ANNUAL REVIEWS Further
Click here to view this article's online features:
- Download figures as PPT slides
- Navigate linked references
- Download citations
- Explore related articles
- Search keywords

Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology

Andrea Danese[1,2,3] and Jessie R. Baldwin[1]

[1]MRC Social, Genetic, and Developmental Psychiatry Research Centre, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London SE5 8AF, United Kingdom; email: andrea.danese@kcl.ac.uk

[2]Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8AF, United Kingdom

[3]National and Specialist Clinic for Child Traumatic Stress and Anxiety Disorders, South London and Maudsley NHS Foundation Trust, London SE5 8AZ, United Kingdom

Annu. Rev. Psychol. 2017. 68:517–44

First published online as a Review in Advance on August 17, 2016

The *Annual Review of Psychology* is online at psych.annualreviews.org

This article's doi: 10.1146/annurev-psych-010416-044208

Copyright © 2017 by Annual Reviews. All rights reserved

Keywords

childhood trauma, maltreatment, psychopathology, psychiatric disorders, inflammation, immunity

Abstract

Childhood trauma is a key risk factor for psychopathology. However, little is known about how exposure to childhood trauma is translated into biological risk for psychopathology. Observational human studies and experimental animal models suggest that childhood exposure to stress can trigger an enduring systemic inflammatory response not unlike the bodily response to physical injury. In turn, these "hidden wounds" of childhood trauma can affect brain development, key behavioral domains (e.g., cognition, positive valence systems, negative valence systems), reactivity to subsequent stressors, and, ultimately, risk for psychopathology. Further research is needed to better characterize the inflammatory links between childhood trauma and psychopathology. Detecting and healing these hidden wounds may help prevent and treat psychopathology emerging after childhood trauma.

Contents

INTRODUCTION 518
CHILDHOOD TRAUMA AND PSYCHOPATHOLOGY 519
- Observational Studies in Humans 519
- Experimental Studies in Animal Models 520
- How Does Childhood Trauma Affect Psychopathology? 520

INFLAMMATION AND PSYCHOPATHOLOGY 522
- Observational Studies in Humans 522
- Experimental Studies in Animal Models and Humans 523
- How Does Inflammation Affect Psychopathology? 524

CHILDHOOD TRAUMA AND INFLAMMATION 528
- Observational Studies in Humans 528
- Experimental Studies in Animal Models 529
- How Does Childhood Trauma Affect Inflammation? 530

DOES INFLAMMATION EXPLAIN THE LINK BETWEEN CHILDHOOD TRAUMA AND LATER PSYCHOPATHOLOGY? 532
- Analogy 532
- Synergy 533
- Specificity 533
- Reversibility 534
- Mediation 534

CONCLUSION 535

INTRODUCTION

The word trauma comes from the ancient Greek word for wound (τραύμα) related to physical injury. It was only in the late nineteenth century that the word trauma started to acquire a new metaphorical meaning in popular culture. During the Industrial Revolution, Victorian surgeons became puzzled by psychological and physical symptoms appearing in victims of railway accidents who did not have apparent physical wounds (Erichsen 1867). The origins of the symptoms then known collectively as railway spine were hotly debated. The leading German neurologist Hermann Oppenheim suggested that symptoms were caused by undetectable physical damage to the spine or brain (Holdorff 2011). In contrast to this organic explanation and in light of the high prevalence of histories of childhood abuse noted among patients with unexplained somatic and emotional complaints (Briquet 1859), the leading French neurologists Jean-Martin Charcot and Pierre Janet theorized that the symptoms were caused by the idea of the trauma—the subjective perception of intensely distressing experiences—which triggered psychological and physical manifestations (hysteria) (Micale 1995). The Austrian psychiatrist Sigmund Freud further developed Charcot and Janet's psychological theory and popularized the notion that intensely distressing experiences—psychological traumas (and particularly those occurring in childhood)—could have significant impact on psychological development and psychopathology (Freud 1962).

The influence of such psychological theories (and the later psychoanalytical focus on imagined experiences or fantasies as triggers of hysteria) was so profound that trauma research was long dominated by intrapsychic explanatory models. Although these models have undeniably advanced the psychological understanding of the response to psychological trauma, they have also created

significant misunderstandings regarding the nature of many of the resulting symptoms and, at times, a culture of blame. Biological theories on psychological trauma, and particularly childhood trauma, have progressively emerged from experimental animal studies revealing how the body adapts to psychosocial stress (Selye 1936), how peripheral biological mediators of the stress response affect the brain (McEwen et al. 1968), and how the development of the biological response to stress is profoundly shaped by early life stressors (Levine et al. 1957).

In this review, we propose that the links between psychological and physical traumas are not, as it is commonly assumed, only metaphorical. Psychological trauma can trigger similar biological responses as physical trauma (Molina 2005), including the activation of the innate immune system. In particular, we discuss how childhood psychological trauma could affect the development of the innate immune system and thus induce a chronically activated and hyperreactive inflammatory response starting in childhood and persisting into adult life. In turn, elevated inflammation can influence brain development and functioning, thereby impacting the risk for psychopathology. Finally, we suggest that these "hidden wounds" caused by childhood psychological trauma have important clinical and treatment implications.

CHILDHOOD TRAUMA AND PSYCHOPATHOLOGY

Observational Studies in Humans

Much of what we know about childhood trauma comes from investigations of the consequences of childhood maltreatment, a prototypical form of severe and chronic interpersonal stress that includes sexual, physical, and emotional abuse as well as physical and emotional neglect. This prevalent form of childhood trauma affects up to one in five children in high-income countries worldwide and has been consistently associated with heightened risk of mental and physical illness in later life (Gilbert et al. 2009b). Childhood maltreatment predicts both high incidence and poor longitudinal course of several psychiatric disorders. For example, individuals with a history of childhood maltreatment have high lifetime risk of major depression, as well as an earlier age of onset and greater comorbidity (Brown & Harris 1978, Kessler et al. 1997). This link is unlikely to be explained by biased retrospective reports of individuals who were depressed at the time of maltreatment assessment because the retrospective findings are consistent with findings based on official records and prospective measures of maltreatment collected in childhood (Danese et al. 2009). Furthermore, this is also unlikely to be explained by the effects of genetic confounding because the high risk of depression in maltreated individuals was also observed within twin-pairs, that is, differences in depression risk were detected between individuals with the same or similar genes but different sexual abuse histories (Kendler et al. 2000). In addition to the elevated lifetime risk of depression, maltreated individuals with depression often show an unfavorable course of illness characterized by recurrent and persistent episodes (Nanni et al. 2012), which accounts for the largest health burden due to depression. Furthermore, individuals with a history of childhood maltreatment are at high risk of poor response to conventional antidepressant treatment and in particular to combined pharmacological and psychological treatment (Nanni et al. 2012). A history of childhood maltreatment is also highly prevalent in patients with bipolar disorder and, among bipolar patients, predicts unfavorable course of illness and clinical features such as greater severity of manic, depressive, and psychotic symptoms; higher risk of comorbid anxiety disorders and of substance or alcohol use disorders; earlier age of onset; higher risk of rapid cycling; greater number of manic and depressive episodes; and higher risk of suicide attempts (Agnew-Blais & Danese 2016). Childhood maltreatment predicts a heightened incidence of psychotic disorders, including schizophrenia, in later life (Varese et al. 2012). Furthermore, childhood maltreatment

is associated with increased risk for incident posttraumatic stress disorder (PTSD) (Widom 1999) and is thought to be related to more complex presentation among patients with PTSD, with symptoms including emotional dysregulation, poor self-concept, and disturbed relationships (complex PTSD) (Maercker et al. 2013).

PTSD: posttraumatic stress disorder

IQ: intelligence quotient

Experimental Studies in Animal Models

In addition to observational studies in humans, experimental studies in animal models have shown that early-life exposure to stressful experiences can cause significant emotional and behavioral abnormalities later in life. Despite the biological and theoretical limitations of using proxy models for human experiences, brain functioning, or behavior (van der Worp et al. 2010), these experimental studies are uniquely placed to address causal inference because of their ability to manipulate the environment and to randomly assign animals to experiences. This is important because individual risk factors of the child and parents, family risk factors, and community risk factors are all associated with increased risk of childhood traumas such as maltreatment (Danese & McCrory 2015). Many of these risk factors [e.g., low intelligence quotient (IQ), family history of mental illness] also predict later psychopathology. These correlated risk factors represent alternative explanations for the link between childhood trauma and later psychopathology and need to be ruled out before inference of causal effects can be drawn (Duncan et al. 2004). Therefore, by manipulating early life experiences independent of the features of individual animals, experimental models can identify unbiased or causal effects of early-life stress. Although experimental studies have stronger internal validity than observational studies, generalization of causal inference from the narrow context of the experiment to the life of living humans requires demonstration (or assumption) that the experiences and physiology in animal models are similar to those of humans (i.e., external or ecological validity).

Building on the pioneering clinical observations of Spitz (1945) and Bowlby (1951) on the effects of maternal separation on psychological development and psychopathology, experimental models in rodents (Francis et al. 1999, Levine et al. 1956) and nonhuman primates (Harlow et al. 1965, Hinde & Spencer-Booth 1971, Sánchez et al. 2001, Suomi 1997) have shown that early-life stress owing to maternal separation or poor maternal care can negatively impact emotional and behavioral development and, thus, impair psychological functioning. Typically, animals experimentally exposed to early-life stress show greater behavioral despair and learned helplessness (depressive-like symptoms measured, for example, through a forced swimming test or tail suspension test in rodents) (Cryan & Holmes 2005), more avoidance behaviors (anxiety-like symptoms measured, for example, through an elevated plus maze or light/dark exploration test) (Cryan & Holmes 2005), and abnormal fear conditioning. Although the effects of experimentally induced early-life stress can vary based on the protocol used and the age and gender of the animals, the overall results of these experimental studies suggest a causal role of early-life stress in later psychopathology.

How Does Childhood Trauma Affect Psychopathology?

Several studies have explored the biological mechanisms underlying the clinical association between childhood trauma and psychopathology. Most of these studies have focused on testing differences in brain and hormonal function between individuals with a history of childhood maltreatment and those without.

Childhood trauma and the brain. To understand how childhood trauma affects the risk of psychopathology, several studies have tested the association of childhood trauma (often assessed through retrospective recall) with neuropsychological tests scores and structural or functional

brain imaging measures. A detailed description of brain abnormalities associated with childhood trauma is beyond the scope of this review; several comprehensive reviews can be consulted for more information (Danese & McEwen 2012, Lim et al. 2014, Lupien et al. 2009, McCrory et al. 2010, Nusslock & Miller 2016, Teicher & Samson 2016, Tottenham & Sheridan 2009). The findings in this area can be summarized using the Research Domain Criteria (RDoC) framework (Insel 2014, Kaufman et al. 2015). Brain function abnormalities associated with childhood trauma include, but are not limited to, changes in the domains of cognition, positive valence, and negative valence.

With regard to cognition, childhood maltreatment has been associated with small-to-moderate and pervasive cognitive impairment. Individuals with a history of childhood maltreatment have lower IQ and poorer declarative memory and executive function than individuals with no history of childhood maltreatment (Pechtel & Pizzagalli 2011). Similar cognitive impairment has been described in animals experimentally exposed to early-life stress (Brunson et al. 2005). Deficits in declarative memory may be related to the macroscopic (smaller hippocampal volume) (Danese & McEwen 2012) and microscopic (impaired adult neurogenesis) (Mirescu et al. 2004) hippocampal abnormalities found in adult animals and humans exposed to early-life stress. Furthermore, deficits in executive function may be related to functional or structural prefrontal cortex abnormalities (Danese & McEwen 2012).

With regard to positive valence, childhood maltreatment has been associated with impaired reward processing. Human studies showed that individuals with a history of childhood maltreatment may be less sensitive to reward, as indicated by blunted subjective responses to reward-predicting cues and blunted activation in the basal ganglia during reward anticipation (Dillon et al. 2009, Guyer et al. 2006, Mehta et al. 2010). Consistent with these findings in humans, animals experimentally exposed to early-life stress showed attenuated sucrose preference and attenuated behavioral responses (self-administration) to powerful artificial reinforcers, such as intravenous cocaine or intra-accumbens amphetamine (Matthews & Robbins 2003, Phillips et al. 1994, Pryce et al. 2004).

With regard to negative valence, childhood maltreatment has been associated with heightened threat perception. Compared to nonmaltreated individuals, those with a history of maltreatment have biased perceptual representations of emotions and tend to overidentify threat signals, such as angry faces (Leppänen & Nelson 2009, Pollak & Kistler 2002). Individuals with a history of maltreatment showed selective heightened amygdala activation in response to angry faces, even when these stimuli were presented preattentively (McCrory et al. 2013, Tottenham et al. 2011, van Harmelen et al. 2013), possibly as a result of impaired functional coupling between the subgenual anterior cingulate cortex (sACC) and the amygdala (Herringa et al. 2013). Consistent with findings in humans, animal studies have highlighted the crucial contribution of the early social environment to amygdala development and functioning (e.g., Moriceau & Sullivan 2006).

Childhood trauma and the neuroendocrine response to stress. Although the link between childhood trauma and brain abnormalities provides biological plausibility for the clinical effects described in the previous section, it does not inform about the underlying biological processes that might have triggered changes in the brain and behavior. Studies of proximal biological processes have traditionally focused on abnormalities and changes in the physiology of the hypothalamic-pituitary-adrenal (HPA) axis (Danese & McEwen 2012, Gunnar & Quevedo 2007, Heim & Nemeroff 2001, Lupien et al. 2009). These studies have stemmed from preclinical findings showing that the HPA axis is a key neuroendocrine pathway involved in the biological adaptation to stress (Selye 1936); that peripheral and central HPA axis mediators affect brain function (McEwen et al. 1968); and that early life experiences can significantly shape the development of the HPA axis and, thus, affect its functioning across the life span (Levine et al. 1957). In humans, studies of children

HPA: hypothalamic-pituitary-adrenal

CRH: corticotrophin-releasing hormone

ACTH: adrenocorticotropic hormone

have shown that the experience of maltreatment is associated with chronic activation of the HPA axis. For example, maltreated children with significant emotional problems showed higher average daily cortisol levels across 1 week (Cicchetti & Rogosch 2001). Similarly, maltreated children with PTSD showed higher 24-h urinary free cortisol and daily salivary cortisol levels compared to a healthy comparison group with no maltreatment history (Carrion et al. 2002, De Bellis et al. 1999). Studies of adults reporting a history of maltreatment found consistent results, including evidence of high corticotrophin-releasing hormone (CRH) levels in the cerebrospinal fluid (Carpenter et al. 2004), greater adrenocorticotropic hormone (ACTH) and cortisol response to a laboratory-based acute psychosocial stress test (Heim et al. 2000), and greater ACTH and cortisol response to a pharmacological challenge with the dexamethasone/CRH test (Heim et al. 2008). These human studies highlight that maltreated individuals have elevated baseline cortisol levels and heightened cortisol reactivity in the context of new stressors. HPA axis hyperactivity may emerge as a compensatory mechanism for primary abnormalities due to insufficient functioning of glucocorticoid receptor–mediated signaling, also known as insufficient glucocorticoid signaling. Consistent with the results of human studies, findings from experimental animal models have shown that early-life stress is associated with altered methylation of the glucocorticoid receptor gene, which is linked to insufficient glucocorticoid signaling (Weaver et al. 2004).

Elevated cortisol levels during early development may have toxic effects on brain development and, thus, have long-term effects on brain function and behavior (Danese & McEwen 2012, Gunnar & Quevedo 2007, Heim & Nemeroff 2001, Lupien et al. 2009). Certain brain areas could be more sensitive to the effects of glucocorticoids and, consequently, more likely to be modified by high levels of glucocorticoids. In particular, high levels of cortisol have been associated with shrinkage of the hippocampus and the prefrontal cortex and with hypertrophy and hypermetabolism of the amygdala. Through these direct effects on the brain, high glucocorticoid levels could have long-term effects on the domains of cognition, positive affect, and negative affect described in the previous section (Danese & McEwen 2012, Gunnar & Quevedo 2007, Heim & Nemeroff 2001, Lupien et al. 2009).

Some thought-provoking new interpretations of these findings highlight the role of the links between the HPA axis systems and other stress-sensitive systems, such as the immune system, in shaping trajectories of brain development. On the one hand, the insufficient glucocorticoid signaling found in individuals with a history of childhood maltreatment could bring about systemic inflammation (Heim et al. 2000, Miller et al. 2002, Raison & Miller 2003). In turn, by affecting the immune system, glucocorticoids could exert significant indirect effects on brain development and functioning. On the other hand, inflammation could trigger HPA axis activation (Besedovsky et al. 1986) and induce glucocorticoid resistance (Barnes & Adcock 2009), thereby potentially acting as the original trigger for neuroendocrine abnormalities. The two-way interaction between the HPA axis and inflammation suggests the need for more complex explanatory models for the effects of childhood trauma on the brain and behavior. The potential involvement of the immune system in brain development and psychopathology is described in the following sections.

INFLAMMATION AND PSYCHOPATHOLOGY

Observational Studies in Humans

The association between inflammation and psychopathology has arguably been best illustrated in the case of major depression (Miller & Raison 2015). Initial conceptualizations of this link emerged from the observations that experimental administration of proinflammatory cytokines produces a clinical response resembling major depression (the macrophage theory of depression)

(Smith 1991) and that immune cell profiling of depressed patients is characterized by systemic immune activation (Maes et al. 1992). In response to these observations, several clinical and population studies have measured cytokines and other proinflammatory mediators in depressed individuals and controls. Meta-analysis of these cross-sectional studies suggests that depression is characterized by a small elevation in circulating levels of inflammation biomarkers (Howren et al. 2009). Longitudinal studies suggest that group differences are likely to result from bidirectional associations between depression and inflammation over time (e.g., Matthews et al. 2010). Notably, high inflammation predicts not only the risk of incident depression but also of poor response to treatment (Strawbridge et al. 2015) and an unfavorable course of illness characterized by recurrent episodes (Ford & Erlinger 2004).

CRP: C-reactive protein

LPS: lipopolysaccharide

IL: interleukin

High levels of circulating inflammation biomarkers have also been found in patients with bipolar disorder. Meta-analytical studies show that bipolar disorder is associated with small to moderate elevation in proinflammatory cytokines (Modabbernia et al. 2013) and C-reactive protein (CRP) (Dargél et al. 2015). Elevation in CRP and in some proinflammatory cytokines is also present in euthymic phases. On the basis of these findings, bipolar disorder is increasingly seen as a multisystem inflammatory disease (Leboyer et al. 2012) in which inflammation contributes to the onset of illness as well as its progression (Berk et al. 2011).

The immune contribution to schizophrenia etiopathogenesis has been investigated for over a century (Khandaker et al. 2015). A meta-analytical investigation has shown that circulating levels of proinflammatory cytokines are moderately elevated in patients with both chronic psychosis and first-episode psychosis (Miller et al. 2011). Furthermore, high baseline levels of inflammation predict poor treatment response in first-episode psychosis patients (Mondelli et al. 2015).

Proinflammatory mediators may also play a role in the symptoms of patients with PTSD. Meta-analytical studies show that PTSD patients have a moderate to large elevation in levels of several proinflammatory cytokines, that these associations are not explained by comorbid depression, and that inflammation is related to illness duration (Passos et al. 2015). Genetic (Michopoulos et al. 2015) and longitudinal (Eraly et al. 2014) studies suggest that inflammation is a preexisting vulnerability factor for the development of PTSD in trauma-exposed individuals.

These findings highlight the transdiagnostic links between inflammation and psychopathology. Despite this evidence, published studies have often been based on a case-control design focused on single diagnoses. Notably, this design does not allow a critical evaluation of the nonspecific links between inflammation and psychopathology and may cause overestimation of the unique contribution of inflammation to single diagnoses. Furthermore, this design is unsuitable for the evaluation of the direction of effects or for the comprehensive assessment of potential confounding factors. Therefore, it is important to consider findings from these observational studies alongside results from experimental studies.

Experimental Studies in Animal Models and Humans

Experimental studies in animal models and humans suggest causal effects of inflammation on affective symptoms and disorders. This research began with the recognition that the onset of febrile infectious diseases was linked to a stereotypical pattern of behaviors in animals and humans that was characterized by lethargy, depression, anorexia, and reduction in grooming (Hart 1988). This sickness behavior was recognized as an organized, evolved behavioral strategy to facilitate the role of fever in combating viral and bacterial infections. Building on this initial theory, pharmacological experiments have been undertaken by manipulating an organism's inflammatory state through systemic or central administration of bacterial cell components [e.g., lipopolysaccharide (LPS), also known as endotoxin] or proinflammatory cytokines [e.g., interleukin (IL)-1β and tumor

necrosis factor (TNF)-α]. These experiments reproduced sickness behavior in animal models, with symptoms including decreased motor activity (fatigue), social withdrawal, reduced food and water intake, increased slow-wave sleep, and altered cognition (Dantzer et al. 2008). Furthermore, consistent with the role of inflammation in these phenomena, the expression of sickness behavior after LPS stimulation was buffered by administration of the anti-inflammatory cytokine IL-10 and exacerbated in IL-10-deficient mice (Dantzer et al. 2008). Similar findings are now accumulating in humans.

TNF: tumor necrosis factor

IFN: interferon

Several experimental studies in humans have tested behavioral changes induced by different proinflammatory compounds. A set of early studies looked at inflammation-related changes in mood and behavior among patients with hepatitis C or cancer that were treated with the proinflammatory cytokine interferon (IFN)-α and were free of depression prior to the beginning of the trial. About half of patients treated with IFN-α developed depressive disorder within weeks of the start of treatment, whereas nearly all treated patients developed neurovegetative symptoms including anorexia, fatigue, psychomotor retardation, and disrupted sleep (Musselman et al. 2001). Consistent with the effects of chronic treatment with IFN-α, acute administration of proinflammatory mediators, such as typhoid vaccination and LPS, can also induce transient depressive-like symptoms (Reichenberg et al. 2001).

Not only can proinflammatory compounds induce depression, but anti-inflammatory medications can have antidepressant effects. A recent meta-analysis of 10 trials with nonsteroidal anti-inflammatory drugs and four trials with cytokine inhibitors found small to moderate antidepressant effects (Köhler et al. 2014). Notably, the meta-analysis also found significant heterogeneity in the effect sizes across trials (Köhler et al. 2014). This latter meta-analytical finding was reinforced by a clinical trial with a potent anti-inflammatory monoclonal antibody that specifically inhibits TNF-α function, commonly known as infliximab (Raison et al. 2013). Treatment with infliximab was not effective overall in a group of treatment-resistant depressed patients. However, infliximab treatment showed some therapeutic effect in the subgroup of depressed patients with high baseline inflammation levels (Raison et al. 2013). These findings highlight the complexity of depression pathophysiology and suggest that inflammation may be an important etiological factor in a large subgroup of depressed patients. Evidence of the treatment effects of anti-inflammatory intervention in other psychiatric conditions is more limited and indirect. For example, a 12-week, randomized, double-blind, placebo-controlled trial of omega-3 polyunsaturated fatty acids, which have complex physiological properties including anti-inflammatory effects, found a reduction in both the risk of progression to psychotic disorders and in psychiatric morbidity over a 7-year follow-up in young people with subthreshold psychotic states (Amminger et al. 2015).

How Does Inflammation Affect Psychopathology?

To complement these clinical studies, much research has focused on the molecular and cellular mechanisms through which inflammation could influence psychopathology. An important discovery in this area came from the evidence that the traditional view that the brain has immune privilege, meaning that the brain is both immunologically inert and immunologically separated from the peripheral immune system, was incorrect (Galea et al. 2007). Researchers increasingly appreciate that the brain immune system actively contributes to normal brain functioning (Yirmiya & Goshen 2011) and that the brain is connected with the peripheral immune system (Dantzer et al. 2008).

The brain immune system and normal brain functioning. The brain has an active immune system that contributes both to surveillance against pathogens and to tissue remodeling.

Consistent with the effects of immunity in other parts of the body, immune activity (and particularly innate immune activity, or neuroinflammation) can be either beneficial or detrimental depending on the level of activation. Low-level activation of the innate immune system in the brain is vital to support tissue remodeling, including molecular (long-term potentiation) and cellular (neurogenesis) mechanisms of brain plasticity. However, both deficient neuroinflammation (e.g., due to immune deficiency or genetic or pharmacological manipulation) and exaggerated neuroinflammation (e.g., due to inflammatory or infectious disorders or, to a lesser extent, psychosocial stress) are associated with symptoms of impaired brain function, such as poor learning and memory (Yirmiya & Goshen 2011). The brain immune system includes specialized cells, such as microglia and T cells, and molecules, such as cytokines.

BBB: blood–brain barrier

CSF: cerebrospinal fluid

BDNF: brain-derived neurotrophic factor

Microglia are macrophage-like cells of myeloid hematopoietic origin that colonize the brain parenchyma during early embryonic development and self-renew locally thereafter (Hanisch & Kettenmann 2007). Microglia continuously scan the surrounding extracellular space for signals of cellular damage or infection. Resting-state microglia play important roles in normal adult brain function, including repairing microdamages [small ischemic events or blood–brain barrier (BBB) lesions], cleaning up cellular debris and inactive or dysfunctional synaptic structures (with overall anti-inflammatory effects), and supporting neurogenesis. In contrast, upon detection of pathogens or inflammatory signals, activated microglia respond by eliminating triggering stimuli through phagocytosis and by producing proinflammatory cytokines, prostaglandins, free radicals, and other mediators. These molecules are helpful in neutralizing a variety of pathogens but can also have neurotoxic effects and suppress neurogenesis.

T cells are cells of lymphoid hematopoietic origin that can migrate to the cerebrospinal fluid (CSF), where they are separated from the brain parenchyma only by the pia mater (in the subarachnoid space) (Kipnis et al. 2012). This vantage point enables T cells to monitor and respond to signals released from the brain into the CSF. T cells, and particularly those that are reactive against brain self-antigens, play a supportive role in learning and memory by stimulating adult neurogenesis. Upon encountering relevant self-antigens, autoreactive T cells produce cytokines (e.g., IL-4) that promote the expression of brain-derived neurotrophic factor (BDNF) by astrocytes and suppress proinflammatory activity in meningeal and parenchymal myeloid cells, including microglia. In contrast, upon detection of pathogens or inflammatory signals, T cells trigger a protective immune response that may have detrimental consequences for brain function.

Cytokines can be produced in the brain by resident cells, including microglia and T cells, in response to local stimuli. Peripheral cytokines can also accumulate in the brain through BBB leaks and the signaling pathways described below (see the following section). Low levels of proinflammatory cytokines support brain plasticity (Yirmiya & Goshen 2011). In particular, low levels of IL-1 play an important role in hippocampus-dependent learning and memory processes, presumably by supporting the induction and maintenance of long-term potentiation. In contrast, high levels of proinflammatory cytokines potentiate neuroinflammation and neurotoxicity, reduce monoaminergic transmission (e.g., by reducing the availability of the precursors or increasing reuptake by presynaptic transporters), stimulate glutamate transmission (e.g., by stimulating glutamate release and inhibiting glutamate reuptake in astrocytes), stimulate the HPA axis–mediated neuroendocrine stress response (with resulting insufficient glucocorticoid signaling after chronic stimulation), inhibit the secretion of BDNF and nerve growth factor, and inhibit cholinergic transmission (Dantzer et al. 2008, Yirmiya & Goshen 2011).

Links between the peripheral immune system and the brain immune system. In the same way that the brain monitors and responds to the external environment and the status of internal organs, it also monitors and responds to the immune system through at least five different pathways

(Dantzer et al. 2008). The neural pathway involves the activation of the afferent fibers of the vagus nerve or the trigeminal nerve by peripherally produced cytokines. The humoral pathway involves the crossing of circulating cytokines into the brain where the BBB is permeable (e.g., the area postrema). The transmembrane pathway involves active transport of cytokines (IL-6, IL-1, TNF-α) through the BBB via saturable carriers. The signal transduction pathway involves stimulation by circulating cytokines of cell surface receptors on astrocytes and on the brain endothelial cells that form the BBB, which, in turn, triggers cytokine production by these cells. Finally, the cellular pathway involves minimal passage of dendritic cells, leukocytes, and lymphocytes via gaps in the epithelial lining of the BBB, the circumventricular organs, and the choroid plexus. Through these pathways, peripheral inflammation can induce neuroinflammation (Dantzer et al. 2008, Perry et al. 2003). For example, peripheral administration of LPS in rodents induces the expression of proinflammatory cytokines in the brain (Breder et al. 1994), the activation of microglia (Monje et al. 2003), and the inhibition of adult neurogenesis (Monje et al. 2003).

The peripheral immune system and abnormal brain functioning. Because the peripheral immune system can affect neuroinflammation, peripheral immune activation can have significant effects on brain functioning. Notably, LPS-induced systemic inflammation affects several domains of brain functioning in humans (Schedlowski et al. 2014). With regard to cognition, peripheral administration of LPS reduces verbal and nonverbal memory functions in humans (Reichenberg et al. 2001). With regard to positive valence systems, peripheral administration of LPS (and also of typhoid vaccine and IFN-α) reduces ventral striatum responses to reward (Capuron et al. 2012, Eisenberger et al. 2010). With regard to negative valence systems, peripheral administration of LPS potentiates amygdala activity in response to socially threatening stimuli (fear faces) (Inagaki et al. 2012), and typhoid vaccine reduces the connectivity of the sACC to the amygdala and increases the activity within the sACC during emotional face processing (Harrison et al. 2009). The specificity of the effects of systemic inflammation on these brain functions is likely due to several factors including the different density of cytokine receptors and different sensitivity to changes in monoamine metabolism in different brain areas. In turn, abnormalities in cognition, reward processing, and threat processing are important putative mediators for the effect of systemic inflammation on behavior.

Long-term effects of early-life immune activation on the brain and behavior. In addition to the broad effect of acute immune stimulation on concurrent measures of brain functioning, immune stimulation during early development can have enduring effects on the brain and behavior. For example, experimental studies found that infection (e.g., by the influenza virus or *Escherichia coli*) and systemic inflammation [e.g., due to synthetic RNA poly(I:C) or LPS] during prenatal or neonatal periods led to stable, long-term impairments in cognition, including deficits in learning, memory, and attention, in rodents (Bilbo & Schwarz 2009, Knuesel et al. 2014, Patterson 2009) and nonhuman primates (Short et al. 2010). Consistent with the evidence in experimental animal models, observational studies in humans have found a link between early-life infection and risks of later neurodevelopmental disorders. For example, some studies, although not all, found an association between prenatal exposure to infection and increased risk of schizophrenia (Khandaker et al. 2013, Mednick et al. 1988) and autism (Atladóttir et al. 2010, Deykin & MacMahon 1979). Furthermore, high levels of systemic inflammation in childhood have been associated with an increased risk of developing depression and psychosis in young adulthood (Khandaker et al. 2014). There are several ways in which early-life immune activation can induce these detrimental effects on the brain, including direct impact on brain development, priming of resident immune cells, and programming of the neuroendocrine response to stress.

The immune system and brain development. The immune system is critical to several aspects of brain development. Although the immune system significantly affects prenatal brain development processes, such as cell proliferation and migration, these effects are beyond the scope of this review and are detailed elsewhere (Boulanger 2009). More relevant to childhood, the immune system also profoundly affects postnatal brain development processes, such as synaptogenesis, synaptic refinement, myelination, and adult neurogenesis (Boulanger 2009). First, synaptogenesis is the formation of synapses between neurons in the nervous system, which begins during fetal life (second trimester) and continues into adulthood. The chemokine CXCL12 and its receptor, CXCR4, regulate axonal elongation and branching and axon pathfinding by modulating neuronal responses to axon guidance cues (e.g., Slit-2, semaphorin 3A, and semaphorin 3C) (Chalasani et al. 2003). Second, synaptic refinement is the activity-dependent modulation of synaptic strength and survival that takes place after birth. Microglia and astrocytes can sense the overall neuronal activity levels and make compensatory changes in synaptic strength by secreting TNF-α. Low synaptic activity induces secretion of TNF-α, which promotes the surface expression of glutamate receptors in neurons, increasing excitability and, thus, synaptic strength (a process known as synaptic scaling). Furthermore, the surface expression of the major histocompatibility complex class I (MHC-I) is necessary for the regulation of both basal synaptic transmission and acute synaptic plasticity. Another activity-dependent mechanism that regulates synaptic survival involves the expression of complement proteins C1q and C3 by synapses that are inactive. Microglia recognize and phagocytize the complement-tagged synapses, thus eliminating them (synaptic pruning) (Boulanger 2009). Third, myelination is the production of myelin by oligodendrocytes, which begins during fetal life (third trimester) and continues into adulthood. Myelin forms an electrically insulating layer around axons to improve the transmission of electrical signals between cells. Microglia secrete proinflammatory mediators and growth factors that are crucial for the survival and functioning of oligodendrocytes and, thus, myelin production (Peferoen et al. 2014). Finally, adult neurogenesis is the process of proliferation and differentiation of neural stem cells that takes place after birth and significantly affects learning and memory. This process can be significantly inhibited by inflammatory mediators in the context of systemic immune activation (Ekdahl et al. 2003, Monje et al. 2003) and can be potentiated by autoreactive T cells (Ziv et al. 2006). Because of these critical effects of the immune system on brain development, postnatal early-life immune activation involving disruption of these fine-tuned processes could exert direct, long-term influence on the brain and behavior. Furthermore, it is possible that early-life immune activation could exert indirect influence by modifying the reactivity of immune cells and the neuroendocrine response to later stimuli.

Early-life immune activation and glial priming. Immune activation in early life can induce long-term functional changes in the microglia. Acute inflammatory stimuli can not only activate microglia (see the section The Brain Immune System and Normal Brain Functioning) but also prime them to show a greater response in the face of subsequent inflammatory stimulation. Compared to rodents with naïve microglia, rodents with primed microglia show heightened production of proinflammatory cytokines in the brain, increased neurotoxicity, and exaggerated fever and sickness behavior in response to subsequent inflammatory stimulation (Perry & Holmes 2014). These priming effects are induced by direct morphological changes and upregulation of cell-surface antigens on glial cells. Furthermore, priming could be due to loss or downregulation of neuronal ligands that inhibit priming or to a reduction in the inhibitory effect of glucocorticoids (see the following section) (Frank et al. 2013, Perry & Holmes 2014). Notably, the long-term priming effects described after early-life exposure to systemic immune activation suggest the potential existence of sensitive periods for microglia priming (Bilbo & Schwarz 2009, Knuesel et al. 2014).

Early-life immune activation and hypothalamic pituitary adrenal axis reactivity. In addition to effects directly mediated by the immune system, early-life immune activation also induces long-term changes in other stress-sensitive systems, such as the HPA axis. Acute immune stimulation elicits activation of both central catecholamines and the HPA axis similar to that seen following stress (Besedovsky et al. 1986, Dunn 2006). Notably, there may be sensitive periods for the programming of HPA axis function by immunity. Research in rodents has shown that early-life immune stimulation with LPS was associated with elevated levels of CRH, greater ACTH and corticosterone responses to restraint stress, decreased negative feedback sensitivity to glucocorticoids, and a reduction in glucocorticoid receptor density across the brain in adult animals (Shanks et al. 1995, 2000). Because these abnormalities in HPA functioning are hallmarks of affective disorders (Pariante & Miller 2001), the immune programming of the HPA axis system could contribute to the effects of early-life immune stimulation on psychopathology.

CHILDHOOD TRAUMA AND INFLAMMATION

Observational Studies in Humans

Because of the association of childhood trauma with abnormal brain and behavioral functioning and the comparable effects of early-life immune activation on these outcomes, we became interested in directly testing the association between childhood trauma and innate immunity in later life. We initially investigated this association in the Dunedin Multidisciplinary Health and Development Study, a birth cohort of 1,037 children born in Dunedin, New Zealand, in 1972–1973 (Danese et al. 2007). Study members had been followed from birth until adulthood through repeated waves of assessment. Crucially, this enabled a longitudinal-prospective assessment of maltreatment experiences as study members grew up, resulting in a cumulative measure of childhood maltreatment that included indicators of maternal rejection, harsh discipline, disruptive caregiver changes, physical abuse, and sexual abuse. We found that cumulative exposure to childhood maltreatment was associated with significant and graded elevation in inflammation levels at the age-32 follow-up (Danese et al. 2007). The association was not sensitive to the particular measure of inflammation used but rather generalized to all inflammation biomarkers available, including CRP, fibrinogen, and white blood cell count, and was independent of key potential confounders, such as low birth weight, disadvantaged socioeconomic conditions of the family, and low IQ. Furthermore, the association was not explained by obvious mediators, such as adult stressors, poor adult health, and unhealthy behaviors, or acute infections at the time of inflammation assessment. Since these initial findings, the association between childhood trauma and adult inflammation has been tested in more than two dozen independent studies, and qualitative and quantitative reviews suggest small but pervasive elevation in inflammation biomarkers among maltreated compared to nonmaltreated individuals (Baumeister et al. 2015, Coelho et al. 2014). Immune abnormalities appeared to be associated not only with maltreatment by adults but also with bullying by peers (Takizawa et al. 2015). Furthermore, immune abnormalities may not be restricted to the innate immune system but may also generalize to impairment in the acquired immune system (Shirtcliff et al. 2009).

In addition to studying the long-term effects of childhood maltreatment, we were interested in testing whether the elevation in inflammation biomarkers in maltreated children was already detectable in childhood years, during sensitive periods of brain development. We investigated this association among a subset of 170 members of the Environmental-Risk (E-Risk) Longitudinal Twin Study, a birth cohort of 2,232 twins born in England and Wales in 1994–1995 (Danese et al. 2011). We compared a group of 12-year-old children for whom we had longitudinal-prospective

evidence of maltreatment to a group of nonmaltreated children matched for sex, socioeconomic status, and zygosity. We found that inflammation levels (derived by measuring CRP in dried blood spots) were elevated in maltreated children who developed depression by age 12 compared to controls (Danese et al. 2011). These initial findings were supported and expanded by later studies showing that elevated inflammation levels were detectable among children exposed to adverse events in the first decade of life (Slopen et al. 2013) and among some children with a Child Protective Services–documented history of maltreatment (Cicchetti et al. 2015).

Individuals with a history of childhood maltreatment show not only elevated levels of unstimulated inflammation but also greater proinflammatory responses in the context of subsequent stressors. For example, individuals with a history of childhood maltreatment showed heightened inflammatory responses to a laboratory-based acute psychosocial stress test (Carpenter et al. 2010). Furthermore, maltreated individuals have greater inflammatory responses in the face of daily stressors and caregiving stress in later life (Gouin et al. 2012, Kiecolt-Glaser et al. 2011). Finally, depressed individuals with a history of childhood maltreatment show both elevated unstimulated inflammation levels (Danese et al. 2008) and greater inflammatory responses to acute psychosocial stress (Pace et al. 2006) compared to controls.

Experimental Studies in Animal Models

Experimental animal models have been used to strengthen causal inference for the link between childhood trauma and immune system abnormalities and to investigate more invasive measures of immune functioning. Evidence for the contribution of early experiences to immune development and function has been found in studies of rodents showing that rats handled before weaning showed a lower rate of development of transplanted tumors (Ader & Friedman 1965) and had greater serum antibody titer in response to flagellin, a protein derived from bacterial flagella (Solomon et al. 1968). Several subsequent investigations have explored the association between different types of early-life stressors and multiple immune measures in later life. A detailed account of all these findings is beyond the scope of this paper, but several comprehensive reviews can be consulted for more information (Ganguly & Brenhouse 2015, Hennessy et al. 2010a, Shanks & Lightman 2001). Results are mixed, reflecting, at least in part, the heterogeneity of stressors and immune system measures used. However, several papers have reported significant associations between maternal separation and inflammation. In nonhuman primates, maternal separation led to an immediate and prolonged increase in macrophage activity (Coe et al. 1988) and peer-rearing induced long-term upregulation in proinflammatory gene transcription in monocytes (Cole et al. 2012). In rodents, maternal separation led to an inflammation-mediated increase in core temperature (Hennessy et al. 2010b) and to an increase in proinflammatory cytokines in the plasma (Wieck et al. 2013).

In addition to elevation in peripheral inflammatory biomarkers, early-life stress has also been linked to markers of neuroinflammation. It is currently challenging to study neuroinflammation in humans because only comparatively nonspecific, expensive, and invasive methods, such as positron emission tomography (PET), exist (Bloomfield et al. 2016, Setiawan et al. 2015). However, this type of investigation is possible in experimental animal models, and initial findings suggest early-life stress has significant and potentially sexually dimorphic effects (Ganguly & Brenhouse 2015). Maternal separation is associated with blunted expression of proinflammatory mediators (such as LPS binding protein) in the hippocampus (Wei et al. 2012) and with reduced microglial cell numbers in midbrain areas (Chocyk et al. 2011) in rodent pups at a time when innate immunity is crucial for brain development. Furthermore, maternal separation is associated with greater hippocampal expression of receptors for proinflammatory cytokines (Viviani et al. 2014), greater

number and motility of cortical microglial processes (Takatsuru et al. 2015), and greater microglia activation (Brenhouse & Thompson 2015).

Similar to the results of human studies, early-life stress in animal studies is associated not only with high unstimulated inflammation levels but also with greater proinflammatory responses in the context of subsequent stressors. In particular, rodents exposed to maternal separation showed a greater increase in core temperature upon a second separation (Hennessy et al. 2010b), greater cytokine expression in response to subsequent viral infection (Avitsur et al. 2006), and greater cortical microglial activation following subsequent exposure to chronic food-restriction stress (Brenhouse & Thompson 2015).

How Does Childhood Trauma Affect Inflammation?

Childhood trauma may become associated with elevated inflammation levels through several mechanisms, including both narrowly defined biological mechanisms and broader behavioral responses to trauma exposure. In addition, although experimental animal studies do not indicate that genetic factors play a significant role in the association between early-life stress and elevated inflammation levels, genetic influences may nevertheless be important in studies of humans who are not randomly allocated to childhood trauma and have greater genetic heterogeneity. These mechanisms are not mutually exclusive. However, the following sections highlight different mechanisms individually because they could potentially be independently targeted for secondary prevention in traumatized children or adults.

Biological mechanisms. Childhood trauma could be linked with innate immune abnormalities through several biological mechanisms. First, the more traditional view is that childhood trauma is indirectly linked to dysregulated innate immunity because of primary neuroendocrine abnormalities. This view builds on the established association between childhood trauma and HPA axis abnormalities and on the link between insufficient glucocorticoid signaling and inflammation (see the section Childhood Trauma and the Neuroendocrine Response to Stress). Chronic activation of the HPA axis during a sensitive developmental period can induce a compensatory reduction in signaling through epigenetic changes in the glucocorticoid receptor (Weaver et al. 2004), leading to resistance to the anti-inflammatory properties of cortisol. For example, human studies showed that reports of childhood trauma were related to allele-specific DNA demethylation in functional glucocorticoid response elements of the *FKBP5* gene, which, in turn, was associated with lower sensitivity of peripheral blood immune cells to the inhibitory effect of glucocorticoids on LPS-induced production of IL-6 in vitro (Klengel et al. 2013). Furthermore, a longitudinal study showed that adolescents from harsh families had declining glucocorticoid sensitivity over time and increasing ex vivo cytokine response to LPS stimulation (Miller & Chen 2010).

Second, childhood trauma may impact immune development because of elevated risk of and susceptibility to infections. On the one hand, traumatized children are more likely to be exposed to physical injury and infections (Gilbert et al. 2009a). On the other hand, childhood trauma might confer vulnerability to infections. Psychological stress in general is known to increase susceptibility to infection (Cohen et al. 1991), and traumatic experiences in children have been associated with recrudescence for latent viral infections (Shirtcliff et al. 2009). In turn, immune activation linked to infections could lead to systemic inflammation.

Third, childhood trauma might affect the colonization and composition of the gut microbiota. In nonhuman primates, maternal separation during the first year of life led to a transient but substantial decrease in fecal lactobacilli (Bailey & Coe 1999). In rats, maternal separation had long-term effects on the composition of the gut microbiota manifested into adult life (O'Mahony

et al. 2009). In turn, altered composition of the gut microbiota in early life could affect immune system development and could directly influence brain development by way of inflammatory signal transmission through the vagus nerve or through metabolic changes (Cryan & Dinan 2012).

Behavioral mechanisms. In addition to biological mechanisms, behavioral mechanisms, including abnormal eating and sleeping patterns and psychopathology, could indirectly explain the link between childhood trauma and inflammation in humans. For example, meta-analytical findings and experimental research in animal models show that childhood trauma is linked to a small increase in the risk of obesity (Danese & Tan 2014). In turn, production of proinflammatory cytokines by adipocytes, particularly IL-6, can induce a systemic inflammatory state commonly observed in obese individuals (Gregor & Hotamisligil 2011). Childhood maltreatment may be associated with a thrifty phenotype characterized by increased energy intake and storage and by reduced energy expenditure (Danese & Tan 2014). Several features associated with childhood trauma might increase energy intake, such as impaired reward processing, heightened HPA axis activation, and impaired executive function. Because individuals with a history of childhood trauma may be less sensitive to reward (see the section Childhood Trauma and the Brain), they may engage in more appetitive behaviors, including eating more high-calorie food. Furthermore, because individuals with a history of childhood trauma may have greater HPA activation (see the section Childhood Trauma and the Neuroendocrine Response to Stress) and related unpleasant feelings, they may eat more in an attempt to dampen HPA axis activation. Finally, individuals with a history of childhood trauma may also have impaired inhibitory control (see the section Childhood Trauma and the Brain), which could limit their ability to suppress unwanted behavior in the context of positive or negative reinforcers. In addition to these effects on energy intake, childhood trauma could be linked to reduced energy expenditure. Individuals with a history of childhood trauma may have impaired functioning in hormonal pathways regulating thermogenesis and lipolysis, such as the HPA axis and leptin pathway (see the section Childhood Trauma and the Neuroendocrine Response to Stress) (Danese et al. 2014). Notably, because of the significant overlap between the brain mechanisms involved in obesity and addiction (Volkow & Wise 2005) and the high prevalence of substance and alcohol abuse disorders among individuals with a history of childhood trauma (Dube et al. 2003), more general addiction behaviors could contribute to the link between childhood trauma and inflammation. For example, childhood trauma is associated with an elevated risk of smoking (Anda et al. 1999), which, in turn, can increase circulating inflammatory biomarkers (Shiels et al. 2014). Because they generally occur later in life, addiction behaviors other than overeating are unlikely to significantly contribute to the biological embedding of stress in children. However, they may contribute to the persistence of high inflammation levels in individuals with a history of childhood trauma.

Disruption of sleep patterns is an additional behavioral mechanism through which childhood trauma could induce heightened inflammation levels. Individuals with a history of childhood trauma are at heightened risk of sleep problems (Gregory & Sadeh 2016, Kajeepeta et al. 2015). Notably, the association appears to be stronger for participants with more severe maltreatment experiences (Gregory & Sadeh 2016) and independent of concurrent PTSD or depression diagnoses (Noll et al. 2006). These epidemiological findings are consistent with evidence from experimental animal models, such as decreased total sleep and disruption in sleep architecture found in rodents separated from their mothers in early life (Mrdalj et al. 2013). In turn, experimentally induced sleep deprivation increases the expression of proinflammatory cytokines in humans (Irwin et al. 2006), and sleep loss is associated with elevated inflammation levels in epidemiological studies, particularly in women (Miller et al. 2009).

Childhood trauma may also induce heightened inflammation levels because of related psychopathology. This might happen in a number of ways. A longitudinal study of humans has described bidirectional associations between psychopathology (e.g., depression) and inflammation over time (Matthews et al. 2010) (see the section Inflammation and Psychopathology). This observation suggests that vulnerabilities linked to emotional symptoms, subjective perception of distress, or related behavioral responses could increase inflammation levels over time. First, individuals, particularly women, suffering from depression appear to be more likely than nondepressed individuals to experience high numbers of negative life events to which they had contributed (i.e., dependent events with interpersonal content) (Hammen 2005). These findings of stress generation could be explained by vulnerabilities of the individual (e.g., cognitive or attachment style, personality traits, values, and expectations) and risk factors within their environment (e.g., socioeconomic disadvantage, domestic violence, or parental mental illness), both of which have notable overlap with risk factors for childhood maltreatment (Danese & McCrory 2015). Second, the subjective perception of distress linked to emotional symptoms can lead to chronic stress. This stress could be due, for example, to the persistence of low mood in depression or the recurrent, intrusive nature of PTSD symptoms (Agnew-Blais & Danese 2016, Nanni et al. 2012). Third, individuals who develop psychopathology could engage in behaviors driven by their emotional symptoms. For example, individuals with emotional symptoms may engage in self harm either to relieve distress or, more dramatically, with intent to end their lives (Agnew-Blais & Danese 2016). In turn, chronic stress and physical injury can induce inflammation.

Genetic mechanisms. Although biological and behavioral mechanisms can help us understand why traumatized children have elevated inflammation, it is important to also consider genetic mechanisms, which offer an alternative, noncausal interpretation of this association. It is possible that shared genetic vulnerability underlies the association between childhood trauma and inflammation, a phenomenon known as gene–environment correlation (Jaffee & Price 2007). For example, genetic pathways related to the immune system predict risk for several psychiatric diagnoses (Netw. Pathw. Anal. Subgr. Psychiatr. Genom. Consort. 2015), and early expressions of liability to these conditions, such as emotional dysregulation or oppositional behavior, might increase the risk of maltreatment in childhood.

DOES INFLAMMATION EXPLAIN THE LINK BETWEEN CHILDHOOD TRAUMA AND LATER PSYCHOPATHOLOGY?

We have reviewed several lines of research highlighting the associations between (*a*) childhood trauma and psychopathology, (*b*) inflammation and psychopathology, and (*c*) childhood trauma and inflammation. However, these associations provide only indirect evidence for the inflammatory links between childhood trauma and psychopathology. More direct evidence of the interplay among these three factors may come, for example, from the examination of the analogy of the effects of childhood trauma and inflammation on psychopathology, the synergy between childhood trauma and innate immunity in predicting psychopathology, the specificity of the link between inflammation and psychopathology within groups of traumatized individuals, and the reversibility of the effects of early life stress with anti-inflammatory compounds.

Analogy

It is possible to identify several analogies between the long-term consequences of childhood trauma and early-life immune activation in humans and animal models (Danese & McEwen 2012). As

detailed above (see the sections Childhood Trauma and Psychopathology and Inflammation and Psychopathology), both childhood trauma and childhood innate immune activation demonstrate presumably causative associations with a wide range of adult mental health outcomes. Emerging evidence suggests that both could be associated not only with an elevated incidence of psychopathology but also with an unfavorable course of illness and poor response to treatment (Agnew-Blais & Danese 2016, Nanni et al. 2012, Strawbridge et al. 2015). Finally, at a more biological level, childhood trauma and childhood innate immune activation are linked to similar domains of brain function, such as cognition, positive valence, and negative valence.

Synergy

There is evidence of cross-sensitization between childhood stress and immune activation and of interaction between childhood trauma and inflammatory genes. On the one hand, we have summarized the evidence for the sensitization of the innate immune system after childhood trauma, including findings of heightened inflammatory responses in the context of subsequent stressors (see the section Childhood Trauma and Inflammation). In addition, we have reviewed evidence for the sensitization of the biological and behavioral responses to stress after childhood immune activation (see the section Long-Term Effects of Early-Life Immune Activation on the Brain and Behavior) and for the link between higher baseline levels of inflammation and greater stress-induced responses in animal models and humans (Hodes et al. 2014). On the other hand, initial evidence suggests that genetic variation in inflammatory genes could moderate the association between a history of childhood maltreatment and the amygdala response to angry and fearful faces (involving the *IFN-γ* gene) (Redlich et al. 2015) or the association between contextual stress and depression in children (involving the *IL-1B* gene) (Ridout et al. 2014). The evidence of sensitization and of gene–environment interaction involving maltreatment and inflammatory genes indicates that both factors are likely to be on the same causative pathways influencing the brain and behavior.

Specificity

If inflammation helps explain the relationship between childhood trauma and psychopathology, inflammation levels should be higher in psychiatric patients with a history of childhood trauma compared to those without. Several studies have tested and found some support for this hypothesis. For example, members of the Dunedin Study who had depression at the time of the study but no prospectively collected evidence of childhood maltreatment showed only a small and statistically nonsignificant elevation in inflammation levels at 32 years old compared to nonmaltreated and healthy controls (Danese et al. 2008). In contrast, depressed individuals with a history of childhood maltreatment showed a moderate elevation in inflammation biomarkers that reached statistical significance (Danese et al. 2008). Overall, the association between inflammation and depression was no longer significant once the effect of childhood maltreatment was controlled for (Danese et al. 2008). We have observed similar stratified findings among 12-year-old members of the E-Risk Longitudinal Twin Study, in which depressed children with a history of maltreatment already had significant elevation in inflammation levels compared to controls, whereas depressed children without a history of maltreatment did not (Danese et al. 2011). Consistent with these findings, longitudinal analyses found that adolescents with a history of early-life stress had greater increases in both IL-6 and CRP when developing depression compared to counterparts without a history of early-life stress (Miller & Cole 2012). In addition, although adolescents with a history of early-life stressors showed persistently elevated inflammation levels even after the remission of

depressive symptoms, their counterparts without a history of early-life stressors showed reductions in inflammation levels as their depressive symptoms abated (Miller & Cole 2012).

Reversibility

Studies in experimental animal models found that administration of medications with anti-inflammatory activity could buffer the effects of early-life stress on the brain and behavior. An experimental model in rats demonstrated that pups separated from their mothers later showed more depressive-like symptoms and lower levels of parvalbumin (a GABAergic marker) in the prefrontal cortex compared to unchallenged pups (Leussis et al. 2012). Notably, these differences between the groups were attenuated in maternally separated rats treated with a cyclo-oxygenase 2 (COX-2) inhibitor, an anti-inflammatory medication (Brenhouse & Andersen 2011), or with IL-10, an anti-inflammatory cytokine (Wieck et al. 2013). In addition to this direct evidence, several other interventions indirectly support the role of anti-inflammatory strategies in buffering the long-term consequences of early-life stress. For example, both physical exercise and antidepressant medications have anti-inflammatory effects (Gleeson et al. 2011, Hannestad et al. 2011) and have demonstrated an ability to buffer the effects of early-life stress on brain and behavioral outcomes (Harrison & Baune 2014).

Mediation

None of the findings discussed in this review can be taken in isolation as definitive evidence for the mediating role of inflammation in the association between childhood trauma and psychopathology. However, cumulatively, these findings do offer significant support for this role. Formal or direct tests of this mediation hypothesis (MacKinnon et al. 2007) will require new studies with peculiar design features. First, studies aiming to formally test mediation will require comprehensive models including assessment of childhood trauma, inflammation biomarkers, and psychopathology. Second, these studies must minimize bias due to reverse causality by capitalizing on prospectively collected information on childhood trauma and on repeated measures of inflammation and psychopathology (to measure longitudinal changes rather than cross-sectional group differences). Third, future studies must minimize bias due to measurement error, for example by using latent inflammation variables derived from multiple inflammation biomarkers (rather than single measures), by using repeated measures of inflammation to capture the chronicity of the effect, and by measuring inflammation early in life, when the effects on brain development are presumably stronger. Finally, future studies must minimize bias due to omitted variables by measuring and accounting for the effects of factors that either are correlated with childhood trauma (e.g., family socioeconomic status, genetic liability to psychopathology) or can offer alternative explanations for the link between inflammation and psychopathology (e.g., genetic liability to inflammation). Although it may not be possible for any single study to include all these design features, research that includes some of these features will be helpful to advance knowledge about the mediating role of inflammation in the association between childhood trauma and psychopathology.

Broader challenges to understanding the mechanisms underlying this association are linked to the inherent heterogeneity of these measures and the limits of causal inference in complex systems. With regard to heterogeneity, the concept of childhood trauma has been applied to stressful experiences ranging widely from child sexual abuse, to parental loss, to road traffic accidents, but different types of trauma may have different correlates and consequences (Terr 1991). In addition, any individual psychiatric diagnosis will likely arise through different pathways (equifinality), and different psychiatric diagnoses have significant pathophysiological overlap (Cicchetti & Rogosch

2009, Kendler et al. 2003). With regard to causal inference, not all cases of psychopathology are associated with childhood trauma, and not all individuals with a history of childhood trauma develop psychopathology. The nonnecessary and nonsufficient nature of this association is not uncommon (Rothman & Greenland 2005), but it counters any attempts to build rigorous models for mediation analyses. Thus, a better characterization of childhood trauma and its association with psychopathology will provide researchers with a better framework to identify mediation pathways.

CONCLUSION

Our understanding of the response to psychological trauma—and particularly childhood psychological trauma—has come full circle to recognize the truth in the analogy with the response to physical trauma or injury, partly reconciling the debate between Oppenheim and Charcot over the origins of trauma-related symptoms. Childhood psychological trauma is associated with similar biological responses as those triggered by physical injury, including activation of the innate immune system (Molina 2005). Notably, because of its occurrence early in life, childhood psychological trauma could influence immune system development, promoting chronic activation and hyperreactivity of the inflammatory response from childhood into adult life. In turn, these "hidden wounds" of childhood psychological trauma could affect the brain and behavior over the course of an individual's lifetime by influencing brain development, potentiating the neuroendocrine and immune responses to subsequent stressors, and biasing key domains of brain functioning. As discussed in the previous section, this hypothesis needs to be more comprehensively tested in future research. If confirmed, it will provide a useful framework to conceptualize adaptive and maladaptive aspects of the response to childhood trauma and to understand and treat trauma-related psychopathology.

Because the immune abnormalities emerging after early-life stress exposure appear to be broadly conserved across species with comparatively distant common ancestors, it is intriguing to speculate about whether the inflammatory response to childhood trauma could, in some ways, be adaptive. The evolutionary forces that have shaped the inflammatory response to childhood trauma presumably acted in a context in which physical threats were frequent and psychological stress was often coupled with injury and infection. In this context, the inflammatory response to childhood psychological trauma could provide adaptive benefits by promoting survival and enabling reproduction (Danese & McEwen 2012, Nusslock & Miller 2016). The increase in unstimulated inflammation levels and heightened inflammatory reactivity could prepare the body to respond to subsequent injury and infection. The reduction in motor activity linked to impaired positive valence systems could promote recovery after injury and infection by channeling metabolic resources to support the immune response. The increase in threat perception and the behavioral responses to threat linked to potentiation of negative valence systems could prevent subsequent injury through avoidance. In addition, routine encounters with minimally pathogenic organisms in rural environments could inhibit chronic elevation in inflammation biomarkers by inducing regulatory T cells and B cells (McDade 2012, Miller & Raison 2015). To the extent that the modern experience of childhood trauma still involves frequent and unpredictable threats to survival, the inflammatory response in traumatized children and adults may promote adaptive strategies reflecting those evolutionary imperatives. However, when psychological stress is no longer coupled with injury and infection, when the response persists years after the original threat has ceased, when the ecological niche does not allow encounters with minimally pathogenic immunomodulatory organisms, and when priorities shift from short-term goals (survival) to long-term goals (wellbeing and aging), the chronic elevation in inflammatory biomarkers becomes maladaptive because of the associated risk of psychopathology and age-related disease (Danese & McEwen 2012).

With regard to clinical implications, the presence of elevated inflammation could help explain the complex clinical presentations related to childhood trauma and could provide innovative targets for intervention. First, because inflammation affects both basic developmental processes (see the section Long-Term Effects of Early-Life Immune Activation on the Brain and Behavior) and broad neurobiological systems (see the section How Does Inflammation Affect Psychopathology?), elevated inflammation could help explain the transdiagnostic psychological correlates of childhood trauma (Caspi et al. 2014). Second, because inflammation is associated with complex presentations and can impair the response to conventional treatments (Strawbridge et al. 2015), elevated inflammation could help explain the stratified clinical effects of childhood trauma across psychopathology (Agnew-Blais & Danese 2016; Danese et al. 2011, 2008; Nanni et al. 2012). Third, because inflammation not only is associated with psychopathology but also contributes to the pathophysiology of several medical conditions (Danese & McEwen 2012), elevated inflammation could help explain the high rate of medical comorbidities in individuals with a history of childhood trauma (Danese et al. 2009, Taylor 2010). Fourth, with regard to interventions, the evidence that both pharmacological and nonpharmacological anti-inflammatory strategies can reverse the long-term consequences of early-life stress in animal models (see the section Reversibility) suggests that similar strategies might be effective in preventing the onset of clinical outcomes in humans (secondary prevention). Provocative findings in animal models also suggest that harnessing the immune response to self-antigens may contribute to psychological stress resilience (Lewitus & Schwartz 2009). An initial mild stressor can increase lymphocyte trafficking to the brain, which in turn reduces secondary neuronal damage by the microglia and produces autoreactive memory T cells that increase neuroprotection in the face of subsequent stressors (Lewitus & Schwartz 2009). Building on these findings, immunization with CNS-derived peptides has been associated with lower anxiety symptoms in rodents exposed to predator odor (Lewitus & Schwartz 2009). However, this immunization approach has not yet been studied in relation to early-life stress. In addition to strategies directly targeting the immune system, psychosocial interventions might be used to reduce inflammation in traumatized children (Pace et al. 2009) and to decrease psychosocial adversity more generally (Miller et al. 2014), although the impact of commonly used psychosocial interventions with established clinical significance (Danese & McCrory 2015) requires further investigation. Finally, similar anti-inflammatory strategies might be effective in improving treatment response and course of illness in trauma-related psychopathology (tertiary prevention) (Agnew-Blais & Danese 2016, Danese et al. 2008, Nanni et al. 2012, Raison et al. 2013).

In addition to its manifest signs and symptoms (Gilbert et al. 2009a), childhood trauma may leave more hidden wounds: immune abnormalities that have the potential to influence brain development and subsequent behavior. Advances in detecting and healing these hidden wounds may help prevent some of the impairing health problems documented in children exposed to psychological trauma.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

Ader R, Friedman SB. 1965. Differential early experiences and susceptibility to transplanted tumor in the rat. *J. Comp. Physiol. Psychol.* 59:361–64

Agnew-Blais J, Danese A. 2016. Childhood maltreatment and unfavourable clinical outcomes in bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* 3:342–49

Amminger GP, Schäfer MR, Schlögelhofer M, Klier CM, McGorry PD. 2015. Longer-term outcome in the prevention of psychotic disorders by the Vienna omega-3 study. *Nat. Commun.* 6:7934

Anda RF, Croft JB, Felitti VJ, Nordenberg D, Giles WH, et al. 1999. Adverse childhood experiences and smoking during adolescence and adulthood. *JAMA* 282(17):1652–58

Atladóttir HO, Thorsen P, Østergaard L, Schendel DE, Lemcke S, et al. 2010. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J. Autism Dev. Disord.* 40(12):1423–30

Avitsur R, Hunzeker J, Sheridan JF. 2006. Role of early stress in the individual differences in host response to viral infection. *Brain Behav. Immun.* 20(4):339–48

Bailey MT, Coe CL. 1999. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. *Dev. Psychobiol.* 35(2):146–55

Barnes PJ, Adcock IM. 2009. Glucocorticoid resistance in inflammatory diseases. *Lancet* 373(9678):1905–17

Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. 2015. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol. Psychiatry* 21:642–49

Berk M, Kapczinski F, Andreazza AC, Dean OM, Giorlando F, et al. 2011. Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors. *Neurosci. Biobehav. Rev.* 35(3):804–17

Besedovsky H, del Rey A, Sorkin E, Dinarello CA. 1986. Immunoregulatory feedback between interleukin-1 and glucocorticoid hormones. *Science* 233(4764):652–54

Bilbo SD, Schwarz JM. 2009. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front. Behav. Neurosci.* 3:14

Bloomfield PS, Selvaraj S, Veronese M, Rizzo G, Bertoldo A, et al. 2016. Microglial activity in people at ultra high risk of psychosis and in schizophrenia: an [^{11}C]PBR28 PET brain imaging study. *Am. J. Psychiatry* 173(1):44–52

Boulanger LM. 2009. Immune proteins in brain development and synaptic plasticity. *Neuron* 64(1):93–109

Bowlby J. 1951. Maternal care and mental health. *Bull. World Health Organ.* 3(3):355–533

Breder CD, Hazuka C, Ghayur T, Klug C, Huginin M, et al. 1994. Regional induction of tumor necrosis factor alpha expression in the mouse brain after systemic lipopolysaccharide administration. *PNAS* 91(24):11393–97

Brenhouse HC, Andersen SL. 2011. Nonsteroidal anti-inflammatory treatment prevents delayed effects of early life stress in rats. *Biol. Psychiatry* 70(5):434–40

Brenhouse HC, Thompson V. 2015. *Maternal separation increases IBA-1 expression: a microglia activation marker in the prefrontal cortex of adolescent males following a second hit of stress*. Presented at Annu. Meet. Soc. Biol. Psychiatry, 70th, May 14–16, Toronto, Canada (Abstr.)

Briquet P. 1859. *Traite clinique et thérapeutique de l'hystérie*. Paris: J.-B. Baillière et Fils

Brown GW, Harris T. 1978. *Social Origins of Depression: A Study of Psychiatric Disorder in Women*. New York: Free Press

Brunson KL, Kramár E, Lin B, Chen Y, Colgin LL, et al. 2005. Mechanisms of late-onset cognitive decline after early-life stress. *J. Neurosci.* 25(41):9328–38

Capuron L, Pagnoni G, Drake DF, Woolwine BJ, Spivey JR, et al. 2012. Dopaminergic mechanisms of reduced basal ganglia responses to hedonic reward during interferon alfa administration. *Arch. Gen. Psychiatry* 69(10):1044–53

Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. 2010. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. *Neuropsychopharmacology* 35(13):2617–23

Carpenter LL, Tyrka AR, McDougle CJ, Malison RT, Owens MJ, et al. 2004. Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. *Neuropsychopharmacology* 29(4):777–84

Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL. 2002. Diurnal salivary cortisol in pediatric posttraumatic stress disorder. *Biol. Psychiatry* 51(7):575–82

Caspi A, Houts RM, Belsky DW, Goldman-Mellor SJ, Harrington H, et al. 2014. The p factor: one general psychopathology factor in the structure of psychiatric disorders? *Clin. Psychol. Sci.* 2(2):119–37

Chalasani SH, Sabelko KA, Sunshine MJ, Littman DR, Raper JA. 2003. A chemokine, SDF-1, reduces the effectiveness of multiple axonal repellents and is required for normal axon pathfinding. *J. Neurosci.* 23(4):1360–71

Chocyk A, Dudys D, Przyborowska A, Majcher I, Maćkowiak M, Wędzony K. 2011. Maternal separation affects the number, proliferation and apoptosis of glia cells in the substantia nigra and ventral tegmental area of juvenile rats. *Neuroscience* 173:1–18

Cicchetti D, Handley ED, Rogosch FA. 2015. Child maltreatment, inflammation, and internalizing symptoms: investigating the roles of C-reactive protein, gene variation, and neuroendocrine regulation. *Dev. Psychopathol.* 27:553–66

Cicchetti D, Rogosch FA. 2001. The impact of child maltreatment and psychopathology on neuroendocrine functioning. *Dev. Psychopathol.* 13(4):783–804

Cicchetti D, Rogosch FA. 2009. Equifinality and multifinality in developmental psychopathology. *Dev. Psychopathol.* 8(4):597–600

Coe CL, Rosenberg LT, Levine S. 1988. Prolonged effect of psychological disturbance on macrophage chemiluminescence in the squirrel monkey. *Brain Behav. Immun.* 2(2):151–60

Coelho R, Viola TW, Walss-Bass C, Brietzke E, Grassi-Oliveira R. 2014. Childhood maltreatment and inflammatory markers: a systematic review. *Acta Psychiatr. Scand.* 129(3):180–92

Cohen S, Tyrrell DA, Smith AP. 1991. Psychological stress and susceptibility to the common cold. *N. Engl. J. Med.* 325(9):606–12

Cole SW, Conti G, Arevalo JMG, Ruggiero AM, Heckman JJ, Suomi SJ. 2012. Transcriptional modulation of the developing immune system by early life social adversity. *PNAS* 109(50):20578–83

Cryan JF, Dinan TG. 2012. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci.* 13(10):701–12

Cryan JF, Holmes A. 2005. The ascent of mouse: advances in modelling human depression and anxiety. *Nat. Rev. Drug Discov.* 4(9):775–90

Danese A, Caspi A, Williams B, Ambler A, Sugden K, et al. 2011. Biological embedding of stress through inflammation processes in childhood. *Mol. Psychiatry* 16(3):244–46

Danese A, Dove R, Belsky DW, Henchy J, Williams B, et al. 2014. Leptin deficiency in maltreated children. *Transl. Psychiatry* 4(9):e446

Danese A, McCrory E. 2015. Child maltreatment. In *Rutter's Child and Adolescent Psychiatry*, ed. A Thapar, DS Pine, JF Leckman, S Scott, MJ Snowling, E Taylor, pp. 364–75. London: Wiley-Blackwell

Danese A, McEwen BS. 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol. Behav.* 106(1):29–39

Danese A, Moffitt TE, Harrington H, Milne BJ, Polanczyk G, et al. 2009. Adverse childhood experiences and adult risk factors for age-related disease: depression, inflammation, and clustering of metabolic risk markers. *Arch. Pediatr. Adolesc. Med.* 163(12):1135–43

Danese A, Moffitt TE, Pariante CM, Ambler A, Poulton R, Caspi A. 2008. Elevated inflammation levels in depressed adults with a history of childhood maltreatment. *Arch. Gen. Psychiatry* 65(4):409–15

Danese A, Pariante CM, Caspi A, Taylor A, Poulton R. 2007. Childhood maltreatment predicts adult inflammation in a life-course study. *PNAS* 104(4):1319–24

Danese A, Tan M. 2014. Childhood maltreatment and obesity: systematic review and meta-analysis. *Mol. Psychiatry* 19(5):544–54

Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. 2008. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.* 9(1):46–56

Dargél AA, Godin O, Kapczinski F, Kupfer DJ, Leboyer M. 2015. C-reactive protein alterations in bipolar disorder: a meta-analysis. *J. Clin. Psychiatry* 76(2):142–50

De Bellis MD, Baum AS, Birmaher B, Keshavan MS, Eccard CH, et al. 1999. Developmental traumatology. Part I: biological stress systems. *Biol. Psychiatry* 45(10):1259–70

Deykin EY, MacMahon B. 1979. Viral exposure and autism. *Am. J. Epidemiol.* 109(6):628–38

Dillon DG, Holmes AJ, Birk JL, Brooks N, Lyons-Ruth K, Pizzagalli DA. 2009. Childhood adversity is associated with left basal ganglia dysfunction during reward anticipation in adulthood. *Biol. Psychiatry* 66(3):206–13

Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. 2003. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics* 111(3):564–72

Duncan GJ, Magnuson KA, Ludwig J. 2004. The endogeneity problem in developmental studies. *Res. Hum. Dev.* 1(1–2):59–80

Dunn AJ. 2006. Cytokine activation of the HPA axis. *Ann. N. Y. Acad. Sci.* 917(1):608–17

Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. 2010. Inflammation-induced anhedonia: Endotoxin reduces ventral striatum responses to reward. *Biol. Psychiatry* 68(8):748–54

Ekdahl CT, Claasen J-H, Bonde S, Kokaia Z, Lindvall O. 2003. Inflammation is detrimental for neurogenesis in adult brain. *PNAS* 100(23):13632–37

Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, et al. 2014. Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. *JAMA Psychiatry* 71(4):423–31

Erichsen JE. 1867. *On Railway and Other Injuries of the Nervous System*. Philadelphia: Henry C. Lea

Ford DE, Erlinger TP. 2004. Depression and C-reactive protein in US adults: data from the Third National Health and Nutrition Examination Survey. *Arch. Intern. Med.* 164(9):1010–14

Francis D, Diorio J, Liu D, Meaney MJ. 1999. Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science* 286(5442):1155–58

Frank MG, Watkins LR, Maier SF. 2013. Stress-induced glucocorticoids as a neuroendocrine alarm signal of danger. *Brain Behav. Immun.* 33:1–6

Freud S. 1962. *The Standard Edition of the Complete Psychological Works of Sigmund Freud*, Vol. IV: *The Interpretation of Dreams (First Part)*. London: Hogarth Press

Galea I, Bechmann I, Perry VH. 2007. What is immune privilege (not)? *Trends Immunol.* 28(1):12–18

Ganguly P, Brenhouse HC. 2015. Broken or maladaptive? Altered trajectories in neuroinflammation and behavior after early life adversity. *Dev. Cogn. Neurosci.* 11:18–30

Gilbert R, Kemp A, Thoburn J, Sidebotham P, Radford L, et al. 2009a. Recognising and responding to child maltreatment. *Lancet* 373(9658):167–80

Gilbert R, Widom CS, Browne K, Fergusson D, Webb E, Janson S. 2009b. Burden and consequences of child maltreatment in high-income countries. *Lancet* 373(9657):68–81

Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. 2011. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat. Rev. Immunol.* 11(9):607–15

Gouin J-P, Glaser R, Malarkey WB, Beversdorf D, Kiecolt-Glaser JK. 2012. Childhood abuse and inflammatory responses to daily stressors. *Ann. Behav. Med.* 44(2):287–92

Gregor MF, Hotamisligil GS. 2011. Inflammatory mechanisms in obesity. *Annu. Rev. Immunol.* 29(1):415–45

Gregory AM, Sadeh A. 2016. Annual research review: sleep problems in childhood psychiatric disorders—a review of the latest science. *J. Child Psychol. Psychiatry* 57(3):296–317

Gunnar M, Quevedo K. 2007. The neurobiology of stress and development. *Annu. Rev. Psychol.* 58:145–73

Guyer AE, Kaufman J, Hodgdon HB, Masten CL, Jazbec S, et al. 2006. Behavioral alterations in reward system function: the role of childhood maltreatment and psychopathology. *J. Am. Acad. Child Adolesc. Psychiatry* 45(9):1059–67

Hammen C. 2005. Stress and depression. *Annu. Rev. Clin. Psychol.* 1:293–319

Hanisch U-K, Kettenmann H. 2007. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat. Neurosci.* 10(11):1387–94

Hannestad J, DellaGioia N, Bloch M. 2011. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* 36(12):2452–59

Harlow HF, Dodsworth RO, Harlow MK. 1965. Total social isolation in monkeys. *PNAS* 54(1):90–97

Harrison EL, Baune BT. 2014. Modulation of early stress-induced neurobiological changes: a review of behavioural and pharmacological interventions in animal models. *Transl. Psychiatry* 4(5):e390

Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Critchley HD. 2009. Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biol. Psychiatry* 66(5):407–14

Hart BL. 1988. Biological basis of the behavior of sick animals. *Neurosci. Biobehav. Rev.* 12(2):123–37

Heim C, Ehlert U, Hellhammer DH. 2000. The potential role of hypocortisolism in the pathophysiology of stress-related bodily disorders. *Psychoneuroendocrinology* 25:1–35

Heim C, Mletzko T, Purselle D, Musselman DL, Nemeroff CB. 2008. The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol. Psychiatry* 63(4):398–405

Heim C, Nemeroff CB. 2001. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. *Biol. Psychiatry* 49(12):1023–39

Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, et al. 2000. Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *JAMA* 284(5):592–97

Hennessy MB, Deak T, Schiml-Webb PA. 2010a. Early attachment-figure separation and increased risk for later depression: potential mediation by proinflammatory processes. *Neurosci. Biobehav. Rev.* 34(6):782–90

Hennessy MB, Deak T, Schiml-Webb PA, Carlisle CW, O'Brien E. 2010b. Maternal separation produces, and a second separation enhances, core temperature and passive behavioral responses in guinea pig pups. *Physiol. Behav.* 100(4):305–10

Herringa RJ, Birn RM, Ruttle PL, Burghy CA, Stodola DE, et al. 2013. Childhood maltreatment is associated with altered fear circuitry and increased internalizing symptoms by late adolescence. *PNAS* 110(47):19119–24

Hinde RA, Spencer-Booth Y. 1971. Effects of brief separation from mother on rhesus monkeys. *Science* 173(3992):111–18

Hodes GE, Pfau ML, Leboeuf M, Golden SA, Christoffel DJ, et al. 2014. Individual differences in the peripheral immune system promote resilience versus susceptibility to social stress. *PNAS* 111(45):16136–41

Holdorff B. 2011. The fight for "traumatic neurosis," 1889–1916: Hermann Oppenheim and his opponents in Berlin. *Hist. Psychiatry* 22:465–76

Howren MB, Lamkin DM, Suls J. 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom. Med.* 71(2):171–86

Inagaki TK, Muscatell KA, Irwin MR, Cole SW, Eisenberger NI. 2012. Inflammation selectively enhances amygdala activity to socially threatening images. *NeuroImage* 59(4):3222–26

Insel TR. 2014. The NIMH Research Domain Criteria (RDoC) project: precision medicine for psychiatry. *Am. J. Psychiatry* 171(4):395–97

Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. 2006. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch. Intern. Med.* 166(16):1756–62

Jaffee SR, Price TS. 2007. Gene-environment correlations: a review of the evidence and implications for prevention of mental illness. *Mol. Psychiatry* 12(5):432–42

Kajeepeta S, Gelaye B, Jackson CL, Williams MA. 2015. Adverse childhood experiences are associated with adult sleep disorders: a systematic review. *Sleep Med.* 16(3):320–30

Kaufman J, Gelernter J, Hudziak JJ, Tyrka AR, Coplan JD. 2015. The Research Domain Criteria (RDoC) project and studies of risk and resilience in maltreated children. *J. Am. Acad. Child Adolesc. Psychiatry* 54(8):617–25

Kendler KS, Bulik CM, Silberg J, Hettema JM, Myers J, Prescott CA. 2000. Childhood sexual abuse and adult psychiatric and substance use disorders in women. *Arch. Gen. Psychiatry* 57(10):953–59

Kendler KS, Prescott CA, Myers J, Neale MC. 2003. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch. Gen. Psychiatry* 60(9):929–37

Kessler RC, Davis CG, Kendler KS. 1997. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. *Psychol. Med.* 27(5):1101–19

Khandaker GM, Cousins L, Deakin J, Lennox BR, Yolken R, Jones PB. 2015. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry* 2(3):258–70

Khandaker GM, Pearson RM, Zammit S, Lewis G, Jones PB. 2014. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life. *JAMA Psychiatry* 71(10):1121–28

Khandaker GM, Zimbron J, Lewis G, Jones PB. 2013. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. *Psychol. Med.* 43(2):239–57

Kiecolt-Glaser JK, Gouin J-P, Weng N-P, Malarkey WB, Beversdorf DQ, Glaser R. 2011. Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. *Psychosom. Med.* 73(1):16–22

Kipnis J, Gadani S, Derecki NC. 2012. Pro-cognitive properties of T cells. *Nat. Rev. Immunol.* 12(9):663–69

Klengel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, et al. 2013. Allele-specific *FKBP5* DNA demethylation mediates gene–childhood trauma interactions. *Nat. Neurosci.* 16:33–41

Knuesel I, Chicha L, Britschgi M, Schobel SA, Bodmer M, et al. 2014. Maternal immune activation and abnormal brain development across CNS disorders. *Nat. Rev. Neurol.* 10(11):643–60

Köhler O, Benros ME, Nordentoft M, Farkouh ME, Iyengar RL, et al. 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry* 71(12):1381–91

Leboyer M, Soreca I, Scott J, Frye M, Henry C, et al. 2012. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J. Affect. Disord.* 141(1):1–10

Leppänen JM, Nelson CA. 2009. Tuning the developing brain to social signals of emotions. *Nat. Rev. Neurosci.* 10(1):37–47

Leussis MP, Freund N, Brenhouse HC, Thompson BS, Andersen SL. 2012. Depressive-like behavior in adolescents after maternal separation: sex differences, controllability, and GABA. *Dev. Neurosci.* 34(2–3):210–17

Levine S, Alpert M, Lewis GW. 1957. Infantile experience and the maturation of the pituitary adrenal axis. *Science* 126(3287):1347

Levine S, Chevalier JA, Korchin SJ. 1956. The effects of early shock and handling on later avoidance learning. *J. Personal.* 24(4):475–93

Lewitus GM, Schwartz M. 2009. Behavioral immunization: immunity to self-antigens contributes to psychological stress resilience. *Mol. Psychiatry* 14:532–36

Lim L, Radua J, Rubia K. 2014. Gray matter abnormalities in childhood maltreatment: a voxel-wise meta-analysis. *Am. J. Psychiatry* 171(8):854–63

Lupien SJ, McEwen BS, Gunnar MR, Heim C. 2009. Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat. Rev. Neurosci.* 10(6):434–45

MacKinnon DP, Fairchild AJ, Fritz MS. 2007. Mediation analysis. *Annu. Rev. Psychol.* 58:593–614

Maercker A, Brewin CR, Bryant RA, Cloitre M, van Ommeren M, et al. 2013. Diagnosis and classification of disorders specifically associated with stress: proposals for ICD-11. *World Psychiatry* 12(3):198–206

Maes M, Lambrechts J, Bosmans E, Jacobs J, Suy E, et al. 1992. Evidence for a systemic immune activation during depression: results of leukocyte enumeration by flow cytometry in conjunction with monoclonal antibody staining. *Psychol. Med.* 22(1):45–53

Matthews K, Robbins TW. 2003. Early experience as a determinant of adult behavioural responses to reward: the effects of repeated maternal separation in the rat. *Neurosci. Biobehav. Rev.* 27(1–2):45–55

Matthews KA, Schott LL, Bromberger JT, Cyranowski JM, Everson-Rose SA, Sowers M. 2010. Are there bidirectional associations between depressive symptoms and C-reactive protein in mid-life women? *Brain Behav. Immun.* 24(1):96–101

McCrory EJ, De Brito SA, Kelly PA, Bird G, Sebastian CL, et al. 2013. Amygdala activation in maltreated children during pre-attentive emotional processing. *Br. J. Psychiatry* 202(4):269–76

McCrory EJ, De Brito SA, Viding E. 2010. Research review: the neurobiology and genetics of maltreatment and adversity. *J. Child Psychol. Psychiatry* 51(10):1079–95

McDade TW. 2012. Early environments and the ecology of inflammation. *PNAS* 109(Suppl. 2):17281–88

McEwen BS, Weiss JM, Schwartz LS. 1968. Selective retention of corticosterone by limbic structures in rat brain. *Nature* 220(5170):911–12

Mednick SA, Machon RA, Huttunen MO, Bonett D. 1988. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch. Gen. Psychiatry* 45(2):189–92

Mehta MA, Gore-Langton E, Golembo N, Colvert E, Williams SCR, Sonuga-Barke E. 2010. Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *J. Cogn. Neurosci.* 22(10):2316–25

Micale MS. 1995. Charcot and les névroses traumatiques: scientific and historical reflections. *J. Hist. Neurosci.* 4:101–19

Michopoulos V, Rothbaum AO, Jovanovic T, Almli LM, Bradley B, et al. 2015. Association of CRP genetic variation and CRP level with elevated PTSD symptoms and physiological responses in a civilian population with high levels of trauma. *Am. J. Psychiatry* 172(4):353–62

Miller AH, Raison CL. 2015. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* 16(1):22–34

Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. 2011. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol. Psychiatry* 70(7):663–71

Miller GE, Brody GH, Yu T, Chen E. 2014. A family-oriented psychosocial intervention reduces inflammation in low-SES African American youth. *PNAS* 111(31):11287–92

Miller GE, Chen E. 2010. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. *Psychol. Sci.* 21(6):848–56

Miller GE, Cohen S, Ritchey AK. 2002. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a glucocorticoid-resistance model. *Health Psychol.* 21(6):531–41

Miller GE, Cole SW. 2012. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. *Biol. Psychiatry* 72(1):34–40

Miller MA, Kandala N-B, Kivimaki M, Kumari M, Brunner EJ, et al. 2009. Gender differences in the cross-sectional relationships between sleep duration and markers of inflammation: Whitehall II study. *Sleep* 32(7):857–64

Mirescu C, Peters JD, Gould E. 2004. Early life experience alters response of adult neurogenesis to stress. *Nat. Neurosci.* 7(8):841–46

Modabbernia A, Taslimi S, Brietzke E, Ashrafi M. 2013. Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biol. Psychiatry* 74(1):15–25

Molina PE. 2005. Neurobiology of the stress response: contribution of the sympathetic nervous system to the neuroimmune axis in traumatic injury. *Shock* 24(1):3–10

Mondelli V, Ciufolini S, Belvederi Murri M, Bonaccorso S, Di Forti M, et al. 2015. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. *Schizophr. Bull.* 41(5):1162–70

Monje ML, Toda H, Palmer TD. 2003. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302(5651):1760–65

Moriceau S, Sullivan RM. 2006. Maternal presence serves as a switch between learning fear and attraction in infancy. *Nat. Neurosci.* 9(8):1004–6

Mrdalj J, Pallesen S, Milde AM, Jellestad FK, Murison R, et al. 2013. Early and later life stress alter brain activity and sleep in rats. *PLOS ONE* 8(7):e69923

Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, et al. 2001. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N. Engl. J. Med.* 344(13):961–66

Nanni V, Uher R, Danese A. 2012. Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *Am. J. Psychiatry* 169(2):141–51

Netw. Pathw. Anal. Subgr. Psychiatr. Genom. Consort. 2015. Psychiatric genome-wide association study analyses implicate neuronal, immune and histone pathways. *Nat. Neurosci.* 18(2):199–209

Noll JG, Trickett PK, Susman EJ, Putnam FW. 2006. Sleep disturbances and childhood sexual abuse. *J. Pediatr. Psychol.* 31(5):469–80

Nusslock R, Miller GE. 2016. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. *Biol. Psychiatry* 80:23–32

O'Mahony SM, Marchesi JR, Scully P, Codling C, Ceolho A-M, et al. 2009. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. *Biol. Psychiatry* 65(3):263–67

Pace TWW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, et al. 2006. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am. J. Psychiatry* 163(9):1630–33

Pace TWW, Negi LT, Adame DD, Cole SP, Sivilli TI, et al. 2009. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology* 34(1):87–98

Pariante CM, Miller AH. 2001. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. *Biol. Psychiatry* 49(5):391–404

Passos IC, Vasconcelos-Moreno MP, Costa LG, Kunz M, Brietzke E, et al. 2015. Inflammatory markers in post-traumatic stress disorder: a systematic review, meta-analysis, and meta-regression. *Lancet Psychiatry* 2(11):1002–12

Patterson PH. 2009. Immune involvement in schizophrenia and autism: etiology, pathology and animal models. *Behav. Brain Res.* 204(2):313–21

Pechtel P, Pizzagalli DA. 2011. Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology* 214(1):55–70

Peferoen L, Kipp M, van der Valk P, van Noort JM, Amor S. 2014. Oligodendrocyte-microglia cross-talk in the central nervous system. *Immunology* 141(3):302–13

Perry VH, Holmes C. 2014. Microglial priming in neurodegenerative disease. *Nat. Rev. Neurol.* 10(4):217–24

Perry VH, Newman TA, Cunningham C. 2003. The impact of systemic infection on the progression of neurodegenerative disease. *Nat. Rev. Neurosci.* 4(2):103–12

Phillips GD, Howes SR, Whitelaw RB, Robbins TW, Everitt BJ. 1994. Isolation rearing impairs the reinforcing efficacy of intravenous cocaine or intra-accumbens *d*-amphetamine: impaired response to intra-accumbens D1 and D2/D3 dopamine receptor antagonists. *Psychopharmacology* 115(3):419–29

Pollak SD, Kistler DJ. 2002. Early experience is associated with the development of categorical representations for facial expressions of emotion. *PNAS* 99(13):9072–76

Pryce CR, Dettling AC, Spengler M, Schnell CR, Feldon J. 2004. Deprivation of parenting disrupts development of homeostatic and reward systems in marmoset monkey offspring. *Biol. Psychiatry* 56(2):72–79

Raison CL, Miller AH. 2003. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am. J. Psychiatry* 160(9):1554–65

Raison CL, Rutherford RE, Woolwine BJ, Shuo C, Schettler P, et al. 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. *JAMA Psychiatry* 70(1):31–41

Redlich R, Stacey D, Opel N, Grotegerd D, Dohm K, et al. 2015. Evidence of an IFN-γ by early life stress interaction in the regulation of amygdala reactivity to emotional stimuli. *Psychoneuroendocrinology* 62:166–73

Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, et al. 2001. Cytokine-associated emotional and cognitive disturbances in humans. *Arch. Gen. Psychiatry* 58(5):445–52

Ridout KK, Parade SH, Seifer R, Price LH, Gelernter J, et al. 2014. Interleukin 1B gene (*IL1B*) variation and internalizing symptoms in maltreated preschoolers. *Dev. Psychopathol.* 26(4 Pt. 2):1277–87

Rothman KJ, Greenland S. 2005. Causation and causal inference in epidemiology. *Am. J. Public Health* 95(Suppl. 1):S144–50

Sánchez MM, Ladd CO, Plotsky PM. 2001. Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Dev. Psychopathol.* 13(3):419–49

Schedlowski M, Engler H, Grigoleit J-S. 2014. Endotoxin-induced experimental systemic inflammation in humans: a model to disentangle immune-to-brain communication. *Brain Behav. Immun.* 35:1–8

Selye H. 1936. A syndrome produced by diverse nocuous agents. *Nature* 138(3479):32

Setiawan E, Wilson AA, Mizrahi R, Rusjan PM, Miler L, et al. 2015. Role of translocator protein density, a marker of neuroinflammation, in the brain during major depressive episodes. *JAMA Psychiatry* 72(3):268–75

Shanks N, Larocque S, Meaney MJ. 1995. Neonatal endotoxin exposure alters the development of the hypothalamic-pituitary-adrenal axis: early illness and later responsivity to stress. *J. Neurosci.* 15(1 Pt. 1):376–84

Shanks N, Lightman SL. 2001. The maternal-neonatal neuro-immune interface: Are there long-term implications for inflammatory or stress-related disease? *J. Clin. Investig.* 108(11):1567–73

Shanks N, Windle RJ, Perks PA, Harbuz MS, Jessop DS, et al. 2000. Early-life exposure to endotoxin alters hypothalamic-pituitary-adrenal function and predisposition to inflammation. *PNAS* 97(10):5645–50

Shiels MS, Katki HA, Freedman ND, Purdue MP, Wentzensen N, et al. 2014. Cigarette smoking and variations in systemic immune and inflammation markers. *J. Natl. Cancer Inst.* 106:dju294
Shirtcliff EA, Coe CL, Pollak SD. 2009. Early childhood stress is associated with elevated antibody levels to herpes simplex virus type 1. *PNAS* 106(8):2963–67
Short SJ, Lubach GR, Karasin AI, Olsen CW, Styner M, et al. 2010. Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. *Biol. Psychiatry* 67(10):965–73
Slopen N, Kubzansky LD, McLaughlin KA, Koenen KC. 2013. Childhood adversity and inflammatory processes in youth: a prospective study. *Psychoneuroendocrinology* 38(2):188–200
Smith RS. 1991. The macrophage theory of depression. *Med. Hypotheses* 35(4):298–306
Solomon GF, Levine S, Kraft JK. 1968. Early experience and immunity. *Nature* 220(5169):821–22
Spitz RA. 1945. Hospitalism; an inquiry into the genesis of psychiatric conditions in early childhood. *Psychoanal. Study Child* 1:53–74
Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. 2015. Inflammation and clinical response to treatment in depression: a meta-analysis. *Eur. Neuropsychopharmacol.* 25(10):1532–43
Suomi SJ. 1997. Early determinants of behaviour: evidence from primate studies. *Br. Med. Bull.* 53(1):170–84
Takatsuru Y, Nabekura J, Ishikawa T, Kohsaka S-I, Koibuchi N. 2015. Early-life stress increases the motility of microglia in adulthood. *J. Physiol. Sci.* 65(2):187–94
Takizawa R, Danese A, Maughan B, Arseneault L. 2015. Bullying victimization in childhood predicts inflammation and obesity at mid-life: a five-decade birth cohort study. *Psychol. Med.* 45(13):2705–15
Taylor SE. 2010. Mechanisms linking early life stress to adult health outcomes. *PNAS* 107(19):8507–12
Teicher MH, Samson JA. 2016. Annual research review: enduring neurobiological effects of childhood abuse and neglect. *J. Child Psychol. Psychiatry* 57:241–66
Terr LC. 1991. Childhood traumas: an outline and overview. *Am. J. Psychiatry* 148(1):10–20
Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ. 2011. Elevated amygdala response to faces following early deprivation. *Dev. Sci.* 14(2):190–204
Tottenham N, Sheridan MA. 2009. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front. Hum. Neurosci.* 3:68
van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, et al. 2010. Can animal models of disease reliably inform human studies? *PLOS Med.* 7(3):e1000245
van Harmelen A-L, van Tol M-J, Demenescu LR, van der Wee NJA, Veltman DJ, et al. 2013. Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Soc. Cogn. Affect. Neurosci.* 8(4):362–69
Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, et al. 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr. Bull.* 38(4):661–71
Viviani B, Boraso M, Valero M, Gardoni F, Marco EM, et al. 2014. Early maternal deprivation immunologically primes hippocampal synapses by redistributing interleukin-1 receptor type I in a sex dependent manner. *Brain Behav. Immun.* 35:135–43
Volkow ND, Wise RA. 2005. How can drug addiction help us understand obesity? *Nat. Neurosci.* 8(5):555–60
Weaver ICG, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, et al. 2004. Epigenetic programming by maternal behavior. *Nat. Neurosci.* 7(8):847–54
Wei L, Simen A, Mane S, Kaffman A. 2012. Early life stress inhibits expression of a novel innate immune pathway in the developing hippocampus. *Neuropsychopharmacology* 37(2):567–80
Widom CS. 1999. Posttraumatic stress disorder in abused and neglected children grown up. *Am. J. Psychiatry* 156(8):1223–29
Wieck A, Andersen SL, Brenhouse HC. 2013. Evidence for a neuroinflammatory mechanism in delayed effects of early life adversity in rats: relationship to cortical NMDA receptor expression. *Brain Behav. Immun.* 28:218–26
Yirmiya R, Goshen I. 2011. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain Behav. Immun.* 25(2):181–213
Ziv Y, Ron N, Butovsky O, Landa G, Sudai E, et al. 2006. Immune cells contribute to the maintenance of neurogenesis and spatial learning abilities in adulthood. *Nat. Neurosci.* 9(2):268–75