



Early Life Stress, Neuroinflammation, and Psychiatric Illness of Adulthood

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Abstract

Stress exposure during early stages of life elevates the risk of developing psychopathologies and psychiatric illness in later life. The brain and immune system are not completely developed by birth and therefore continue develop after birth; this post birth development is influenced by several psychosocial factors; hence, early life stress (ELS) exposure can alter brain structural development and function. A growing number of experimental animal and observational human studies have investigated the link between ELS exposure and increased risk of psychopathology through alternations in the immune system, by evaluating inflammation biomarkers. Recent studies, including brain imaging, have also shed light on the mechanisms by which both the innate and adaptive immune systems interact with neural circuits and neurotransmitters, which affect psychopathology. Herein, we discuss the link between the experience of stress in early life and lifelong alterations in the immune system, which subsequently lead to the development of various psychiatric illnesses.

Keywords

Early life stress · Psychopathology · Psychiatric illness · Inflammation · Cytokines · Neuroinflammation · Immune system

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6.1 Introduction

Both positive and negative experiences in early life can have profound effects on mammalian brain development. In particular, early life stress (ELS) is associated with increased risk of both mental and physical health deterioration throughout life [1–3]. Approximately 12% of youth, from infancy to age 18 years, experiences ELS to such an extent that they will have mental and physical health discrepancies throughout life [4, 5]. These individuals who account for almost half of all mental disorders [6] experience approximately 44% increase in strokes and heart attacks [7] and elevated risk of death by age 50 years [8, 9].

Generally, two main criteria, namely, the developmental age range of early life and the characteristics of stressful events, should be considered when defining ELS. Previous studies have considered an upper age limit between 12 and 18 years as early life. Regarding the stress criterion, various models have proposed that stress is experienced when an individual faces a threatening situation for which adequate coping skills are not available. Disruption to physiological homeostasis also induces stress responses. A certain event occurring within a defined developmental term may be classified as ELS. Thus, ELS can be defined as an injury, potential of injury, or threat of injury generally caused by a child's caregiver [10]. This definition includes different stressful experiences, such as the death of a caregiver, neglect, bullying, emotional maltreatment, and physical and sexual abuse. However, emotional and physical abuse and neglect are the most common patterns of harm reported [11].

The most major forms of ELS in individuals are neglect (physical or emotional), abuse (physical, emotional, or sexual), and parental loss (death, or separation). The number of abused children reached approximately 520,000 in the United Kingdom in 2011, which has since increased [12]. According to a large-scale epidemiological study on adverse childhood events, approximately 65% of individuals in the United States have been exposed to at least one event, while 12.5% have been exposed to as many as four [13]. Adults reporting ≥ 4 ELS are 4.6 times more likely to experience depression and 12.2 times more likely to attempt suicide compared to those with no ELS exposure. Gilbert et al. found that children self-reporting physical and emotional abuse is estimated at up to 29% and 33%, respectively, in Eastern Europe [14].

Approximately 8% of males and 20% of females experience childhood sexual abuse, with the highest prevalence in Africa (34.4%), followed by Asia, America (10.1%), and Europe (9.2%) [15]. Physical abuse, the intentional use of physical force that harms the child's development, survival, or dignity, is estimated at 17.6% [16]. Meanwhile, psychological abuse, the failure to give children enough supportive environment, may also be more than physical and sexual abuse but is more difficult to estimate [17]. Neglect, the failure of a caregiver to provide for a child's basic needs, is the most major ELS affecting 78.5% of children in the general population. Other forms of ELS include natural disasters, physical diseases, surgeries, accidents, and events such as terrorism or war. Less salient experiences with significant distress on children include poverty, unstable families, poor parental care, and dysfunctional relationships between parent and children. ELS can be often

complex, with different forms simultaneously coexisting and can happen as chronic or ongoing stress.

ELs are associated with an elevated risk of noncommunicable diseases in adulthood [18–21] and premature mortality [22], possibly mediated by a dysfunctional immune system, particularly chronic low-grade inflammation [23–25]. The dysregulated immune responses could be prone to developmental programming attributed to ELS exposure that only trigger an excessive stress response at onset, but also influencing long-term stress responses, leading to chronic low-grade inflammation [26, 27]. The immune system responds to foreign invaders [28], and both human and animal researches have shown that ELS can cause persistent inflammation, which could develop psychiatric problems through effects on brain development and response to stressors [29].

The brain and immune system are not fully developed at birth, yet have minimal functions in newborns that enable adjustment to limited and expected stimuli. The ongoing maturity of the immune system throughout infant and childhood indicates that environmental effects and stimulation during childhood can seriously affect the immune system. Therefore, the brain and immune system experience during early postnatal development progressively increases their repertoire to maximize adaptation to stimuli specific to the individual's own environment [1, 30, 31]. Notably, ELS gives rise to various aberrations in brain circuitry, cognitive function, and general health [32–34] and the immune system may also play a unifying role in the pathophysiology of these multifactorial diseases related to ELS. Herein, we provide an overview of the current evidence connecting ELS to elevated inflammation and subsequent risk of psychiatric disorders.

6.2 Early Life Stress and Inflammation

6.2.1 Experimental Animal Studies

The first report for the effect of ELS on the immune system came to light from experimental animal models more than half a century ago. Mouse handled before the process of weaning exhibited a decreased rate of development in transplanted tumor [35] and elevated serum antibody titer in response to the bacterial protein flagellin [36]. These results attracted interest in the area of developmental psychoneuroimmunology [37–39], which facilitated subsequent studies on the association between ELS and immune functioning in later life in rats and nonhuman primates [40, 41].

Experimental animal models have expanded our understanding of the relationship between ELS and immune system abnormalities and allowed for invasive procedures to investigate immune function since components in the immune system can be targeted with drugs during and after ELS to determine the adverse health outcomes. ELS in rats has been manipulated through various experimental models with heterogeneous effects on parental caregiving behavior, such as nursery rearing, maternal separation (MS), maternal deprivation, neonatal handling, and dexamethasone exposure. Measures of immune function range from pro-inflammatory

cytokines and chemokines in the plasma and antigen-specific immune response to pro-inflammatory gene expression in the brain and gut microbiota.

MS has been commonly used in animal models of ELS. In nonhuman primates, MS increased macrophage activity [42] and upregulated long-term pro-inflammatory gene transcription in monocytes [43]. In rats, MS elevated core temperature [40] and pro-inflammatory cytokines in the plasma [44, 45]. These findings demonstrated the association between MS and inflammatory processes in later life.

Using a mouse model, a previous study has reported that MS results in a loss of prefrontal cortex (PFC) interneurons [46], underlying a supposed mechanism of schizophrenia associated with inflammatory and excitotoxic damage [47]. In an animal model undergoing repeated MS (RMS), elevated hippocampal interleukin-1 β (IL-1 β) mRNA levels approximately 20 times that of the control have been reported [48]. One study also showed elevated NF- α expression in the PFC of animals sacrificed on the day of their final MS episode [49], while another reported that MS animals sacrificed immediately after their final episode had higher hypothalamic tumor necrosis factor- α (TNF- α) than those with a single episode of MS sacrificed simultaneously [48]. In animals sacrificed on the final day of MS, elevated interleukin-10 (IL-10) expression was identified in the PFC and small intestine but not the hippocampus or serum [49, 50].

In pups, MS during brain development is associated with reduced lipopolysaccharide-binding protein expression in the hippocampus [51] and decreased microglial cell numbers in the midbrain [52]. In contrast, early MS in adult animals increases synaptic levels of pro-inflammatory cytokine interleukin-1 (IL-1) receptor [53], elevates the number and motility of cortical microglial processes [54], and exacerbates microglial activation [55]. Moreover, mice experiencing MS have a higher elevation in body core temperature after a second MS, increased cytokine expression followed by viral infection [56], and greater cortical microglial activation following exposure to chronic food-restriction stress [55]. Although the peripheral response to ELS may not be mostly activated or suppressed, ELS-linked early immune programming seems to sensitize later pro-inflammatory processes and result in higher risk to depression and anxiety in adulthood [57]. Increased heart rate and inflammatory responses to a physiological stressor [58], as well as elevated TNF- α and interferon- γ (IFN- γ) and corticosterone levels, and anxiety-like behavior [59] in maternally deprived rodents have been shown.

ELS studies have recently reported overall increases in activation and number of microglial cells in various brain regions. Microglial cells sensitized in early life could show a dysregulated response and morphological changes in later life [60]. ELS may therefore convert a neuroprotective state to a pro-inflammatory state in microglia [48]. Moreover, microglial activation and increases could facilitate brain maturation [61]. Ex vivo studies on the early MS-induced damage on microglia have reported an overall elevation in the proportion of cells with an activated morphology in the hippocampus [48, 62, 63] and medulla [64]. Furthermore, using captured microglial cells in vivo, one study showed that somatosensory stimulation in adulthood caused a significantly higher increase in microglial motility

in MS mice compared to controls which could also affect microglia–synapse interactions and neuronal function [54].

Psychosocial stressors other than immune stimuli can also provoke a microglial response that may induce different responses to threats [65]. Gong et al. reported that 1 day of brief social isolation at postnatal day (P)14 elevated microglial density in the hippocampus, presumably by facilitating increases of these cells [66]. Four days following isolation (P14–17), the number of cells was restored to normal levels. In contrast, a week of brief social isolation (P14–21) in adulthood decreased microglial cell number in the dentate gyrus of the hippocampus. Concordantly, social defeat in adolescent mice triggers early increase of ionized calcium-binding adapter molecule (IBA-1) in the hippocampus and a following decrease in microglial cells and IBA-1 expression in adulthood [67, 68]. Furthermore, a milder social defeat paradigm adopted during the adolescent stage elevated microglia number, IBA-1 expression, and the size of soma in the ventral tegmental area of pups [69]. Adult mice experiencing repeated social defeat show significant elevation in neutrophils and CD11b⁺LyC6^{high} monocytes in the spleen and circulation [70, 71]. Splenic dendritic cells from mice experiencing repeated social defeat have shown greater surface expression of major histocompatibility complex class I, CD80, and CD44, suggesting an activated state [72]. Exposure to repeated social defeat in mice and low socioeconomic status in humans can also lead to a relative expansion of a transcriptional protein associated with immature pro-inflammatory monocytes in peripheral blood mononuclear cells [73]. Therefore, various types of social stressors in early life independently impact the development of the immune system, although the dysfunctional relationship between mother and infant may negatively affect health outcome.

Recent studies on the gut microbiota found that MS in rodent and nonhuman primate models also has transient and long-term effects on gut microbiota [59, 74]. ELS-induced changes of the microbiome in murine models continue during adulthood [75–77] and are linked to anxiety-like behaviors and activation of systems involved in stress [78]. Rats exposed to stress show inflammation, altered gastrointestinal function and leaky gut, and disturbances of immune activity [78]. Moreover, gut microbiota and dysregulated inflammation in rats or mice exposed to stress can regulate the metabolism of tryptophan to kynurenine or 5-hydroxytryptamine (5-HT) [79–81]. Inflammatory cytokines such as IFN- γ and interleukin-6 (IL-6) enhance indoleamine-2,3-dioxygenase (IDO) production, which subsequently metabolizes tryptophan to kynurenine, increasing kynurenine production and decreasing 5-HT levels [80]. Elevated kynurenine/tryptophan ratios have been recognized in rats with depression-like behavior, together with elevated pro-inflammatory cytokines and altered gut microbiota [81]. Furthermore, a study on *Flexibacter* and *Prevotella*, in connection with colitis, revealed that they were more abundant in the gut of MS rats [82], and concordantly, Wong et al. showed that caspase-1 inhibition, an inflammasome factor, restored stress-induced gut microbiota alterations [83].

6.3 Early Life Stress and Inflammation

6.3.1 Observational Human Studies

ELS can affect the immune system at the time of exposure [57, 84] and alter its normal developmental trajectory [85]. The exaggerated effects of ELS on the immune system are long term, resulting in chronic low-grade inflammation throughout life [86]. A large population-based study of almost 12,000 participants observed an association between increased white blood cell counts and ELS [87].

A meta-analysis demonstrated that adults with ELS have higher levels of C-reactive protein (CRP) and the major pro-inflammatory cytokines IL-6 and TNF- α as compared to adults without ELS [88]. Another meta-analysis reported a significant correlation between ELS and inflammatory markers, with effect sizes being greatest for TNF- α , followed by IL-6 and CRP. A recent meta-analysis showed a relationship between ELS and IL-1 β , IL-6, TNF- α , and CRP, but not interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-8 (IL-8), IL-10, or fibrinogen [89]. Moreover, Baumeister et al. reported that various types of ELS exposure differentially resulted in alterations of inflammatory markers [88]. Notably, physical and sexual abuse were associated with significantly elevated TNF- α and IL-6, but not CRP, which is mainly associated with parental absence during the early developmental period. Although the underlying pathophysiology remains nebulous, factors such as situation and duration of stress exposure may interact with individual stress types to regulate immune response.

Furthermore, a meta-analysis of 27 studies conducted by Kuhlman et al. evaluated the relation between ELS and inflammation in those under 18 years of age [90] and found small associations between ELS and inflammation that were statistically significant only for CRP. Meanwhile, other longitudinal studies have reported an association between ELS and elevated inflammatory markers in early adulthood [91, 92], thereby providing evidence for the relationships between ELS and increased peripheral CRP levels, particularly profound in those who develop subsequent depression in adult life [93, 94]. Danese et al. reported elevated inflammation levels in abused children who had depression at the age of 12 years compared to normal controls [95]. Increased CRP levels were also identified in 10-year-old children with recent onset of maltreatment and a genotype predisposing to elevated CRP levels [93]. Exposure to stressful events before the age of 8 years is associated with increased CRP at 10 and 15 years old [25]. Peripheral low-grade inflammation may describe the relationships between early-life stress and various physical or mental health outcomes [96–98]. To the best of our knowledge, there has been one study investigating the relationship between ELS and inflammation in preschool-aged children (3–5 years) which showed increased IL-1 β levels in connection with ELS [99]. In healthy community samples, ELS has been related to elevated IL-6, in response to the Trier Social Stress Test [100] and IL-1 β , interleukin-12 (IL-12), and TNF- α levels [101]. Furthermore, recent findings suggest that repeated exposure to ELS is connected with significant increases in soluble urokinase plasminogen activator receptor (suPAR) in young adulthood [102] and mid-adulthood

[92]. During activated immune and pro-inflammatory states, suPAR is discharged into the systemic bloodstream by cleavage of the membrane-bound urokinase receptor (uPAR) [103, 104] expressed on endothelial cells and immune cells [105]. While CRP and IL-6 are influenced by acute fluctuations in inflammation, such as during infections [106, 107], suPAR reflects a person's overall immune activity level and is predicted to be involved in low-grade chronic inflammation, tissue and organ damage [108, 109], development and progression of disease, adverse clinical outcomes, and mortality [110, 111] and thus is an effective and additional measure of persistent inflammatory response. Concordantly, suPAR is associated with ELS [92, 102] and adult stressful life events [112], whereas IL-6 and CRP are not persistently related to these kinds of stressors.

Granulocyte function, evaluated by ex vivo killing of *Staphylococcus aureus*, is decreased by 20% in children with divorced parents [113], which is in line with the findings of elevated vulnerability to *Staphylococcus aureus* in children exposed to acute or chronic family stress [114]. Moreover, reduced natural killer (NK) cell activity was related to stressful events in adolescents with depression or conduct disorder [115] and adult females with breast cancer [116]. However, increased NK cell activity has been identified in children whose parents showed more chronic stress, which is also associated with greater rates of febrile diseases in childhood, while this was not associated with NK cell activity [117]. Furthermore, Wyman et al. studied a younger population undergoing immune assessment [117] and observed an elevation in NK cell activity [118]. Meanwhile, Ayaydin et al., in a relatively small number of participants, also showed no significant difference in NK cell activity between control and sexually abused adolescents [119]. Sexual or physical abuse is associated with lower salivary IgA levels in young females, even though adult sexual victimization appeared to mediate this relationship [120].

Evidence of the relationship between ELS and increased reactive oxygen species (ROS) production, oxidative stress, and mitochondrial activity, which are associated with pro-inflammatory cytokine from different immune cells, has been reported [121]. Dysfunctional cellular immunity caused by repeated viral infections and reactivation of viruses elevates inflammatory markers including IL-6 and CRP [122]. Also, individuals exposed to ELS showed increased immune activation with higher CD25 expression, major histocompatibility complex, class II, DR (HLA-DR), or implicating CD8 T cells [123]. Moreover, adolescents exposed to ELS have decreased NK and NK T cells and increased circulating and senescent T cells with the activation markers CD3+/CD69+ and CD2+/CD4+/CD25+ [124, 125].

Positron emission tomography (PET) imaging of the mitochondrial translocator protein (TSPO) can provide insights on the microglial activation in the human brain. One study found that after peripheral lipopolysaccharide (LPS) injection, TSPO expression uniformly increased across the brain [126]. These findings allow for deeper assessment of neuroinflammatory markers to investigate microglial activation during brain injury and neurodegeneration. Interestingly, only one study has investigated microglial activation using TSPO-PET in individuals exposed to ELS [71, 127]; therefore, further investigations on the relationship between ELS and microglial activation are warranted.

Also, in line with findings from animal studies, results from human studies suggest that females may have higher sensitivity to stressful events in provoking a pro-inflammatory response than males [128, 129]. Moreover, evidence from an environmental risk study indicates that the levels of inflammation were already increased in children exposed to ELS who developed depression at the age of 12 years as compared to controls [95], while sex differences may influence the susceptibility to cause a pro-inflammatory state post ELS exposure [130]. CRP concentrations in 18-year-old females were significantly correlated with childhood victimization, yet no such correlation was observed in their male counterparts. According to the study by Entringer et al., the relationship between CRP levels and maltreatment was significantly mediated by child sex and were higher in the maltreated girls compared to the control group which was stable over the 2-year follow-up period, whereas no relationship between maltreatment and CRP levels was shown, suggesting that following ELS exposure at a very young age in girls, the effect of maltreatment may immediately emerge in an inflammation process and exacerbate over time.

In summary, peripheral inflammation caused by ELS can influence the brain and change neural activity through various routes, such as humorally via active transport of cytokines stimulated by the release of second messenger or cellular routes involving macrophage-like cells residing in circumventricular organs. Microglia can be activated by peripheral inflammation that enter the brain across the blood-brain barrier (BBB) with different routes [131]. Subsequently, microglia cells affect cell proliferation and survival in the brain based on their inflammatory state [126]. Microglial cells can undergo several alterations [132] such as pro-inflammatory cytokine production and expression of cell surface antigens related to oxidative stress in the brain. Peripheral LPS injection, used for immune challenge in primates, can increase TSPO expression uniformly across the brain. Recently, alterations in the gut microbiome have been reported in adults with ELS-induced PTSD [133]. Children exposed to ELS have also been reported in a study to exhibit gut microbiome alterations, with gut bacteria levels associated with PFC activation in an emotional face experiment [134]. Generally, the association between ELS-linked gut dysbiosis and inflammation is likely bidirectional [135, 136].

6.4 Inflammation and Psychiatric Illness

6.4.1 Experimental Animal Studies

Animal models are beneficial to investigate the pathophysiology due to their flexibility in randomly assigning animals to different rearing environments and allow for directly investigating the brain and immune system using techniques thought to be too invasive in humans. Inflammation can increase animals' responses to rewarding stimuli with reinforcers such as food or electrical stimulation [137]. Initial findings linking the immune function and psychiatric etiology, particularly mood disorders, originated from studies involving humans and animals with acute infection showing

stereotypical behaviors as featured by anhedonia, anorexia, and reduced grooming [138]. In line with the hypothesis of this “sickness behavior” with evolutionarily inflammatory origins, gene knockout models in rodents have been strongly beneficial in emphasizing the causal relationship of inflammatory cytokines (including IL-1 β and TNF- α) in developing social withdrawal, sickness behaviors, and anhedonia [137]. Also, the development of sickness behavior led by a pro-inflammatory state is attenuated by treatment with IL-10 and aggravated in mice that are IL-10-deficient [137]. An elevation in cytokine serum levels may correspondingly elevate oxidative stress and reduce availability of serotonin and other neurotransmitters, along with activities of the hypothalamic-pituitary-adrenal (HPA) axis in the brain [137, 139]. Acute induction of pro-inflammatory agents, such as LPS or typhoid vaccination, can trigger transient and similar symptoms [140]. Rodents exposed to MS show dysfunction in PFC-mediated behaviors including social interactions [141], learned helplessness [142], and cognitive function [46] in adolescence and elevated peripheral inflammatory cytokines IL- β and IL-6 [45]. Findings in rodents have suggested that this immune-to-brain traffic can control the cortico-amygdala circuitry involved in threat processing and is connected with enhanced anxiety-like behaviors [143–145]. Pigs with MS show sickness-like behavior that is buffered with anti-inflammatory treatment [146, 147], indicating that pro-inflammatory processes can influence early responses to ELS. Social withdrawal, lethargy, and anhedonia related to exposure to pro-inflammatory agents may be part of the organism’s evolutionary effort to use all its resources for fighting foreign invaders and overcoming diseases [148]. Giovanoli et al. have investigated if an anti-inflammatory medication with minocycline in early life during peripubertal adversity exposure could prevent the following occurrence of adult behavioral problems [149]. Notably, rats deficient in the inflammasome NLRP3 showed improvement in both pro-inflammatory state and cognitive function and reduced both systemic inflammation and functional decline during aging [150].

6.5 Inflammation and Psychiatric Illness

6.5.1 Observational and Experimental Human Studies

Experimental findings suggest that inflammation can decrease neural activity to reward circuit, as shown by studies that induced inflammation with low-dose bacterial stimuli [151] or investigating the effects of immune-activating treatments on neural reward circuit [152]. Induction of pro-inflammatory states in humans produces a clinical response similar to major depression [153]. Patients with some types of cancer or hepatitis C treated with interferon- α (IFN- α) also develop depressive symptoms within weeks [140, 154]. Additional experimental evidence related to the inflammation as the pathophysiology of mood disorders comes from the antidepressant effects of anti-inflammatory medications. These experimental human studies proposed that inflammation can modulate neural circuit activity linked to rewards

independently in different processes that may lead inflammation in those exposed to ELS.

Recently, a meta-analysis showed that cytokine inhibitors and nonsteroidal anti-inflammatory drugs can have small to moderate antidepressant effects [155]. Moreover, patients administered minocycline exhibited a greater decrease in negative symptoms in two clinical trials comparing minocycline versus placebo [156, 157]. Pro-inflammatory cytokines may also reduce executive control-related processes associated with PFC in the brain where it is linked to decision making, executive control, and regulation of reward and threat-related predisposition [158, 159]. Cytokine increase may alternate microglia in the cortex, thereby causing structural and functional changes, which increases the risk of mental illness [160]. Concordantly, alterations in microglial activation have been observed in several psychiatric disorders including schizophrenia [161], depression [162], and anxiety [163].

Microglia plays a major role in the adaptive immune response in the central nervous system (CNS) that can modulate neuronal function not only during inflammation but also in synaptic pruning [164] and plasticity during development [165, 166]. A recent TSPO-PET study showed elevated microglial activity in patients with schizophrenia and persons who are even at ultrahigh risk of psychosis. Moreover, increased microglial activity was positively associated with greater symptom severity in the high-risk population [167], suggesting a relationship between neuroinflammation and psychotic symptoms.

In line with these findings, human observational studies over the past 30 years have emphasized the role of the immune function in the pathophysiology of several psychiatric disorders, including schizophrenia, depression, bipolar affective disorder [168, 169], obsessive–compulsive disorder [170, 171], and posttraumatic stress disorder (PTSD), along with an increase of suicidal attempt [172]. A meta-analysis controlling the effect of antipsychotics in schizophrenia showed persistently increased levels of several immune proteins released from macrophages, such as IL-12, TNF- α , and IFN- α [97]. Interestingly, cell cultures from patients with schizophrenia also produce greater levels of circulating IL-1 and IL-8, thereby confirming the role of immunity-related pathophysiology in schizophrenia. Studies on obsessive–compulsive disorder reported polymorphisms in the TNF- α gene [173] and elevation in plasma TNF- α cytokine levels [174–176]; based on the individual, cytokine gene polymorphisms may manifest differently [173]. Other prospective studies also showed that elevated IL-6 and CRP were significantly associated with depressive symptoms later in life. Longitudinal studies have found that increase inflammatory levels in patients with depression likely result from a bidirectional relationship between inflammation and depression over time [177]. A meta-analysis of clinical studies found that patients with depression show a slight elevation in several inflammatory biomarkers [178]. Concordantly, longitudinal associations between inflammation and subsequent psychopathology were shown in participants with psychosis [179], depression [171], and PTSD [180, 181].

Associations between inflammation and psychopathology have been best investigated in depression [182]. Patients with depression show immune cell profiles

featured by systemic low-grade inflammation [183]. A cross-sectional meta-analysis investigated alterations in inflammation in depressed adults and characterized depression by a small increase of serum inflammatory markers [178]. Anti-inflammatory medications showed antidepressant effects in a subset of depressed patients with elevated baseline levels of inflammation [184]. Group differences between inflammation in patients with depression and controls likely attributed to the bidirectional relationship between depression and inflammation [29, 177]. Increased levels of pro-inflammatory cytokines, such as IL-6 and TNF- α , are associated with depressed mood [185–187], and decreased levels of the anti-inflammatory cytokine IL-10 have been shown in depression [188]. A meta-analysis demonstrated increased TNF- α and IL-6 in patients with depression [189]. Moreover, a study by Miller and Cole showed that the transition to depression was associated with relative increases in CRP and IL-6 levels in individuals exposed to ELS, indicating that ELS can potentially enhance a phenotype wherein depression and inflammation occurred simultaneously [190].

Concordantly, patients with bipolar disorder also have increased levels of inflammation [191], TLR-mediated intracellular signaling [45], and toll-like receptors (TLRs) in peripheral monocytes and lymphocytes. Moreover, elevated NLRP3 levels were found in the frontal cortex of patients with bipolar disorder, which is associated with elevated levels of IL-6, IL-1, TNF- α , and IL-10 [192]. Meta-analyses of clinical studies found that patients with bipolar disorder have small to moderate elevation of both pro-inflammatory cytokines [193] and CRP [194] levels compared to controls. An elevated inflammation state can predict poor treatment prognosis in bipolar disorder [195]. These relationships can reflect the negative outcomes in individuals exposed to ELS [29]. Systemic inflammation in patients with bipolar disorder can be identified not only during active episodes, but also in euthymic phases [194], indicating that inflammation may be a trait marker rather than a state marker for bipolar disorder.

Although there have been limited findings from cross-sectional human studies, increased IL-6 and CRP levels is associated with psychosis [3, 196], as supported by longitudinal studies involving the general population, including the Avon Longitudinal Study of Parents and Children birth cohort. Furthermore, greater levels of pro-inflammatory cytokines in childhood are associated with an elevated risk for psychosis in adolescence and young adulthood [179, 197]. A meta-analysis controlling antipsychotics persistently showed increased TNF- α , interleukin-12 (IL-12), and IFN- γ in patients with schizophrenia [97]. Furthermore, schizophrenic patients show a moderate to large increase in pro-inflammatory cytokines [97] and CRP [198]. Initial evidence also suggests that elevated baseline inflammatory levels can be predictive of poor treatment response in first-episode psychosis [126]. Indeed, a study on both chronic psychotic disorders and first-episode psychosis showed that several inflammatory markers appear to be trait markers and showed no reduction following antipsychotic medication [97, 198].

Patients with PTSD also exhibited increased inflammation levels. A meta-analysis suggests that patients with PTSD have moderate to large elevation in several pro-inflammatory cytokines [199] after controlling the effect of comorbid depression

[199]. Genetic [181] and longitudinal [180] studies have suggested that inflammation can be a preexisting susceptibility factor for patients with PTSD exposed to ELS rather than a simple correlation of disease severity, subjective distress, or dysfunctional coping strategies after PTSD development.

6.6 Early Life Stress and Psychiatric Illness

6.6.1 Experimental Animal Studies

Animal studies of ELS on psychiatric disorders found that associations between early contexts of stress and later emotional and behavioral abnormalities are likely causal in nature [200–206]. Studies using mouse [202, 205] and nonhuman primate models [203, 204, 206] have found that ELS from MS can negatively influence the emotional and behavioral development and impair cognitive functioning, in line with the seminal studies of clinical observations by Spitz [207] and Bowlby [208] on the effects of MS on psychiatric disorders. Indeed, animals exposed to ELS show behavioral despair and learned helplessness [200], dysfunctional fear conditioning [200], and avoidant behaviors. Surprisingly, sensitization in guinea pigs was first identified when two, 3-h separations at a 24-h interval increased the number of 1-min intervals that guinea pig pups spent showing a passive, depressive-like response on the second day of separation [40]. Although the effects of induced ELS can be different based on the protocol used and the animals' gender and age, the findings of these experimental studies strongly indicate a causative role of ELS in psychopathology in the late stage.

6.7 Early Life Stress and Psychiatric Illness

6.7.1 Observational Human Studies

Individuals exposed to ELS are 1.3–3.1 times more likely to result in lifetime major depressive disorder or dysthymia, based on the frequency, type and severity, and stressful events [209–211]. Although exposure to ELS can increase the risk of many psychiatric disorders, the relationship between ELS and various types of psychiatric etiology have not been clarified [6, 212–215]. One study showed that ELS predicts several psychiatric disorders, including schizophrenia, depression, bipolar disorder, and PTSD [216–218]. ELS from childhood neglect has also been related to later changes in reward function in individuals [219]. Activation of the nucleus accumbens [220] and other basal ganglia regions [221] associated with the reward system decreases in teenagers exposed to ELS. Therefore, individuals exposed to ELS have an increased lifelong risk of major depression including an early-onset and elevated comorbidity [213, 222]. Individuals with present depression and a history of ELS are also more likely to show high levels of high-sensitivity CRP compared to controls. Notably, this association is not likely to be suggested by retrospectively

biased reports of individuals in depression at the time of ELS assessment as the evidence is persistent with those from official records and prospective evaluations of maltreatment investigated in childhood [223]. Moreover, this is also unlikely to be described by the effects confounded genetically because a higher risk of depression in individuals exposed to ELS has been identified within twin studies [209].

Also, a history of ELS is highly associated with patients with bipolar disorder and can predict an unfavorable illness course and clinical symptoms such as higher severity of manic, psychotic, and depressive symptoms, a higher suicidal attempt, higher risk of comorbid substance use disorders, anxiety disorders, elevated risk of rapid cycling, and increased occurrence of depressive and manic episodes [224]. Moreover, ELS predicts an increased number of psychotic disorders such as schizophrenia or schizoaffective disorder later in life [217]. Furthermore, ELS is related to an elevated risk of PTSD [218] and is associated with more complex symptoms including dysfunctional interrelationship, dysregulated emotion, and poor self-concept [225].

6.8 Discussion

In this chapter, we provided an overview of the literature on early-life stress, inflammation, and psychiatric illness. This section reviews how ELS affects the psychopathology of psychiatric illness via inflammation. In the past, the brain is thought to be immune-privileged with highly controlled innate and adaptive immunity, especially inflammation in the blood-brain barrier. It has increasingly become evident that the immune-privileged property of the brain is complicated and not absolute [226]. The brain immune system is not only associated with the peripheral immune system [137] but also actively contributes to normal brain development and functioning [227]. The immune system in the brain has different cells, such as T cells and microglia, and proteins such as chemokines or cytokines that play essential roles to maintain homeostasis in the CNS resting state. Microglia monitor the surrounding extracellular space during the resting state for infection and eliminate cellular debris as well as maintain neurogenesis and inactive or dysfunctional synaptic structures. Conversely, during a pro-inflammatory state, microglia produce inflammatory cytokines and other molecules and clean up triggering foreign invaders through phagocytosis. T cells originating from the lymphoid hematopoietic cell scan and detect signals cascaded from brain into the CSF during the resting state. Meanwhile, during the pro-inflammatory state, T cells release cytokines (e.g., IL-4) that stimulate astrocytes to lead the production of brain-derived neurotrophic factor (BDNF) and control inflammatory activity in parenchymal and meningeal myeloid cells such as microglia and induce a protective immune response that may be associated with aggravated results for brain function. Moreover, cytokines accumulating in the microglia and T cells at the resting states play a critical role in hippocampus-linked learning and memory processes, putatively via supporting long-term potentiation, whereas cytokines during the pro-inflammatory state enhance neuroinflammation and decrease monoaminergic transmission and trigger glutamate transmission and

the HPA axis-mediated neuroendocrine stress response. Furthermore, a higher level of cytokines inhibits BDNF and cholinergic transmission [137, 227]. Notably, there are various routes through which inflammatory cytokines can increase synaptic monoamine availability; these routes can play a fundamental role in the mechanism underlying the pathophysiology of psychiatric illness [228]. An increased level of IDO is also associated with cytokine-induced monoamine neurotransmitter changes by converting the metabolism of tryptophan more into the kynurenine pathway but less into the 5-hydroxyindoleacetic acid, thereby reducing serotonin production. Subsequently, the neurotoxic metabolite quinolinic acid from microglia, monocytes, and macrophages in the CNS originates from kynurenine [229, 230]. Quinolinic acid stimulates N-methyl-D-aspartate receptors for glutamate and glutamate release by astrocyte and blocks glutamate reuptake by astrocytes [231], which directly affect glutamate metabolism to ultimately increase excitotoxicity and decrease efficient neurogenesis, finally resulting in increased glutamate both inside and outside the synapse. Therefore, elevated glutamate also increases excitotoxicity and decreases the production of BDNF [232].

Concordantly, high levels of nitric oxide (NO) [233] released from microglia in the inflammatory state can promote more neuronal cytotoxicity and apoptosis [234, 235] and contribute to neuronal loss in schizophrenia and Alzheimer's diseases [236–238]. Thus, ELS sensitize microglial activation resulting in a lower threshold for a reactive state and subsequently increasing inflammatory cytokine levels and dysregulated neurotransmission, which can explain psychopathologies of psychiatric illness caused by ELS.

As mentioned above, previous studies have linked the peripheral immune system and the brain immune system; researchers have recognized that the immune-privileged property of the brain is complicated and not absolute. The humoral pathway refers to the cytokine passage through regions such as the circumventricular organs with increased permeability in the BBB and elevated binding of cytokines to saturable transport molecules on the BBB. The neural pathway [137] refers to the binding of peripheral cytokines to peripheral afferent nerve fibers, such as the vagus nerve, which subsequently triggers ascending catecholaminergic fibers in the CNS and/or brings back cytokine signals in the central part [139]. The signal transduction pathway refers to the triggering by peripheral cytokines from cell surface receptors on endothelial cells and astrocytes in the brain that maintain the BBB, subsequently stimulating more cytokine production by these cells. The transmembrane pathway refers to the active transport of cytokines (TNF- α , IL-6, IL-1) through saturable carrier proteins to enter the BBB. Finally, the cellular pathway refers to the trafficking of activated immune cells, typically monocytes, to the brain vasculature and parenchyma. Through these pathways, peripheral inflammation can trigger neuroinflammation in the brain [137, 239]. For example, peripheral induction of LPS in rodents increases the production of pro-inflammatory cytokines [240] and microglia activation and inhibited adult neurogenesis in the brain [241].

Chronic stress in early life causes repeated and prolonged HPA overactivation, which can subsequently cause less compensation in reduced signaling through epigenetic alterations in the glucocorticoid receptor [242] and promote resistance

to the function of cortisol to control the inflammatory state. Experimental human studies have found that traumatic experiences during childhood are associated with allele-specific DNA demethylation related to glucocorticoid response elements (FKBP5 gene), which is related to the subsequently reduced sensitivity of peripheral blood immune cells to the inhibitory function of glucocorticoids on LPS-induced production of IL-6 *in vitro* [243]. A longitudinal study also showed that adolescents exposed to harsh familial treatment showed decreased sensitivity of glucocorticoid over time and elevated *ex vivo* cytokine responses to LPS administration [244].

Furthermore, the alteration of colonization and composition of the gut microbiota might be influenced by ELS, which could affect immune development as well as brain development via inflammatory signal transmission through metabolic alterations or the vagus nerve [135]. Experimental animals findings also showed that MS during the first year of life causes a significant reduction in fecal lactobacilli [74] with long-term alterations on the composition of the microbiota in the gut being apparent in later life [59].

Interestingly, recent meta-analytical findings in animal models showed that ELS is linked to a small increase in the risk of obesity [19], as individuals with ELS may be less sensitive to reward and hence may be involved in more dysfunctional appetitive behaviors, such as eating fast foods or more high-calorie food items. Also, given that ELS can potentiate HPA axis activation and related unpleasant feelings, individuals with ELS eat more to decrease HPA axis activation. Elevated pro-inflammatory cytokines by adipocytes can trigger a systemic inflammatory state in individuals with obesity [245]. Moreover, individuals with ELS may have dysfunction in hormonal pathways regulating thermogenesis and lipolysis including the leptin pathway or the HPA axis [19].

Previous studies have also reported that individuals exposed to ELS are at increased risk of sleep disturbances [246, 247], which showed stronger relationship for participants with more severe maltreatment exposures [246] regardless of concurrent PTSD or depressive disorders [248]. Furthermore, MS in rodents can disrupt sleep architecture and decrease total sleep; meanwhile, in humans, MS can induce sleep deprivation and loss, which elevates the expression and levels of pro-inflammatory cytokines [249, 250].

In line with the biological and evolutionary aspects of the bidirectional associations between the brain and immune system, the critical targets primary related to inflammation in the brain include those brain regions associated with both motivation and motor activity such as arousal, anxiety, and alarm. In other words, the main neurocircuits affected by inflammation involve the reward and anxiety circuits. Dopamine as a core neurotransmitter plays a critical role in the reward circuit and inflammatory cytokines have been demonstrated to reduce the production of dopamine in the basal ganglia, which is involved in decreased motivation and activation of the reward circuit in the ventral striatum [151, 152, 251]. Accumulated imaging studies such as PET, functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS) have shown decreases in reward activation in the striatum, showing strong reproducibility and validity of the cytokine-induced alterations of the brain in nondepressed individuals peripherally administered LPS,

typhoid vaccination, or IFN- α [151, 152, 252–254]. Notably, fMRI studies also found that inflammation-mediated reduction of positive reward activation is related to elevated sensitivity to negative stimuli and decreased activations in the substantia nigra in the basal ganglia [254, 255]. According to studies on positive valence systems, peripheral administration of typhoid vaccine and LPS decreases responses to reward in the ventral striatum [151, 152]. Inflammatory cytokines in dopaminergic pathways also induce a state of reduced motivation. Moreover, elevated inflammation is related to elevated responses to anxiety and threat neurocircuitry, involving the amygdala, dACC, and insula [155, 256, 257]. Notably, the dACC and amygdala are regions with elevated responses in patients with depression, anxiety, and neuroticism [258]. Thus, elevated oral IL-6 expression is strongly associated with increased response of the amygdala to social evaluation stressor, with subjects showing the highest IL-6 responses to stress, indicating greatest functional connectivity within threat circuitry, which involves the dorsomedial PFC and amygdala [259]. Similarly, elevated concentrations of oral IL-6 and soluble TNF receptor 2 in response to an induced social anxiety condition, such as a public speaking, are strongly associated with the activation of the dACC to a social rejection task [257]. Indeed, these findings are related to the trafficking of monocytes to the amygdala led by social defeat stress in rodents [145]. Considering negative valence systems, typhoid vaccine decreases the relationship between the sACC and the amygdala and elevates the activation in the sACC while processing emotional faces [158]; peripheral administration of LPS also enhances activation in the amygdala in conditions of socially threatening stimuli [260]. Subsequently, alterations in reward and threat processing are critical potential mediators led by the effect of systemic inflammation on behavioral responses.

As immune stimulation also profoundly affects the perinatal brain development processes involved in cognitive function, some experimental animal studies showed that infection and systemic inflammation during prenatal or neonatal periods impair learning, memory, and attention [261–264]. Meanwhile, observational human studies found a relationship between prenatal exposure to infection and elevated risk of schizophrenia [265, 266]. Elevated levels of the systemic inflammatory marker IL-6 during childhood are significantly related to an elevated risk of causing psychosis and depression in young adult [179].

Accumulated experimental and observational studies in animals and humans have suggested bidirectional relationships between psychiatric illness and inflammation in peripheral and neuroinflammation over time [177], indicating that susceptibilities associated with emotional and behavioral symptoms and dysfunctional perception of distress could elevate inflammatory responses and sensitization over time or vice versa. Thus, the severities and frequencies of stressful events could be affected by an individual's susceptibilities, such as personality traits or attachment style, and their environmental risk factors, both of which are critical risk factors for ELS [267].

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