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Review article

Studying longitudinal trajectories in animal models of psychiatric illness and their translation to the human condition

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ABSTRACT

Many forms of psychopathology and/or psychiatric illness can occur through the pathways of altered environmental sensitivity, impulsivity, social functioning, and anxious responding. While these traits are also heritable, environmental conditions are known to play a critical role. The genetic factors that contribute to these traits may be adaptive in certain contexts, but can – under the environmental conditions commonly faced among modern humans – also be key moderators of risk for psychopathological outcomes. This article will discuss how animal studies inform us of the various environmental mechanisms through which prenatal or early postnatal environmental challenge can produce long-term effects on behavior and will briefly address how pre-copulatory, pre-natal and early postnatal epigenetic effects can contribute to persistent alterations in offspring behavior. Its main focus will be how nonhuman primate studies have helped us to understand how genetic vulnerability factors can moderate responses to early environmental factors, suggesting pathways through which early stress might produce long-term effects, thus pointing to systems that might moderate risk for psychiatric illnesses in humans.

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nonhuman primate studies have helped us to understand how genetic vulnerability factors can moderate responses to early environmental factors, suggesting pathways through which early stress might produce long-term effects, thus pointing to systems that might moderate risk for psychiatric illnesses in humans.

1. The role of early life stress on future vulnerabilities to reactivity and psychopathology

"Stress" is a universal condition of life but, if it is chronic, severe or occurs during critical developmental windows, it contributes to a variety of disease vulnerabilities, particularly disorders of the brain (McEwen, 2006, 2007). In humans, there are known links between prenatal or early stress and a variety of psychiatric and developmental disorders, including depression, schizophrenia, autism spectrum disorders, post-traumatic stress disorder, anxiety disorders, and substance use disorders (Neigh et al., 2009; Sinha, 2008; Sinha and Li, 2007). A major advantage to using animal models is the ability to follow animals prospectively from or before birth or and to then control environmental exposure. As such, many studies have been performed using animal models in order to determine how early manipulation of the mother or offspring induces long-lasting changes in neurophysiology and behavior.

One of the most commonly used "stressors" in this type of research is to subject infants to short-term or prolonged maternal deprivation. Mothers, caregivers and alloparents are critical to offspring development, not only because they provide nourishment, but because they also provide protection from predation and danger (reviewed in Barr, 2013). Mothers and infants develop strong attachment bonds, which serve to keep an infant in close proximity and also afford its localization during periods of separation. Because of this strong attachment bond, mothers are thought to be able to "buffer" environmental stressors and down-modulate their infants' levels of emotionality during periods of real or perceived stress, while providing security, allowing the infant to eventually become self-reliant as it uses its mother as a secure base from which to explore (Harlow, 1969; Harlow and Harlow, 1965). In addition to these factors, mothers are critical to the development of the behavioral inhibition system, as they teach their infants how to inhibit inappropriate or dangerous social and non-social behaviors while reinforcing appropriate social behaviors with contact and grooming (Harlow, 1969; Harlow and Harlow, 1965).

Early infant development is a time of high brain plasticity and intense mother-infant interaction. For an infant, the mother's behaviors and other cues (i.e., hormones in the milk, pheromones, etc.) are the main source of information about the external environment and about the environment to which an infant must adapt. An early period of enhanced environmental sensitivity has been documented in wild, laboratory, and domestic animals, alike. In 1937, the ethologist, Konrad Lorenz, defined a "critical period" for social bonding during early development (Lorenz, 1937). In 1979, Bateson later modified the nomenclature, instead referring to a "sensitive period", which he described as a developmental phase during which events are particularly likely to produce prolonged effects on an individuals (Bateson, 1979). For domestic animals, it is known that early exposure to other conspecifics and members of other species can influence the degree to which an animal interacts socially with members of other species as an adolescent or adult. At the same time, during this period, if animals are deprived of maternal care at an early time-point, despite the potential for extensive interaction with human "alloparents", they may be at risk for developing inappropriate behaviors, heightened anxiety, and social attachment disorders (reviewed in Overall, 1997).

More than 50 years ago, studies performed by Levine (Levine, 1970) showed that, in rodents, early experience as determined by the extent and quality of maternal care, produced long-lasting alterations in HPA (hypothalamic-pituitary-adrenal) axis activity (the major endocrine stress system), fearfulness and social behaviors. In the laboratory, these studies were rapidly replicated and expanded (Meaney and Szyf, 2005; Roman et al., 2005, 2006). While these studies performed in rodents are foundational and have been critical to our understanding of the epigenetic mechanisms driving behavioral effects related to variation in maternal care, there are limitations to the rodent models. The relative levels of expression and distributions of key mediators of stress responses differ between catarrhine primates (old world monkeys, apes and humans) and other animal species, and of particular relevance to studies modeling effects of early adversity, other laboratory animal species (rodents) are hyporesponsive to stress during the first several weeks of development, with delayed maturation of the endocrine stress response. This is not the case in humans and other catarrhine primates, such as the rhesus macaque (Sanchez et al., 1999) (Fig. 1).

One manipulation that has been demonstrated to produce long-lasting effects on behavior in nonhuman primates (rhesus macaques, *M. mulatta*) is maternal deprivation in the form of nursery or peer rearing. As with other primate species, rhesus macaque mothers invest much of their energy into defending, comforting and caring for their infants, and this maternal buffering appears to be critical to normal infant development (Suomi, 1982). In the so-called "peer rearing" condition, subjects are removed from their parents at birth and reared with other age-matched infants, so that they develop in the absence of adult influence (Chamove et al., 1973; Harlow and Suomi, 1974). Peer-reared (PR) monkeys develop strong bonds with their age mates and use them as bases from which to explore. When compared to their mother-reared counterparts, however, peer-reared subjects exhibit evidence of insecure attachment, higher levels of anxiety, and lower levels of exploration in novel settings (Suomi, 1982). Because their peers do not necessarily punish inappropriate behavior, they also can have impaired development of the behavioral inhibition system, and, as in humans, macaques that have been exposed to early adversity (in the form of peer-rearing) show long-lasting differences in brain function and behavior (Higley et al., 1991; Spinelli et al., 2009, 2010; Suomi, 1982).

Other forms of early stress involving manipulation of the mother-infant interaction, but not the infant itself, have been proposed to be more translatable to the human condition and have demonstrated very interesting, while potentially more subtle and varied, effects. Notable among these is a "Foraging Demand" paradigm, in which the environmental factor acts as a stressor for both mother and infant independent of active human intervention (Rosenblum and Paully, 1984). In these paradigms, the degree to which a mother must work to obtain food is varied. As such, this is a stressor that produces energetic demands on the mother and emotional stress for both mother and infant, resulting in variation in both the quality and quantity of maternal care. In a macaque species closely related to the rhesus macaque (the bonnet macaque, *M. radiata*), studies have been performed to examine the effects of constantly high levels foraging demand on measures of stress reactivity and infant attachment. When tested later, it had been reported that infants were more reactive to maternal separation than were infants raised under a low foraging demand condition (Andrews and Rosenblum, 1991; Kinnally et al., 2013; Rosenblum and Paully, 1984). In later studies, animals were assessed longitudinally after having been subjected to a condition in which mothers were intermittently exposed to food scarcity, making the environment unpredictable for both mother and infant, and also resulting in repeated, cyclical exposures to stress. These studies examined not only infant reactivity during maternal separation, but also looked at the responses to mother interaction during periods