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The impact of developmental timing for stress and recovery

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ABSTRACT

Stress can have lasting effects on the brain and behavior. Delineating the impact of stress on the developing brain is fundamental for understanding mechanisms through which stress induces persistent effects on behavior that can lead to psychopathology. The growing field of translational developmental neuroscience has revealed a significant role of the timing of stress on risk, resilience, and neuroplasticity. Studies of stress across species have provided essential insight into the mechanisms by which the brain changes and the timing of those changes on outcome. In this article, we review the neurobiological effects of stress and propose a model by which sensitive periods of neural development interact with stressful life events to affect plasticity and the effects of stress on functional outcomes. We then highlight how early-life stress can alter the course of brain development. Finally, we examine mechanisms of buffering against early-life stress that may promote resilience and positive outcomes. The findings are discussed in the context of implications for early identification of risk and resilience factors and development of novel interventions that target the biological state of the developing brain to ultimately ameliorate the adverse consequences of stress during childhood and adolescence.

1. Introduction

Stress is a potent environmental risk factor for both mental and physical illness. The effects of stress on the brain depend critically on the timing (age of onset and duration). When stress occurs early in life it can have profound and lasting effects on brain organization and function. Approximately 10% of youth have anxiety and stress-related disorders (Newman et al., 1996; Kim-Cohen et al., 2003; Kessler et al., 2005), and early childhood adversity accounts for over 30% of all mental illnesses (Green et al., 2010). Yet not all children who experience stressful life events develop mental illness. Understanding the mechanisms by which stress alters the developing brain is fundamental for: 1) delineating adaptive and maladaptive changes; 2) identifying resilience and risk factors; and 3) developing interventions for ameliorating risk. This article highlights recent studies that examine the neurobiological effects of the timing and buffering of stressful life events.

2. Brain development and sensitive periods

The brain undergoes dynamic changes throughout the course of development, with important implications for how stress influences the brain and the efficacy of treatments targeting stress-related mental illness at different developmental time points. Nonhuman primate studies show that typical brain development is marked by an initial period of overproduction of synapses, followed by selective stabilization and elimination of a substantial proportion of synapses (Huttenlocher, 1979; Huttenlocher et al., 1982; Bourgeois and Rakic, 1993; LaMantia and Rakic, 1994). Human neuroimaging studies show corresponding patterns, in which gray matter volumes typically peak around 10–12 years of age (Giedd et al., 1999), with significant gray matter loss throughout adolescence and adulthood (Sowell et al., 2001, 2003). Simultaneously, increases in white matter occur through myelination of axons (Brody et al., 1987; Benes et al., 1994). Substantial regional variation exists, with maturation of low-level sensory and motor cortices occurring prior to prefrontal and temporal cortices involved in higher-level cognition and regulation of behavior (Yakovlev and Lecours, 1967; Benes et al., 1994; Sowell et al., 1999, 2001; Gogtay et al., 2004). Such regional changes in brain structure and function across development, as well as changes in the availability of neurochemicals and patterns of cortical cell firing, are posited to lead to transient imbalances that underlie behavioral changes

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during adolescence (Galvan et al., 2006; Casey, Galvan, Getz, 2008). These dynamic changes in brain and behavioral development likely influence how stress at unique developmental time periods alters the brain and how children and adolescents cope with stressors. Exacerbations of transient imbalances in brain circuitry, such as the effects of acute or chronic stress, may lead to altered stress reactivity and ultimately increase the risk for mental illness.

Understanding neurodevelopmental changes that influence stress reactivity and recovery are critical for enhancing mental health. Sensitive periods refer to times in development when heightened neuroplasticity renders the brain especially amenable to environmental influences (Moriceau and Sullivan, 2006; Callaghan and Richardson, 2011; Yang et al., 2012). The timing of sensitive periods differs by neural circuit and behavioral system, but it may be that sensitive periods occur when brain development is most dynamic, such as infancy and adolescence (Fig. 1). During these periods, environmental input can lead to a series of developmental cascades (Masten and Cicchetti, 2010) that ultimately have significant influences on behavior, of a positive *or* negative nature. A sensitive period may render the brain more capable of responding to stress in adaptive ways. It could also magnify consequences of stressful life events in maladaptive ways. By contrast, stress that occurs during windows of reduced plasticity (e.g., after the closing of a sensitive period) may yield a brain that is less capable of remodeling itself. Thus, sensitive periods in neurodevelopment may render the developing brain more vulnerable to the effects of later stress, but they could also serve as windows of opportunity, during which there is increased potential for positive adaptation or effective intervention.

Delineating sensitive periods could reveal how the effects of stress differ depending on when in development and what type of stress occurs, as well as when in development certain types of intervention may be most effective for buffering against maladaptive consequences of stress. In this way we may begin to direct the timing and type of interventions at the level of the individual and the nature of the stressor. The extent to which neuroplasticity and brain function change throughout childhood and adolescence suggests that interventions based on the adult brain cannot be simply applied to youth who experience stress-related mental health disorders (Lee et al., 2014). Understanding how sensitive periods shift, constrict, or expand in individuals at different points in development will allow treatments to precisely target the biological state of the developing brain to optimize stress-related interventions.

3. Neurobiology of stress

Studies of mature animals have provided the majority of extant knowledge on the effects of stress at the cellular level and show that stress can significantly remodel brain structure and function (reviewed in McEwen, 2012). Stress results in changes in frontolimbic circuitry that are regional in nature. Chronic stress can lead to hypermetabolism and morphological changes within the amygdala, which is critical for learning about the emotional significance of environmental cues and helping the organism react to the challenge or threat of these cues. In contrast, chronic stress downregulates the hippocampus and prefrontal cortex (PFC), which regulate the stress response. Specifically, studies of rodents show that stress increases dendritic arborization and spine density of the amygdala, with concomitant increases in anxiety-like behaviors (Vyas et al., 2002; Vyas et al., 2003; Mitra et al., 2005). By contrast, stress results in atrophy of the hippocampus and medial PFC (mPFC) (Magariños et al., 1997; Vyas et al., 2002; Radley et al., 2006). Parallel findings of increased amygdala volume and functional reactivity, smaller hippocampal volume, and altered prefrontal function and connectivity have been observed in humans following stress (Ganzel et al., 2007, 2008; Liston et al., 2006; Liston et al., 2009; Sheridan et al., 2012a,b).

The reversibility of the effects of stress is regional as well. There is a growing body of evidence to suggest that the hippocampus and PFC may have greater capacity for change or plasticity following stress with many of the effects being reversible following the termination of stress (McEwen, 1999; Vyas et al., 2004; Liston et al., 2009). In contrast, stress-induced amygdala morphology and volume changes seem to persist (Vyas et al., 2002; Adamec et al., 2005; Tottenham et al., 2010). Due to its cellular properties, the amygdala

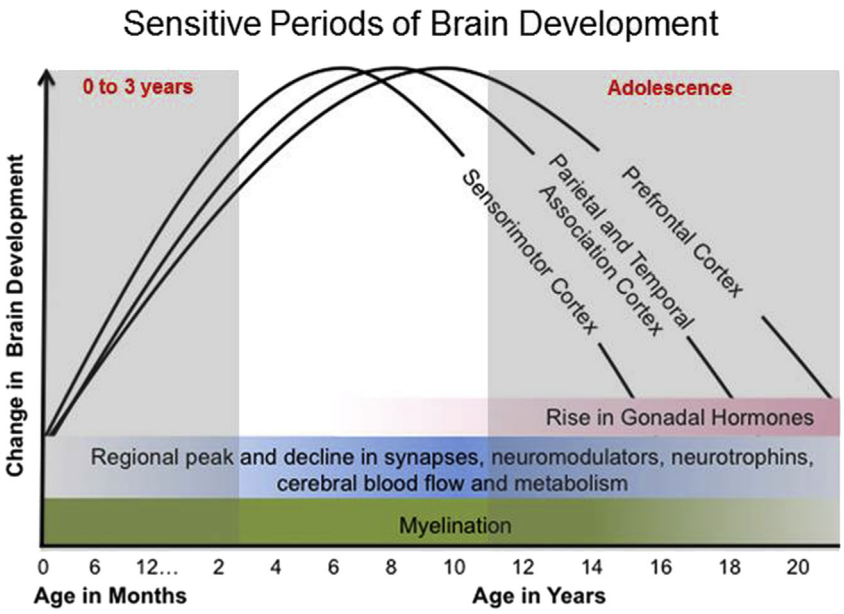

Fig. 1. Model of sensitive periods of brain development. Periods of rapid and substantial changes in brain development, such as the first three years of life and adolescence (shaded in gray), may provide the most opportunity for adaptive behavioral changes. These sensitive periods of neural development may also render the developing brain most vulnerable to the effects of stress. Figure adapted with permission from Lee et al., 2014 (Copyright 2014 AAAS).