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Broken or maladaptive? Altered trajectories in neuroinflammation and behavior after early life adversity

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ABSTRACT

Exposure to adversity and stress early in development yields vulnerability to mental illnesses throughout the lifespan. Growing evidence suggests that this vulnerability has mechanistic origins involving aberrant development of both neurocircuitry and neuroimmune activity. Here we review the current understanding of when and how stress exposure initiates neuroinflammatory events that interact with brain development. We first review how early life adversity has been associated with various psychopathologies, and how neuroinflammation plays a role in these pathologies. We then summarize data and resultant hypotheses describing how early life adversity may particularly alter neuro-immune development with psychiatric consequences. Finally, we review how sex differences contribute to individualistic vulnerabilities across the lifespan. We submit the importance of understanding how stress during early development might cause outright neural or glial damage, as well as experience-dependent plasticity that may insufficiently prepare an individual for sex-specific or life-stage specific challenges.

1. Introduction

Early life experiences—both positive and negative—can have profound effects on brain development in mammals. Rearing environments that are enriched with good parental care, suitable protection, and engaging sensory stimulation offer resilience to insults later in life such as psychological stressors (Francis et al., 2002) or even pathological infection (Johnson et al., 2014). In contrast, early life adversity (ELA) such as parental deprivation, neglect, abuse, or exposure to threats has been repeatedly shown to yield a myriad of deviations in brain circuitry, stress-responsivity, cognitive function, and general health (Anda et al., 2008; Dube et al., 2009; Brown et al., 2010). In this review, we will discuss the current progress in understanding intervening variables that underlie vulnerability, resilience, and behavior after ELA, with a focus on the evolving knowledge of neuroimmune influences. We will present findings from both human and animal research, since a comprehensive and clinically relevant view will only come from a synthesis of both realms. Models of ELA vary widely across studies, and each provides a distinct characteristic of exposure and effects. A full comparison of all models is beyond the scope of this review; therefore we will present different models throughout and highlight the implications of differences when possible.

The idea of modeling the correct kind of ELA is irrelevant, since there is no single type of exposure, and the remarkable plasticity exhibited by the brain is largely

Abbreviations: ADHD, attention deficit hyperactivity disorder; COX-2, cyclooxygenase-2; ELA, early life adversity; HPA, hypothalamic-pituitary axis; IFN, interferon; IL, interleukin; PFC, prefrontal cortex; PTSD, post-traumatic stress disorder; SHP, stress hyporesponsive period; SHRP, spontaneously hypertensive rats; TNF, tumor necrosis factor.

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experience-dependent. For example, growing evidence from human studies strongly suggests that gray matter volume, cortical thickness, and white matter integrity are differentially altered across brain areas depending on the type of ELA exposure (Tomoda et al., 2009). Animal work has revealed that stressful experiences in general can have functionally relevant effects on dendritic arbor, spine, and synapse number in many brain regions, including the hippocampus, amygdala, and the prefrontal cortex (PFC), with effects on cognition, emotional regulation and neuroendocrine function (McEwen and Gianaros, 2011). These effects can occur through excitotoxicity (Moghaddam, 1993), oxidative stress (Madrigal et al., 2001; Manikandan et al., 2006; Spiers et al., 2013), and inflammation (Munhoz et al., 2010). When presented early in life, these processes can prevent typical developmental patterns of innervation and receptor activity, and cause unhealthy sensitization of the immune response (Hennessy et al., 2011). For example, stress-induced activity of the immune and neuroendocrine systems (McEwen and Magarinos, 1997; Goshen and Yirmiya, 2009; Sorrells et al., 2009) reportedly causes neuronal damage in areas such as the hippocampus (Schneider et al., 1998; Avital et al., 2003; Ross et al., 2003; Frank et al., 2012), striatum (Relton and Rothwell, 1992) and PFC (de Pablos et al., 2006). At the same time, altered neurotransmission (Gunn et al., 2013), synaptogenesis (Aisa et al., 2009; Jutapakdeegul et al., 2010), and immune responsivity are consequences of ELA that could be interpreted as adaptations to the environment in preparation for future challenges (Tottenham and Sheridan, 2009). Indeed, ELA represents stressors that impact the brain during a time of rapid development and, importantly, during a time preceding the tumultuous period of adolescence. Here, we will explore the young but growing landscape of how neural and immune developmental trajectories that drive behavior intersect (or fail to intersect) with environmental demands over the lifespan.

ELA impacts the immune system at the time of exposure (Hennessy et al., 2010, 2011), and can also alter the normal developmental trajectory of certain immunological processes (e.g., Coe et al., 1989). One consequence of these early alterations is a heightened immune response to stressors later in life (see Tables 1 and 2). The adaptive advantage of heightened immune function in response to stress can be seen from an evolutionary perspective, since a psychological stressor would typically occur alongside a threat to an animal's physical well-being (e.g., injury, predator). Therefore, a sensitized immune response to future stressors could better prepare an animal for future threatening environments. In one well-characterized example, a behavioral consequence of heightened inflammation is the phenomenon of sickness behavior. The lethargy, social avoidance, and anhedonia associated with being exposed to an immunostimulant (e.g., a pathogen) can be viewed as a part of the organism's effort to recruit all of its resources for fighting against the invading pathogen and overcoming the disease (Hartung et al., 1988). Sickness behavior purportedly shares phenomenology and immunological physiology with major depressive disorder (Maes et al., 2012). In this very simple sequence, we begin to see a role of immunity in ELA-attributable depression. Therefore, the life-long consequences of ELA could be viewed very differently as either a result of, or a response to, these stressful experiences. This conceptual distinction is worthy of attention as we attempt to understand the what's and why's of vulnerability to mental illness after ELA.

2. Behavioral effects of early life stress across the lifespan

ELA causes children to experience their environment as threatening, perceiving themselves as having no value and regarding the future as being not trustworthy (Dube et al., 2003). A history of ELA consequentially increases the risk of developing a psychiatric disorder in adulthood (Rojo-Moreno et al., 1999; Ritchie et al., 2009; Wright et al., 2009; Carr et al., 2013). Models of plasticity such as the allostatic load and reactive scope models have been useful to understand the mechanisms underlying psychopathology after ELA (Howell and Sanchez, 2011). In these models, the pathological consequences of ELA have been attributed to a dysfunction in homeostasis of neural, endocrine, or immune functions. It has also been proposed that the effects of ELA on allostatic load can contribute to diathesis for stress-mediating disorders later in life (Grassi-Oliveira et al., 2008; Rogosch et al., 2011; Danese and McEwen, 2012).

Notably, ELA-exposed individuals have an earlier age of onset for several disorders such as depression and substance abuse (Andersen and Teicher, 2008; Scott et al., 2012) compared to the general population. These individuals also have a greater risk of self-harm and have poorer response to treatment in comparison to non-maltreated people with same psychopathologies (Nemeroff et al., 2003). These findings are indicative of the major differences between individuals affected by ELA versus later stressors, and show a need to understand the underlying biology and behavior caused by ELA over a lifespan.

3. Neuroinflammation and psychopathology

The immune system has been implicated in vulnerability to psychopathologies over the lifespan. For example, many clinical studies have provided evidence for the influence of immunological activation during the prenatal or early postnatal period on behavioral, psychological and neurological consequences such as schizophrenia and Parkinson's disease (Brown et al., 2004; Bilbo and Schwarz, 2009; Kohman and Rhodes, 2013). This research has shed light on how the interactive influence of the hypothalamic pituitary axis (HPA), sympathetic nervous system, and immune system can contribute to the effects of ELA.

The well-orchestrated mammalian immune system has two major kinds of immune responses: innate and adaptive. Both are responsible for detecting and regulating foreign threats, and inflammation resulting from both has been associated with psychopathology (Miuller and Schwarz, 2007; McNally et al., 2008; Raison and Miller, 2011). The innate immune system is the first line of the host defense, and involves a rapid response of patrolling cells such as macrophages and microglia. The adaptive

Table 1
Rodent studies of ELA inflammatory effects. Papers were identified using search terms "early life stress" or "maternal separation" or "neonatal stress" with "inflammation" or "inflammatory", excluding transgenic models or sensitive lines (to eliminate the complication of interactive effects). White cells: infancy; shaded cells: adolescence; gray cells: adulthood.

ELA paradigm	ELA period	Species	Age at measure	Tissue/sample	What was measured	ELA Effect (sex affected)	Sex	Sex difference?	Reference
Maternal Deprivation 24h	P9	Wistar Rat	P13	spleen	LPS-induced lymphoproliferation	↓(males)	both	Effects in males only	(Viveros et al., 2009)
Maternal Separation 3h/day	P2-14	Wistar Rat	P16	Whole brain mRNA	IL-1β; IL-10	↓	male	N/A	(Dimatelis et al., 2012)
Maternal Separation 15 min/day[a]	P1-21	Mouse	P14, P21	Hippocampus mRNA	Lipopolysaccharide Binding Protein (LBP)	↓	male	N/A	(Wei et al., 2012)
Maternal Deprivation 24h	P9	Wistar Rat	P40	spleen	Con-A lymphoproliferation	↓(both)	both	none	(Viveros et al., 2009)
Maternal Separation 4h/day	P2-20	SD Rat	P40	Plasma protein	IL-1β; IL-6	↑	male	N/A	(Wieck et al., 2013)
Maternal Separation 3h/day	P1-10	Mouse	P45	Bronchoalveolar fluid protein	Ovalbumin-induced: macrophages IL-4 IFNγ Lymphocytes	 ↑(both) ↓(both) ↓(both) ↓(males)	both	yes	(Vig et al., 2010)
Maternal Separation 4h/day	P2-20	SD Rat	P40	PFC protein	Cyclooxygenase-2	↑(males) ⃠(females)	both	yes	(Holland et al., 2014; Holland et al., 2014 (in press))
Maternal Separation 4h/day	P2-20	SD Rat	P40	HIP protein	Cyclooxygenase-2	⃠	male	N/A	(Brenhouse and Andersen, 2011b)
Maternal Deprivation 24h	P9	Wistar Rat	P75	spleen	LPS-induced lymphoproliferation	↓(males) ⃠(females)	both	yes	(Viveros et al., 2009)
Maternal Separation 6h/day	P1-14	Mouse	P56-70	Lung mRNA	Influenza-induced: IL-1α, β; TNFα; IL-12; IFNγ (fold-increase from controls)	↑(females)	both	yes	(Avitsur et al., 2006)
Maternal Separation 2h/day	P1-28	F344 Rat	P150	Brochoalveolar fluid	Ovalbumin-induced lymphocytes	↑	male	N/A	(Kruschinski et al., 2008)
Maternal Separation 2h/day	P1-28	F344 Rat	P150	Blood plasma protein	Ovalbumin-induced IL-6	⃠	male	N/A	(Kruschinski et al., 2008)
Maternal Separation 3h/day	P1-14	Mouse	P76	Mesenteric lymph node protein	DSS colitis-induced[a] IFN-γ; TNFα	↑	male	N/A	(Veenema et al., 2008)
Maternal Separation 6h/day	P1-14	Mouse	P49-70	Serum protein	LPS-induced TNFα LPS-induced IL-1β LPS-induced IL-6	↓(females) ↓(males) ⃠	both	yes	(Avitsur et al., 2013)
Maternal Separation 3h/day	P2-12	SD Rat	adult	Colonic mucosa protein	Toll-Like Receptors 3,4,5	↑	male	N/A	(McKernan et al., 2009)
Maternal Separation 15 min/day[b]	P1-14	Mouse	P70-80	Striatum mRNA	Ischemia-induced IL-1β; TNFα	↑	male	N/A	(Craft et al., 2006)

[a] Fifteen-minute maternal separation is typically referred to as Handling, which can induce increased maternal behavior and have opposite effects from ELA; however in this paradigm, a highly stress-reactive mouse strain was used which displays heightened corticosterone release in response to this type of separation.
[b] In this paradigm, pups were also separated from bedding and were not thermoregulated, thus this was presented as ELA.

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[b] In this paradigm, pups were also separated from bedding and were not thermoregulated, thus this was presented as ELA.

Table 2
Human studies of ELA inflammatory effects. Papers were identified using search terms "early life stress" or "childhood adversity" or "childhood maltreatment" or "childhood trauma" with "inflammation" or "inflammatory". Anti-inflammatory modulators are in italics. Light gray cells: childhood; shaded cells: adolescence; gray cells: adulthood.

ELA assessment	ELA type	ELA period	Age at measure	What was measured*	ELA effect	Sex	Sex difference	Reference
Longitudinal Birth Cohort	adversity	6-8 yrs	10 yrs	C-Reactive Protein IL-6	↑ ↑	Both	Not assessed	(Slopen et al., 2013)
Longitudinal Birth Cohort	adversity	0-6 yrs	10 yrs	C-Reactive Protein IL-6	⊘ ⊘	both	Not assessed	(Slopen et al., 2013)
Longitudinal Birth Cohort	adversity	1.5 yrs	15 yrs	C-Reactive Protein IL-6	↑ ⊘	both	Not assessed	(Slopen et al., 2013)
Longitudinal Birth Cohort	adversity	2-7 yrs	15 yrs	C-Reactive Protein IL-6	⊘ ⊘	both	Not assessed	(Slopen et al., 2013)
Risky Families Questionnaire	Harsh family environment	0-14 yrs	15-19 yrs	IL-6	⊘	females	N/A	(Miller and Chen, 2010)
Risky Families Questionnaire	Harsh family environment (cohort at familial risk for depression)	0-14 yrs	15-19 yrs	LPS-induced IL-6	↑	females	N/A	(Miller and Chen, 2010)
Childhood Trauma Questionnaire	maltreatment	<18 yrs	Adult	TNFα TNFα receptor	↑ ↑	females	N/A	(Levandowski et al., 2013)
Childhood Trauma Questionnaire	physical neglect	<18 yrs	Adult	Fibrinogen *adiponectin*	↑ ⊘	both	Not assessed	(Zeugmann et al., 2013)
Childhood Trauma Questionnaire	maltreatment	<18 yrs	Adult	Acute stress-induced IL-6	↑	both	Not assessed	(Carpenter et al., 2010)
Adverse Childhood Experiences Questionnaire	adversity	<18 yrs	Adult	*adiponectin* TNFα TGFβ 1 IL-6	↓ ↑ ↑ ↑	females	N/A	(Tietjen et al., 2012)
Longitudinal Birth Cohort	maltreatment	3-11 yrs	Adult	Hs C-Reactive Protein Fibrinogen White Blood Cell count	↑ ↑ ↑	both	Not assessed	(Danese et al., 2007)
Longitudinal Birth Cohort	Parental separation; low material and psychosocial resources	0-16 yrs	44 yrs	C-Reactive Protein	↑	both	Not assessed	(Lacey et al., 2013)
Questionnaire	Physical and/or sexual abuse	childhood	49-63 yrs	*adiponectin* Resistin	↓ ⊘	both	Not assessed	(Lehto et al., 2012)
Childhood Trauma Questionnaire	trauma	childhood	~34-40 yrs	IL-6 TNFα IL-1ß IL-8	↑ ↑ ⊘ ⊘	both	Not assessed	(Dennison et al., 2012)

system is uniquely associated with the production of immune memory responses that are protective and also can be easily activated upon later encounters with specific pathogens (Chaplin, 2006). When these responses are inappropriately provoked, harmful inflammation is induced from pro-inflammatory cytokines such as IL-1β, IL-2, IL-6 and TNF-α secreted by activated microglia, macrophages and lymphocytes (Miuller and Schwarz, 2007; Haroon et al., 2012). Inflammatory activity is countered by other subsets of astrocytes, T lymphocytes, macrophages and monocytes that secrete anti-inflammatory cytokines including IL-10, IL-5 and IL-4 (Muller et al., 2000; Raison et al., 2010; Haroon et al., 2012). Innate and adaptive immunity both play critical roles in early development and aging (Schwarz and Bilbo, 2011), but very few studies have looked at normative lifespan development of the immune system (Siegrist and Aspinall, 2009), which may impact pathogenesis of mental illnesses.

Pro-inflammatory immune activation has been linked to psychiatric disorders such as depression, schizophrenia and obsessive–compulsive disorder (Jones and Thomsen, 2013; Valkanova et al., 2013). For example, a meta-analysis controlling for antipsychotics revealed consistently elevated levels of several immune molecules released from macrophages, such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ and interleukin (IL)-12 in cases with schizophrenia (Miller et al., 2011). Cell cultures obtained from individuals with schizophrenia also produced higher levels of circulating IL-8 and IL-1β, further implicating immunity in schizophrenia pathology. In obsessive–compulsive disorder studies, polymorphisms in the TNF-α gene have been described (Cappi et al., 2012), as well as both increases and decreases in plasma TNF-α cytokine levels (Monteleone et al., 1998; Denys et al., 2004; Konuk et al., 2007). It has been proposed that cytokine gene polymorphisms can have variable effects between individuals (Cappi et al., 2012). In another meta-analysis, raised levels of the pro-inflammatory proteins IL-6 and C-reactive protein were significantly associated with the later development of depressive symptoms in prospective studies. In order to understand how these changes in the immune response can lead to susceptibility to a number of psychopathologies, we review the two major ways in which neuroinflammation can affect the brain: neuronal damage and altered neurotransmission.

A neuroinflammatory response typically occurs when signals involving infection or irritation are evoked in the brain, or through vagal afferents, transport of cytokines into the brain through the blood–brain-barrier (BBB), or infiltration of cytokines where the BBB is absent (Schoderboeck et al., 2009; Northrop and Yamamoto, 2012; reviewed by Schwarz and Bilbo, 2011). Microglia are resident immune cells in the brain and are known to play a major mediating role in neuroinflammation. Although the mechanism by which neuroinflammation causes etiology of behavioral and psychological disorders is not fully understood, the damaging effects of microglial and astrocyte activation on neuron function and circuitry are being elucidated. Under normal circumstances, resting microglia continuously survey the brain parenchyma (Nimmerjahn et al., 2005). Microglia become activated in response to various danger signals posed by neurons and/or astrocytes (Davalos et al., 2005) and have local protective effects via regulated release of cytokines and phagocytosis of cellular debris. Under conditions of serious injury, microglia become reactive, characterized by heightened release of inflammatory mediators. When reactive, microglia can be neurotoxic and damage otherwise healthy neurons (Banati and Graeber, 1994). For example, activated microglia release nitric oxide (NO) (Chao et al., 1992). While low levels of NO function as signaling molecules, high levels of this free radical can cause neuronal cytotoxicity (Uttara et al., 2009). Several studies have shown that excess production of free radicals such as NO contributed significantly to neuronal loss in schizophrenia, Parkinson's and Alzheimer's disease (Mahadik and Mukherjee, 1996; Christen, 2000; Beal, 2003), likely through excitotoxicity and apoptosis (Kehrer, 2000). These mechanisms may partially explain the etiology of psychopathologies that emerge after ELA. It is noteworthy that different insults may summate upon microglia and potentiate each other to worsen the outcome of the response (Luo and Chen, 2012). It is therefore plausible that ELA acts to sensitize microglia toward a lower threshold for a reactive state, leading to increased inflammatory cytokine levels and altered neurotransmission. Alternatively, activated microglia can express anti-inflammatory cytokines and play a role in tissue protection and repair.

Neuroinflammatory influences on neurotransmission and morphology also rely largely on glial activity. Activated microglia may contribute to neuroplastic changes through synaptic remodeling, excitatory transmission, and phagocytosis of newborn neurons and cellular debris (reviewed by Kovacs, 2012). Monoamine transmission is also affected by neuroinflammation. In activated microglia, tryptophan is metabolized by indoleamine to the NMDA agonist quinolinic acid instead of serotonin (Steiner et al., 2011). Microglial activity has therefore been directly linked to depressive symptoms through a reduction in serotonin production (Muller, 2014). Importantly, neural-immune interactions begin during fetal development (Schwarz and Bilbo, 2011), and a growing landscape of data supports an active role for these interactions on the programming of lifelong function.

4. The neuroinflammatory link between ELA and behavioral changes

Pioneering work describing how ELA can alter immunological development was conducted in the 1980s in primates (Laudenslager et al., 1982, 1990; Coe et al., 1987, 1988, 1989). Since then, the growing appreciation for an immunological contribution to mental illness has led to a resurgence of interest in neuroimmune interactions. Tables 1 and 2 display studies over the past 15 years directly investigating the effect of ELA on later immune function in rodents (Table 1) and humans (Table 2). Despite stress paradigms, species/strain differences, and age differences, a pattern emerges suggesting ELA leads to increased pro-inflammatory responsivity in early adolescence or later. This heightened response is likely a consequence of the

early response to ELA during and immediately following exposure.

4.1. Immediate immune effects of ELA

Measurements taken during or immediately after ELA, which understandably have largely been studied in non-humans (Table 1 and (Laudenslager et al., 1982, 1990; Coe et al., 1987, 1989), often reveal a *suppression* of inflammatory responses in stressed infants. Many of the studies showing immune suppression targeted the adaptive immune responses of lymphocyte proliferation, while other studies that measured circulating cytokines or macrophage proliferation (Coe et al., 1988) reported mixed results including an increased response in preweanlings and infants. While the peripheral response to ELA may not be an overall activation or suppression, early immune programming through ELA appears to sensitize later pro-inflammatory processes and lead to greater vulnerability to depression and anxiety in adulthood (Hennessy et al., 2010).

In the brain, glial proliferation, glial activity and direct neuronal response to cytokines are crucial for healthy brain development (Eyo and Dailey, 2013). The importance of immune activity during early development is gleamed from the peak of cytokine concentrations, cytokine receptor densities, and glial activity shown in rodent and ex vivo models during this period (Giulian et al., 1988; Gadient and Otten, 1994). Glia-mediated mechanisms control synaptogenesis (Chamak et al., 1995; Christopherson et al., 2005), apoptosis (Frade and Barde, 1998), synaptic pruning (Stevens et al., 2007; Garay and McAllister, 2010), and myelination (Pang et al., 2013). The impact of ELA on developmental processes therefore likely involves aberrant glial activity.

ELA from maternal separation has been shown to decrease microglial number in midbrain areas (Chocyk et al., 2011), decrease cytokine expression (Dimatelis et al., 2012), and decrease acute-phase proteins like lipopolysaccharide binding protein (Wei et al., 2012) in the rodent brain. Taken together, it appears that suppression of glial activity during early development is the earliest neuroimmune response to ELA. Behavioral consequences have also been noted early on, as this suppressed neuroinflammation co-occurred with anhedonic and withdrawal behaviors (Hennessy et al., 2010) and altered fear learning (Callaghan and Richardson, 2011) in rodents. However, guinea pigs that are separated from their mother exhibit a characteristic behavior that resembles sickness behavior, and is reportedly blocked with anti-inflammatory treatment (Hennessy et al., 2007, 2011; Perkeybile et al., 2009), suggesting that pro-inflammatory processes play a role in these early responses to ELA as well. In mature animals, glucocorticoid exposure has been shown to activate neuroinflammatory processes, leading to a sensitization of microglia to a pro-inflammatory state (Frank et al., 2012). However, during early postnatal life, microglia display an immature phenotype (Schwarz and Bilbo, 2012) and sensitization of immature microglia to psychological stress has not been directly investigated.

Direct effects of early life infection, as elegantly presented by Bilbo and colleagues, further highlight the critical role of the immune system in brain development with particular influence from microglia. For example, healthy levels of microglial activity are necessary for phagocytosing apoptotic neurons and unneeded synapses during development (Schafer et al., 2012; reviewed by Bilbo and Frank, 2013). Infection or otherwise exacerbated inflammation in neonate rats can sensitize microglia to become over-activated upon future infections in adulthood, causing impaired cognitive flexibility (Bilbo and Frank, 2013; Williamson and Bilbo, 2014). This is one example of how early life programming is affected by experience. Notably, neonatal infection leads to transient neuroinflammation in the brain (Lieblein-Boff et al., 2013), which differs from the apparent suppression of neuroimmune activity during ELA. It is unclear—and an important topic of investigation—how early suppression of microglial activity translates to the heightened neuroinflammatory state observed later in life after ELA. However, we will generalize here to acknowledge that altered neuronal-glial programming could incite neuronal circuitry to compensate for an unpredictable environment.

4.2. Delayed and prolonged immune effects of ELA

As mentioned above, ELA has been shown in the short-term to suppress some types of inflammatory activity in the brain and periphery; however ELA often leads to exacerbated pro-inflammatory activity later in life (see Tables 1 and 2). Given the important role of the immune system in normal brain development, it is not surprising that an altered trajectory of inflammatory responses will lead to atypical brain development after ELA. However, the immune-related effects of ELA are not yet fully understood. It will be important to determine whether different types or time-courses of ELA can differentially affect immunity depending on the presence of a secondary insult, the developmental stage of assessment, or the sex of the individual.

ELA has been observed to produce developmentally distinct psychiatric outcomes. In humans, externalizing disorders such as aggression and cognitive dysfunction are apparent during childhood and early-adolescence (Egeland et al., 2002; reviewed by Gunnar and Fisher, 2006), while disorders such as depression, schizophrenia, and drug addiction are often not observed until adolescence or early adulthood (Lewis and Levitt, 2002; Andersen and Teicher, 2009; Teicher et al., 2009). The display of cognitive deficits and aggression during childhood compared to the later presence of depressive, addictive, or psychotic symptoms raises the question whether inflammatory activity after ELA prospectively affects distinct circuits in the brain at different developmental stages. Inflammatory cytokine receptors are dense in several areas controlling cognitive function such as the hippocampus (Tancredi et al., 2000; Vereker et al., 2000; Curran and O'Connor, 2003; Butler et al., 2004) and PFC (del Rey et al., 2013), and pro-inflammatory interventions have been shown to directly impair cognitive processing in people (Harrison et al., 2009). A direct relationship between aggression and pro-inflammatory processes in humans has also been reported

(Coccaro et al., 2014). It is therefore likely that a sensitized inflammatory response yields impaired cognition and externalizing behaviors after ELA.

Depression and schizophrenia, which manifest in adolescence or later, are also purportedly linked to pro-inflammatory processes, however this link is not fully understood. While ELA in humans has been associated with elevated inflammatory C-reactive protein and IL-6 in late childhood (age 10) (Slopen et al., 2013), inflammatory markers during late childhood and adolescence do not consistently predict later episodes of depression (Copeland et al., 2012; Slopen et al., 2013). That said, Miller and Cole (Miller and Cole, 2012) recently reported that female adolescent women exposed to ELA expressed higher levels of IL-6 that forecasted depression 6 months later. In patients with schizophrenia, 40% of individuals displayed increased microglial activation and inflammatory cytokine mRNA expression in the dorsolateral PFC, with the greatest effect in those who had been most recently diagnosed, suggesting inflammation might be an early causative factor. It is also likely that the subset of patients with schizophrenia who also displayed an inflammatory profile represented a unique population that had undergone ELA, since patients with childhood trauma—but not those without such experience—reportedly have heightened inflammatory markers than healthy controls (Dennison et al., 2012). However, these inflammatory changes do not reveal a mechanism for the delayed manifestation of illnesses like depression and schizophrenia after ELA. It is possible that the late and protracted development of the prefrontal cortex (PFC)—which is not fully mature until early adulthood (Giedd et al., 1999)—delays the full impact of a sensitized immune response after ELA on affective control.

In a rodent model, we have observed that maternal separation ELA leads to a loss of PFC interneurons (Brenhouse and Andersen, 2011a), which is a purported mechanism of schizophrenia that is linked to inflammatory and excitotoxic damage (Behrens and Sejnowski, 2009). We have also observed that rats exposed to maternal separation display deficits in PFC-mediated behaviors such as learned helplessness (Leussis et al., 2012), social interaction (Holland et al., 2014), and working memory (Brenhouse and Andersen, 2011b) in adolescence, with increased peripheral levels of the inflammatory cytokines IL-β and IL-6 (Wieck et al., 2013). It is possible that development of the neuroinflammatory response partially underlies the delayed effects of ELA, since maternal separation in rats was shown to yield neuroinflammatory changes in the PFC that correlated with interneuron deficits and manifested in adolescence, but not before (Brenhouse and Andersen, 2011a). Specifically, the neuroinflammatory mediator cyclooxygenase-2 (COX-2) was upregulated in the PFC in adolescent males, and PFC interneuron loss was prevented with pre-adolescent COX-2 inhibition (Brenhouse and Andersen, 2011a). ELA-exposed males did not display this increase of COX-2 in juvenility. Since these changes co-occurred with altered glutamatergic NMDA receptor expression (Wieck et al., 2013), we hypothesize that aberrant glutamatergic innervation from subcortical regions during adolescence could play a role in increased neuroinflammatory activity within the PFC. Indeed, ELA has been shown in several species to induce a dysbalance between inhibitory and excitatory signaling in the PFC (Bock et al., 2014). Both depression and schizophrenia in humans have been attributed to both dysfunctional glutamate signaling and related inflammatory mechanisms (Myint et al., 2012; Muller, 2014). Furthermore, microglia contribute to inflammatory mechanisms through glutamate release and may be overactivated in a sensitized state after ELA.

Rodent investigations of behavior and neuroanatomy and functional connectivity studies in humans have shed some light onto how corticolimbic development after ELA might yield age-dependent vulnerability to neuroimmune activity. These studies have revealed that PFC connections with subcortical limbic structures such as the amygdala are immature during childhood and become adult-like during adolescence (Cunningham et al., 2002; Gee et al., 2013b). However, development of other corticolimbic circuits, such as that of the PFC-nucleus accumbens projections in rodents, have been reported to display transient changes during adolescence that are different from both juveniles and adults (Brenhouse et al., 2008). The interplay of altered glial programming in early-developing structures with the later maturation of interconnected regions is largely unknown. However, given the complexity of these intersecting trajectories it is not surprising that lifelong effects of ELA are mediated by the time of exposure as well as the time of assessment.

ELA from childhood neglect has also been associated with later alterations in reward processing in humans (Mueller et al., 2012). Reactivity of the nucleus accumbens (Goff et al., 2013) and other basal ganglia regions (Mehta et al., 2010) in response to emotion or reward is reduced in ELA-exposed teenagers. These effects on reward circuitries are likely due to altered trajectories of connectivity with cortical regions, such as the premature maturation of cortical-amgydala functional connectivity seen after maternal deprivation in rodents (Gee et al., 2013a). We know of no direct investigations into neuroimmune effects from ELA on reward-related regions. However, recent observations in rats raised with *enhanced* maternal care through an early handling paradigm reveal early glial programming in the nucleus accumbens (Schwarz et al., 2011). Specifically, early short-term handling protected rats from later morphine-induced microglial activation within the nucleus accumbens, through an anti-inflammatory mechanism. Microglial activation in reward-related areas has been associated with heightened drug-associated conditioning (Schwarz et al., 2011; Zhang et al., 2012), drug-seeking, and drug-induced neuroplasticity (Kovacs, 2012) in rodents. Astrocyte activity in the nucleus accumbens was also shown to mediate drug reward in mice (Narita et al., 2006). Moreover, changes in innate immune gene expression have been proposed to directly contribute to the development of addiction through cortical hyper-excitability (Crews and Vetreno, 2011), which is exacerbated during adolescent development (Brenhouse et al., 2008). Whether ELA shifts cortical excitatory signaling earlier is not known, however related studies examining prefrontal-amygdala connectivity in previously institutionalized children suggest that other glutamatergic connections with the PFC do indeed develop earlier than in

controls (Tottenham, 2012, 2013). Inflammatory processes thereby likely interact with developing connectivity to contribute to the association of ELA with earlier manifestation of addictive behaviors, e.g. the 2- to 4-fold increase in the likelihood of illicit drug use by age 14 (Dube et al., 2003).

As reviewed by Tottenham and Sheridan (2009), once environmental exposure occurs, it modifies the architecture of the circuit in such a way that certain patterns of future activity are preferred (Knudsen, 2004). We acknowledge here that ELA occurs at a time when the brain is learning how to adapt to its lifelong environment. As these modifications develop, the brain encounters developmental time-points that require particular function. Mental illness or dysfunction may arise if the trajectory of the brain has left it unprepared for transient changes during early through late adolescence. This concept was presented in Greenough's "experience-expectant" model (Greenough et al., 1987), whereby the brain expects and "waits" to interact with the environment by shaping itself based on early experiences during critical periods. Here we have reviewed evidence that neuroimmune development plays an important role in such programming after ELA.

5. Neuroimmune mechanisms underlying sex differences

Measuring developmental and life-long effects of ELA exposure produces a moving baseline from which to gauge anatomical and functional differences. Therefore the addition of sex as a factor in developmental studies is challenging. While some animal studies report stronger effects of maternal separation ELA in females on measures such as HPA axis responsivity (Desbonnet et al., 2008), others report a stronger effect in males (Kunzler et al., 2013) on measures such as catecholamine fiber density. When accounting for sexually dimorphic moderators like HPA responsivity (Klein and Corwin, 2002), neuroimmune development (Schwarz and Bilbo, 2012), and rates of circuitry maturation (Brenhouse and Andersen, 2011b), it becomes clear that the idea of one sex being resilient or vulnerable to ELA is oversimplified.

5.1. Sex differences in HPA responsivity and stress coping

Sex differences in the effects of ELA on HPA responsiveness have been reported. For example, ELA was found to yield higher cortisol levels in females only, both immediately after maternal separation ELA in infant monkeys (Sanchez et al., 2005) and in adolescence after ELA in humans (Burghy et al., 2012). Furthermore, only in females was increased HPA activity during childhood shown to predict lower functional connectivity between the amygdala and PFC and internalizing symptoms (Burghy et al., 2012). These data have been interpreted as a greater sensitivity to the neuroendocrine effects of ELA in females (Desbonnet et al., 2008). However, it is interesting to note that in rats, stress exposure in adolescence yielded increased microglial activation and neuroinflammation in males, but not females (Pyter et al., 2013), suggesting a sex difference in inflammatory response to glucocorticoids.

5.2. Sex differences in glial programming and neuroinflammation

Few studies have directly investigated the sex-specific effects of ELA on immune programming. As Table 2 illustrates, human studies of inflammatory changes after ELA often include both sexes, but typically do not assess sex differences (likely due to limited participants of each sex). Animal studies of ELA have traditionally focused on male models, however a small number of reports have emerged that suggest sexually dimorphic developmental changes after ELA. For example, we recently reported that maternally separated female rats displayed earlier changes in PFC inhibitory interneurons, with concurrent social interaction deficits after maternal separation; male deficits were seen as well, only later in adolescence (Holland et al., 2014). Male deficits were correlated with increases in COX-2 in the PFC, yet ELA-exposed females did not display COX-2 effects (Holland et al., 2014). We also observed in preliminary studies that maternally separated males, but not females, displayed higher circulating levels of pro-inflammatory cytokines during pre-adolescence that predict later cognitive dysfunction (unpublished observations). Additionally, Chocyk et al. (2011) reported decreased glial cells (type unspecified) in the basal ganglia of maternally separated juvenile males, but not females.

Interestingly, microglial colonization of the brain occurs much earlier in males than in females in several regions including the parietal cortex, hippocampus, and amygdala (Schwarz et al., 2012). It has been proposed that sex differences in the colonization and function of glia within the normal developing brain may contribute to distinct windows of vulnerability between males and females (Schwarz and Bilbo, 2012). One might hypothesize that early stress exposure during a period when microglia have colonized these regions in males but not females could lead to preferential sensitization of the neuroimmune response in males, however this has not been determined.

Further supporting evidence of sexually-dimorphic glial programming is gleamed from work by Bilbo and colleagues, who reported that males were more sensitive than females to the long-term effects of early-life immune challenges (Bilbo et al., 2012; Schwarz and Bilbo, 2012). Therefore, males may be more vulnerable than females to the inflammatory consequences of ELA. By adolescence in many species glial activation is greater in typically-developing females, and peripheral inflammatory responses are reportedly more robust in females than males (reviewed by Klein, 2000; Schwarz and Bilbo, 2012). Whether or not ELA or subsequent challenges can impact this dimorphism is not known. In contrast to the above evidence suggesting that males are preferentially affected by ELA via glial mechanisms, a separate study reported that in prenatally-stressed mice, sex-specific hippocampal glial decreases were found only in juvenile female but not male offspring (Behan et al., 2011). As seen in Tables 1 and 2, and as discussed in the previous section, other studies investigating adult females have indeed shown inflammatory changes after ELA [e.g., Miller and Cole, 2012]. These inconsistencies are likely due to the timing, duration, and type

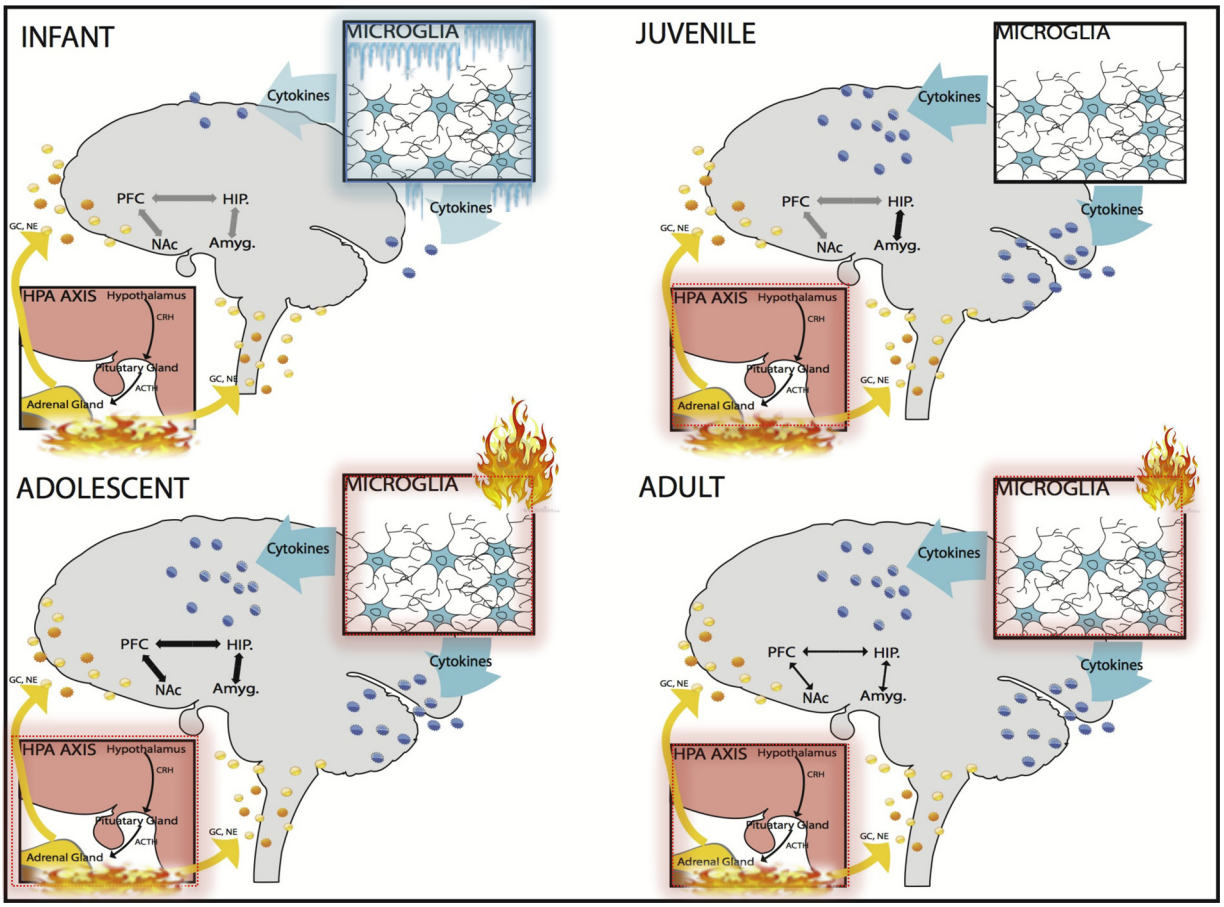

Fig. 1. Hypothetical schematic showing neuroimmune and neuroendocrine influences over development after ELA. Microglial activity is aberrantly suppressed during ELA (illustrated as freezing). Early neuroimmune dysfunction leads to a heightened neuroimmune response later in life (illustrated as heat), which impacts developing corticolimbic circuitries. Concurrently, HPA activity is aberrantly overactivated during ELA (which is more pronounced in females). This leads to a hypersensitivity of the HPA axis later in life which impacts both immune activity and corticolimbic function—themselves developmentally dynamic. Grayed arrows depict immature connections that can be programmed through immune and neuroendocrine influences; bold arrows depict maturing connections that can cause latent behavioral changes after ELA.

of ELA assessed. Indeed, sexual dimorphism has also been observed in circuitry changes after ELA, which can lead to differential vulnerability to neuroinflammation over development. For example, ELA in humans has been shown to decrease amygdala-hippocampus functional connectivity in adolescent females, but not males (Herringa et al., 2013). Amygdala development is in particular flux during adolescence, completing a shift from positive to negative functional connectivity with the PFC (Gee et al., 2013b). Therefore a female-specific effect in the adolescent amygdala is noteworthy when considering potential impacts of ELA and subsequent stress exposure.

Taken together, we present the perspective that males and females might be impacted by ELA differently, with females more vulnerable to early neuroendocrine-induced changes in corticolimbic circuitry, and males more vulnerable to later neuroinflammation, possibly through microglial sensitization. These ideas are entirely understudied and currently speculative, however they highlight the importance of parsing mechanistic changes based on sex and development, and of questioning why these sexually dimorphic responses would exist.

6. Future directions and conclusions

Here we have reviewed the converging evidence that ELA can deleteriously suppress normal inflammatory and neuroinflammatory processes during early development, which may lead to a sensitized immune response and heightened neuroinflammation later in life. Fig. 1 illustrates a simplified hypothetical schematic of how development of the ELA-exposed brain is influenced by neuroimmune and neuroendocrine actions. Both age and sex of an individual can influence the impact of neuroinflammation, since males and females display different time-courses of glial development, proliferation, and colonization. Since neuroinflammation involves aberrant glutamate signaling, altered monoamine synthesis, and synaptogenesis, immune sensitization directly influences circuitry development, which itself is altered after ELA through separate neuroendocrine mechanisms. Concurrently, neuroinflammation causes oxidative damage and excitotoxicity that can directly impair normal development, which also will have discrete impacts on behavior in separate sexes and ages.

Revisiting the philosophy that brain development aims to meet the demands of each stage-specific environment, we see here how ELA derails the typical trajectory. On a psychosocial level, children that are exposed to threatening or negligent environments are met with two forces on their development: First, the stress coping mechanisms in place during early development are over-activated, leading to long-term changes that may be evolutionarily ideal for survival in similarly threatening later life environments, but are not ideal for typical adolescent and adult challenges. Second, neuroimmune systems that are vulnerable to stress during early life are damaged at a time when they are necessary for circuit formation. Therefore, when encountered with day-to-day challenges (i.e., a need for new decision-making in adolescence), the circuits in a severely ELA-exposed brain are—at best—wired for a very different type of challenge or—at worst—mis-wired and dysfunctional.

Given the remarkable plasticity of the brain we expect that many of the deleterious effects of ELA can be treated with interventions that account for gender and target neuro-immune interactions over the lifespan. Notably, targeted prevention—not just treatment, should be a high priority goal of research. ELA exposure may yield a vulnerable population with neurodevelopmental deficits that can particularly benefit from interventions aimed at the mechanisms we review here, possibly during a sex-dependent critical period.

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