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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.

Keywords

Primate; Genetic; Stress; Social attachment; OPRM1; CRH; Serotonin transporter

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 maybe 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

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Appendix A. Supplementary data

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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 Pauly, 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 of reunion, in order to more accurately model human attachment studies (Ainsworth et al, 1978). Following brief periods of maternal separation, for infants reared by mothers subjected to unpredictable forage, there was increased reluctance to leave close contact with the mother in order to explore. This is reminiscent of certain subtypes of insecurely attached human toddlers as reported by Ainsworth and colleagues (Strange Situation Test).

However, the effects of these types of manipulations are sensitive to variations and differently so across species. The early studies performed in rats that described effects of daily brief maternal separations demonstrated long-term suppression of behavioral and endocrine stress responses (Meaney et al., 1991). Though initially believed to be counterintuitive, it was later determined that the separation itself was not important, but that maternal attention during periods of reunion (with increased arched back nursing and licking and grooming) was the factor that produced long-lasting effects on stress resilience (Caldji et al., 1998). Similar findings have been reported in other rodents or nonhuman primates. Squirrel monkeys (*S. sciureus*) that are repeatedly exposed to maternal separation and reunion exhibit a “stress inoculated” phenotype, in that they exhibit persistent stress resistance (Parker et al., 2004). However, unlike in rats, this resistance is independent of maternal behavior during periods of reunion. Similarly, there are species differences in responses to foraging demand manipulations of the dam. For example, while when rat dams are required to leave the nest cage in order to feed, they provide higher levels of licking and grooming during periods of mother-litter contact, the same manipulation in mice results in the in a more passive nursing style/posture, a measure of deficient maternal care (Coutellier et al, 2008). To further complicate the picture, rat pups reared under these paradigms demonstrate long-lasting resilience, as would be expected, but mouse pups are differentially reactive, and in a sex limited way (Coutellier et al., 2009). For both species, however, there were increased incidences of socio-positive behaviors, indicating that the effects of maternal manipulation produces similar effects on motivations to seek social contact across species.

2. Expanding the window of exposure and definition for “early life stress”

Decades ago, Hans Selye described the physiological response to stress as the general adaptation syndrome (Selye, 1956, 1973). He defined stress as “the nonspecific response of the body to any demand made upon it”. Various stimuli, including hemorrhage, extremes of temperature, exercise, ischemia, infectious disease, and emotional stress, are considered to be “stressors.” The endocrine stress response occurs in order to counter these “threats to homeostasis” and is comprised of the secretion of corticosteroids from the adrenal cortex as

well as that of catecholamines from the adrenal medulla. Selye described the stress response as being composed of three discrete phases: 1) the “alarm reaction,” which pertains to the release of stress hormones from the adrenal gland; 2) “resistance,” which refers to the successful adaptation of the organism to the stress; and 3) “exhaustion” of the system, where the ability to adapt is lost. In other words, although the acute stress response is an adaptive one, it will ultimately become maladaptive after repeated or chronic stimulation. As a result, chronic stress can potentially have deleterious consequences. Selye also proposed that every individual is born with a given amount of “adaptive energy” and that this energy is progressively reduced with each stressor. An animal will, therefore, become less able to adapt to novel stressors as a function of age or chronicity of stress exposure (Selye, 1956,1973).

In a wide variety of animal species, individuals or strains that are particularly stress-reactive may be more likely to survive and reproduce successfully in highly variable or stressful environments. Over the course of human evolution, however, selective pressures have shifted, as have the nature and chronicity of stress exposures. In fact, in modern society, highly stress-reactive individuals, who are no less likely to be eaten by a predator (predation not being a major cause of mortality in modern humans), may instead be more likely to fall susceptible to various-stress related disorders, including chronic infections, diabetes, heart disease, accelerated brain aging, stress-related psychiatric disorders, and even drug and alcohol problems. In his book “Why Zebras Don’t Get Ulcers”, Robert Sapolsky explains how the human condition is such that we are constantly overburdening our supply of adaptive energy (Sapolsky, 2004). Whereas our stress response evolved for the benefit of short-term gain at the expense of other non-emergent functions, such as reproduction, inflammation, food intake, and neuroplasticity, we have adopted a lifestyle that embraces chronic emotional stress, which has wreaked havoc on our abilities to cope and has led to a condition in which the chronicity and nature of stress exposures to our offspring are at an extreme. Besides the lifestyle of chronic work and social related stress adopted by some modern humans, there is the potential for concomitant addition of “new” exposures to agents of our own design, for example, environmental contaminants in foodstuffs, psychotropic medications, or drugs of abuse/alcohol. Such factors could produce long-lasting effects on behavior and reactivity in infants, but could also act similarly during fetal development. These are discussed in the sections below.

2.1. Toxins

There are certain anthropogenic agents that are thought to affect pre-and post-natal development in humans (for example, polychlorinated biphenyls, Bisphenol A, and pesticides- (Boersma and Lanting, 2000; Faroon et al, 2000; Komada et al., 2014; Naule et al, 2014; Panagiotidou et al., 2014). Animal studies have shown that there are neurodevelopmental effects resulting from exposures to such compounds, with behavior and neuroendocrine responses persistently dysregulated (Naule et al., 2014; Panagiotidou et al, 2014). Some of these effects have been shown to persist across generations, pointing to a potential role for epigenetic mechanisms, though they may also produce effects via alterations in maternal behavior (reviewed in Rosenfeld, 2015). Many of these compounds have been shown to influence estrogen and androgen receptor signaling in tissue- and dose-

dependent manners (Grimaldi et al., 2015), and there is evidence that dams exposed during pregnancy and after exhibit deficits in maternal care (Boudalia et al., 2014). The trans-generational effects of these toxins on infant neurodevelopmental outcomes could also be attributable to epigenetic phenomena, to a suboptimal early post-natal environment, or to both (Cummings et al., 2010; Wolstenholme et al., 2013).

2.2. Alcohol

Alcohol and drugs of abuse may produce similar patterns. For example, among women who consume alcohol during pregnancy, there is risk for neurodevelopmental defects in the offspring (Vall et al., 2015). For those who continue to drink in the post-partum period, there is not only risk for continued exposure to alcohol among infants of lactating mothers, but also, if consumed at levels producing high levels of intoxication, disruption in maternal care (Popoola et al., 2015; Workman et al., 2015). In studies performed with rats, exposure of the fetus to alcohol in utero via maternal intake and/or postnatally can produce persistent alcohol preference in offspring. While intoxication of the dam postnatally impairs pup retrieval and nursing, adversely affecting maternal care, dams exposed to alcohol throughout pregnancy, on the other hand, are better able to tolerate alcohol, retrieve pups during periods of intoxication, and thus facilitate access of pups to alcohol-contaminated milk (Pueta et al., 2008). Because interaction with the mother, nursing, and alcohol exposure are all factors that could recruit the reward system, it is not surprising that alcohol preference persists among these offspring (Pepino et al., 2004; Ponce et al., 2011; Pueta et al., 2008). Studies in rhesus macaques show that prenatal exposures to alcohol result in persistent differences in pre-pulse inhibition (Schneider et al., 2013), and other studies show interactive effects of stress and alcohol, such that offspring show alterations in dopamine-system function, HPA-axis activity, and exhibit a sensory processing disorder-like phenotype, all of which are observed among individuals with autism spectrum disorders, ASD (Converse et al., 2013; Schneider et al., 2004, 2008). Since alcohol preference and stress reactivity are traits that are heritable, it may be that genetic vulnerability factors could interact with pre-and post-natal ethanol exposure to predict future vulnerabilities. One such candidate could be the Mu-Opioid receptor (*OPRM1*) gene (Fig. 2).

2.3. Inflammation

As stated above, one role of the activation of the stress axis (and both corticotropin releasing hormone, or CRH, and corticosteroid release) is to decrease inflammation. Interestingly, under certain circumstances or in specific tissue types, stress has been shown to produce the opposite effect. Maternal stress and infection have been associated with increased risk for neurodevelopmental disorders, such as schizophrenia, attention deficit hyperactivity disorder (ADHD) and the ASDs (Brown, 2012; Howerton and Bale, 2012). The developing placenta is critical to the transmission of information from the mother to its offspring, and studies performed in rodents and cavies demonstrate that early prenatal stress produces heightened stress sensitivity and diminished cognitive function in a stress-exposed dam's offspring, especially among males (Bronson and Bale, 2014). These effects have been shown to occur through inflammatory mediators, including pro-inflammatory cytokines. In dams exposed to prenatal stress, both cytokine levels and the resultant behavioral

phenotypes of the male offspring are rescued when dams are treated with anti-inflammatory agents (Bronson and Bale, 2014).

Other studies show a role for neuroinflammation independent of stress on offspring behavioral stress regulation and neurodevelopment (Howerton et al, 2014). When targeted post-natally, both male and female animals in which neuroinflammation is induced at the dorsal raphe nucleus (the origin of most serotonergic pathways in brain) exhibit a “manic”-like phenotype, that is, increased stress-induced locomotion and reduced risk aversion and fearfulness. This is of interest in that among patients presenting with psychosis, such as those with schizophrenia or bipolar disorder, altered cytokine profiles have been observed clinically (Kalia and Costa, 2015; McNamara and Lotrich, 2012; Mitchell and Goldstein, 2014; Myint, 2013; Reus et al., 2015). Also of interest, many autoimmune conditions include symptoms such as irritability, irregularity in emotionality, impaired impulse control, and distractibility, and patients with synaptic autoimmune encephalitis are commonly first treated following presentation with manic behavior (discussed in Rege and Hodgkinson, 2013). All of these point to a potential role for neuroinflammation in the etiology and progression of various psychiatric phenotypes.

There is also a literature examining the role of neuroinflammation in the etiologies of schizophrenia and autism. Various findings support these links (Arion et al., 2007; Patterson, 2009; Vargas et al, 2005), and epidemiological studies show that maternal infection can increase an offspring’s risk for developing these disorders. It is proposed that prenatal infection/inflammation could not only induce neurodevelopmental effects, but could produce a “subclinical, inflammatory-like state” (Patterson, 2009), resulting in alterations in behavior across the lifespan. Various animal models have supported a role for infection and inflammation in adolescent and adult behavioral outcomes. Rodent dams infected with the flu virus or given immune system stimulators, such as poly I:C or lipopolysaccharide (LPS), produce offspring exhibiting long-lasting deficits in social interaction, sensorimotor gating, and exploration (Shi et al, 2003). In pregnant mice and rhesus monkeys, it has been shown that by administering antibodies obtained from human mothers that had given birth to children with autism, offspring are observed to exhibit persistent deficits in social behavior, increased acoustic startle, and altered frontal lobe volumes, particularly among males (Singer et al., 2009).

3. The role for epigenetic processes in driving persistent effects of early stress exposures

Adaptations to unpredictable or stressful environmental conditions can occur at both the species and the individual levels. While adaptation at the species level occurs through genetic polymorphism, short-term adaptation (which can also be heritable, albeit for a limited number of generations) can occur through epigenetic processes. It is proposed that epigenetic effects act as a potential conduit for informing offspring and preparing them for potential environmental challenges (Agrawal et al, 1999). One prominent example of such an epigenetic phenomenon as it relates to early life stress exposure and maternal care comes from work by Meaney, Szyf and colleagues (Meaney and Szyf, 2005). This body of work

demonstrates, among many other epigenetic effects, that early life stress in both rodents and humans results in long-lasting, epigenetically-driven decreases in hippocampal expression of glucocorticoid receptor (GR, or *NR3C1*) (McGowan et al, 2009) via alterations in DNA methylation. Hippocampal GR is thought to be involved in engaging the fast-feedback “brake” on the HPA axis and, therefore, to be important for termination of the endocrine stress response (Liberzon et al, 1999). Disruption of this brake and a resultant persistence of elevated levels of corticosteroid have been observed in a number of stress-related psychiatric disorders.

It is difficult to disentangle epigenetic effects and environmental effects when considering epigenetic transmission through the maternal germ line, since stress or other factors (i.e., alcohol or drugs of abuse) can both produce epigenetic effects and influence early maternal care (reviewed by Toth, 2015). This being said, there is evidence that stress exposures in the sire can also induce long-lasting effects in behavior and responsivity in the offspring. Rodent studies indicate that male exposures to social stressors, dietary challenge, and drugs of abuse can be transmitted through epigenetic marks present in spermatozoa. Although epigenetic processes are typically considered to occur through histone or deoxyribonucleic acid (DNA) modifications, microRNAs present in the gametes can also produce trans-generational effects. MicroRNAs represent dynamic, rapidly responding mechanisms for epigenetic regulation that, unlike other epigenetic marks, are less subject to being “erased” during early embryogenesis and, therefore, have the potential to persistently regulate gene expression and behavior in the offspring. Rodent studies support a role for this mechanism. Bales and colleagues have shown that offspring of sires exposed to pre-copulatory stress exhibit persistent dysregulation of HPA-axis responses to stress, identifying some of the microRNA species (and their downstream targets) that are potentially involved (Rodgers et al., 2013).

4. Early stress exposure and alternative strategies

Whereas environmental reactivity and both behavioral and endocrine stress responses are critical to an individual’s survival, both hyper- and hypo-activation of these systems can lead to various stress-related pathologies. Yet, across a wide variety of animal species, it is common for there to be individuals on both extremes that are highly represented (Korte et al., 2005). Several decades ago, Maynard Smith applied “Game Theory” to animal behavior and found that aggression and fearfulness are traits that tend to balance each other in any social population (Maynard Smith, 1976). He described the “Hawk-Dove game” in which ‘Hawks’ (aggressive individuals, who were proactive and exhibited a fight-or-flight response to stress) and ‘Doves’ (who were fearful, cooperative and adopted a freeze-and-hide stress response) were likely to co-occur in the same species. He determined that both ‘Hawk’ and ‘Dove’ strategies could potentially be adaptive, perhaps especially so in certain environmental contexts. While ‘Hawks’ would do better when food was abundant and population density high, since they are better at fighting for access to mates than foraging), ‘Doves’ would likely outcompete ‘Hawks’ when the opposite were true since they would excel at getting food during periods of scarcity and avoiding danger during times of increased conflict. The two temperaments must be balanced in any given population; in a population comprised completely of ‘Hawks’, excessive aggression would reduce the chances of an individual surviving to successfully reproduce, while an all-‘Dove’ population

would quickly be killed off by some other, more aggressive species. In other words, the presence of both behavioral types may be critical to the survival of the species, while at the same time, there will be selective pressure at the individual level, depending on life history, sex, and environmental context. It then stands to reason that the genetic factors that underlie these two alternative strategies would be likely to be subject to balancing selection and that, as a result, both types of traits or strategies will be observed among individuals of any social species.

There are a number of research groups that have been investigating genetic variations in the rhesus macaque that contribute to the expression of traits that have been linked with human personality and psychiatric disorders, all of which may map well onto the Hawk vs. Dove model (i.e., stress reactivity, behavioral dyscontrol, aggression and reward seeking/sensitivity) (Barr and Driscoll, 2014). Many of the variants that have been identified and studied in macaques are functionally similar to those present in humans, and some findings suggest convergent evolution, with the variants maintained by selection in both species (Barr et al, 2008a; Vallender et al., 2008). The macaque model has proven useful for learning how relatively common genetic variants, which are associated with traits that may be adaptive in certain environmental contexts, can also increase vulnerability to behavioral pathology (see supplemental text box and Lindell et al, 2012).

5. Longitudinal trajectories - candidate gene studies aid in understanding individual differences

More than a decade ago, two landmark papers were published in *Science* that demonstrated that early life adversity could predict future behavior in human subjects, but only as a function carrying a risk allele for the behavior. In the first of these, Caspi, Moffit and colleagues demonstrated that functional variable number tandem repeat (VNTR) in the monoamine oxidase A (*MAOA*) gene (previously linked to aggressive behaviors) resulted in increased incidence of conduct disorder as a function of prior stress exposure (Caspi et al., 2010). In the second, this same group demonstrated that a loss of function variant for serotonin transporter linked polymorphic region (*HTTLPR*), which had previously been linked to increased anxious responding (Heils et al., 1997), predicted increased vulnerability to depressive episodes in a dose-dependent manner (Caspi et al, 2002); Both the number of alleles and the number of stress exposures contributed to an individuals' risk. In other words, genetic variation moderated risk for developing behavioral or psychiatric problems in the face of environmental challenge. These studies created a lot of excitement and were foundational for gene by environment interaction ($G \times E$) studies in psychiatric genetics, but since then, much controversy over the validity of these approaches has arisen (Caspi et al., 2010; Risch et al, 2009). This section will discuss in detail several examples of how early stress exposure influences an individual's longitudinal trajectory as a function of genetic variation in the rhesus macaque. Both the neurobiological systems involved and the nature of the responses will be considered as they pertain to potential adaptive roles and risk for psychiatric illnesses, including the addictions.

5.1. Genetic factors that predict long-term increases in stress reactivity and anxious responding

Genetic vulnerability factors can moderate responses to early environmental stressors. Rhesus macaques provide an opportunity to examine $G \times E$ interactions in a controlled, prospective manner (Barr and Goldman, 2006; Barr et al., 2003, 2004a, 2004c). Not only can variables like diet, light-dark cycle, and other factors that are contributors to “noise” in human genetic studies be controlled, but environmental factors that might contribute to $G \times E$ interactions can also be applied in a controlled manner. Such factors commonly studied in behavioral research include alcohol exposure (prenatal or in adolescence/adulthood), acute challenge (e.g., the presentation of an intruder or separation from attachment sources), response to treatment (pharmacogenetics, including alcohol response), or early life stress (variable foraging demand or peer/nursery rearing) (reviewed in Barr and Goldman, 2006).

Of particular interest for the study of $G \times E$ interactions is variation within regulatory or coding regions of genes encoding stress-responsive signaling molecules, which may contribute to stress vulnerability or resiliency. The corticotropin releasing hormone (CRH, also known as corticoliberin and CRF, corticotropin releasing factor) system is the key integrator of behavioral and physiological adaptations to stress (Owens and Nemeroff, 1991). Hypothalamic release of CRH drives the “fight or flight” hormonal cascade that enables the life-preserving endocrine response to stress (Sapolsky, 2001). In concert, release of CRH from extrahypothalamic brain regions, such as the locus coeruleus, bed nucleus of the stria terminalis (BNST), and amygdala, mediates the autonomic and behavioral responses to stress (Vale et al, 1983) that underlie fear and emotionality (Schulkin et al, 2005). As such, the CRH system is critical for survival. However, chronic overactivity of the system can lead to stress-related pathology (Korte et al, 2005; McEwen, 2006). Studies in both non-primate and primate species have shown that upregulation of the CRH system can produce anxiety- and/or depression-like behavioral phenotypes (Gold and Chrousos, 2002; Kalin et al., 2000) and that CRH system upregulation, whether innate or due to environmental factors, can lead to escalated alcohol drinking (Sommer et al., 2008). The majority of the effects listed above are mediated through the corticotropin releasing hormone-1 (CRHR1) receptor subtype (Heinrichs and Koob, 2004), and for this reason, CRHR1 antagonists have been proposed for the treatment of stress-related disorders, including alcohol dependence (Heilig and Koob, 2007).

Most studies demonstrating a role for CRH system up-regulation in driving anxiety, stress reactivity, and alcohol seeking have been performed in rodents. However, the relative levels of expression and distributions of key mediators of stress responses differ between rodents and catarrhine primates (Sanchez et al., 1999). As such, demonstrating a link between increased CRH system activity and individual differences in behavior in a primate species provides critical support for the notion that rodent findings may translate to humans. There is a *CRH* gene promoter single nucleotide polymorphism (SNP) in rhesus macaques (−248C/T) (Barr et al., 2009), which is located in a region that is under purifying selection and has been demonstrated empirically to be critical for regulation of *CRH* expression (King and Nicholson, 2007). In vitro studies show that the −248T allele increases cAMP-stimulated *CRH* promoter activity, but also disrupts glucocorticoid-mediated repression,

indicating that this particular SNP would result in augmented *CRH* expression in response to stress. When effects of –248C/T genotype on stress responding are examined, the T allele predicts increased behavioral and endocrine responses to stress among monkeys with a history of early stress exposure. A similar pattern is observed for alcohol consumption. The fact that there is an SNP in the corresponding human region (–201C>T) (<http://genome.ucsc.edu/>) suggests that *CRH* promoter variation could interact with environmental stressors to increase stress responding and alcohol consumption in humans.

In humans, *CRHR1* haplotype predicts risk for developing alcohol dependence in the context of stress (Blomeyer et al, 2008; Schmid et al., 2010). In addition, it has been shown that individuals who are sexually abused as children are more likely to develop alcohol problems that persist into adulthood if they also are homozygous for the ancestral, H1 *CRHR1* haplotype. In all of these reports, what is demonstrated is that the rs1876831T allele-containing haplotype (H2) is protective against stress-induced alcohol problems. The study by Nelson et al. is of particular relevance to this review, as it demonstrates that genotype moderates the effects of early stress exposure on alcohol use, but that there are no effects of genotype alone for adult alcohol use or dependence (Nelson et al., 2010). More importantly, it examines dependent variables that are temporally distant from the timing of stress exposure (from childhood stress exposure to alcohol dependence during adulthood).

Perhaps the most extensively studied gene in psychiatric genetics and in nonhuman primate neurobehavioral studies is that encoding the serotonin transporter (Bennett et al, 2002). The serotonin transporter is a protein critical to regulating serotonin function in the brain since serotonin's action in the synapse is terminated by reuptake. In mice, targeted disruption of the serotonin transporter gene results in increased adrenocorticotrophic hormone (ACTH) and corticosterone responses to immobilization stress, as well as increased anxiety during the elevated plus maze and light/dark exploration tasks (Holmes et al, 2003; Lanfumey et al., 2000; Li et al., 1999). Gene expression studies demonstrate that monkeys with high levels of stress reactivity have lower gene expression levels for the serotonin transporter (Bethea et al., 2004, 2005).

In humans, there is a common, functional repeat length variant in the regulatory region for the serotonin transporter gene (*5-HTT*, or *SLC6A4*), producing long (*l*) and short (*s*) alleles. The *s* allele for this serotonin transporter linked polymorphic region (*HTTLPR*) predicts certain personality traits related to anxiety, depression, and aggression, such as neuroticism, harm avoidance, and disagreeableness (Lesch et al., 1997; Mazzanti et al, 1998). There is variation in the serotonin transporter gene regulatory region in many non-human primate species (Lesch et al., 1997; Wendland et al., 2006). In rhesus, a 21-bp insertion/deletion polymorphism, rh5-*HTTLPR*, has been shown to alter transcriptional efficiency (Bennett et al., 2002), resulting in decreased serotonin transporter mRNA levels in brains of macaques carrying the *s* allele, and this may be further regulated by epigenetic mechanisms (Kinnally et al., 2010). The 5-*HTTLPR* polymorphism has been studied extensively in both rhesus and human G × E studies.

Studies in multiple, independent laboratories demonstrate that the rh5-*HTTLPR* *s* allele predicts anxiety and responses to stress in rhesus macaques (Bethea et al., 2004; Champoux

et al., 2002). It has also been shown that *rh5HTT-LPR* genotype interacts with duration and number of stress exposures to predict the patterns and types of behavioral responses that macaque infants exhibit during early development (Spinelli et al., 2012). Other studies in rhesus show that *rh5HTT-LPR* genotype can interact with controlled exposures to prenatal stress/alcohol or early life adversity to result in long-lasting differences in stress reactivity, sensation seeking, aggression, and alcohol consumption (Barr et al., 2004c; Kraemer et al., 2008; Schneider et al., 2011; Schwandt et al., 2010; Spinelli et al., 2007). Alcohol consumption appears to decrease anxiety in various primate species. Consistent with this, studies have demonstrated that peer-reared female rhesus macaques carrying the *s* allele exhibit higher levels of alcohol preference than do *l/l* animals (Barr et al., 2004b), suggesting that they may be seeking alcohol for its anxiolytic effects. It may be that independent effects of genotype on anxiety and alcohol response converge to increase alcohol consumption among these subjects (Barr, 2013). These studies in rhesus have provided support for the notion that human *5-HTTLPR* variation may interact with stressful life experiences to moderate risk for stress-related alcohol consumption and other related disorders in humans (Caspi et al., 2003, 2010; Caspi and Moffitt, 2006).

5.2. G × E interactions and impulsivity in a high-risk environment

Impulsivity is a trait that is observed in many psychopathological conditions, from the personality disorders to attention deficit hyperactivity disorder (ADHD) to the addictions. It is a coping mechanism that, at certain life history stages and in certain environmental contexts, might be an adaptive one. The CRH system is one that is critical to behavioral responses to stress, and studies utilizing experimental manipulations of CRH system activity suggest that naturally occurring CRH gene variation may mediate individual variability in behavioral traits that are key to determining an individual's coping style. One of the most consistent behavioral correlates of CRH system activity is the way an organism approaches novelty and unfamiliar conspecifics (Kalin et al., 2000; Korte et al., 2005). Individuals that readily seek out and investigate novel stimuli are considered “exploratory” or “bold”; those more likely to show fear or withdrawal when confronted with new objects or individuals are described as more “inhibited” or “shy” (Kagan et al., 1988).

In humans, *CRH* haplotype has been shown to predict behavioral inhibition in children (Smoller et al., 2003), and studies in rhesus macaques suggest that human *CRH* variation may also moderate risk for alcohol use disorders, perhaps through the pathway of behavioral inhibition. A rhesus polymorphism (−2232C/G) that has similar in vitro functional effects to some *CRH* haplotypes reported in humans (Wagner et al., 2006) predicts decreased cerebrospinal fluid (CSF) levels of CRH, an intermediate phenotype demonstrated in individuals or strains characterized as being particularly extroverted, aggressive, or bold. Infant macaques carrying the G allele are characterized as being more exploratory and bold (Barr et al., 2008b), and, following adolescence, males that are G allele carriers exhibit a bolder and more active response to an unfamiliar conspecific. In rhesus macaques, this allele and early environmental stress in the form of peer-rearing produce additive effects on high-risk alcohol consumption and suggests that *CRH* variation may influence early or uncontrolled alcohol consumption in human populations (Barret al., 2008b).

Dopamine neurotransmission underlies many reward-dependent and reinforcing processes and also contributes to prefrontocortical inhibitory control. Tandem repeats in the third exon of the dopamine receptor D4 gene (*DRD4*) exist across a variety of species, including humans, vervets, dogs, dolphins, bears, raccoons, horses, and chimpanzees (see Larsen et al., 2005). Some species, including rhesus, pigtail, and Tonkean macaques, exhibit variation in the number of repeats present, with various alleles differing in frequencies across species (Livak et al, 1995; Wendland et al., 2006). In humans, the *DRD4* 7-repeat allele (7R) reduces efficacy of the receptor and is linked with traits such as sensation seeking (reviewed in Ptacek et al, 2011). A *DRD4* length variant has also been associated with novelty seeking in vervet monkeys (Bailey et al, 2007). In the dog, which has been subject to intense artificial selection, a repeat polymorphism predicts social impulsivity and activity-impulsivity endophenotypes (Hejjas et al., 2007; Wan et al, 2013). We recently identified 4R, 5R, 6R, and 7R alleles in a colony of rhesus macaques (Barr and Driscoll, 2014). Compared to the ancestral allele (4R), the loss-of-function 7R allele predicted increased physical aggression toward an unknown age- and sex-matched conspecific. Though little work has been published in animal models to examine stress by *DRD4* genotype interactions, studies performed in humans suggest that maternal stress during pregnancy predicts offspring vulnerability to ADHD, aggression and antisocial outcomes (Buchmann et al., 2014; Grizenko et al., 2012; Zohsel et al., 2014).

Another gene at which variation is linked to impulsivity and impulsive aggression in both animal models and in humans is the monoamine oxidase A (*MAOA*) gene. Monoamine oxidase A degrades the monoamine transmitters (dopamine, norepinephrine, and serotonin) and therefore can influence synaptic concentrations of these neurotransmitters. A variable number of tandem repeats (VNTR) polymorphism in the transcriptional control region for the human *MAOA* gene (*MAOA*-LPR) has been shown to produce differential transcriptional activity in vitro (Sabol et al., 1998). In humans, the *MAOA*-LPR low-activity alleles predict decreased prefrontocortical and increased amygdalar responses to emotional stimuli, suggesting impaired ability to control emotional responses during arousal (Meyer-Lindenberg et al., 2006). The low-activity *MAOA*-LPR allele has also been associated with trait-like, alcohol-independent antisocial behavior in alcohol-dependent populations (Samochowiec et al., 1999; Tikkanen et al., 2009), and various studies have shown that early environmental factors interact with genotype to predict antisocial behavior, aggressiveness, and violence (Caspi et al., 2002; Sjöberg et al., 2008). Other studies show that *MAOA* genotype is associated with alcohol dependence, age of onset of dependence, and comorbid drug abuse (Contini et al., 2006).

In rhesus macaques, the low-activity allele of rh*MAOA*-LPR contributes additively with peer-rearing to increase impulsivity, aggression, and alcohol consumption (Barr et al., 2004a; Newman et al., 2005). These studies in rhesus macaques support the notion that *MAOA* gene promoter variation may specifically increase the risk for conduct or personal disorders in which impaired impulse control and aggressivity are features, particularly among those exposed to early stress or lack of parental influence.

5.3. Early environment and the ontogeny of empathy

As a result of the importance of social connections and coalitions for mammalian survival and fitness, the neurobiological and behavioral systems driving sociality are highly conserved across species. The ability to share and be affected by the emotional state of a conspecific (social cognition, or empathy) is organized by basic systems subserving social attachment-related processes (Panksepp et al., 1997). These behavioral systems are critical because they not only predict social interactions, but are thought to be critically important in determining maternal behavior, which, as stated above, can have long-lasting effects on offspring health and behavior. Furthermore, the quality of early mother-infant interactions can also predict parenting style in the offspring.

Pharmacological and genetic studies suggest some of the processes relating to social attachment and cognition to exploit the physical pain system; The experience of social pain alerts an individual to environmental threats, inducing coping strategies aimed at their mitigation via increased social connections (Macdonald and Leary, 2005). Systems known to be involved in the evolution of these processes are those affecting the vasopressin/oxytocin systems, the endogenous opioids and the dopamine and serotonin systems (Decety et al., 2012). These motivations are also adaptive through driving caregiving behavior and development of the mother-infant bond, and can even extend to phenomena such as paternal altruism.

The endogenous opioid system is critically involved in alleviating pain and in driving the euphoric and stimulating effects of rewarding experiences. In both humans and rhesus macaques, polymorphisms in the *OPRM1* gene (*OPRM1* A118 G and C77G, respectively) alter affinity for β -endorphin in vitro (Bond et al., 1998; Miller et al., 2004). In both species, HPA responses to stress are blunted among G allele carriers, suggesting functional similarities of the polymorphisms among the respective species (Bond et al., 1998; Schwandt et al., 2011). The *OPRM1* variants present in human and in rhesus macaques not only predict responses to artificial rewards, such as alcohol, but to natural, social rewards as well (a.k.a., social rejection in humans; see Way et al., 2009). In free-ranging rhesus macaques, *OPRM1* genotype affects maternal care, but only among maternal subjects with high levels of oxytocin, the neurohormone critically important in parturition and lactation, but also in the formation of the mother-infant bond (Higham et al., 2011). Longitudinal studies performed in rhesus show that the 77G allele predicts increased expression of attachment of an infant to its mother, and this is particularly true following repeated exposure to periods of maternal separation (Barr et al., 2008a). This finding has been supported by a cross-sectional study performed using a sample of human children aged 9–13, in which various measures of attachment to the caregiver were increased as a function of parental inconsistency or unavailability (Copeland et al., 2011). Of interest, polymorphisms affecting this system have also been implicated in alcohol-mediated reward and may, therefore, also increase vulnerability to alcohol abuse and addiction. Considering the epigenetic effects that result from both maternal care and alcohol exposure, variation within this system could produce trans-generational and wide-spread (if not convoluted) effects on offspring stress reactivity and psychiatric outcome (Fig. 2). Whether variation within this system contributes to individual differences in social cognition or empathy is yet to be

explored, but it may be that *OPRM1* genotype could predict risk for individuals with developmental or personality disorders that present with aberrant affective and empathic responses.

6. Conclusions

Because they can be prospectively controlled, animal studies are critical in studying the longitudinal trajectories of early environmental challenge as they relate to risk for psychopathology. Longitudinal animal studies have elucidated mechanisms by which pre- and post-natal exposures to “stress” can potentially lead to aberrations in stress axis activity and behavioral pathology, and nonhuman primate studies have informed us of how genetic factors can moderate the long-term effects of early stress exposure. Candidate gene-based studies performed in nonhuman primates appear to have translational value for investigating effects of genetic variation on traits that increase risk for stress-related disorders among stress-exposed human subjects. It is possible that behavioral traits and environmental sensitivities could have, on the one hand, conferred selective advantage at some point in the evolutionary history of humans, while also increasing risk for stress-related disorders in modern humans.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Rhesus Macaques in the Field and the Laboratory

(A) Free-ranging macaques grooming one another in their social group (Cayo Santiago). Rhesus macaques have long-term social attachments and extended social networks founded on matrilineal. (B) Mother and infant (Cayo Santiago). Like humans, rhesus macaques commonly give rise to singleton births. (C) Self-biting (NIHAC). Self-biting is a form of behavioral pathology more commonly exhibited by animals exposed to early adversity. (D) Peer-reared macaques (NIHAC). Peer-reared macaques are highly stress-responsive, show insecure attachment styles, and will cling to one another with very little provocation.

Fig. 2. A Potential Role for the *OPRM1* Gene in the Ontogeny of Empathy

The ontogeny of empathy is founded on the development of early attachment relationships, which influence future social interactions and parenting style. Functional polymorphisms in the *OPRM1* gene exist in both rhesus macaques and humans, and these influence both alcohol response/preference and mother-infant attachment in infant (as a function of social separation) and mother (as a function of oxytocin (OT) levels). Studies of early exposures in rodents show that variation in maternal intoxication can influence maternal care and offspring alcohol preference. Genetic variation that predicts differences in *OPRM1* receptor functioning could simultaneously result in variation in levels of early alcohol exposure and epigenetic effects, via dose-dependent alcohol-induced effects on maternal care. These factors could result in pleiotropic and trans-generational effects on offspring stress reactivity and empathic responses.