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Early life adversities, psychopathologies and novel pharmacological strategies

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ABSTRACT

Exposure to adversities during early life stages (early life adversities - ELA), ranging from pregnancy to adolescence, represents a major risk factor for the vulnerability to mental disorders. Hence, it is important to understand the molecular and functional underpinning of such relationship, in order to develop strategies aimed at reducing the psychopathologic burden associated with ELA, which may eventually lead to a significant improvement in clinical practice. In this review, we will initially recapitulate clinical and preclinical evidence supporting the link between ELA and psychopathology and we will primarily discuss the main biological mechanisms that have been described as potential mediators of the effects of ELA on the psychopathologic risk, including the role for genetic factors as well as sex differences. The knowledge emerging from these studies may be instrumental for the development of novel therapeutic strategies aimed not only at correcting the deficits that emerge from ELA exposure, but also in preventing the manifestation of a full-blown psychopathologic condition. With this respect, we will specifically focus on adolescence as a key time frame for disease onset as well as for early therapeutic intervention. We believe that incorporating clinical and preclinical research data in the context of early life adversities can be instrumental to elucidate the mechanisms contributing to the risk for psychopathology or that may promote resilience. This will ultimately allow the identification of 'at risk' individuals who may benefit from specific forms of interventions that, by interfering with disease trajectories, could result in more benign clinical outcomes.

Contents

Abbreviations: 5-HT, 5-hydroxytryptamine; 5-HTTLPR, Serotonin-transporter-linked promoter region; BDNF, Brain-derived neurotrophic factor; CRH, Corticotropin-releasing hormone; CRHR1, Corticotropin-releasing hormone receptor 1; CRP, C-reactive Protein; ELA, Early life adversities; FKBP5, FKBP prolyl isomerase 5; GABA, Gamma-aminobutyric acid; GABA, γ-Aminobutyric acid; GRS, Glucocorticoid receptors; HPA, Hypothalamus-pituitary-adrenal; IL-10, Interleukin 10; IL-1β, Interleukin 1 beta; IL-6, Interleukin 6; LPS, Lipopolysaccharides; LTP, Long-term potentiation; MD, Maternal deprivation; MS, Maternal separation; NAc, Nucleus accumbens; NR3C1, Nuclear receptor subfamily 3 group C member 1; PFC, Prefrontal cortex; PND, Postnatal day; PV, Parvalbumin; SERT, serotonin transporter; SLC6A4, Solute Carrier Family 6 Member 4; TGF-β, Transforming Growth factor beta; TNF-α, Tumor Necrosis Factor alpha.

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1. Introduction

1.1. The link between early life adversities and psychopathology

Early life adversities encompass a broad spectrum of negative experiences that can occur prenatally or early postnatally until childhood and adolescence, such as maltreatment, neglect, and trauma. Early life adversities (ELA) have long been recognized as a significant factor influencing psychological well-being and mental health outcomes (Norman et al., 2012). Importantly, evidence suggests that partially distinct mechanisms may underlie the association between different dimensions of ELA and psychopathology later in life. However, while there is evidence that different types of ELA are associated with specific psychopathology outcomes, it is also known that specific dimensions of ELA increase the transdiagnostic risk of mental health problems across the internalizing and externalizing spectra.

For these reasons, investigating the link between ELA and psychopathology is extremely important to establish causal relationships between adverse experiences and clinical features and to understand the molecular and functional underpinning of such relationship, overall contributing to improve clinical practice.

Among the different types of adversities, those occurring during the prenatal, early postnatal period as well as childhood appear to be associated with the most relevant negative outcomes.

1.1.1. The finding from human studies

1.1.1.1. Prenatal adversities. It is well known that prenatal adversities are associated with an increased risk, in the exposed offspring, to develop behavioral problems, with symptoms that can be observed already during the first years of life. Among prenatal adversities, maternal stress, depression, and obesity represent the two most common complications during pregnancy and are associated with severe health risks for both the mother and the child. In the mother, the risks include gestational hypertension, pre-eclampsia, gestational diabetes, cesarean, preterm delivery, decreased breastfeeding initiation and duration, and a poor bonding of the mother with her child (Sullivan et al., 2015). In the exposed children we can observe increased risk of preterm birth and lower birth weight, of suboptimal physical, cognitive, and socio-emotional development, of poorer academic performance, and of physical and mental disorders in later life. This is mainly due to biological alterations occurring in the intrauterine environment, known to shape the fetal development and the subsequent child's health or disease risk via the well-known phenomenon of "*early life programming*" (Lindsay et al., 2019). Given the well-known effect of social and environmental exposure during pregnancy on the development of adverse outcomes in the exposed offspring, several studies have assessed maternal status with particular interest on maternal stress or depression, and obesity, as risk factors for the onset of negative behavioral outcomes in the offspring.

1.1.1.2. Maternal stress, anxiety and depression. Maternal stress, anxiety, and depression during pregnancy have been widely associated with effects during the in utero development, with consequences such as intrauterine growth restriction, prematurity, and low birth weight (Keenan-Devlin et al., 2023; Matsas et al., 2023), but also with a wide range of altered neurodevelopmental outcomes, including difficult temperament, emotional and behavioral problems in the offspring, both during infancy and childhood (Hantsoo et al., 2019; Loomans et al., 2011; Pickles et al., 2017; Van Batenburg-Eddes et al., 2013). Importantly, specific temporal windows of exposure during pregnancy have been shown to have the strongest impact on offspring outcomes. For example, maternal stress during middle and late pregnancy has the largest effect on infant negative affective behaviors. Also, the presence of increased maternal stress during late pregnancy has been linked to stronger effects on brain morphology and functionality in neonates (Marr et al., 2023).

Indeed, behavioral consequences in children exposed to maternal stress and anxiety are mirrored by changes on offspring's brain morphology such as gray matter volume reductions in several brain areas, including the prefrontal cortical and the medial temporal regions changes (Buss et al., 2010). Also accelerated fetal neurological maturation has been observed in babies exposed to maternal psychological stress in pregnancy, suggesting that the human brain requires sufficient but not excessive stress to promote neural development, both before and after birth (DiPietro et al., 2010). Amygdala and hippocampus are the brain regions primarily affected by maternal stress and anxiety, possibly because their development starts at an early embryonic stage and they appear to be particularly sensitive to elevated levels of glucocorticoids (Buss et al., 2012; Qiu et al., 2017; Wen et al., 2017). Indeed, the presence of high maternal glucocorticoids concentrations in association with maternal stress during early gestation may represent the main players for later dysfunction, since they are associated with larger right amygdala volumes in female offspring, also suggesting that the intrauterine environment may interact with foetal sex, in shaping the vulnerability of developing altered behavior (Buss et al., 2012).

Also, maternal depression during pregnancy has been widely associated with negative child's mental health outcomes and altered brain neurodevelopmental trajectories at adolescence or adulthood. For example, children of mothers with severe depressive symptoms during pregnancy were those with the most severe neurodevelopmental disadvantages in gross motor, communication, problem solving, and personal/social skills, and higher risk for both internalizing and externalizing problems (M. Lahti et al., 2017), Moreover, an additive effect of depressive symptoms during pregnancy and in the post-partum on child neurodevelopment has been also demonstrated (Tuovinen et al., 2018).

The effect of mothers' depression and children's behavioral problems or emotional functioning has been confirmed by meta-analyses where depression in the mothers has been associated with children's internalizing, externalizing problems, and general psychopathology. Interestingly, the association between maternal depressive symptoms and internalizing problems was stronger in girls, suggesting that girls are more sensitive to the postnatal stress context and to the style of parenting associated with depression in the mother as compared to boys (Goodman et al., 2011). Plant and colleagues also demonstrated that offspring exposed to maternal depression in utero are at higher risk to develop depressive symptoms at adolescence or adulthood (Plant et al., 2015). Similarly, in the ALSPAC Cohort it has been shown an increased risk of anxiety disorders as well as comorbid anxiety and depression in adolescents exposed to maternal depression in utero. Interestingly no effect of paternal depression on children's outcomes was observed, supporting the main role of foetal programming in mediating the effect of exposure to stress/depression in the mother on offspring's mental outcomes (Capron et al., 2015).

Behavioral negative outcomes in offspring exposed to maternal depression are also associated with structural changes in brain regions involved in behavioral regulation, such as prefrontal cortex, frontal and inferior temporal areas (Lebel et al., 2016), amygdala (Rifkin-Graboi et al., 2013), and in neural connectivity between amygdala and fronto-striatal areas (Qiu et al., 2015). For example, a significant cortical thinning primarily in the right frontal lobes was observed in children exposed to prenatal maternal depression, suggesting that cortical thinning may represent a brain-based endophenotype for the development of depression (Scheinost et al., 2017; Soe et al., 2018).

Interestingly, as for the behavioral outcomes, the effects of depression in pregnancy on children's brain morphology are sex specific. For example, a larger right amygdala volume was associated with prenatal maternal depression in girls, but not in boys, suggesting independent and differential influences of pre and postnatal depressive symptoms

in the mother on the structural development of the amygdala, with sex-specific effects (Wen et al., 2017). These data emphasize the importance of the timing of exposure to maternal depression, as well as the importance of considering gender differences when planning intervention strategies for the prevention of adverse outcomes in exposed children.

1.1.1.3. Maternal obesity. It is well known that maternal nutrition represents another important risk factors that influences not only foetal development, but also the offspring's long-term behavioral and physical features. Indeed, both a restricted diet or a condition of obesity of the future mother during pregnancy may lead to several negative outcomes in the offspring, including dysfunctions in cognitive abilities (Ars et al., 2019), language delay (C. Roth et al., 2011), internalizing and externalizing behaviors (Lichtwald et al., 2023), and affecting brain regions mainly involved in language and emotions (Lee et al., 2023).

As an example, conditions such as obesity or exposure to high fat diet can enhance the offspring's vulnerability for neurodevelopmental disorders by inducing metabolic related changes, such as increased maternal leptin, insulin, glucose, triglycerides, and by inducing a pro-inflammatory status which in turn can contribute to a brain mal-programming and to impairments in reward circuitry and in synaptic plasticity (Cattane et al., 2021).

Maternal obesity during pregnancy can affect offspring's brain development, increasing the risk for a wide range of neurodevelopmental disorders (Contu & Hawkes, 2017; Edlow, 2017; O'Donnell & Meaney, 2017; Rivera et al., 2015; Sullivan et al., 2015). It has been reported that children born from obese mothers or from mothers who gained excessive weight during pregnancy have a twofold increased risk of developing ADHD as compared to controls (Q. L. C. Reynolds et al., 2014; Rodriguez, 2010). Moreover, overweight and obesity in pregnancy have been associated with delays in communication, problem solving and personal-social skills, whereas early pregnancy overweight was associated only with delay in fine motor skills and mild delay in communication skills (Girchenko et al., 2018).

For example, by investigating the mother–offspring pairs in the ALSPAC study, it has been shown that prenatal maternal depression is related to unhealthy prenatal diet, which, in turn, is prospectively associated with reduced cognitive functions in the offspring (Barker et al., 2013). Higher maternal depressive symptoms are associated with lower levels of healthy nutrition as well as higher levels of unhealthy nutrition, and each of them was in turn associated with reduced cognitive functions in children (Barker et al., 2013).

Moreover, although the literature suggests that the sex-dependent impact of prenatal maternal stress and depression is time and brain region-specific, still little is known about the mechanisms underlying the vulnerability for the development of negative outcomes in male and female offspring (Goldstein et al., 2016). More research should be performed to identify and characterize sex specific mechanisms, which will eventually help to plan sex specific interventions in at risk individuals.

These findings clearly indicate that ELA exert a key role on fetal developmental programming, causing both short and long-term consequences on the exposed offspring. This suggests the importance of interventions designed to reshape the biological alterations associated with such exposures as they could have profound protective effects on fetal development and also long-term health.

1.1.1.4. Stress exposure during childhood and adolescence. Childhood is an important period for the development of socioemotional and cognitive skills given the high degree of brain plasticity that facilitates learning and adaptation to the environment. It has been estimated that one in four children will experience child abuse or neglect at some point in their lifetime, although, it has been suggested that these numbers are underestimated especially because certain childhood trauma events, such as those related to emotional abuse and neglect are unreported. The presence of traumatic and stressful experiences occurring in this period of life has a huge impact on brain development and mental health outcomes. Accordingly, a large body of evidence has demonstrated that exposure to childhood maltreatment is associated with the development of mood disorders, since about 50% of patients suffering from depression have reported such experiences.

Childhood trauma is not only shaping the risk to develop depression and other mental disorders, but it has also been shown, both in longitudinal and prospective studies, to have an impact on the overall clinical symptomatology and illness course. Indeed, patients with childhood trauma experiences report an earlier age at onset, more recurrence, greater persistence of depressive symptoms, greater symptom severity and poorer treatment response to pharmacotherapy (Comijs et al., 2013; Nanni et al., 2012; Nelson et al., 2017; Nemeroff, 2016; Quilty et al., 2016; Romero et al., 2009; Withers et al., 2013). Importantly depressed patients with childhood trauma history have also a higher risk for suicide ideation, attempts, and completion (Agnew-Blais & Danese, 2016; Castellví et al., 2017; J. Liu et al., 2017; Nemeroff, 2016; Norman et al., 2012). For example, in the Adverse Childhood Experiences Study conducted in 17,337 adults, adverse childhood experiences led to a two-to-five-fold increase in the risk for suicide attempts (Dube et al., 2001). In another study, among the 9272 adolescents of the U.S. National Comorbidity Survey Adolescent Supplement a history of physical and sexual abuse increased the odds of suicide ideation, planning, and attempts (Gomez et al., 2017).

Importantly, although sexual and physical abuse are the ones having the strongest association both with enhanced risk for mood disorders and suicide attempts (Maniglio, 2011), it must be borne in mind that all types of childhood maltreatment may exert a negative impact. Moreover, experiencing multiple maltreatment subtypes, also including other early-life stressors, such as divorce, domestic violence, household substance abuse, and parental loss, further elevate such risk (Anda et al., 2006; J. G. Green et al., 2010; Putnam et al., 2013), indicating the presence of additive effects of stressful events over time on the onset of mental disorders and on their course.

1.1.2. The findings from animal models

The study of ELA and their impact on psychopathology is a challenging field, often limited by ethical constraints and by the complexities of human experiences. With this respect, animal models are instrumental to gain insights on this critical relationship, as well as to establish possible causal relationships between a given adverse condition within a selected time frame and the possible psychopathologic consequences. Moreover, these models provide valuable insights into the biological and behavioral mechanisms underlying the link between ELA and psychopathology.

Animal models have been developed to mimic and replicate different types of life adversities commonly encountered by humans during early development. By exposing animals to controlled adverse experiences, researchers can investigate the short- and long-term consequences on behavior, neurobiology, and physiology. While there are obvious differences between humans and animals, the commonalities in stress response systems, neural circuits, and behavioral outcomes suggest that animal models can be fundamental for unraveling the neurobiological mechanisms underlying the complex relationship between early life adversities and psychopathology.

Different animal models have been developed and characterized with the aim to cover different time windows of vulnerability as well as different types of adversities that may interfere with brain development leading to enhanced risk for psychopathology (Cattane et al., 2022). However, although different models are available, they can be grouped according to the timing of the exposure that may reproduce specific clinical situations.

1.1.2.1. Gestational adversities. Several models for maternal stress or depression have been developed. In all these paradigms, pregnant animals are exposed to stressors during gestation, a procedure that by affecting

the developing offspring, may lead to behavioral disturbances resembling specific symptoms observed in mental disorders (Weinstock, 2008). The best characterized model of prenatal stress is based upon the exposure to immobilization, a psychophysical stressor that also causes discomfort in animals. The stressor is applied for 45 min under bright light 3 times a day in a random order, during the last week of gestation (Luoni et al., 2014). Variations of this model are reported in the literature, using restraint stress, with or without bright light, either as the sole stressor, or with additional stressors including forced swim, exposure to cold, food deprivation, prevention of sleep, overcrowding, social isolation, cage tilting and noise. The duration and the frequency of stress sessions can also vary, ranging from 30 min to 6 h, one to three times daily (Weinstock, 2017).

The effects of prenatal stress on anxiety-like and depressive-like behaviors have been largely studied. Several works reported that the offspring of animals exposed to stress during gestation show an anxious phenotype in the elevated plus maze as well as in the open field, have increased immobility in the forced swim test and exhibit an anhedonic phenotype when tested in the sucrose preferences as well as social impairment (Creutzberg et al., 2023; Weinstock, 2017). Learning deficits have been similarly reported when the animals were tested in the Morris water maze and novel object recognition tests (Cattaneo et al., 2020; Weinstock, 2008). These results have been observed both in female and male rats during adolescence as well as at adulthood.

Nevertheless, these models do not consider the social component of stress exposure and are confined to a specific phase of the gestational window. In the clinical scenario, depression is mostly elicited by social stress and most importantly, it may be present before, during and/or after pregnancy. With this respect, a novel murine model to study the impact of gestational depression is based on rearing female mice in social isolation prior to mating, a paradigm that leads to a depressive-like state before and during pregnancy (Scarborough et al., 2021). Adult female mice exposed to social isolation for 10 weeks exhibit emotional impairment, as shown by increased anxiety-like behavior, decreased sociability and a depressive-like phenotype (increased immobility time in the forced swim test), with normal cognitive performance. Such behavioral alterations before and during pregnancy lead to a pathologic phenotype in the adult offspring, with increased anxiety-like behavior and disrupted cognitive performances, although the latter effect was limited to males. All in all, this model is extremely important considering that numerous studies have established a clear link between untreated prenatal maternal depression with increased infant morbidity and neurodevelopmental abnormalities, as described in the previous paragraph.

Although experiences of chronic severe stress during gestation account for a large body of evidence, phycological stressors may not be the only environmental risk factors for later mental disorders. Indeed, exposure to maternal infections (i.e. toxoplasma gondii, rubella virus, cytomegalovirus, herpes simplex viruses, Zika virus), chemicals (i.e. tobacco smoke, air pollution) and dietary habits also represent relevant risk factors for the development of psychopathologic conditions (Maitre et al., 2021; Reuben et al., 2022; Vermeulen et al., 2020). A good example is represented by maternal infection since immune activation experienced during early life can exert substantial influences on both physiology and behavior later in life (Meyer, 2019). Moreover, such adverse experiences can prime the immune system, affecting how it may respond to subsequent infections and immune challenges. Maternal immune activation can be induced during different periods of gestation via immunogenic stimuli including poly I:C and lipopolysaccharides (LPS) (Mueller et al., 2018). Successfully recapitulating key behavioral aspects of mental disorders, poly I:C results in a signaling cascade that leads to the transcription of inflammatory cytokines while LPS stimulates the innate immune system leading to subsequent inflammation and increased corticosterone levels.

1.1.2.2. Adversities during early postnatal life. Clinical studies on untreated maternal depression showed that, besides neurodevelopment consequences in the offspring, the mother–infant relationship is also impaired, potentially enhancing the risk for the negative outcomes in the infant. In line with this, preclinical studies have shown that prenatal stress exposure can induce deficits in maternal care during the first 10 days of postnatal life (Creutzberg et al., 2023). Several forms of stressful paradigms during early postnatal life based on the disruption of adequate dam-offspring interaction, namely maternal separation and maternal deprivation, have been developed to investigate how such experience may impact on the offspring's behavior.

The maternal separation (MS) model implicates separating neonatal animals from their mothers for relatively brief periods during the early postnatal period. Separation typically lasts for a few hours each day, often ranging from 3 to 6 h during the first two to three weeks of life. A recent systematic review and meta-analysis on maternal separation showed that it is associated with increased anxiety-like behaviors tested in the elevated plus maze and open field tests (D. Wang et al., 2020). This is in line with clinical data showing that childhood maltreatments largely correlate with anxiety disorders (Teicher & Samson, 2013). In addition, depressive-like phenotypes were consistently found associated with such manipulation (Tractenberg et al., 2016). Moreover, cognitive functions, such as learning and memory and cognitive flexibility, in rodent offspring exposed to maternal separation are also impaired, thus resembling the alterations found in psychiatric patients (Hedges & Woon, 2011; Ou-Yang et al., 2022).

On the other end, the maternal deprivation (MD) model consists in a prolonged single episode (24 h) of maternal withdrawal on PND 9. Contrary to MS, a lack of maternal care for 24 h leads to other indirect stressors including lack of nutrients and hypothermia (Marco et al., 2015). Both emotional and cognitive behaviors are impaired following MD. Depressive-like phenotypes have been observed in animals exposed to MD, together with cognitive impairments and deficits of sensorimotor gating, as measured by prepulse and latent inhibition (Ellenbroek et al., 2004; Guo et al., 2022; Janetsian-Fritz et al., 2018).

Slightly different, the limited bedding and nesting paradigm (LBN) disrupts the pattern and quality of maternal care by limiting the dam's access to sufficient bedding and nesting material early after the birth of the offspring (Walker et al., 2017). The paradigm is usually applied from PND2 to 9. It does not change the amount of maternal care while rather leads to fragmented maternal care, for instance increasing the frequency of exits of the dam from the nest (Walker et al., 2017). Long-term effects on fear and anxiety have been reported in several studies applying the limited bedding and nesting model. Similarly, anhedonic behaviors were observed both during adolescence and adulthood. The exposure to limited bedding and nesting also produces dysfunctional social behaviors and impaired learning and memory performances, as tested in the water maze and novel object recognition tests (Walker et al., 2017).

1.1.2.3. Adversities during adolescence. The adolescent period is characterized by profound changes in social, cognitive, and emotional behaviors accompanied by a significant shaping of brain neural circuitry. Moreover, the first manifestation of mental disorders often occurs at adolescence and may be precipitated by the exposure to adverse life situations. Accordingly, several stress-based animal models during adolescence have been developed with differences related to the timing of stress exposure, ranging from juvenile and early adolescence (from PNDs 27-35 until PND 45) as compared to late adolescence (from PND 42-45 until PND 55-58) (Spear, 2000). Furthermore, stress paradigms can be divided into non-social and social. In non-social stress models, adolescent animals are exposed to various non-social mild stressors including forced swim, elevated platform, foot shock, restraint, loud noise, food and water deprivation and cold exposure (Isgor et al.,

2004; Tsoory & Richter-Levin, 2006). Cognitive deficits and anxiety-like behaviors have been associated with exposure to variable stressors during adolescence, as shown by the reduction of exploratory behaviors in the open-field test and poor avoidance learning tested in the two-way shuttle avoidance task (Tsoory & Richter-Levin, 2006). On the contrary, social stressors include social isolation, social instability, exposure to novel environment, crowding and social defeat (Buwalda et al., 2011; Isgor et al., 2004). Indeed, social behaviors and social experience are crucial for adolescent individuals as they spend more time with peers, shifting their social orientation from adults to peers. These increased interactions provide an important source of experiences that may help to develop and shape social skills and promote independence (Spear, 2000).

For these reasons, social isolation paradigms that deprive adolescent animals of social contacts are well-established and produce long-lasting behavioral alterations related to different psychopathologic domains. For example, we found that male and female rats reared in isolation during adolescence, show an anhedonic phenotypes at adulthood without significant cognitive impairments (Begni et al., 2020). Learning and memory deficits were instead found when the animals were tested immediately after the end of stress exposure (M. R. Green & McCormick, 2013). Moreover, social isolation in adolescence does produce an anxiety behavior immediately after the end of the adverse experience, an effect that persists into adulthood (Lukkes et al., 2009).

The social defeat paradigm, which has been used to model exposure to physical abuse and bullying, has also been applied during adolescence. Under these conditions, defeated animals showed reduced social behaviors associated with increased anxiety and depressive-like behaviors, as inferred from increased social avoidance, increased immobility in the forced swim test, reduced sucrose preference and reduced exploratory behaviors in the open-field test (Iñiguez et al., 2014; Reguilón et al., 2022; Shimizu et al., 2020). A similar phenotype can also be observed using the social instability paradigm that involves periods of isolation and periods of overcrowding, (i.e. daily short social isolation sessions followed by pair housing with an unfamiliar partner) (Graf et al., 2023).

All in all, the functional effects of early in life stress exposure are clear and highlight the perinatal period and adolescence as critical timeframes in an individual's life as stress exposures during these periods have profound and lasting consequences on behavior. The available animal models provide an opportunity to investigate time-specific environmental adversities, such as maternal stress and dysfunctional parenting behaviors for the perinatal period or emotional and social stressor during adolescence. The data emerging from these models suggest that regardless of the type or timing of stress, they can similarly impact a plethora of behavioral domains including depression, anxiety, cognition, and sociability, potentially leading to long-term consequences for mental health. It may also be inferred that such exposure can produce a state of vulnerability, which can enhance the susceptibility toward subsequent events that may precipitate a full-blown pathologic condition. Understanding the unique biological vulnerabilities and molecular consequences associated with each developmental window is crucial for developing targeted interventions.

2. Biological mechanisms contributing to the psychopathological outcomes following exposure to early life adversities

Considering the strong link between exposure to ELA and the risk for psychopathology, it is important to identify and characterize the biological mechanisms and the molecular underpinning of such relationship. This will eventually lead to the development of strategies that, by correcting or modulating such alterations, may reduce the negative consequences of ELA.

With this regard, different systems have been investigated in preclinical models as well as at clinical level, including the glucocorticoid-related signaling, the immune and inflammatory function, neuroplastic and neurotrophic mechanisms, the redox balance as well as more global processes in brain function and activity. In the next sections, we will recapitulate the main findings on these mechanisms, and we will try to provide functional interpretation of such alterations.

2.1. The hypothalamic-pituitary-adrenal axis

Based on the role of the hypothalamus-pituitary-adrenal (HPA) axis in the stress response, alterations of its functional activity represent a key mechanism in mediating the link between stress and mental health. Indeed, changes at this level can be responsible for the inability to cope with stress, which in turn can lead to the vulnerability of a plethora of health-related disorders associated with prolonged exposure to stress.

The first step of the HPA axis system activation is represented by the corticotropin-releasing hormone (CRH)-driven sympathetic response, which is mediated by the CRH1 receptor (CRHR1). CRH induces the synthesis of the adrenocorticotropic hormone (ACTH), which in turn stimulates the synthesis and release of the stress hormones (cortisol in humans and corticosterone in rodents) (de Kloet et al., 2005). Upon release, stress hormones reach peripheral and central targets, allowing a coordinated response of brain and body to activate coping strategies, as well as recovery and adaptation processes.

Exposure to ELA can influence HPA maturation and its responsiveness to stress, which may contribute to the increased vulnerability toward psychiatric illness. For example, at preclinical level, exposure to MS produces a reduction in the baseline plasma levels of corticosterone (Plotsky & Meaney, 1993). On the other hand, some studies have also found that short periods of MS can induce opposite effects, such as reduced anxiety-like behavior and decreased HPA responsiveness to stressors in adulthood (Macrì et al., 2008).

Besides the results from the preclinical studies, also clinical evidence has pinpointed the connection between ELA exposure and HPA axis disruption. Childhood trauma, such as maltreatment, is associated with increased cortisol levels, both measured in blood and saliva (Bernard et al., 2017; Fogelman & Canli, 2018; Zajkowska et al., 2022). Moreover, the effect of ELA on the HPA axis function appears to be modulated by other stress-related factors, such as the age of maltreatment, parental responsiveness, subsequent re-exposure to stress, and type of maltreatment (e.g., physical, sexual, or emotional abuse), and both baseline and stress induced HPA axis activation have been described to be either increased or reduced following childhood maltreatment.) (Fogelman & Canli, 2018).

The altered function and responsiveness of the HPA axis following ELA is due, at least to some extent, to a disruption of the HPA negative feedback. The HPA axis is switched off by cortisol itself, as it negatively regulates CRH and ACTH synthesis and secretion via a mechanism known as “negative feedback”, which is mediated by the glucocorticoid receptors (GRs). In preclinical models of ELA, the HPA axis impairment has been associated to GR and MR expression and functioning (de Kloet et al., 1998). For example, GR mRNA expression is reduced following ELA exposure, in different brain structures including amygdala, hippocampus and the paraventricular nucleus of the hypothalamus (Arnett et al., 2015). Moreover, ELA may exert long-lasting effects on HPA functioning also via epigenetic changes of the GR (McGowan et al., 2009; Weaver et al., 2004). The impaired negative feedback is responsible of the elevation in circulating cortisol levels that may expose the brain, as well as other peripheral organs, to the detrimental effects of glucocorticoids (Herman et al., 2016). Clinical investigations have confirmed a disruption in the negative feedback the HPA axis possibly due to a reduction in bothGR expression and sensitivity. Indeed, antidepressant treatment has been shown to resolve this impairment, as the study of Carvalho and colleagues has shown that the negative feedback disruption is specifically linked to GR dysfunction in depressed patients (Carvalho et al., 2008). Moreover, the capacity of the antidepressant drugs has been shown to reduce GR function in peripheral blood cells in clinically resistant patients with MDD (Carvalho et al., 2010, 2008).

Another player that may contribute to HPA disruption and GR resistance following ELA is FKBP5, a co-chaperon protein that regulates GR and MR affinity for cortisol and modulates its nuclear translocation. Non-human primates spontaneously over expressing the FKBP5 gene show GR resistance (P. D. Reynolds et al., 1999; Scammell et al., 2001), suggesting that increased expression of FKBP5 may be associated with HPA axis hyperactivity. Moreover, FKBP5 polymorphisms can interact with early life stressors, such as childhood trauma, conferring higher risk for depression in adolescence and adulthood (Appel et al., 2011; Kohrt et al., 2015; J. Lahti et al., 2016; Zimmermann et al., 2011). Moreover, the interaction between ELA and FKBP5 in vivo has been studied by using mouse model which overexpresses human FKBP5 throughout the forebrain; this model does not show any anxiety-like or depression-like phenotypes basally but the interaction of high FKBP5 and ELA has been observed to induce neuropsychiatric-like symptoms such as anxiety-like behavior and changes in the molecular pathways involved in cell survival and growth in the hippocampus (Criado-Marrero et al., 2019).

All these data suggest that the exposure to ELA is associated with altered function and responsiveness of the HPA axis, which may contribute to the onset of psychopathology (Herman et al., 2016).

2.2. Immune and inflammatory mechanisms

The role of inflammation and its interplay with stress has an important role in shaping the risk for psychopathology, such as depression, as demonstrated by several meta-analysis showing higher levels of peripheral inflammatory mediators in adult patients with major depressive disorder (MDD) Furthermore, the hyperactivation of the immune system is considered a risk factor for the development of depression as higher serum or plasma levels of pro-inflammatory cytokines, such as IL-6, IL-10, IL-12, IL-13, IL-18, and TNF-α have been observed in individuals with MDD, as compared to controls (Himmerich et al., 2019; Raison et al., 2006).

Clinical studies have provided support for a link between early in life experiences and changes in inflammatory and immune mechanisms. For example, in the pioneering study of Danese and colleagues, maltreated children had higher levels of serum CRP, as compared to those without an history of childhood trauma even after twenty years from the adverse experience (Danese et al., 2009). Such results were confirmed also in subsequent metanalytic analyses (Kuhlman et al., 2020; Slopen et al., 2012), including the study from Baumeister and colleagues who demonstrated consistent increased levels of CRP, IL-6, and TNF-α in individuals with a history of childhood trauma (Baumeister et al., 2016).

In line with the clinical evidence, preclinical studies have demonstrated the long-lasting effects of ELA on inflammation (Creutzberg et al., 2021; Orso et al., 2023). The meta-analysis of Dutcher and colleagues has shown increased levels of IL-1β, IL-6, IL-10, and TNF-α following both repeated or single MS in rodents, although such effects appear to be more pronounced in selected brain regions such as hippocampus and PFC, rather than in the blood or other peripheral tissues (Dutcher et al., 2020). However, repeated MS shows limited long-term effect on cytokines expression without a re-exposure to stress later in life. Indeed, increased expression of IL-1β, IL-6, IL-10 and TNF-α were found in different brain regions of animals exposed to MS and challenged with a subsequent stress in adulthood, suggesting that the perinatal manipulation may sensitize the immune system to over-react under adverse conditions (Dutcher et al., 2020). Transcriptomic analysis have shown a modulation of inflammatory-related pathways, such as the dendritic cell maturation, neuroinflammation and p38 MAPK signaling pathway in the PFC of adult animals subjected to PNS, as compared to controls, and a modulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling was also observed in both PFC and hippocampus (Anacker et al., 2013; Lopizzo, Mazzelli, et al., 2021). Also, postnatal stress exposure appears to affect neuroinflammation. For example, exposure to the LBN paradigm produces long-term impairment in hippocampal microglia by altering the distribution of morphological subtypes of microglia and its transcriptomic profile at adulthood (Reemst et al., 2022). Moreover, the exposure to stress during adolescence has also been shown to induce long-term inflammatory changes. For example, Lopizzo and colleagues have shown increased levels of several pro-inflammatory molecules in the dorsal hippocampus (TGF-β) and ventral hippocampus (IL-1β and IL-6) of female rats following the social isolation stress paradigm during adolescence, as well as increased expression levels of MIF and TGF-β in the dorsal hippocampus and IL-1β and IL-6 in the ventral hippocampus of adult male rats compared to controls. Moreover, in the same socially isolated male rats, increased expression levels of microglia related markers such as IBA1, CX3CL1, CX3CR1, CD40 and CD68 were found in the dorsal and ventral hippocampus (Lopizzo, Marizzoni, et al., 2021).

2.3. Redox mechanisms

Oxidative stress is defined as an imbalance between pro- oxidants and antioxidants, which may result in toxic mechanisms leading to structural and functional alterations of target proteins. Oxidative stress has been also described as a central hub bridging important players involved in the etiology and manifestation of psychiatric disorders, including major depression and schizophrenia (Cuenod et al., 2022; Rossetti et al., 2020). Interestingly, as described in this chapter, several players that interact with redox mechanisms also display significant alterations as a consequence of stress exposure, particularly occurring during early life stages.

Redox dysregulation appears to be an important component for the effects produced by prenatal stress and such changes may start in the womb and can persist after birth until adulthood. Indeed, exposure to stress during gestation alters the activity of antioxidant enzymes and the expression of redox-related genes in the embryonic forebrain. Interestingly, it has been demonstrated that increased oxidative markers are associated with delayed interneuron migration after prenatal stress exposure, which may lead to behavioral impairment after birth. Interestingly maternal supplementation of antioxidants was able to ameliorate such alterations (Bittle et al., 2019).

A role of placental oxidative stress in conveying the effects of maternal stress to the fetus has also been demonstrated, which may ultimately contribute to adverse outcomes in the offspring. Indeed, maternal stress increases reactive oxygen species at placental level and the blockade of oxidative stress using the antioxidant mitoquinone, which targets mitochondrial activity, was able to prevent the prenatal stress-induced anxiety phenotype as well as the neurobiological changes in male offspring (Scott et al., 2020).

Interestingly, we have recently demonstrated that the depressive-like phenotype observed in adolescent rats born from prenatally stressed dams is associated with a dysregulation of oxidative stress, with a significant elevation of inducible nitric oxide synthase (iNOS), NADPH oxidase 1 (NOX1) and NOX2 levels in the hippocampus (Fidilio et al., 2022).

The role of oxidative mechanisms in the prenatal environment is also suggested by a study in humans that has revealed that elevated exposure to prenatal negative life events in combination with lower antioxidant (vitamins A, C, and E, magnesium, zinc, selenium, β-carotene) intakes in pregnancy increases the likelihood of heightened child temperamental negative affectivity. On the other end, increased antioxidant intakes during pregnancy may protect against the effects of prenatal stress on the child temperament (Lipton et al., 2017).

Exposure to stressful experience in the early postnatal life is also associated with aberrant expression and function of redox mechanisms. For example, rats that were deprived of maternal care in the first 10 days of life, a manipulation that is associated with depressive-like behavior, show an increase of lipid peroxidation and protein carbonylation in males and females at adulthood, as well as decreased SOD and CAT

activities. Interestingly, some of these changes were ameliorated by ketamine treatment at adulthood, suggesting the potential for pharmacological intervention in counteracting the 'redox' component (Abelaira et al., 2021).

At clinical level, it has been shown that childhood maltreatment is associated with increased oxidative stress markers in adolescents suggesting that, independently from the pathological condition, the adverse experience can alter redox mechanisms, which may represent a predisposing state toward secondary challenges that may precipitate a pathologic condition (do Prado et al., 2016).

Recent studies have corroborated these results showing that markers of systemic DNA and RNA damage caused by oxidation (8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) and 8-oxo-7,8-dihydroguanosine (8-oxoGuo) were found higher in individuals who had experienced childhood maltreatment (Eriksen et al., 2022).

One key question is to understand how an unbalance of the redox state may contribute to the clinical phenotype. With this respect, a study from Alameda and coworkers has characterized a group of patients with early psychosis (EPP), to establish the relationships between childhood trauma, blood antioxidant defenses with psychopathologic and brain dysfunction. The authors showed that traumatized patients with high peripheral oxidative status, as measured by the glutathione peroxidase activity, had smaller hippocampal volumes and more severe symptoms, while those with lower oxidative status showed better cognitive performances, suggesting that the ability to regulate antioxidant systems may allow for compensatory mechanisms preventing long-term neuroanatomical and clinical impacts (Alameda et al., 2018).

It is important to bear in mind that oxidative stress has also been described in rodents exposed to chronic stress in adulthood, suggesting that it may represent a consequence of stress response independently from the time of occurrence (Rossetti et al., 2018). However, an unbalance of redox mechanisms during critical developmental windows can produce more detrimental effects, which may lead to persistent changes in brain function. One prototypical example of this concept is represented by parvalbumin (PV) positive GABAergic inhibitory neurons that can generate action potentials at very high frequency and, for this reason, may be particularly susceptible to oxidative stress and mitochondrial damage. While a dysfunction of PV neurons has been well established in schizophrenia, and possibly in other mental disorders, cumulating evidence indicates that redox dysregulation appears as a common pathological mechanism leading to PV neuron-associated network anomalies in schizophrenia. The implication of redox dysregulation in the abnormal development of PV neurons has been further corroborated in neurodevelopmental animal models of schizophrenia that do not involve direct manipulation of the redox system (Cuenod et al., 2022). Interestingly, a redox dysregulation, due to impaired synthesis of glutathione, renders parvalbumin interneurons vulnerable to an additional oxidative challenge in preweaning or pubertal but not in young adult animals, suggesting that early-life environmental challenges may lead to protracted impairment of parvalbumin interneurons due to redox unbalance. The enhanced sensitivity of PV neurons during early life stages may be due to the immaturity of perineuronal nets that enwrap and protect these neurons form 'damaging' with mature are better protected than immature PV cells surrounded by less condensed perineuronal nets (Cabungcal et al., 2013).

2.4. Neuronal and synaptic plasticity

Neuronal and synaptic plasticity are important features of the nervous system, and they are always considered one of the mechanisms through which life experiences can be embedded in the brain. Hence, changes in neuronal and synaptic plasticity can play a significant role for the protracted effects of the exposure to stressful experiences during the perinatal period, which may eventually contribute to the increased risk for mental illnesses, including depression, schizophrenia, addiction, and posttraumatic stress disorder. (Hübener & Bonhoeffer, 2014; Rice & Barone, 2000).

One of the most important forms of synaptic plasticity is represented by long-term potentiation (LTP), which involves changes in synaptic strength. With this regard, the hippocampus is the brain region where such mechanism has been extensively characterized. Starting from the pioneer work by Levine and colleagues (Foy et al., 1987), different studies have demonstrated that exposure to ELA leads to a reduction of hippocampal LTP (Lesuis et al., 2019; X. D. Wang et al., 2011). Wang and colleagues showed that ELA effects on LTP are dependent on persistent forebrain corticotropin-releasing factor (CRF) receptor 1 (CRF1) signaling (X. D. Wang et al., 2011). Interestingly, it has been shown that a reduction of maternal care, often observed in relation to ELA, correlates with impaired LTP (Champagne et al., 2008). Likewise, MS may lead to an attenuation of LTP within the prefrontal cortex (Chocyk et al., 2013).

Adult neurogenesis, a critical form of plasticity, is similarly reduced by ELA exposure within the hippocampus. These studies also reported that adult neurogenesis is needed for hippocampus-dependent function, indicating that ELA has lasting consequences not only on hippocampal structure but also on its function (Naninck et al., 2015). Likewise, exposure to prenatal stress impairs adult neurogenesis, leading to a decrease in cell proliferation both in the hippocampus and in the prefrontal cortex (Lemaire et al., 2000; Z. Zhang et al., 2021). These deficits were paralleled by altered gene expression profiles in embryonic cortices characterized by a down-regulation of synaptic transmission, synaptic plasticity, and cell adhesion related genes (Z. Zhang et al., 2021).

A key player and prototype marker of neuronal plasticity is the neurotrophin brain-derived neurotrophic factor (BDNF) (Begni et al., 2017; Huang & Reichardt, 2001; H. Park & Poo, 2013). Decreased BDNF levels have been reported in animals exposed to gestational stress or maternal separation (Luoni et al., 2014; Marco et al., 2013; Roceri et al., 2002). For example, we have shown that the expression of BDNF is significantly reduced in the hippocampus and in the prefrontal cortex of animals that were exposed to prenatal stress, an effect that becomes fully manifested during the transition between adolescence and adulthood. The delay between the actual stressful experience and the observed neuroplastic changes suggests that such modifications may represent a developmental consequence possibly involving complex changes occurring across adolescence. Interestingly, we also showed that these deficits can be prevented by a pharmacological intervention during adolescence (Luoni et al., 2014). Moreover, we found that the modulation of BDNF expression following an acute stressful challenge is selectively altered in the prefrontal cortex of female animals prenatally exposed to stress, suggesting an impairment of coping mechanisms with brain region and sex selectivity (Luoni et al., 2016). Remarkable alterations of BDNF levels have also been reported in peripheral samples of individuals affected by mood and psychotic disorders in association with early traumatic experiences (Di Benedetto et al., 2022). Furthermore, some studies showed a link between lower BDNF levels and cognitive impairment. Instead, the data on the peripheral levels of BDNF in control subjects exposed to ELA are controversial, showing both lower and higher levels of the neurotrophin (Di Benedetto et al., 2022). Specifically, Do Prado and colleagues found that adolescents aged between 13 and 17 years with a history of ELA had significantly lower BDNF levels, as compared to healthy controls without a history of ELA (do Prado et al., 2017). Conversely, when examining the levels of BDNF in younger children aged between 3 and 12 years with or without trauma, Bücker and coworkers showed increased BDNF levels (Bücker et al., 2015). It is possible that ELA may initially promote BDNF expression as a compensatory mechanism, although the transition through adolescence may lead to a reduction of its expression that will eventually contribute to the behavioral and pathologic phenotype, a hypothesis that is in line with our preclinical data on BDNF expression following prenatal stress exposure (Luoni et al., 2014).

In parallel, changes in the levels of other markers of synaptic plasticity including PSD-95, synaptophysin and the neural cell adhesion molecule NCAM have been observed both in the hippocampus and in the prefrontal cortex of adolescent male and female animals exposed to maternal separation (Cui et al., 2020; Marco et al., 2013). In addition, an altered excitatory/inhibitory synaptic balance, characterized by changes of glutamatergic and/or GABAergic markers, were found in the hippocampus (Akillioglu et al., 2015; Ku et al., 2008; Lesuis et al., 2019), in the PFC (Ganguly et al., 2015; Marchisella et al., 2021; Roshan-Milani et al., 2021) as well as in the amygdala (Guadagno et al., 2020) of animals exposed to ELA. This is particularly important since it may provide an important target for future strategies aimed at preventing the long-lasting ELA effects on synaptic plasticity. A study by Lesuis and colleagues indeed reported that pharmacological blockade of GluN2B was less effective to reduce synaptic plasticity in animals exposed to ELA, as compared to controls, suggesting a reduced contribution of the NMDAR subunit to synaptic plasticity (Lesuis et al., 2019). In addition, aberrant glutamatergic functioning has been implicated in ELA-induced mood disorders, potentially leading to impairment of synaptic connections and eventually to reduced neuroplasticity (Averill et al., 2020; Tamman et al., 2023).

It is important to note that the detrimental effects of ELA on synaptic plasticity were observed independently from the specific time window of exposure. Eventually, the disruption of synaptic plasticity by early adversities may contribute to alterations occurring at behavioral level. Indeed, as mentioned earlier, dysfunctions of neuronal plasticity were associated with a concomitant impairment in cognition, learning and memory tasks following exposure to early life stress (D. Liu et al., 2000; Naninck et al., 2015).

2.5. Brain morphology and neuronal circuits

Besides a decrease in brain plasticity, significant structural alterations have been reported as a result of ELA. Human studies have shown that exposure to childhood maltreatment, including both physical or sexual abuse and emotional neglect, is associated with smaller hippocampal volumes later in life (Frodl & O'Keane, 2013). Similarly, animals exposed to LBN show reduced hippocampal volume at adulthood (Y. Chen & Baram, 2016; Naninck et al., 2015). A selective volumetric loss of the dorsal hippocampus following ELA exposure was similarly observed already during late adolescence (Molet et al., 2016). Additional results showed that MD causes similar changes in the prefrontal and orbitofrontal cortex (Sarabdjitsingh et al., 2017). Furthermore, decreased white matter volume was found in prefrontal cortex and dorsomedial striatum as a consequence of MD (Sarabdjitsingh et al., 2017). Regional gray matter changes have also been identified by MRI studies in the frontal lobe, parietal lobe, thalamus, caudate, pallidum, putamen, and temporal lobes in patients with depression (Peng et al., 2016; van Eijndhoven et al., 2013). Alterations in the cortical and subcortical structures have been widely observed together with a loss of cerebral parenchyma and increased ventricular space in the prefrontal cortex, hippocampus, amygdala, and cerebellum in subjects who have experienced early-in-life adversities (González-Acosta et al., 2021).

A reduced dendritic arborization could contribute to the observed volume loss. Several preclinical studies showed that exposure to ELA -either maternal separation or LBN- is associated with dendritic atrophy both in the PFC and in the hippocampus, as assessed during adolescence as well as in adulthood (Chocyk et al., 2013; Cui et al., 2020; Molet et al., 2016). Furthermore, LBN has been shown to alter neurogenesis in the mouse dentate gyrus (Naninck et al., 2015) and can also lead to an earlier temporal decline in the expression of markers of hippocampal neurogenesis over the postnatal period (Bath et al., 2016).

Changes in brain morphology may contribute to the disruption of selected brain circuits. It has been demonstrated that exposure to fragmented maternal care from PND 8 to PND 12 leads to an impairment of amygdala-PFC connectivity, which increases as a developmental process from adolescence to adulthood (Yan et al., 2017). Hence, failure in the maturation of this circuit may be particularly relevant considering its functional role in emotion regulation (Marek et al., 2013). In line with these studies, depressed patients with a history of childhood maltreatment show significant reductions in the connectivity of prefrontal-limbic regions (L. Wang et al., 2014). On the contrary, experiencing ELA from PND2 to PND9 leads to aberrant structural connectivity of stress and reward circuits of the amygdala to the PFC of late-adolescent animals (Bolton et al., 2018). Similarly, a combination of maternal deprivation and fragmented maternal care was found to increase amygdala–prefrontal cortex and amygdala–hippocampus connectivity correlating with anxiety-like behavior at adulthood (Johnson et al., 2018).

In addition, Bolton and colleagues suggested a specific role for CRF-producing neurons of the amygdala in the emotional consequences of ELA (Bolton et al., 2018). Indeed, clinical and preclinical data suggest that stress exposure may alter the circuits controlling the activity of the HPA axis (see paragraph 1.1), modulating the release of corticotrophin releasing hormone (CRH) and glucocorticoids. As an example, ELA can increase glutamatergic activity onto the neurons of the paraventricular nucleus (PVN) of the hypothalamus associated with a modest decrease in GABAAR-mediated inhibition, leading to a dramatic upregulation of excitatory transmission within stress-activated neuronal circuits (Gunn et al., 2013). In turn, augmented CRH signaling after ELA results in altered hippocampal plasticity as shown by dendritic atrophy and LTP attenuation in hippocampal CA1 subregion (Ivy et al., 2010). On the contrary, augmented maternal care early in life induced by brief 15-min daily separation of pups from the dam during the first week of life, immediately and transiently reduces functional glutamatergic innervation of CRH neurons in the hypothalamus (Korosi et al., 2010; Singh-Taylor et al., 2018).

Furthermore, chemogenetic and optogenetic stimulation of a CRH/GABA projection connecting basolateral amygdala and nucleus accumbens has been found linked to disrupted reward behaviors while inhibiting the projection in adult animals exposed to ELA could restore typical reward behaviors (Birnie et al., 2023).

As said, the PFC has connections to different subcortical limbic regions, including the amygdala, thalamus, and basal forebrain. Several studies support the idea that ELA exposure may affect cortical excitation and inhibition (E/I) balance, critical for appropriate responsiveness to stress, leading to alterations of PFC circuitry. Different studies have demonstrated that exposure to ELA produces significant changes of inhibitory interneurons within the PFC with a prominent role in the disruption of the functionality and responsiveness of this brain region (McKlveen et al., 2019). Additionally, reduced PFC-dorsal striatum connectivity was observed in stressed animals both at adolescence and adulthood, leading to impaired reward processing (Yan et al., 2017).

The dysfunction of selected circuits may contribute to specific pathologic domain. For example, exposure to maternal separation produces a depressive phenotype that persists into adulthood is associated with reduced connectivity between inhibitory somatostatin-positive basal forebrain neurons and the lateral habenula, which may prompt a sensitized state more responsive to subsequent challenges (Webster et al., 2023).

Moreover, exposure to ELA produces morphological changes in dendritic spine head diameter within lateral ventral tegmental area (VTA) DAergic neurons, despite no changes in the dendritic morphology or spine density (Spyrka et al., 2020). The VTA forms a functional loop with the hippocampus that is involved in learning and memory (Lisman & Grace, 2005). In addition, different studies have shown that ELA alters the VTA to nucleus accumbens (NAc) dopaminergic circuit, leading to alterations of motivation and reward-related behaviors (Arborelius & Eklund, 2007; Bonapersona et al., 2018; Gracia-Rubio et al., 2016; Hanson et al., 2021).

3. Epigenetic mechanisms and early life adversities

3.1. Gene x environment interaction

While exposure to ELA has been associated with the enhanced risk to develop psychiatric disorders, different players can mediate such association. With this respect, the genetic background represents a major element that may contribute to the psychopathologic outcomes of ELA exposure (Heim & Binder, 2012).

The first studies investigating the interaction between genes and environment (GxE) in the etiology of mental diseases focused on the serotonergic system, which is one the major target for pharmacological intervention in major depression and anxiety-like disorders. In the milestone study by Caspi et al., it has been shown that the short allele of 5-HTTLPR, a functional polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) that reduces SLC6A4 expression and serotonin reuptake, is associated with increased sensitivity to stress exposure (Caspi et al., 2003; Nugent et al., 2011). This interaction has been extensively investigated, with an association of the short allele of 5-HTTLPR and childhood trauma with decreased cognitive performance (Aas et al., 2012). Moreover, it has been documented that healthy subjects carrying the short allele of the 5-HTTLPR show reduced peripheral BDNF gene expression, potentially conferring vulnerability to mood disorders (Molteni et al., 2010). In line with the clinical evidence, we showed alterations of BDNF as well as of HPA axis-related genes in the hippocampus and prefrontal cortex of serotonin transporter knockout (SERT−/−) rats in association with ELA exposure (Calabrese et al., 2015; van der Doelen et al., 2014). SERT−/− rats indeed exhibited an impairment in neuroplasticity that starts early in development, as inferred by decreased expression of BDNF at birth. This reduction is sustained by epigenetic changes at the promoter regions of BDNF exons IV and VI, supporting the possibility that impaired plasticity because of abnormal SERT function may have a persistent a role in mood disorders susceptibility and could interact and synergize with life adversities (Calabrese et al., 2013).

As discussed above, the HPA axis plays an important role in ELA response. With this respect, another set of studies demonstrated that polymorphisms in the corticotrophin receptor 1 (CRHR1) gene interact with childhood trauma and predict depressive-like phenotypes (Polanczyk et al., 2009). Polymorphisms in FKBP5, a chaperone protein involved in the functional activity of GR, have been associated with stress response and the risk of psychiatric disorders (Binder, 2009). These genetic variations are associated with an alteration GR-dependent transcription of FKBP5. Accordingly, individuals carrying these alleles display an extended cortisol response to psychological stressors, suggesting a state of GR resistance. Furthermore, sex-dependent differences in the interaction between FKBP5 polymorphisms and ELA have been reported, showing reduced social preference as well as impaired rhythmicity HPA and higher reactivity of the HPA axis in female mice carrying the genetic variation (Nold et al., 2022).

Considering that changes in neuronal plasticity may mediate short- and long-term effects of ELA on brain function, some studies focused on the functional BDNF Val66Met polymorphism. On these bases, the presence of the Met allele, which is associated with reduced neurotrophin secretion, may increase the risk of depressive symptoms following childhood abuse (Aguilera et al., 2009; Gatt et al., 2009). Moreover, genetic variations in the oxytocin receptor (OXTR) gene have been implicated in the interaction with other environmental risk factors such as ELA (Myers et al., 2014).

In addition, interactions between multiple genes and the environment have also been reported. For instance, interactions between 5-HTTLPR, BDNF, COMT and CRHR1 genes and adverse events have been reported, which may predict mental health disorders (Aguilera et al., 2009; Conway et al., 2010; Ressler et al., 2009). However, more recent combined analyses focusing on the interaction between ELA and 5-HTTLPR genotype (Culverhouse et al., 2018) as well as candidate gene polymorphisms (Border et al., 2019) do not support such hypotheses, while they suggest that these interactions should not be broadly generalizable and must be of modest effect size only observable in limited situations.

A recent genome-wide association study (GWAS) meta-analysis found 14 genetic variants associated with childhood trauma and mental health problems. These variants were significantly enriched for regulatory chromatin marks in brain tissues and for genes that are highly expressed in excitatory neurons (Warrier et al., 2021). Childhood maltreatment has been associated with two genome-wide specific variants of FOXP genes, that have been implicated in development and cognition (Dalvie et al., 2020).

3.2. Epigenetic mechanisms as mediator of adversities early in life on psychopathology

Rather than altering DNA sequence, epigenetic changes, including miRNA, histone modifications and DNA methylation, alter chromatin architecture and regulate gene transcription. During development, epigenetic mechanisms undergo dynamic and tightly regulated changes; global genome demethylation followed by de novo methylation and chromatin remodeling mechanisms create a dynamic epigenetic environment. The accentuation of these mechanisms during development is of fundamental importance, enabling a timely and accurate regulation of gene expression, and may contribute to the lasting outcomes on environmental events that shape the susceptibility to diseases. Indeed, several studies have demonstrated that epigenetic processes may explain how exposure to stress during critical developmental periods may result in severe long-term behavioral and molecular changes. A seminal work by Weaver and colleagues found that ELA in the form of reduced maternal care produced an increased methylation of the glucocorticoid receptor gene (NR3C1) in the offspring, which was associated with reduced hippocampal mRNA and protein expression (Weaver et al., 2004). Interestingly, such effects emerged over the first week of life and persisted into adulthood. In parallel, they found that reduced maternal care resulted in reduced histone H3-K9 acetylation in the hippocampus of adult offspring. To confirm the role of epigenetic changes in ELA, treatment with HDAC inhibitor at adulthood normalized both methylation and acetylation differences due to maternal care (Weaver et al., 2006). In line with these findings, McGowan and colleagues found that the NR3C1 promoter was hypermethylated in the hippocampus of adult individuals with a history of childhood abuse (McGowan et al., 2009). Likewise, increased methylation of the NR3C1 promoter was observed in blood cells from adult patients with major depressive disorders who experienced ELA (Perroud et al., 2011). In addition, the severity and number of stressful experiences positively correlated with the level of NR3C1 DNA methylation (Perroud et al., 2011). Furthermore, clinical studies showed that prenatal maternal psychological distress increases peripheral NR3C1 DNA methylation in male infants at 2 months of age (Braithwaite et al., 2015), confirming that epigenetic modifications may appear soon after stress exposure and endure until adulthood, permanently impacting the HPA axis function and responsiveness.

In addition, preclinical research showed that high maternal care results in enhanced resilient phenotypes associated with reduced DNA methylation at the NR3C1 gene and increased histone H3-K9 acetylation in the hippocampus of adult offspring (Fish et al., 2006). Similarly, in humans, high quality parental care correlated with decreased methylation of N3CR1 (Provenzi et al., 2020).

Along the same line of reasoning, allele-specific DNA demethylation of FKBP5 was detected in adult individuals experiencing sexual and physical child abuse, which may contribute to the long-term dysregulation of stress response as a consequence of exposure to early in life adversities (Klengel et al., 2013; Tozzi et al., 2018). Specifically, FKBP5 risk allele carrier status and early trauma exposure has been shown to lead to demethylation of intron 7 CpGs in FKBP5, ultimately altering the

peripheral regulation of several GR-responsive genes mostly involved in the T cell receptor signaling, TGF-β signaling pathway, Wnt signaling pathway and pluripotency and inflammatory response pathway (Klengel et al., 2013).

ELA, in the form of maternal separation, has been associated with decreased methylation of the CRH promoter in the hypothalamic paraventricular nucleus of adult rats, along with higher plasma corticosterone (J. Chen et al., 2012). On the contrary, augmented maternal care produces increased histone-3 lysine 27 tri-methylation (H3K27me3) at the Crh gene in the hypothalamus of neonatal and adult rats, with a repressive activity that may produce enduring effects on emotional resilience (Singh-Taylor et al., 2018).

All in all, epigenetic modifications at HPA-related genes provide important insights into how early life stressors can lead to enduing changes in stress function and responsiveness that will eventually impact on health outcomes.

Epigenetic alterations of 5-HT-related genes are also well-documented because of ELA exposure. In a clinical cohort of 12-year-old twins experiencing bullying induced increased SLC6A4 DNA methylation. Interestingly, epigenetic modification correlated with blunted cortisol responses when facing a challenging condition, suggesting that epigenetic alterations of 5-HT-related genes may also affect HPA axis reactivity (Ouellet-Morin et al., 2013). In a preclinical model of maternal deprivation, epigenetic changes of the monoamine oxidase A (Maoa) gene have been reported in the nucleus accumbens at adulthood (Bendre et al., 2019). Moreover, DNA methylation changes in the 5-HT3AR gene have been implicated in the enhanced severity of several psychiatric disorders in adult individuals who experienced childhood maltreatment (Perroud et al., 2016).

As mentioned above, immune-inflammatory mechanisms have also been associated with ELA exposure and the risk to develop mental illnesses. Childhood trauma exposure reduces the methylation of the IL6 gene promoter, along with increased IL6 expression and a blunted cortisol response at early adulthood (Janusek et al., 2017).

Interestingly, the effects of ELA on BDNF expression and function can also occur through epigenetic changes. Increased DNA methylation of BDNF exon IV in the hippocampus of prenatally stressed animals was found associated with higher Dnmt3a gene expression (Boersma et al., 2014; S. W. Park et al., 2018). Similarly, ELA exposure during the first week of life is associated with brain-region specific and sexually dimorphic epigenetic consequences on global and gene-specific DNA methylation. Specifically, stressed adolescent female rats showed increased DNA methylation at BDNF exon IV in the amygdala and hippocampus, while males had up-regulated global levels of DNA methylation in the hippocampus with no specific alterations of the BDNF gene (Doherty et al., 2016). In similar fashion, Roth and colleagues demonstrated that LBN exposure led to deficits in BDNF gene expression within the adult PFC that was associated with a lasting increase in BDNF exon IV DNA methylation, highlighting the perpetuation of changes in BDNF DNA methylation throughout the lifespan. Interestingly, the epigenetic changes in the adult animals exposed to ELA could be rescued by chronic treatment with a DNA methylation inhibitor (T. L. Roth et al., 2009). In a clinical setting, prenatal maternal psychological distress decreased BDNF IV DNA methylation in both male and female infants (Braithwaite et al., 2015). Similarly, decreased acetylation of H3 and H4 on BDNF promoter IV was observed in the hippocampus following maternal separation, associated with a decrease in exon IV BDNF mRNA at adulthood (Seo et al., 2016).

More recently, ELA has been associated with demethylation of lysine 79 of histone H3 (H3K79me2) in D2-type medium spiny neurons of the nucleus accumbens of adult male mice. Combined with this, increased transcriptional regulation of the writer (Dot1l) and eraser (Kdm2b) of H3K79 methylation in NAc has been detected, mirroring the histone modifications (Kronman et al., 2021). Decreased H3K9 mono- and trimethylation in the frontal cortex of adult female rats has been similarly observed as consequence of exposure to early life maternal separation (Kao et al., 2012).

As mentioned above, ELA influences VTA structure and functions. In line, exposure to maternal deprivation is associated with reduced acetylation at H3K9 and increased expression of HDAC2 in VTA DA neurons from 14- to 21-day-old rats (Authement et al., 2015; Shepard et al., 2020).

Another well investigated epigenetic mechanism involved in the long-lasting effects of ELA is represented by microRNAs (miRNAs) which are short non-coding RNAs that regulate protein synthesis through translational repression or mRNA degradation. With this respect, different studies have identified significant miRNAs changes in response to ELA, thus affecting different systems that may be relevant for the long-term changes and their psychopathologic implications.

Preclinical studies associated ELA with increased levels of miR-16 and miR124a in the hippocampus and miR-504 in the nucleus accumbens, and decreased miR-9 in the striatum (Bahi, 2016; Bai et al., 2012; Y. Zhang et al., 2015, 2013). Increased miR-16 and miR124a correlated negatively with BDNF expression in the hippocampus at adulthood (Bahi, 2016; Bai et al., 2012) and were found similarly upregulated in the blood of individuals exposed to childhood trauma (Cattane et al., 2019; Prados et al., 2015). MiR-504 expression correlated negatively with dopamine receptor D1 (DRD1) gene expression in the nucleus accumbens (Y. Zhang et al., 2013), while miR-9 directly targets dopamine receptor D2 mRNA inhibiting its expression (Y. Zhang et al., 2015). We have recently demonstrated that miR-30a levels are upregulated in the blood of adult male and female individuals exposed to childhood trauma with a diagnosis of depressive disorder. In addition, miR-30a levels were elevated in the prefrontal cortex of male rats subjected to prenatal stress. The up-regulation of miR-30a became evident at the transition between adolescence at adulthood and it was also associated with a significant reduction in the expression of some of its target genes that play an important role in neuronal plasticity and exon guidance. Furthermore, miR-30a itself undergoes epigenetic changes, showing hypomethylated DNA following PNS exposure (Cattaneo et al., 2020). On the contrary, a long-term decrease of miR-19 levels was observed in the hippocampus of adult rats previously exposed to prenatal stress, an effect that correlated with an increased expression of its target genes NRCAM, IL4R and RAPGEF2 that are involved in neural development, inflammatory and immune response pathways and cell migration, respectively (Mazzelli et al., 2020). Using a combined approach of miRNAs datasets across different tissues and species, miR-125-1-3p has been found commonly down-regulated (Cattane et al., 2019). Predicted and validated target genes of miR-125-1-3p are involved in inflammatory and immune response as well as in neurodevelopment pathways. Similarly, miR132 and miR29a, which are involved in morphogenesis and apoptotic pathways respectively, have been implicated in ELA effects within the prefrontal cortex (Uchida et al., 2010). Specifically, young rats exposed to maternal separation showed higher expression levels of REST4, a neuron-specific splicing variant of the transcriptional repressor element-1 silencing transcription factor (REST), associated with an upregulation of brain-enriched miRNAs, such as miR132 and miR29a, containing REST-binding sequences. Importantly, transient overexpression of REST4 led to depressive-like behaviors under a stressful situation at adulthood, suggesting the involvement of REST4-mediated gene transcription in stress vulnerability. Moreover, the exposure to the LBN paradigm has been linked to a reduced expression of few miRNAs, such as miR-200c-3p and miR-182-5p, which are associated with hippocampal Protein Kinase A Signaling, Ephrin Receptor signaling and AMP-activated protein kinase signaling (Reemst et al., 2024).

All in all, studies in both animals and humans have provided compelling evidence of the link between ELA and epigenetic modifications such as DNA methylation and histone acetylation. These modifications can translate environmental experiences into changes in gene expression that may persist throughout an individual's lifetime, ultimately

increasing the vulnerability to mental disorders. Identifying epigenetic signatures associated with ELA opens the door to targeted interventions and preventive measures aimed at mitigating the long-term effects of early life stress.

4. Sex differences in the response to early life adversities

In this section we will discuss differences pertaining to an individual's sex chromosomes, sex hormone levels, and reproductive phenotype, which is referred as biological sex. There will be no referring to any discussion of gender, which is determined by self-identification, rather than any measurable biological factor.

4.1. Temporal windows and vulnerability traits in males and females

The incidence of several pathological conditions, including mental and stress-related disorders, is strongly dependent on the biological sex. As an example, the incidence of depression is double in females as compared to males, suggesting that sex represents an important driver for the onset of these disorders and may therefore contribute to the link between etiological factors and clinical outcomes. In line with this possibility, clinical and preclinical studies have shown that significant differences between males and females exist in the response to ELA (Hodes & Epperson, 2019; Novais et al., 2017; Weinstock, 2011). For example, cognitive deficits have been observed only in male offspring following exposure to stress during gestation, whereas prenatally stressed females appear to be more susceptible to emotional dysfunction, with increased anxiety and depressive-like behaviors (Nishio et al., 2001; Weinstock, 2007). Moreover, exposure to early life stress in rodents has been shown to reduce functional connectivity within cortical areas in female offspring (Bolton et al., 2018; Molet et al., 2016). On the other hand, cognitive deficits have been observed in males, but not in females, specifically in association with changes in hippocampal excitability (Brunson et al., 2005). These sex differences might be explained considering that female fetuses are more vulnerable both to high levels of glucocorticoid exposure and prenatal stress than male fetuses (Richardson et al., 2006) and this has been linked to differences in the biology of placental function between male and female fetuses. To this point, studies in mice have shown that more corticosterone crosses from the maternal bloodstream to the placenta in females, as compared to males (Montano et al., 1993).

The timing of stress exposure has been proposed to play a key role in the different response to ELA in males and females. For example, it has been shown that exposure to stress from P2 to 12 did not significantly alter depression-like behaviors in both male and female mice, and this may be due to immature stress-response circuitry or timing of the molecular cascades that mediate adaptations to stressful stimuli; on the other hand, shifting the timing of stress to the period from P10 to P17 did not alter depression-like behaviors at baseline, but instead increased the risk that a second stress in adulthood would result in depression-like behaviors (Peña et al., 2017, 2019). These findings are in contrast with other ELA paradigms in rodents that report baseline depression-like behaviors from very early postnatal stressors in female mice (Goodwill et al., 2019).

The long-term effects of maternal separation can also differ across sexes. For example, an enhanced fear memory during adulthood was observed in male, but not in female, rats exposed to stress during early postnatal life, an effect that was associated with an increased activation of the amygdala (Diamantopoulou et al., 2013). On the other hand, a reduction of hippocampal neurogenesis was observed in female rats, whereas opposite results were observed in males, suggesting that the same early stressful experience can lead to divergent outcomes in a sex-dependent manner (Oomen et al., 2009), which may be related to the differential regulation by gonadal hormones of proliferation and survival of hippocampal cells (Galea, 2008).

Lastly, it is not surprising that the susceptibility to stress in adolescence is strongly affected by sex, considering that such adversities may overlap in time with puberty and with the maturation of gonadal hormones (Marceau et al., 2015; Morrison et al., 2014). At preclinical level, it has been observed that female and male adolescent rats exposed to stress show a different profile of adaptation, and such differences persist also at adulthood. Indeed, while stress in adolescence produces an anhedonic phenotype only in females, deficits in avoidance learning exposed were specifically observed in male animals (Horovitz et al., 2014).

Clinical studies have also attempted to identify sex differences in the response to ELA. For example, the study of Quarani and colleagues showed that maternal antenatal depression was associated with an increased risk of depression in 18-year-old girls as compared to same-age boys, whereas maternal postnatal depression was associated with an increased risk of depression in 18-year-old boys, as compared to girls (Quarini et al., 2016). Furthermore, exposure to proinflammatory cytokines in utero was associated with sex-dependent differences in brain activity and connectivity in response to negative stressful stimuli 45 years later- Indeed, lower maternal TNF-α levels were associated with higher hypothalamic activity in both men and women as well as with an increased functional connectivity between the hypothalamus and the anterior cingulate only in men. On the other hand, increased maternal levels of IL-6 were associated with higher hippocampal activity in women alone. Overall, these results suggested that altered levels of proinflammatory cytokines in utero may produce long-lasting changes in brain development of the offspring in a sexually dimorphic manner (Goldstein et al., 2021).

Overall, preclinical and clinical data suggest that the exposure to early in life adversities show a stronger impact on cognitive ability in males, which may contribute to symptoms associated with autism spectrum disorder, attention deficit disorder and the relationship between depression and autism disorder later in life. On the other hand, while females may be more resilient to the effects of early life stress on cognition, such adverse experiences can primarily affect the emotional domains (Hodes & Epperson, 2019).

4.2. Biological substrates underlying sex differences to stress response

Several evidence suggests that the behavioral responses to stress in males and females are complex, depending on the time window of stress exposure, the intensity of the exposure, and individual responses. However, the biological mechanism and substrates underlying the sexually dimorphic responses to stress remains largely unknown.

While considering the complexities and heterogeneity of the changes produced by ELA exposure, it becomes important to establish anatomical and molecular mechanisms that may contribute to functional changes in a sex-dependent manner. For instance, among the brain regions known to be involved in stress response, the prefrontal cortex (PFC) is particularly sensitive to stress exposure both in humans and in rodents (Perry et al., 2021). Sexual dimorphism in the PFC has been observed in human and rodents, as earlier maturation has been shown in females compared with males, which may contribute to sex differences in anxiety and depressive-like behaviors (Perry et al., 2021). In a recent study of Zhang and colleagues, sex-specific transcriptional signatures were observed in the medial PFC of adult rats exposed to early-in-life stress and to restrain stress during adulthood, and such transcriptional differences have been linked to the different sex-specific behavioral responses to stress (Y.-D. Zhang et al., 2023). Moreover, previous studies have identified significant sex differences in the transcriptional response to stress in different brain areas, such as NAc, PFC, hippocampus, and ventral tegmental area (Hodes et al., 2015; Parel & Peña, 2022; Peña et al., 2019). The studies of Pena and colleagues have shown that there are similarities in the biological signatures modified by ELA in the PFC among females and males, whereas opposite genome-wide signatures of response to ELA among females

and males have been shown in VTA and NAc (Parel & Peña, 2022). We have recently shown that, although exposure to PNS produced emotional impairment through different pathological domains, such as anhedonia, anxiety, and sociability, in males and females, sex differences were observed in the activity state of different brain regions in relation to vulnerability or resilience to the prenatal manipulation (Creutzberg et al., 2023). Moreover, Musillo and colleagues have recently demonstrated two sex-dimorphic phenotypic pathways affected by both PNS and maternal high fat diet, specifically a disrupted neuroendocrine regulation that characterize the long-term effects in male mice, while an impairment of inflammation and-redox balance were found in female mice (Musillo et al., 2023).

Beside the role of sex hormones, also the differential modulation of neurotransmitter systems may contribute to sex differences in the response to ELA. For example, the expression of selected ionotropic and metabotropic glutamatergic receptors was increased only in adult male offspring that were exposed to PNS (Y. Wang et al., 2016). Moreover, maternal immune activation was shown to increase PFC glutamate levels in both juvenile male and female offspring (J. Zhang et al., 2018), but only males showed reduced glutamate levels at adulthood (Bitanihirwe et al., 2010). On the other hand, adult female rats prenatally exposed to LPS have shown a reduced number of parvalbumin and glutamate decarboxylase expressing neurons in the medial prefrontal cortex, whereas in males these changes have been detected in the hippocampus, suggesting a key role for the GABA system following PNS exposure and that the observed changes are sex-dependent (Basta-Kaim et al., 2015).

With regards to monoamines, Perry and colleagues showed that the effects of prenatal stress on frontal cortex monoaminergic systems is sexually dimorphic (Perry et al., 2021). Indeed, while dopamine metabolites are increased in females exposed to PNS, a reduction was found in males (Bowman et al., 2004). Similarly, serotonin metabolites were decreased in males but not in females (Bowman et al., 2004), while the levels of tryptophan hydroxylase, the enzyme responsible for serotonin biosynthesis, were unaffected in both sexes (Dang et al., 2018; Van den Hove et al., 2014). Considering the inconsistencies observed in the literature, there remains a significant lack of conclusive findings regarding the specific biological signatures able of discerning between males and females; however, as previously mentioned, this variability might depend on stage of development where stress is experienced, the time at which effects are measured, and the type of stress experienced (Perry et al., 2021).

However, although there is a great variety of studies on the relationship between sex hormones and depression, only a few have investigated the role of sex hormones in depression following ELA. This association has been investigated mainly in preclinical studies, and both prenatal and early postnatal stress have been shown to induce an effect on sexual hormone levels, specifically in adulthood. For example, lower testosterone levels in adulthood have been observed in males following PNS, and lower adult estradiol and testosterone observed in females. On the other hand, more inconsistent results have been observed following early postnatal stress, as in males both lower or no effect were observed for testosterone, whereas no effect on estradiol in females (Eck & Bangasser, 2020). These results might indeed suggest that the sex differences observed following ELA does not rely only on the effect or ELA on sex hormones.

5. The implications of early life adversities for the treatment of mental disorders

5.1. The role of ELA in disease diagnoses and therapeutic response

As mentioned in the above paragraphs, a history of childhood trauma, independently to the type of trauma experienced, increases the risk for psychopathology, and it is also associated with specific clinical features, such as an earlier onset of symptoms, more severe symptomatology, more severe illness course, increased risk for suicide and reduced quality of life also because of the higher frequency of comorbidities (Lippard & Nemeroff, 2020).

Above to influence the risk for psychopathology and its course, childhood trauma has also a huge impact on treatment response, regardless of the diagnosis. Indeed, it is widely reported that depressed patients with history of childhood trauma often fail to respond to pharmacological interventions, they are at markedly increased risk for developing recurrent and persistent depressive episodes and are at high risk to develop treatment resistant depression (Nanni et al., 2012; Williams et al., 2016; Yrondi et al., 2020).

Although less data is available, treatments' efficacy is influenced by childhood trauma history also in bipolar disorder (Cakir et al., 2016; Lippard & Nemeroff, 2022; Wrobel et al., 2022) and in schizophrenia (Mansur et al., 2020; Mørkved et al., 2022).

Although childhood trauma cannot be considered a feature to improve diagnosis, such information could be used to improve clinical practice, and to plan personalized interventions. Indeed, it has been shown that individuals with a history of these adverse events can benefit more of some interventions than others. Again, most of the available data are focused on depressed patients. For example, adults with chronic depression and early life stress had a more beneficial response to Cognitive Behavioral Analysis System of Psychotherapy than antidepressants and they also had a more favorable response to psychotherapy than chronically depressed individuals without early life stress (Nemeroff et al., 2003). It is worth noting that emerging evidence suggest that trauma-focused psychotherapies may produce global DNA methylation changes (Carvalho Silva et al., 2024). Moreover, preliminary evidence suggests that cognitive behavior therapy may improve depressive symptoms also through the modulation of inflammation (Lopresti, 2017), whereas psychological interventions appear efficacious in reducing pro-inflammatory biomarker levels (O'Toole et al., 2018).

Interestingly, patients with refractory depression with a history of childhood trauma were also those showing a substantially better response to intravenous ketamine than refractory depressed patients with no history of early life trauma (O'Brien et al., 2021).

Interestingly, anti-inflammatory drugs (including non-steroidal anti-inflammatory drugs, cytokine inhibitors, statins, pioglitazone, glucocorticoids and minocycline) have emerged as adjuvant therapies able to improve depressive symptoms in specific clusters of patients and in particular treatment-resistant patients characterized by exposure to childhood trauma (Köhler-Forsberg et al., 2019). The use of anti-inflammatory drugs as adjuvant therapy in non-responder patients come from biological evidence, as both childhood trauma and the non-response condition are characterized by the presence of higher levels of peripheral inflammation, which in turn negatively influence treatment response. In line with this, it has been shown that several agents with anti-inflammatory properties (i.e., polyunsaturated fatty acids, nonsteroidal anti-inflammatory drugs, cytokine inhibitors, statins, pioglitazone, corticosteroids, minocycline or modafinil) have been studied and included in previous reviews. Celecoxib, and minocycline have been found to reduce depressive symptoms in individuals with depression although only in patients showing a pro-inflammatory profile (Anmella et al., 2024; Köhler-Forsberg et al., 2019; Simon et al., 2023).

A recent meta-analysis showed that minocycline treatment may improve depressive symptoms compared to placebo in both unipolar and bipolar depression, given as an add-on treatment as well as in monotherapy (Cai et al., 2020). However, the conclusions are still not clear, possibly because such analyses are limited by the overall lack of trials that have attempted to identify those clinical subgroups that are more likely to benefit from minocycline treatment, or from other anti-inflammatory agents, as specific patients' subtypes, with a specific immune profile, that are preferentially responsive certain treatments exist.

Indeed, it has been suggested, that heterogeneity in the results of minocycline's efficacy could be associated with the profile of different

immune mediators (CRP versus IL-6) that in turn may activate specific inflammatory cascades ultimately differentially influencing treatment response (Dean et al., 2017; Husain et al., 2017; Nettis et al., 2021). This adds further evidence on the importance of stratifying patients for individual baseline inflammatory markers before selecting the anti-inflammatory drugs to be used as add-on treatment.

To move even more into the era of precision medicine, the use of monoclonal antibody-assisted therapy that is customized based on the specific levels of certain inflammatory cytokines shows promise in improving the precision, effectiveness, and safety of psychiatric disorders' treatment. Several data on the use, in depressed and bipolar patients, of different monoclonal antibodies (Infliximab, Tocilizumab, Adalimumab, Canakinumab, Siltuximab, Sarilumab, Golimumab) targeting different cytokines are available (Bavaresco et al., 2020; Shamim et al., 2023; Wu & Zhou, 2024). While the safety of these monoclonal antibodies remains to be thoroughly addressed, such approach may represent a valuable targeted strategy of immunotherapy for psychiatric patients showing a particular immune profile often in association with a history of childhood trauma.

Overall, these data suggest that the identification of clinical subgroups of patients based on specific clinical features, such as childhood trauma history and a pro-inflammatory status, will be instrumental to identify specific adjuvant therapies, that will ultimately contribute to symptomatology improvement. However, larger clinical trials are needed to compare the effect of different anti-inflammatory agents with other strategies (psychotherapy and other non-pharmacological approaches), as well as to identify clusters of patients who will take advantage from a specific intervention (e.g presence of childhood trauma history, elevated inflammatory markers, presence of comorbidities) in order to implement treatment personalization.

5.2. Therapeutic strategies to overcome the effects of early life stress

As mentioned above, the presence of ELA within the context of a given pathologic condition appears to be associated with reduced treatment responsiveness (Nanni et al., 2012; Nelson et al., 2017). How can we overcome this problem? Which strategies can be implemented in order to take into account the role of ELA in a specific psychopathologic context and orchestrate a better treatment strategy?

Several therapeutical options are available for depressive disorders during pregnancy including psychotherapy and antidepressants, although most women are discontinuing antidepressant medications before and during pregnancy because they are worried on the possible consequences of these drugs on their baby (Hayes et al., 2012; Xing et al., 2020). Nevertheless, different preclinical studies have provided important support to the possibility that early interventions can minimize or prevent the negative consequences associated with stress exposure early in life.

At the experimental level a distinction must be done between treatments that overlap in time with a given manipulation (for example stress exposure) with respect to treatments that are initiated after the adverse event or when a phenotype is already present.

When considering the first approach, some studies have investigated with mixed results the effect of prenatal stress (PNS), as to mimic a depressive-like condition in pregnancy, in association with antidepressant treatments. For example, Amani and coworkers have shown that fluoxetine administration was able to ameliorate PNS-induced anxiety-and depressive-like behavior and increased HPA-axis function in pregnant and postpartum dams. Moreover, such treatment was also able to counteract some of the behavioral alterations found in the offspring of stressed dams, in a dose-dependent fashion (Amani et al., 2021). Conversely, Ehrlich et al. found that stress exposure during gestation produced age-dependent deficits in anxiety-like behavior and amygdala function in female offspring, regardless of in utero treatment with the SSRI escitalopram (Ehrlich et al., 2015).

In a recent study, Scarborough et al. have shown that maternal fluoxetine treatment was effective in preventing some of the behavioral and molecular abnormalities emerging in the offspring born to mothers characterized by an antenatal depression-like condition based on social isolation prior to mating (Scarborough et al., 2021).

In a recent study, we have also shown that prenatal administration of the antioxidant *N*-acetyl-cysteine administration, by restoring the redox balance, was able to exert long-term protective effects on brain development in mice exposed to high-fat diet or stress during gestation, which mimic maternal obesity and maternal adversities, respectively (Musillo et al., 2023). Evidence suggests that a diet high in fat and sugar post weaning can ameliorate the LBN-induced anxiety-like behavior and revert the down-regulation of molecules linked to neural plasticity (Walker et al., 2017). Similarly, exposure to a diet enriched with low ω6/ω3 polyunsaturated fatty acid (PUFA) ratio early in life show protection against LBN-induced cognitive impairments (Reemst et al., 2024). Lastly, maternal supplementation with essential micronutrients, such as methionine and B vitamins, can also prevent the lasting effects of LBN (Naninck et al., 2017).

These data suggest that nutritional interventions aimed at boosting endogenous protective mechanisms during critical time frames may prove useful to buffer the potential consequences of different types of adversities.

A large number of studies used the second approach and investigated different treatments after the exposure to a specific stress paradigm. For example, since exposure to PNS can alter the expression of serotonin and dopaminergic receptors already in adolescence, we have shown that the multi-receptor antipsychotic drug lurasidone administered during the peripubertal period was able to prevent the significant down-regulation of the neurotrophin Bdnf in PNS rats (Luoni et al., 2014). More recently, we have demonstrated that the transient up-regulation of different inflammatory markers in adolescent rats previously exposed to PNS can also be prevented by lurasidone treatment (Lopizzo, Mazzelli, et al., 2021). Other studies have examined the potential effects of standard antidepressant treatments during adulthood in counteracting the adverse effects of early life stress, with heterogeneous responses on functional and neurobiological changes. For example, fluoxetine, venlafaxine and tianeptine given at adulthood were able to counteract the depressive-like behavioral alterations in male rats exposed to PNS and show anti-inflammatory effects that are more pronounced in the hippocampus (Trojan et al., 2019). On the other end, sertraline was able to reduce the behavioral impact of PNS in females, with no significant effects in male animals (Pereira-Figueiredo et al., 2017). Considering the significant differences among the experimental designs, including the type and length of treatments as well as the functional and molecular readouts investigated, it is difficult to reconcile the findings from such experiments. More work is indeed needed to establish possible differences between early (adolescence) and late (adulthood) intervention and to understand the relationship between a given pathologic domain and the type of treatment that may prove more effective.

Considering, as discussed above, that changes in immune-inflammatory systems as well as oxidative stress may represent important mechanisms in mediating the short and long-term effects of early life stress, it will be important to test specific interventions that, either alone or in combination with psychotropic drugs could result in more effective therapeutic responses.

6. Conclusions and future perspectives

Understanding the factors that contribute to the onset and progression of a pathologic condition is an important step for a more precise diagnosis and treatment approach. With this in mind, exposure to traumatic or adverse experiences early in life, from the womb until adolescence, represents a major causative factor for the development of different psychiatric conditions, including (but not limited to) anxiety,

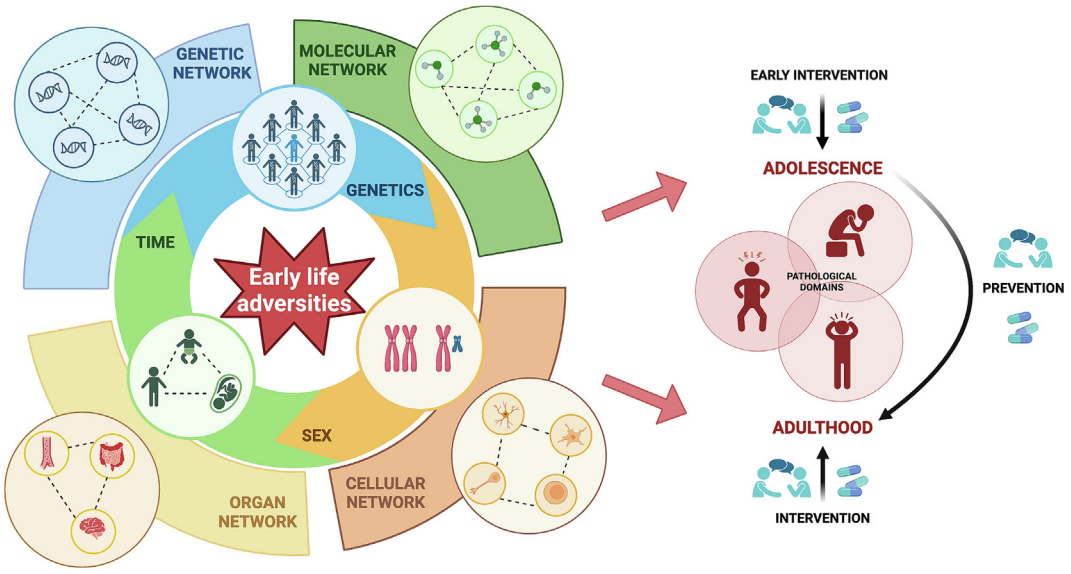

Fig. 1. Schematic view of the factors mediating the effects of early life adversities on psychopathology and their implications for novel treatment approaches.
The exposure to stress from gestation to adolescence, together with genetics and sex, plays a major role in the development of psychiatric conditions characterized by the disruptions of different pathological domains, such as cognition, anxiety, and depression. Moreover, a variety of interrelated biological mechanisms may contribute to the onset of psychiatric disorders as a consequence of the exposure to adverse experiences early in life.
The characterization of such mechanisms has important clinical implications with a better phenotyping of patients who will eventually benefit from specific pharmacological and non-pharmacological approaches not only aimed at counteracting specific pathogenetic mechanisms but also with the goal of preventing the occurrence of a full-blown pathologic condition.

major depression, bipolar disorder and schizophrenia. As we have discussed in this review, the link between such adverse experiences and their psychopathologic consequences is modulated by several biological factors and is mediated by different molecular mechanisms (see Fig. 1), although we must acknowledge in the limitations of our review that some aspects, including neuropsychological and neuroimaging changes resulting from ELA exposure, were not discussed in great details.

The characterization of this association has potential implications, primarily related to the selection of the most appropriate therapeutic approaches to improve individual responsiveness. Indeed, it is not surprising that treatment resistant depression is often associated with exposure to childhood trauma (Nanni et al., 2012; Nelson et al., 2017), suggesting that a given therapeutic approach may not be able to overcome or counteract the functional and molecular alterations that sustain the pathologic phenotype developing as a consequence or with the contribution of the exposure to early in life adversities.

This may imply that different subtypes of a specific pathologic condition, such as major depression, can be identified based on the presence (or not) of early life adversities. It will be important to establish if the type, the timing, and the duration of a given early in life adversity may be associated with specific outcomes. It is known that some brain circuits or cellular populations may be more vulnerable within selected time frames or to specific types of trauma, and this will eventually lead to the impairment of specific pathologic domains, which may be shared by different psychiatric disorders (anhedonia, reduced sociability, cognitive impairment).

Experimental work suggests that, while exposure to stress early in life or in adulthood may produce similar functional and behavioral alterations, differences in the molecular underpinnings of such alterations may exist. Moreover, although similar changes between ELA and adult stress have been demonstrated, including reduced plasticity, enhanced inflammation, altered HPA axis function, a clear difference may exist with respect to the duration of such changes. This may also explain the different responsiveness to a given treatment in patients who, for example, develop a depressive disorder with or without the contribution of early traumatic experiences.

It has been wisely suggested by Teicher et al. that it will be crucial to recognize the importance of ELA/childhood trauma in the etiology and manifestation of mental disorders by incorporating such information into the diagnostic criteria in order to develop better classification systems with an increasing focus on etiology and pathophysiology (Teicher et al., 2022).

Some of the alterations produced by ELA and discussed in the present review may be modifiable targets, including the changes of inflammatory-immune mechanisms, the dysregulation of HPA axis and redox mechanisms, as well as different neurotransmitter-related changes. With this respect, a recent study reported that adjunctive treatment with infliximab, a monoclonal antibody targeting tumor necrosis factor, was able to reduce depressive symptoms only in a subpopulation of adult bipolar patients with a history of childhood maltreatment (McIntyre et al., 2019).

However, the role of a given alteration on the pathologic outcome may depend on specific time windows, particularly if such alterations are contributing to the disease onset. On these bases, the potential effectiveness of treatments that will interfere with such mechanisms may be limited to an early disease stage or must anticipate a full-blown condition. Interestingly, the onset of stress-induced conditions, peaks between mid and late adolescence and become fully manifest during the transition from adolescence to adulthood (Paus et al., 2008; Solmi et al., 2022), suggesting that such period is crucial to establish intervention strategies aimed at mitigating or preventing the long-term outcomes that develop as a consequence of early life stress exposure.

As an example, as previously discussed, an imbalance in the pro/anti-oxidative homeostasis may contribute to the etiology and manifestation of different psychiatric disorders (Rossetti et al., 2020) and such alterations can be particularly relevant during development. Indeed, it has been demonstrated that juvenile antioxidant treatment is able to prevent adult deficits in a developmental model of schizophrenia (Cabungcal et al., 2014).

Such approach must also rely on measurable peripheral (as well as genetic) biomarkers, which still represent a major problem in psychiatry. Such biomarkers may not necessarily reflect a specific condition or psychopathologic domain but could rather identify a subgroup of

patients with specific features, who may be more prone to respond to a given treatment or who will benefit from specific strategies aimed at delaying or mitigating the consequence of an enhanced disease vulnerability. For example, Nasca and coworkers have shown that the endogenous levels of acetyl-L-carnitine (LAC) are significantly reduced in patients with major depressive disorder. Interestingly, such decrease was larger in patients with a history of treatment-resistant depression (TRD), with a strong prediction due to previous exposure to childhood trauma suggesting that decreased LAC may identify specific endophenotype of patients who could benefit of adjunctive treatment with LAC (Nasca et al., 2018).

One big challenge for the cure of mental disorders is represented by early intervention, considering that most of the pharmacological treatments are usually initiated with significant delays as compared to the manifestation of symptoms. We believe that early signs of impairment such as reduced sociability, reduced motivation, anhedonia, affective blunting and distractibility may serve to sense a condition that may progress into a full-blown disease, particularly if associated with traumatic experience early in life.

One difficulty in trying to apply the concept of ELA for a better diagnosis and treatment in mental disorders, relates to the fact that a specific traumatic experience may not act in isolation and that there may be cumulative effects of early adverse experiences. As mentioned, the 'original' experience may sensitize toward subsequent events to which an individual may show exacerbated responsiveness with harmful consequences for brain function and mental health. Moreover, it has been proposed that the early adverse experience can reduce cognitive adaptation and produce a 'social thinning' that may amplify the negative consequences of an adverse environment during adolescence in presence of reduced protective factors that will ultimately increase the risk of psychiatric disorder (McCrory et al., 2022). While acknowledging such complexity in the human conditions, animal models must try to reproduce these conditions to better capture the variability emerging from a 'first hit' and to identify the systems or circuits that will ultimately be relevant for disease onset.

Animal models are also important to characterize resilience, which must be considered an active mechanism that, by promoting protective factors, can allow adaptation strengthening the ability to cope under challenging conditions (Bhatnagar, 2021). Boosting these systems can also represent a strategy to overcome the adverse consequences of the exposure to early life adversities (Cathomas et al., 2019; Holz et al., 2020). Once again adolescence can be a critical time window for such strategies: indeed, while its heightened plasticity may amplify environmental inputs to unmask the effects of stress exposure that occurred earlier in life, protective and pro-resilience intervention may also be more effective to counteract the adverse consequences of such stressful experiences.

In summary, we have tried to show and discuss neurobiological mechanisms that may cross diagnostic boundaries in conferring a heightened risk for psychopathology, linking the different forms of early life trauma with the vulnerability for detrimental outcomes.

In order to improve mental health care and reduce the enormous burden and economic costs associated with such conditions, a paradigmatic shift toward prevention is needed (Arango et al., 2018; McCrory et al., 2022). Such shift must rely on scientific advancement as well as on the education and training of families and professional working routinely with children and adolescents to identify those 'at risk' individuals who may benefit from specific forms of interventions. Moreover, enhanced longitudinal analyses in at high-risk individuals may be essential to characterize individual disease trajectories in order to decide treatment options that may lead to more benign clinical outcomes.

CRediT authorship contribution statement

Annamaria Cattaneo: Writing – original draft, Visualization, Investigation, Funding acquisition, Conceptualization. **Veronica Begni:** Writing – original draft, Visualization, Investigation, Conceptualization. **Valentina Zonca:** Writing – original draft, Visualization, Investigation, Conceptualization. **Marco A. Riva:** Writing – original draft, Visualization, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

M.A.R. has received compensation as speaker/consultant from Angelini, Lundbeck, Otzuka, Sumitomo Pharma, and Sunovion, and he has received research grants from Sumitomo Pharma. A.C. received compensation as a speaker from Sumitomo Pharma. All the other authors declare that there are no conflicts of interest.

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