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Neuroinflammation, early life adversity, and brain development

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Abstract

The overarching objective is to review how early exposure to adversity interacts with inflammation to alter brain maturation. Both adversity and inflammation are significant risk factors for psychopathology. Literature relevant to the effects of adversity in children and adolescents and brain development is reviewed. These studies are supported by research in animals exposed to species-relevant stressors during development. While it is known that exposure to adversity at any age increases inflammation, the effects of inflammation are exacerbated at developmental stages when the immature brain is uniquely sensitive to experiences. Microglia play a vital role in this process, as they scavenge cellular debris and prune synapses to optimize performance. In essence, microglia modify the synapse to match environmental demands, which is necessary for someone with a history of adversity. To achieve the main objective, clinical and preclinical research areas are pieced together to show how adversity uniquely sculpts the brain. Microglia interactions with the inhibitory neurotransmitter GABA (specifically, the subtype expressing parvalbumin) are discussed within contexts of development and adversity. A review of inflammation markers in individuals with a history of abuse is combined with preclinical studies to describe their effects on maturation. Inconsistencies within the literature are discussed, with a call for standardizing methodologies in the areas of the age of assessment of adversity effects, measures to quantify stress and inflammation, and more brain-based measures of biochemistry. Preclinical studies pave the way to interventions for anti-inflammation-based agents (COX-2 inhibitors, CB2 agonists, meditation/yoga) by identifying where, when, and how the developmental trajectory goes awry.

Keywords

accelerated aging; maltreatment; microglia; prevention; sensitive period

Introduction

Exposure to early life adversity affects brain development differentially, depending on the type of adversity, the sex/gender of the individual, and the timing of exposure. When an individual is exposed to a real or potential threat, the body perceives that event as stressful. Such responses to stressors are found in all mammalian systems that are relevant to each species and activate the hypothalamic-pituitary-adrenal axis (HPA). Sources of stress that occur during childhood and adolescence and associated with psychopathology, including physical and sexual abuse or neglect that occurs before the age of 18 years, are considered for the current review. The studies included here on adversity exposure in humans use

standardized measures such as the Adverse Childhood Experiences Scale (ACES:[1]) or the Childhood Trauma Questionnaire (CTQ).[2]

For animal models, developmental stressors include separation from parents[3] or peers[4], or physical stress[5], or limited bedding model[6]; we did not include the resident intruder for late adolescents.[7] Comparisons of these various stressors reveal similarities and differences[8] that are discussed in more detail.[9] Differences are found across the maternal separation paradigm, with paradigms varying in duration of separation, the timing of ages of separation, and the use of males and females within each litter.

No standard scale exists for animal studies to quantify adversity. The activation of the HPA axis is used as evidence of the stress, as measured by corticosterone (the animal analog of cortisol), corticotropin-releasing hormone (CRH), adrenal corticotropin hormone (ACTH). However, like in humans, these measures show tremendous variation and are subject to the time of collection. The nature of the stressors used in animals may or not reflect the same phenomenon in humans. Most paradigms alter maternal behavior (e.g., maternal separation or limited nesting); other stressors, like shock, are more physical than we would expect to model child sexual abuse; the resident intruder model is only effective in adolescents and adult animals.[7] Despite these issues, modifying the mother's behavior has been useful as a model and is used herein, unless described otherwise.

If sufficiently potent, exposure to these stressors increases the risk of psychopathology. Anxiety, depression, and post-traumatic stress disorder (PTSD) are expected outcomes of adversity, as are increased substance use disorders, schizophrenia, obesity, and heart disease.[10] Animal studies find parallel behavioral outcomes of adversity exposure, including increased fear and anxiety[11], depressive-like behavior[4], and increased drug use, especially alcohol.[12] Adversity exposure is a risk factor for these disorders whose negative effects can be mitigated with novel treatments to prevent serious outcomes.

The objective of the current review is to integrate knowledge about the effects of neuroinflammation, early life adversity (keywords: maltreatment, stress, abuse, deprivation), and brain development. Additional key terms used for the literature search include microglia, phagocytosis, inflammation, maturation, and brain. An emphasis was placed on how preclinical research can inform the neurophysiological mechanisms and how these mechanisms may be used to develop possible interventions of the human condition. The following two sections focus on brain maturation and explain how exposure to adversity and its effects on development depend on the timing of the stressor and the age of assessment. In the three sections after that, the interconnections between early life stress, microglia, and inflammation are discussed in relation to maturation and the potent effects of stress experienced during sensitive periods of development. Finally, the review surveys what is known about specific inflammation markers and developmental stress.

Sensitive periods are experience-expectant stages in development when events can influence and sculpt brain maturation. They are not experience-dependent, such as the necessity of light for the formation of the visual system during a critical period of development.[13] The greatest impact of childhood or adolescent adversity on brain development occurs during

sensitive periods by producing regional effects on the brain that are associated with the timing of exposure.[14,15] As discussed below, sensitive periods are related to changes in plasticity, including the overproduction and elimination of synapses/gray matter in a process that is highly conserved across species.[15–17]

Factors important in predicting clinical outcomes include the nature of experience, the brain regions underlying a given function (e.g., fear, emotion, reward), and the timing of exposure and assessment. Attention to these factors is critical if a comprehensive timeline of the course of the sequelae of adversity is to be ascertained. When possible, the age/stage when the adversity occurred is presented for the clinical studies. By raising awareness of the importance of tracking the stages, it is the author's hope that we can arrive at more consensus findings of the effects of "adversity" on brain maturation.

The effects of early adversity on behavior and brain maturation

Depression occurs in ~ 67% of an early life stress population (reviewed by[18,19]) with an age of onset that is an average of nine years earlier than the non-early life stress exposed population.[20,21] Early life adversity preferentially impacts brain circuits associated with threat detection, emotional regulation, reward anticipation, executive functioning, autonomic functions, and sleep/wake regulation.[22,23] Elevated inflammation exacerbates the underlying brain regions associated with these behaviors.[24]

The age when the abuse occurs is associated with different developmental trajectories; children with abuse occurring before 6 years of age exhibit significant levels of depression and anxiety later in life compared to children with abuse occurring between 6–11 years of age, who were more at risk for externalizing disorders.[25] This earlier abuse/depression track is associated with changes in emotional regulation pathways. Exposure to maltreatment during adolescence results in abnormal development of cortical structures that results in immediate manifestation of depression in humans[26] and in animals following a significant social stressor.[4,27] Additional research on older stressed animals is outside the scope of this review.

Physical, sexual abuse, and neglect have unique effects on brain development, suggesting that different mechanisms underlie the enduring consequences[28,29] that are partially due to the brain regions that are activated. An early manifestation of early sexual abuse exposure includes fear processing, which typically appears in infancy. For example, the human amygdala, which is involved in fear processing, is reduced in volume following childhood sexual abuse.[30] In rodent models of adversity (e.g., the limited bedding model), offspring show reduced fear expression before adolescence, mediated by changes in the amygdala.[11] Behaviorally, both human and rodent species exhibit anxiety following exposure to adversity.[9,31,32]

The expression of more complex behavioral symptoms is delayed after the initiation of childhood abuse, likely due to the engagement (or lack thereof) of higher cortical areas involved in regulation.[4,11,20] Adversity-associated depression involves regions regulating emotional responses[33], including the anterior cingulate cortex, dorsolateral cortex, and orbital cortex.[26] Increased risk for depression in the early abuse window occurs at the

same stage when elevated amygdala activity is observed in children with an early life stress history.[34,35]

The adolescent emergence of depression reflects a dysfunction in emotional regulatory circuits[36] as they mature, with delayed effects as maturity unmasks earlier the consequences of abuse (childhood). Cortical connections to subcortical regions must play a role. For example, the younger vulnerability to depression coincides with the stage when the prefrontal cortex (PFC) innervates the amygdala[11] and amygdala innervation into the PFC[37], which increases in female rodents exposed to early stress.

Abuse-related changes in connectivity are also found in the hippocampus, where early childhood maltreatment reduces hippocampal volume in adolescence, but not earlier.[38,39] Studies in animals exposed to early stress (maternal separation) show reduced overproduction of hippocampal synapses during adolescence.[16] The hippocampus informs us about the context which is used by the prefrontal cortex to interpret our emotional responses.[40] In children with a maltreatment history, connectivity between the hippocampus and prefrontal cortex and cortical activity to threat (as revealed by the angry faces MRI paradigm) is reduced.[41] The sensitive period for environmental manipulations to affect the connectivity between the hippocampus and cortical structures is during early adolescence in animals.[42] As a result, early abuse manifests when these hippocampal/cortical connections are becoming functional later in adolescence.

Processes of brain maturation at the synaptic level

The process of how exposure to early adversity alters the course of development at the anatomical/functional level is not well understood. Figure 1 illustrates the fundamental players in brain maturation (left side) and the impact of exposure to early adversity (right side). Typical synaptogenesis results in a balance between excitatory (E) information (mainly glutamate) and inhibitory (I) information (mainly GABA). This balance has been referred to as the E/I balance. During a sensitive period of development, the balance shifts to more excitatory activity (encoding the environment) and less inhibitory activity leading to increased brain responsiveness to the environment.[43] Increases in the fast-spiking GABA neuron that expresses parvalbumin ends the sensitive period by increasing inhibition.[44,45] The timing of parvalbumin expression is unique for each brain region[46] and reports differ across laboratories[47–49], complicating the story. Nevertheless, parvalbumin rises in concert with brain-derived growth factor (and its receptor Tropomyosin receptor kinase B; [TrkB]), which facilitates synaptogenesis.[44,45] Finally, a perineuronal net wraps around the parvalbumin neuron, limiting its plasticity by acting as a physical barrier.[50]

In keeping with a sensitive period framework, the overall impact of early adversity depends partly on the timing of exposure and the brain region examined. Differences across the timing of stress exposure and assessment can explain discrepant results across studies. Maternal separation reduces parvalbumin and TrkB levels in the prefrontal cortex in adolescence (35 days of age) in males[51] and earlier in females.[52] The stress-related reduction in parvalbumin occurs earlier than the control subject, and levels rise to control groups with age. The maturational timeline is also advanced after early stress and closes the amygdala and PFC sensitive periods earlier than controls as indicated by increased

parvalbumin expression.[11,48] By adulthood, parvalbumin levels appear normal, with no quantitative difference between experimental and control subjects. Thus, if the timing of assessment is too late (adulthood), it would appear as if there was no effect.

Maternal separation in animals also increases the glutamate receptors GluN2A NMDA[53], mGluR5[54], further shifting the E/I balance. Glutamatergic projections from the amygdala to the prefrontal cortex increase after exposure to maternal separation or the limited bedding rodent models.[11,37] Finally, the perineuronal nets are more robust in animals exposed to early life stress[55], but occur later than in controls.[56] Together, low parvalbumin, increased glutamate, and delayed perineuronal net expression suggest that early life stress extends the sensitive period, allowing the neuron to remain vulnerable to “experiences” longer by starting earlier.

Clinically, the underlying mechanism of these changes is difficult to ascertain, but proxies exist. For example, magnetic resonance spectroscopy reveals that adolescents with anhedonia have lower levels of GABA in prefrontal cortical areas.[57] Figure 1 shows how GABA, as measured with spectroscopy, reflects changes in parvalbumin in rats. Parvalbumin activity in humans is also reflected in cortical gamma activity, whereby the strength and coherence of the electroencephalogram reflect the E/I balance of the region[58], but see.[59] Gamma activity is lower in the superior temporal gyrus in a population with elevated Childhood Trauma Questionnaire (CTQ) scores.[60] Similarly, exposure to adversity increases connectivity between the amygdala and cortical regions, presumably via glutamatergic projections–although the nature of these projections is not known in humans.[61,62] These imaging studies used resting state and functional connectivity measures. Whether these changes are indeed glutamatergic could be ascertained with magnetic resonance spectroscopy.

Data from animals with maternal separation demonstrate either increased[63] or decreased glutamate (relative to the stable neuro metabolite creatine) in the hippocampus.[64] In a different study, GABA and glutamate + glutamine (Glu+Gln) levels in the prefrontal cortex were reduced (a trend).[63] These animals were adults, leaving open the possibility that glutamate measured during adolescence is elevated. In the single study on the subject, hippocampal glutamate levels were inversely correlated with the degree of stress exposure indexed by ACES.[65]

Neuroinflammation

Inflammation, independent of early life stress, alters developmental processes in several ways. Studies that examine the effects of inflammation produced by an immune challenge, such as lipopolysaccharide (LPS), find reduced cell proliferation and migration; synaptogenesis, and pruning (reviewed in[66]). Changes in myelination and expression of other support cells are also observed.[67,68] It is the tenet of this paper that inflammation resulting from stress during a sensitive period is a trifecta for exerting significant and enduring damage.

As the story builds, the next objective of this review is to discuss the role of inflammation on the effects of early life adversity on synaptic plasticity. In general, stress challenges the body causing it to react by increasing the sympathetic nervous system and the HPA system. As part of the sympathetic nervous system response, norepinephrine phosphorylates mitogen-activated protein kinases (MAPKs) that in turn influence the immune system.[69] The HPA system releases glucocorticoids that stimulate both anti- and pro-inflammatory responses. Acute stressors increase the release of glucocorticoids to reduce inflammation.[70] Over time, chronic stress shifts the response to pro-inflammatory[71], allowing the organism to respond to sustained threat.[72] Indeed, glucocorticoid levels or glucocorticoid responses in humans[73] and animals[74] are suppressed in some, but not all, individuals following chronic stress.[75] The inconsistent findings can be due to methodology of sample ascertainment, age of assessment, types or the age of abuse, or other underlying differences in subjects.[76,77] With prolonged immune activation, markers including C-reactive protein[78] and interleukin-6 can be measured readily (discussed in more detail below).

The interaction of stress that occurs during a sensitive period of development to effect inflammation produces a permanent change in neural circuitry. Inflammation associated with the stress[79] affects neurons at all ages by reducing dendritic branching.[80] However, these early descriptions show that dendrites resume their exuberance when the stress abates. In contrast, dendritic branching following exposure to early adversity does not return to normal. Loss of gray matter/synapses is exaggerated following stress at a specific stage or may not be detectable until age-appropriate pruning occurs.[16] The structural/functional changes in the brain following early life stress exposure are more pronounced, however, if the stressor occurs during a sensitive period.[15] Early life stress-induced inflammation interacts with synaptogenesis in two ways. First, inflammation activates microglia, which are one of several cells in the brain involved in inflammatory responses and the pruning of neurons. Microglia express glucocorticoid receptors[81], which are highly expressed in the PFC and hippocampus at the ages coinciding with the sensitive periods discussed here.[15,82] Second, inflammation directly impacts GABA/parvalbumin neurons to shift the E/I balance (Figure 1), further exacerbating the effects of stress on regional development.

Inflammation is associated with exposure to early life adversity

Physicians have long recognized the link between psychological stress and healing in their patients.[83–86] Multiple reviews establish a role for inflammatory processes in adverse outcomes[66,87–91], and the relationship between inflammation and depression has been established for some time in adults.[92] Inflammation is associated with depression in teens[93,94], and mood dysregulation following vaccinations in children[95] Individuals with a history of maltreatment or animals exposed to maternal separation have increased inflammation.[48,96,97]

The objective of the following section is to synthesize what is known about neuroinflammation and integrate this information with developmental processes. Currently, little of this vast knowledge is applied to developmental processes. The proposed framework explains why inflammation during a sensitive period may be vital to producing a permanent effect on circuitry versus the more temporary changes when inflammation occurs at other

stages. Stress increases inflammation via microglia (the focus here), astrocytes[98], and by causing the blood-brain barrier to leak, allow peripheral cytokines to enter the brain.[99] Changes in HPA axis activity, inflammation, and most importantly, circuit changes, will produce sustained vulnerability to depression and other emotion-regulating conditions in individuals with maltreatment. As a result, psychopathology associated with adversity, especially depression, is generally more severe, recurring, and more resistant to treat as reviewed by.[100]

The role of microglia and inflammation to facilitate pruning

There is still limited understanding of how inflammation permanently alters the immature brain following exposure to adversity. Recent investigations shine a light on microglia as critical cells of interest due to their dual role in inflammation and phagocytotic pruning that occurs during normal development.[101–103] Contact between microglia and a synapse activates the cell under normal conditions and synchronizes their activity; such synchrony is absent when the cell is inflamed.[104] Microglia have been called the “guards of homeostasis” and are activated when homeostasis is disrupted.[105] When an environmental disruption such as adversity occurs, microglia and neurons undergo asynchronous development.

Microglia transition between two fundamental (and oversimplified) states: M1 during inflammation and M2 when the cell is involved in phagocytosis. Microglia produce cytokines such as TNF-α and IL-1β during the pro-inflammatory phase (M1). Microglia in the M2 phase are neuroprotective and produce the anti-inflammatory cytokines IL-10 and TGF-β.[106,107] A ramified morphology characterizes the resting (M2) phenotype that constantly scans its environment.[106,108] The ramified morphology increases microglia/neuron interactions and is observed following chronic stress or elevated glutamate activity.[109–112] However, studies in neurodegenerative models show that ramification is reduced as the microglia cell is no longer able to perform its neuroprotective role.[113]

During development, microglia in the M2 state aid in the pruning of synapses[102,114] and other markers (e.g., dopamine signaling[101,115] to optimize neural circuits and signaling pathways to match the demands of the environment.[102,116–118] The synchronized activity of the microglia/synapse pair support synaptogenesis. In other words, the microglia/neuron pair that fires together wires together. Exposure to adversity desynchronizes activity, resulting in abnormal development.

A meta-analysis of microglia number in animal models of stress not restricted to development (e.g., including adulthood) and seven different types of social stressors found an increase in microglia number using the marker ionised calcium-binding adaptor molecule 1 (Iba-1).[81] In the case of early maternal separation in animals, the cell count of microglia in prefrontal structures did not differ overall from control animals[119], but did in cortical subregions.[120] This observation, however, is misleading given that the state of the cell (M1 or M2, which is based on morphology) is vital to microglia impact. By adolescence, not at a younger age, the number of processes on each microglial cell (M2) is elevated in females (but not males) following exposure to adversity and an immune challenge. Soma size is increased in both sexes after stress. This study[118] highlights several important details that can influence the interpretation of the results: age of assessment, sex, and cell state. It

further suggests that additional metrics of microglia activity are needed to study the effects of inflammation on microglia/synapse interactions in development.

The signal for pruning is mediated in part by interactions between the Complement component 1q (C1q), part of the innate immune system, and complement 3 fractalkine (C3) and its receptor (C3R).[102,121] C1q and C3 promote microglia engulfment of developing synapses during pruning marked by a "tag" containing the complement protein C3. The tag molecule binds to a C3 receptor, CD11b, that is expressed exclusively on microglia and is directly involved in synaptic elimination (pruning).[102] CD11b orchestrates inflammatory and anti-inflammatory activity. Under typical developmental conditions, the innate immune signaling protects synapses from being pruned erroneously.[122] A loss of C1q and C3 prevents pruning, resulting in excess synapses in adulthood[102,116,121]; we would expect the opposite whereby increased C1q or C3R enhances pruning. Evidence is emerging suggesting that early life stress alters C1q and C3R.[123]

Phagocytic activity by microglia increases earlier in life (e.g., childhood in mice) in animals that underwent early maternal separations compared with controls.[124] Given the role that the CD11b receptor plays in pruning[125], it is not surprising that animals exposed to early life stress have elevated CD11b receptors (Andersen, unpublished observation). Increased CD11b provides a mechanism for explaining enhanced pruning in animals exposed to early life stress.

Another microglia marker, fractalkine (CX3CL1; CX3 chemokine ligand [L] 1), is associated with pruning during a sensitive period. Changes in CX3CR are necessary for glutamatergic synaptogenesis during development.[126–128] CX3CL1 activation of microglia modulates the overproduction of inducible nitric oxide synthase (iNOS), IL-1β, TNFα, and IL-6. Decreased CX3CR1 (CX3 chemokine receptor [R] 1) signaling in young mice (early childhood) enhances long-term depression in the hippocampus, but reductions in CX3CR1 at adolescence have no effect.[129]

One way chemokines work is to modify glutamate. Reduced expression of the chemokine CXCR1 during a sensitive period is associated with less glutamatergic AMPA activity and delays the developmental switch in GluN2B to GluN2A NMDA receptors.[105] Animal studies show that early stress increases GluN2A NMDA receptor expression, but GluN2B was not measured in this study.[53] GluN2B was decreased in the adult hippocampus after maternal separation in rats.[130] Early stress exposure is expected to reduce plasticity as the synapse matures, as suggested by the GluN2B: Glu N2A ratio.

Manipulating the CX3CR1 changes developmental plasticity and the effects of inflammation, but the result is not universal across all brain regions.[131] Since every brain region has a unique period of plasticity, the possibility exists that the timing of assessment prevented the detection of CX3CR1 changes in various brain regions. The single study that examined CX3R after early stress exposure failed to find an effect within a single age group in one brain area.[132] However, increased inflammation at four days of age in mice (due to LPS treatment) elevated microglia engulfment of synapses via a CX3CR1-mediated mechanism in the adolescent prefrontal cortex.[133] Possible reasons for the lack of CX3CR1

change following early stress include differences in the timing of stress, LPS activates the HPA or immune systems more than maternal separation, or the timing of assessment was not appropriate for the sensitive period of the region. These pervasive issues in the field hamper our progress to detect important factors relevant to psychiatry. By aiming for a more systematic approach across laboratories that includes the use of key ages of a stressor that produces a maximal effect, duration of stress manipulation, and key ages to measure outcome, we will improve our ability to identify important changes. The paper by[11] provides an example of such a foundational analysis.

In addition to microglia, astrocytes enable synaptic pruning by directly engulfing synapses and indirectly by increasing the release of different measures of the complement system and IL-33.[134–136] For a more expanded review of the role of inflammatory markers involved in synaptogenesis in other conditions, such as Parkinson's disease, Alzheimer's disease, and schizophrenia, the reader is referred to a review by.[105]

Pathways of inflammation

The objective of the following section is to review the limited number of studies that examine the effects of inflammation that affect brain development following early adversity. Several inflammation markers that are associated with adversity, depression, or aging have been identified. Behaviorally, increased inflammation and stress are associated with depression, memory impairment, and cognitive dysfunction in humans[66,137,138] and animals.[48,51,139] Inflammation is also associated with neurodegeneration, as evidenced by structural brain changes in gray and white matter.

Figure 2 focuses on markers that have been examined clinically or preclinically or are of potential interest. The signal 1 initiating cascade includes pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs). DAMPs are responsible for the activation of the TLR pathway.[140] The interleukins (IL) IL-6, IL-1b, IL-10, and tumor necrotic factor-alpha (TNFa) are studied frequently. C-reactive protein (CRP) is a systemic marker of inflammation and is considered a downstream product of the IL-6 cascade.[141]

Inflammation, adversity, and development

The following discussion focuses on the relationship between early adversity, inflammation, and how they relate to brain and behavior changes when data are available. Changes in *systemic* inflammatory markers in populations with a history of maltreatment are reviewed elsewhere.[66,87–91] Keeping in mind that stress allows peripheral cytokines to enter the brain[99], these references are important when considering biomarkers. The review here discusses clinical findings of inflammation on the brain and will be supported further with preclinical studies that are experimental and not correlational.[142,143]

Inflammation (IL-6)

IL-6 is one of the most well-known interleukins and can be measured readily in blood samples. Elevated levels of IL-6 are reported in children with a maltreatment history in

several studies. IL-6 decreases CX3CR1 levels[144,145] resulting in reduced plasticity. For example, IL-6 dose-dependently inhibits synaptic plasticity in the hippocampus, whereas blocking IL-6 activity improves long-term memory.[146,147]

Maltreatment-related depression is often associated with inflammation. The level of childhood trauma as measured by the CTQ correlates positively with serum levels of IL-6 for physical abuse and emotional abuse.[148] IL-6 levels are inversely associated with the volume of the hippocampus and prefrontal cortex regions in humans.[149]

Studies in rats that underwent maternal separation show increased IL-6 levels in the hippocampus, but not the prefrontal cortex.[120] Mechanistically, preclinical studies show that IL-6 identifies parvalbumin cells as “sick” and dying[150]. Animal studies reveal an inverse correlation between IL-6 in the plasma and parvalbumin in the prefrontal cortex.[53] IL-6 levels are increased in the prefrontal cortex and hippocampus of males, but not female rats exposed to maternal separation.[151] Notably, the time course of parvalbumin loss in an animal model is delayed until adolescence in females and occurs earlier in males.[49] These data suggest that increased IL-6 opens the sensitive period early, making the individual more plastic (vulnerable?) to their experiences.[152]

IL-1β

IL-1β is another cytokine that inhibits cell proliferation[153,154,155], reduces CX3CR1 levels in vivo[144,145] and reduces LTP and calcium currents in culture. In addition, IL-1β induces the expression of cyclo-oxygenase-2 (COX2;[156]), the target of non-steroidal anti-inflammatories. An interaction between the IL-1β genotype, the NR3C1 haplotype (a variant that encodes the glucocorticoid receptor), and adversity exposure is associated with thinning of the left subgenual anterior cingulate cortex in humans.[157]

IL-1β is often, but not always, associated with depression[158] and impair memory-related behaviors in humans.[144,145] Depressive symptoms in males, but not females, with a history of adversity, were higher if they had the single nucleotide polymorphism GG IL-1β polymorphism in the rs16944.[159] IL-1β correlates with gray matter volumes in the left occipitotemporal area, left superior occipital gyrus, and left inferior parietal lobule in older adults (non-abused).[160]

Changes in IL-1β are also associated with increased GABA-A receptor expression in animals.[155,161] The GABA-A receptor is the site of action for benzodiazepines. GABA-A receptor activity is very dynamic the first month of life in the rat (corresponding to childhood in humans;[162]), and thus susceptible to changes in maternal care.[163] Reduced GABA activity during peri-adolescence increases amygdala innervation into the prefrontal cortex in animals[164–167] This observation is consistent with the lower GABA/glutamate balance found in affective disorders in humans[168] and increased glutamate activity in individuals with a history of maltreatment.[169]

Studies in animals show that this GABA loss can be rescued by increasing GABA during the first two weeks of life.[170] In depression-resilient humans, greater cortical activity and less amygdala activity facilitate adapting to stress quickly.[62] Thus, intervening early in life

(see below) may mitigate the effects of maltreatment. In animal models of early adversity (e.g., the maternal separation model), IL-1β levels inversely correlate with performance on the win-shift maze task (a memory task;[49]) and are elevated in the hippocampus.[171]

Pro-inflammatory tumor necrosis factor-alpha (TNFα)

TNFα regulates glutamate and GABA receptor trafficking and neuronal connectivity.[172–174] Children with a history of trauma have elevated levels of TNFα.[175] Decreases in gray matter in individuals with a history of childhood trauma negatively correlate with a composite measure of IL-6, CRP, and TNFα. Affected regions the bilateral posterior cingulate cortex/precunei, postcentral gyri, inferior/superior parietal lobules.[176] Changes in these regions implicate social processing. These results are supported by a second study, finding TNFα significantly correlated with gray matter volumes of the left occipitotemporal area, left superior occipital gyrus, left inferior parietal lobule, and the medial prefrontal cortices[160] Finally, the effects of inflammation can be mediated via social means. Increased inflammation in caregivers is associated with elevated children's inflammation markers (a composite measure of IL-1B, Il-6, IL-8, TNFα, but not CRP) where both had adverse experiences.[177] A significant interest in caregiver mediation is building in the field, in general.

While individuals with an abuse history showed deficits in both the inhibitory control when tested with a Go-No Go task and a behavioral rating scale, levels of TNFα were associated with deficits only at a trend level with the Go-No Go performance.[158] The effects of treatment with inflixamib, which targets the TNFα receptors, is moderated by a history of physical abuse in bipolar patients.[178] These data highlight the vital role that maltreatment and inflammation play in mediated psychopathology later in life.

Toll-like receptors

The TLR pathway is the subject of extensive research in other fields[179], but emerging evidence suggests this pathway changes in response to early experiences. TLR activity increases nuclear factor kappa B (NF-κB)-mediated signaling to increase pro- IL-1β formation (Figure 1). Basic research from slice culture shows that the TLR pathway, namely TLR2 and TLR3, is activated by lipopolysaccharide, causing microglia to release IL-6 and TNFa. Maternal separation increases TLR4 activity in the hypothalamus[180] and the hippocampus.[181] Voluntary, but not mandatory, exercise reduces TLR4 levels in these rats.

NF-kB

Lymphocytes can be collected from blood in humans and used to assay systemic, but not brain, immune function. Studies of NF-kB activity following exposure to early adversity show a pattern of gate keeping, where only high levels of NF-kB are associated with extreme stress in the form of PTSD. Cellular levels of NF-kB are elevated in women with child abuse-related PTSD.[182] However, when not stimulated (or the trauma experienced does not lead to PTSD), peripheral levels of NF-kB in a population defined by Adverse Childhood Events (ACEs) were not altered relative to controls.[183] NF-kB in lymphocytes need to be stimulated in resilient, healthy adolescents with a history of maltreatment to evoke an increase relative to controls.[184] For example, a history of childhood physical neglect, but

not CTQ scores, are associated with NF-kB expression in response to the Trier Social Stress Test.[185] These studies illustrate the importance of defining the population of interest (discussed below).

Animals separated from their mothers (a model of early life stress) also show elevated levels of NF-kB[186] and greater NF-kB responsivity to challenge (i.e., to cocaine) than controls.[187] Together, these data suggest that NF-kB requires a minimum threshold of activity for activation following early adversity.

Inflammasome (NLRP3)

The inflammasome is a multi-protein, intracellular complex that detects outside pathogens as part of the innate immune system. While much is known about the inflammasomes and their role in depression, the inflammasome may represent a novel avenue of investigation to treat abuse. The inflammasome can detect danger signals, including stress and metabolic distress[188] Microglia contain inflammasomes.[189] The nucleotide-binding and oligomerization domain (Nod)-like receptor family pyrin domain-containing 3 (NLRP3) is one of many different proteins that makes up the inflammasome. The inflammasome is integral to the cascade of IL-1b synthesis.[190] Maternal separation increases NLRP3 expression in the prefrontal cortex, secondary to a 20% reduction in MARCH7 (an enzyme that regulates caspase activity). Inflammasome expression in the hippocampus is elevated in an animal model of social isolation and reversed by the inhibitor, MCC950.[191] MCC950 reduced cognitive impairment also.

Preventing the inflammatory cascade

COX-2 inhibitors

Cyclo-oxygenase-2 (COX-2), an inflammation marker, is elevated in individuals with depression and in early life stress animals with depressive behaviors.[48,51,192,193] Treatment with a COX-2 inhibitor reduces depressive behavior, restores working memory impairment, and increases parvalbumin levels in early stress animals.[48,51,53] At the same time, COX-2 inhibition demonstrated positive effects as a depression intervention; the drug influences other mechanisms. Some COX-2 inhibitors (e.g., rofecoxib) have been deemed unsafe by Merck but remain supported by the Food and Drug Administration. In any event, new and safer targets are needed to alter depression following exposure to early life stress.

IL-10—Neuronal development and synaptic function are modulated by microglial interleukin-10 (IL-10), which binds to IL-10 receptors on neurons.[194] IL-10 downregulates the expression of Th1 cytokines, major histocompatibility class II antigens, and co-stimulatory molecules on macrophages.[195] It also enhances B cell survival, proliferation, and antibody production. IL-10 can block NF-κB activity and regulates the JAK-STAT signaling pathway.[196] Taken together, the effects of IL-10 are beneficial.

IL-10 abrogates the IL-1β -induced inhibition of glutamate release and LTP.[196] In animal models of early adversity (e.g., the maternal separation model), IL-10 levels positively correlate with performance on the win-shift maze task.[49] Microinjections of IL-10 into the ventricles also prevented memory impairment in maternally separated animals.[53]

CB2 Receptors: Maltreatment during early childhood is a significant predictor of cannabis dependence[197–199], even after adjustment for genetic vulnerability.[200] Cannabis use by depressed individuals thus can be considered self-medication.[201] CB2 receptors play a role in social behavior[202] and modulate GABA activity.[203] Studies in late adolescent rats show that CB2 agonist treatment reduces anxiety levels. The effect is partly due to a normalization of cortical glucocorticoid receptors in both males and females.[204]

The CB2 receptor is found on microglia.[205–208] CB2 activity reduces inflammation by inhibiting the inflammasome protein NLRP3[209] Activation of CB2 receptors increases IL-10[210,211], which we have found prevents PV loss in MS animals.[53] CB2 agonists activate the MAPK-ERK pathway via a Gβγ subunit and alter cell migration and increases neurogenesis.[212–215]

While a cannabis intervention has yet to be examined in an animal model of early maltreatment, we know that treatment with a CB1/2 agonist during a sensitive period can impair function. Treatment in early or mid-adolescence, but not in late adolescence or adulthood, alters GABA-A activity; frequency-dependent activity in the prefrontal cortex is disinhibited to juvenile-like levels in adults (arrested development).[216] Increased CB2 receptor expression, on the other hand, produces an anti-depressant-like action.[217] Consistent with an intervention occurring before pruning begins, the existing literature on adolescent THC/CB1 exposure in animals suggests that a sensitive period occurs before adulthood, with most studies suggesting exposure before puberty onset in males as critical.[216,218–220]

Non-pharmacological interventions that reduce inflammation—A host of other approaches are under development to reduce inflammation/increase GABA levels as a means of treatment for a maltreated population. Yoga and meditation have been studied for years. Meditation can reduce brain aging[221], and reductions of stress-induced changes in emotional regulation dysfunction[222], and IL-6 are reported.[223] A recent review of the appropriateness of mindfulness for maltreatment patients, including pros and cons, of mindfulness-based interventions, exists.[224,225]. Researchers find that yoga is helpful.[226]

Another approach is to manipulate the microbiome to reduce inflammation.[227,228] Studies associating food intake with major depression exist, but studies including maltreatment, hopefully, are forthcoming. Finally, there is nothing better than human touch. Adoption studies in humans[229] or manipulations in rats[230] show that social interaction can have a positive impact.

Discussion

Early adversity mediates part of its effects on brain development by increased inflammation. One objective of the current review was to discuss the differential impact that the occurrence of adversity during a sensitive period has on maturation, and to highlight its importance for predicted effects and maximum vulnerability. The second objective was to introduce the role of microglia as a key mediator for both developmental changes and inflammation. Finally,

the third objective presents specific examples of neuroinflammatory agents, adversity, and neuroanatomical and behavioral change.

One important facet to discuss is the role of individual differences. Not all individuals exposed to early adversity show changes in brain development, increased inflammation, or psychopathology. Clinical studies that examine group differences may miss the effect of adversity by assuming otherwise. Data showing individual data points show this plainly. Such differentiation is not always possible, with MRI analyses requiring group analyses as an example. Markers that can help segregate groups to allow for a more refined analysis are key to both predictions of who will be adversely affected and those who are resilient. These markers are also the key to identify the middle group: those whose trajectory of development predicts adverse consequences, but intervention can redirect this course. Possible biomarkers are GABA/parvalbumin and inflammation in combination.

We also need to get the timing right, in a sex-dependent manner. When individual data points are published, it is easier to see why certain group differences are not significant. More importantly, individual data allow us to see those subjects that are more vulnerable[231] The animal data, with more experimental control than human studies, also show trends to two groups of outcomes after early exposure to adversity.[11,51,119] What additional data might we need? Maybe some of the markers are found here.

Conclusions

Stress is known to increase inflammation. Depending on the state of development, microglia increase or decrease inflammation. If the region of interest is undergoing active synaptogenesis, the microglia are activated and over-prune the synapses. While details of this process are an active area of investigation, we know that elevated inflammation adversely affects the GABAergic parvalbumin cells. As they are lost, the excitatory/inhibitory balance shifts, and the brain over-prunes. The rationale is that the brain matures in a way to match its environment. Here, the brain exposed to maltreatment has fewer synapses, is less plastic, and is less flexible in its behavioral repertoire.

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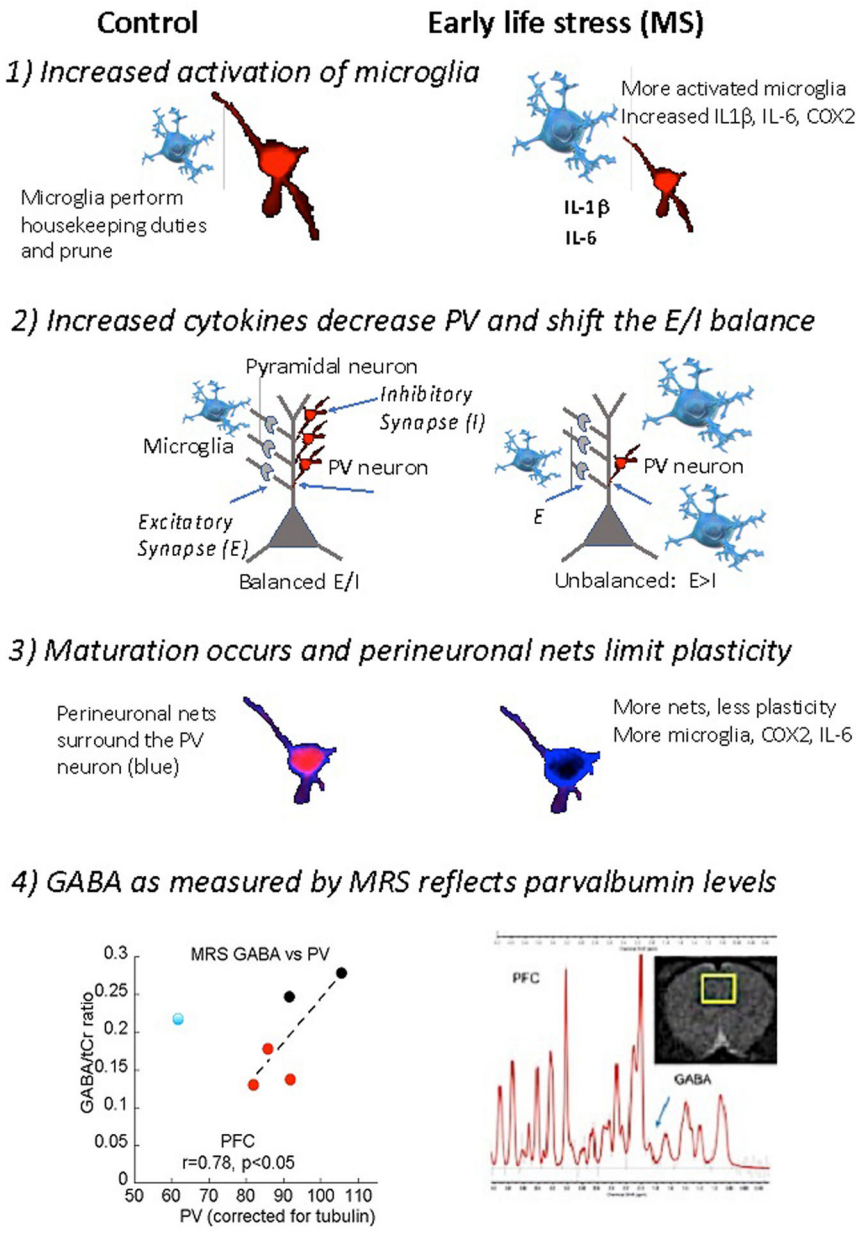

Figure 1.

A simplified model of the interactions of microglia (blue), parvalbumin neurons, and pyramidal neurons (gray) across age. Typically, microglia aid in pruning but will switch to an activated form and increase inflammatory factors. Second, cytokines decrease parvalbumin (PV; red) neurons and shift the balance to more excitation. Third, eventually, the neurons are surrounded by perineuronal nets (blue), and plasticity is limited. (Bottom) Voxel placement on the right in adolescent male rats. MRS data of GABA/tCr versus PV levels from the same animals as assayed by Western immunoblot[152]. We can detect GABA levels with magnetic resonance spectroscopy (MRS) and compare them to PV levels later. Shown are controls animals (black dots), rats with a history of maternal separation (red dots). Levels of PV were quantified with Western Immunoblot, using our standard methods.

The spectrograph and the location of the voxel are on the right. Credit to Dr. Dionyssios Mintzopoulos for the MRS data.

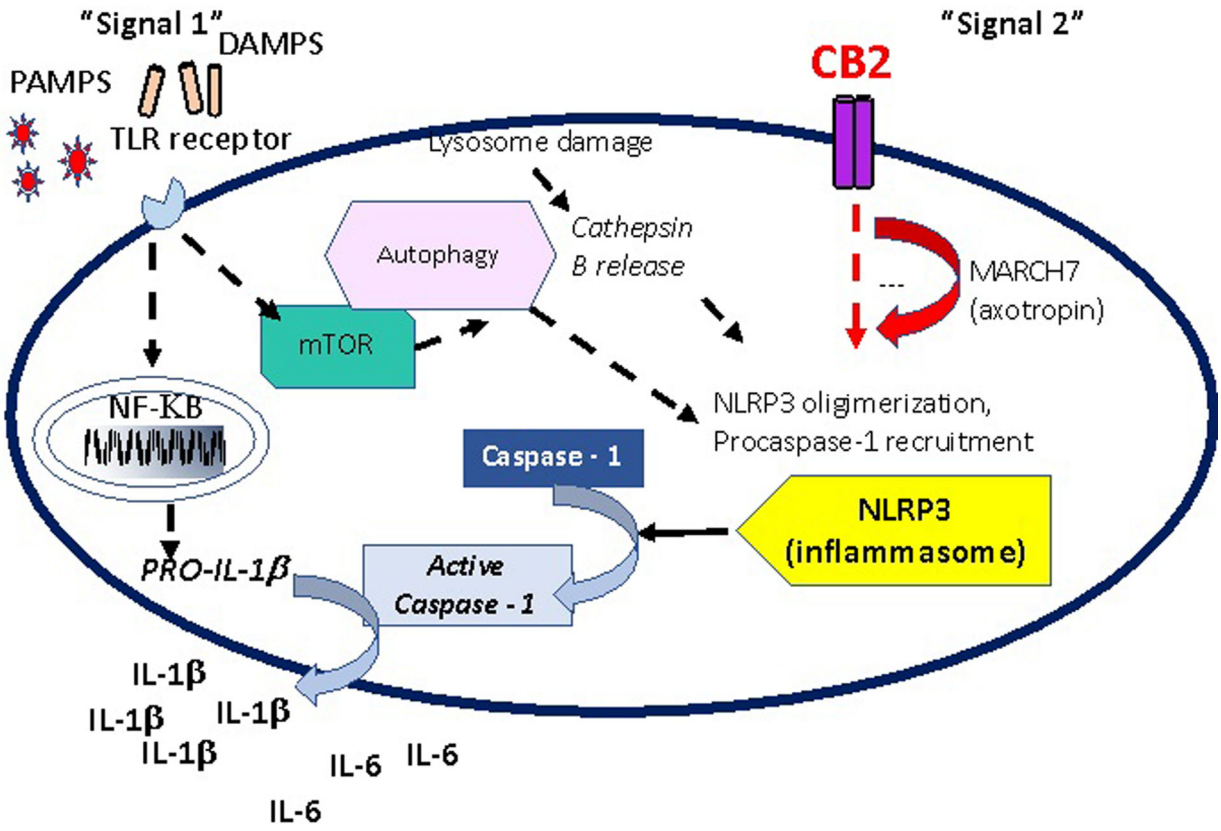

Figure 2.

Two different types of signals activate the innate immune system. The first pathway, mediated by the toll receptors (TLRs), recognizes an initiating pro-inflammatory signal. The second is mediated by the inflammasome, which has a well-recognized role in depression. The key protein complex, (Nod)-like receptor family pyrin domain-containing 3 (NLRP3), is a target of novel therapeutics. This complex is modulated by the cannabinoid receptor 2 (CB2), MARCH7 (axotropin). Signal 1 via the TLRs initiates the synthesis of NF-KB, which is involved in the synthesis of a Pro-IL-1b. The NLRP3 activates Caspase-1, which then results in a cleaved and active IL-1b. This simplified diagram suggests that there are two different points of access to regulate inflammation.