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Review

Identifying key features of early stressful experiences that produce stress vulnerability and resilience in primates

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ABSTRACT

This article examines the complex role of early stressful experiences in producing both vulnerability and resilience to later stress-related psychopathology in a variety of primate models of human development. Two types of models are reviewed: Parental Separation Models (e.g., isolate-rearing, peer-rearing, parental separations, and stress inoculation) and Maternal Behavior Models (e.g., foraging demands, variation in maternal style, and maternal abuse). Based on empirical evidence, it is argued that early life stress exposure does not increase adult vulnerability to stress-related psychopathology as a linear function, as is generally believed, but instead reflects a quadratic function. Features of early stress exposure including the type, duration, frequency, ecological validity, sensory modality, and developmental timing, within and between species, are identified to better understand how early stressful experiences alter neurobiological systems to produce such diverse developmental outcomes. This article concludes by identifying gaps in our current knowledge, providing directions for future research, and discussing the translational implications of these primate models for human development and psychopathology.

Contents

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1. Introduction

The long-term effects of early social experiences on developmental outcomes are of high significance. This is because early experiences occur during a time of extraordinary brain plasticity, when the brain is maximally capable of being programmed in an enduring way (Knudsen, 2004). In an effort to understand the role of social relationships in fostering normative brain development, non-human primate (hereafter primate) models have historically focused on the developmental neuropathology of disrupted parent-offspring relationships. This research has shown that the stress of early parental loss, neglect, or abuse produces enhanced fear and anxiety, increased anhedonia, impaired cognition, abnormal brain neurochemistry and neurobiology, and alterations in baseline activity as well as stress reactivity of the hypothalamic-pituitary-adrenal (HPA) axis (Coplan et al., 1998; Law et al., 2009; Maestripieri et al., 2005; Pryce et al., 2005; Rosenblum et al., 2001; Sanchez et al., 1998; Stevens et al., 2009; Suomi, 1997). Parallel research in human populations likewise has established that traumatic experiences in childhood impair the acquisition of appropriate coping skills, impair corticolimbic brain systems that regulate stress and anxiety, produce abnormal baseline and stimulated HPA axis functioning, and increase the risk for the development of mood and anxiety disorders in the aftermath of subsequent stressors experienced in adulthood (Agid et al., 1999; Heim et al., 2004; Lupien et al., 2009; McEwen, 2007; Repetti et al., 2002). These collective research efforts have produced profound scientific insights, but have also lead to the prevailing notion that the consequences of early life stress exposure are invariantly deleterious. This view of early life stress exposure is thus best conceptualized as a linear function, whereby each incremental "dose" of early life stress increases subsequent vulnerability to later psychopathology.

There is accumulating evidence, however, that early life stress exposure produces a diverse range of developmental outcomes, including resilience to subsequent stressors encountered in adulthood. For example, in humans, childhood stress has been linked to diminished increases in salivary cortisol responses to the Trier Social Stress Test (Gunnar et al., 2009), lower cerebrospinal fluid (CSF) levels of corticotropin-releasing-factor (CRF) in healthy adults (Carpenter et al., 2004), and diminished cardiovascular responses during stressful laboratory tests (e.g., mental arithmetic, videogame performance, hand submersion in ice water) (Boyce and Chesterman, 1990). Prior stressful experiences also diminish emotional distress in day care settings and hospital admissions (Holmes, 1935; Stacey et al., 1970), and women and men are found to better cope with stressful events (e.g., spousal loss, major accident, illness, work stress) if they previously experienced and successfully coped with stressors in childhood (Forest, 1991; Khoshaba and Maddi, 1999). When early life stress exposure is examined across a continuum, adults exposed to moderate levels of early life stress exhibit lower levels of state anxiety (Edge et al., 2009) and more resilient cardiovascular responses to a stressful motivated performance task (i.e., what subjects believed was an intelligence test) (Seery, under review) compared to individuals exposed to either low or high levels of early life stress. These empirical studies suggest that early life stress exposure may be best conceptualized as a quadratic, rather than linear, function.

In the early 1980s, Garmezy et al. (1984) detailed a process-oriented "Challenge" framework by which to view the effects of early life stress exposure. In this model, stress exposure is viewed as a potential enhancer of future competence, provided the degree of stress is not excessive. Whereas severe early life stress exposure generally undermines the development of resilience and leads to vulnerability (Bebbington et al., 1993; Brown et al., 1994; Frank et al., 1994; Paykel, 1978), mild or moderate early life stress exposure may protect against these deleterious effects. Specifically, milder forms of adversity may provide a challenge, that when overcome, produces competence in the management of, and enhanced resistance to, subsequent stressors (Boyce and Chesterman, 1990; Fergus and Zimmerman, 2005; Garmezy et al., 1984; Haglund et al., 2007; Huether et al., 1999; O'Leary, 1998; Rutter, 1993). This phenomenon has been variously described in the literature as "inoculating" (Boyce and Chesterman, 1990; Eysenck, 1983; Parker et al., 2004), "immunizing" (Levine et al., 1989; Rutter, 1987; Seligman et al., 1975), "steeling" (Rutter, 1985, 1993), "toughening" (Dienstbier, 1989; Miller, 1980), and "thriving" (O'Leary and Ickovics, 1995).

Despite a growing appreciation for the complexity of early life stress effects on developmental outcomes, progress in this research field has been hampered by a tendency to label early life stress exposure based on the outcomes it produces. Thus, early stressful experiences that produce vulnerability to stressors later in life are labeled "severe" or "adverse" and those that induce resilience to subsequent stressors are labeled "mild" or "moderate". Not only are these definitions circular, they also preclude identification and detailed analyses of the key components of stressors, which contribute to whether stressful experiences produce deleterious or adaptive outcomes. Such detailed analyses may be difficult to do in human studies, in which early stress exposure is often documented retrospectively and through subjective rather than objective measures. Primate models of early stress and development therefore allow us to more clearly assess the relationships between the characteristics of early stressors (e.g., type, duration, frequency, ecological validity, sensory modality, developmental timing) and their developmental outcomes (i.e., stress vulnerability or resilience).

In this article we review various primate models of early stress and development within the broader context of animal model research. Examples from two types of animal models (maternal separation paradigms and maternal behavior paradigms) are reviewed. We discuss the benefits and limitations of each model in terms of its feasibility of use, its effectiveness in generating the expected developmental outcomes, its ecological validity, and its potential to enhance our understanding of how early stressful experiences produce stress vulnerability and resilience in human populations.

2. Necessity of animal models of early stress and development

Animal models of early stressful experiences are required because human studies have a variety of important limitations. Randomized longitudinal studies of stress exposure under otherwise identical conditions are rare in children. Because randomization to stress vs. no-stress control conditions is required for causal inference, and opportunities for randomization of children to stress exposure are limited due to ethical concerns, many studies of childhood stress exposure are thus necessarily correlational in nature. The collection of long-term follow-up data from longitudinal studies may take decades to complete, and cost considerations for such longitudinal studies are often prohibitive in humans. Given these constraints, animal research that examines how early experiences shape social, emotional, and cognitive capacities that have a lasting impact in adulthood is extremely valuable and provides a viable addition to human studies (Knudsen, 2004).

The benefits of animal models of human development are numerous. Animal studies using randomization allow for strong causal inference. Early life environments can be rigorously controlled in animals, and this allows for the exclusion of extraneous sources of variation inherent in developmental or retrospective