Risk, Resilience, and Gene × Environment Interactions in Rhesus Monkeys

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ABSTRACT: Recent research with both humans and rhesus monkeys has provided compelling evidence of gene–environment (GxE) interactions throughout development. For example, a specific polymorphism ("short" allele) in the promoter region of the serotonin transporter (5-HTT) gene is associated with deficits in neurobehavioral functioning during infancy and in poor control of aggression and low serotonin metabolism throughout juvenile and adolescent development in monkeys who were reared with peers but not in monkeys who were reared with their mothers and peers during infancy. In contrast, monkeys possessing the "long" allele of the 5-HTT gene exhibit normal neurobehavioral functioning, control of aggression, and serotonin metabolism regardless of their early social rearing history. One interpretation of these GxE interaction data is that the "long" 5-HTT allele somehow confers resiliency to adverse early attachment relationships on those individuals who carry it ("good genes"). An alternative interpretation of the same data is that secure attachment relationships somehow confer resiliency to individuals who carry alleles that may otherwise increase their risk for adverse developmental outcomes ("maternal buffering"). These two interpretations are not mutually exclusive, but the difference in their respective implications for developing prevention and even intervention strategies is considerable. Moreover, the allelic variation seen in certain genes in rhesus monkeys and humans but apparently not in other primate species may actually contribute to their remarkable adaptability and resilience at the species level.

KEYWORDS: rhesus monkeys; fear; aggression; GxE interactions; species differences

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Ann. N.Y. Acad. Sci. 1994: 52–62 (2006).
doi: 10.1196/annals.1376.006

INTRODUCTION

Why are some individuals more resilient than others? In study after study of the emotional, psychological, and physiological sequelae of trauma and other forms of stress, one basic finding stands out: There are dramatic differences among individuals of all ages and in every culture in the manner in which they respond to stress, be it acute or chronic. On the one hand, even in the face of an overwhelming disaster such as the Pacific tsunami of 2004 or Hurricane Katrina of 2005 many individuals with direct exposure to traumatic events exhibit only minimal immediate effects on their biological, psychological, and emotional functioning and subsequently show scant evidence of any lasting consequences. Many children subjected to the chronic stress of being raised in socially impoverished orphanages have shown remarkable recovery of social, cognitive, and biological functions following adoption into middle- and upper-class families. On the other hand, some individuals consistently respond to even the slightest changes in their physical or social environment with profound emotional, psychological, and physiological distress that often reappears without any obvious subsequent provocation. What are the factors that underlie such dramatic individual differences in response to stress? Are they largely the product of differences in the individuals' genetic heritage, differences in their social and emotional experiences early in life, differences in their current biological and psychological makeup—or some combination of these factors?

Similar questions can be raised about nonhuman primates. This chapter will examine factors contributing to resiliency in rhesus monkeys (*Macaca mulatta*). There are dramatic differences among rhesus monkeys in their behavioral and biological responses to environmental stress throughout development, and numerous studies have identified both genetic and environmental factors that clearly contribute to such individual differences. Recent research has demonstrated that such factors can actually *interact* to shape individual developmental trajectories. The chapter will review some of the relevant findings regarding these gene–environment (GxE) interactions and discuss some implications of those findings from a comparative perspective.

Over the past two decades, my colleagues and I have been studying the development of individual differences in personality or temperament—and the biological substrates that apparently underlie such differences—in the rhesus monkeys we maintain in large social groups at the National Institutes of Health Animal Center (NIHAC) in rural Maryland. During this time we have found that approximately 20% of the monkeys growing up in these naturalistic settings (as well as at two long-term field sites) consistently react to novel, mildly stressful social situations with unusually fearful and anxious-like behavior, accompanied by prolonged hypothalamic-pituitary-adrenal (HPA) axis activation, as indexed by significant and extended elevations of both salivary and plasma cortisol.[1] Another 5–10% of the monkeys growing up in these naturalistic settings are likely to exhibit impulsive and/or inappropriately aggressive

patterns of behavioral response under similar circumstances; monkeys in this latter subgroup also show chronic deficits in serotonin metabolism, as indexed by unusually low cerebrospinal fluid (CSF) concentrations of the primary central serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA).[2]

Development of Individual Differences in Stress Reactivity

Rhesus monkeys growing up in naturalistic settings normally spend virtually all of their first month of life in intimate physical contact with their biological mother, during which time a strong and enduring attachment bond is established between mother and infant. In their second month these infants begin to explore their immediate physical and social environment, using their mother as a "secure base" from which to launch brief exploratory ventures but remaining in physical contact with her at most other times. In the weeks and months that follow the infants spend increasing amounts of time away from their mothers and begin to establish relationships with other members of their social group, most notably with same-aged peers. Throughout the rest of their childhood most juveniles spend several hours each day in active social play with these peers. Virtually every social behavior that will be important for normal adult functioning is developed, practiced, and perfected during the course of peer play, most notably behaviors leading to successful reproduction, as well as the socialization of aggression, which usually first appears in each monkey's behavioral repertoire between 4 and 6 months of age.[3]

Both excessively fearful and excessively aggressive monkeys tend to show significant deviations from this species-normative pattern of social development, beginning very early in life. Fearful infants start leaving their mother to explore their environment at a later age than the rest of their birth cohort, and they continue to exhibit low rates of exploratory behavior in subsequent weeks and months. They also seem reluctant to interact with monkeys other than their mother, and as a result they tend to spend less time playing with peers than others in their birth cohort throughout their childhood years.[4] When these fearful young monkeys become physically separated from their mothers, either in natural settings during the annual breeding season, when females typically leave their social group for short periods to mate with different males, or in the course of laboratory simulations of such maternal separations, they consistently exhibit far greater behavioral distress, accompanied by higher and more prolonged elevations of cortisol, than the rest of their birth cohort.[5] Moreover, such differences in adrenocortical response to separation are predictive of differential responses to other situations later in life. For example, Fahlke and colleagues found that monkey infants who exhibited highly elevated levels of plasma cortisol following brief separations at 6 months of age subsequently consumed significantly more alcohol in a "happy hour" situation when they were 5 years of age than did monkeys whose 6-month cortisol responses were

more moderate.[6] Heritability analyses have demonstrated that these individual differences in behavioral and adrenocortical response to separation have a significant genetic component.[7,8]

Overly aggressive infants, especially males, typically display their aggressive tendencies initially in the context of social play with peers. Unlike their fearful counterparts, these youngsters readily respond to play invitations from other monkeys, and they often initiate rough-and-tumble play bouts themselves. However, their rough-and-tumble play bouts with peers often turn out to be *too* rough, escalating into episodes of actual physical aggression with their play partners. Not surprisingly, other monkeys in the social group soon learn to avoid most interactions with these aggressive young males, and as a result they become increasingly isolated socially, even though they are continually in the presence of potential playmates.[9] CSF samples collected from free-ranging juvenile males have revealed a significant negative relationship between the incidence of aggression in the context of play and 5-HIAA concentrations, that is, the most aggressive males tend to have the lowest CSF 5-HIAA concentrations.[10] Laboratory studies have demonstrated that individual differences in CSF 5-HIAA are remarkably stable from infancy to early adulthood in both male and female subjects[11,12] and, as was the case for adrenocortical responses to social separation, they are also highly heritable.[13] Other laboratory studies have demonstrated that like their highly fearful counterparts, impulsively aggressive monkeys consume excessive amounts of alcohol in a "happy hour" situation as adolescents and young adults.[14]

Effects of Differential Social Rearing Environments

The individual differences in behavioral and biological responses to environmental challenges described above were all observed in rhesus monkeys growing up either in naturalistic environments or in captive settings that provided unrestricted access to both their biological mothers and same-aged peers (MP-rearing). However, other rhesus monkeys in our colony at the NIHAC have been reared from birth in the absence of any access to their biological mothers or any other adults but in the continuous presence of 3–4 other like-reared peers after an initial month in our neonatal nursery. After 6 months of such peer-only (PO) rearing, these infants have typically been placed in large social groups containing other same-aged PO-reared monkeys in addition to MP-reared age mates; both the PO- and MP-reared subjects have usually remained in these large social groups until puberty.

PO-reared monkeys rapidly develop strong attachment-like bonds with one another within days of being placed together following their initial month of nursery rearing. However, these "hyperattachments" tend to be essentially nonfunctional, if not outright dysfunctional, largely because a peer is not nearly as good as a mother—even a relatively nonresponsive or punitive mother—in

either providing a secure base for exploration or soothing an infant whenever it becomes frightened or otherwise upset.[15] Perhaps as a result, PO-reared infants tend to explore little and play less than their MP-reared counterparts during their first six months. What few play bouts they do experience with one another tend to be rudimentary in nature and short-lived in duration, far less complex than routine play bouts among MP-reared monkeys of comparable age. PO-reared monkeys as a group also exhibit more extreme behavioral and adrenocortical responses to social separation at 6 months of age.[16]

In addition, PO-reared monkeys display many of the same behavioral and serotonergic characteristics that differentiate overly impulsive and aggressive monkeys growing up in naturalistic settings from others in their birth cohort. Perhaps because they are essentially experiencing play deprivation even though they are in the continuous presence of potential playmates, as they grow older they become increasingly aggressive, far more so than most of their MP-reared fellow group members.[17] Importantly, they also consistently exhibit significantly lower CSF 5-HIAA concentrations than MP-reared monkeys from early infancy to early adulthood.[18,19] In addition, as adolescents and young adults they consume more alcohol than MP-reared subjects in a "happy hour" situation.[20] In sum, PO-reared monkeys exhibit many of the same behavioral and biological patterns of response to environmental challenge and social stress that are shown by excessively fearful monkeys and overly impulsive and aggressive monkeys growing up in naturalistic settings. Clearly, at least for rhesus monkeys, early social experiences such as maternal deprivation can have significant and long-lasting effects on behavioral and biological development over and above any contributions to individual differences attributable to heritable factors.

GxE Interactions

In recent years there has been increasing interest in the study of possible GxE interactions, especially in the face of reports such as those of Caspi, Moffitt, and their colleagues, who followed a large sample of young adults prospectively from early childhood onward. Those investigators demonstrated convincingly that allelic variation in the promoter region of the serotonin transporter (5-HTT) gene was associated with significant differences in the number of depressive symptoms observed in these young adults—but *only* if they also had experienced childhood neglect or abuse or were experiencing high levels of concurrent stress.[21] Rhesus monkeys have essentially the same 5-HTT gene and functional polymorphism as do humans.[22] We have recently been able to genotype most monkeys in our colony at the NIHAC, and as a result we have been able to search for possible GxE interactions involving differential early experience (MP- vs. PO-rearing) and allelic variation in the 5-HTT gene.

To date we have found such interactions to be ubiquitous. Monkeys carrying the "short" allele of the 5-HTT gene show delayed early neurobiological development, impaired serotonergic functioning, and excessive aggression, HPA reactivity, and alcohol consumption as they are growing up—*but only if they have been PO-reared.* MP-reared monkeys carrying the "short" 5-HIAA allele exhibit species-normative patterns of early neurobiological development, serotonin metabolism, levels of aggression, and HPA reactivity following separation comparable to those shown by both MP- and PO-reared carrying the "long" 5-HTT allele.[23–26] In addition, MP-reared adolescent and young adult monkeys carrying the "short" 5-HTT allele actually consume *less* alcohol than their MP-reared counterparts carrying the "long" 5-HTT, raising the intriguing possibility that having the functionally less efficient 5-HTT allele may represent a significant risk factor for PO-reared monkeys but may actually be a protective factor for their MP-reared counterparts carrying the same 5-HTT allele.[27] Other studies examining possible GxE interactions involving MP- and PO-reared monkeys carrying functionally different alleles of the MAO-A gene and various measures of aggression have yielded findings paralleling the pattern of GxE interactions involving MAO-A allelic variation and presence/absence of a history of childhood neglect/abuse reported by Caspi and colleagues in the above-mentioned sample of young adults studied prospectively since early childhood.[29,30]

Although it seems apparent that significant GxE interactions involving the 5-HTT gene and differential early experience do occur and are associated with different long-term outcomes for a variety of behavioral and biological measures in both rhesus monkeys and humans, the demonstration of such interactions has been largely statistical to date and hence subject to multiple interpretations. An interpretation initially put forward by Caspi *et al*. for the MAO-A polymorphism is essentially that the more efficient allele "protected" individuals who carried it from possible effects on aggressive behavior stemming early adverse experiences of childhood neglect and/or abuse,[30] that is, a "good" gene offered protection from a "bad" environment. An equally plausible interpretation of a similar pattern of GxE interactions involving the 5-HTT polymorphism and differential early social rearing for a variety of measures of behavioral and biological functioning in rhesus monkeys is essentially that MP-rearing "buffers" individuals carrying the less efficient allele from developing the aberrant patterns exhibited by PO-reared monkeys carrying the same allele,[31] that is, a "good" environment can protect individuals carrying a "bad" gene from deleterious developmental outcomes.

It can be argued that these apparently competing interpretations of the same or similar data sets are not necessarily mutually exclusive, and indeed I believe that different developmental processes representing both interpretations can be taking place in the same individual, even during the same periods of development. Definitive resolution of this potential conflict of interpretation awaits further empirical evidence regarding the actual behavioral and biological

process that might underlie such statistical interactions. Some relevant evidence is already beginning to be reported. For example, Meaney, Szyff, and colleagues have demonstrated that differential maternal licking and grooming of rat pups during the second postnatal week can actually alter gene expression in the pups' brains via demethalation processes, with consequences that are not only life-long but actually transmitted to the next generation of offspring.[32] Given such findings, the possibility that specific early social experiences can similarly alter gene expression in primates no longer seems particularly farfetched. If true, this could have enormous implications for the development of strategies for prevention of adverse outcomes in individuals carrying the less efficient allele of these and other "candidate" genes. At the very least, these recent findings regarding GxE interactions should provide important insights regarding the issue of individual difference in resiliency in the face of experiences with acute and chronic stress in primates, human and nonhuman alike.

A Comparative Perspective

Clearly, there are *both* specific genetic *and* environmental factors that can put individuals at risk for developing adverse responses to environmental stress and challenge, often with long-term consequences. On the other hand, it seems increasingly likely that individual differences in resiliency to such environmental adversity represent the product of complex interactions among multiple genes and characteristics of the physical and social environments within which development takes place. Identifying, characterizing, and understanding the basis for such complex interactions certainly represents a considerable—even daunting—challenge for future research endeavors.

Nevertheless, such endeavors may well be warranted. To put the above-described GxE results from studies of rhesus monkeys and humans into a broader comparative perspective, consider some recent findings regarding the 5-HTT and MAO-A genes carried by other members of the *Macaca* genus. Wendland *et al*.[33] characterized the 5-HTT gene in rhesus monkeys and six other species of macaques. To our considerable surprise, we found that in *none* of these other species was there any allelic variability in the promoter region of the 5-HTT gene. Instead, all of the samples for each species were homozygous for a specific repeat number in that region: Pigtail (*M. nemestrina*), stumptail (*M. arctoides*), Tonkenean (*M. tonkeana)*, and crab-eating (*M. fasicularis*) macaques all were homozygous for the "long" rhesus monkey 5-HTT allele, whereas Barbary macaques (*M. silvanus*) all had an "extra-long" version of this gene and all Tibetan macaques (*M. tibetana*) sampled had an "extra-short" (fewest repeats) 5-HTT promoter region.

Interestingly, there appeared to be a systematic relationship between number of repeats in this region and relative aggressivity at the species level: whereas

Barbary, Tonkenean, stumptail, pigtail, and crab-eating macaques are all generally thought to be considerably less aggressive than rhesus monkeys,[34] a recent field study of Tibetan macaques suggests that this species may be even more aggressive than rhesus monkeys.[35]

But perhaps of potentially greater significance is the finding that *none* of the samples obtained from these other macaque species revealed *any* functional polymorphisms in the 5-HTT gene readily apparent in both humans and rhesus monkeys—nor have any comparable functional 5-HTT polymorphisms been reported for any of the baboon or anthropoid ape species. A similar situation seemingly exists for the MAO-A gene: functional polymorphisms in the promoter region of this gene have been found in humans and rhesus monkeys but to date not in any of the other aforementioned species.[36] What other characteristics might these species' differences in the presence/absence of polymorphisms in these and other genes be related to—what is it about humans and rhesus monkeys that differs from these other primate species?

One characteristic shared by humans and rhesus monkeys—but not these other species—is that they are two of the very few "weed" species of primates.[37] They can live in an extraordinarly wide range of physical range of physical habitats and social environments, and when moved into new settings, more often than not they flourish and actually expand their initial founder populations, unlike all of the other aforementioned species (and most other species of primates).[37] So, to take an admittedly speculative leap, perhaps one of the factors underlying the relative adaptive "success" of both humans and rhesus monkeys derives not from some sort of exquisite genetic specialization but instead from more general genetic *variation*. Consider the truism that there can be no GxE interactions in the absence of any genetic variability. Maybe—just maybe—one of the secrets to the remarkable resiliency shown at the species level by rhesus monkeys and ourselves alike could actually be genetic *diversity*.

SUMMARY

Like humans, rhesus monkeys exhibit striking individual differences in their reactions to environmental stress and challenge. Some rhesus monkeys are excessively fearful in response to changes in their environment throughout development; others are overly impulsive and aggressive. It is possible to identify both genetic and environmental factors that contribute to these different response patterns, but recent evidence suggests that GxE interactions may actually be at least as important in shaping individual developmental trajectories in this species, possibly through mechanisms by which specific aspects of the environment influence the expression of specific genes at specific times during development. Finally, because GxE interactions require genetic variation at the species level in order to take place, the fact that rhesus monkeys—and

humans—apparently possess greater allelic variability in certain candidate genes than many other primate species may in fact contribute to their remarkable resilience and adaptive success relative to other primates.

ACKNOWLEDGMENTS

The research summarized in this report was supported by funds from the Division of Intramural Research, National Institute of Child Health & Human Development, National Institutes of Health, DHHS.

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