Neuroscience and Biobehavioral Reviews 186 (2026) 106710

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

From juvenile stress to adult depressive-like behavior: A systematic review of biomarkers, developmental timing, and sex differences

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ARTICLE INFO

Keywords:
Juvenile stress
Adult vulnerability
Depression
Sex-differences
Biomarkers

ABSTRACT

Early adversity during the peripubertal period is a well-established risk factor for the emergence of adult psychopathology, particularly depression. Notably, depression arising from early stress often presents with greater symptomatic complexity and reduced responsiveness to conventional treatments, underscoring the need to identify biomarkers that can predict long-term vulnerability. Despite this, a major research gap persists regarding the effects of juvenile stress in females, even though clinical evidence indicates that women show heightened susceptibility to stress-related depression. To address these issues, we conducted a systematic review of the literature examining the behavioral and biological consequences of juvenile stress and the biomarkers associated with depression-like outcomes in adulthood. Across studies, juvenile stress rarely left brain or behavior unaffected; instead, it biased developmental trajectories toward a range of maladaptive outcomes, with depression being common but not exclusive. The resulting phenotype was strongly shaped by sex, developmental timing, stressor type and duration, and genetic background. Among biological markers, only two domains showed partial convergence. Functional changes, which were consistently linked to anxiety-related behaviors, and neuroplasticity impairments, which were associated with classical depressive-like outcomes. Overall, biomarker profiles were highly context-dependent, supporting the notion that juvenile stress gives rise to multiple neurobiological pathways rather than a single depressive mechanism. A deeper understanding of these divergent trajectories may improve preventive strategies and guide more personalized therapeutic interventions for depression rooted in early-life stress.

1. Introduction

Accumulating epidemiological evidence suggests that adversity during childhood and adolescence, including experiences of abuse, neglect, or bereavement, constitutes a significant risk factor for the development of psychopathology in adulthood (Caspi and Moffitt, 2006; Heim et al., 2008; Heim and Binder, 2012; Walker and Sandi, 2018). These adverse experiences constitute a profound disruption to normative development, challenging the child's adaptive capacity and often leading to multi-level impairments in biological, psychological, and social functioning (Humphreys and Zeanah, 2015; Nelson et al., 2020; Rizeq et al., 2025). Depression represents one of the most common affective outcomes of such adversity and is among the most prevalent and comorbid psychiatric conditions (Kessler et al., 2013; Moreno-Fernández et al., 2017, 2018, 2023; Bobo et al., 2022; Platona et al., 2024). Although its aetiology is multifactorial, early environmental adversity is a key determinant of vulnerability (Humphreys and Zeanah, 2015; Nelson et al., 2020; Zajkowska et al., 2021; Rizeq et al., 2025). Beyond increasing the likelihood of developing depression, trauma exposure during the peripubertal period contributes to greater symptom heterogeneity and poorer treatment response (Nanni et al., 2012; Allen et al., 2023). Notably, fewer than 18% of individuals with major depressive disorder (MDD) and a history of childhood trauma respond to specialized interventions, compared with response rates exceeding 84% in those without such history, highlighting profound clinical disparities (Williams et al., 2016). These differences underscore the need to

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https://doi.org/10.1016/j.neubiorev.2026.106710
Received 24 January 2026; Received in revised form 28 March 2026; Accepted 23 April 2026
Available online 25 April 2026
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elucidate the neurobiological mechanisms that may drive altered treatment responsiveness, and the increased symptom complexity observed in trauma-exposed individuals (Nemeroff et al., 2003; Nanni et al., 2012; Williams et al., 2016; Tapocik et al., 2021; Dos Santos et al., 2026).

Such outcomes are thought to arise, at least in part, from dynamic interactions between environmental inputs and the developing nervous system. (Boyce, 2016; Pillai and Franze, 2024; Whittle et al., 2025). However, despite the well-established link between early adversity and adult mental health disorders, the specific neurobiological pathways through which such experiences confer increased risk for the development of depression remain incompletely understood.

On the other hand, depression is approximately twice as prevalent in women compared to men, and evidence suggests that the neurobiological substrates of stress and depression may differ by sex (Bangasser and Cuarenta, 2021; Mengelkoch and Slavich, 2024; Da Silva et al., 2025). However, the literature has historically exhibited a strong male bias, both in clinical and preclinical research. Until relatively recently, most animal models and experimental frameworks currently in use have either excluded female subjects or failed to analyze sex as a biological variable (Miller et al., 2017; Rechlin et al., 2022). Consequently, the neurobiological effects of early-life adversity in females remain insufficiently studied and poorly characterized, limiting progress toward the development of targeted, sex-specific interventions (Kang et al., 2020; Harris et al., 2022a, 2022b; Mohammadi et al., 2023).

In addition to sex differences, the impact of peripubertal and juvenile stress is modulated by a range of contextual and individual factors. These include the type of stressor, whether psychological, physical, or physiological, as well as its controllability, duration, and perceived threat level (Kubala et al., 2012; Tapocik et al., 2021). Distinct types of stress may activate different neural circuits and molecular pathways, resulting in divergent symptom profiles. The timing of stress exposure also appears to play a crucial role, as the developing brain may be differentially sensitive to adversity depending on the maturational stage at which it occurs (Vaidya et al., 2024).

Given this complexity, there is a pressing need to identify robust and specific biomarkers that can capture individual and sexual differences in susceptibility or resilience to the effects of juvenile stress. Biomarkers, whether molecular, hormonal, neuroimaging-based, or physiological hold promise not only for elucidating underlying mechanisms, but also for informing early detection, risk stratification, and the development of targeted preventive or therapeutic strategies. Identifying such markers may eventually lead to personalized interventions tailored to the neurobiological and psychosocial profile of everyone.

In this context, the present systematic review was designed to address several interrelated objectives: a) To determine whether juvenile stress is associated with an increased risk of developing depressive-like behavior in adulthood in animal models; b) To assess whether the specific characteristics of stress exposure, namely its type (emotional, physical, social), duration (acute vs. chronic), and timing (i.e., the developmental stage during which adversity occurs), differentially influence vulnerability to adult depressive-like behavior; c) To identify and evaluate biological markers that have been proposed as predictors of depressive-like behavior, following early-life stress, including markers of neuroinflammation, HPA axis dysregulation, neurogenesis, epigenetic modifications, and alterations in brain connectivity; d) To explore sex- and individual-dependent differences in both the effects of juvenile stress and the predictive value of identified biomarkers.

By integrating findings across preclinical studies, this review seeks to advance our understanding of the neurodevelopmental mechanisms that link juvenile stress with adult depressive-like behavior. The synthesis highlights key moderators, particularly sex and individual variability, which strongly influence vulnerability and shape long-term outcomes. Together, the findings support a view of depressive-like behavior as a heterogeneous condition arising from multiple etiological pathways, some specifically rooted in early-life stress. A clearer understanding of these mechanisms may ultimately guide the development of more targeted, mechanistically informed preventive and therapeutic strategies for high-risk individuals.

2. Methods

2.1. Search strategy

We searched the literature using four primary electronic databases: Web of Science, Scopus, PsycINFO, and Medline. The search was performed in February 2025 and restricted to articles published between the year 2000 and the 31st of December 2024. To maximize the search results and capture all relevant articles, we combined the terms (1) “Juvenile stress”, (2) “Early stress”, (3) “Adolescent stress” and (4) “Peripubertal stress” with the key terms *(A) “Depressi*”, (B) “Biomarker*” and (C) “Gender differenc*”, resulting in a total of four search combinations. One example of the Boolean search would be “Juvenile stress” AND (“depressi*” OR “Biomarker*” OR “Gender differenc*”), and this strategy was repeated for “Early stress”, “Adolescent stress” and “Peripubertal stress”.

Two authors (V.M.A. & A.Z.D.) independently searched and reviewed the selected studies according to the established inclusion and exclusion criteria. Discrepancies were resolved by consensus and discussed with a third author (C.P.B.). The search and selection of articles followed the Cochrane and PRISMA guidelines (Page et al., 2021; Higgins et al., 2024).”

2.2. Inclusion and exclusion criteria

Study selection was guided by the PICO framework, defining the population as healthy male and female rodent models (mice and rats) of different strains assessed in adulthood following stress exposure during juvenile or adolescent developmental periods. Human studies, other animal species, and rodent models with pathological conditions were excluded. The intervention consisted of stress exposure (e.g., social isolation, chronic unpredictable mild stress, physical restraint, predator odor exposure) applied during the juvenile/adolescent period, approximately PND 21–65 in mice and PND 21–70 in rats. The comparison included age-, sex-, and strain-matched non-stressed control animals housed under standard conditions. The primary outcome was depressive-like behavior in adulthood following juvenile stress exposure, together with associated neurobiological biomarkers. Following this framework, inclusion criteria were: (1) empirical, peer-reviewed articles in English or Spanish; (2) use of rodent models; (3) stress exposure during juvenile or adolescent phases; and (4) assessment of depressive-like behavior and biomarkers in adulthood. Studies were excluded if they were theoretical or review articles, measured outcomes exclusively during adolescence, lacked biological markers, or utilized models of comorbid clinical disorders such as schizophrenia, bipolar disorder, or epilepsy.

To ensure developmental accuracy within this framework and taking into account species- and sex-specific differences (Bell, 2018; Tirelli et al., 2003; Arellano et al., 2024), developmental stages were defined as follows. The juvenile/pre-pubertal period extends from weaning (PND 21) to puberty onset, approximately PND 26 in female mice, PND 30 in male mice, PND 34 in female rats, and PND 45 in male rats (Arellano et al., 2024). Adolescence is generally considered to span from PND 21 to PND 59 in mice and up to PND 65–70 in rats and has been further subdivided into early (pre-pubertal; PND 21–34), mid- (peri-adolescent; PND 34–46), and late adolescence (PND 46–59) based on developmental milestones (Tirelli et al., 2003). Adulthood begins around PND 60 for mice and female rats, whereas male rats typically reach full maturity at PND 70 (Arellano et al., 2024; Bell, 2018). However, these boundaries should be considered approximate, as developmental transitions may vary depending on species, sex, and experimental context and the precise timing may differ between mice and rats. Accordingly, some studies extend adolescence up to approximately PND 65, highlighting a partial overlap between late adolescence and early adulthood (Borsini et al., 2023).

2.3. Identification

The initial search across the four databases identified a total of 2497 articles (749 from Web of Science, 490 from Scopus, 463 from PsycINFO, and 795 from MedLine). After removing duplicates, 918 articles remained. An initial title and abstract screening eliminated 847 articles that were either outside the scope of this review or did not meet the inclusion/exclusion criteria. The remaining 71 articles were considered for full-text review. Thirty articles were excluded from this selection for the following reasons: Lack of juvenile stress (15 articles), lack of an adult measurement of depression (10 articles), and lack of biomarker (5 articles). Consequently, 41 articles fully met all the established criteria and were included in the systematic review. Finally, another 9 articles were included through the snowballing process. The literature search and study selection process are summarized in the flow chart presented in Fig. 1.

3. Results

3.1. Behavioral paradigms used to assess depressive-like phenotypes

Across the reviewed studies, juvenile stress exposure was induced using a variety of experimental procedures designed to model early-life adversity. The most common paradigms included social stress (e.g., social isolation or social instability), chronic unpredictable mild stress (CUMS), restraint stress, predator-related stressors, and mixed or

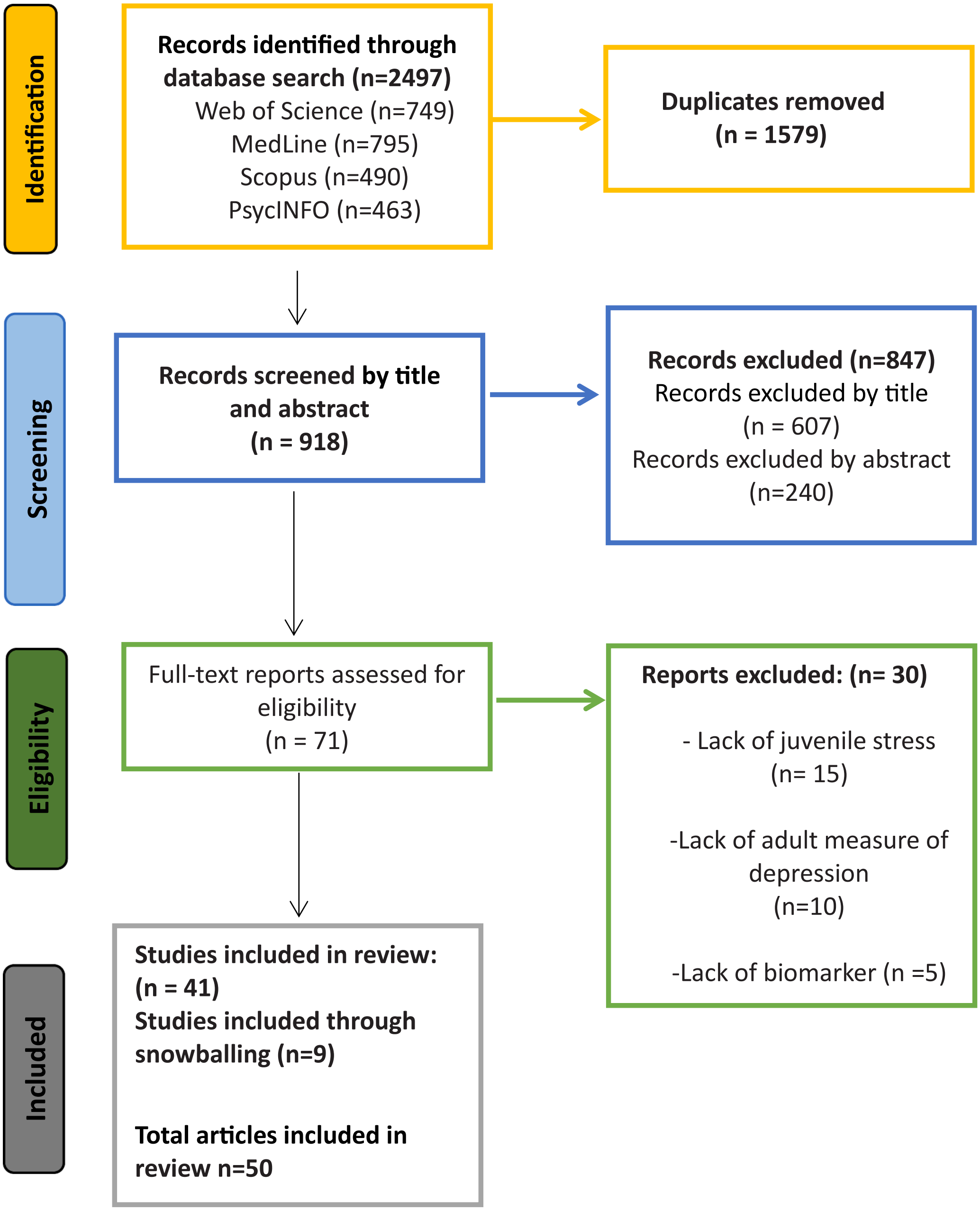

Fig. 1. Search and study selection flowchart. The flowchart illustrates the identification phase, with the number of records retrieved from each database; the screening phase; the eligibility phase, including the number of articles excluded for each criterion; and the inclusion phase, showing the final number of studies included in the systematic review.

variable stress protocols. Although the specific stressors and their duration varied across studies and species, these procedures are widely used in preclinical research to induce long-lasting alterations in affective and motivational behavior. A structured overview of these paradigms, including their characteristics and validity, is provided in Table 1.

To characterize depressive-like outcomes following juvenile stress exposure, the reviewed studies employed a range of behavioral paradigms targeting different affective and motivational domains. In line with the Research Domain Criteria (RDoC) framework proposed by the National Institute of Mental Health (NIMH), affective disorders are increasingly conceptualized as multidimensional constructs (Carcone and Ruocco, 2017; Insel et al., 2010). These involve alterations across negative valence systems, prominently including anxiety and overlapping distress (Ahmed et al., 2018; Böttger et al., 2023), as well as cognitive (von Mücke-Heim et al., 2023; Woody and Gibb, 2015), and motivational systems (Ahmed et al., 2018; von Mücke-Heim et al., 2023). Accordingly, behavioral domains such as anxiety-related responses and cognitive impairments are often evaluated in preclinical studies as components of the broader depressive-like phenotype rather than as entirely independent outcomes. In this context, the Forced Swim Test (FST) was the most frequently employed tool to assess the consequences of juvenile stress (76% of studies). Although traditionally interpreted as a measure of 'behavioral despair', it is important to note that this interpretation is currently under scrutiny (Molendijk and de Kloet, 2015; Gorman-Sandler and Hollis, 2022); contemporary perspectives suggest that increased immobility may represent an adaptive energy-saving strategy or a specific coping style rather than a purely depressive-like state (Molendijk and de Kloet, 2015).

Similarly, other tasks were used to infer different dimensions of depressive-like phenotypes, such as the Sucrose Preference Test (SPT, 48%) (Primo et al., 2023) and the Splash Test (ST), which assess anhedonia-like behaviors and self-care deficits (Butelman et al., 2019), respectively. The Social Interaction Test (SIT) provided indices of social withdrawal (Mancha-Gutiérrez et al., 2021). The Tail Suspension Test (TST), applied in a smaller subset of studies, is conceptually like the FST and measures the duration of immobility when animals are suspended

Table 1

Classification of Juvenile stress protocols by stressor types.

Protocol/Main category	Nature of Stressor	Specific stressors used (frequency)	Description/Primary Impact	Validity
1. CUMS/ Mixed stressors (32 articles)	**Physical/ sensorimotor**	Restraint (18), Forced swimming (11), Cold (7), Tail puncture (6), Footshock (5), Shaking (4), Heat exposure (4), Rotation (2), Water immersion, Tail suspension	Induces physical fatigue, direct pain activation, or thermal discomfort. Triggers a strong HPA axis response.	**Construct Validity:** Originally proposed by Willner et al. (1987) to model chronic, unpredictable socio-environmental stress (Nollet, 2021). **Face Validity:** Strongly associated with anhedonic behavior (sucrose preference loss) and environmental loss of control (Antoniuk et al., 2019). **Predictive Validity:** Robust; symptoms are successfully reversed by chronic antidepressant treatment (Zhang et al., 2019; Pałucha-Poniewiera et al., 2023).
	Psychological/ Environmental	Elevated platform (10), Lights exposure (8), Cage tilt/slanted cage (8), Wet bedding (5), Predator odor (fox 5, rat 2, snake), Noise (4), Day and night reversal (4), Lights off (3), No bedding (2), Dirty/soiled cages, Open field (2), Novel environment.	Disrupts circadian rhythms, creates a sense of threat (odors/ heights), and induces a loss of environmental control.	
	Metabolic/ Homeostatic	Water deprivation (9), Food deprivation (8), Hypoxia (2).	Directly compromises energy resources and basic survival needs	
	Social (within CUMS)	Isolation (5), Social crowding (2), New partner (2), Exchange of residents, Intruder, Paired housing, Social defeat stress.	Acute social instability paradigms to cause social stress or isolation	
	Pharmacological	Lithium chloride injection.	Induces gastric distress/nausea (interoceptive stress).	
2. Social stress	**Psychological/ Social**	Chronic Variable Social Stress/CVSS (5), Isolation (5).	Interferes with the development of prosocial behaviors, social hierarchies, and social behavior	**Construct Validity:** High ethological relevance; mimics human psychosocial stress, bullying, and social subordination (Golden et al., 2011). **Face Validity:** Effectively induces social avoidance, withdrawal, and anhedonia-like phenotypes (Antoniuk et al., 2019). **Predictive Validity:** Crucial for identifying "Resilient" vs. "Susceptible" phenotypes and testing novel rapid-acting antidepressants (Hollis and Kabbaj, 2014)
3. Physical stress	**Physical**	Footshock (5), Restriction/Restraint stress (2).	Monotypic (non-mixed) protocols. Generate an acute or chronic response based primarily on pain or immobilization.	**Construct Validity:** Uses footshock/restraint to model both Depression and PTSD (Bali and Jaggi, 2015). Shows circuit-level convergence with human pathology (Gyles et al., 2024). **Face Validity:** Replicates core human symptoms like anhedonia and specific neurochemical shifts (Mao et al., 2022). **Predictive Validity:** Validated via reversal of effects by antidepressants, including Ketamine and Fluvoxamine (Lyttle et al., 2015; Aikawa et al., 2020).
4. Endocrine stress	**Pharmacological/ Physiological**	CORT (Corticosterone) exposure.	Simulates the effect of chronic stress by bypassing stressor perception (direct impact on glucocorticoid receptors).	**Construct Validity:** Directly manipulates the primary effector of the **HPA axis**, bypassing the variability of environmental stressors (Shoji et al., 2024). **Face Validity:** Produces a robust phenotype mirroring core human symptoms: **anhedonia**, anxiety, and cognitive dysfunction (Wang et al., 2024). **Predictive Validity: Limited/Inconsistent;** unlike CUMS or Physical Stress, its pharmacological reversal has not been consistently documented.

by the tail, typically interpreted as reflecting passive coping (Gencturk and Unal, 2024)

Regarding other domains, anxiety-related behaviors were widely assessed (in nearly 80% of the studies), most commonly using the Elevated Plus Maze (EPM), Open Field (OF), and Light-Dark Box (LDBT) (Gencturk and Unal, 2024). While cognitive functions were explored less frequently, tasks such as the Morris Water Maze (MWM). Object Recognition Test (ORT) (Vorhees and Williams, 2024), Object–Context Mismatch Test (OCMT), and the Attention-Shift Task (ACT) (Heisler et al., 2015) provided insights into executive and memory deficits. It should be noted that the references cited in this paragraph are not derived from the systematic search but are included to support the interpretation and functional relevance of these behavioral paradigms. Nevertheless, while these paradigms are widely used in preclinical research to model behavioral domains relevant to depressive-like phenotypes, their interpretation is not universally agreed upon and should be considered within the broader behavioral context of each study. For a detailed overview of these behavioral tests and their specific parameters across studies, see Table 2."

3.2. Association between juvenile stress and adult depression

Evidence from the reviewed studies supports a link between peri-adolescent stress and later depression risk, with very few exceptions. Only six of the reviewed studies failed to report depressive-like behavior following juvenile stress exposure (Luo et al., 2014; Azogu et al., 2018; Page and Coutellier, 2018; Walker and Sandi, 2018; Lovelock and Deak, 2019; Drzewiecki et al., 2021). However, even in these cases, increases in anxiety-like behaviors (Luo et al., 2014; Page and Coutellier, 2018; Walker and Sandi, 2018), or cognitive impairment, particularly in males (Page and Coutellier, 2018), both of which fall within the broader depressive-symptom spectrum. Drzewiecki et al. (2021) additionally reported impaired prepulse inhibition (PPI), more often associated with schizophrenia, yet also documented in some depressed patients (Perry et al., 2004; reviewed in Santos-Carrasco and De la Casa, 2023).

Two studies, however, showed non-orthodox forced swimming test/tail suspension test (FST/TST) outcomes with increased latency to immobility with enhanced exploration (De Lima et al., 2017) and reduced immobility accompanied by elevated plus maze/locomotion test (EPM/LOC) indices of hyperactivity (Simó et al., 2012), patterns observed in males and compatible with sex-specific depressive phenotypes (Krahe et al., 2015; Pietrantonio et al., 2025). Similarly, several studies in Sprague–Dawley rats reported no anhedonia (Harris et al., 2022a; Xue et al., 2023), with the absence of anhedonia in Xue et al., 2023 observed only after 30 days of stress, whereas shorter 14-day exposure induced anhedonia, highlighting strong strain-dependent resilience. Additional null findings appeared in C57BL/6N NMRI and Wistar rats (Luo et al., 2014; Eidson et al., 2019; Ranaei et al., 2020; Fariborzi et al., 2021), particularly when sucrose ≥ 2% likely produced ceiling effects.

By contrast, most studies consistently reported increased immobility or reduced latency to immobility in the FST/TST and/or anhedonia following juvenile stress. In particular, elevated immobility emerged across a wide range of stress paradigms, including chronic unpredictable mild stress (CUMS, isolation, mixed stressors, predator exposure, restriction, social instability, and footshock), and across species such as mice (Schmidt et al., 2010; Yohn and Blendy, 2017; Fariborzi et al., 2021; Aleksic et al., 2022; Takaba et al., 2022; Niwa et al., 2024) and rats (Bourke and Neigh, 2011; Wilkin et al., 2012; Veenit et al., 2014; Lyttle et al., 2015; Wulsin et al., 2016; Arcego et al., 2018; Cotella et al., 2018; Ghalandari-Shamami et al., 2019; Aikawa et al., 2020; Brás et al., 2022; Harris et al., 2022b; Sun et al., 2023). Anhedonia also emerged frequently, especially after long CUMS exposure (>20 days) in Wistar rats (Wang et al., 2018; Xu et al., 2019, 2024) or C57BL/6J mice (Takaba et al., 2022), t was also reliably induced by shorter peripubertal or mixed-modality stressors (Bourke and Neigh, 2011; Márquez et al., 2013), mid-adolescent isolation (Niwa et al., 2024), and predator stress in rats (Tapocik et al., 2021). These effects were sometimes sex-specific or dependent on stress sensitivity (Bourke and Neigh, 2011; Caruso et al., 2017; Bràs et al., 2022).

Importantly, anhedonia and immobility did not always emerge or co-occur; however, affective disturbances were almost invariably present, often manifesting as anxiety-like responses following footshock or mixed stress (Azogu et al., 2018; Lovelock and Deak, 2019; Fariborzi et al., 2021), CUMS (Page and Coutellier, 2018) or as altered emotional behaviors such as risk-seeking in predator-based paradigms (Eidson et al., 2019). Cognitive impairments, though less extensively assessed, emerged in the object recognition test (ORT), Morris Water Maze (MWM) and related tasks (Page and Coutellier, 2018; Xu et al., 2019; Sun et al., 2023).

Furthermore, a subset of studies employed two-hit paradigms in which juvenile stress was combined with either earlier developmental insults or subsequent environmental challenges. In these models, behavioral outcomes were typically more severe than after juvenile stress alone, indicating that both prior and subsequent stressors can potentiate the impact of juvenile stress, thereby amplifying vulnerability to later depressive-like phenotypes (Raftogianni et al., 2012; Arcego et al., 2018; Ranaei et al., 2020; Huang et al., 2021; Niwa et al., 2024). Although Jaric et al. (2019) reported attenuated anxiety when juvenile stress followed early-life stress.

3.3. Influence of stress type, duration, and developmental timing during the peripubertal period on adult depression susceptibility

Although findings remain heterogeneous, the evidence can be organized according to developmental timing, stress type, and exposure duration, which jointly shape, but do not fully determine, susceptibility to depressive-like behaviors in adulthood.

Stress exposure during pre-pubertal (juvenile) stages (before PND 34) generally produced weaker or inconsistent depressive-like outcomes, particularly in short protocols (3–7 days). Some brief stressors produced subtle changes in anxiety or active coping with stress (Harris et al., 2022a) or affected anxiety without altering depressive-like behavior (Luo et al., 2014). In contrast, other paradigms yielded clearer effects. For example, variable stress at PND 27–29 increased anxiety and passive coping (Ilin and Richter-Levin, 2009), and variable stress + social isolation (VS/IS) combinations at PND 24–26 induced contextual fear generalization, while isolation increased immobility (Müller et al., 2014). Similarly, isolation-based protocols, whether applied alone or following early adversity, increased FST immobility (Raftogianni et al., 2012; Arcego et al., 2018).

Similarly, footshock paradigms during this stage also showed clear duration- and intensity-dependent effects. Repeated footshock (PND 28–33) increased anxiety-like behavior (Li et al., 2015), whereas a mild protocol increased immobility without affecting anxiety (Lyttle et al., 2015). Similarly, daily footshock (PND 21–25) increased immobility but did not alter anhedonia (Aikawa et al., 2020), while a single exposure at PND 29 selectively affected anxiety-related responses in males (Lovelock and Deak, 2019).

Longer protocols yielded more consistent changes, particularly under mixed or ethologically relevant stressors. Across mixed paradigms, stress effects depended on timing, complexity, and individual susceptibility. Early-to mid-adolescent mixed stress reduced self-care behavior, particularly in females (Alcaide et al., 2024) and increased anxiety in both sexes but immobility only in males, whereas applying the similar paradigm slightly later increased both exploration and immobility (Wilkin et al., 2012). More complex combinations produced robust outcomes. Thus, social defeat (PND 28–42) increased anxiety and aggression (Kovalenko et al., 2014), while a restriction + light–noise protocol (PND 30–40) induced male-specific memory deficits and female-specific anxiety. Moreover, both sexes showed reduced latency to immobility after 30 days of recovery (Fariborzi et al., 2021).

Table 2
Characteristics and main findings of the selected articles (organized in alphabetical order of first author's name) divided into single and double stress studies.

REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
Articles with a single stress protocol									
Aikawa et al., 2020	Wistar rats	M	Footshock	Age-, sex-, and strain-matched controls with vehicle injections. There is an experimental group receiving treatment with ketamine (not shown)	P21–25	FST SPT	↑ Immobility in the FST of juvenile stressed groups. No effects in anhedonia measured with SPT	Synaptic plasticity/ Synaptic proteins Excitatory/Inhibitory balance	↓ Apical spine density of pyramidal neurons in layer V of mPFC in the juvenile stressed group ↓ Excitatory neurotransmission, affecting the Excitatory/ Inhibitory balance in the mPFC in the juvenile stressed group ↑ Frequency of mIPSCs in the mPFC in the juvenile stressed group
Alcaide et al., 2024	C57BL/6J-tg (PV-tdTomato) 15 Gfng/6J mice	M/ F	Mixed stressors: 7 stressors in 7 non-following days: Novel environment, fox odor (TMT), tail puncture, elevated platform, restraint, tail suspension, forced swimming	Age-, sex-, and strain-matched naïve controls	P28–42	OFT ST	MF: No behavioral differences in OFT after stress. ↓ Licking in ST in the stressed group	Brain morphology Synaptic plasticity/ Synaptic proteins Excitatory/Inhibitory balance. Neuroinflammation	F: ↓ volume of the thalamic reticular nucleus in the juvenile stressed group F: ↑ WFA-labeled PNN fluorescence intensity and ↓ density of PSA-NCAM in the thalamic reticular nucleus in the juvenile stressed group F: ↑ PV+ puncta fluorescence intensity in the lateral posterior nucleus of the thalamus in the juvenile stressed group M: ↓ Fluorescence intensity points expressing inhibitory synaptic markers in the thalamic reticular nucleus (VGLUT1, VGLUT2, and VGAT) in the juvenile stressed group MF: No changes in Iba1 or GFAP Significative negative correlation in PPS males between TRN volume and immobile episodes
Aleksic et al., 2022	C57BL/6J mice	M/ F	CUMS Cold, cage tilt, lights off, shaking, rat odor, forced swim, restraint, new partner, no bedding	Age-, sex-, and strain-matched naïve controls	P28–40	OFT EPM NSFT TST FST	MF: stress caused ↑ Anxiety-like behaviors. ↓ Time spent and entries to the center of OFT. ↓ Time in open arms in EPM and ↑ latency to eat in the NSFT ↑ Depressive-like behaviors. ↑ Immobility in FST and TST	HPA axis Gene expression and epigenetics. BDNF/Neurotrophins	M: stress caused ↑ GR25 and 40 glucocorticoid receptor isoforms in the hippocampus. ↑ GR50 isoform in PFC in the juvenile stressed group ↑ Levels of glucocorticoid receptor mRNA in the hippocampus and BDNF mRNA in the PFC F: stress caused ↓ GR25 and ↑ GR40 glucocorticoid receptor α isoforms in the hippocampus. ↑ GR25 and 40 isoforms in PFC. ↓ Levels of glucocorticoid receptor and BDNF mRNA in the hippocampus and PFC. ↑ expression of FKBP5 and IL-1β in the hippocampus

(*continued on next page*)

Table 2 (*continued*)

REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
Azogu et al., 2018	Wistar rats	M/ F	Mixed Stressors: Restriction + Forced swimming	Age-, sex-, and strain-matched controls with vehicle injections. There is an experimental group receiving treatment with TrKb receptor agonist (not shown)	P26–36	OFT EPM FST	MF: ↓ Open arm entries in the EPM. No effect of FST in the juvenile stressed group	Gene expression and epigenetics. BDNF/Neurotrophins	M: ↑ levels of TrkB receptor isoforms TrkBT.1 (truncated) and FL (full length) in both PFC, NAc, and hippocampus compared to F on a physiological basis M: ↓ Levels of both isoforms in the nucleus accumbens and ↑ levels in the PFC, in the juvenile stressed group. This suggests a site-specific expression of TrkB receptors Under stress, there are brain region differences in the isoform expression ratios, with the hippocampus having 3.41 T1 to FL isoform ratio, 1,73 for the PFC, and 1,76 for the Nac. ↑ PFC ratio is related to alterations
Bertholomey et al., 2022	Sprague-Dawley rats	M/ F	Chronic CORT exposure	Age-, sex-, and strain-matched naïve controls	P30–50	EPM CFC SPT FST	F: ↓ Anhedonia (SPT), ↓ anxiety-like (greater percent open arm entries), depressive-like (less immobile time), and fear-related behaviors (↓ freezing) irrespective of treatment. ↑ Immobility in FST in the juvenile stressed group. M: No differences in behavior in the juvenile stressed group	HPA axis Neurotransmitters	F: stress caused ↑ CORT consumption and plasma levels regardless of age F: Control ↑ basal expression of GluA1 and GluA2/3 of AMPA in the BLA compared to males. Adolescent CORT treatment ↓ GluA1 and GluA2/3 expression in females M: Adolescent CORT treatment ↑ GluA1 and GluA2/3 subunits in comparison female
Bourke and Neigh, 2011	Wistar rats	M/ F	Mixed stressors: Isolation, restriction, and social defeat stress	Age-, sex-, and strain-matched naïve controls	P37–49	EPM ASR FST SPT	F: ↑ Depressive-like behaviors both in SPT (↑ anhedonia) and FST (↓ latency to immobility). In EPM, chronic stress increased locomotor activity but not exploration in the stressed group M: No effect of stress	HPA axis	F: Blunted ↑ in plasma CORT after stress M: Not affected
Brás et al., 2022	Wistar Han rats	M	Mixed stressors: Open field, synthetic fox odor, and elevated platform.	Age- and sex-, matched naïve controls from two different strains: High and low CORT responsive group	P28–42	OFT EPM SIT SPT FST	↓ Sociability and exploring motivation in SIT in all experimental conditions subjected to juvenile stress ↑ Time in periphery (OFT), ↑ anhedonia (SPT), and ↑ immobility time (FST) in the high CORT-responsive group subjected to juvenile stress	Neuroinflammation/ Immune activation	↑ Levels of IL-1β, IL-6, and IBA-1 in mPFC and ↑ levels of IL-1β and IL-6 in the nucleus accumbens in the high CORT-responsive group alone ↑ TNF-α in the nucleus accumbens of the high CORT-responsive group subjected to juvenile stress ↑ TNF-α in the hippocampus in all groups subjected to juvenile stress, and correlates with

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
									worsened depressive behaviors ↑ IBA-1 and morphological alterations in hippocampal microglia of the high CORT-responsive group subjected to juvenile stress. The alterations studied are reduced arborization volume, decreased total number of branches, and a shift toward an amoeboid shape ↑ microRNA (miR-342) expression in the high CORT-responsive group subjected to juvenile stress. This correlated with TNF- α expression, depressive-like behaviors, and microglial arborization volume
Caruso et al., 2017	BALB/cJ mice	M/F	CVSS Chronic variables social stress: repeated cycles of individual-housing (3 days) and re-socialization with two unfamiliar same-sex cagemates (4 days)	Age-, sex-, and strain-matched naïve controls	P22–50	EPM SPT FST	MF: stress caused ↓ Time in open arms, ↓ open arm entries, and ↓ locomotion in EPM (anxiety-like behaviors). No effects in the FST F: ↑ Anhedonia after stress	HPA axis	MF: ↓ Concentrations of fecal corticoids in the stress group suggest hypoactive HPA in adulthood F: ↓ Concentrations of fecal corticoids during daytime in the juvenile stressed group Positive correlation between corticoids and SPT in F
Cotella et al., 2018	Wistar rats	M	CVS Hypoxia, rotation, cold exposure, foot shock, lithium chloride injection, restriction, and novel environment	Age-, sex-, and strain-matched naïve controls	P40–54	EPM FST	↓ Entries to the center in EPM and ↑ immobility time in FST caused by stress	HPA axis Fos-B	No differences in the HPA axis response of the juvenile stressed group ↓ Fos-B expression in PVN of the hypothalamus in the juvenile stressed group
De Lima et al., 2017	Balb/c mice	M	CUMS Water deprivation, wet bedding, cold, exchange of residents, restraint, intruder, forced swim, slanted cage, dirty bedding	Age-, sex-, and strain-matched naïve controls	P28–38	LDBT OFT NORT TST	↓ Time in the center of the OFT and ↑ latency to immobility in the TST of the juvenile stressed group. No differences in the LDBT. ↑ Exploratory behaviors towards the object in NORT in the control group	HPA axis Neurotransmitters	↑ CORT levels in serum and adrenal weight in the stressed group ↓ 5-HT levels in PFC, hippocampus and hypothalamus. ↑ 5-HIAA in the PFC of the juvenile stressed group ↓ Noradrenaline in the hippocampus and hypothalamus. ↑ VMA in the hippocampus of the juvenile stressed group ↑ Dopamine turnover in general. Significant ↓ in metabolite HVA in the hypothalamus caused by stress
Drzewiecki et al., 2021	Long Evans rats	M/F	Restriction and isolation stress Rats were divided into: Pubertal stress (PS), post-pubertal stress (post-PS) and unstressed (US) groups	Age-, sex-, and strain-matched naïve controls	M: P41–47/49–55 F: P32–38/40–46	EPM PPI OFT NORT FST	M: ↑ Anxiety-like behavior compared to F MF: stress reduced PPI, indicating impaired inhibitory processing, but only during puberty onset and not at later	Brain morphology	MF: ↓ Volume of mPFC. F: ↑ Neuronal density in mPFC in the PS group

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
							stages. F: ↓ Passive behavior compared to M, independent of stress (FST) MF: No differences in exploration behavior (OFT). No differences in anxious or depressive-like behaviors long-term		
Eidson et al., 2019	C57BL/6J mice	M/F	Intermittent predator stress	Age-, sex-, and strain-matched controls with vehicle injections. There is an experimental group receiving treatment with solTN (not shown)	P34–64	SIT OFT SPT	M: More affected in social interaction. Stressed males took longer to enter the strange chamber and to sniff the stranger F: More affected in OFT, increasing risk-seeking behaviors. Stressed females took longer to freeze and spent more time in the center and less in the borders of the OF compared to controls. MF: Stress did not alter sucrose preference when tested at 2 or 4 weeks.	Neuroinflammation/Immune activation Metabolism/Microbiota Body weight/Body composition	M: ↑ weight in gonadal fat. ↓ CXCL1 in the cortex in the juvenile stress group. *Stress did not change fecal inflammatory protein levels… There was no main effect of stress condition on… indicators of gut dys-function* F: ↑ plasma IL-4 and CXCL1 compared to M, where there was a decrease. ↑ CCL2 in the cortex. ↑ TNF-α in the hippocampus. ↓ IL-6 in cortex of stressed animals. ↑ CCL2 in the amygdala in the juvenile stress group MF: ↑ IL-1β, ↓ TNF-α, LCN2, and TLR4 levels in the cortex of stressed animals. ↑ Lcn2 and CCL2 in the hippocampus. ↓ TNFR1 and TNFR2 in the intestines in the juvenile stress group Stress did not change fecal inflammatory protein levels.
Fariborzi et al., 2021	C57BL/6J mice	M/F	Mixed stressors: Restriction and light-noise exposure.	Age-, sex-, and strain-matched naïve controls	1 h for 10 days P30–40	YMT LDBT FST SPT	MF: ↑ Immobility in the FST. No differences in SPT in the juvenile stress group M: ↓ Performance in YMT in the juvenile stress group F: ↓ Entries in open arm in LDBT and ↑ anxious behavior in LDBT in the juvenile stress group	Excitatory/Inhibitory balance	M: The juvenile stress group had ↓ Excitatory impulses in the deep layers of the posterior parietal cortex, measured using whole-cell voltage clamp recordings from pyramidal neurons F: Not affected by stress. Correlation with deficits in visuospatial working memory in the YMT
Ghalandari-Shamami et al., 2019	Wistar rats	M	Restriction stress	Age-, sex-, and strain-matched naïve controls	P30–40	EPM FST	↑ Anxiety (↓ percent of open arm time and open arm entries in EPM) and depressive-like behaviors (↑ immobility time) in the juvenile stress group	HPA axis Brain morphology	Juvenile stress caused: ↑ CORT levels and adrenal weight ↓ Dendritic length of pyramidal neurons of infralimbic and prelimbic regions of PFC. ↓ Dendritic branch points of pyramidal neurons in the infralimbic region

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
Harris et al., 2022a	Sprague-Dawley rats	M/F	Mixed stressors: Forced swimming, elevated platform, Restriction	Age-, sex-, and strain-matched naïve controls	P27–29	NIH OFT SPT FST	MF: ↓ Latency to drink a palatable solution (NIH). ↓ Climbing and ↑ swimming (escape-oriented behaviors), but no effect on immobility in the FST. No effect of stress on SPT F: ↓ Number of rearings in OFT, although no anxiety effect as evidenced by crossings in the juvenile stress group	Neurotransmitters Neurogenesis Cell markers	MF: stress ↑ tyrosine hydroxylase in PFC only. Catecholaminergic innervation in the PFC might explain reward-seeking behavior deficits, the authors suggest MF: No effect of stress on hippocampal neurogenesis (DCX+ count)
Harris et al., 2022b	Sprague-Dawley rats	M/F	Mixed stressors: Forced swimming + elevated platform + restriction	Age-, sex-, and strain-matched naïve controls	M: P35–37 F: P45–47	OFT NIH FUST SPT FST	MF: ↑ Immobility and reduced climbing in FST caused by juvenile stress M: Stress ↑ Anhedonia in SPT F: Stress ↓ Rearings in OFT	HPA axis Neurotransmitters	MF: No changes in CORT levels in adulthood. ↓ 5-HT turnover in the striatum of the juvenile stressed group M: ↓ Dopamine turnover in striatum F: ↑ Dopamine turnover in striatum
Ilin and Richter-Levin, 2009	Sprague Dawley rats	M	Mixed stressors: forced swimming, elevated platform, and restriction	Age-, sex-, and strain-matched naïve controls	P27–29	OFT EPM NSE TWSAT	↑ Anxious and depressive behaviors as evidenced by less exploration in the OFT and EPM. Learned helplessness in the TWSAT with fewer escape attempts in the juvenile stress group	HPA axis Synaptic plasticity/ Synaptic proteins	↑ CORT concentrations in the group that underwent juvenile stress ↓ Levels of L1-CAM (related to axon growth, neural migration, and survival) in BLA and thalamus
Jankord et al., 2011	Sprague-Dawley rats	M	CVS during early adolescence, late adolescence or adult period (not shown) Plastic restraint tube, shaker stress, hypoxia, open field, and cold room	Age-, sex-, and strain-matched naïve controls	P35–50 or P50–64	FST	No differences in behavior in the FST of the early juvenile stressed group (P35–50) or late juvenile stressed group (P50–64)	HPA axis Metabolism/ Microbiota Body weight/Body Composition	↑ Basal CORT plasma levels and reduced oxytocin expression in PVN in the late juvenile stressed group ↓ Body weight and body weight gain, ↑ adrenal size, ↓ and body fat composition in the early juvenile stressed group ↓ body weight, body weight gain, thymus size and ratio, fat tissue in the late juvenile stressed group
Kim et al., 2021	Wistar Kyoto rats	M/F	Footshock to induce CFC	Age- and sex- matched naïve controls from two different strains (high and low reactivity to stress). Animals were classified as high or low immobility responders	P32–34	CFC OFT SIT FST	MF: ↑ Immobility time in FST in the genetically less stress-reactive strain subjected to juvenile stress M: ↑ Freezing and ↓ time in the center of the genetically less stress-reactive strain subjected to juvenile stress, compared to the genetically more stress-reactive strain also	HPA axis Gene expression and epigenetics. BDNF/Neurotrophins	F: ↑ Nr3c1 glucocorticoid receptor expression in PFC of females of the more stress-reactive strain compared to males (for both control and stressed conditions) ↑ Nr3c1 glucocorticoid receptor expression in the hippocampus of the genetically less stress-reactive strain compared to the genetically more stress-reactive strain M: ↑ Nr3c1 glucocorticoid

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
							subjected to stress F: ↓ Immobility in FST in a genetically more stress-reactive strain subjected to juvenile stress. No effect in OFT or SIT. F shows less vulnerability to stress in general compared to M		receptor expression in the hippocampus of the genetically less stress-reactive strain. (both control and stressed males, in comparison to the control and stressed males of the higher reactive strain) MF: ↑ BDNF expression in PFC in the control groups of the genetically more stress-reactive strain compared to the less reactive. This difference was not found in the juvenile stressed groups. In the hippocampus, ↓ BDNF in the more stress-reactive strain subjected to juvenile stress No correlation between behavioral phenotypes and BDNF levels
Kovalenko et al., 2014	C57BL/6 J mice	M	Social Defeat Stress	Age-, sex-, and strain-matched naïve controls	P28–42	PT EPM SIT AIT FST	↓ Latency to move in OFT. ↑ Anxious behavior in EPM (↓ open arm entries and number of head dips and peepings). ↑ Aggressivity in AIT in the juvenile stressed group	Neurogenesis Cell markers	Juvenile stress initially reduced BrdU levels, but no differences in DG cell proliferation/survival were observed 3 weeks later.
Li et al., 2015	Wistar rats	M	Footshock	Age-, sex-, and strain-matched controls with vehicle injections. There is an experimental group receiving treatment with central corticotropin-releasing factor receptor 1 (not shown)	P28–33	EPM YMZ OFT	↓ Time in central squares, horizontal and vertical movement scores and number of groomings of juvenile stressed group compared to controls in the OFT. ↑ Number of fecal boli ↓ Ratio of entry to open arms and time in the open arms of the juvenile stressed group compared to controls in the EPM Y maze (spatial memory) registered ↓ ratio of entry to novel arm and ratio spent in the novel arm in the stress group	HPA axis	Juvenile stress ↓ Basal CORT levels. ↑ DEX negative feedback inhibition and displayed exacerbated and longer-lasting reactions to CRH challenge as evidenced by the DEX-CRH test Juvenile stress ↑ Expression of CRFR1 in PFC, amygdala and hypothalamus but reduced in hippocampus
Lovelock and Deak, 2019	Sprague-Dawley Rats	M/ F	Footshock	Age-, sex-, and strain-matched naïve controls	P29	SIT LOC LDBT FST	M: ↑ Anxiety (LDBT). No depressive-like behaviors or socialization deficits (SIT) F: Not affected	HPA axis C-FOS IL-1β Gene expression and epigenetics	MF: ↑ IL-1β after FST. HPA axis genes not affected by stress MF: ↑ C-Fos in medial amygdala caused by juvenile stress
Luo et al., 2014	Wistar rats	M	CVS Restraint (2 h, P27) Elevated platform (30 min,	Age-, sex-, and strain-matched naïve controls	P27–33	EPM OFT	↑ Anxiety-like behaviors were evidenced by fewer entries in the open arms	Neurotransmitters	↑ Levels of dopamine in mPFC (correlating with anxious response) induced by juvenile

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			P29, P33) Foot shock (40 times in 20 min, P31)			AST SPT	of EPM. No differences in anhedonia (SPT) or AST produced by juvenile stress		stress. ↓ Levels of 5-HIAA and noradrenaline in the amygdala induced by juvenile stress. Noradrenergic activity in the amygdala might mediate the modulatory effects of GABAergic transmitters in memory, the authors suggest
Lyttle et al., 2015	Wistar rats	M	Footshock	Age-, sex-, and strain-matched controls with vehicle injections. There is an experimental group receiving treatment with fluvoxamine (not shown)	P21–26	OFT FST	↑ Immobility in the FST and reduced locomotor activity. No effect of juvenile stress on anxious behavior in OFT	Brain morphology	↓ Thickness in prelimbic and infralimbic regions of mPFC after stress ↓ Dendritic length and basal-apical spine densities of pyramidal neurons in the layers II and III of the infralimbic region of mPFC. No reduction was found in the prelimbic region for the juvenile stress group
Márquez et al., 2013	Wistar Han rats	M	VS Fox odor (TMT) and elevated platform, both under bright light (administered a total of seven random days)	Age-, sex-, and strain-matched naïve controls	P28–42	RIT SIT EPM SPT FST	↑ Aggressivity in RIT. ↑ Number of attacks on non-violent individuals, vulnerable zones, and ↓ discrimination between individuals in the juvenile stress group Juvenile stress ↑ Anxiety and depression-like behaviors. ↓ % of time in open arms, ↓ distance in open arms, ↑ latency to enter in open arms for anxiety and ↑ % time floating in the FST and ↓ sucrose consumption in the SPT	HPA axis HPG axis Neurotransmitters Gene expression and epigenetics	Juvenile stress changed: ↑ Testosterone/CORT ratio ↑ MAOA enzyme and 5-HTT receptor mRNA expression in PFC ↑ Histone H3 acetylation in the MAOA gene promoters in PFC, suggesting increased transcription ↓ activity of the medial orbitofrontal cortex (region of PFC) and increased activity of the amygdala
Mathews et al., 2008	Long Evan rats	M/ F	CSS Isolation stress + peer-change stress + acute stress (one day only, 1 h of isolation containers)	Age-, sex-, and strain-matched naïve controls	P30–45	FST	M: No differences in behavior ↑climb F: ↑ immobility time in FST and ↓ climb	HPA axis	MF: No differences in CORT concentrations
Moradi-Kor et al., 2020	Wistar rats	F	Restriction stress	Age-, sex-, and strain-matched naïve controls	P30–40	OFT EPM FST	↓ Number of center visits, time in center, and total distance in the OFT. ↓ Open arm entries in the EPM and ↑ immobility time in the FST in the juvenile stressed group	BDNF/Neurotrophins Gene expression and epigenetics. Neurotransmitters. Neuroinflammation/ Immune activation	Juvenile stress group had: ↓ BDNF levels that correlated with FST behavior (PFC). Both protein and mRNA ↓ BDNF mRNA expression levels in the PFC ↑ 5-HT3 receptor expression (mRNA, PFC) ↓ FRAP levels and ↑ MDA levels, indicating ↓ antioxidant capacity and ↑ oxidative damage, respectively. In this line, an ↑ activity of SOD and GPx enzymes

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
									was found, suggesting a compensatory mechanism of these antioxidant enzymes
Müller et al., 2014	C57BL/6N and male heterozygous GAD (+/-) mice	M	Variable stress + Isolation stress Variable stress: immobilization for 30 min, bright light three times for 30 min, and forced swim for 15 min	Age-, sex-, and strain-matched naïve controls	P24–26	OFT EPM CFC LDBT SIT TST	5 main factors accounted: 1) Generalized contextual fear (CFC) and anxiety: stress ↑ the scores in the wildtype as well as in the GAD group, except for the variable stress group 2) Pre-conditioning activity (EPM/OFT): stress-reduced activity, being significant in the isolation stress group, no effect for the GAD group 3) Pre-conditioning anxiety (EPM/OFT): either variable stress or isolation stress ↑, the score in the wildtype, no effect for the GAD group 4) Depression-like behavior: either variable stress and variable stress + isolation stress ↑ depression, without effect in the GAD group 5) Cued fear memory: no effects	Neurotransmitters	Haplodeficiency of GAD infers protection against anxiety and depression by delaying GABAergic system maturation during the stress period
Page and Coutellier, 2018	C57BL/6J mice	M/ F	CUMS Absence of nesting material for 24 h, 20 cage-tilt along the vertical axis for 6 h, absence of bedding for 8 h, restraint stress for 8 min in the dark, and restraint stress for 4 min under bright light. Stressors were applied during 2 weeks, daily exposure to a random stressor)	Age-, sex-, and strain-matched naïve controls	P28–42	EPM OFT OCMT FST	MF: ↑ Anxiety-like behaviors (↓ time in open arms in EPM and ↓ time in the center of OFT, no significant differences due to stress in the FST). No depressive-behaviors. Males show cognitive impairment in the OCMT with a lower discrimination ratio F: Resiliency in cognitive impairments. While males were affected by stress, females stressed during the juvenile period were not affected	Neurotransmitters Synaptic plasticity/ Synaptic proteins Excitatory/Inhibitory balance Body weight	M: The juvenile stress group had the following differences: ↑ body weight ↓ PV+ cells in the prelimbic region of mPFC. PNN not affected ↑ NMDA receptor subunit NR2B expression. ↑ the ratio NR2B:NR2A F: were not affected by stress
Ros-Simó et al., 2012	CD1 mice	M	Isolation stress	Age-, sex-, and strain-matched naïve controls	P21–70	LOC EPM Dark-light	↑ Horizontal activity in LOC, ↓ entries, and time spent in open arms in EPM, and ↓ immobility	HPA axis.	↓ Levels of basal CORT. ↑ Levels of CORT after stressor (DLB) in the group subjected to isolated housing in comparison with the

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
						box (DLB) FST	in FST in the group subjected to isolated housing. ↓ Time spent in the white box is consistent with EPM results		rest of the experimental conditions (Exacerbated HPA axis)
Schmidt et al., 2010	CD1 mice	M	CSS In a highly unstable social and hierarchical situation, the group composition of each cage is changed twice a week for 7 weeks Then, they were divided into high and low responders	Age-, sex-, and strain-matched naïve controls	P30–80	OFT EPM TST	↑ Distance travelled in OFT (hyperactivity). ↓ Time spent and entries to open arms in EPM. ↑ Immobility in TST in the juvenile stressed group with vulnerability to stress (higher CORT levels) These changes happen in the vulnerable group, compared to both the resilient and the control group	HPA axis	↑ CORT in a subset of the juvenile stressed group with vulnerability to stress ↑ CRH in PVN in the juvenile stressed group with vulnerability to stress (High CORT levels) compared to resilient and control mice (Lower CORT levels) ↓ Mineralocorticoid receptor expression in the hippocampus and PVN in the juvenile stressed group with vulnerability to stress (High CORT levels). No changes in the expression of the glucocorticoid receptor
Sun et al., 2023	Specific pathogen free Sprague-Dawley rats	M	CUMS Food deprivation (24 h), water deprivation (24 h), wet bedding (24 h), tail pinch (1 min), day and night reversal (24 h), cold swimming for 5 min, restriction 24 h, inversion of the light/dark cycle (24 h)	Age-, sex-, and strain-matched naïve controls	P28–49	OFT EPM NORT FST	↓ Distance travelled, exploration time, and center time in OFT. ↑ Time in closed arms and closed arm entries in EPM and immobility in the FST. ↓ Novel object exploration in NORT in the juvenile stressed group	Gene expression and epigenetics.	↑ Expression of genes in the hippocampus, related to metabolic pathways like oxidative phosphorylation and neurodegenerative disorders. Specifically, some of these genes were related to iron ion binding, nerve growth factor receptor binding, and apoptotic processes. These genes were upregulated in the juvenile stressed group compared to the control group Suppressed glycolysis and activated the immune response in the hippocampus, as reported by the GSEA analysis in the juvenile stress group ↑ Expression of genes in mPFC, related to metabolic pathways and neuroactive ligand-receptor interaction, mainly related to NOD-like receptor/ErbB/TNF signaling pathways in the juvenile stress group
Takaba et al., 2022	C57BL/6 J mice	M	CUMS Food and water deprivation (24 h), 30° tilted cage (24 h), shaking (10 min), tail clamping (1 min), damp bedding cage (24 h), confinement (2 h), isolation rearing (24 h),	Age-, sex-, and strain-matched naïve controls	P28–50	OFT MBT SIT SPT TST	↑ Anxious-like behavior in the OFT and MBT, ↑ immobility in the FST, and anhedonia in the SPT. Deficits in social interaction (SIT) in the juvenile stressed group	HPA axis Body weight Gene expression and epigenetics BDNF/Neurotrophins	↑ CORT levels in the juvenile stressed group ↓ Body weight levels in the juvenile stressed group ↓ Sirt1 levels in the PFC and hippocampus in the juvenile stressed group. Sirt1 is involved in dendritic development and synaptic growth

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
			illumination (100 lx, 24 h), empty cage (24 h)						No changes in BDNF expression or housekeeping genes like GAPDH and beta-actin
Tapocik et al., 2021	Wistar rats	M	Restriction + Predator stress (live snake)	Age-, sex-, and strain-matched naïve controls	P31, 46, 61	EBT EPM Alcohol consumption SPT	↓ Exploratory behavior, ↓ percentage of time in the open arm in the EPM, and ↑ anhedonia (SPT) in the juvenile stress group	HPA axis C-Fos Body weight	↓ CORT levels in the juvenile stressed group after stress exposure (blunted HPA response) ↑ C-Fos expression in the lateral habenula and dorsal raphe nucleus. ↑ C-Fos in BLA, medial amygdala, medial habenula, and lateral habenula (lateral part), and dorsal raphe nucleus in adulthood, compared to activation during the juvenile period (P31) ↓ Body weight in the stress group
Tóth et al., 2008	Sprague-Dawley rats	M	CUMS Cage tilt, low intensity stroboscopic light, intermittent white noise, soiled cages, food and water deprivation, empty water bottle, restricted food, paired housing, and lights overnight	Age-, sex-, and strain-matched naïve controls	P30–58	LOC Spontaneous male sexual behavior NSE FST SPT	No differences in behavior in SPT or FST in the juvenile stressed group	HPA axis Neurotransmitters BDNF/Neurotrophins Synaptic plasticity/ Synaptic proteins Neurogenesis Cell markers	↓ CORT levels in the juvenile stressed group ↓ GluR1 subunit of the AMPA receptor in the PFC ↑ BDNF levels in the dorsal dentate gyrus and in the ventral hippocampus in rats exposed to CUMS compared to their age-matched controls ↑ Number of BrdU-positive cells in the DG of the dorsal hippocampus
Veenit et al., 2014	Wistar Hans rats	M	Exposure to the synthetic fox odor and the elevated platform	Age-, sex-, and strain-matched naïve controls	P28–42	EPM SPT FST SIT	↑ Anxiety-like behaviors in the EPM (↓ time and percentage of time in center) and depressive-like behaviors in the FST (↑ immobility) in the juvenile stress group- ↓ Sociability	HPA axis Gene expression and epigenetics	↑ CHRH1 mRNA expression in the hippocampal CA1 and central nucleus of the amygdala in the juvenile stress group
Walker and Sandi, 2018	Wistar rats	M/ F	Mixed stressors: Elevated platform Synthetic fox odor (TMT) Performed in two strains: High and Low glucocorticoid responders to stress	Age- and sex-, matched naïve controls from two different strains: high and low glucocorticoid responders	P28–42	EPM RIT FST	MF: ↑ Anxious behavior in the EPM (↑ time in closed arms). No effects on FST in the juvenile stressed group ↑ Anxious behavior (↑ immobility time in the FST) and more aggressive behaviors in the RIT of the juvenile stressed group with a high CORT response. High CORT lines (both stressed and non-stressed) show anxious behavior in the EPM (↑ time in closed arms) and ↑ time floating in the	Metabolism/ Microbiota Body weight/Body composition	MF: ↑ 2-DG reuptake in the dorsal hippocampus in the juvenile stressed group with a high CORT response ↑ 2-DG reuptake in ventral and medial orbitofrontal cortex and prelimbic cortex in the juvenile stressed group, independently of CORT levels This activation is negatively correlated with distance in the EPM No sex differences found

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REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
							FST, as well as aggressive behavior ↑ Aggressivity with aberrant responses in the juvenile stressed group, with a low CORT response No sex differences found		
Wang et al., 2018	Wistar rats	M	CUMS Water deprivation, food deprivation, pinching tail, footshock, heat, light/dark cycle reversal, noise, water deprivation	Age-, sex-, and strain-matched naïve controls	P28–50	OFT EPM MWM SPT	↓ Sucrose preference affected the behavior in the OFT (rearing, grooming, number of crossings), ↑ anxiety in the EPM (fewer entries in the open arm), and impaired memory in the Morris maze in the juvenile stresss group	Neuroinflammation/ Immune activation	Juvenile stress ↑ Levels of IL-β and IL-6, microglial reactivity, iNOS activation, and Jmjd3. ↓ Levels of H3K27me3. Changes found in both the PFC and hippocampus
Wilkin et al., 2012	Long-Evans rats	M/ F	Mixed stressors: Water immersion, elevated platform, and forced swimming.	Age-, sex-, and strain-matched naïve controls	P22–33 or P35–46	EPM SPBT FST	MF: ↓ Exploration in the open arm in EPM and ↑ the duration of burying in SPBT when the stress period was in prepuberal (P22–33). ↑ Exploration and immobility in FST when the stress period is in mid adolescence (P35–46) M: ↑ Immobility in the FST when the stress period was in prepuberal (P22–33)	HPA axis	MF: ↓ Basal levels of CORT in plasma in the groups that underwent stress in the juvenile period
Wulsin et al., 2016	Sprague-Dawley rats	F	CVS Cold room, shaker, hypoxia, and restriction, open field	Age-, sex-, and strain-matched naïve controls	P45–58	FST	↑ Immobility time in the FST in the juvenile stressed group	HPA axis Gene expression and epigenetics.	↓ ACTH and CORT levels in plasma after FST in the juvenile stressed group (Blunted HPA axis), although the immediate effect is ↓ body weight gain and a transient ↑ in central HPA axis drive, as indicated by ↑ CRH mRNA expression in the PVN and ↑ baseline CORT secretion ↓ Vasopressin mRNA expression in PVN. ↑ Magnocellular OXT in the PVN of the juvenile stress group
Xu et al., 2019	Wistar rats	M	CUMS or Dexamethasone Food deprivation (24 h), water deprivation (24 h), noise (2 h), pinching tail (1 min), hot stress (5 min), footshocks, day and night reversal 24 h	Age-, sex-, and strain-matched naïve controls	P28–49	OFT EPM MWM SPT	↑ Anhedonia in SPT, ↓ locomotor activity in OFT, ↓ time in open arms in the EPM and impaired memory in the MWM in juvenile stressed animals	HPA axis Gene expression and epigenetics.	Both CUMS and dexamethasone (separately) induced: ↓ Glucocorticoid receptor mRNA expression ↑ FKBP5 levels in PFC and hippocampus ↑ Micro RNA (miR-18 and 124) in PFC and hippocampus. ↓ miR-511 in PFC

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Table 2 (*continued*)

REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
Xu et al., 2024	Specific pathogen-free Wistar rats	M	CUMS Food deprivation (24 h), water deprivation (24 h), empty water bottle (1 h), tail pinch (1 min), cage tilting 45º 24 h, wet padding for 24 h, horizontal vibration for 30 min, overnight illumination, moist bedding for 24 h, social crowding for 24 h, horizontal vibration for 30 min	Age-, sex-, and strain-matched controls with vehicle injections. There is an experimental group receiving treatment with S-adenosylmethionine (not shown)	P28–56	OFT YMT EPM SPT	↓ Open arm entries, open arm time, and total distance in EPM and ↑ anhedonia in SPT caused by juvenile stress	Brain morphology Neuroinflammation/ Immune activation Metabolism/ Microbiota Body weight/Body composition Neurogenesis Cell markers	↑ Neuronal damage in the hippocampus, with unclear neuronal outlines in the juvenile stressed group ↓ Nissl bodies and ↑ cytoplasmic cavitations in the juvenile stressed group ↑ Inflammatory cell infiltration into the colon and reduced intestinal glands ↑ Firmicutes, deferribacteres, lactobacillus, clostridium_XIVb, enterococcus, butyrivibrio, roseburia, clostridium_XlVa, pseudoflavonifractor and muscisprillum in the juvenile stressed group ↓ Romboustia, phascolarctobacterium, turicibacter, bacteroides and barnesiella ↓ Ratio of Bacteroidetes to Firmicutes phylum **CUMS** ↑: Absolute abundance of firmicutes and deferribacteres, elevates abundances of lactobacillus, clostridium_XlVb (inversely related to BDNF levels) enterococcus (which has a positive correlation with depressive behaviors), elevates butyrivibrio, roseburia and clostridium_XlVa (also correlated with depressive-behaviors), abundance of pseudoflavonifractor and musciprillum. **CUMS** ↓: Lower radio of Bacteroidetes to firmicutes, romboustia, phascolarctobacterium and turicibacter levels, reduces absolute abundance of bacteroides and barnesiella (also correlated with depressive behaviors)
Xue et al., 2023	Sprague-Dawley rats	M	CSC Experimental rats observed higher-ranking rats with environmental stimuli through a transparent acrylic plate	Age-, sex-, and strain-matched naïve controls	P28–42–59 (14 or 31 days of stress)	3-CSIT LOC OFSIT OF EPM SPT FST	↑ Immobility in the FST and anxious behaviors in the EPM or OF, with ↑ closed-arm entries, and OF ↓ in the center area after 30 d stress. ↓% Sniffing the novel rat	BDNF/Neurotrophins	↓ BDNF levels in the mPFC and hippocampus. Interestingly, ↓ BDNF levels in the mPFC correlated with immobility in the juvenile stress group

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Table 2 (*continued*)

REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
							cage and SPT after 14 days stress.		
Yohn and Blendy, 2017.	C57BL/6 J mice	M/ F	CUMS Rotate, restraint, forced swimming, rat odor, cold, new partner, lights off, cage tilt, wet bedding, dividers, isolation, food deprivation, lights	Age-, sex-, and strain-matched naïve controls	P28–40	MBT EZM ASR FST	MF: ↑ Depressive-like behaviors (↑ immobility in FST) in the juvenile stress group ↑ anxiety F: ↓ Immobility than M in the control group	HPA axis Gene expression and epigenetics	M: Changes in Crfr2 in amygdala. Significant upregulation in the juvenile stress group F: Not affected
Articles with a double stress protocol									
Arcego et al., 2018	Wistar rats	M	Isolation stress Chronic High-fat diet	Age-, sex-, and strain-matched naïve controls	P21–28 for isolation stress P21–70	SPT FST	↑ Immobility (FST) in the groups following isolation stress. ↑ Immobility (FST – only day 1) in the groups with a high-fat diet following isolation stress	HPA axis Synaptic plasticity/ Synaptic proteins BDNF/Neurotrophins Neurotransmitters Neuroinflammation/ Immune activation	↓ Levels of glucocorticoid receptors in groups with isolation stress and a high-fat diet ↓ Phospho-AKT following isolation. ↓ βIII tubulin, PSD95, SNAP-25 and neurotrophin-3 Impaired glutamatergic transmission (↑ NR2A subunit of NMDA receptor levels) after isolation. Impaired GABAergic and glutamatergic transmission (reduced GAD-65, GLUTA2 and phospho-NR2B, subunits of AMPA receptor) No changes in levels of GFAP or BDNF
Huang et al., 2021	Sprague-Dawley rats	F	Maternal separation+CUMS Food deprivation (24 h) water deprivation (24 h), thermal water stimulation for 5 min, reversal for 24 h, ice water stimulation 5 min, cage tilting 45° 24 h, wet padding for 24 h, crowded squirrel cage 24 h, empty water bottle 2 h	Age-, sex-, and strain-matched naïve controls	P1–21 and P28–61	OFT EZM SPT	↑ Anhedonia in SPT. ↓ Time in the center of OFT and time in the open areas of EZM of the juvenile stressed group. The effect is aggravated in the group that combined maternal separation and juvenile stress	Synaptic plasticity/ Synaptic proteins Neurogenesis Cell marker	↓ Nissl-stained bodies in the juvenile stressed group in the DG or CA1 of the hippocampus. The effect is aggravated in the group that combined maternal separation and juvenile stress ↓ Expression of synaptic and neural signalling proteins (PSD95, GAP43, and SYN) in the juvenile stressed group. The downregulation is aggravated in the group that combined maternal separation and juvenile stress
Jaric et al., 2019	C57BL/6J mice	M/ F	Maternal separation + Social isolation	Age-, sex-, and strain-matched naïve controls	P1–14 and P35–56	OFT EPM SPT FST	MF: ↑ Locomotor activity in the OFT in the group that combined maternal separation during infancy and social isolation in the juvenile period. ↑ Latency to enter the center of OFT in the group subjected to social isolation only	Gene expression and epigenetics.	F: ↓ Levels of Cacnac1 (a gene related to psychiatric disorders) in the group that combined maternal separation during infancy and social isolation in the juvenile period. M was not affected MF: ↑ Expression of Dnmt1 (epigenetic regulation) in the group that combined maternal separation during infancy and social isolation in the juvenile period. Dnmt1 could be related to ↑ hyperactivity in OFT

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Table 2 (*continued*)

REF.	SPECIES/ STRAIN	SEX	STRESS	CONTROL GROUP	STRESS WINDOW	BEHAVIOR TEST	ADULT BEHAVIOR RESULTS	BIOMARKER	BIOMARKER RESULTS
Niwa et al., 2024	CBL57/6J mice postpartum	F	Isolation stress from week 5–8 The isolation stress (juvenile) is combined (or not) with a second stressor (partum)	Age-, sex-, and strain-matched naïve controls	Juvenile stress	SIT TST FST SPT	↑ Immobility (FST, TST), ↑ anhedonia (SPT), and deficits in social novelty recognition but not sociability in SIT in the group that combined isolation stress and partum	HPA axis	Higher CORT levels were in the group that combined isolation stress and partum. Positive correlations with the behavioral changes seen in TST and FST No changes in ACTH and CORT levels with a low dose of DEX (DEX-CRH test) in the isolation group
Raftogianni et al., 2012	Wistar rats	F	Maternal contact-reward denial + Isolation stress	Age-, sex-, and strain-matched naïve controls	P10–13 P30–38	FST	↑ Immobility time in the group whose maternal contact-reward was denied during infancy, and underwent stress in the juvenile period	HPA axis Neurotransmitters	↓ Levels of 5-HT and ↑ 5-HIAA/5-HT in the amygdala, 5-HIAA, and 5-HIAA/5-HT ratio in the PFC. These changes in serotonin concentrations are evidenced mostly in the group whose maternal contact-reward was denied during infancy. Stress in all conditions ↓ levels of 5-HT1A in the PFC and ↑ 5-HT1A only in control groups
Ranaei et al., 2020	NMRI mice	M	Maternal LPS injection + Postnatal mixed stressors: footshock, restriction, and forced swimming	Age-, sex-, and strain-matched controls that were the offspring of vehicle-treated mothers that did not undergo the stress protocol	LPS on GD 17 P30, P34, P38	NSFT SPT TST FST	M: ↑ Latency to feed in the NSFT, ↑ anhedonia (SPT), and immobility time in the TST and FST in the group that combined maternal LPS injection during gestation and juvenile stress	HPA axis HPG axis	M: ↑ Basal and stress-induced CORT levels in the group that combined maternal LPS injection during gestation and juvenile stress compared to control and to F M: ↓ testosterone levels in the group that combined maternal LPS injection during gestation and juvenile stress F: ↓ Estradiol levels in the group that combined maternal LPS injection during gestation and juvenile stress. There are positive correlations between the tests and CORT level, and a negative correlation between FST and NSFT with testosterone levels, as well as CORT and estradiol M offspring seem to be more vulnerable to stress than F offspring, evidenced by the HPA axis and gonadal hormones

Acronyms in alphabetical order:

2-DG: 2-Deoxy-D-glucose, **3-CSIT:** Three chamber social interaction test**,** **5-HIAA:** 5-hydroxyindoleacetic acid, **5-HT:** 5-hydroxytryptamine, **5-HT1A:** 5-hydroxytryptamine receptor 1A, **ACTH:** Adrenocorticotropic hormone, **AIT:** Agonistic interaction test, **AMPA:** α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, **ASR:** Acoustic startle response, **AST:** Attention-shift task, **BDNF:** Brain-derived neurotrophic factor, **BLA:** Basolateral amygdala, **BrdU:** 5-Bromo-2′-deoxyuridine, **CA1:** Cornu ammonis 1, **CFC:** Contextual fear conditioning, **CORT:** Corticosterone, **CRFR:** Corticotropin-releasing factor receptor, **CRH:** Corticotropin releasing hormone, **CSC:** Chronic social comparison stress, **CSS:** Chronic social stress, **CUMS:** Chronic unpredictable mild stress (Note that the original studies may have referred to this paradigm as Chronic Unpredictable stress (CUS) or Chronic Mild Stress (CMS); this terms have been unified into CUMS for clarification), **CVS:** Chronic variable stress, **CVSS:** Chronic variable social stress, **DEX:** Dexamethasone, **DG:** Dentate gyrus, **EBT:** Exploratory behavior test, **EPM:** Elevated plus maze, **EZM:** Elevated zero maze test, **F:** Females, **FRAP:** Ferric reducing antioxidant power, **FST:** Forced swimming test, **FUST:** Female urine sniffing test, **G:** Gestation day, **GAD:** Glutamic acid decarboxylase, **GFAP:** Glial fibrillary acidic protein, **GPx:** Glutathione peroxidase, **HVA:** Homovanillic acid, **LDBT:** Light-dark box test, **LOC:** Locomotion test, **M:** Males, **MDA:** Malondialdehyde, **MAOA:** Monoamine oxidase A, **MBT:** Marble burying task, **mIPSCs:** Miniature inhibitory postsynaptic currents, **mPFC:** Medial prefrontal cortex, **MRI:** Magnetic resonance imaging, **MWM:** Morris water maze, **NIH:** Novelty induced hypophagia, **NORT:** Novel object recognition test, **NSE:** Novel-setting exploration, **NSFT:** Novelty suppression feeding test, **NMDA:** N-methyl-D-aspartate, **OCMT:** Object/context mismatch test, **OFT:** Open field test**,**

OFSIT: Open Field social interaction test, **P:** Postnatal day, **PNN:** Perineural nets, **PPI:** Prepulse inhibition, **PSA-NCAM:** Polysialylated neural cell adhesion molecule, **PT:** Partition test, **PV:** Parvalbumin, **PVN:** Paraventricular nucleus, **RIT:** Resident-intruder test, **SIT:** Social interaction test, **SOD:** Superoxide dismutase, **SPBT:** Shock-probe burying test, **SPT:** Saccharine/Sucrose preference test, **ST:** Splash test, **TST:** Tail suspension test, **TWSAT:** Two-way shuttle avoidance task, **VMA:** Vanillylmandelic acid, **WFA:** Wisteria floribunda agglutinin, **YMT:** Y maze test.

↑ Indicates an increase and ↓ indicates a decrease.

Biological vulnerability further modulated outcomes. Following prenatal immune activation, early-to mid-adolescent stress (PND 30–38) selectively increased feeding latency, anhedonia, and immobility in males (Ranaei et al., 2020). Predator-based stressors (synthetic fox odour + elevated platform, PND 28–42) produced strong anxiety, and immobility (Veenit et al., 2014; Walker and Sandi, 2018), particularly in high-CORT responders (Walker and Sandi, 2018). Other paradigms, such as chronic social comparison (Xue et al., 2023) or social isolation, mainly increased anxiety, with isolation also reducing immobility, suggesting hyperactivity rather than despair (Ros-Simó et al., 2012). Strain-dependent stress reactivity also emerged. In this sense, less-reactive Wistar Kyoto lines showed increased immobility, whereas highly reactive females showed the opposite (Kim et al., 2021).

Long-term social stress produced mixed outcomes. Hierarchy instability or prolonged isolation increased anxiety and promoted passive coping, particularly in vulnerable animals (Schmidt et al., 2010). However, chronic social stress from PND 30–45 combining isolation, repeated peer changes and an acute isolation session, induced depressive-like behavior, and stressed female Long–Evans rats even showed increased immobility and less climbing compared with controls (Mathews et al., 2008). In contrast, 31 days of chronic social comparison stress (CSC) increased immobility in the FST and anxiety-like behavior in the EPM (more closed-arm entries, reduced center exploration) and OFT, while leaving social interaction and hedonic responses unaffected (Xue et al., 2023).

CUMS during early-to mid-adolescence yielded contrasting outcomes depending on intensity and duration and, in some cases, produced atypical profiles, such as increased latency to immobility rather than the expected immobility in the TST (De Lima et al., 2017) or selective cognitive impairment in males accompanied by overt affective changes (Page and Coutellier, 2018). In contrast, more intense protocols consistently increased immobility, anhedonia, anxiety, social withdrawal, reduced self-care, and/or cognitive impairments, the latter mainly in males (Yohn and Blendy, 2017; Wang et al., 2018; Xu et al., 2019, 2024; Aleksic et al., 2022; Takaba et al., 2022; Sun et al., 2023). A 28-day CVSS protocol (PND 22–50) induced anxiety in both sexes and anhedonia in females (Caruso et al., 2017). Combined maternal separation + CUMS (PND 28–61) produced stronger anhedonia and reduced exploration than either stressor alone (Huang et al., 2021).

Consistent with these findings, mixed stress paradigms applied during a comparable developmental window (PND 28–42) also induced affective alterations, including reduced sociability and, in high-CORT responders, increased anhedonia and immobility (Brás et al., 2022). Likewise, exposure similar procedure, such as fox odour combined with elevated platform, increased anxiety, immobility, and aggression (Márquez et al., 2013). Restriction-based paradigms applied during this period (restriction alone or combined with forced swimming) were associated with increased anxiety-like behavior (Azogu et al., 2018; Ghalandari-Shamami et al., 2019; Moradi-Kor et al., 2020) and immobility (Ghalandari-Shamami et al., 2019; Moradi-Kor et al., 2020). These findings suggest that even relatively simple physical stressors can induce affective alterations when applied during this developmental window.

Stress applied slightly later (during mid-adolescence (≈ PND 34–46) produced a distinct and often more sexually divergent profile. Isolation + predator stress (PND 34–64) induced male-specific social deficits and female-specific risk-seeking (Eidson et al., 2019). Early-life adversity increased vulnerability in females, and when combined with isolation (PND 35–56), it further amplified hyperactivity without altering anxiety or immobility (Jaric et al., 2019). Mixed paradigms revealed selective vulnerabilities. Mixed stress (PND 37–49) induced depressive-like behavior in females only (Bourke et al., 2011), while juvenile isolation increased immobility, anhedonia, and impaired social behavior during the postpartum period, which can be considered a second stressor (Niwa et al., 2024). Pharmacological stressors also produced sex-specific effects: chronic corticosterone exposure (PND 30–50) increased immobility in females but had no effect in males (Bertholomey et al., 2022).

Predator-based stress paradigms during this period reduced exploration and increased anhedonia (Tapocik et al., 2021). In contrast, short restriction protocols, even when paired with social isolation, failed to elicit typical depressive-like behaviors but impaired prepulse inhibition (PPI), indicating a sensorimotor gating deficit rather than canonical affective disruption (Drzewiecki et al., 2021). Short mixed stress or mid-adolescent CVS increased immobility and reduced open-arm exploration (Cotella et al., 2018; Harris et al., 2022b).

Although less extensively studied, stress applied during late-adolescent stages (≈ PND 47–59) was still associated with affective alterations. For example, CVS applied during this window (PND 45–58) increased immobility in females exclusively when tested in adulthood (Wulsin et al., 2016). However, a comparative design spanning mid- to late adolescence (PND 35–50 vs. PND 50–64) found no differences in FST outcomes, suggesting that sensitivity to this protocol may not differ across these developmental windows (Jankord et al., 2011).

3.4. Candidate biomarkers of adult depression after juvenile stress

Identifying reliable biomarkers is crucial for understanding how peripubertal stress enhances long-term vulnerability to mood disorders and for guiding early interventions. Among preclinical candidates, the hypothalamic–pituitary–adrenal (HPA) axis stands out due to its central role in stress regulation. HPA-related parameters were assessed in 59% of the reviewed studies, underscoring their relevance (see Table 2). It should be noted that only a small subset of the reviewed studies explicitly distinguished between resilient and vulnerable animals within the stress-exposed population (Schmidt et al., 2010; Walker and Sandi, 2018; Kim et al., 2021; Brás et al., 2022). In most cases, biological and behavioral outcomes were reported by comparing stress-exposed animals with non-stressed controls, without stratifying individuals according to their later behavioral phenotype (see Table 2). Studies employing two-hit paradigms, where juvenile stress was combined with an additional stressor occurring either before (most frequently during early development) or after the juvenile period, reported biological alterations that differed from those observed after single-stress exposure. Rather than simple quantitative increases, these models revealed distinct molecular and endocrine profiles (Raftogianni et al., 2012; Arcego et al., 2018; Jaric et al., 2019; Ranaei et al., 2020; Huang et al., 2021; Niwa et al., 2024), suggesting that combined developmental stress exposures may help uncover biological signatures associated with heightened vulnerability that are not readily detectable in single-stress designs. Notably, only two of these studies applied juvenile stress as the first hit followed by a second stressor, an approach particularly relevant for assessing its long-term impact. However, the effects of the combined stress exposure varied by study and type of second stressor. Thus, Niwa et al. (2024) reported that alterations emerged specifically after the second stressor, whereas in Arcego et al. (2018), where the second challenge was a high-fat diet, effects were more complex, with some neurobiological changes reverting to control levels despite persistent depressive-like behavior. These findings suggest that the impact of juvenile stress depends on the nature of the subsequent stressor and may involve dissociations between behavioral and biological outcomes.

3.4.1. The hypothalamic–pituitary–adrenal (HPA) axis and stress-related hormones

Although HPA axis alterations are among the most consistent findings following stress exposure, the direction and magnitude of these changes vary considerably across studies. Depending on the nature, duration, and developmental timing of the stressor, stress can lead to either hyperactivation or attenuation of the axis, both of which may represent maladaptive responses. Such variability likely reflects differences in feedback regulation, adrenal sensitivity, and steroid receptor plasticity, as well as sex-specific hormonal modulation.

In this sense, a hyporeactive phenotype, characterized by reduced basal and stress-induced corticosterone (CORT) release or enhanced negative feedback sensitivity, typically emerges after early intermittent or mixed stress (Wilkin et al., 2012; Li et al., 2015; Wulsin et al., 2016; Caruso et al., 2017), and is also observed in studies using predator and restriction protocols during adolescence (Tapocik et al., 2021), where animals showed reduced CORT levels after stress and increased immobility or anhedonia. This profile appears particularly evident in females (Wulsin et al., 2016). Conversely, a hyperreactive HPA profile, characterized by elevated basal CORT, adrenal hypertrophy, and exaggerated stress responses, is frequently observed following social or environmental stress (De Lima et al., 2017; Ranaei et al., 2020), mixed stressors like forced swim, elevated platform and restraint (Ilin, Richter-Levin, 2009) or CVS combined with restriction (Jankord et al., 2011) restriction stress (Ghalandari-Shamami et al., 2019). CUMS models showed variable outcomes, including upregulation of GR in male and a differential expression of GR isoforms in females (Aleksic et al., 2022). In contrast, in a two-hit model combining juvenile isolation with a high-fat diet, basal CORT remained unaffected, yet a significant down-regulation of hippocampal GR was observed (Arcego et al., 2018).

Adolescent CUMS or dexamethasone induced long-term molecular changes related to depressive-like behavior in males, including miR-124a and miR-18a overexpression, which reduced GR levels, and FKBP5 upregulation, which inhibited GR activity, disrupting HPA regulation (Xu et al., 2019). Peripubertal stress increased Crhr1 mRNA in hippocampus and amygdala, without affecting Crhr2, and was associated with social deficits and increased immobility (Veenit et al., 2014).

In a two-hit model (maternal separation + adolescent isolation), females showed increased Nr3c1 and Egr1 expression and reduced Nr3c1 methylation, primarily driven by maternal separation, while isolation modulated these effects. Conversely, Dnmt1 expression reached its highest levels in the combined stress group, a distinct molecular change that was associated with synergistically amplified hyperactivity, a phenotype in which males were more strongly affected (Jaric et al., 2019). Sex- and strain-specific responses were also evident. Distinguishing between highly and less stress-reactive animals, less rats showed generally higher hippocampal Nr3c1 expression than WMI, with modest sex-specific differences, while early adolescent stress did not significantly alter Nr3c1 levels, indicating these patterns reflect constitutive strain effects (Kim et al., 2021).

In adulthood, adolescent stress exposure also led to reduced GR and AVP mRNA and increased OXT mRNA in the PVN, associated with HPA hyporresponsivity and delayed-onset depressive-like behavior (Wulsin et al., 2016). Still, behavioral symptoms and endocrine output do not always align. Thus, hypocorticosteronaemic mice showed mild hyperlocomotion despite enhanced CORT reactivity, while transient CORT elevations normalized in adulthood even though behavioral deficits persisted (Ros-Simó et al., 2012; Brás et al., 2022). Furthermore, altered GR isoforms and increased FKBP5 expression in the PFC without changes in circulating CORT (Aleksic et al., 2022).

Finally, some models exhibit depressive- and anxiety-like behaviors in the absence of HPA axis alterations. In this sense, Lovelock and Deak (2019) reported increased anxiety and reduced sociability in males following adolescent footshock without changes in HPA-related genes, whereas Bourke and Neigh (2011) observed increased immobility and anhedonia in females without HPA alterations. Together, these findings suggest that glucocorticoid measures alone are insufficient predictors of stress-related behavior, supporting a more integrative framework encompassing endocrine, neural, and immune mechanisms.

Mid-to late-adolescent chronic variable stress reduced oxytocin levels and increased vasopressin. However, despite increased susceptibility to the central and peripheral effects of chronic stress, late-adolescent animals remained resistant to its behavioral consequences (Jankord et al., 2011).

3.4.2. Neurotransmission systems and stress response

Neurochemical markers, particularly glutamatergic and GABAergic, were reported in ∼27% of studies. Glutamatergic signaling, emerged as a consistent feature of adolescent stress although not always directly correlated with behavioral alterations. Thus, in C57BL/6J males exposed to adolescent CUMS; NR2B upregulation and an increased NR2B:NR2A ratio were observed in the PFC, accompanied by heightened anxiety-like behavior (Page and Coutellier, 2018). Similarly, early social isolation in Wistar rats led to NR2A elevation in the hippocampus, associated with depressive-like behavior in adulthood (Arcego et al., 2018). Chronic corticosterone exposure markedly reduced BLA levels of GluA1 and GluA2/3 in females, accompanied by behavioral alterations, whereas in males it increased these markers, consistent with a resilient phenotype (Bertholomey et al., 2022). Additionally, females showed an increase in GluN1 density in PV+ neurons of the thalamic reticular nucleus, alongside significant depressive-like behavior (evidenced by reduced number of licks in the sucrose splash test) (Alcaide et al., 2024).

Additional evidence supports the role of inhibitory signaling in stress susceptibility. GAD65+/– mice showed resilience to variable stress but not to prolonged isolation, suggesting that delayed GABAergic maturation selectively modulates stress vulnerability, whereas complete GAD65 deficiency increases susceptibility to stress-induced behavioral alterations (Müller et al., 2014). Furthermore, high-fat diet, either alone or combined with early social isolation, reduced hippocampal GABAergic marker GAD 65, indicating impaired inhibitory transmission, whereas stress alone had no significant effect (Arcego et al., 2018).

Multiple studies have shown long-lasting alterations in the monoaminergic system, classically linked to depression, following early or adolescent stress, often in a sex- and region-specific fashion. In female Wistar rats, neonatal reward deprivation combined with adolescent isolation reduced 5-HT levels and increased serotonin turnover in the amygdala and PFC, alongside increased immobility in the FST. In contrast, early reward exposure increased baseline 5-HT and 5-HT1A receptor levels but did not confer resilience (Raftogianni et al., 2012).

Adolescent CUMS induced persistent reductions in serotonin and noradrenaline in the hippocampus and hypothalamus, as well as decreased cortical serotonin, alongside increased dopamine turnover in the cortex. These neurochemical alterations were associated with emotional hyperarousal, hyperactivity, and memory deficits in adulthood (De Lima et al., 2017). Similarly, adolescent stress upregulated 5-HT$_3$ receptor mRNA in the PFC, which was linked to elevated anxiety- and depression-like behaviors, potentially via BDNF downregulation (Moradi-Kor et al., 2020). Early life stress also induced increased MAOA and 5-HTT mRNA expression and H3 histone acetylation at the MAOA promoter in the PFC, associated with heightened aggression, anxiety, and depressive-like behavior, suggesting an epigenetic mechanism of serotonergic dysregulation (Márquez et al., 2013).

Moreover, in the PFC, juvenile stress has been shown to increase dopamine levels in association with heightened anxiety (Luo et al., 2014), and to elevate tyrosine hydroxylase (TH) expression, a change linked to increased risk-taking behavior (Harris et al., 2022a).

Sex-dependent changes were also reported. In this regard, pubertal stress induced opposite changes in dopamine turnover in males and females, with striatal dopamine turnover increasing in females but decreasing in males, effects that persisted into adulthood (Harris et al., 2022b). In an exclusively male cohort, chronic juvenile stress increased anxiety-like behavior, associated with reduced noradrenaline in the amygdala and lower 5-HIAA in the mPFC, while dopamine levels in the mPFC were elevated and correlated with behavioral outcomes (Luo et al., 2014). Increased TH+ fiber density in the prelimbic cortex was also observed independently of sexes (Harris et al., 2022b), along with further evidence of 5-HT$_3$ upregulation in adult female PFC (Moradi-Kor et al., 2020).

3.4.3. Neuroinflammatory mechanisms linking stress and depression

In recent years, dysregulation of the immune system and increased inflammation have been increasingly implicated in stress-induced depression.

Acute adult stress increased IL-1β and IL-6 expression, which was not further sensitized by footshock-induced juvenile stress (Lovelock and Deak, 2019). In contrast, adolescent CUMS produced a persistent upregulation of IL-1β and IL-6 in the PFC and hippocampus, accompanied by increased Jmjd3 and reduced H3K27me3, epigenetic changes linked to greater stress vulnerability in adulthood (Wang et al., 2018). Adolescent predatory stress induced sex-dependent neuroinflammatory dysregulation, with reduced cortical IL-1β, IL-6, and TNF mRNA, and increased hippocampal TNF, Lcn2, and CCL2, as well as amygdalar CCL2 and elevated plasma cytokines (IL-10, IFN-γ, IL-2) in females. These molecular alterations were accompanied by reduced social interaction and social novelty preference in males and altered open-field behavior in females, and unchanged sucrose preference, indicating selective socio-emotional vulnerability without anhedonia (Eidson et al., 2019).

Changes in microglia, the main immune cells of the brain, have been consistently associated with neuroinflammation. Thus, the increase in amoeboid, stress-reactive microglia was linked to anhedonia, as minocycline treatment, a microglial activation inhibitor, prevented this phenotype (Wang et al., 2018). Similarly, peripubertal stress elevated hippocampal IBA-1 and TNF-α expression and promoted microglial activation, evidenced by reduced branching, particularly in rats with high corticosterone responses, which also exhibited anhedonia and passive coping behaviors (Brás et al., 2022). Increased miR-342 levels were also reported (Brás et al., 2022) that potentially may perpetuate the inflammatory response. Moreover, animals with a high corticosterone responder phenotype (H-CSR) showed elevated IL-6 levels in the mPFC and nucleus accumbens, independent of stress exposure, indicating a baseline pro-inflammatory profile associated with this phenotype (Brás et al., 2020). Finally, adolescent stress induced neuronal damage in the hippocampus, characterized by disrupted neuronal morphology and reduced Nissl bodies, observed in CA1 and CA3 with no significant changes in the dentate gyrus (Xu et al., 2024), and in CA1 and DG when aggravated in a two-hit stress paradigm (Huang et al., 2021). These alterations were associated with anhedonia and depressive-like behaviors, including reduced sucrose preference (Xu et al., 2024; Huang et al., 2021).

Adolescent chronic restraint stress increased malondialdehyde (MDA) levels, a marker of lipid peroxidation, and enhanced the activity of antioxidant enzymes (glutathione peroxidase and superoxide dismutase), while significantly reducing total antioxidant capacity in the PFC. These oxidative alterations were accompanied by anxiety and depressive-like behaviors, particularly impaired stress-coping strategies (Moradi-Kor et al., 2020).

3.4.4. Neuroplasticity alterations as biomarkers of stress-induced depression

Other widely studied biomarkers in depression include indicators of neuroplasticity and neurotrophic support, particularly adult hippocampal neurogenesis, dendritic remodeling, and neurotrophin signaling (e.g., BDNF). These mechanisms are highly sensitive to early-life stress and have been consistently associated with long-term emotional and cognitive vulnerability (Leschik et al., 2021; Takahashi and Shelton, 2025).

Stress-related impairments in neurotrophic and synaptic plasticity are evidenced by decreased BDNF levels in the medial PFC and dorsal hippocampus following chronic social comparison stress, paralleled by depression- and anxiety-like behaviors (Xue et al., 2023). Similarly, restraint stress in adolescent females reduced BDNF content and mRNA in the PFC, correlating with increased anxiety and depressive-like behavior (Moradi-Kor et al., 2020). In contrast, early- to mid-adolescent CUMS induced sex-specific alterations in BDNF mRNA expression. In females, BDNF mRNA levels decreased in the hippocampus and the prefrontal cortex (PFC), whereas in males, CUMS increased BDNF mRNA in the PFC, with no reported increase in the hippocampus. These changes were associated with depressive-like behavior (Aleksic et al., 2022). Altered BDNF signaling through TrkB has also been observed. Thus, early-life social isolation reduced TrkB receptor and phospho-AKT levels in the hippocampus, reflecting impaired neurotrophic signaling (Arcego et al., 2018). In contrast, combined adolescent stress decreased TrkB.FL and TrkB.T1 expression in the nucleus accumbens of males, while increasing their expression in the prefrontal cortex, changes that were accompanied by heightened anxiety-like behavior (Azogu et al., 2018). Moreover, downregulation of SIRT1, a NAD$^+$-dependent deacetylase, has been reported in the PFC and hippocampus of adult mice. Reduced SIRT1 expression disrupts synaptic and neurotrophic plasticity, independently of BDNF, and has been linked to depressive-like phenotypes, including behavioral despair, anxiety, anhedonia, and social withdrawal (Takaba et al., 2022).

Beyond neurotrophins, several studies highlight structural and molecular alterations linked to reduced synaptic remodeling. Combined or two-hit stress paradigms, such as maternal separation plus juvenile CUMS, aggravated these effects, producing greater reductions in synaptic plasticity proteins (SYN, PSD-95, GAP-43) and more severe emotional disturbances than single stress (Huang et al., 2021). Similarly, mixed adolescent stress reduced PSA-NCAM in the thalamic reticular nucleus specifically in females (Alcaide et al., 2024), and footshock-induced juvenile stress decreased apical spine density of mPFC pyramidal neurons while increasing immobility (Aikawa et al., 2020).

Regarding hippocampal cell proliferation, social defeat stress (SDS) impaired adolescent neurogenesis and induced emotional disturbances. Although proliferation levels normalized over time and these neural deficits did not persist into adulthood, the emotional disturbances remained (Kovalenko et al., 2014). By contrast, SDS or mixed stressors do not significantly affect adult neurogenesis or long-term neuronal survival (Harris et al., 2022a).

3.4.5. *Neuronal activation and brain energetic metabolism*

In addition, various adolescent stress paradigms have been linked to sustained changes in immediate-early gene expression and neuronal activation. For instance, acute footshock during juvenile period in rat (PND 29–30) selectively enhanced c-Fos expression in the medial amygdala (MeA) in response to adult stress, without promoting depressive-like behavior but increasing anxiety and neophobia in adult males (Lovelock and Deak, 2019). Similarly, repeated live predator exposure across adolescence (PND 31, 46, 61) increased c-Fos expression in the dorsal raphe nucleus and lateral habenula, regions implicated in mood and stress regulation, and was associated with reduced saccharin preference, diminished exploration, a behavioral profiles consistent with anhedonia and anxiety (Tapocik et al., 2021).

By contrast, chronic variable stress during late adolescence (PND 40–54) led to reduced Fos-B like immunoreactivity in the PVN following adult stress exposure, suggesting increased inhibitory tone in central stress circuits. This was accompanied by enhanced passive coping (increased immobility in the FST) and reduced exploratory behavior (Cotella et al., 2018).

Similarly, peripubertal stress altered basal brain metabolism, as evidenced by increased 2-DG uptake in the orbitofrontal and prelimbic cortex, indicating heightened neuronal activity in stressed and high-line rats. An increase in the dorsal hippocampus was observed in high-line rats regardless of stress exposure. These findings suggest that adolescent stress modifies both neuronal activation and baseline metabolic function, contributing to long-term emotional vulnerability, particularly in animals with a high corticosterone response (Walker and Sandi, 2018).

3.4.6. *Changes in brain morphology*

Adolescent stress has also been shown to alter brain morphology. Specifically, peripubertal stress reduced the volume of the thalamic reticular nucleus in adult females, measured using PV+ cell boundaries, and was associated with depressive-like behavior emerging in adulthood (Alcaide et al., 2024). Juvenile footshock stress consistently impaired medial PFC structure and cortical thickness and reduced dendritic complexity and apical spine density in infralimbic pyramidal neurons (Lyttle et al., 2015) or in mPFC (Aikawa et al., 2020). These convergent alterations were associated with depressive-like outcomes emerging in adulthood. Pubertal isolation and restriction stress reduced medial PFC gray matter volume, likely reflecting loss of neurons, synapses, and dendritic spines in males. This structural change predicted behavioral vulnerability, including impaired sensorimotor gating (Drzewiecki et al., 2021). Adolescent chronic variable stress reduced dendritic length and branching in pyramidal neurons of the infralimbic and prelimbic cortex, measured in adulthood, and was associated with persistent anxiety- and depression-like behaviors (Ghalandari-Shamami et al., 2019).

3.4.7. *Body weight and microbiota*

Several studies reported reduced weight gain during or after juvenile stress exposure (Jankord et al., 2011; Wulsin et al., 2016; Eidson et al., 2019), whereas others found rebound weight gain or metabolic shifts later in adulthood (Bourke and Neigh, 2011). Some models showed altered adiposity (Eidson et al., 2019) or altered hormone profiles (e.g., decreased testosterone and estradiol) correlated with depressive-like immobility (Ranaei et al., 2020). Conversely, other stress paradigms resulted in reduced body weight associated with anhedonia and anxiety (Tapocik et al., 2021). However, weight changes alone were not a reliable predictor of psychopathology, as they were not consistently associated with behavioral alterations. Instead, persistent physiological changes, such as adrenal hypertrophy or reduced thymus size and body fat following late-adolescent stress (Jankord et al., 2011), may reflect underlying stress-related adaptations, even in the absence of overt behavioral deficits. Consistent with this, several studies identified stress-induced gut dysbiosis as a relevant pathway. Changes in microbial composition were associated with depressive-like behaviors. For example, increased abundance of Enterococcus, Butyrivibrio, Roseburia, Clostridium_XlVa and Mucispirillum correlated positively with depression-like behaviors, whereas Barnesiella showed a negative, possibly protective, association (Xu et al., 2024). Adolescent CUMS produced persistent alterations in microbiota diversity and composition, including increases in Enterococcus and shifts in the Firmicutes/Bacteroidetes ratio, changes directly linked to anxiety- and depression-like behaviors (Xu et al., 2024). In contrast, adolescent predatory stress did not alter faecal inflammatory protein levels or other gut dysfunction markers, though it did increase retroperitoneal fat in males (Eidson et al., 2019).

3.5. *Sex- and individual-dependent differences in both the effects of juvenile stress and the predictive value of identified biomarkers*

Depression is nearly twice as prevalent in women as in men, with stress being one of the main environmental contributors to its onset. Although it is well established that women are more vulnerable to stress-related disorders than men (Bourke and Neigh, 2011), sex differences in the long-term impact of juvenile stress on adult depression remain underexplored. Some animal studies have shown that female rodents exhibit stress sensitivity comparable to that of women (Desbonnet et al., 2008; Marchette et al., 2018; Kuske and Trainor, 2022), suggesting that these models may offer valuable insights into the sex-specific effects of juvenile stress on depressive outcomes in adulthood. However, of the 50 studies that met the inclusion criteria for this review, only 20 included both sexes and analyzed sex differences. While this reflects a notable improvement compared to earlier literature, it still represents a limited proportion given the fundamental relevance of sex as a biological variable in stress and depression research (Prendergast et al., 2014; Becker et al., 2016; Shansky, 2019, Shansky, Murphy, 2021; Rechlin et al., 2022; Holloway and Lerner, 2024). Among the studies specifically assessing sex differences, three reported no male–female differences in anxiety- or depressive-like outcomes following juvenile stress (Yohn and Blendy, 2017; Aleksic et al., 2022; Drzewiecki et al., 2021). Across these protocols, following 12-day CUS from P28–40 (Aleksic et al., 2022), male and female animals showed overlapping adult phenotypes. Similarly, 12 days of CUS administered either in adolescence (P28–40) or adulthood (P70–82) produced equivalent anxiety indices and comparable increases in FST immobility in both sexes but only adolescent stress induced long-lasting anxiety-like behavior (Yohn and Blendy, 2017). Similarly, peripubertal restriction and isolation induced prepulse inhibition (PPI) deficits in both males and females, but only at puberty onset and not at later stages, indicating disrupted sensorimotor gating (Drzewiecki et al., 2021). However, even when affective phenotypes overlap, distinct sexually dimorphic trajectories can emerge in other systems (Yohn and Blendy, 2017).

Conversely, several studies identified behavioral endpoints that were equally affected in both sexes. Intermittent physical stress during early adolescence reduced open-arm exploration in the EPM to a similar degree in male and female Long-Evans rats. During mid adolescence the same paradigm increased immobility and altered EPM exploration in both sexes (Wilkin et al., 2012). Together, these findings suggest that some anxiety- and exploration-related measures remain sex-neutral despite variation in adolescent stress paradigms.

Beyond this shared effect, clear baseline dimorphisms were evident. Specifically, sex differences spanned locomotor, social, and affective domains, sometimes appearing independently of adolescent stress exposure. Females consistently showed greater horizontal activity (Lovelock and Deak, 2019) and increased open-arm exploration in the elevated-plus maze (Bertholomey et al., 2022), as well as more stretch-attend postures and unprotected head-dips in an ethological EPM battery (Azogu et al., 2018), whereas vertical activity was variable across studies (Azogu et al., 2018; Lovelock and Deak, 2019). They displayed higher sucrose preference in basal test sessions or upon reaching adulthood (PND 84) (Bertholomey et al., 2022), suggesting lower basal anxiety-like behavior and greater reward sensitivity. Other behavioral measures have reinforced the view that females display a more active and less reactive behavioral profile, as evidenced by increased swimming and reduced immobility in the forced-swim test (Lovelock and Deak, 2019; Drzewiecki et al., 2021; Bertholomey et al., 2022) and diminished acoustic startle responses (Drzewiecki et al., 2021). Conversely, male controls tend to freeze longer than females during fear-extinction sessions, indicating greater persistence of conditioned fear (Bertholomey et al., 2022). Taken together, these findings delineate a multifaceted baseline sex dimorphism, marked by heightened behavioral activation in females and more sustained fear responses in males, which should be taken into account when evaluating the consequences of adolescent stress.

Despite these baseline differences, the impact of adolescent stress revealed a more nuanced and sex-specific pattern. Although several investigations reported sex-dependent alterations in particular behavioral domains, these effects were not consistently biased toward heightened female susceptibility. In fact, multiple studies demonstrated that males often showed greater vulnerability across anxiety, social, and cognitive domains, whereas females were either less affected or displayed distinct adaptive responses. For instance, adolescent footshock exposure increased anxiety-related behaviors in males, evidenced by reduced time in the light, increased latency to re-enter it, fewer transitions, and diminished exploratory head pokes, while females remained unaffected (Lovelock and Deak, 2019). In C57BL/6J mice subjected to chronic unpredictable mild stress (CUMS), females did not exhibit significant cognitive deficits compared to males (Page and Coutellier, 2018). Similarly, under a chronic adolescent paradigm combining predator cues and social isolation (PND 34–64), stressed males showed robust social-interaction deficits at late-adolescent to early adulthood (PND 65–67) stages, while females remained socially intact (Eidson et al., 2019). In Long–Evans rats, prepubertal juvenile stress (PND 22–33) increased forced-swim immobility in males, whereas mid-adolescent exposure (PND 35–46) produced a sex-neutral increase in exploration (Wilkin et al., 2012). Ranaei et al. (2020) reported that male offspring of LPS-treated dams exposed to peripubertal stress displayed marked increases in latency to feed, anhedonia, and immobility in both the tail-suspension and forced-swim tests, effects absent in females and in those exposed to stress alone, supporting a male-selective vulnerability. Likewise, brief juvenile stress (PND 27–29 in Sprague–Dawley rats) combining forced swimming, elevated platform, and restraint produced altered motivational responses in the novelty-induced hypophagia test (Harris et al., 2022a). Finally, in C57BL/6J mice exposed to 10 days of combined restraint, bright light, and noise, males displayed working-memory impairments in the Y-maze, while females showed elevated anxiety behavior in the light/dark box, but preserved cognitive performance (Fariborzi et al., 2021).

Nevertheless, other studies describe the opposite trend, with female-selective increases in anxiety, anhedonia, or passive coping, consistent with epidemiological data showing higher rates of stress-related psychopathology in women. For example, female C57BL/6J mice exposed to a 10-day repeated-stress protocol exhibited increased avoidance in light/dark box, an effect absents in males (Fariborzi et al., 2021). Similarly, brief juvenile stress (PND 27–29 in Sprague–Dawley rats) reduced rearing behavior in Sprague–Dawley females but not in males (Harris et al., 2022a). In addition, adolescent predator-based stress combined with isolation caused females to enter the center of the open field more quickly, suggesting altered risk processing relative to males (Eidson et al., 2019).

In affective domains, female Sprague-Dawley rats chronically treated with corticosterone from PND 30 to PND 50 showed increased forced-swim immobility (Bertholomey et al., 2022), and similar effects emerged in stressed Wistar females subjected to combined isolation, restraint, and social defeat (PND 37–49) (Bourke and Neigh, 2011). Chronic social stress also increased immobility in Long-Evans females (Mathews et al., 2008), and reduced sucrose preference, indicative of anhedonia, was consistently observed in females across diverse paradigms, including BALB/cJ mice exposed to chronic variable social stress (Caruso et al., 2017) and C57BL/6J mice with early-life maternal separation but not after adolescent isolation (Jaric et al., 2019).

Collectively, these findings indicate that, although several behavioral endpoints remain sex-neutral after adolescent stress, clear divergence emerges across functional domains. Males more often exhibit pronounced impairments in cognitive, social, sensorimotor, and anxiety-related behaviors, whereas females show particularly salient vulnerabilities in emotional and hedonic dimensions. Altogether, these patterns underscore that adolescent stress gives rise to complex and domain-specific sex differences, rather than uniform susceptibility across sexes.

4. Discussion

The present review provides convergent evidence that juvenile stress constitutes a robust environmental risk factor for the emergence of depression-related phenotypes in adulthood. Across species, strains, and paradigms, most studies reported persistent alterations in emotional, motivational, or social domains following adolescent stress exposure. Only a minority of studies failed to show canonical “depressive-like” outcomes. However, even in these cases, increases in anxiety-like behaviors (Luo et al., 2014; Page and Coutellier, 2018; Walker and Sandi, 2018) or cognitive impairment, particularly in males (Page and Coutellier, 2018), were reported, both of which fall within the broader depressive-symptom spectrum. Taken together, these findings support the notion that juvenile stress rarely leaves brain and behavior unaffected but instead biases developmental trajectories toward maladaptive outcomes, among which depression is common but not exclusive. Moreover, the nature of these outcomes depends critically on the timing, type, and duration of the stressor, the animal strain, and sex, which consistently shapes vulnerability and the specific phenotype that emerges.

Looking across studies, our analysis further indicates that the behavioral impact of juvenile stress is strongly modulated by the characteristics of the stressor itself. Early adolescent (before ~PND 34) or mid adolescent exposures tended to yield weaker or inconsistent depressive-like outcomes, particularly when stressors were brief or of low intensity (Raftogianni et al., 2012; Harris et al., 2022b). Under these conditions, studies frequently reported anxiety changes or even reduced immobility, patterns that likely reflect hyperactivity rather than true resilience (Ros-Simó et al., 2012; Luo et al., 2014). In contrast, longer-lasting or more complex paradigms, especially those combining physical, social, and ethologically relevant threats, produced robust and enduring alterations, including increased immobility, anhedonia, social withdrawal, and cognitive impairments, and in several cases these effects differed between sexes (Bourke and Neigh, 2011; Márquez et al., 2013; Kovalenko et al., 2014; Xu et al., 2019, 2024; Fariborzi et al., 2021). Mixed stressors, social defeat, predator-based cues, and chronic variable stress during the peripubertal period were particularly effective at inducing persistent emotional dysregulation (Schmidt et al., 2010; Veenit et al., 2014; Wulsin et al., 2016; Fariborzi et al., 2021). Moreover, juvenile stress is often exacerbated by pre-existing vulnerabilities such as such as early-life maternal immune activation (Ranaei et al., 2020) or strain-dependent reactivity (Kim et al., 2021).

In line with this heterogeneity, identifying biomarkers that reliably predict divergent outcomes remains challenging. Among these, HPA axis studies showed the greatest inconsistency, with juvenile stress producing both hyporeactive (Li et al., 2015; Wulsin et al., 2016; Caruso et al., 2017; Tapocik et al., 2021) and hyperreactive profiles (Ilin, Richter-Levin, 2009; Jankord et al., 2011; De Lima et al., 2017; Ghalandari-Shamami et al., 2019; Ranaei et al., 2020; Niwa et al., 2024). These alterations were sometimes behaviorally aligned (Ghalandari-Shamami et al., 2019) particularly in males (Ranaei et al., 2020), sometimes opposite (Caruso et al., 2017; Tapocik et al., 2021), and in other cases completely uncoupled from behavior (Mathews et al., 2008; Arcego et al., 2018; Aleksic et al., 2022; Bertholomey et al., 2022; Brás et al., 2022). Such variability underscores that HPA output alone cannot account for stress-induced phenotypes.

Peripheral markers were again heterogeneous, with some models showing adrenal hypertrophy or reduced thymus/body fat (Jankord et al., 2011), while others revealed microbiota alterations associated with emotional outcomes (Xu et al., 2024) or no detectable changes (Eidson et al., 2019).

Despite the marked heterogeneity across neurotransmission studies, much of this variation stems from methodological differences, as studies rarely assess the same neurotransmitter systems, regions, or molecular endpoints. Even so, a coherent vulnerability pattern emerges. In this sense, disruptions in glutamatergic signaling, particularly increased NMDA receptor subunits (Arcego et al., 2018; Page and Coutellier, 2018), and monoaminergic transmission (Raftogianni et al., 2012; Luo et al., 2014) or 5-HT$_3$ receptor upregulation (Moradi-Kor et al., 2020) consistently align with heightened susceptibility, whereas preserved or enhanced AMPA-mediated plasticity or higher GluA1 and GluA2/3 expression in the BLA tends to be associated with resilience (Bertholomey et al., 2022).

In the inflammatory domain, variability is also evident. While some paradigms show no sensitization after juvenile stress of cytokine responses (Lovelock and Deak, 2019), others report persistent elevations or sex- and region-specific increases (Wang et al., 2018; Eidson et al., 2019). Across studies, changes in IL-1β, IL-6 and TNF-α were more consistently associated with anxiety-related outcomes, whereas links with classical depressive-like measures were more variable and often dependent on individual stress reactivity profiles (Lovelock and Deak, 2019; Wang et al., 2018; Eidson et al., 2019; Aleksic et al., 2022; Bràs et al., 2022). In particular, pro-inflammatory increases (e.g., IL-1β, IL-6, TNF-α) were most prominent in high corticosterone-responsive animals, where they were accompanied by both anxiety- and depressive-like behaviors, while in other conditions inflammatory changes were not consistently associated with anhedonia or immobility (Lovelock and Deak, 2019; Wang et al., 2018; Eidson et al., 2019; Aleksic et al., 2022; Bràs et al., 2022).

By contrast, neuroplastic alterations showed the clearest convergence among biomarker domains. Rather than a simple downregulation of neurotrophins, juvenile stress precipitated a multifaceted collapse of neuroplasticity. This was characterized by profound dysregulation of the BDNF/TrkB signaling pathway (Azogu et al., 2018; Moradi-Kor et al., 2020; Aleksic et al., 2022; Xue et al., 2023), alongside severe structural and functional synaptic impairments (Aikawa et al., 2020; Huang et al., 2021; Takaba et al., 2022 (limited to SIRT1); Alcaide et al., 2024; Xu et al., 2024), but not hippocampal neurogenesis long-term changes (Kovalenko et al., 2014, Harris et al., 2022a).

Adolescent stress has also been shown to consistently alter brain morphology, with the PFC, a region critically involved in emotional regulation, emerging as the most frequently affected structure, which may help explain the heightened vulnerability observed in adulthood (Lyttle et al., 2015; Ghalandari-Shamami et al., 2019; Aikawa et al., 2020; Drzewiecki et al., 2021). In addition to these structural alterations, adolescent stress also modifies neuronal activation patterns and baseline metabolic function, further contributing to long-term emotional vulnerability (Walker and Sandi, 2018).

Taken together, the evidence indicates that juvenile stress gives rise to multiple, partially distinct neurobiological trajectories rather than a single depressive pathway. Even so, when specific biological domains are examined, they often show coherent alterations following juvenile stress. In this regard, the findings of the review reveal marked heterogeneity in HPA-axis and peripheral markers, which limits their utility as standalone biomarkers. By contrast, more consistent patterns emerge in neuroplasticity, PFC structural changes, and alterations in neuronal activation and baseline metabolic function, suggesting that these domains may offer more reliable indicators of long-term vulnerability.

Establishing the pathological nature of these biological alterations, however, requires a careful methodological consideration. These findings should be interpreted considering potential biases across the included studies, which may contribute to the observed heterogeneity. Because most studies compared stress-exposed animals with non-stressed controls, the observed changes cannot always be interpreted unequivocally as markers of vulnerability to stress. In the present review, biomarker alterations are therefore interpreted in relation to functional outcomes. In line with the NIMH Research Domain Criteria (RDoC) framework, a biological change is considered indicative of vulnerability when it is statistically associated with a deficit in a relevant behavioral domain. Notably, only a very limited number of studies explicitly distinguished between resilient and vulnerable individuals within the stress-exposed population. The few studies that did stratify animals according to stress susceptibility reported biological alterations selectively in the vulnerable subgroup, supporting the interpretation of these changes as vulnerability-related signatures rather than generalized adaptive responses to juvenile stress (Schmidt et al., 2010; Walker and Sandi, 2018; Kim et al., 2021; Brás et al., 2022). Although several studies employed two-hit paradigms and generally reported that combined stress exposure produces greater behavioral and biological alterations than a single stressor (Raftogianni et al., 2012; Jaric et al., 2019; Ranaei et al., 2020; Huang et al., 2021; Niwa et al., 2024), only two specifically applied a second stressor following juvenile stress, and in these cases the findings were inconsistent, with Niwa et al. (2024) reporting exacerbated effects, whereas Arcego et al. (2018) found no additional impact beyond juvenile stress alone.

Future studies should incorporate designs capable of distinguishing resilient from susceptible individuals, for example through phenotypic stratification or the identification of predictive biomarkers prior to phenotype expression. In parallel, the use of two-hit paradigms, where juvenile stress is followed by a second challenge, may provide a complementary framework to uncover vulnerability-related biomarkers by revealing latent susceptibilities not evident after a single stress exposure.

Together such strategies would help to more precisely identify biological markers specifically associated with vulnerability to stress.

Finally, sex differences provide an additional layer of complexity and help explain part of the heterogeneity observed across behavioral and biological outcomes. Sex is a major determinant of stress responsivity and depression risk, yet only ~38% of the included studies assessed males and females separately, which limits the strength of conclusions and may partially account for inconsistent biomarker patterns reported above.

At baseline, females and males already differ in emotional reactivity and reward sensitivity (Lovelock and Deak, 2019; Drzewiecki et al., 2021; Bertholomey et al., 2022), indicating that juvenile stress acts upon sex-specific starting points rather than a neutral substrate. This baseline dimorphism is essential for interpreting downstream changes. Although clinical evidence shows greater stress sensitivity in females, this vulnerability did not emerge uniformly across preclinical paradigms. No clear sex-specific effects were detected in anxiety- or depressive-like outcomes after CUMS (Yohn and Blendy, 2017; Aleksic et al., 2022). Peripubertal restraint and isolation specifically impaired PPI (Drzewiecki et al., 2021). This suggests that sex differences are not universal but depend strongly on the nature, timing, and intensity of the stressor.

When differences were found, they followed two complementary patterns. Thus, males tended to be more sensitive to physical or high-intensity early-to-mid adolescent stress, showing cognitive impairments, anxiety-like behavior, or learned helplessness (Wilkin et al., 2012; Page and Coutellier, 2018; Lovelock and Deak, 2019; Fariborzi et al., 2021; Harris et al., 2022b). By contrast, females were more affected by mid-to-late adolescent stressors, particularly social or chronic paradigms, displaying marked socio-emotional alterations and hedonic deficits (Bourke and Neigh, 2011; Caruso et al., 2017). Conversely, stress restricted to the pubertal window has been shown to induce anhedonia selectively in adult males (Harris et al., 2022b). These findings indicate that sex differences do not conform to a strict male–cognitive/female–affective dichotomy, but instead depend critically on the nature, timing, and genetic background of the stressor.

These findings collectively suggest that sex interacts with developmental timing to shape behavioral outcomes, rather than conferring uniform vulnerability in one sex. Corresponding biomarker patterns reflect these sex-dependent trajectories, with females generally showing higher baseline GluA1 and GluA2/3 expression in the BLA (Bertholomey et al., 2022) and more pronounced neuroimmune and neuroplastic alterations after stress (Alcaide et al., 2024), including changes in hippocampal IL-1β and BDNF expression. In contrast, males display distinct stress-induced responses, such as increased PFC BDNF expression (Aleksic et al., 2022) and opposite patterns of serotonergic and noradrenergic turnover (Harris et al., 2022a, 2022b), while volumetric mPFC loss is generally more pronounced in females (Drzewiecki et al., 2021). These sex-specific molecular and neurochemical signatures typically correspond to different patterns of depressive-like behavioral alterations, as reflected in coping styles and emotional responses.

In summary, sex differences in biomarkers are meaningful but highly context-dependent, reinforcing the view that juvenile stress gives rise to multiple neurobiological trajectories rather than a single depressive pathway. Sex interacts with both the type of stressor and the developmental window in which it occurs, shaping behavioral outcomes and the underlying biological signatures. This diversity of trajectories likely contributes to the limited effectiveness of conventional treatments, which are often designed around more uniform mechanisms of adult-onset depression. A more precise understanding of the sex- and timing-specific neurobiological profiles emerging after juvenile stress may therefore open the door to more targeted prevention strategies and tailored therapeutic interventions.

In addition, greater attention to sex-specific developmental windows and stressor characteristics will be essential for improving the translational relevance of preclinical models. Ultimately, integrating these factors into biomarker discovery may facilitate the development of early identification strategies and more personalized interventions for individuals exposed to stress during sensitive developmental periods. Future studies should prioritize identifying 'latent biomarkers', biological changes that occur immediately after stress but only manifest as behavioral deficits after reaching adulthood, to enable early-stage preventive interventions before the clinical phenotype fully crystallizes.

Funding

This study was supported by Ministerio de Ciencia, Innovación y Universidades—Plan Nacional I+D+I from Spain Grant PID2020-117464RB-I00 and PID2023-151537OB-I00 funded by MICIU/AEI/10.13039/501100011033 to CP and MP-M; Consejería de Conocimiento, Investigación y Universidades, Junta de Andalucía P20_00460-Co-financing by the European Regional Development Fund (ERDF/FEDER) to CP; VMA, AZD and JMM hold a FPU PhD fellowship from the Spanish Ministry of Science, Innovation and Universities (FPU21/05694, FPU24/01652, and FPU21/01318, respectively). PCP is supported by an FPI predoctoral fellowship from the Spanish Ministry of Science Innovation and Universities, associated with project (PRE2021-099225) funded by MICIU/AEI/10.13039/501100011033. Funding for open access costs: University of Málaga / CBUA.

Acknowledgements

The authors are grateful to the University of Málaga (UMA) and the Consortium of University Libraries of Andalusia (CBUA) for covering the article processing charges (APC).

References

Ahmed, A.T., Frye, M.A., Rush, A.J., Biernacka, J.M., Craighead, W.E., McDonald, W.M., Bobo, W.V., Riva-Posse, P., Tye, S.J., Mayberg, H.S., Hall-Flavin, D.K., Skime, M.K., Jenkins, G.D., Wang, L., Krishnan, R.R., Weinshilboum, R.M., Kaddurah-Daouk, R., Dunlop, B.W., 2018. Mood Disorders Precision Medicine Consortium (MDPMC). Mapping depression rating scale phenotypes onto research domain criteria (RDoC) to inform biological research in mood disorders. J. Affect. Disord. 238, 1–7. https://doi.org/10.1016/j.jad.2018.05.005.

Aikawa, K., Yoshida, T., Ohmura, Y., Lyttle, K., Yoshioka, M., Morimoto, Y., 2020. Subanesthetic ketamine exerts antidepressant-like effects in adult rats exposed to juvenile stress. Brain Res. 1746, 146980. https://doi.org/10.1021/bi00694a011.

Alcaide, J., Gramuntell, Y., Klimczak, P., Bueno-Fernandez, C., Garcia-Verellen, E., Guicciardini, C., Sandi, C., Castillo-Gómez, E., Crespo, C., Perez-Rando, M., Nacher, J., 2024. Long term effects of peripubertal stress on the thalamic reticular nucleus of female and male mice. Neurobiol. Dis. 200, 106642. https://doi.org/10.1016/j.nbd.2024.106642.

Aleksic, M., Brkic, Z., Petrovic, Z., Francija, E., Lukic, I., Adzic, M., 2022. Sex-specific contribution of glucocorticoid receptor alpha isoforms to anxiety and depressive-like behavior in mice. J. Neurosci. Res. 100 (5), 1239–1253. https://doi.org/10.1021/bi00694a011.

Allen, E.C., Goslawski, M.M., Taple, B.J., Sakowicz, A., Alvarado-Goldberg, M., Miller, E. S., 2023. The association between adverse childhood experiences and perinatal depression symptom trajectories. Am. J. Obstet. Gynecol. MFM 5, 101039. https://doi.org/10.1016/j.ajogmf.2023.101039.

Antoniuk, S., Bijata, M., Ponimaskin, E., Wlodarczyk, J., 2019. Chronic unpredictable mild stress for modeling depression in rodents: meta-analysis of model reliability. Neurosci. Biobehav. Rev. 99, 101–116. https://doi.org/10.1016/j.neubiorev.2018.12.002.

Arcego, D.M., Toniazzo, A.P., Krolow, R., Lampert, C., Berlitz, C., Dos Santos Garcia, E., do Couto Nicola, F., Hoppe, J.B., Gaelzer, M.M., Klein, C.P., Lazzaretti, C., Dalmaz, C., 2018. Impact of high-fat diet and early stress on depressive-like behavior and hippocampal plasticity in adult male rats. Mol. Neurobiol. 55 (4), 2740–2753. https://doi.org/10.1007/s12035-017-0538-y.

Arellano, J.I., Duque, A., Rakic, P., 2024. A coming-of-age story: adult neurogenesis or adolescent neurogenesis in rodents? Front. Neurosci. 18, 1383728. https://doi.org/10.3389/fnins.2024.1383728.

Azogu, I., Liang, J., Plamondon, H., 2018. Sex-specific differences in corticosterone secretion, behavioral phenotypes and expression of TrkB. T1 and TrkB. FL receptor isoforms: impact of systemic TrkB inhibition and combinatory stress exposure in adolescence. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 86, 10–23. https://doi.org/10.1016/j.pnpbp.2018.05.002.

Bali, A., Jaggi, A., 2015. Electric foot shock stress: a useful tool in neuropsychiatric studies. Rev. Neurosci. 26 (6), 655–677. https://doi.org/10.1515/revneuro-2015-0015.

Bangasser, D.A., Cuarenta, A., 2021. Sex differences in anxiety and depression: circuits and mechanisms. Nat. Rev. Neurosci. 22 (11), 674–684. https://doi.org/10.1038/s41583-021-00513-0.

Becker, J.B., Prendergast, B.J., Liang, J.W., 2016. Female rats are not more variable than male rats: a meta-analysis of neuroscience studies. Biol. Sex Differ. 7, 34. https://doi.org/10.1186/s13293-016-0087-5.

Bell, M.R., 2018. Comparing postnatal development of gonadal hormones and associated social behaviors in rats, mice, and humans. Endocrinology 159 (7), 2596–2613. https://doi.org/10.1210/en.2018-00220.

Bertholomey, M.L., Nagarajan, V., Smith, D.M., Torregrossa, M.M., 2022. Sex-and age-dependent effects of chronic corticosterone exposure on depressive-like, anxiety-like, and fear-related behavior: role of amygdala glutamate receptors in the rat. Front. Behav. Neurosci. 16, 950000. https://doi.org/10.3389/fnbeh.2022.950000.

Bobo, W.V., Grossardt, B.R., Virani, S., St Sauver, J.L., Boyd, C.M., Rocca, W.A., 2022. Association of depression and anxiety with the accumulation of chronic conditions. JAMA Netw. Open 5 (5), e229817. https://doi.org/10.1001/jamanetworkopen.2022.9817.

Borsini, A., Giacobbe, J., Mandal, G., Boldrini, M., 2023. Acute and long-term effects of adolescence stress exposure on rodent adult hippocampal neurogenesis, cognition, and behaviour. Mol. Psychiatry 28 (10), 4124–4137. https://doi.org/10.1038/s41380-023-02229-2.

Böttger, S.J., Förstner, B.R., Szalek, L., Koller-Schlaud, K., Rapp, M.A., Tschorn, M., 2023. Mood and anxiety disorders within the research domain criteria framework of positive and negative valence systems: a scoping review. Front. Hum. Neurosci. 17, 1184978. https://doi.org/10.3389/fnhum.2023.1184978.

Bourke, C.H., Neigh, G.N., 2011. Behavioral effects of chronic adolescent stress are sustained and sexually dimorphic. Horm. Behav. 60 (1), 112–120. https://doi.org/10.1016/j.yhbeh.2011.03.011.

Boyce, W.T., 2016. Differential susceptibility of the developing brain to contextual adversity and stress. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 41 (1), 142–162. https://doi.org/10.1038/npp.2015.294.

Brás, J.P., Bravo, J., Freitas, J., Barbosa, M.A., Santos, S.G., Summavielle, T., Almeida, M. I., 2020. TNF-alpha-induced microglia activation requires miR-342: impact on NF-kB signaling and neurotoxicity. Cell Death Dis. 11 (6), 415. https://doi.org/10.1038/s41419-020-2626-6.

Brás, J.P., de Suduiraut, I.G., Zanoletti, O., Monari, S., Meijer, M., Grosse, J., Barbosa, M. A., Santos, S.G., Sandi, C., Almeida, M.I., 2022. Stress-induced depressive-like behavior in male rats is associated with microglial activation and inflammation dysregulation in the hippocampus in adulthood. Brain Behav. Immun. 99, 397–408. https://doi.org/10.1016/j.bbi.2021.10.018.

Butelman, E.R., McElroy, B.D., Prisinzano, T.E., Kreek, M.J., 2019. Impact of pharmacological manipulation of the κ-opioid receptor system on self-grooming and anhedonic-like behaviors in male mice. J. Pharmacol. Exp. Ther. 370 (1), 1–8. https://doi.org/10.1124/jpet.119.256354.

Carcone, D., Ruocco, A.C., 2017. Six years of research on the national institute of mental health’s research domain criteria (RDoC) initiative: a systematic review. Front. Cell. Neurosci. 11, 46. https://doi.org/10.3389/fncel.2017.00046.

Caruso, M.J., Kamens, H.M., Cavigelli, S.A., 2017. Exposure to chronic variable social stress during adolescence alters affect-related behaviors and adrenocortical activity in adult male and female inbred mice. Dev. Psychobiol. 59 (6), 679–687. https://doi.org/10.1002/dev.21541.

Caspi, A., Moffitt, T., 2006. Gene–environment interactions in psychiatry: joining forces with neuroscience. Nat. Rev. Neurosci. 7, 583–590. https://doi.org/10.1038/nrn1925.

Cotella, E.M., Scarponi Gómez, A., Lemen, P., Chen, C., Fernández, G., Hansen, C., Herman, J.P., Paglini, M.G., 2018. Long-term impact of chronic variable stress in adolescence versus adulthood. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 88, 303–310. https://doi.org/10.1016/j.pnpbp.2018.08.003.

Da Silva, F.E.R., Yucel, A., Menezes, A.P.M., Ruiz, A.C., Carbajal Tamez, M.C., Barichello, T., Scaini, G., Quevedo, J., 2025. Mechanisms underlying treatment-resistant depression: exploring sex-based biological differences. J. Neurochem. 169 (9), e70215. https://doi.org/10.1111/jnc.70215.

De Lima, A.P.N., Sandini, T.M., Reis-Silva, T.M., Massoco, C.O., 2017. Long-lasting monoaminergic and behavioral dysfunctions in a mice model of socio-environmental stress during adolescence. Behav. Brain Res. 317, 132–140. https://doi.org/10.1016/j.bbr.2016.09.024.

Desbonnet, L., Garrett, L., Daly, E., McDermott, K.W., Dinan, T.G., 2008. Sexually dimorphic effects of maternal separation stress on corticotrophin-releasing factor and vasopressin systems in the adult rat brain. Int. J. Dev. Neurosci.: Off. J. Int. Soc. Dev. Neurosci. 26 (3-4), 259–268. https://doi.org/10.1016/j.ijdevneu.2008.02.004.

Dos Santos, M.A.B., Guerra, A.E.P., Sayão, M.M.A., da Silva Selani, A.L., Betarelli, B.C., de Faria Siqueira, I., Forgerini, M., 2026. The role of adverse childhood experiences in the development of major depressive disorder and treatment-resistant depression. Child Psychiatry Hum. Dev. 1–17. https://doi.org/10.1007/s10578-026-01977-w.

Drzewiecki, C.M., Willing, J., Cortes, L.R., Juraska, J.M., 2021. Adolescent stress during, but not after, pubertal onset impairs indices of prepulse inhibition in adult rats. Dev. Psychobiol. 63 (5), 837–850. https://doi.org/10.1002/dev.22111.

Eidson, L.N., deSousa Rodrigues, M.E., Johnson, M.A., Barnum, C.J., Duke, B.J., Yang, Y., Chang, J., Kelly, S.D., Wildner, M., Tesi, R.J., Tansey, M.G., 2019. Chronic psychological stress during adolescence induces sex-dependent adulthood inflammation, increased adiposity, and abnormal behaviors that are ameliorated by selective inhibition of soluble tumour necrosis factor with XPro1595. Brain Behav. Immun. 81, 305–316. https://doi.org/10.1016/j.bbi.2019.06.027.

Fariborzi, M., Park, S.B., Ozgur, A., Lur, G., 2021. Sex-dependent long-term effects of prepubescent stress on the posterior parietal cortex. Neurobiol. Stress 14, 100295. https://doi.org/10.1016/j.ynstr.2021.100295.

Gencturk, S., Unal, G., 2024. Rodent tests of depression and anxiety: construct validity and translational relevance. Cogn. Affect. Behav. Neurosci. 24 (2), 191–224. https://doi.org/10.3758/s13415-024-01171-2.

Ghalandari-Shamami, M., Nourizade, S., Yousefi, B., Vafaei, A.A., Pakdel, R., Rashidy-Pour, A., 2019. Beneficial effects of physical activity and crocin against adolescent stress induced anxiety or depressive-like symptoms and dendritic morphology remodeling in prefrontal cortex in adult male rats. Neurochem. Res. 44 (4), 917–929. https://doi.org/10.1007/s11064-019-02727-2.

Golden, S.A., Covington, H.E., 3rd, Berton, O., Russo, S.J., 2011. A standardized protocol for repeated social defeat stress in mice. Nat. Protoc. 6 (8), 1183–1191. https://doi.org/10.1038/nprot.2011.361.

Gorman-Sandler, E., Hollis, F., 2022. The forced swim test: giving up on behavioral despair (Commentary on Molendijk & de Kloet, 2021). Eur. J. Neurosci. 55 (9-10), 2832–2835. https://doi.org/10.1111/ejn.15270.

Gyles, T.M., Nestler, E.J., Parise, E.M., 2024. Advancing preclinical chronic stress models to promote therapeutic discovery for human stress disorders. Neuropsychopharmacol.: Off. Publ. Am. Coll. Neuropsychopharmacol. 49 (1), 215–226. https://doi.org/10.1038/s41386-023-01625-0.

Harris, E.P., Villalobos-Manriquez, F., Melo, T.G., Clarke, G., O'Leary, O.F., 2022b. Stress during puberty exerts sex-specific effects on depressive-like behavior and monoamine neurotransmitters in adolescence and adulthood. Neurobiol. Stress 21, 100494. https://doi.org/10.1016/j.ynstr.2022.100494.

Harris, E.P., McGovern, A.J., Melo, T.G., Barron, A., Nolan, Y.M., O'Leary, O.F., 2022a. Juvenile stress exerts sex-independent effects on anxiety, antidepressant-like behaviors and dopaminergic innervation of the prelimbic cortex in adulthood and does not alter hippocampal neurogenesis. Behav. Brain Res. 419, 113725. https://doi.org/10.1016/j.bbr.2021.113725.

Heim, C., Binder, E.B., 2012. Current research trends in early life stress and depression: review of human studies on sensitive periods, gene-environment interactions, and epigenetics. Exp. Neurol. 233 (1), 102–111. https://doi.org/10.1016/j.expneurol.2011.10.032.

Heim, C., Newport, D.J., Mletzko, T., Miller, A.H., Nemeroff, C.B., 2008. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrinology 33 (6), 693–710. https://doi.org/10.1016/j.psyneuen.2008.03.008.

Heisler, J.M., Morales, J., Donegan, J.J., Jett, J.D., Redus, L., O'Connor, J.C., 2015. The attentional set shifting task: a measure of cognitive flexibility in mice. J. Vis. Exp.: JoVE 51944 (96). https://doi.org/10.3791/51944.

Higgins J.P.T., Thomas J., Chandler J., Cumpston M., Li T., Page M.J., Welch V.A. 2024. Cochrane Handbook for Systematic Reviews of Interventions. Versión 6.5. Cochrane.

Hollis, F., Kabbaj, M., 2014. Social defeat as an animal model for depression. ILAR J. 55 (2), 221–232. https://doi.org/10.1093/ilar/ilu002.

Holloway, A.L., Lerner, T.N., 2024. Hidden variables in stress neurobiology research. Trends Neurosci. 47 (1), 9–17. https://doi.org/10.1016/j.tins.2023.10.006.

Huang, J., Shen, C., Ye, R., Shi, Y., Li, W., 2021. The effect of early maternal separation combined with adolescent chronic unpredictable mild stress on behavior and synaptic plasticity in adult female rats. Front. Psychiatry 12, 539299. https://doi.org/10.3389/fpsyt.2021.539299.

Humphreys, K.L., Zeanah, C.H., 2015. Deviations from the expectable environment in early childhood and emerging psychopathology. Neuropsychopharmacology 40 (1), 154–170. https://doi.org/10.1038/npp.2014.165.

Ilin, V.A., Richter-Levin, G., 2009. Enriched environment experience overcomes learning deficits and depressive-like behavior induced by juvenile stress. Behav. Brain Res. 201 (1), 51–58. https://doi.org/10.1371/journal.pone.0004329.

Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D.S., Quinn, K., Sanislow, C., Wang, P., 2010. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167 (7), 748–751. https://doi.org/10.1176/appi.ajp.2010.09091379.

Jankord, R., Solomon, M.B., Albertz, J., Flak, J.N., Zhang, R., Herman, J.P., 2011. Stress vulnerability during adolescent development in rats. Endocrinology 152 (2), 629–638. https://doi.org/10.1210/en.2010-0658.

Jaric, I., Rocks, D., Cham, H., Herchek, A., Kundakovic, M., 2019. Sex and estrous cycle effects on anxiety- and depression-related phenotypes in a two-hit developmental stress model. Front. Mol. Neurosci. 12. https://doi.org/10.3389/fnmol.2019.00074.

Kang, H.J., Park, Y., Yoo, K.H., Kim, K.T., Kim, E.S., Kim, J.W., Kim, S.W., Shin, I.S., Yoon, J.S., Kim, J.H., Kim, J.M., 2020. Sex differences in the genetic architecture of depression. Sci. Rep. 10 (1), 9927. https://doi.org/10.1038/s41598-020-66672-9.

Kessler, R.C., Berglund, P.A., Chiu, W.T., Deitz, A.C., Hudson, J.I., Shahly, V., Xavier, M., 2013. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. Biol. Psychiatry 73 (9), 904–914. https://doi.org/10.1146/annurev-publhealth-031912-114409.

Kim, S., Gacek, S.A., Mocchi, M.M., Redei, E.E., 2021. Sex-specific behavioral response to early adolescent stress in the genetically more stress-reactive Wistar Kyoto more immobile, and its nearly isogenic Wistar Kyoto less immobile control strain. Front. Behav. Neurosci. 15, 779036. https://doi.org/10.3389/fnbeh.2021.779036.

Kovalenko, I.L., Galyamina, A.G., Smagin, D.A., Michurina, T.V., Kudryavtseva, N.N., Enikolopov, G., 2014. Extended effect of chronic social defeat stress in childhood on behaviors in adulthood. PLoS One 9 (3), e91762. https://doi.org/10.1371/journal.pone.0091762.

Krahe, T.E., Medina, A.E., Lantz, C.L., Filgueiras, C.C., 2015. Hyperactivity and depression-like traits in Bax KO mice. Brain Res. 1625, 246–254. https://doi.org/10.1016/j.brainres.2015.09.002.

Kubala, K.H., Christianson, J.P., Kaufman, R.D., Watkins, L.R., Maier, S.F., 2012. Short- and long-term consequences of stressor controllability in adolescent rats. Behav. Brain Res. 234 (2), 278–284. https://doi.org/10.1016/j.bbr.2012.06.027.

Kuske, J.X., Trainor, B.C., 2022. Mean girls: social stress models for female rodents. Curr. Top. Behav. Neurosci. 54, 95–124. https://doi.org/10.1007/7854_2021_247.

Leschik, J., Lutz, B., Gentile, A., 2021. Stress-related dysfunction of adult hippocampal neurogenesis—an attempt for understanding resilience? Int. J. Mol. Sci. 22 (14), 7339. https://doi.org/10.3390/ijms22147339.

Li, C., Liu, Y., Yin, S., Lu, C., 2015. Long-term effects of early adolescent stress: dysregulation of hypothalamic–pituitary–adrenal axis and central corticotropin releasing factor receptor 1 expression in adult male rats. Behav. Brain Res. 288, 39–49. https://doi.org/10.1016/j.bbr.2015.04.007.

Lovelock, D.F., Deak, T., 2019. Acute stress imposed during adolescence yields heightened anxiety in Sprague Dawley rats that persists into adulthood: sex differences and potential involvement of the Medial Amygdala. Brain Res. 1723, 146392. https://doi.org/10.1016/j.brainres.2019.146392.

Luo, X.-M., Yuan, S.-N., Guan, X.-T., Xie, X., Shao, F., Wang, W.-W., 2014. Juvenile stress affects anxiety-like behavior and limbic monoamines in adult rats. Physiol. Behav. 135, 7–16. https://doi.org/10.1016/j.physbeh.2014.05.035.

Lyttle, K., Ohmura, Y., Konno, K., Yoshida, T., Izumi, T., Watanabe, M., Yoshioka, M., 2015. Repeated fluvoxamine treatment recovers juvenile stress-induced morphological changes and depressive-like behavior in rats. Brain Res. 1616, 88–100. https://doi.org/10.1016/j.brainres.2015.04.058.

Mancha-Gutiérrez, H.M., Estrada-Camarena, E., Mayagoitia-Novales, L., López-Pacheco, E., López-Rubalcava, C., 2021. Chronic SOcial Defeat during Adolescence Induces Short- and Long-term Behavioral and Neuroendocrine Effects in Male Swiss-webster mice. Front. Behav. Neurosci. 15, 734054. https://doi.org/10.3389/fnbeh.2021.734054.

Mao, Y., Xu, Y., Yuan, X., 2022. Validity of chronic restraint stress for modeling anhedonic-like behavior in rodents: a systematic review and meta-analysis. J. Int. Med. Res. 50 (2). https://doi.org/10.1177/03000605221075816 (3000605221075816.

Marchette, R.C.N., Bicca, M.A., Santos, E.C.D.S., de Lima, T.C.M., 2018. Distinctive stress sensitivity and anxiety-like behavior in female mice: strain differences matter. Neurobiol. Stress 9, 55–63. https://doi.org/10.1016/j.ynstr.2018.08.002.

Márquez, C., Poirier, G.L., Cordero, M.I., Larsen, M.H., Groner, A., Marquis, J., Magistretti, P.J., Trono, D., Sandi, C., 2013. Peripuberty stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal MAOA gene expression. Transl. Psychiatry 3 (1), e216. https://doi.org/10.1038/tp.2012.144.

Mathews, I.Z., Wilton, A., Styles, A., McCormick, C.M., 2008. Increased depressive behavior in females and heightened corticosterone release in males to swim stress after adolescent social stress in rats. Behav. Brain Res. 190 (1), 33–40. https://doi.org/10.1016/j.bbr.2008.02.004.

Mengelkoch, S., Slavich, G.M., 2024. Sex differences in stress susceptibility as a key mechanism underlying depression risk. Curr. Psychiatry Rep. 26 (4), 157–165. https://doi.org/10.1007/s11920-024-01490-8.

Miller, L.R., Marks, C., Becker, J.B., Hurn, P.D., Chen, W.J., Woodruff, T., McCarthy, M. M., Sohrabji, F., Schiebinger, L., Wetherington, C.L., Makris, S., Arnold, A.P., Einstein, G., Miller, V.M., Sandberg, K., Maier, S., Cornelison, T.L., Clayton, J.A., 2017. Considering sex as a biological variable in preclinical research. FASEB J.: Off. Publ. Fed. Am. Soc. Exp. Biol. 31 (1), 29–34. https://doi.org/10.1096/fj.201600781R.

Mohammadi, S., Seyedmirzaei, H., Salehi, M.A., Jahanshahi, A., Zakavi, S.S., Dehghani Firouzabadi, F., Yousem, D.M., 2023. Brain-based sex differences in depression: a systematic review of neuroimaging studies. Brain Imaging Behav. 17 (5), 541–569. https://doi.org/10.1007/s11682-023-00772-8.

Molendijk, M.L., de Kloet, E.R., 2015. Immobility in the forced swim test is adaptive and does not reflect depression. Psychoneuroendocrinology 62, 389–391. https://doi.org/10.1016/j.psyneuen.2015.08.028.

Moradi-Kor, N., Moradi, N., Alizadeh, A.M., Mohseni, S., 2020. Protective effects of Spirulina platensis, voluntary exercise and environmental interventions against adolescent stress-induced anxiety and depressive-like symptoms, oxidative stress and alterations of BDNF and 5HT-3 receptors of the prefrontal cortex in female rats. Neuropsychiatr. Dis. Treat. 16, 2257–2274. https://doi.org/10.2147/NDT.S247599.

Moreno-Fernández, R.D., Pérez-Martín, M., Castilla-Ortega, E., Rosell Del Valle, C., García-Fernández, M.I., Chun, J., Estivill-Torrús, G., Rodríguez de Fonseca, F., Santín, L.J., Pedraza, C., 2017. maLPA1-null mice as an endophenotype of anxious depression. Transl. Psychiatry 7 (4), e1077. https://doi.org/10.1038/tp.2017.24.

Moreno-Fernández, R.D., Nieto-Quero, A., Gómez-Salas, F.J., Chun, J., Estivill-Torrús, G., Rodríguez de Fonseca, F., Santín, L.J., Pérez-Martín, M., Pedraza, C., 2018. Effects of genetic deletion versus pharmacological blockade of the LPA_1 receptor on depression-like behavior and related brain functional activity. Dis. Models Mech. 11 (9), dmm035519. https://doi.org/10.1242/dmm.035519.

Moreno-Fernández, R.D., Sampedro-Piquero, P., Gómez-Salas, F.J., Nieto-Quero, A., Estivill-Torrús, G., Rodríguez de Fonseca, F., Santín, L.J., Pedraza, C., 2023. Social avoidance and altered hypothalamic-pituitary-adrenal axis in a mouse model of anxious depression: The role of LPA_1 receptor. Behav. Brain Res. 455, 114681. https://doi.org/10.1016/j.bbr.2023.114681.

von Mücke-Heim, I.A., Urbina-Treviño, L., Bordes, J., Ries, C., Schmidt, M.V., Deussing, J.M., 2023. Introducing a depression-like syndrome for translational neuropsychiatry: a plea for taxonomical validity and improved comparability between humans and mice. Mol. Psychiatry 28 (1), 329–340. https://doi.org/10.1038/s41380-022-01762-w.

Müller, I., Obata, K., Richter-Levin, G., Stork, O., 2014. GAD65 haplodeficiency conveys resilience in animal models of stress-induced psychopathology. Front. Behav. Neurosci. 8, 265. https://doi.org/10.3389/fnbeh.2014.00265.

Nanni, V., Uher, R., Danese, A., 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. Am. J. Psychiatry 169 (2), 141–151. https://doi.org/10.1176/appi.ajp.2011.11020335.

Nelson, C.A., Bhutta, Z.A., Harris, N.B., Danese, A., Samara, M., 2020. Adversity in childhood is linked to mental and physical health throughout life. bmj 371. https://doi.org/10.1136/bmj.m3048.

Nemeroff, C.B., Heim, C.M., Thase, M.E., Klein, D.N., Rush, A.J., Schatzberg, A.F., Ninan, P.T., McCullough, J.P., Jr, Weiss, P.M., Dunner, D.L., Rothbaum, B.O., Kornstein, S., Keitner, G., Keller, M.B., 2003. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. Proc. Natl. Acad. Sci. USA 100 (24), 14293–14296. https://doi.org/10.1073/pnas.2336126100.

Niwa, M., Lockhart, S., Wood, D., Yang, K., Kanes, S.J., 2024. Prolonged HPA axis dysregulation in postpartum depression associated with adverse early life experiences: a cross-species translational study. Nat. Ment. Health 2 (5). https://doi.org/10.1038/s44220-024-00217-1.

Nollet, M., 2021. Models of depression: unpredictable chronic mild stress in mice. Curr. Protoc. 1 (8), e208. https://doi.org/10.1002/cpz1.208.

Page, C.E., Coutellier, L., 2018. Adolescent stress disrupts the maturation of anxiety-related behaviors and alters the developmental trajectory of the prefrontal cortex in a sex- and age-specific manner. Neuroscience 390, 265–277. https://doi.org/10.1016/j.neuroscience.2018.08.030.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj 372. https://doi.org/10.1136/bmj.n71.

Pałucha-Poniewiera, A., Bobula, B., Rafało-Ulińska, A., 2023. The antidepressant-like activity and cognitive enhancing effects of the combined administration of (*R*)-ketamine and LY341495 in the CUMS model of depression in mice are related to the modulation of excitatory synaptic transmission and LTP in the PFC. Pharmaceuticals 16 (2), 288. https://doi.org/10.3390/ph16020288.

Perry, W., Minassian, A., Feifel, D., 2004. Prepulse inhibition in patients with non-psychotic major depressive disorder. J. Affect. Disord. 81 (2), 179–184. https://doi.org/10.1016/S0165-0327(03)00157-5.

Pietrantonio, A.F., Urian, R.A., Hardy, D.B., Allman, B.L., Willmore, K.E., 2025. Hyperactivity in male and female mice manifests differently following early, acute prenatal alcohol exposure and mild juvenile stress. Front. Behav. Neurosci. 19, 1501937. https://doi.org/10.3389/fnbeh.2025.1501937.

Pillai, E.K., Franze, K., 2024. Mechanics in the nervous system: from development to disease. Neuron 112 (3), 342–361. https://doi.org/10.1016/j.neuron.2023.10.005.

Platona, R.I., Căiță, G.A., Voiță-Mekeres, F., Peia, A.O., Enătescu, R.V., 2024. The impact of psychiatric comorbidities associated with depression: a literature review. Med. Pharm. Rep. 97 (2), 143–148. https://doi.org/10.15386/mpr-2700.

Prendergast, B.J., Onishi, K.G., Zucker, I., 2014. Female mice liberated for inclusion in neuroscience and biomedical research. Neurosci. Biobehav. Rev. 40, 1–5. https://doi.org/10.1016/j.neubiorev.2014.01.001.

Primo, M.J., Fonseca-Rodrigues, D., Almeida, A., Teixeira, P.M., Pinto-Ribeiro, F., 2023. Sucrose preference test: a systematic review of protocols for the assessment of anhedonia in rodents. Eur. Neuropsychopharmacol.: J. Eur. Coll. Neuropsychopharmacol. 77, 80–92. https://doi.org/10.1016/j.euroneuro.2023.08.496.

Raftogianni, A., Diamantopoulou, A., Alikaridis, F., Stamatakis, A., Stylianopoulou, F., 2012. Effects of interaction of an early experience of reward through maternal contact or its denial with social stress during adolescence on the serotonergic system and the stress responsiveness of adult female rats. Neuroscience 209, 84–96. https://doi.org/10.1016/j.neuroscience.2012.01.032.

Ranaei, E., Torshizi, S., Amini, A., Heidari, M.H., Namvarpour, Z., Fathabady, F.F., Salari, A.A., 2020. Peripubertal stress following maternal immune activation sex-dependently alters depression-like behaviors in offspring. Behav. Brain Res. 393, 112800. https://doi.org/10.1016/j.bbr.2020.112800.

Rechlin, R.K., Splinter, T.F.L., Hodges, T.E., Albert, A.Y., Galea, L.A.M., 2022. An analysis of neuroscience and psychiatry papers published from 2009 and 2019 outlines opportunities for increasing discovery of sex differences. Nat. Commun. 13 (1), 2137. https://doi.org/10.1038/s41467-022-29903-3.

Rizeq, J., Kennedy, M., Miseih, K., Liao, W., Sonuga-Barke, E.J., 2025. Early childhood deprivation and the impact of negative life events on mental health in later life: a test of the stress sensitization hypothesis. Front. Psychiatry 15, 1393107. https://doi.org/10.3389/fpsyt.2024.1393107.

Ros-Simó, S., Lecourtois, M., Charrier, V., Bailly, J., Givalois, L., 2012. Early-life social experiences in mice affect emotional behavior and hypothalamic-pituitary-adrenal axis function. Pharmacol. Biochem. Behav. 102 (3), 434–441. https://doi.org/10.1016/j.pbb.2012.06.001.

Santos-Carrasco, D., De la Casa, L.G., 2023. Prepulse inhibition deficit as a transdiagnostic process in neuropsychiatric disorders: a systematic review. BMC Psychol. 11 (1), 226. https://doi.org/10.1186/s40359-023-01253-9.

Schmidt, M.V., Scharf, S.H., Sterlemann, V., Ganea, K., Liebl, C., Holsboer, F., Müller, M. B., 2010. High susceptibility to chronic social stress is associated with a depression-like phenotype. Psychoneuroendocrinology 35 (5), 635–643. https://doi.org/10.1016/j.psyneuen.2009.10.002.

Shansky, R.M., 2019. Are hormones a "female problem" for animal research? Science 364 (6443), 825–826. https://doi.org/10.1126/science.aaw7570.

Shansky, R.M., Murphy, A.Z., 2021. Considering sex as a biological variable will require a global shift in science culture. Nat. Neurosci. 24 (4), 457–464. https://doi.org/10.1038/s41593-021-00806-8.

Shoji, H., Maeda, Y., Miyakawa, T., 2024. Chronic corticosterone exposure causes anxiety-and depression-related behaviors with altered gut microbial and brain metabolomic profiles in adult male C57BL/6J mice. Mol. Brain 17 (1), 79. https://doi.org/10.1186/s13041-024-01146-x.

Sun, L., Ma, S., Yu, Y., Li, X., Wei, Q., Min, L., et al., 2023. Transcutaneous auricular vagus nerve stimulation ameliorates adolescent depressive- and anxiety-like behaviors via hippocampus glycolysis and inflammation response. CNS Neurosci. Ther. 30 (2), e14614. https://doi.org/10.1111/cns.14614.

Takaba, R., Ibi, D., Watanabe, K., Hayakawa, K., Nakasai, G., Hiramatsu, M., 2022. Role of sirtuin1 in impairments of emotion-related behaviors in mice with chronic mild unpredictable stress during adolescence. Physiol. Behav. 251, 113971. https://doi.org/10.1016/j.physbeh.2022.113971.

Takahashi, M., Shelton, R.C., 2025. From trauma to depression: structural, synaptic, epigenetic, and molecular pathways linking early stress to lifelong vulnerability. Front. Psychiatry 16, 1666599. https://doi.org/10.3389/fpsyt.2025.1666599.

Tapocik, J.D., Schank, J.R., Mitchell, J.R., Damazdic, R., Mayo, C.L., Brady, D., Elmer, G. I., 2021. Live predator stress in adolescence results in distinct adult behavioral consequences and dorsal diencephalic brain activation patterns. Behav. Brain Res. 400, 113028. https://doi.org/10.1016/j.bbr.2020.113028.

Tirelli, E., Laviola, G., Adriani, W., 2003. Ontogenesis of behavioral sensitization and conditioned place preference induced by psychostimulants in laboratory rodents. Neurosci. Biobehav. Rev. 27 (1-2), 163–178. https://doi.org/10.1016/s0149-7634(03)00018-6.

Tóth, E., Gersner, R., Wilf-Yarkoni, A., Raizel, H., Dar, D.E., Richter-Levin, G., Levit, O., Zangen, A., 2008. Age-dependent effects of chronic stress on brain plasticity and depressive behavior. J. Neurochem. 107 (2), 522–532. https://doi.org/10.1111/j.1471-4159.2008.05642.x.

Vaidya, N., Marquand, A.F., Nees, F., Siehl, S., Schumann, G., 2024. The impact of psychosocial adversity on brain and behavior: an overview of existing knowledge and directions for future research. Mol. Psychiatry 29 (10), 3245–3267. https://doi.org/10.1038/s41380-024-02556-y.

Veenit, V., Riccio, O., Sandi, C., 2014. CRHR1 links peri puberty stress with deficits in social and stress-coping behaviors. J. Psychiatr. Res. 53, 1–7. https://doi.org/10.1016/j.jpsychires.2014.02.015.

Vorhees, C.V., Williams, M.T., 2024. Tests for learning and memory in rodent regulatory studies. Curr. Res. Toxicol. 6, 100151. https://doi.org/10.1016/j.crtox.2024.100151.

Walker, S.E., Sandi, C., 2018. Long-term programing of psychopathology-like behaviors in male rats by peripubertal stress depends on individual's glucocorticoid responsiveness to stress. Stress 21 (5), 433–442. https://doi.org/10.1080/10253890.2018.1435639.

Wang, H., Wang, X., Wang, H., Shao, S., Zhu, J., 2024. Chronic corticosterone administration-induced mood disorders in laboratory rodents: features, mechanisms, and research perspectives. Int. J. Mol. Sci. 25 (20), 11245. https://doi.org/10.3390/ijms252011245.

Wang, R., Wang, W., Xu, J., Liu, D., Jiang, H., Pan, F., 2018. Dynamic effects of early adolescent stress on depressive-like behaviors and expression of cytokines and JMJD3 in the prefrontal cortex and hippocampus of rats. Front. Psychiatry 9, 471. https://doi.org/10.3389/fpsyt.2018.00471.

Whittle, S., Rakesh, D., Simmons, J.G., Schwartz, O., Vijayakumar, N., Allen, N.B., 2025. Prospective associations between structural brain development and onset of depressive disorder during adolescence and emerging adulthood. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.20240588 (appi-ajp.

Wilkin, M.M., Waters, P., McCormick, C.M., Menard, J.L., 2012. Intermittent physical stress during early- and mid-adolescence differentially alters rats' anxiety- and depression-like behaviors in adulthood. Behav. Neurosci. 126 (2), 344–360. https://doi.org/10.1037/a0027258.

Williams, L.M., Debattista, C., Duchemin, A.M., Schatzberg, A.F., Nemeroff, C.B., 2016. Childhood trauma predicts antidepressant response in adults with major depression: data from the randomized international study to predict optimized treatment for depression. Transl. Psychiatry 6 (5), e799. https://doi.org/10.1038/tp.2016.61 (-e799.

Willner, P., Towell, A., Sampson, D., Sophokleous, S., Muscat, R.A., 1987. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology 93 (3), 358–364. https://doi.org/10.1007/BF00187257.

Woody, M.L., Gibb, B.E., 2015. Integrating NIMH research domain criteria (RDoC) into depression research. Curr. Opin. Psychol. 4, 6–12. https://doi.org/10.1016/j.copsyc.2015.01.004.

Wulsin, A.C., Waugh, C.E., Harkness, K.L., 2016. Adolescent chronic stress causes hypothalamo-pituitary-adrenocortical hypo-responsiveness and depression-like behavior in adult female rats. Psychoneuroendocrinology 65, 109–117. https://doi.org/10.1016/j.psyneuen.2015.12.004.

Xu, J., Wang, R., Liu, Y., Liu, D., Jiang, H., Pan, F., 2019. Short- and long-term alterations of FKBP5-GR and specific microRNAs in the prefrontal cortex and hippocampus of male rats induced by adolescent stress contribute to depression susceptibility. Psychoneuroendocrinology 101, 204–215. https://doi.org/10.1016/j.psyneuen.2018.11.008.

Xu, J., Wang, X., Xu, W., Zhang, Y., Pan, L., Gao, J., 2024. The protective effect of S-adenosylmethionine on chronic adolescent stress-induced depression-like behaviors by regulating gut microbiota. Eur. J. Pharmacol. 982, 176939. https://doi.org/10.1016/j.ejphar.2024.176939.

Xue, B., Ma, Y.-Y., Zhu, J.-Y., Mu, Y., Li, Y.-H., Shen, F., Liang, J., Zhang, J.-J., 2023. Chronic social comparison elicits depression- and anxiety-like behaviors and alterations in brain-derived neurotrophic factor expression in male rats. Anim. Cogn. 26 (5), 1505–1519. https://doi.org/10.1007/s10071-023-01798-7.

Yohn, N.L., Blendy, J.A., 2017. Adolescent chronic unpredictable stress exposure is a sensitive window for long-term changes in adult behavior in mice. Neuropsychopharmacology 42 (10), 1670–1678. https://doi.org/10.1038/npp.2017.11.

Zajkowska, Z., Walsh, A., Zonca, V., Gullett, N., Pedersen, G.A., Kieling, C., Mondelli, V., 2021. A systematic review of the association between biological markers and environmental stress risk factors for adolescent depression. J. Psychiatr. Res. 138, 163–175. https://doi.org/10.1016/j.jpsychires.2021.04.003.

Zhang, S.S., Tian, Y.H., Jin, S.J., Wang, W.C., Zhao, J.X., Si, X.M., Jin, J.Y., 2019. Isoflurane produces antidepressant effects inducing BDNF-TrkB signaling in CUMS mice. Psychopharmacology 236 (11), 3301–3315. https://doi.org/10.1007/s00213-019-05287-z.