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Title: A Review of Immune and Histological Brain Changes Following Early Life Adversity

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Abstract

Exposure to stressors in early life is an important factor in shaping an individual's health in later stages of life. Besides, the growing range of stressors during the very first 1000 day of human life may lead to critical biophysiological consequences. The results of previous studies have shown that ELA contact to a stressor reduces the capacity of the immune system to produce subsequent generations of naive cells, as well as, the capacity of neuronal stem cells to proliferate. In today's modem societies, stressors and their later-life outcomes have significantly increased, yet the molecular mechanisms behind them are still not well understood. Due to the above reasons, animal models of postnatal stress have been widely developed. Since in the first days of life, a reciprocal relationship between the mother and baby is needed for proper growth and development, disruption of this relationship may lead to permanent changes in neurobiology and neurobehavioral mechanisms of individuals.

Keyword

Astrocytes/ Cognition/ Early life adversity (ELA)/ Early life Stress (ELS)/ Maternal separation (MS)

Introduction

Early development of the brain and other body tissues requires the integration of various environmental factors, including stress hormones, nutrition, and immune responses (Vázquez et al. 2002; Gordon and Hen 2004; Lowry 2002; Barr et al. 2004; Erickson et al. 2005; Fahlke et al. 2000; Spinelli et al. 2009). Early life experiences are critical for brain development, with early life adversity (ELA) such as trauma, abuse, neglect, or malnutrition associated with cognitive decline and adult psychopathology (De Bellis 2005; Teicher et al. 2003; Teicher et al. 2004; De Bellis et al. 2002). For example, social deprivation in institutionalized children leads to reduced cognitive abilities. Childhood trauma, neglect or emotional abuse also affect cognitive functioning and can lead to adult depression (Banasr and Duman 2007; Herman et al. 2005; Liberzon and Martis 2006; De Bellis et al. 1999; Kitayama, Quinn, and Bremner 2006). In addition, prenatal malnutrition is associated with cognitive impairment in adulthood and a higher risk of schizophrenia. This work reviews how ELA correlates with various mental disorders and the role of neuroinflammation in these conditions. It discusses how such adversity may specifically impact neuro-immune development and highlights the influence of sex differences on individual vulnerabilities.

1. Stress and the Limbic-Hypothalamic-Pituitary-Adrenal Axis

Stress is the biological response that appears when the body detects a real or expected threat. This response uses neural, endocrine, and autonomic pathways (Oubaid 2023). The limbic-HPA system is a central part of this response. The amygdala, hippocampus, and medial prefrontal cortex help the brain assess danger and choose the proper response. The amygdala usually increases HPA axis activity. In contrast, the hippocampus and prefrontal cortex help reduce this activity through feedback pathways (Herman et al. 2020; Murphy et al. 2022).

During stress, the hypothalamus releases corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). These peptides stimulate the anterior pituitary to release adrenocorticotropic hormone (ACTH). ACTH then reaches the adrenal cortex and increases cortisol secretion in humans and corticosterone secretion (Sheng et al. 2020). Glucocorticoids support energy supply and help the body respond to the stressor. They also send negative feedback to the hypothalamus, pituitary, hippocampus, and prefrontal cortex. This feedback helps stop excessive HPA axis activity and helps the system return toward baseline (Raise-Abdullahi et al. 2023).

Short-term activation of this system can be adaptive. However, repeated or long-term stress can disturb the normal balance of the system. It may change daily cortisol rhythm, stress reactivity, immune activity, and neural plasticity. This issue is highly relevant in early life because the brain and HPA axis are not fully mature (De Kloet, Joëls, and Holsboer 2005). Childhood trauma, neglect, deprivation, and unstable care can change the maturation of prefrontal-hippocampal-amygdala circuits and HPA axis responses. These changes may increase the later risk of depression, PTSD, psychosis, and other stress-related disorders (Birnie and Baram 2025; Murphy et al. 2022; Ochi and Dwivedi 2023; Smith and Pollak 2020).

The pattern of HPA axis change is not the same in all studies. Some people show higher cortisol responses after early adversity, whereas others show weak cortisol responses after chronic or severe stress. This difference may depend on the type, timing, length, and social context of stress. Sex may also affect this pathway because males and females can show different HPA axis, serotonin, and hormone-related responses after ELS. Therefore, the limbic-HPA system helps explain how early adverse experiences may link to long-term changes in brain function, immunity, and mental health (An et al. 2022; Gotlib et al. 2026; Heck et al. 2020; Maier et al. 2022).

1.2. The Link Between Childhood Stress and Chronic Diseases: The Role of Timing and Biological Changes

Since the early studies of David Barker linking birth weight to cardiovascular disease, the relationship between environmental influences during the first 1000 days has expanded to include many mental illnesses, immune disorders, and metabolic problems such as diabetes and obesity (Grova et al. 2019; McEwen 1998; Gluckman et al. 2009; Cao-Lei et al. 2015). ELA primarily affects the central nervous system and the immune system. Long-term studies have linked ELA to higher risks of stress-related disorders, mental health problems, diabetes, obesity, asthma, cardiovascular disease, and depression. The exact mechanisms behind these associations are unclear. However, there appears to be significant interaction between the immune system and the central nervous system, particularly the HPA stress axis. The hippocampus plays a critical role in this process, influencing the hormonal

response to stress and regulating glucocorticoid levels and the duration of HPA axis activation. The hippocampus regulates the endocrine stress response through the HPA axis and continues to produce new dentate granule cells throughout life, which are essential for its function. Neurogenesis here is influenced by metabolic factors and neurotransmitters such as GABA. In addition, stem cells in the striatum and lateral ventricles can also differentiate into glial and neuronal cells. However, early stress can inhibit their proliferation and differentiation, leading to cognitive impairments associated with reduced reparative capacity caused by ELA. The "perinatal sensitive window" may be a time when stem cells are most vulnerable to reprogramming and help the body adapt to its environment, especially in the brain and immune system, which are most affected by ELA. The 1998 Quebec ice storm, which left residents without power for weeks, resulted in altered metabolic parameters and increased HPA axis reactivity in children exposed in utero or shortly after birth (Roseboom, de Rooij, and Painter 2006; Cao-Lei et al. 2011; Ziegler and Herman 2000; Fee et al. 2020; Jankord and Herman 2008). Early stress therefore increases the risk of lifelong disorders, making this period crucial for biological development and environmental adaptation. In vivo models also show that short-term stress exposure can significantly increase the risk of disease (Ping et al. 2020; BT 2009; Schulz 2010; Roseboom, de Rooij, and Painter 2006; Susser et al. 1996; Tobi et al. 2009; McDonald et al. 2011). The mother-infant bond is formed immediately after birth, and negative events can disrupt this relationship. Previous research has shown that the caregiver-infant relationship is crucial for long-term health, with psychosocial factors being the most influential parameters. Caregiving, even in a supportive environment, negatively impacts physical and cognitive development and affects stress and immune functions for years, and even short periods of adoption (approximately 2 months) can result in lasting behavioral effects that are observable 24 years later. Rodent studies show that maternal deprivation induces behavioral and hippocampal changes alongside immune system changes, including neuroinflammation and increased inflammatory markers. Similarly, human institutional adoption leads to behavioral changes and increased mental health risks (Reid et al. 2019; Palma-Gudiel et al. 2020; Brunson et al. 2005; Turner et al. 2010). ELA accelerates immune system aging, affecting both innate and adaptive responses. CD8+ T cells are significantly affected, disrupting the CD4/CD8 balance and displaying signs of aging. CD4+ T helper cells are also increased in senescent forms. In addition, the percentage of B cells decreases for no apparent reason. Innate immunity shows a decrease in the number of macrophages and NK cells, which is likely due to premature stress (ELS) and its function is reduced. These changes may lead to a less effective immune response (Turner et al. 2014; Armstrong et al. 2014). systematic review and meta-analysis of animal studies showed that ELA leads to an increase in pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α in brain tissue, particularly in the hippocampus of adult mice. These changes were associated with the duration of exposure to ELA, but no significant changes were found in anti-inflammatory cytokines like IL-10. This suggests that ELA induces long-term immune changes in the brain and These studies highlight that ELA can lead to long-lasting changes in immune function and brain structure, which are associated with psychiatric and neurodegenerative disorders. They underscore the need for early interventions to mitigate the negative effects of ELA on mental and physical health. In addition, the sympathetic nervous system stimulates immune tissues such as the spleen and creates immune synapses that transmit environmental information to pro-inflammatory and anti-inflammatory macrophages and influence various other factors. These effects are thought to be stabilized through epigenetic mechanisms such as DNA methylation. Similarly, the Dutch Hunger Winter (1943-1944) highlighted a critical time of stress exposure that led to lifelong mental health problems and metabolic changes associated with DNA methylation changes. While much research has examined epigenetic changes in somatic cells, these cells have a limited lifespan, often shorter than their associated phenotypes, with tissues such as heart and brain cells having long lifespans being pitted against short-lived immune cells. Most cell types, with a few exceptions, live less than 1.5 years. A recent study in mice showed that social stress inhibits cell growth in the hypothalamus and reduces hypothalamic neural stem cells by up to 4 months. Another study showed that by reducing adult neural stem cells, it also affects hippocampal development, and the literature suggests that hippocampal neurogenesis adapts to challenges. Focusing solely on differentiated brain cells ignores the underlying issues arising from neural stem/progenitor cells. Therefore, it is very important to consider these stem/progenitor cells because they are the origin of these abnormalities. Blood cells, like hippocampal cells, are continuously produced from stem cells. Research in mice has shown that social stress induces hematopoietic stem progenitor cells to migrate from the bone marrow to the spleen, where they expand and differentiate into monocytes, neutrophils, and red blood cells. As a result, the constant turnover of stem cells and their interaction with the environment that influences these stem cells can have lasting effects. Epigenetic changes in stem cells

persist as they proliferate and differentiate, potentially leading to more significant health consequences than changes in differentiated cells. This “stem cell hypothesis” suggests that ELA can have lasting effects, influencing health and disease in the future (Dammann et al. 2011). Since the work of Weaver and Meaney in the early 2000s, it has become clear that changes in the epigenetic landscape, DNA methylation, and gene transcription, are key to the ELA phenotype. Significant DNA methylation changes occur in various tissues, particularly in blood and brain regions such as the hippocampus and prefrontal cortex. While many genes have been studied, the glucocorticoid receptor (GR) and brain-derived neurotrophic factor (BDNF) play a central role. Epigenetic regulation of the GR gene (Nr3C1) is notable, particularly due to its complex 5' untranslated region that influences tissue-specific expression and protein production. In rodents, maternal care influences Nr3c1 methylation and influences stress responses. In humans, prenatal adversity such as anxiety and violence has been associated with increased NR3C1 methylation (Daskalakis et al. 2015; Byun et al. 2016). BDNF promoter methylation is influenced by early life environments. While GR regulates HPA axis reactivity throughout life, BDNF is critical for brain development. Although the effects of GR and BDNF methylation are different, both affect mitochondrial processes. GR proteins are predominantly cytosolic but can enter mitochondria and regulate energy processes, while BDNF contributes to mitochondrial biogenesis and transport. Environmental factors can lead to epigenetic changes that prevent mitochondria from adapting to stress. Mitochondria regulate stress pathways in the endocrine, immune, and central nervous systems by regulating their functions (Mposhi et al. 2022). Studies also show that exposure to ELA leads to persistent stress-related changes in the telomere/telomerase system and impairs the differentiation of stem cells into functional somatic cells. Telomerase activity decreases during cell differentiation, affecting its critical roles in mitochondria, such as regulating membrane potential and superoxide production. Telomerase reduction leads to mitochondrial dysfunction and increased reactive oxygen species (ROS), which cause DNA damage and aging. These processes are significant in the immunophenotype of ELA and may influence stem cell fate. DNA repair and the telomere system are crucial during ELA and show significant adaptations (Cheng et al. 2012; Blackburn 2005; Chatterjee and Walker 2017; Masutomi et al. 2005). Factors such as gestational diabetes, inflammation, and maternal mental health affect telomere length at birth. In addition, exposure to air pollution, smoking, and low birth weight increase DNA damage and reduce repair capacity (Sobinoff and Pickett 2017; Entringer 2023). However, the autophagy network in adult neural stem cells is crucial for proteostasis and the maintenance of lifelong neurogenesis. Immunometabolic differences are influenced by cellular activation states and environmental factors, including nutrients and microbiome metabolites. This interaction is crucial in regulating immune responses, balancing tolerance, and inflammation. Notably, specific metabolites have been associated with ELA-induced immune senescence, highlighting their role in promoting immune senescence. Differences in glutamine and arginine metabolism are consistent with the ELA immunophenotype. Glutamine is critical for T-cell and macrophage proliferation and promotes the M1 inflammatory phenotype, both of which are critical for ELA. Furthermore, declining glutamine levels with age may lead to decreased immune cell function, reflecting aspects of the ELA immunophenotype. Nutrient metabolism has been linked to ELA, inflammation, and long-term disease risk (Lazarides et al. 2019). In addition, adequate intake of macronutrients and micronutrients is essential for immune development. Psychosocial stress can disrupt nutrient absorption and metabolism, affecting the microbiome and immune development. Iron deficiency is a major problem affecting 40% of children under 5 years of age in the United States and is associated with ELA. This deficiency increases proinflammatory responses and alters immune function, which is not reversible even after iron levels are restored to normal. Iron deficiency may not only affect the immunophenotype associated with ELA, but is also critical for postnatal development. It is essential for brain structure and function, as well as for the production of key neurotransmitters such as dopamine, norepinephrine, and serotonin, suggesting its potential impact on other elements of the overall ELA phenotype (Moreli et al. 2016). Reactive oxygen species (ROS) are also associated with psychosocial stress. Glucocorticoids increase ROS production and affect mitochondrial function and energy production. Stem cells rely on anaerobic glycolysis to limit ROS and switch to oxidative phosphorylation during differentiation. This balance helps prevent senescence and maintain proliferation. Immune cells also alter metabolism based on activity, reflecting the dynamic nature of mitochondrial metabolism in response to stress and differentiation. Endogenous ROS are implicated in stress-related inflammation, endocrine, and metabolic issues. Stem cells primarily utilize anaerobic glycolysis for energy to limit ROS production and switch to mitochondrial OXPHOS (oxidative phosphorylation) during differentiation (Moreli et al. 2016). Glycolysis supports rapid growth despite its lower ATP yield, while OXPHOS is more efficient for energy-demanding cells

but produces more ROS. Mitochondrial dysfunction and ROS accumulation are associated with cellular aging. By reducing ROS, stem cells retain their ability to proliferate and differentiate. Even after differentiation, hematopoietic cells can switch between glycolysis and OXPHOS, as observed in activated macrophages and during neural differentiation. Stem/progenitor cells exhibit a dynamic energy profile that is influenced by the stages of differentiation, and mitochondrial metabolism is crucial for the transition from glycolysis to OXPHOS. Exposure to ELA increases mitochondrial ROS, reduces ATP production, and inhibits mitochondrial biogenesis (Audesse et al. 2019). This alteration in mitochondrial metabolism may lead to senescent immune cell phenotypes (Aschbacher et al. 2021; Alwarawrah, Kiernan, and MacIver 2018). The integration of the immune system and the brain suggests that lifelong turnover of differentiated cells explains the long-term effects of ELA, and one of the tissues most severely affected by ELA is the brain (Mposhi and Turner 2023). A 2023 review explored the interplay between early-life adversity, the immune system, and the microbiome. It highlighted that ELS can disrupt the developing microbiome, leading to altered immune responses and increased inflammation. These disruptions may contribute to the long-term physical and mental health consequences observed in individuals exposed to ELS, underscoring the complex interactions between the brain, immune system, and microbiome(Reemst et al. 2022). A study by Kinderlehrer, D.A. et al discussed inflammation as a central mechanism linking stress to various health issues, including mental illness, autoimmunity, and chronic diseases. It emphasized that ELA can prime the immune system, leading to chronic inflammation and increased susceptibility to these conditions. The review suggests that targeting inflammation could be a potential therapeutic approach for mitigating the effects of ELS on health(Kinderlehrer 2024) also demonstrated the focusing on women aged 30–60 years found that those who experienced significant stress or trauma in childhood exhibited higher levels of biomarkers indicating neuroinflammation and neurodegeneration. Additionally, they had lower brain volumes and displayed more cognitive problems. These findings suggest that ELS contributes to accelerated brain aging, increasing the risk of developing neurodegenerative disorders later in life (Kinderlehrer 2024; Herbers, Wallace, and Tebepah 2025).

2. From ELA to Adult Disease: The DOHaD Hypothesis and Epigenetic Regulation

Recent research emphasizes how early-life environmental factors influence adult health. The Developmental Origin of Adult Health and Disease (DOHaD) hypothesis suggests that harmful early conditions can lead to chronic diseases later in life. Initially focused on prenatal and neonatal malnutrition, it now recognizes that non-nutritional factors, like psychological stress, also significantly impact long-term health, with epigenetic regulation playing a crucial role. Early postnatal stages are essential for development (Hanson and Gluckman 2015; Eriksson 2016). Research in rodents shows poor mother-infant interactions can disrupt neuroendocrine regulation, increasing GR and stress hormones. This early adversity can lead to adult behavioral issues like learning deficits and anxiety. Studies indicate that offspring of dams with high licking and grooming (LG) show less stress and better cognitive performance than those from low-LG dams. These changes are linked to significant epigenetic modifications, including DNA methylation and histone alterations. Epigenetic mechanisms, which alter gene expression without changing DNA, are crucial in linking ELS to adult neurobehavioral outcomes. While DNA remains stable, epigenetic marks change significantly during early development, influencing tissue-specific expression. Key epigenetic regulation methods in mammals include DNA methylation, histone modifications (like acetylation and phosphorylation), and non-coding RNA regulation (Vaiserman and Koliada 2017).

3. Brain Imaging Insights: How ELA Shapes Neurodevelopment and Mental Health

Brain imaging shows structural changes in adults who faced ELS, as well as in abused children and those with PTSD from maltreatment (De Bellis et al. 2002). These findings indicate that brain abnormalities might exist before disease onset, posing a risk for stress-related neuropsychiatric disorders. However, interpreting retrospective studies is challenging due to varying traumatic experiences, stressor timing and intensity, and medication effects (Cohen et al. 2006). Clearly defining and controlling the type and duration of stressors, as well as the developmental stage during stress exposure, is crucial to determine if brain abnormalities existed before illness or are due to disease progression. Studies show that the hippocampus, cerebellum, prefrontal cortex, and corpus callosum are particularly vulnerable to ELS due to their prolonged postnatal development, high

glucocorticoid receptor levels, and, in the case of the hippocampus, postnatal neurogenesis. ELA to cause epigenetically regulated, vulnerability to depression changes and induced programming astrocytes and ELS accelerates behavioral and neural maturation(Molet et al. 2016).

3.1. ELA: Balancing Resilience and Vulnerability in Behavioral and Mental Health

ELA significantly impacts behavioral and mental health. While ELA leads to dysfunctions, brief exposure may enhance resilience (Bahari-Javan et al. 2017; Bock et al. 2014; Burkholder et al. 2016). In a mouse model, long-term separation stress (LTSS) caused depressive behaviors, while short-term separation stress (STSS) reduced them. STSS increased dopamine receptor D1 (DRD1) expression and decreased DARPP-32 levels, linked to epigenetic changes. Conversely, LTSS raised DARPP-32 without affecting DRD1 or histone acetylation. These results suggest that ELA alters dopaminergic pathways, influencing depressive symptoms based on exposure duration (Cirulli et al. 2015; Walker et al. 2017). The effects of ELA vary based on the type, intensity, and duration of the stress experienced. Most studies on stress focus on vulnerability and negative behaviors, but emerging evidence suggests that brief or intermittent ELA can enhance behavioral flexibility and adaptation. This occurs through cellular mechanisms that promote stress resilience (Gröger et al. 2016; Kunzler, Braun, and Bock 2015; Peña et al. 2014; Ziabreva et al. 2003). Essential factors for adapting to environmental challenges include temporary or lasting epigenetic changes, as demonstrated in various animal and human studies. Cognitive deficits, particularly memory impairments, are linked to ELA and are often seen in neuropsychiatric disorders like depression and schizophrenia. These conditions arise from genetic and environmental factors, especially after early stress. However, not all individuals exposed to such adversity experience cognitive issues, making it difficult to identify those at risk and implement targeted interventions (Azzinnari et al. 2014; Jin et al. 2015).

3.2. Hippocampal Vulnerability: How ELA Influences Depression Risk

Early adverse experiences like parental loss and maltreatment increase the risk of depression later in life. Research suggests that stress during critical developmental periods leads to lasting changes in the limbic-hypothalamic-pituitary-adrenal system, making individuals more sensitive to stress and contributing to depression's onset and persistence. Preclinical research shows the hippocampus is vulnerable to stress due to its development and high GR. Smaller hippocampal volumes are linked to ELA and depression, but the connections among these factors are unclear (Rao et al. 2008; Gould and Tanapat 1999; MacMaster et al. 2008; Kim et al. 2004). The hippocampus is not only sensitive to stress hormones. Its vascular network also supports memory, spatial tasks, and emotional control. Damage to hippocampal vessels and endothelial cells can disturb local blood flow and tissue function. This point is relevant to ELA because early stress is linked to hippocampal structural change and later cognitive problems (Azedi and Joghataei 2026). Maternal separation is a common animal model for the study of ELS. A recent study in adolescent male rats assessed intranasal oxytocin after maternal separation and focused on hippocampal histophysiology. This evidence supports the idea that early separation can be linked to hippocampal tissue changes and that oxytocin may be relevant to stress-related hippocampal changes (Najafabadi et al. 2026).

One theory suggests ELA may indirectly lead to depression through reduced hippocampal size. Alternatively, ELA could exacerbate depression in those with smaller hippocampi, or both factors might together cause hippocampal changes, particularly in depressed individuals with ELA. Smaller hippocampal size may result from a depressive disorder rather than indicating vulnerability, with size decreasing as the illness worsens. However, research shows mixed results; some adults with longer illness durations have smaller hippocampal volumes, while depressed adolescents often have shorter illness durations yet also show reduced volume. Studying at-risk individuals could clarify if hippocampal deficits precede depression. Currently, there are no reports on hippocampal volume in high-risk groups, though one study noted standard hippocampal shape in non-affected co-twins of depressed individuals (Rao et al. 2010). A 2025 study examined 179 women aged 30–60 years, assessing the impact of ELS on neuroinflammation, brain volume, and cognitive function. Findings revealed that higher ELS severity correlated with increased serum concentrations of neurofilament light chain (NfL) and GFAP, indicating neurodegeneration. Additionally, participants exhibited reduced total and subcortical gray matter volumes, increased third ventricular volume, and cognitive impairments. These results suggest that ELS exacerbates peripheral, neurostructural, and cognitive markers of brain aging, highlighting the need for early prevention strategies targeting developmental stress impacts.

3.3 The Influence of ELA on Microglial Function and Brain Health

Another study found that ELA led to the activation of microglia in the hippocampus and prefrontal cortex of mice. These changes were linked to increased immobility in the forced swim test and reduced ability to recognize new objects in memory tasks. Additionally, genes like BDNF and Arc were altered in the hippocampus. The effects were gender-dependent, suggesting that ELA impacts microglial function and behavior differently between sexes (Bachiller et al. 2022). A study revealed that ELA induces immune memory in microglia, which could increase the risk of neurodegenerative diseases later in life. This study emphasizes the role of microglia in linking ELA to these diseases and ELA resulted in cortical thinning and increased glial density in the prefrontal cortex in adults. These structural changes were linked to cognitive and psychiatric disorders, indicating that ELA may alter the normal development of the brain and Research showed that ELA leads to microglial activation and an enhanced inflammatory response after brain injury in adulthood. These changes were associated with increased neuronal death and worsened recovery of function, suggesting that ELA may exacerbate brain damage. A 2024 study investigated the long-term effects of early-life stress on microglial gene expression and function. The research found that ELS leads to persistent alterations in microglial transcriptomic profiles, affecting their response to immune challenges. These changes may contribute to neuroinflammatory processes and neurodegenerative diseases later in life, emphasizing the importance of understanding microglial dysfunction in the context of early-life adversity (Reemst et al. 2022).

3.4. The Influence of ELA on Astrocyte Function and Brain Health

ELA in humans is linked to neurological issues like MDD (Major depressive disorder) and (SCZ) schizophrenia (Akhondzadeh 1999; Allen 2013, 2014; Allen and Eroglu 2017). A study demonstrated that ELA leads to dysfunction in astrocytes in the amygdala of mice. These dysfunctions were associated with increased neuronal excitability, reduced synaptic plasticity, and generalized fear memory. This suggests that astrocytes play a crucial role in emotional memory and its connection to ELA and Research indicated that ELA causes vascular damage and increased amyloid-beta deposition in a mouse model of Alzheimer's disease. These changes were more pronounced in female mice, suggesting that ELA may accelerate the progression of Alzheimer's disease (Guayasamin et al. 2022). Studies show that astrocyte dysfunction is significant in MDD, particularly in younger patients, with postmortem findings revealing reduced astrocyte numbers and abnormal morphology in key brain regions. In SCZ, astrocyte changes are inconsistent, but some studies indicate both increases and decreases in numbers (Alvarez, Katayama, and Prat 2013). Treatments for MDD have been shown to restore astrocyte function, suggesting that targeting astrocytes could be crucial for therapeutic strategies and understanding their role in mood disorders related to ELA (André et al. 2017; Araque et al. 2014). Astrocytes integrate various signals from their environment to modulate neuronal function, playing key roles in brain processes like glutamate recycling, myelination, and energy metabolism. They promote synaptogenesis and influence dendritic maturation in adult neurons, suggesting a role in neurogenesis regulation. Astrocytes form the tripartite synapse, affecting up to 140,000 synapses, and synchronize neuronal activity. They also regulate synapse development and modulate transmission quickly, clearing glutamate to prevent excitotoxicity(Araque et al. 1999; Argente-Arizon et al. 2018). Additionally, astrocytes respond to environmental changes by adjusting extracellular factors, including metabolites and neurotransmitters. Astrocytes can sense and coordinate various signals from the early-life environment. ELA may affect astrocytes, leading to lasting impacts on brain development and function. Astrocytes are vital for brain development, with their maturation influenced by ELA (Autry et al. 2006; Balasingam et al. 1996; Balland and Cowley 2017). In rodents, they originate from neural progenitor cells, radial glia, or local proliferation, starting development late in embryogenesis and peaking in the first month postnatal. By the second week, astrocytes form distinct domains and mature further by weeks three and four (Barros et al. 2006; Bazargani and Attwell 2016). In humans, astrogenesis begins late in gestation and continues postnatal. Astrocytes integrate local and systemic signals from their environment, including neurotransmitters, nutrients, hormones, and factors related to metabolism, inflammation, and stress. This integration is crucial for neuronal development and function throughout life. (Berkiks et al. 2019; Bilbo and Schwarz 2009; Bilbo and Schwarz 2012; Bland et al. 2010). Astrocytes play a crucial role in sensing and supplying nutrients to neurons, especially during the brain's rapid development, which requires high energy. A lack of nutrients early on can affect brain function later. Positioned around blood vessels, astrocytes regulate the blood-brain barrier and nutrient entry (Bohn et al. 1991). They specifically sense glucose levels, using GLUT1 to absorb glucose, which is stored as

glycogen for energy. Astrocytes can also convert glucose to lactate for neurons under high-energy demands, though this is debated (Boneva et al. 2011; Boyles et al. 1985; Braun et al. 2009). Astrocytes are vital for brain lipid metabolism, essential for development and function. Lipids, particularly polyunsaturated fatty acids (PUFAs), support neurite growth, synaptic transmission, and neurogenesis. Astrocytes also synthesize lipids, including cholesterol, and transport them to neurons, unlike neurons that struggle with lipid synthesis. The brain's lipid uptake is debated, with some lipids entering freely while others require synthesis (Brown and Susser 2008). Astrocyte lipid uptake also influences energy regulation and body weight control. Defective lipid metabolism in astrocytes can lead to neurological issues. The high nutrient and energy needs for brain development suggest that ELA may impair astrocytes' ability to support neurons, potentially leading to long-term effects on brain structure and function.

Astrocytes and microglia collaborate in brain immunity, with astrocytes responding to inflammatory signals and producing cytokines (Buckman et al. 2015; Burke et al. 2013). ELA alters neuroimmune profiles and impacts brain function. Microglia initiate immune responses, influencing astrocyte behavior, which can lead to reactive gliosis and glial scar formation. Reactive astrocytes can be neurotoxic (A1) or protective (A2), affecting neuronal health. Astrocytes also regulate microglial activity and can phagocytose synapses(Bushong, Martone, and Ellisman 2004). The interplay between astrocytes and microglia in response to ELA is not fully understood, but initial evidence suggests early inflammatory events may program astrocyte functions. Astrocytes are the first brain cells to encounter stress hormones like glucocorticoids, which bind to their receptors and affect their function. Stress hormone corticosterone (CORT) reduces GFAP expression and inhibits astrocyte proliferation, while lower CORT levels increase GFAP (Bushong et al. 2002; Calderon and Kim 2004; Camargo et al. 2012; Camargo et al. 2017). Glucocorticoids also impair glucose transport and glycogen levels in astrocytes, potentially disrupting energy supply to neurons. Elevated glutamate during stress can impact synaptic transmission. Overall, stress hormones significantly influence astrocyte functions essential for normal brain activity, but the effects of ELA on astrocytes and glucocorticoids require further investigation (Cano et al. 2014; Carter, Hamilton, and Thompson 2013). ELA influences astrocytes through environmental signals, including nutrition, immune responses, and stress. Astrocytes play a key role in integrating these signals, which may affect brain development and the risk of disorders linked to ELS. Rodent models, such as maternal deprivation and malnutrition, are crucial for studying these effects. Most research uses GFAP expression as a marker for astrocytes, but changes in GFAP levels may not accurately reflect overall astrocyte numbers, as they can alter their expression profiles instead (Catalani et al. 2002; Champeil-Potokar et al. 2016; Chih and Roberts Jr 2003). Experimental evidence from rat brain injury models also supports this point. Babaee et al. studied the effect of melatonin after traumatic brain injury in rats. They measured GFAP-positive astrocytes and apoptotic neurons in the hippocampus and dentate gyrus. Melatonin reduced astrocyte reactivity and neuronal apoptosis after neural damage. These findings are not direct evidence from an ELA model, but they support the idea that hippocampal astrocytes are sensitive to neural injury and can change after a protective treatment. This evidence may help explain why early-life stress can affect later glial responses in vulnerable brain regions such as the hippocampus (Babaee et al. 2021). Human iPSC models (induced pluripotent stem cell model) are crucial for studying astrocytes in ELA, highlighting the genetic risk for neuropsychiatric disorders. These disorders involve polygenic risks, making rodent models inadequate. GWAS for SCZ and MDD reveal hundreds of implicated genes. IPSC technology enables the creation of human-specific models that reflect the donor's genetic background, facilitating studies on how genetic and environmental factors interact to influence pathology. Recent studies highlight the potential of iPSC technology in understanding neuropsychiatric disorders like SCZ and MDD, particularly through astrocyte dysfunction linked to ELA. While iPSC models have revealed cell-autonomous deficits in SCZ, further research is needed on astrocyte subtypes and their roles in these diseases. Enhanced knowledge of astrocyte biology and their environmental responses could illuminate how ELA influences astrocyte programming, ultimately improving our understanding of these conditions (Choi, Maulucci-Gedde, and Kriegstein 1987; Chowen et al. 2016; Christopherson et al. 2005; Chugani et al. 2001; Chung et al. 2013; Cirulli 2017). Maternal deprivation (MD) and Maternal separation (MS) are common models for studying ELS effects. Male rats showed decreased GFAP reactivity and cytoskeletal complexity in the hippocampus and cortex after MS and MD within 24 hours. In Octodon degus, MD reduced GFAP+ astrocyte density and altered astrocytic processes, while increasing S100β+ cells. Initially, GFAP levels dropped, but increased weeks later in various brain regions, suggesting a delayed response to stress. This pattern may relate to the dynamics of CORT response during stress, where acute CORT elevation reduces GFAP,

followed by a compensatory increase once CORT levels normalize, indicating a potential shift in astrogenesis. Studies show that daily MS increases GLAST and GLT-1 in hippocampal astrocytes of rats, while limited nesting decreases GLAST in the hypothalamus, affecting glutamate uptake. This suggests that glutamate transporter expression is altered by brain region and stress model. Glucocorticoids may play a role, as stress raises glutamate and GLT-1 levels. MS may upregulate transporters to manage excess glutamate. Additionally, GFAP loss could impair GLT-1 trafficking, affecting glutamate metabolism regionally (Claessens et al. 2012; Cobb et al. 2016; Connor et al. 2012; Couvreur et al. 2011; Crossin et al. 1997). ELS, such as MD or MS, appears to temporarily impact GFAP expression and permanently change astrocytic glutamate transporter levels, despite being based on a limited number of studies.

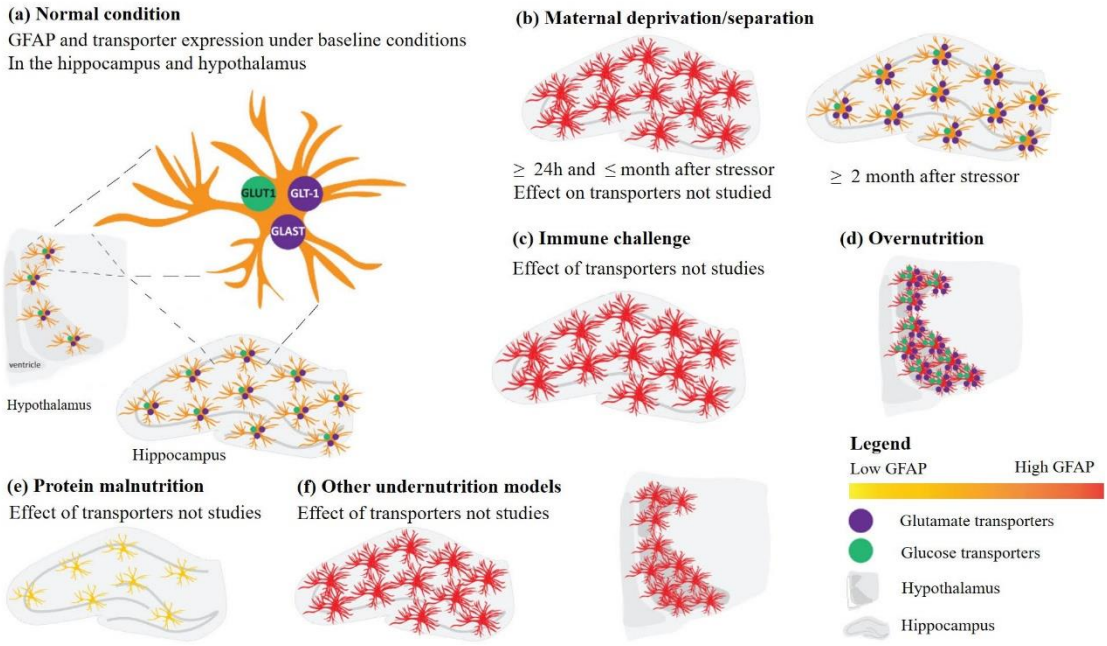

Figure. 1 The long-term effects of ELA on astrocyte characteristics. This figure summarizes the lasting effects of different forms of ELA on the expression of GFAP+ astrocytes and glutamate and glucose transporters. In panel a, a healthy astrocyte under basal conditions is depicted. The remaining panels represent deviations from this following the various forms of ELA. For the conditions where transporter expression was not studied, transporter expression is not included in the figure. (a) Astrocyte under healthy basal conditions in hippocampus and hypothalamus express GFAP, glutamate transporters (GLT-1 and GLAST), and glucose transporters (GLUT1). (b) MD and MS increase GFAP on the short-term. On the long-term, while GFAP returns to basal levels, there is a persistent increase in glutamate transporters. (c) Early-immune challenge increases GFAP expression. (d) Overnutrition increases GFAP, glutamate transporter, and glucose transporter expression. (e) PMN decreases GFAP expression. (f) Other undernutrition models increase GFAP expression (Abbink et al. 2019)

Studies show that neonatal exposure to substances like LPS and Poly I: C leads to increased astrocyte size and numbers in the hippocampus, lasting until weaning and beyond. In contrast, postnatal E. coli exposure did not affect astrocyte proliferation by P33, indicating that effects may vary by immune challenge. Prenatal IL-6 exposure also raised astrocyte density and GFAP levels in the hippocampus by 24 weeks. Microglial activation was noted but normalized over time. Alterations in astrocytes due to ELA may not be evident until a subsequent stressor occurs, revealing increased vulnerability. Studies indicate that offspring exposed to stress show heightened sensitivity of astrocytes to immune challenges later in life. ELA could induce a proinflammatory state in glial cells, leading to exaggerated infection responses. The nature of astrocyte priming whether beneficial or harmful is debated. Additionally, early-life factors like diet and metabolism may influence the effects of ELA, contributing to cognitive decline and psychopathology (Dalvi et al. 2017; Danielewicz, Trenk, and Hess 2017; De

Rooij et al. 2010; Derks et al. 2016; Ganguly and Brenhouse 2015). Recent studies highlight the impact of unhealthy high-fat and high-sugar diets on brain function, mainly focusing on hypothalamic astrocytes, which regulate food intake and respond to metabolic changes. Maternal high-fat diets during pregnancy and lactation increase astrocyte density and complexity in offspring, affecting brain regions like the arcuate nucleus and hippocampus. These changes persist into later life, with evidence of altered protein levels and astrocytic processes, although the specific causes related to omega-3 deficiency or high-fat intake remain unclear (Abbink et al. 2019).

3.5. Neural Development Disruption Due to ELA A Pathway to Behavioral Issues

ELA disrupts neural development by reducing cell birth, increasing cell death, and changing neuronal structure, linked to behaviors suggesting early maturation. ELA affects neural development, raising the risk of cognitive and emotional issues. It disrupts neural circuitry, contributing adverse outcomes. (Avishai-Eliner et al. 1999). In the developing hippocampus and cortex, ELA or stress hormones result in reduced cell growth and increased cell death. Enhanced turnover and loss of dendritic structures, decreased synaptic density, and reduced brain volume occur during adolescence and adulthood. Stress in adults leads to similar effects, including dendritic simplification and cell death, suppressing neurogenesis. These findings suggest that ELA disrupts neural development, resulting in behavioral issues often seen as developmental delays(Champagne and Meaney 2001). ELA resulted in an earlier onset of developmental suppression of fear behavior linked to the hippocampus. Gene expression and immunohistochemistry revealed that ELA accelerated the appearance of neural maturation biomarkers while silencing those related to cell growth and differentiation. This supports the idea that ELA triggers an early transition from growth processes to neural and behavioral maturation in the hippocampus (Bath, Manzano-Nieves, and Goodwill 2016).

4. ELA: Implications for Lifelong Mental Health and Emotional Regulation

Early experiences significantly influence lifelong functioning, with the average onset of mental health disorders at age 14, primarily during childhood or adolescence. This indicates that early adversity increases the risk of mental health issues later in life. Most research focuses on existing disorders, but understanding the developmental pathways is crucial for identifying and treating at-risk individuals early. Animal models are essential to studying ELA due to ethical challenges in human research. Research, mainly in rodents, shows that ELA impacts emotional learning systems, increasing mental illness risk (Chao et al. 1992; Ashbolt 2004; Babenko, Kovalchuk, and Metz 2015). For instance, stressed infant rats shift from approaching to avoiding shock-associated odors earlier than non-stressed peers. They also retain learned fear longer and show more significant relapse after extinction training. These findings indicate that ELA can lead to heightened emotional responses and persistent fear, contributing to future mental health issues (Bale 2015; Banyard 1997). For instance, MS increases corticosterone in infant rodents and primates, while elevated CRF in adolescents correlates with amygdala growth and anxiety. Additionally, stressed animals show early development of fear responses linked to amygdala activity, suggesting that early stress may accelerate emotional regulation development (Beach et al. 2011; Bercik et al. 2011; Betancourt 2015). Early stress exposure impacts children's neural development, evidenced by altered cortisol levels and neuroendocrine changes. While human findings vary due to different methodologies, studies show that stress leads to advanced emotional neural circuitry.

Early stress can significantly impact biology and behavior, potentially leading to adverse effects on future generations (Betancourt et al. 2015; Boles et al. 2005; Bruce et al. 2013).

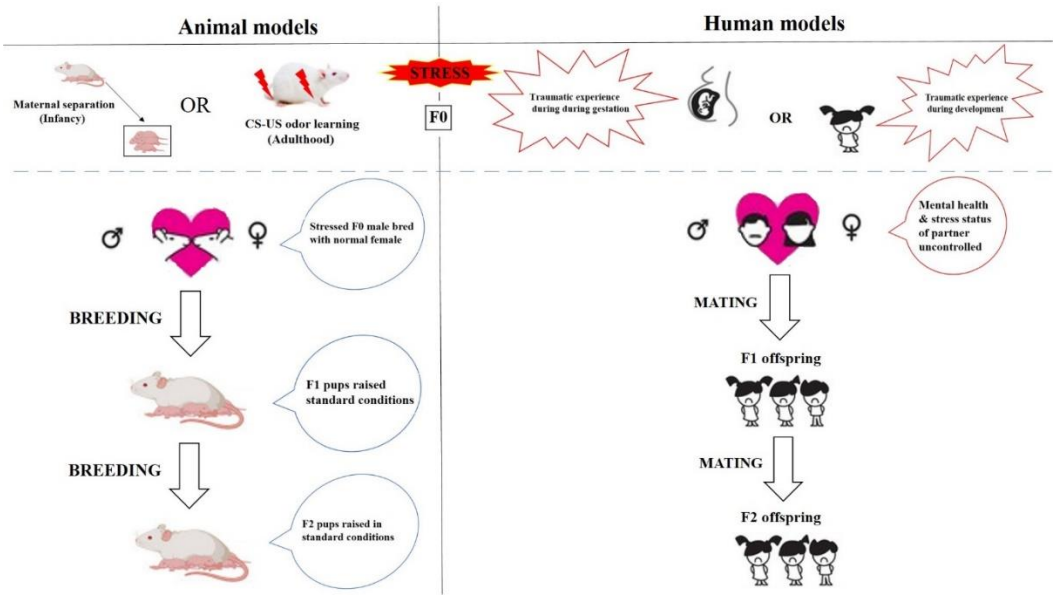

Figure. 2 Various models of early-life stress and stressful learning experiences have been used to study the transmission of stressed phenotypes across generations in both humans and rodents. In this review, the terminology 'F0' is used to refer to the individual/generation directly exposed to stress. In rodent studies, F0 males are typically bred with experimentally naïve, unstressed females to produce the next generation. These offspring, known as the 'F1' generation, are not directly exposed to stress. Similarly, F1 males can be bred with naïve females to produce a further 'F2' generation. In studies of humans, the children and grandchildren of stressed individuals can be similarly labeled as the F1 and F2 generations, respectively. However, the stress exposure of mating partners and offspring is difficult to control in humans (Cowan et al. 2016)

Significant historical events, like the Dutch famine (1944-1945), have allowed researchers to study intergenerational stress transmission. Prenatal malnutrition leads to physical underdevelopment and increased coronary heart disease risk in offspring. Additionally, those exposed in utero showed higher rates of schizophrenia and depression(Cowan et al. 2016). Similar effects were noted in children of mothers exposed to disasters or violence, such as the Tangshan earthquake and the 2001 World Trade Centre attacks, where maternal PTSD correlated with low cortisol levels in infants. These findings highlight how parental trauma influences offspring development. The effects of stress can be passed down through generations, as seen in children of combat veterans and Holocaust survivors, who show higher rates of psychological issues like depression and PTSD. Studies indicate that these risks are linked to parental trauma, with maternal PTSD particularly influencing offspring. Additionally, research from Sierra Leone shows that caregiver mental health impacts adolescent symptoms. Overall, these findings demonstrate the increased risk of psychiatric disorders in children of trauma-exposed parents, suggesting a biological and behavioral transmission of stress-related traits (Dias et al. 2015; DiLillo and Damashek 2003; Dinan, Stanton, and Cryan 2013; Ehrensaft et al. 2015). Parental behavior can transmit trauma to offspring through altered parenting styles. Post-trauma, caregivers often exhibit atypical behaviors, such as role-reversing parenting, where children fulfill parents' emotional needs, hindering the child's autonomy. Studies show that trauma leads to destructive parenting, increased violence, and emotional neglect, impacting child mental health. Adult children of trauma survivors report higher childhood abuse levels (Fairbanks et al. 2011; Field et al. 2011; Field, Muong, and Sochanvimean 2013). Additionally, parents with a history of abuse tend to be emotionally disengaged and use harsh discipline. These patterns suggest that parental trauma has lasting effects, increasing the risk of mental health issues in future generations. Animal studies support that parental care influences offspring development amid environmental stress. Meaney's research emphasizes maternal care's role, linking low care to increased stress responses and the passing of behaviors through generations (Francis et al. 1999; Franklin et al. 2010; Gapp et al. 2014; Gardner et al. 2010). Female rodents in social isolation exhibited reduced maternal care, affecting their offspring's behavior, leading to decreased exploration and increased anxiety-like traits in the next generation. Research on rodent stress transmission includes both vertical (across generations)

and horizontal (within generations) studies. One study showed that stressed mothers exhibited less nurturing behavior, leading to increased anxiety in their offspring, which persisted in subsequent generations without further stress (Gareau et al. 2006; Gareau et al. 2007; Gee and Casey 2015; Cowan et al. 2016).

5. From ELA to Lifelong Challenges: The Neurodevelopmental and Immune Impacts of ELA

Early exposure to stress can lead to lifelong mental health vulnerabilities due to disrupted neurodevelopment and neuro-immune functions. Early life experiences significantly impact mammalian brain development. Positive environments with reasonable care and stimulation foster resilience against later stress and health issues (Andersen and Teicher 2009). Conversely, ELA, like neglect or abuse, leads to various brain and health problems. Modeling ELA is irrelevant as there's no single exposure type; brain plasticity is experience-dependent. Studies show that gray matter, cortical thickness, and white matter vary with ELA exposure. Animal research indicates that stress affects dendritic structure and synapse numbers in key brain areas like the hippocampus and PFC, impacting cognition, emotional regulation, and neuroendocrine function. These changes can result from excitotoxicity(Behan et al. 2011; Behrens and Sejnowski 2009; Bilbo, Smith, and Schwarz 2012). ELA highlights stressors affecting the brain during crucial developmental stages before adolescence. ELA affects the immune system during exposure and can change the development of immunological processes, leading to more potent immune responses to stress later in life. This heightened response offers an evolutionary advantage, as stress often coincides with physical threats (Brown et al. 2004). A notable effect of increased inflammation is sickness behavior, characterized by lethargy, social withdrawal, and lack of pleasure, which helps the organism focus resources on combating pathogens and recovering from illness. Sickness behavior resembles major depressive disorder in both symptoms and immune response. This suggests that immunity plays a role in depression linked to ELA. The long-term effects of ELA can be interpreted as either a consequence of or a stress reaction, highlighting the need to explore the reasons behind mental illness vulnerability following ELA. ELA makes children view their surroundings as threatening, feel worthless, and distrust the future. This history heightens the risk of psychiatric disorders in adulthood. Models like allostatic load and reactive scope help explain the psychopathological effects of ELA, linking them to dysfunctions in neural, endocrine, or immune systems. Additionally, ELA's impact on allostatic load may predispose individuals to stress-related disorders later in life. Individuals exposed to ELA experience earlier onset of disorders like depression and substance abuse, along with higher self-harm risk and poorer treatment responses compared to non-maltreated individuals. These findings highlight significant differences between ELA-affected individuals and those facing later stressors, emphasizing the need to explore the biological and behavioral impacts of ELA throughout life (Burghy et al. 2012; Carr et al. 2013; Chao et al. 1992).

CONCLUSION

This review demonstrates that ELA significantly affects various living tissues, the nervous system and its cells, as well as the immune system. These effects are associated with structural and metabolic changes that may impact neural and other physiological functions. Most research on the CNS has focused on glial cells specifically astrocytes and the expression of GFAP. However, the functional consequences of changes in GFAP expression remain unclear. Notably, ELA can lead to functional deficits even without alterations in GFAP levels. Given the role of astrocytes in cognitive impairment, it is crucial to understand their contribution to adult psychopathologies associated with ELA. Technological advances, such as induced pluripotent stem cell (iPSC) models, may enhance our understanding of these mechanisms and their relevance to ELA-related disorders. Therefore, a comprehensive understanding of the adverse environmental conditions experienced in early postnatal life may help prevent the development of cognitive and functional disorders such as depression and anxiety as well as transient and permanent changes in body tissues.

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Data Availability:

This study includes no data deposited in external repositories. See also Guide for Source Data Submission.

Ethics, Consent to Participate, and Consent to Publish declarations:

Not applicable.

Conflict of interests:

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