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Brain Behav Immun. Author manuscript; available in PMC 2021 May 01.

Published in final edited form as:

Brain Behav Immun. 2020 May ; 86: 1–3. doi:10.1016/j.bbi.2019.11.005.

Special Issue: Contexts and Consequences of Childhood Inflammation

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1. Preface

This special issue aims to highlight the latest insights into the links between adverse experiences early in life and their immediate and lasting effects on human health and well-being. Factors such as poverty, psychosocial stress, trauma, familial psychopathology, and compromised relationships predict physical and mental health problems in adulthood. Interest in how early forms of adversity embed themselves biologically to engender disease has focused largely on developmental implications for the brain, autonomic, and neuroendocrine stress response systems. Given the immune system's mechanistic role in linking early environmental challenge with disease, more recent attention has focused on stress-induced alterations to inflammatory processes. The vast majority of this work has examined inflammation in adults, with retrospective recall of early adversity (Baumeister et al., 2016). Of late, however, evidence has begun to emerge that reveals how contexts of adversity shape a pro-inflammatory phenotype early in childhood development, with both immediate and lasting consequences. Recent evidence suggests that adverse experiences during early life, specifically infancy, are especially worth compiling given the immune system's early vulnerability and rapid, experience-dependent development (e.g., Measelle et al., 2017).

Accordingly, the time to compile newer evidence from this exciting line of research has arrived, and insights from the work presented in this special issue may help to pinpoint the earliest origins of disease vulnerability among children exposed to early adversity. Possible insights and answers that emerge from this line of research may prove helpful to the identification of bio-behavioral sources of risk and resilience very early in life that have significant near- and long-term health implications and that might emerge to be prime targets for intervention. Moreover, the public-health implications of this work cannot be overstated. Starting with the Centers for Disease Control and Prevention (CDC) and American Heart Association's consensus statement in 2003 (Pearson et al., 2003), and the more recent report on childhood and adolescent adversity from the American Heart Association (Suglia et al., 2018), the need to identify inflammatory processes and their most relevant immunologic

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biomarkers early in life is critical given the public health costs (Luengo-Fernandez et al., 2006) and human toll (Prince et al., 2015) of cardiovascular disease alone. If indeed the origins of costly adult disease can be traced back to links between early-life adversity and contemporaneous inflammatory modifications, the opportunity to consolidate newer findings is timely and warranted.

2. Summary of findings

It has been suggested that such changes in both psychiatric and physical symptoms may be mediated by changes in neuroimmune pathways (Loftis et al., 2010), including brain function (Byrne et al., 2016). However, much of this evidence is from short-term, experimental paradigms. We understand less about the more real-world situations of long-term changes in immune function after or during significant or ongoing adversity, and how these may play a role in the etiology and onset of psychiatric disorders. Until now, even less of this research was examined from a developmental lens that measures adversity and immune functioning during key developmental stages or longitudinally. However, the collection of papers in this special issue will help researcher understand how these associations are linked over time beginning early in life. This is especially critical if early life adversity is shown to alter trajectories of neuroimmune development. Without comprehensive research from a developmental perspective, the mechanisms linking early stress, immune dysfunction, and disease will not be clear.

Importantly, all empirical papers in this special issue examine longitudinal associations (Alloy et al., this issue; Blomström et al., this issue; O'Connor et al., this issue; Nelson et al., this issue; Reid et al., this issue) at key stages of development, such as infancy and adolescence. Several papers also focus on early life stress or adversity as the context in which the immune system develops (Alloy et al., this issue; Kuhlman et al., this issue; O'Connor et al., this issue; Nelson et al., this issue; Reid et al., this issue). Critically, the issue also includes a review that considers experimental evidence in animal models that link early life streptococcal infection and neuropsychiatric disorders (Moreno et al., this issue). Overall, this collection highlights critical steps in the field that begin to elucidate the developmental mechanisms of the association between adversity and inflammation, and identify potential sensitive periods in psychoneuroimmunology more generally. For a summary of study design in the included papers, refer to Table 1.

Two papers focus on early life infection as the measure of stressful context and associated inflammatory response in childhood. First, Moreno and colleagues (this issue) present a systematic review aggregating evidence from animal models that suggest that postnatal Group A streptococcus (GAS) exposure is related to several cognitive and somatic behaviors that may be related to neuropsychiatric disorders. This is supplemented by a large-scale human population cohort study in Sweden (approximately 2 million people) that found that registered diagnoses of infections in childhood (especially in the first year of life and in the central nervous system) were associated with violent criminal behavior later in life, partially mediated by a diagnosis of psychiatric disorder (Blomström et al., this issue). Together, this evidence suggests that infection may trigger an inflammatory response that alters behavioral trajectories across development.

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The other papers in the special issue measure levels of inflammation during infancy, childhood, and adolescence, across a number of different stressful contexts and health consequences. A comprehensive systematic review and meta-analysis of 27 studies by Kuhlman and colleagues (this issue) showed that the effect between early life adversity and inflammation measured in childhood and adolescents was not significant, but emphasized, as discussed here, the small number of studies and the inconsistencies in methodology (namely in the measurement of early life stress and the measurement of inflammatory markers), which limited their ability to compare and aggregate results across studies. The remaining empirical studies in this issue (all longitudinal in nature) were able to look at associations between adversity and inflammation over time in focused cohorts. All found that early adversity is critically associated with poor health outcomes later. First, one study found that individual differences in the immune response to early stress may be especially important to consider for psychological outcomes: Kautz and colleagues (this issue) showed that adolescents who experienced stressful life events and showed an exaggerated inflammatory response over time had higher levels of depressive symptoms at follow up. The remaining studies showed that it may be interpersonal- and family-specific adversity early in life that is important for immunological development. Focusing first on infancy, Nelson and colleagues (this issue) found that maternal parenting stress and social support prospectively predicted levels in inflammation in infants six months later. But the consequences of this early life stress may be even longer lasting. In a study of working-class communities in Chile (Reid et al., this issue), early interpersonal conflict stress in infancy predicted inflammation in adolescence, especially for children who had increased BMI over time. Additionally, another study found that poor inflammatory outcomes in development may be specific to caregiver stress: O'Connor and colleagues (this issue) found that caregiver depressive symptoms in early childhood predicted levels of inflammation in adolescence, even after controlling for SES, health behaviors, and BMI. Overall, the results presented in this special issue make clear the urgent need for researchers, policy makers, and healthcare providers to consider the effects of maternal and caregiver stress on children's health and wellbeing.

3. Methodological considerations for future research

Research that investigates the inflammatory processes and relevant immunologic biomarkers early in life is complex and presents a number of important methodological challenges. To maximize feasibility, scientific rigor, and reproducibility across these studies, a number of protocol design and methodological factors should be considered. Table 2 summarizes the measures of stress and adversity as well as the associated immunologic indices used in the collection of original (empirical) research papers presented in this special issue. As can be seen, a number of different measures have been used to measure stress and immune functioning.

Measures: stress and adversity.

In clinical research studies, assessment of stress and adversity should be expanded beyond Adverse Childhood Experiences (ACE) scoring to better appreciate the complexities of stress exposure during key developmental stages. This includes consideration for how risk, stress and adversity are conceptualized and measured. The current issue presents several

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contexts in which stress exposure was measured. Other suggestions for future research may also include the Stress and Adversity Inventory for Adolescents (Adolescent STRAIN), which was recently developed, evaluated, and found to have high concurrent and predictive validity (Slavich et al., 2019). This measure was designed using the conceptual framework that life stress is not a singular construct; stressors can appear in different forms (acute or chronic); and adversity can occur in a variety of environments (*e.g.* home, school, intimate relationships) with different effects on health (Epel et al., 2018).

Biological specimen type.

Most of the studies in the current issue focused on inflammation measured in serum (Reid, et al., this issue; O'Connor et al., this issue) or plasma (Kautz et al., this issue), while one study measured salivary inflammation (Nelson, et al., this issue). However, unique to this field in general has been the range of biological specimens, beyond peripheral blood samples, potentially available for investigating immune mechanisms (*e.g.*, amniotic fluid, colostrum, breast milk, and umbilical cord blood). Increasingly, studies are utilizing multiple sources of cytokines and immune cells during pregnancy to characterize the maternal-fetal interface and to better understand the fetal inflammatory response [*e.g.*, (Abioye et al., 2019; Gomes Fagundes et al., 2016)]. Given that immunoregulation is critical for the maintenance of viable pregnancy and normal development (Denney et al., 2011), it is important for future research to take into account the source of and potential for interaction across inflammatory signals to better understand the role of neonatal immunity on human health and well-being.

Other considerations for future research.

Determination of the sampling time point(s) is another methodological consideration. The sampling design includes, but is not limited to, parameters such as 1) frequency of sample collection, 2) time of day for collection, and 3) fasting versus non-fasting sample collection. When interpreting results from studies of early life experiences, it is important to consider how or whether gestational ages are estimated. It is well-known that gestational age, as well as maternal age, can have significant effects on immune factor expression (*e.g.*, Weissenbacher et al., 2012). Longitudinal studies and cross-sectional studies can also be influenced by seasonal effects. Preclinical and clinical studies report significant seasonal variation for many chemokines and cytokines (Thorsen et al., 2014). Thus, seasonal changes in the immune system may contribute to variability across studies and to challenges in combining data from multiple studies.

Some studies in the current issue measured one marker of inflammation and others measured several, or measured infection instead of inflammation. Deciding whether to use a targeted assay strategy (*e.g.*, assessment of a single or limited number of factors) or an unbiased, multi-analyte assessment approach will depend on the goals of the research. In both discovery research and clinical studies, there can be advantages to using multiple indicators of inflammation. Large scale profiling at the protein level, for example, can be used to analyze signaling pathways, assess proteomic biomarkers, and evaluate treatments, but costs may limit the feasibility of this approach. Single-analyte measurements are more affordable but can have limited utility especially when biological specimens are rare or in small quantities. Relatedly, there are inconsistencies in this research for data cleaning, data

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reduction (especially for multiple markers), and other quantification strategies that require a review of best practice guidelines. Lastly, strategies to address co-morbidities, particularly those that are common in childhood and associated with inflammatory processes, such as asthma and diabetes, are critical and should be included in the analytic plan.

4. Summary and future directions

To highlight the latest research findings into the links between adverse experiences early in life and their immediate and lasting effects on human health and well-being, this special issue features data-driven articles that provide insights into: early adversity (poverty, trauma, toxins, etc.); early stress (stressful, harsh family climates, etc.); perinatal and early life exposure to adversity inflammatory processes – acute and chronic; neurodevelopment, neuroplasticity, and neurogenesis; epigenetic mechanisms; microbiome-brain-gut axis communication; neurocognitive outcomes, socioemotional outcomes, and health or mental health outcomes. Collectively, the papers included in this special issue represent a collection of studies focused on illuminating potential links between early-life adversity and immediate and protracted immune and inflammatory responses. The methods used and the results reported in these studies will enable important next steps in this burgeoning field, including the progression of animal to human and back to animal research.

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Table 1

Summary of study design in the current special issue.

Authors	Empirical or Review	Longitudinal	Type of sample	Context	Consequences
Kautz, et al.	Empirical	Yes	Adolescents	Stressful life events	Depressive symptoms
Blomstrom, et al.	Empirical	Yes (population study)	Infant/Child/Adolescent	Psychiatric disorder	Violent criminal behavior
Kuhlman, et al.	Review	N/A	Child/Adolescent	Early life adversity	Elevated inflammation
Moreno, et al.	Review	N/A	Animal	Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS)	Psychomotor, cognition and socioemotional outcomes
Nelson, et al.	Empirical	Yes	Infants	maternal parenting stress and social support	Elevated inflammation and telomere length
O'Connor, et al.	Empirical	Yes	Child/Adolescent	economic adversity, family and caregiving stress	Elevated inflammation
Reid, et al.	Empirical	Yes	Infant/Child/Adolescent	Family adversity in infancy; depressive symptoms and BMI in childhood	Elevated inflammation in adolescence
Reid, et al.	Empirical	Yes	Infant/Child/Adolescent	Family adversity in infancy; depressive symptoms and BMI in childhood	Elevated inflammation in adolescence

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Table 2

Measures to evaluate stress, adversity, and immune response in the special issue.

Stress/adversity assessment	Immune measures	Reference
Modified Social Readjustment Rating Scale and Center for Epidemiological Studies Depression scale were used to assess interpersonal conflict stress, financial stress, and maternal depression	Serum C-reactive protein (CRP) was measured by high sensitivity immunoturbidimetry	Reid et al.
Adolescent Life Event Questionnaire and Life Events Interview were used to measure stressful life events	Plasma IL-6, IL-8, IL-10, and TNF-α were measured by multi- cytokine array, and CRP was measured in a single-plex assay	Kautz et al.
Early stress exposure was measured using an income/needs ratio, the Conflict Tactics Scale, and the Brief Symptom Inventory (to assess caregiver depressive symptoms)	Serum IL-6, TNF-α, and CRP were measured using standard and high sensitivity enzyme-linked immunosorbent assay (ELISA) kits	O'Connor et al.
Infections during childhood, as defined by ICD-10 diagnoses of infection before age 14, were evaluated for association with subsequent violent crimes	N/A	Blomstrom et al.
The Social Support Questionnaire 6 and the Parent Stress Scale were used to assess maternal support and stress	Salivary CRP was measured by enzyme immunoassay kit	Nelson et al.