

Special Issue Article

Challenges in researching the immune pathways between early life adversity and psychopathology

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Abstract

Exposure to childhood adversity is a critical risk factor for the development of psychopathology. A growing field of research examines how exposure to childhood adversity is translated into biological risk for psychopathology through alterations in immune system functioning, most notably heightened levels of inflammation biomarkers. Though our knowledge about how childhood adversity can instantiate biological risk for psychopathology is growing, there remain many challenges and gaps in the field to understand how inflammation from childhood adversity contributes to psychopathology. This paper reviews research on the inflammatory outcomes arising from childhood adversity and presents four major challenges that future research must address: (a) the measurement of childhood adversity, (b) the measurement of inflammation, (c) the identification of mediators between childhood adversity and inflammation, and (d) the identification of moderators of inflammatory outcomes following childhood adversity. We discuss synergies and inconsistencies in the literature to summarize the current understanding of the association between childhood adversity, a proinflammatory phenotype, and the biological risk for psychopathology. We discuss the clinical implications of the inflammatory links between childhood adversity and psychopathology, including possibilities for intervention. Finally, this review concludes by delineating future directions for research, including issues of how best to detect, prevent, and understand these “hidden wounds” of childhood adversity.

Keywords: childhood adversity, immunity, inflammation, maltreatment, psychiatric disorders, psychopathology

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Introduction

Childhood adversity is widespread and associated with increased risk for mental health problems and psychopathology in adulthood (Danese, 2020; Humphreys & Zeanah, 2015; McLaughlin, 2016; Teicher & Samson, 2013). Childhood adversities are defined as exposures to circumstances that represent a deviation from the expectable environment, either chronic or severe and acute, during childhood or adolescence that require significant adaptation by an average child (McLaughlin, Sheridan, & Lambert, 2014). We will center our discussion of early life adversity (ELA) around the construct of child victimization, which includes experiences of maltreatment by an adult (i.e., emotional, physical, or sexual abuse, and physical or emotional neglect) and bullying by peers (Danese & Lewis, 2017). ELA is associated with greater risk for developing mental disorders early and across the life course in humans, and the odds of developing psychopathology increase as exposure to adversity increases (Kessler, Davis, & Kendler, 1997; Khandaker, Pearson, Zammit, Lewis, & Jones, 2010;

Schaefer et al., 2018). Animal models of ELA experimentally show that the associations between early contexts of stress and later emotional and behavioral abnormalities is likely causal (Cryan & Holmes, 2005; Francis, Diorio, Liu, & Meaney, 1999; Harlow, Dodsworth, & Harlow, 1965; Hinde & Spencer-Booth, 1971; Levine, Chevalier, & Korchin, 1956; Sanchez, Ladd, & Plotsky, 2001; Suomi, 1997).

While exposure to ELA increases the odds of many psychiatric disorders, the association between ELA and different types of psychopathology is generally nonspecific (Green et al., 2010; Kessler et al., 1997; Kessler et al., 2010; McLaughlin et al., 2012; Schaefer et al., 2018). For example, childhood maltreatment predicts several psychiatric disorders, including depression, bipolar disorder, posttraumatic stress disorder (PTSD), and schizophrenia (Gilbert et al., 2009; Varese et al., 2012; Widom, 1999). Childhood maltreatment is associated with an unfavorable course of mental illness, higher rates of comorbid disorders, and more complex presentation of symptoms (Agnew-Blais & Danese, 2016; Maercker et al., 2013; Nanni, Uher, & Danese, 2012). In addition, ELA is associated with many physical health outcomes, including metabolic syndrome, cardiovascular disease, neurodegenerative diseases, cancer, asthma, and aging (Scrivo, Vasile, Bartosiewicz, & Valesini, 2011). Given the nonspecific associations and the co-occurring risk for psychopathology and physical health disorders, inflammation has been proposed as the “common soil” by

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which adversity becomes biologically embedded to influence later psychological and physical functioning (Scriver et al., 2011). The immune system, via inflammation, is increasingly recognized as a pathway to developing psychopathology (Danese & Baldwin, 2017; Nusslock & Miller, 2016). In longitudinal studies of depression, high levels of inflammation predict an increased risk of developing depression, poor response to treatment (Strawbridge et al., 2015), and an unfavorable course of illness (Ford & Erlinger, 2004). In bipolar disorder, high levels of inflammation predict poor treatment response (Mondelli et al., 2015). All of these associations echo the negative psychopathology outcomes in individuals exposed to ELA (Danese & Baldwin, 2017).

Research continues to find that ELA confers specific brain, behavioral, and physiological vulnerabilities to inflammation. There are several excellent reviews that outline the links between ELA, inflammation, and psychopathology (Danese & Baldwin, 2017; Danese & Lewis, 2017). This area is an exciting frontier in the understanding of the etiology and incidence of mental illness arising from ELA. Thus, with the availability of multiple reviews, meta-analyses, and new data, this review outlines the outstanding questions on the links from ELA to inflammation to psychopathology. We provide an overview of the current evidence that connects ELA to increased inflammation and subsequent risk for psychopathology. Then, we identify four challenges for the field going forward. The first is the issue of measuring ELA, which includes the type and timing, dimensional approaches to the construct of ELA, and construct invariance across longitudinal studies. The second challenge is measuring inflammation itself, which includes questions about biomarker selection and tissue specificity in the study of ELA, inflammation, and psychopathology. Third, we review a number of proposed mechanistic pathways that could mediate the relationship between childhood adversity and inflammation to ultimately prevent ELA-exposed children from developing increased inflammation and psychopathology. As a great deal of heterogeneity exists in the literature on ELA and inflammation, we propose that the fourth challenge of the field is a better understanding of moderators at play. We put forward the hypotheses that differences in an individual's age at the inflammation assessment, sex, and population context can explain the heterogeneity in outcomes. We conclude with a discussion of the clinical and intervention implications as the field continues to mature.

Inflammation and psychopathology

The immune system consists of two interconnected branches: innate and adaptive immunity. These branches detect and eliminate molecules and cells that represent a threat to our body, including foreign antigens, altered self-antigens, or cellular damage. Inflammation is part of the innate immune system and works to protect against pathogens and repair tissue in contexts of illness, injury, or infection. Innate immunity serves as the first line of defense and is evolutionally older than adaptive immunity (Medzhitov, 2008). The innate immune system is composed of immune cells, such as monocytes, macrophages, and dendritic cells, that constantly circulate in the body and detect a wide variety of pathogens. When activated, these cells begin a rapid (i.e., minutes to hours) cascade of processes to contain infection and promote healing (Medzhitov, 2008). Inflammatory cytokines promote vascular permeability and cellular adhesion so that immune cells can leave the blood vessels, migrate to tissues, and eliminate pathogens. Proinflammatory cytokines signal sites of injury or

infection to recruit immune cells to the site of inflammatory activity (Murphy, 2011). However, if the regulatory processes in immunity fail, this can result in a prolonged, chronic, and nonresolving inflammatory response associated with cellular and tissue damage and poor mental and physical health outcomes (Nusslock & Miller, 2016). Low-grade inflammation is frequently assessed in human studies using the acute-phase protein C-reactive protein (CRP) and the proinflammatory cytokine interleukin-6 (IL-6), both of which can be measured in blood.

Inflammation is implicated in the pathogenesis of psychopathology in nonhuman animal models and human studies. In experimental animal models, the administration of bacterial cell components (e.g., lipopolysaccharide (LPS)) or proinflammatory cytokines manipulates the organism's inflammatory state and produce symptoms that mirror psychopathology (e.g., disruptions in sleep, food and water intake, social engagement, motor activity, and cognition) (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). These symptoms are worse in mice deficient in anti-inflammatory cytokines but improve if mice are subsequently administered anti-inflammatory cytokines (Dantzer et al., 2008). Experimental studies in humans have replicated these findings. Early studies found that the experimental administration of proinflammatory cytokines produced a clinical response that resembles that of major depression (Smith, 1991). Later studies demonstrate that the administration of proinflammatory mediators induces depressive-like symptoms in healthy participants and cancer patients (Musselman et al., 2001; Reichenberg et al., 2001).

Human studies of depression, bipolar disorder, PTSD, and schizophrenia show evidence of a link between inflammation and psychopathology development (Berk et al., 2011; Dargel, Godin, Kapczinski, Kupfer, & Leboyer, 2015; Leboyer et al., 2012; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Modabbernia, Taslimi, Brietzke, & Ashrafi, 2013). Of these, the association between inflammation and psychopathology has been best characterized in the case of depression (Miller & Raison, 2016). Patients with depression had immune cell profiles characterized by systemic inflammation (Maes et al., 1992). Moreover, a meta-analysis of cross-sectional studies that investigate the differences in inflammation in depressed adults and healthy controls found that depression is characterized by small elevations of inflammatory biomarkers in the blood (Howren, Lamkin, & Suls, 2009). In addition, anti-inflammatory medications have been found to have antidepressant effects in trial with a subgroup of depressed patients with high baseline levels of inflammation (Raison et al., 2013) and in a meta-analysis of trials (Kohler et al., 2014). The group differences between inflammation in depressed patients versus controls is likely due to bidirectional associations between depression and inflammation (Danese & Baldwin, 2017; Matthews et al., 2010). Concordantly, longitudinal associations between inflammation and subsequent psychopathology are reported in participants with depression (Valkanova, Ebmeier, & Allan, 2013), psychosis (Khandaker et al., 2014), and PTSD (Eraly et al., 2014; Michopoulos et al., 2015).

Proposed mechanisms of inflammation and psychopathology

While inflammation contributes positively to brain development, high levels can result in changes at multiple levels of brain function and increase risk for psychopathology. In rodents and nonhuman primates, experimental studies show that infection and systemic inflammation in the prenatal and neonatal periods lead to long-term impairments in learning, memory, and attention (Bilbo & Schwarz, 2009; Knuesel et al., 2014; Patterson, 2009;

Short et al., 2010). Observational studies in humans demonstrate links between prenatal infection and later risk for neurodevelopmental disorders, including schizophrenia and autism (Atladdottir et al., 2010; Deykin & MacMahon, 1979; Khandaker, Zimbron, Lewis, & Jones, 2013; Mednick, Machon, Huttunen, & Bonett, 1988). Experimental activation of the peripheral system with LPS and other proinflammatory stimulants has significant effects on brain functioning in humans (Schedlowski, Engler, & Grigoleit, 2014). These effects include changes in cognition with the reduction of verbal and nonverbal memory functions (Reichenberg et al., 2001) and changes in positive valence systems with the reduction of ventral striatum responses to reward (Capuron et al., 2012; Eisenberger et al., 2010). These effects include changes in negative valence systems, with increased amygdala activity in response to socially threatening stimuli (fear faces) (Inagaki, Muscatell, Irwin, Cole, & Eisenberger, 2012), reduced connectivity of the subgenual anterior cingulate cortex (sACC) to the amygdala, and increases in the activity within the sACC during emotional face processing (Harrison et al., 2009). Inflammation can affect brain and behavior mechanistically through (a) brain neurochemistry, (b) brain development, (c) microglial priming, and (d) neuroendocrine programming (i.e., hypothalamic–pituitary–adrenal; HPA). We briefly review these mechanistic pathways and direct the reader to Danese and Lewis (2017) for a more comprehensive review.

First, inflammation can affect brain neurochemistry through monoamine and glutamate metabolism. Inflammatory cytokines can affect monoamine transmission through reduced monoamine synthesis and increased expression of the presynaptic transporter, reducing monoamine availability in the brain (Miller & Raison, 2015). Inflammatory cytokines can increase glutamate transmission through reduced expression of the presynaptic transporter, thereby increasing glutamate release and availability in the brain (Miller & Raison, 2016).

Second, inflammation plays an integral role in brain development. Prenatally, the immune system affects cell proliferation and migration (Boulanger, 2009). Postnatally, the immune system affects brain synaptogenesis (Chalasan, Sabelko, Sunshine, Littman, & Raper, 2003; Lieberam, Agalliu, Nagasawa, Ericson, & Jessell, 2005; Tran & Miller, 2003), synaptic refinement (Beattie et al., 2002; Huh et al., 2000; Paolicelli et al., 2011; Shatz, 2009; Stellwagen & Malenka, 2006; Stephan, Barres, & Stevens, 2012), myelination (Peferoen, Kipp, van der Valk, van Noort, & Amor, 2014), and adult neurogenesis (Ek Dahl, Claasen, Bonde, Kokaia, & Lindvall, 2003; Monje, Toda, & Palmer, 2003; Ziv et al., 2006). Early exposure to inflammation has long-term impacts on the brain and behavior of rodents (Bilbo & Schwarz, 2009; Knuesel et al., 2014; Patterson, 2009) and nonhuman primates (Short et al., 2010). In humans, higher levels of serum inflammation in childhood has been associated with increased risk of depression and psychosis in adulthood (Khandaker et al., 2014).

The brain's specialized immune cells (e.g., microglia and T cells) and cytokines contribute to normal brain functioning and thus may be directly affected by disruptions in immune functioning (Boulanger, 2009; Deverman & Patterson, 2009; Yirmiya & Goshen, 2011). The innate immune system supports tissue remodeling involved in mechanisms of brain plasticity. For example, microglia in their resting state play important roles in adult brain function (Hanisch & Kettenmann, 2007). T cells in the brain monitor and respond to signals in the cerebrospinal fluid and play a role in learning and memory in adults by stimulating neurogenesis and promoting the expression of brain-derived neurotrophic factor (BDNF) (Kipnis, Gadani, & Derecki, 2012). Low levels of

proinflammatory cytokines, produced by microglia and T cells, support brain plasticity (Yirmiya & Goshen, 2011). Exaggerated or chronic neuroinflammation, however, is associated with impaired brain function such as poor learning and memory (Yirmiya & Goshen, 2011). Microglia produce proinflammatory cytokines upon detection of inflammatory signals, prostaglandins, and free radicals, all of which can have neurotoxic effects and suppress neurogenesis (Hanisch & Kettenmann, 2007). Upon detection of inflammatory signals, T cells are involved in triggering protective immune responses that could be detrimental to brain function.

Third, inflammation affects microglial reactivity and can prime immune cells to be more reactive upon subsequent psychosocial stressors, resulting in increased inflammation. Early life inflammation can activate and prime microglia to subsequent inflammatory stimuli, thereby influencing later inflammatory responses to stressors (Perry & Holmes, 2014). Inflammation may downregulate neuronal ligands responsible for inhibiting this priming response (Perry & Holmes, 2014). Similar effects may occur if microglia are less sensitive to the inhibitory effect of glucocorticoids (Frank, Watkins, & Maier, 2013). Rodents with primed microglia exhibit increased proinflammatory cytokine production in the brain, increased neurotoxicity, and exaggerated sickness behavior when exposed to subsequent inflammatory stimulation (Perry & Holmes, 2014). Thus, microglia can be activated and primed by inflammatory stimuli and mount a greater inflammatory response from subsequent immune stimulation. Early life seems to be a sensitive period for this microglial priming (Bilbo & Schwarz, 2009; Knuesel et al., 2014).

Fourth, inflammation can sensitize the neuroendocrine and immune systems in a bidirectional fashion (Danese & Lewis, 2017). In acute immune stimulation, the HPA axis is activated similar to activation following exposure to a stressor (Besedovsky, del Rey, Sorkin, & Dinarello, 1986; Dunn, 2000). Evidence from animal models suggests that the immune system may program the HPA axis response during sensitive periods of development. In rodents, early life immune stimulation with LPS is associated with HPA axis abnormalities that are linked to psychopathology, including increased corticotropin-releasing hormone (CRH) levels, increased adrenocorticotropic hormone (ACTH) and corticosterone production in response to stress, decreased negative feedback sensitivity to glucocorticoids, and reductions in glucocorticoid receptor (GR) density in the brain (Pariante & Miller, 2001; Shanks, Larocque, & Meaney, 1995; Shanks et al., 2000). If cytokines chronically stimulate the HPA axis, this can result in insufficient glucocorticoid signaling, inhibited BDNF secretion, inhibited nerve growth factor secretion, and inhibited cholinergic transmission (Dantzer et al., 2008; Yirmiya & Goshen, 2011). These results suggest that the immune system's programming of the HPA axis programming is part of the causal pathway between early life immune stimulation and psychopathology (Danese & Lewis, 2017). Together, the brain neurochemistry, developmental, priming, and neuroendocrine effects demonstrate evidence of direct and long-term risk for psychopathology (Boulanger, 2009).

Early life adversity and inflammation

As ELA cannot be randomly assigned or manipulated in humans, animal models provide a support for causal inference in the link between early life stress and increased inflammation. Evidence from animal models point to associations between early life stress paradigms and immune system functioning (for comprehensive

reviews, we point the reader to (Ganguly & Brenhouse, 2015; Hennessy, Deak, & Schiml-Webb, 2010a; Shanks & Lightman, 2001). Although not analogous to all forms of ELA in humans, maternal separation as an ELA paradigm in nonhuman animal models paints the most consistent picture linking ELA with inflammation. Rodent and nonhuman primate models of maternal separation provide evidence for increased peripheral inflammatory biomarkers, markers of neuroinflammation, and greater proinflammatory response in response to subsequent stress (Coe, Rosenberg, & Levine, 1988; Cole et al., 2012; Hennessy, Deak, Schiml-Webb, Carlisle, & O'Brien, 2010b; Wieck, Andersen, & Brenhouse, 2013). Markers of neuroinflammation include blunted expression of proinflammatory mediators in the hippocampus (Wei, Simen, Mane, & Kaffman, 2012), reduced microglial cell numbers in the midbrain areas of rodent pups (Chocyk et al., 2011), increased expression of proinflammatory cytokine receptors in the hippocampus (Viviani et al., 2014), changes in cortical microglial processes (Takatsuru, Nabekura, Ishikawa, Kohsaka, & Koibuchi, 2015), and increased microglia activation (Brenhouse & Thompson, 2015). Maternal separation in rodent models show a greater proinflammatory response in the brain and periphery when animals are exposed to later stressors (Avitsur, Hunzeker, & Sheridan, 2006; Brenhouse & Thompson, 2015; Hennessy et al., 2010b).

Research Questions

Many thoughtful reviews, theoretical papers, and meta-analyses have been written on studies of ELA and inflammation in humans (Baumeister, Akhtar, Ciufolini, Pariante, & Mondelli, 2016; Danese & Baldwin, 2017; Danese & Lewis, 2017; Kuhlman et al., 2020; Nusslock & Miller, 2016). This domain of research is rapidly expanding, and this review brings together the outstanding and developmentally focused research questions moving forward. As the field has relatively heterogeneous inflammation outcome measures, we focus our discussion on CRP, IL-6, and tumor necrosis factor (TNF)-alpha, a common trio of inflammatory markers associated with psychopathology in humans (Yuan, Chen, Xia, Dai, & Liu, 2019).

We take a developmental focus because, in contrast to the studies on ELA and inflammation in adults, the literature on ELA and inflammation in infants, children, and adolescents is still in its early stages. A meta-analysis of 13 studies on ELA and inflammation in pediatric samples highlight the relative lack of studies overall, the high levels of heterogeneity of ELA and inflammation measures, and mixed results (Kuhlman et al., 2020). Though this recent meta-analysis did not find a statistically significant association between ELA and inflammation, the authors argued that this was due to too much heterogeneity across pediatric studies (Kuhlman et al., 2020). The ELA constructs, types of inflammation assessment, and timing of the inflammation assessment varied widely in these studies. The mixed results are not all together surprising when looking toward reviews of the animal literature, which find mixed results due to a multiplicity of stressors and inflammatory measures (Ganguly & Brenhouse, 2015; Hennessy et al., 2010a; Shanks & Lightman, 2001). Therefore, as the field continues to grow, the field must address how to consistently measure ELA, consistently measure inflammation, test mediators, and account for moderators with a developmental lens. We refer the reader to Table 1, which codes the studies discussed relevant to the following research question sections.

Measuring early life stress

Are there features of ELA experiences or its measurement that are more strongly associated with inflammation? Within the study of ELA and inflammation in pediatric populations, we must clarify if there is a difference in inflammatory outcomes when measuring ELA prospectively versus retrospectively and when assessing ELA with objective or subjective measures. Further, would dimensional approaches to the measurement of ELA clarify research on ELA and inflammation if applied? For example, researchers have proposed that experiences of “deprivation” and “threat” in ELA contexts act as different dimensions and interact to produce a range of different outcomes (McLaughlin et al., 2014). Finally, how does construct invariance in the measurement of ELA impact the research examining inflammatory outcomes longitudinally? Precision in the measurement and definition of ELA, then, is the first challenge if the field seeks to better understand the relationship between ELA, inflammation, and psychopathology across development.

Measurement of early life adversity

How adversity is assessed, whether through objective or self-report measures, prospectively or retrospectively, has long been a consideration in the study of child adversity. A recent study highlights this reporting discrepancy, as it found poor agreement between prospective and retrospective reports of childhood maltreatment within the same individuals (Baldwin, Reuben, Newbury, & Danese, 2019). The literature provides no clarity about how the reporting of ELA affects inflammatory outcomes. Part of this lack of clarity arises from a lack of formal delineation between prospective measures and retrospective measures of ELA. Few studies on inflammation arising from ELA have prospective and retrospective measures to compare directly. One study that makes the comparison is the Dunedin Multidisciplinary Health and Development Study, which showed that inflammation at age 32 y was more strongly associated with prospective compared to retrospective measures of ELA (Reuben et al., 2016). However, data from the 1958 British Cohort ($N = 7,661$) that included prospective and retrospective measures of victimization found more mixed results, with positive associations between ELA and inflammation dependent on the type of ELA exposure (Pinto Pereira et al., 2019).

Another related area that requires clarification is how the source of information on ELA influences outcomes. Retrospective measures are, by necessity, self-reports, while prospective measures can include objective information (e.g., court reports), parent reports, or self-reports on ELA. The few studies that do use objective measures of ELA found inconsistent evidence for a link between ELA and inflammation. Osborn and Widom (2019) have recently shown that individuals with official reports of child maltreatment (specifically physical abuse) had significantly higher levels of CRP than nonmaltreated individuals, yet two studies using Child Protective Services (CPS) referrals found no association between CRP and maltreatment (Bernard et al., 2019; Cicchetti et al., 2015). Other studies of adolescents and adults exposed to objectively and prospectively assessed ELA in the form of institutional care have found no association between neglect exposure and inflammatory biomarkers (Elwenspoek et al., 2017; Reid et al., 2019; Slopen et al., 2019).

Perhaps the ultimate challenge across measures is that the effect sizes between ELA and inflammation are small, and without adequately powered studies the outcomes are predictably

Table 1. Studies of early life adversity and peripheral inflammation, arranged by mean age (years) at inflammation assessment

Study	Sample size	Tissue	Mean Age (years)	% Female	Design	Exposure	Exposure details	Age of exposure (years)	Outcome notes	CRP	IL-6	TNF
Tyrka, Parade, Valentine, Eslinger, and Seifer (2015)	40	Saliva	4.2	N/A	Retrospective	Maltreatment	Maltreatment, traumatic life events	4	Number of past month contextual stressors, lifetime contextual stressors, and traumatic life events were associated with higher IL-1 β .	∅		
Bernard, Hostinar, and Dozier (2019)	84	DBS	4.9	50	Prospective	Maltreatment	CPS-referred (abuse, neglect)		CPS-referred children with insecure or disorganized attachments higher CRP levels than both low-risk children and CPS-referred children with secure attachments; CPS-referred children with secure attachments did not differ from low-risk children.	∅		
Flouri, Francesconi, Papachristou, Midouhas, and Lewis (2019)	4,583	Blood	9	49.02	Prospective	Adversity, including victimization	Life events reported by mother (death, illness, divorce, family violence, accident, lower income)	<9		∅	✓	
Bucker et al. (2015)	62	Blood	9.4	40.3	Prospective	Maltreatment	Trauma: using DSM criteria for trauma, children with trauma background recruited from foster care and child protection program compared to community controls	3–12	∅ for IL-12p70, IL-8, IL-10, and IL-1 β		∅	✓

(Continued)

Table 1. (Continued.)

Study	Sample size	Tissue	Mean Age (years)	% Female	Design	Exposure	Exposure details	Age of exposure (years)	Outcome notes	CRP	IL-6	TNF
Cicchetti, Handley, and Rogosch (2015)	485	Saliva	9.7	47.6	Prospective	Maltreatment	Determined via dept of human services records	<5	Not associated with age of exposure and CRP; association between maltreatment and salivary CRP levels depends on CRP genetic variation.	∅		
Kilic, Ozlem, and Murat (2017)	27	Blood	15	74.1	Concurrent	Maltreatment	Sexual abuse	3–17	Assessed at clinic to determine sexual abuse, within 72 hr of sexual abuse ∅ for IL-10		✓	
Slopen et al. (2019)	127	DBS	16	52.8	Prospective	Neglect	Institutionalization	~1.5	∅ for IL-8 and IL-10. Youth with accelerated BMI trajectory had higher CRP	∅	∅	∅
Reid et al. (2019)	84	Blood	16.3	56	Prospective	Neglect	Institutionalization	~1.5	Differences in the CD4/CD8 ratio and T cell profile	∅		
Walsh et al. (2016)	133	Blood	16.5	100	Retrospective	Maltreatment	Exposure to child abuse (CTQ)	<14–17	Pregnant population.	∅	∅	
Baldwin et al. (2018)	1,732	Blood	18	51.3	Prospective	Maltreatment, Victimization	Domestic violence, peer bullying, physical maltreatment, sexual abuse, emotional abuse and neglect, physical neglect	5–12	Females exposed to victimization had higher CRP (not males); twin study, Latent genetic influences on CRP levels did not explain the association in females.	✓		
Miller and Chen (2010)	135	Blood	18.5	100	Retrospective	Maltreatment	Harsh family climate; Risky Families Questionnaire	<14	In vitro: found cortisol was hampered in ability to properly regulate inflammatory responses.		∅	

Elwenspoek et al. (2017a)	109	Blood	22.7	61	Prospective	Neglect	Institutionalization	<1.25	Proinflammatory T cell status associated with ELA	∅	∅	
Carpenter et al. (2010)	69	Blood	26.8	60.9	Retrospective	Maltreatment	(CTQ)	<17				✓
Carpenter, Gawuga, Tyrka, and Price (2012)	92	Blood	30.5	51.1	Retrospective	Maltreatment	CTQ, SES disadvantage, neonatal stress (birth complications)	<17		∅		
Danese, Pariante, Caspi, Taylor, and Poulton (2007)	862	Blood	32	48	Prospective	Maltreatment	Maltreatment	<10	Low birth weight (LBW) associated with increased CRP	✓		
Hartwell et al. (2013)	38	Blood	35.69	51.3	Retrospective	Trauma	Early Trauma Inventory (ETI), 18 years and younger; Total number of traumas	<18	Positive association with IL1-β	∅	∅	✓
Carroll et al. (2013)	765	Blood	40	57.3	Retrospective	Maltreatment	Risky Families Questionnaire maltreatment subscale	<18		✓	✓	
Taylor, Lehman, Kiefe, and Seeman (2006)	3,248	Blood	40.1	54.7	Retrospective	Maltreatment	Risky families questionnaire, SES, maltreatment	<18		✓		
Kraynak, Marsland, Hanson, and Gianaros (2019)	303	Blood	40.3	49.2	Retrospective	Maltreatment	Childhood physical abuse	<17		∅		✓
Bertone-Johnson, Whitcomb, Missmer, Karlson, and Rich-Edwards (2012)	702	Blood	42.67	100	Retrospective	Maltreatment	Reports of abuse (physical & sexual)	<11		∅	∅	
Bertone-Johnson et al. (2012)	702	Blood	42.67	100	Retrospective	Maltreatment	Reports of abuse (physical & sexual)	11–17		✓	✓	
Runsten et al. (2014)	116	Blood	42.89	100	Retrospective	Victimization	Victimization	<18		✓		
Pinto Pereira, Stein Merkin, Seeman, and Power (2019)	7,661	Blood	45.2	50	Retrospective	Neglect	emotional neglect	<16	British Cohort	∅		

(Continued)

Table 1. (Continued.)

Study	Sample size	Tissue	Mean Age (years)	% Female	Design	Exposure	Exposure details	Age of exposure (years)	Outcome notes	CRP	IL-6	TNF
Pinto Pereira et al. (2019)	7,661	Blood	45.2	50	Prospective	Neglect	neglect	11-Jul	British Cohort, associated w/ higher BMI; associations attenuated after adjustment for adult SES disadvantage	✓		
Pinto Pereira et al. (2019)	7,661	Blood	45.2	50	Retrospective	Maltreatment	Physical abuse	<16	British Cohort, association abolished when including adult adiposity	✓		
Pinto Pereira et al. (2019)	7,661	Blood	45.2	50	Retrospective	Maltreatment	Psychological abuse	<16	British Cohort	✓		
Pinto Pereira et al. (2019)	7,661	Blood	45.2	50	Retrospective	Maltreatment	Sexual abuse	<16	British Cohort	∅		
Matthews, Chang, Thurston, and Bromberger (2014)	443	Blood	45.7	100	Retrospective	Maltreatment	CTQ	<17	Mediated through BMI: emotional & sexual abuse, physical neglect, & total number of types of abuse. Not mediated through BMI: emotional abuse & neglect	✓		
Rooks, Veledar, Goldberg, Bremner, and Vaccarino (2012)	482	Blood	55	0	Retrospective	Maltreatment	Early Trauma Inventory (ETI)		Attenuated in obese individuals; twin study; familial factors shared by the twins because levels of inflammation were highest when both twins were exposed to trauma.	✓		

Pinto Pereira et al. (2019)	1,255	Blood	57.3	56.8	Retrospective	Maltreatment	Sexual abuse	<18	MIDUS Adversity & inflammation only significant for nonwhites; association abolished when including adult adiposity	✓	✓
Pinto Pereira et al. (2019)	1,255	Blood	57.3	56.8	Retrospective	Maltreatment	Psychological abuse	<18	MIDUS	∅	∅
Pinto Pereira et al. (2019)	1,255	Blood	57.3	56.8	Retrospective	Maltreatment	Physical abuse	<18	MIDUS	∅	∅
Pinto Pereira et al. (2019)	1,255	Blood	57.3	56.8	Retrospective	Neglect	Emotional neglect	<18	MIDUS, associated w/ higher BMI	∅	∅
Slopen et al. (2010)	999	Blood	57.9	55.4	Retrospective	Victimization		<18	Associations only significant for African Americans	✓	✓
Gouin, Glaser, Malarkey, Beversdorf, and Kiecolt-Glaser (2012)	130	Blood	65.13	82.3	Retrospective	Maltreatment	CTQ	<17		∅	✓
Kiecolt-Glaser et al. (2011)	132	Blood	69.69	72	Retrospective	Maltreatment	CTQ abuse subscales (emotional, physical, sexual)	<17			✓

∅ = null association between ELA exposure and inflammatory outcome.

✓ = positive association between ELA exposure and inflammatory outcome.

BMI = body mass index; CPS = Child Protective Services; CRP = C-reactive protein; CTQ = Child Trauma Questionnaire; ELA = early life adversity; IL-6 = interleukin-6; MIDUS = Midlife in the United States; SES = socioeconomic status; TNF = tumor necrosis factor

inconsistent. A meta-analysis of 25 studies on ELA and plasma levels of inflammation in adulthood found small but significant effect sizes, though most studies included ELA measured broadly and retrospectively in adulthood (Baumeister et al., 2016). Prospective studies of ELA in large cohorts have also found positive associations between ELA and inflammation, though the significant inflammation biomarker outcome differs between them (Baldwin et al., 2018; Bucker et al., 2015; Flouri, Francesconi, Midouhas, & Lewis, 2020). Adequately powered studies in large, longitudinal cohorts with both prospective and retrospective measures of ELA and a consistent set of inflammation biomarkers could help clarify the issue of ELA measurement as it relates to inflammation risk.

Dimensional approaches to the measurement of early life stress type

A second question is whether inflammation outcomes differ depending on the dimension or type of adversity exposure. Numerous studies have found different outcomes when examining separate types of childhood adversity. In meta-analysis of ELA exposure and inflammation in pediatric populations, the types of ELA exposure were too different to compare dimensionally (Kuhlman et al., 2020). Future research would benefit from outlining diversity in the *type* of adversity exposure to examine the development of a proinflammatory phenotype and risk for psychopathology. McLaughlin et al. (2014) propose a dimensional approach to disentangle the effects of ELA on neurodevelopment, and we propose that this dimensional approach could be applied to the study of inflammatory outcomes. The approach distinguishes “threat,” or experiences that threaten an individual’s physical integrity, and “deprivation,” which encompasses the lack of species-expected environmental inputs and/or environmental complexity (McLaughlin et al., 2014). While deprivation and threat often co-occur in contexts where children are victimized, measuring both may clarify differential inflammation and psychopathology outcomes. In this section, we review a few select studies to highlight the measurement questions that remain in this area.

Experiences of threat include those that involve physical or sexual violence, threat of death, or other physical harm (McLaughlin et al., 2014). In adult populations, there are a few examples of examining “threat” types of childhood adversity as they relate to inflammatory outcomes. In subgroup analyses in a meta-analysis, the type of ELA exhibited contrasting results in specific inflammatory outcomes (Baumeister et al., 2016). Childhood sexual abuse was positively associated with TNF- α but not with IL-6 or CRP. Childhood physical abuse was associated with TNF- α and IL-6 but not CRP (Baumeister et al., 2016). An analysis of two large adult cohorts mentioned previously examined different types of childhood adversity on adult levels of inflammation (Pinto Pereira et al., 2019). In the British cohort, increased inflammation in adulthood was positively associated with physical abuse but not sexual abuse (Pinto Pereira et al., 2019). In the US cohort, physical abuse was not associated with either IL-6 or CRP in adulthood (Pinto Pereira et al., 2019). However, childhood sexual abuse was significantly associated with IL-6 and CRP for nonwhites only (Pinto Pereira et al., 2019). In studies of pediatric populations, threat experiences of maltreatment and victimization are positively associated with inflammation in some studies (Baldwin et al., 2018; Bucker et al., 2015; Danese et al., 2007; Flouri et al., 2019; Kilic et al., 2017) but not all (Bernard et al., 2019; Cicchetti et al., 2015; Miller & Cole, 2012).

One component of the dimensional approach to measuring ELA is the grounding of the dimensions in current evidence on neurodevelopment (McLaughlin et al., 2014). Threat experiences may result in changes to emotional learning networks (Johansen, Cain, Ostroff, & LeDoux, 2011; LeDoux, 2003; McLaughlin et al., 2014). Kraynak et al. looked at pathways from childhood abuse to systemic inflammation and corticolimbic functionality in healthy adults and found that childhood abuse was associated with increased IL-6 and indirectly associated with reduced amygdala–ventromedial prefrontal cortex (vmPFC) connectivity (2019). Consistent with recent neurobiological models of early life threat experiences, associations between childhood physical abuse and adulthood corticolimbic circuit functionality may be partially explained by inflammatory processes (Kraynak et al., 2019). Interestingly, while CRP associated negatively with amygdala–ventromedial prefrontal cortex connectivity, it did not statistically associate with childhood physical abuse (Kraynak et al., 2019). This study provides preliminary evidence of how a dimensional and neurobiological approach may elucidate ELA–inflammation–psychopathology connections.

In contrast to the construct of “threat,” deprivation experiences are defined as the absence of expected environmental inputs (i.e., cognitive inputs, social inputs, and environmental stimuli that are species- and age-typical in their complexity (McLaughlin et al., 2014). Experiences of deprivation are central for children who have been institutionalized (i.e., orphanage care), children experiencing neglect, and children in contexts of poverty. Few studies of adult cohorts operationalize neglect as a separate dimensional construct, and the definition of neglect is heterogeneous across and within these studies. For example, emotional neglect was not associated with either IL-6 or CRP in a large US cohort and physical neglect but not emotional neglect was positively associated with inflammation in a large British cohort (Pinto Pereira et al., 2019). The Baumeister meta-analysis demonstrated that parental absence was significantly and positively associated with CRP, though the measures of deprivation across the studies were highly inconsistent (Baumeister et al., 2016).

Studies of adults and children who experienced institutional care early in life provide an opportunity to examine the dimension of deprivation as it relates to inflammatory outcomes. Institutional care typically involves environmental deprivation, caregiver separation, and neglect. Two studies that focused on neglect exposure and subsequent inflammation compared previously institutionalized (PI) adolescents to community controls. One study examined youth adopted out of institutional care before the age of 2 y into well-resourced families in the United States (Reid et al., 2019) and another examined youth who either remained in institutional care or were randomly assigned to a foster care intervention (Slopen et al., 2019). These studies of adolescents removed from institutional care as infants provide opportunities to look at sensitive periods of adversity exposure as it relates to inflammation and compare differences in behavioral and environmental inputs. Neither study found evidence of increased peripheral inflammation in PI adolescents (Reid et al., 2019; Slopen et al., 2019). One study found no differences in plasma levels of inflammation in PI and comparison adolescents (Reid et al., 2019), which replicated findings in PI adults (Elwenspoek et al., 2017a). These studies are consistent with a study with the Bucharest Early Intervention Project, in which inflammation (CRP, IL-6, IL-8, TNF- α) was measured in dried blood spots in adolescent follow-up of institutionalized infants randomized to care as usual ($n = 68$) or foster care intervention

($n = 68$), and compared to never institutionalized controls ($n = 127$). The study found no differences in levels of peripheral inflammation markers between the PI and comparison adolescents (Slopen et al., 2019). However, further post hoc analyses found differences in CRP only in PI adolescents who exhibited an increasing adiposity trajectory and glucose dysregulation, though this group of adolescents was a small subset of the full PI sample (Tang et al., 2018).

Unfortunately, none of the studies reviewed have a dimensional measure of threat and deprivation, and many of the conditions of threat and deprivation co-occur. Current studies suggest that inflammatory outcomes can be diverse even between different threat and deprivation exposures. The field would be well served by research that includes dimensional measures of threat and deprivation in better understand how dimensional constructs of ELA do – or do not – result in a proinflammatory phenotype.

Construct invariance from infancy to childhood and adolescence

Longitudinal construct invariance is the third measurement research question for the study of ELA and inflammation. Many studies measure the family environment in infancy and early childhood, as this proximal family environment is thought to best capture experiences of adversity at very young ages. David, Measelle, Ostlund, and Ablow (2017) found that salivary CRP was positively and independently associated with socioeconomic disadvantage and maternal stress in 18-month-olds. In contrast, a study of 125 5-year-olds found no association between family level adversity and salivary IL-6 or TNF-alpha (Riis et al., 2016). In a prospective, longitudinal cohort of 600 adolescents, exposure to family-level adversity in infancy predicted higher levels of CRP, mediated through higher BMI in childhood (Reid et al., 2020). Finally, a study of 337 11-year-olds found no association between family-level adversity in infancy and IL-6 or TNF-alpha. The study found significant associations only between caregiver depressive symptoms in infancy and higher levels of CRP in childhood (O'Connor et al., 2020). Few studies examine ELA in infancy and early childhood, and none yet provide clarity around construct invariance from family adversity to later forms of ELA and inflammation.

Measuring inflammation/immune biomarkers

Questions on the measurement of inflammation are equally important to the questions of measuring ELA. Namely, what are the best inflammation biomarkers to measure associations between ELA, inflammation, and psychopathology? The nature of human research on psychopathology is that we are limited primarily to inflammatory biomarkers in the periphery, not the brain. This some challenges, which include (a) the interpretation of peripheral blood biomarkers of inflammation to brain measures of inflammation (i.e., tissue specificity) and (b) the selection of inflammation biomarkers from many different inflammatory cytokine options.

Tissue specificity

Though the connection between peripheral inflammation and neuroinflammation has been made (Miller & Raison, 2016), there are still open questions that researchers should continue to acknowledge when studying adversity, inflammation, and psychopathology risk. A meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and postmortem brain tissue in patients with depression found that patients with

depression have higher cerebral spinal fluid levels of IL-6 and TNF- α than controls. However, there was little correlation between central and peripheral markers of inflammation in the studies reviewed, which may reflect a lack of connection between central and peripheral inflammation or other possible moderating factors (Enache, Pariante, & Mondelli, 2019). Nonetheless, measures in blood, and therefore blood draws, are considered the gold standard for inflammatory biomarker measurement in population-based studies. Most studies investigating the links between ELA and inflammation focus on blood as the target tissue of interest in populations of adults, adolescents, and many studies of children.

Large-scale studies and studies of infants and children often use less invasive biomarkers for acceptability and cost. Blood draws can be cost-prohibitive, not feasible, and are not minimally invasive. One less invasive methods of collection for inflammatory biomarkers involve finger prick and blood spot (McDade, Williams, & Snodgrass, 2007). The blood spot cards are let to dry and can be stored until laboratory analysis with good stability. Levels of inflammation biomarkers, such as CRP, in dried blood spot correlate highly with levels in serum ($r = 0.96$) (McDade, Burhop, & Dohnal, 2004). Analysis of ELA-related inflammation abnormalities in dried blood spot showed results comparable to those in serum (Copeland et al., 2014; Danese et al., 2011). As such, there is interest in developing further inflammation biomarkers including cytokines from dried blood spots.

Blood draws and dried blood spots may be considered too invasive in studies with healthy infants or young children. Reflecting this, the majority of the studies in infancy and early childhood (0–5 years) in this review use salivary markers of inflammation, which limits our ability to compare these with studies in older children and adults. Several studies have reported poor correlations between saliva and blood for inflammatory markers (Dillon et al., 2009; Riis et al., 2016), likely due to the relative difficulty that most proteins have in passing the multiple barriers between blood and saliva compartments. Cytokines are too large to enter the mouth from the periphery through passive diffusion and instead enter through sites of inflammation or tissue damage, producing large variability between individuals (Bosch, 2014). Thus, while salivary cytokines are mostly indicative of local inflammation (Bosch, 2014), they may still serve as important indicators of health status while taking care to control for dental health confounds (Slavish, Graham-Engeland, Smyth, & Engeland, 2015). As in any tissue, the type of inflammatory biomarker assessed is important. CRP from saliva has been associated with CRP in circulating blood more consistently than other inflammatory biomarkers, perhaps because CRP is produced in the liver, not in the mouth, and its most likely route into saliva is via blood (Slavish et al., 2015). A validation study of a high-sensitivity CRP assay in saliva allowed prediction of serum CRP in healthy adults (Ouellet-Morin, Danese, Williams, & Arseneault, 2011). Markers of salivary inflammation have been stable across time in adolescent samples in the short and long term (when averaging across multiple assessments) (Shields, Slavich, Perlman, Klein, & Kotov, 2019). More research is needed to establish both the health relevance and the mechanisms driving salivary inflammation generally and across development. Further research is needed to determine how ELA relates to salivary inflammation, what increased salivary inflammation means for infants and young children in the short term, whether this measure is associated with blood levels of inflammation, or what the long-term implications of increased salivary inflammation are.

Biomarker (cytokine) selection

Diverse inflammatory markers have been used to test the association between ELA and inflammation. To counteract the literature's heterogeneity, longitudinal and system-wide studies of inflammation regulation with multiple biomarkers that can differentiate trait- and state-specific changes in the context of childhood adversity would improve our understanding of etiology and establish valuable biomarkers. Del Giudice and Gangestad make the argument that IL-6 and CRP assays alone are not enough to establish the existence of inflammatory states due to their multiple roles and states in the body, a concept accepted in immunology research but rarely addressed in behavioral research (Del Giudice & Gangestad, 2018). For example, IL-6 and CRP might be elevated for maintenance functions and not necessarily indicative of an aberrant and chronic inflammatory state. Future studies should consider using IL-6 and CRP alongside additional inflammatory biomarkers (e.g., IL-1B, TNF-alpha, and circulating levels of soluble IL-6 receptors such as sIL-6R) (Del Giudice & Gangestad, 2018). A meta-analysis of 704 publications on psychopathology and 44 inflammatory biomarkers found that related disorders share similar patterns of inflammatory changes (Yuan et al., 2019). Longitudinal studies of inflammation regulation with multiple biomarkers could help differentiate trait- and state-specific changes in psychopathology to establish valuable biomarkers in the ELA literature (Yuan et al., 2019).

Mediation: Mechanisms linking early life stress and inflammation

Mechanisms through which ELA could contribute to chronic inflammation include genetic risk, exposure to acute immune responses early in life, behavior, neuroendocrine dysregulation, adipose tissue, gut microbiome dysbiosis, and stress-induced disruptions to nutrient metabolism, among others. This review is not exhaustive but seeks to highlight important and modifiable pathways by which ELA could contribute to inflammation and increase the subsequent risk for psychopathology. We integrate insights from provide support for the current theoretical mechanisms and offer alternative or contradicting evidence to inform research agendas going forward.

Gene-environment correlation

The genetic vulnerability of inflammation is estimated to account for between 13%–30% of within-subjects variability of CRP (Pankow et al., 2001), and there may be shared, underlying genetic vulnerability to ELA, psychopathology, and inflammation (2017). Immune-related genetic pathways have been found to predict risk for several types of psychopathology (Network & Pathway Analysis Subgroup of Psychiatric Genomics, 2015). Danese & Baldwin (2017) note that an individual exhibiting early behavioral expressions of genetic vulnerability to psychopathology (e.g., emotional dysregulation, oppositional behavior) might increase their risk of maltreatment in childhood. However, the study on victimization by Baldwin et al. (2018) with a genetically informative sample of twins found that exposure to ELA was associated with increased inflammation above and beyond the genetic risk for increased inflammation, further suggesting that while genetics plays a role, additional mechanisms are at play.

Acute inflammatory responses

Acute inflammation in response to physical trauma, infection, or exposure to pathogens during sensitive periods early in life may

stimulate microglia and neuroendocrine activity and affect brain development. Acute inflammatory responses can be incited through psychological stress or in the context of physical trauma, as children exposed to ELA are more likely to be exposed to physical injuries (Gilbert et al., 2009). Children exposed to ELA are more likely to be exposed to infection (Gilbert et al., 2009) and psychological stress and traumatic experiences can increase susceptibility to both infections and recurrent viral infections (Cohen et al., 2012; Shirtcliff, Coe, & Pollak, 2009). ELA could contribute to systemic inflammation through these recurrent acute immune perturbations, but this pathway may not be applicable in all contexts. For example, in the studies of PI adolescents and young adults mentioned earlier in this paper, ELA-exposed youth have been found to exhibit higher levels of cytomegalovirus (CMV) titers, likely due to increased exposure to infectious disease and pathogens in institutional care (Elwenspoek et al., 2017b; Reid et al., 2019). ELA and CMV exposure were associated with acquired immune system perturbations and markers of T-cell senescence, but not higher levels of inflammation (Elwenspoek et al., 2017b; Reid et al., 2019). In addition, McDade's study of a prospective birth cohort in the Philippines found that ELA was associated with adult levels of inflammation only in individuals with low levels of microbial exposure in infancy (McDade, Rutherford, Adair, & Kuzawa, 2010). It is unclear how ELA and early infection interact, the salience of specific pathogen exposures, and how infection affects the developing immune system. For instance, PI youth are not at increased risk of more inflammation (Elwenspoek et al., 2017a; Reid et al., 2019; Slopen et al., 2019), but they are at increased risk of psychopathology (Gunnar & Reid, 2019). In the Philippines cohort, there was no evidence of association between depressive symptomology in adulthood and increased inflammation (McDade, Borja, Adair, & Kuzawa, 2013). In contexts where infectious disease burden is high, pathogen exposure may act as a protective factor in the pathway from ELA, inflammation, and psychopathology (McDade, 2012). Future work should consider operationalizing pathogen and infection exposure across development to better understand inflammation and psychopathology risk.

Neuroendocrine dysregulation

Psychological stress can indirectly contribute to inflammation by inducing neuroendocrine abnormalities and changes in HPA axis physiology. The HPA axis is a key neuroendocrine pathway involved in processes critical to homeostasis, including an organism's responses to challenge, metabolism, and immune activity. Peripheral and central HPA axis mediators affect brain function (McEwen, Weiss, & Schwartz, 1968), and early life experiences can significantly shape the development and subsequent functioning of the HPA axis (Levine, Alpert, & Lewis, 1957). Furthermore, the HPA axis and the immune system relate to each other in dynamic and bidirectional ways. Inflammation can activate the HPA axis and cortisol activates anti-inflammatory and suppresses proinflammatory responses (Barnes & Adcock, 2009; Besedovsky et al., 1986). In situations where chronic stress leads to HPA upregulation, immune cells can become insensitive to the GR-mediated inhibitory effects of cortisol after excessive exposure over long periods, thought to be indicative of "glucocorticoid resistance" (Cohen et al., 2012; Kuhlman et al., 2020; Miller, Chen, & Parker, 2011b).

HPA biology in humans is typically measured in the context of cortisol reactivity to stress and the diurnal rhythm of cortisol secretion, which reflect the ability of the HPA axis to regulate

responses to stress and to modulate circadian rhythm. In chronic ELA exposures, the evidence suggests that the HPA axis responsiveness can either upregulate, where cortisol becomes chronically elevated, or downregulate, where the HPA axis becomes become flat and unresponsive (McEwen, 2007, 2012). In general, current evidence shows that childhood adversity is associated with heightened activity of the axis (Koss & Gunnar, 2018; Sanchez et al., 2001). If the axis is chronically elevated, it may produce a blunted cortisol response (Koss & Gunnar, 2018; Sanchez et al., 2001).

Blunted cortisol patterns have been found in studies of PI children (Koss, Hostinar, Donzella, & Gunnar, 2014; Koss, Mliner, Donzella, & Gunnar, 2016) and in children experiencing neglect and maltreatment (Bernard, Hostinar, & Dozier, 2015; Bruce, Fisher, Pears, & Levine, 2009). Blunted cortisol patterns may lead to different Neuroendocrine×Immune System interactions. Inflammatory cytokine production is typically inhibited when cortisol binds to GRs in healthy immune cells (Barnes & Adcock, 2009). Thus, in the case of downregulated HPA activity, low circulating levels of cortisol might induce elevated levels of inflammatory cytokines (Del Giudice & Gangestad, 2018). Studies have found insufficient glucocorticoid signaling in adolescents and adults with a history of childhood maltreatment, which could bring about systemic inflammation (Heim, Ehlert, & Hellhammer, 2000; Miller, Cohen, & Ritchey, 2002; Miller, Freedland, Carney, Stetler, & Banks, 2003). However, this finding is not always consistent: the study of 11-year-olds mentioned previously found no association between glucocorticoid resistance and either ELA exposure in infancy or inflammation at 11 years, even though early adversity exposure was positively associated with inflammation (O'Connor et al., 2020). It is unclear whether this discrepancy is a result of the need for cumulative adversities to result in glucocorticoid resistance, a level of adversity that was not severe enough to impact glucocorticoid resistance, or an indication of multiple adversity-to-inflammation pathways across development.

Proinflammatory effects on immune cells in development may only be reliably observed when immune cells are stimulated in vitro, not when measured in circulation (Kuhlman et al., 2020). If youth exposed to ELA exhibit elevated concentrations of cortisol, this upregulation may be masking the proinflammatory phenotype in children if inflammation is measured with circulating markers (Kuhlman et al., 2020; Tarullo & Gunnar, 2006). Chronic HPA activation during sensitive developmental periods can induce epigenetic changes in the GR, reducing signaling in a compensatory manner (Weaver et al., 2004). This signal reduction could lead to resistance to cortisol's anti-inflammatory properties. ELA is associated with DNA demethylation in the glucocorticoid response elements of the FK506 binding protein 5 (*FKBP5*) gene and reduced sensitivity to glucocorticoids' inhibitory effect on IL-6 production in peripheral blood immune cells stimulated in vitro (Klengel et al., 2013). A study in 18-year-old females retrospectively reporting ELA did not find higher levels of peripheral IL-6, but in vitro analyses found pronounced cytokine responses to bacterial challenge and evidence for decreased efficacy of cortisol to regulate the inflammatory response (Miller & Chen, 2010). HPA axis and immune system interactions highlight the need to consider how neuroendocrine responses to adversity may increase risk for psychopathology through alterations in the co-regulation of multiple systems. Few studies on childhood adversity investigate HPA axis functioning with immune functioning (Kuhlman et al., 2020). More complex models might

clarify how childhood adversity impacts the brain and behavior through both HPA- and immune-mediating systems.

Gut microbiome dysbiosis

Growing evidence suggests that the microbiome plays a role in the pathway between ELA, stress-mediating and immune-system development, and mental health. The gut microbiome is involved in the immune system development and function (Hooper, Littman, & Macpherson, 2012). Its effects include changes in inflammation (Cani, Osto, Geurts, & Everard, 2012; Wells et al., 2017) and immune competence in response to pathogen exposure and infection (Mackos, Maltz, & Bailey, 2017; Zanella Terrier, Simonet, Bichard, & Frossard, 2014). Gut microbiome dysbiosis has been associated with psychological impairments (Cryan & Dinan, 2012; McVey Neufeld, Mao, Bienenstock, Foster, & Kunze, 2013). ELA may alter communication between the gut and the brain through altered vagus nerve and enteric nervous system signaling, HPA axis activation, immunomodulation, and inflammation (Cryan & Dinan, 2012; Gareau, Silva, & Perdue, 2008; Konturek, Brzozowski, & Konturek, 2011; Segerstrom & Miller, 2004). Psychosocial stress has been associated with changes in gut microbiota structure and activity (Mackos et al., 2017). In rodent and nonhuman primate models, early maternal separation has transient and long-term effects on the gut microbiota (Bailey & Coe, 1999; O'Mahony et al., 2009). In murine models, ELS-induced alterations of the microbiome persist into adulthood (Garcia-Rodenas et al., 2006; Jasarevic, Howard, Mistic, Beiting, & Bale, 2017; Jasarevic, Rodgers, & Bale, 2015). Changes to the gut microbiome in these models have been associated with anxiety-like behaviors and activation of stress-mediating systems (Gareau et al., 2008). Rodents exposed to stress exhibit inflammation, altered gastrointestinal (GI) function and permeability, and differences in immune activity (Gareau et al., 2008). In humans, differences in the gut microbiome have been found in adults who have developed PTSD after trauma exposure and adults with a history of childhood trauma (Hemmings et al., 2017). ELA-exposed children have also been found to exhibit gut microbiome differences (Callaghan et al., 2020). Although conducted in a small sample of children, this study observed that gut bacteria levels were correlated with prefrontal cortex activation to emotional faces (Callaghan et al., 2020). The relationship between ELA-induced gut dysbiosis and inflammation are likely bidirectional (Cryan & Dinan, 2012; Hooper et al., 2012).

Stress-induced nutrient metabolism disruptions

Disruptions to nutrient metabolism is an unexplored pathway by which ELS can lead to inflammation. To function properly, the developing immune system requires macronutrients (i.e., protein, fat, carbohydrates) and micronutrients (e.g., iron, zinc, B vitamins etc.). Psychosocial stress and dysregulated neuroendocrine pathways can disrupt nutrient metabolism even in the context of adequate nutrient intake (Monk, Georgieff, & Osterholm, 2013; Suchdev et al., 2017) and lead to through disruptions in immune functioning. There are many required nutrients for immune system development, but we will use iron as an illustrative example. Iron deficiency is one of the most common forms of malnutrition, with an estimated 4 in 10 children under 5 being affected (Stevens et al., 2013), and children exposed to ELA are often at higher risk of iron deficiency. Adequate iron intake and utilization is necessary for normal white blood cell and cytokine function (Coe, Lubach, & Shirtcliff, 2007). In murine models, early iron deficiency increased expression of proinflammatory cytokine gene

pathways in the adult brain even after iron repletion. Neonatal iron deficiency also reduced anti-inflammatory gene expression and altered cell-mediated immune response genes in infant mice (Tran, Singh, Wallin, & Georgieff, 2018). Research from a nonhuman primates showed that exposure to early life stress resulted in lower levels of iron and iron status subsequently predicted greater deficits in innate immune system functioning (Coe et al., 2007). Few studies exist in human models, but one study found that a randomized control trial of iron supplementation was associated with decreased levels of inflammation in a cohort of adolescents, even after exposure to ELA in infancy (Reid et al., 2020). ELA-induced nutrient dysregulation could be a mediator that is ripe for research and intervention.

Adipose tissue

Adipose tissue generates and regulates about one-third of circulating inflammatory markers (Black, 2003). Obesity in childhood is associated with low-grade inflammation (Visser, Bouter, McQuillan, Wener, & Harris, 2001), and ELA is a risk factor for obesity in experimental animal models and human studies (Bzostek & Beck, 2011; Danese & Tan, 2014; Gundersen, Mahatmya, Garasky, & Lohman, 2011; Jelleyman & Spencer, 2008; Weinberg et al., 2013). The links between ELA and increased adiposity could arise from a biologically and behaviorally driven “thrifty” phenotype characterized by increased energy intake, increased storage, and/or decreased energy expenditure (Danese & Tan, 2014). Childhood stress has been linked with emotional eating and unhealthy dietary patterns (Michels et al., 2012), perhaps due to “self-medicating” with energy dense foods (Baldwin & Danese, 2019). Impaired reward processing and reduced self-control from ELA may lead to increased intake of high-fat, high-sugar foods (Evans, Fuller-Rowell, & Doan, 2012; Hostinar, Ross, Chen, & Miller, 2015b). The neuroendocrine pathway between ELA, obesity, and inflammation could be a potent one, as glucocorticoids contribute to adipose tissue development (Dallman et al., 1993) and cortisol plays a central role in regulating food intake and metabolism (Dallman, 2010; Dallman, Pecoraro, & la Fleur, 2005). Thus, early adversity exposure could increase the risk for children and adolescents to engage in eating behaviors that contribute to increased adiposity and inflammation.

ELA could result in obesity through decreased energy expenditure from metabolic hormone alterations and mental health problems (Baldwin & Danese, 2019). ELA is associated with changes in leptin levels, which are responsible for lipolysis (Danese et al., 2014; Panagiotaropoulos et al., 2004). Mental health problems associated with child adversity are also associated with physical inactivity (Baldwin & Danese, 2019). Impaired functioning in neuroendocrine and leptin pathways could dysregulate thermogenesis and lipolysis, leading to decreased energy expenditure and increased adipose tissue growth (Danese & Tan, 2014). Inflammation itself can induce fatigue (Dantzer et al., 2008), and thus inflammation from ELA exposure could cyclically contribute to reduced energy expenditure, increased adipose tissue, and increased inflammation.

Studies have found that ELA was associated with adolescent levels of inflammation only in the context of accelerated BMI growth trajectories (Reid et al., 2020; Tang et al., 2018). In a number of studies, adiposity attenuated or abolished several of the associations between ELA and inflammation (Matthews et al., 2014; Pinto Pereira et al., 2019), though others have found that the association between adversity and inflammation was

independent of obesity in both adult and pediatric samples (Baldwin et al., 2018; Danese et al., 2011; Danese et al., 2007; O'Connor et al., 2020). This adversity–obesity–inflammation pathway seems to be of increased importance in studies of childhood adversity and inflammation in adolescence.

Brain functioning and behavior

ELA can instantiate a chronic inflammatory state through brain and behavioral changes. The Neuroimmune Network Hypothesis outlines the process by which ELA prompts crosstalk between the neural and immune systems to create a loop of increased threat sensitivity, inflammation, and unhealthy behaviors that can result in increased risk for chronic inflammation (Nusslock & Miller, 2016). ELA is associated with impaired executive function, impaired reward processing, and hippocampal and prefrontal cortex abnormalities in human and nonhuman animal studies, which could lead to impaired ability to suppress unwanted behavior (Brunson et al., 2005; Danese & McEwen, 2012; Dillon et al., 2009; Matthews & Robbins, 2003; Mehta et al., 2010; Pechtel & Pizzagalli, 2011; Phillips, Howes, Whitelaw, Robbins, & Everitt, 1994; Pryce, Dettling, Spengler, Spaete, & Feldon, 2004). Individuals exposed to ELA are at a higher risk of substance and alcohol abuse disorders (Anda et al., 1999; Dube et al., 2003), which contribute to increased inflammation (Shiels et al., 2014). Though less relevant for children, adolescence might be a salient time for proinflammatory phenotypes to emerge due to increases in risky behaviors, such as smoking and habits that contribute to weight gain (Raposa, Bower, Hammen, Najman, & Brennan, 2014), and impulsive behaviors that increase stress exposure (Lovallo, 2013; Raposa et al., 2014).

Another behavioral pathway that could follow from ELA to promote inflammation is through persistent or recurring distress and self-harming behaviors. Maltreatment has been associated with heightened threat perception (Leppanen & Nelson, 2009; Pollak & Kistler, 2002) and heightened amygdala activation in response to negative emotional stimuli (McCrorry et al., 2013; Tottenham et al., 2011). Depression and inflammation are bidirectionally associated in longitudinal studies of adults and adolescents (Matthews et al., 2010; Miller & Cole, 2012). An individual's perception of stressors, emotional symptoms, and behavioral responses when distressed could increase their inflammation levels (Danese & Lewis, 2017). An individual's increased exposure to stressors and their emotional symptoms can further lead to chronic levels of stress and individuals may engage in self-harm to relieve feelings of distress (Baldwin, Arseneault, Caspi et al., 2019), offering another behavioral pathway by which ELS can contribute to increased inflammation.

Sleep

There are reciprocal links between sleep and inflammation, and we direct the reader to a thorough review by Irwin (2015). Sleep can regulate the immune response: sleep disturbance has been linked with reduced vaccine efficacy (e.g. Prather et al., 2012; Spiegel, Sheridan, & Van Cauter, 2002), impaired response to infectious challenge (Cohen, Doyle, Alper, Janicki-Deverts, & Turner, 2009; Toth, 1995), and upregulation of inflammation (Irwin, 2015). Sleep influences the HPA axis, which in turn regulates the immune system through the diurnal cortisol rhythm (Irwin & Cole, 2011; Slavich & Irwin, 2014). In experimental and naturalistic epidemiological studies, sleep deprivation is associated with increased expression of proinflammatory cytokines and elevated inflammation (Irwin, Wang, Campomayor, Collado-Hidalgo, & Cole, 2006;

Miller et al., 2009). Maternal separation in rodent models decreased sleep duration and disrupted sleep architecture for stress-affected animals (Mrdalj et al., 2013). A history of childhood trauma is associated with increased sleep problems (Gregory & Sadeh, 2016), independent of current PTSD or depression diagnoses (Noll, Trickett, Susman, & Putnam, 2006). Unfortunately, prospective evidence that demonstrates a mediating role for inflammation in the association between sleep disruptions and psychopathology is not yet available (Irwin, 2015). To our knowledge, no studies have extended this work to investigate the specific pathways between ELA and sleep disruption as they relate to inflammation and psychopathology.

Moderation

Meta-analyses of pediatric and adult populations have found heterogeneity in outcomes in the association of ELA and inflammation (Baumeister et al., 2016; Kuhlman et al., 2020). We propose three moderating factors that are currently underexamined in the literature: (a) age at inflammation assessment, (b) sex differences, and (c) population context differences. First, when are ELA's effects on inflammation instantiated and measurable? Do inflammatory phenotypes from ELA differ based on the timing of immune assessment? Second, there are questions on the timing of adversity exposure: are there sensitive periods for exposure to adversity and maximal impact on the immune system, or is a cumulative model of adversity exposure most salient to impacts on the immune system? Further, animal models of early life stress and inflammation routinely find sex differences (Ganguly & Brenhouse, 2015), though few studies examine sex differences in human populations. Finally, though much of the ELA and inflammation literature has been conducted with participants from Western, educated, industrialized, rich and democratic ("WEIRD") societies, a handful of studies in different country contexts paint a different picture of the associations between ELA and inflammation. Thus, does societal context act as a yet-unexplored moderator? While studies and meta-analyses have tested for moderation in adult samples, more work is needed to understanding how moderation functions in pediatric samples.

Age of assessment

More research is needed to understand how ELA across development contributes to an inflammatory phenotype and how inflammatory phenotypes change across development. As noted, acute psychosocial stress activates peripheral inflammation and chronic psychosocial stress is associated with systemic, low-grade inflammation. This transition is thought to be a driver of psychopathology, especially after exposure to childhood adversity. However, it is unclear when an acute stressor becomes a chronic stressor (Rohleder, Nater, Wolf, Ehlert, & Kirschbaum, 2004), and this gap is especially prevalent in studies of children. Longitudinal assessments of inflammation over longer periods of time, repeat assessments of inflammation over a shorter window (for an example, see McDade et al., 2012), and studies on repeated acute stress might help fill this gap. As these studies do not yet exist, we review the ELA and inflammation literature with a developmental lens.

Adulthood. Much of the evidence linking ELA and later inflammation has been found in adults. Consistent with the animal literature, adults exposed to childhood maltreatment are at greater risk of increased levels of circulating inflammatory markers (Baumeister et al., 2016; Danese & Lewis, 2017) and greater

proinflammatory responses in response to subsequent stressors (Carpenter et al., 2010; Gouin et al., 2012; Kiecolt-Glaser et al., 2011). In clinical adult populations, depressed individuals with a history of ELA exhibit increased inflammatory responses to acute psychosocial stress (Pace et al., 2006) and show higher levels of inflammation in unstimulated plasma (Danese et al., 2008). Table 2 collates the studies of adult clinical populations from the Baumeister meta-analysis, specifically focusing on populations with psychiatric diagnoses of first episode of psychosis (FEP), major depressive disorder (MDD), and PTSD as compared with health controls (Baumeister et al., 2016). A history of ELA appears drive increased inflammation in clinical samples (Baumeister et al., 2016), as patients without ELA had immune profiles similar to healthy controls (Dennison et al., 2012). Further, psychologically healthy controls with a history of ELA exhibited higher IL-1B compared to controls without ELA exposure (Di Nicola et al., 2013).

The Baumeister meta-analysis found that age did not have a moderating effect on the relationship between ELA and inflammation in adulthood (Baumeister et al., 2016). It could be possible that the moderating effect of age is most salient in pediatric populations. Alternatively, adulthood could be a life stage in which the cumulative effects of ELA are easier to capture through peripheral inflammatory cytokines. One study of adults in midlife found support for the stress accumulation model: ELA and recent life event stressors were independently associated with higher levels of inflammation, controlling for each other's effects, and their interaction was not significant (Hostinar, Lachman, Mroczek, Seeman, & Miller, 2015a). In that study, mediation analyses found that ELA and recent life stressors had unique and additive contributions to inflammation through norepinephrine pathways, adiposity, and inflammation-inducing behaviors (Hostinar et al., 2015a). In adults, inflammation might depend on behavioral mediators rather than age.

Childhood and adolescence. Descriptive analyses from the meta-analysis of ELA and inflammation associations in a pediatric population found that adversity was positively associated with CRP when inflammation was assessed in adolescence, but not with IL-6 or TNF- α (Kuhlman et al., 2020). A study of 1,789 female adolescents found that greater exposure to childhood maltreatment and victimization predicted higher CRP levels at age 18 (Baldwin et al., 2018). This study included prospectively collected information from 5 to 12 years of age about ELA exposure, but the study took a cumulative approach rather than testing ELA exposure at different developmental periods. A study of sexual abuse in a clinic setting found that individuals getting a medical assessment for sexual abuse (occurring in the 72 hr preceding the assessment) did exhibit higher levels of IL-6 than their non-abused peers (Kilic et al., 2017). However, the sample size was small and, while the mean age of assessment was 15 years, the age range spanned from 3 to 18 years, which makes it difficult to interpret as it pertains to time in development. Given the temporal proximity of the sexual abuse to the inflammation metric, it is unclear if this study is indicative of acute physical injury or chronic inflammation.

The pediatric meta-analysis previously mentioned also found in descriptive analyses that ELA was positively associated with CRP when inflammation was assessed in later childhood (Kuhlman et al., 2020). Two found positive associations with maltreatment exposure and circulating levels of TNF- α , but not IL-6 (Bucker et al., 2015). In contrast, a larger study of 9-year-olds

Table 2. Early adversity and inflammation: adult at inflammation assessment, clinical populations

Study	Sample size	Tissue	Population	Mean age (years)	% Female	Design	Exposure	Exposure details	Age of exposure (years)	Outcome notes	CRP	IL-6	TNF
Hepgul et al. (2012)	80	Blood	Clinical – FEP patients versus HC	26.69	34.4	Retrospective	Maltreatment	Physical, sexual abuse	<17		✓		
Di Nicola et al. (2013)	48	Blood	Clinical – FEP patients versus HC	27.35	35.4	Retrospective	General trauma	Childhood Experience of Care and Abuse (CECA)	<17	HC w/ trauma = higher mRNA levels of IL-1 β compared w/ HC w/out trauma. No other associations found serum interleukin(IL)-1 α , IL-1 β , IL-2, IL-4, IL-6, IL-8, IL-10, Interferon- γ (IFN- γ),		∅	✓
Lu et al. (2013)	65	Blood	Clinical – MDD patients versus HC	29.32	55.4	Retrospective	General trauma	CTQ	<17			✓	✓
Dennison, McKernan, Cryan, and Dinan (2012)	80	Blood	Clinical – FEP (schizophrenia) patients versus HC	37.27	53.8	Retrospective	General trauma	CTQ	<17	Patients with no trauma had similar immune profiles to controls.	✓		✓
Frodl et al. (2012)	83	Blood	Clinical – MDD patients versus HC	39.12	59	Retrospective	General trauma	CTQ	<17		✓	∅	
Zeugmann et al. (2013)	23	Blood	Clinical – MDD patients	47.8	68	Retrospective	General trauma	CTQ, Maltreatment	<17	Fibrinogen significant only with physical neglect	∅		∅
Smith et al. (2011)	177	Blood	Clinical – PTSD patients versus HC	NA	NA	Retrospective	Maltreatment	Child abuse CTQ	<17				✓

∅ = null association between ELA exposure and inflammatory outcome.

✓ = positive association between ELA exposure and inflammatory outcome.

CTQ = Child Trauma Questionnaire; CRP = C-reactive protein; ELA = early life adversity; FEP = first episode of psychosis; HC = “heathy controls”; IL-6 = interleukin-6; MDD = major depressive disorder; PTSD = posttraumatic stress disorder

exposed to maltreatment found no associations between ELA and salivary CRP, even when examining the contributions of timing and chronicity of exposure (Cicchetti et al., 2015). It is difficult to compare the studies, as the inflammatory cytokines and tissue selection differed. However, both studies measured maltreatment prospectively and measured inflammation at age 9, highlighting the need for more studies on ELA and inflammation in childhood.

Few studies have examined ELA and inflammation in infancy and early childhood but descriptive analyses from the previously mentioned meta-analyses found that ELA was positively associated with CRP in infancy but negatively associated with CRP in early childhood (Kuhlman et al., 2020). This meta-analysis included studies with a very broad definition of ELA that are not included in our definition of victimization. A study of salivary CRP in 40 4-year-olds found no association between ELA and CRP, though ELA was positively associated with salivary IL-1 β (Tyrka et al., 2015). In a study using dried blood spot measures of CRP, no group differences were found in CRP levels between 4–6 year old CPS-referred children and low-risk children (Bernard et al., 2019). The study did find that both insecure and disorganized attachments in CPS-referred children were associated with more inflammation compared to securely attached CPS-referred children and low-risk children (Bernard et al., 2019).

The Avon Longitudinal Study of Parents and Children (ALSPAC) study, a prospective cohort study of 4,525 individuals with data on IL-6 and CRP in childhood (age 9 years), provides a wealth of longitudinal data on ELA, inflammation, and psychopathology-related outcomes. One analysis found that prospective measures of adversity predicted IL-6 but not CRP in 9-year-olds (Flouri et al., 2020). IL-6 partially mediated the relationship between ELA and later internalizing symptoms (Flouri et al., 2019). However, IL-6 did not explain the association between ELA and externalizing symptoms. A separate study on this cohort found that IL-6 levels at 9 years partially mediated the association between ELA in childhood and depressive symptoms at the beginning of adolescence (Flouri et al., 2019). Internalizing symptoms at age 9 years fully mediated the association between levels of IL-6 in childhood and subclinical psychotic symptoms (psychotic-like experiences, PLEs) at age 18 (Flouri et al., 2020). CRP was not associated with either internalizing symptoms or psychotic-like experiences. Though it is unclear how IL-6 tracks across development, these studies provide evidence that that specific markers of inflammation in childhood mediate the relationship between ELA and symptoms of psychopathology.

Timing and duration of exposure. Cumulative adversity throughout childhood may be needed to see associations with inflammation. Early intervention and removal from adversity may protect an individual from developing an inflammatory phenotype and instead instantiate risk for psychopathology through other mechanisms. As mentioned previously, studies of adolescents and young adults removed institutional care indicate no evidence of a proinflammatory phenotype after exposure to deprivation (Reid et al., 2019; Slopen et al., 2019; Tang et al., 2018). As these studies did find changes in acquired immunity indicative of immune senescence (Elwenspoek et al., 2017a; 2017b; Reid et al., 2019), adolescence might be a time to capture early perturbations to acquired immunity that are either on the path to or distinct from the pathogenesis of inflammation and psychopathology. In the Avon Longitudinal Study of Parents

and Children study mentioned previously, there was also no evidence that IL-6 or CRP levels mediated the association between ELA exposure in infancy and depressive symptoms in adolescence (Flouri et al., 2020). The link from ELA in infancy to depressive symptoms in adolescence was direct, and therefore elevated levels of IL-6 in childhood partially explained the link between adolescent depressive symptoms from proximal childhood stressors only (Flouri et al., 2020). Thus, there may be qualitatively different pathways to depression from very early ELA exposure. Associations between ELA and inflammation may not emerge without substantial environmental or behavioral input (Miller et al., 2011b). Future studies that address the auto-correlation of early and concurrent adversity can help tease apart how the timing of childhood adversity contributes to increased risk of psychopathology and inflammation.

Summary. What does it mean, functionally and regarding psychopathology risk, to have higher levels of inflammatory cytokines in infancy versus childhood versus adolescence? Relatively little is known about the relationship between adversity and inflammation longitudinally from infancy to adolescence. Even less is known about the pathogenesis of inflammation from ELA in infants and young children. Thus, given the meta-analytical findings that show increased inflammation in infancy, no association in childhood, and increased inflammation in adolescence, it is unclear whether the association between ELA and inflammation across development is linear or nonlinear. This might suggest support for theoretical sensitive periods of immune development in infants and adolescents (Kuhlman et al., 2020). However, the picture becomes less clear when examining ELA exposure limited to infancy compared to cumulative exposure. Developmentally focused research is needed to understand the “hidden wounds” of ELA.

Sex differences

Experimental, nonhuman animal models suggest that early life stress has sexually dimorphic effects on immune dysregulation (Ganguly & Brenhouse, 2015). In adult populations, a meta-analysis found no evidence of a moderating effect of sex on the relationship between ELA and inflammation (Baumeister et al., 2016). The pediatric meta-analysis was underpowered to examine sex differences. Nonetheless, the association between ELA and CRP was specific only to young women in the genetically informed twin study mentioned previously (Baldwin et al., 2018). Sex differences could arise from sex differences in neuroendocrine regulation. For example, male, not female, adolescents exposed to violence in the past year exhibited lower cortisol reactivity to a laboratory stressor (Peckins, Dockray, Eckenrode, Heaton, & Susman, 2012). Sleep disruption may be another avenue by which sex moderates the relationship between ELA, inflammation, and psychopathology. Women appear more likely to develop dysregulated inflammatory responses from sleep disturbance while men appear to be more likely to develop cardiovascular disease and cancer, but not depression (Irwin, 2015). The field needs studies that are well-powered to examine sex differences in pediatric populations, as exposure to ELA and the biological sequelae of inflammation could exhibit important sexually dimorphic effects in humans.

Ecological and demographic differences

Examination of heterogeneous populations and contexts could reveal important mechanisms of how ELA contributes to

inflammation and psychopathology. Many of the studies reviewed have been conducted in high-income country contexts, though children in low- and middle-income country contexts are no less exposed to ELA. However, the processes by which ELA may instantiate inflammation might be different for children outside of high-income country and often urban contexts. Studies in representative cohorts in the Philippines, as mentioned previously, and Tanzania suggest that the typical high-adversity, high-inflammation associations may be moderated by contextual factors that are unique to high-microbial, rural, or low- or middle-income country contexts (Hadley & Decaro, 2014; McDade, Hoke, Borja, Adair, & Kuzawa, 2013). In a pediatric population, a large study of Tanzanian children under 5 found that CRP was positively associated with adversity quantified as maternal illiteracy, larger household size, and disease load (Hadley & Decaro, 2014). Interestingly, membership in the *least* poor wealth category was associated with higher levels of CRP. As this sample of Tanzanian children were more likely to be stunted, with an average height-for-age of -1.66 , and an average CRP level of 4.4 mg/l, it is difficult to compare with the studies of infants conducted in higher-income countries (Hadley & Decaro, 2014). However, this study points to important contextual considerations when researching young children, ELA, and inflammatory biomarkers in more diverse country contexts.

Even in the context of Western, educated, industrialized, rich and democratic (WEIRD) societies, under-represented ethnic and race groups in predominantly white countries might experience differences in context that contribute to increases in inflammation after ELA exposure. For example, Pereira's analysis of the large US cohort mentioned previously found that sexual abuse was associated with all inflammatory markers in nonwhite adults but not white adults in the United States. IL-6 was higher by 36.3% in nonwhite adults exposed to childhood sexual abuse versus 9.89% in white adults exposed to childhood sexual abuse (Pinto Pereira et al., 2019). Experiences of racial or ethnic discrimination may constitute an aspect of child victimization or threat perception that is currently understudied. In a study of perceived discrimination, there was a positive association between child-reported discrimination and CRP, as measured by dried blood spots in a group of children with a mean age of 12 y (Goosby, Malone, Richardson, Cheadle, & Williams, 2015). This was a small study, but emphasizes the need to operationalize, measure, and assess how different forms of child adversity, such as racial discrimination, can contribute to inflammatory outcomes and risk for psychopathology. Thus, specific populations may experience moderating factors such as discrimination in addition to the types of adversity that are typically measured in the context of childhood adversity exposure and inflammation (Goosby et al., 2015; Pinto Pereira et al., 2019; Slopen et al., 2010).

Interventions

The accumulated evidence suggests that the study of inflammation could help explain and plan a course of treatment for individuals with psychopathology after exposure to ELA. Nevertheless, there are a number of questions that can only be answered with animal models. For example, animal models could help elucidate developmental pathways from ELA and inflammation, assist in biomarker selection, clarify tissue specificity issues. As ELA is typically associated with later adversity in humans, animal models can help answer questions about the timing of inflammation assessment. In humans, clinical interventions can begin to address

the heterogeneity in outcomes that might be experience- or population-dependent. Lifestyle and psychosocial interventions can begin to clarify the outstanding questions on mediation. Here, we address some of the evidence from human intervention models.

Clinical interventions

There is still much to understand about treating inflammation-associated psychopathologies with anti-inflammatory medications and supplements. Experimental studies on anti-inflammatory treatments in depression offer promise, especially in subgroups of patients who exhibit high levels of inflammation in the case in ELA-exposed individuals with depression (Danese & Lewis, 2017; McIntyre et al., 2019; Raison et al., 2013). Meta-analyses examining inflammation before and after treatment in depressed patients found that IL-6 levels decreased with antidepressant treatment regardless of outcome, whereas elevated TNF α was associated with treatment resistance (Strawbridge et al., 2015). Patients who were nonresponders had higher baseline inflammation, suggesting that elevated levels of inflammation contribute to treatment resistance (Strawbridge et al., 2015). Studies of major depressive disorder and bipolar disorder patients with high levels of systemic inflammation and a history of physical abuse demonstrated a superior response to the TNF- α blocker infliximab (McIntyre et al., 2019). This initial evidence points to the potential benefit of pharmacological anti-inflammatory interventions in patients' subgroups but requires further investigation before any clinical implementation.

Lifestyle interventions

Beyond clinical interventions, diverse lifestyle interventions could reduce inflammation and either prevent or reduce psychopathology symptoms. Ideally, lifestyle interventions such as diet, physical activity, and sleep can be tailored and used across development with minimal adverse side effects.

In the last decade, numerous studies report inverse associations between diet quality and depressive disorders and symptoms in adults (Jacka, Mykletun, Berk, Bjelland, & Tell, 2011b; Jacka et al., 2013; Kuczmarski et al., 2010; Nanri et al., 2010), adolescents (Jacka et al., 2011a; Jacka et al., 2009; Weng et al., 2012), and children (Kohlboeck et al., 2012). Diet quality is associated with inflammation in population-based studies (Chrysohoou, Panagiotakos, Pitsavos, Das, & Stefanadis, 2004; Fung et al., 2001; Lopez-Garcia et al., 2004) and intervention studies (Esposito et al., 2004; Watzl, Kulling, Moseneder, Barth, & Bub, 2005). These associations may be due to specific aspects of diet quality that either contribute to or protect from inflammatory processes.

For example, magnesium intake is highly correlated with diet quality and is negatively associated with levels of CRP (King, Mainous, Geesey, & Woolson, 2005). Omega-3 fatty acids and polyunsaturated fatty acids are associated with reduced inflammation (Clarke, Shipley, Armitage, Collins, & Harris, 2009; Rangel-Huerta, Aguilera, Mesa, & Gil, 2012), and a randomized controlled trial of omega-3 fatty acids found a reduction in psychotic disorder progression and psychiatric morbidity over a 7-year follow-up (Amminger, Schafer, Schlogelhofer, Klier, & McGorry, 2015). Foods high in fiber could have positive impacts on immune functioning due to high levels of beta-glucans, phytochemicals, and influences on the gut microbiome (Bilici et al.,

2001; Parikh et al., 2012; Tachon, Zhou, Keenan, Martin, & Marco, 2013; Volman, Ramakers, & Plat, 2008). As noted in the nutrient metabolism mechanism section, adequate iron intake during infancy may act as a protective factor from increased levels of CRP in adolescence (Reid et al., 2020). In contrast, diets high in refined carbohydrates, added sugars, and trans-fatty acids are associated with higher levels of inflammation in human and animal models (Iwata et al., 2011; Levitan et al., 2008; Liu et al., 2002; Pistell et al., 2010). Saturated and trans-fat intake may increase LPS release from microbiota in the gut to promote immune system activation (Moreira, Texeira, Ferreira, Peluzio Mdo, & Alfenas Rde, 2012). More studies on adversity, diet, and inflammation are needed in adult and child cohorts to test the impact of dietary interventions in ELA-exposed populations.

Physical activity is another area of intervention. Exercise can reduce depressive symptoms (Conn, 2010) and the risk of new depressive episodes in adults (Brown, Ford, Burton, Marshall, & Dobson, 2005; Pasco et al., 2011; Strawbridge, Deleger, Roberts, & Kaplan, 2002). Physical inactivity in childhood has been associated with an increased risk of adult depression (Jacka et al., 2011c). A longitudinal study of 3,809 nondepressed men and women found that physical activity mediated the association between inflammation and depressive symptoms (Frank et al., 2019). A meta-analysis of 83 studies found that exercise training was negatively associated with CRP levels regardless of the age or sex of the individual (Fedewa, Hathaway, & Ward-Ritacco, 2017). Few studies have been conducted in children, and most studies are in overweight or obese samples of children (Michigan, Johnson, & Master, 2011). Physical activity is a modifiable health behavior that could be used to target inflammation and depressive symptoms. However, to our knowledge, no studies have investigated physical activity and inflammation in the context of ELA.

Behavioral interventions that target sleep have the potential to reduce inflammation and possibly reduce inflammatory disease risk in contexts of psychopathology (Irwin, 2015). Sleep health can theoretically be used to therapeutically control chronic infectious, inflammatory, and neuropsychiatric diseases (Irwin, 2015). Several behavioral (e.g., cognitive behavioral therapy for insomnia) and mind-body (e.g., tai chi and yoga) interventions have potential to modulate certain aspects of the immune functioning. For example, mind-body interventions have been found to improve insomnia (Irwin, Olmstead, & Motivala, 2008), augment vaccine responses (Irwin, Olmstead, & Oxman, 2007), and reduce levels of IL-6 (Irwin & Olmstead, 2012), and reduce proinflammatory response gene profiles (Creswell et al., 2012). Similarly, behavioral therapy in patients with rheumatoid arthritis improved depressive symptoms, reduced the stimulated production of the proinflammatory cytokine IL-6 (Zautra et al., 2008), and decreased levels of CRP up to a year after treatment (Irwin et al., 2014). Interventions might be specifically helpful for adolescents, as a study of 315 adolescents found that nightly variability in sleep duration was associated with higher levels of CRP (Park et al., 2016). For younger adolescents, shorter average sleep duration was associated with higher CRP (Park et al., 2016). While more studies are needed in younger children and infants, this suggests that targeting sleep duration could reduce inflammation following ELA.

Psychosocial interventions

Interventions to reduce the incidence of ELA itself are clearly necessary to reduce the rates of mental and physical illness. However,

interventions in the context of ongoing childhood adversity show promise in reducing harmful outcomes. A study of positive childhood experiences in a cross-sectional study of 6,188 adults found that self-reports of positive childhood experiences showed a dose-response association with lower odds of adult depression and/or poor mental health (Bethell, Jones, Gombojav, Linkenbach, & Sege, 2019). These associations held after controlling for exposure to adverse childhood experiences, and support the prioritization of providing children with safe, stable nurturing relationships for better mental health outcomes (Bethell et al., 2019). Positive family and caregiving environments are associated with low inflammation across a range of developmental ages. A study in infants found that attachment security moderated the association between ELA and inflammation, where securely attached infants did not exhibit a heightened inflammatory phenotype (Measelle & Ablow, 2018). As noted earlier, attachment quality in infancy has been found to predict early childhood CRP among CPS referred children (Bernard et al., 2019). Children who had insecure or disorganized attachments in infancy had higher CRP levels in early childhood than children who had secure attachments in infancy, controlling for covariates (Bernard et al., 2019). Interventions such as the Attachment and Biobehavioral Catch-up (ABC) intervention have demonstrated efficacy in improving attachment quality in families at high risk of developing insecure attachment (Bernard et al., 2012), and parenting interventions early in life therefore may be a promising avenue to pursue reducing later inflammatory phenotypes.

In addition to prevention, the therapeutic improvement of social support and community belonging could be promising in reducing the associations between child adversity and adult inflammatory outcomes. One study investigated whether belonging to the tribal community in a sample of 90 adults living on the Blackfeet reservation may moderate the relationship between ELA and levels of IL-6 and CRP (John-Henderson et al., 2020). Independent of age, gender, annual income, body mass index, and depressive symptoms, ELA exposure predicted IL-6 and CRP levels, but self-reports of belonging to the tribal community moderated the relationship between reports of ELA and markers of inflammation (John-Henderson et al., 2020). Outside of parenting interventions, one study found that the presence of supportive role models and positive cognitive models to deal with stress may act as a buffer against proinflammatory phenotypes for adolescents experiencing adversity (Chen, Lee, Cavey, & Ho, 2013). In this study, youth with supportive role models had lower IL-6 levels. Youth who were better able to reframe stressors a benign and better able to persisting with optimism (“shift-and-persist”) had lower IL-6 (Chen et al., 2013). These benefits seemed to especially benefit the low-SES youth, as benefits were not found among high-SES adolescents (Chen et al., 2013). This study suggests that identifying psychological buffers in adolescents has could have implications for inflammation levels and possibly mental health disparities. Despite many possible avenues of intervention and prevention, more research is needed in this space and in the basic science of understanding how childhood adversity contributes to psychopathology through inflammatory pathways.

Conclusion

Exposure to ELA is a critical risk factor for the development of psychopathology, and the understanding of how early adversity gets “under the skin” is growing with increased research on the

biological risk for increased inflammation. Nevertheless, the heterogeneity present in the current literature leaves many questions and many opportunities for future research. Studies that are developmentally informed and grounded in an understanding of immune- and stress-mediating systems are needed as the field grows. In addition to population-based studies, mechanistic and experimental work is needed to understand what increased inflammation means in the context of adversity at specific times in development and longitudinally. In addition to a better understanding of moderation and measurement, more research is needed to elucidate how ELA contributes to inflammation through neuroendocrine dysregulation, brain functioning and behavior, sleep, adipose tissue, the gut microbiome, and stress-induced nutrient dysregulation. All of these possible mechanistic pathways emphasize the myriad intervention and prevention routes that could be pursued to reduce the mental health burden on individuals and communities that arises from the hidden wounds of childhood adversity.

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