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

Prabarna Ganguly, Heather C. Brenhouse*

Northeastern University, Psychology Department, 125 Nightingale Hall, 360 Huntington Avenue, Boston, MA 02115, USA

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ABSTRACT

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

1. Introduction

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

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

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

* Corresponding author. Tel.: +1 617 373 6856.
E-mail addresses: prabarna@gmail.com (P. Ganguly), h.brenhouse@neu.edu (H.C. Brenhouse).

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

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

2. Behavioral effects of early life stress across the lifespan

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

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

3. Neuroinflammation and psychopathology

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

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