

Risk, Resilience, and Gene-Environment Interplay in Primates

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Abstract

Objectives: The primary objectives of the body of research reported here was to demonstrate significant interactions between genetic and social environmental factors that clearly influenced both the biological and behavioral responses of rhesus monkeys to social stressors such as separation from familial and/or familiar conspecifics throughout development and to investigate possible mechanisms underlying such interactions. **Methods:** Prospective longitudinal studies of rhesus monkeys reared in both captive and naturalistic settings have examined individual differences in biological and behavioral responses to stress throughout the lifespan. **Results:** Approximately 20% of monkeys in both settings consistently display unusually fearful and anxious-like behavioral reactions to novel, mildly stressful social situations and depressive-like symptoms following repeated separations from familial and/or familiar conspecifics during their infant and juvenile years, as well as profound and prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis in both situations. Both genetic and experiential factors – as well as their interaction -- are implicated in these reactions to social stress. For example, a specific polymorphism in the serotonin transporter gene is associated with deficits in neonatal neurobehavioral functioning and in extreme behavioral and adreno-cortical responses to social separation among infant and juvenile monkeys who experienced insecure early attachments but not in monkeys who developed secure attachment relationships with their mothers during infancy (maternal “buffering”). Similar instances of maternal “buffering” have been demonstrated in significant gene-environment interplay involving several other “candidate” gene polymorphisms. Moreover, because the attachment style of a monkey mother is typically “copied” by her daughters when they become mothers themselves, similar “buffering” is likely to occur for the next generation of infants carrying so-called “risk” alleles. **Conclusions:** Specific gene-environment interactions can influence behavioral and biological reactions to social stress not only throughout development but also across successive generations of rhesus monkey families.

Key words: *risk, resilience, gene-environment, primates*

Résumé

Objectifs: Montrer les interactions significatives entre les facteurs génétiques et socio-environnementaux qui influencent clairement les réponses biologiques et comportementales des singes rhésus à des stressseurs sociaux comme la séparation d'avec les conspécifiques familiaux ou familiaux au cours de leur développement; étudier les mécanismes sous-jacents tels que les interactions. **Méthodologie:** Observation de singes rhésus élevés en captivité et dans leur environnement naturel dans le cadre d'études longitudinales prospectives sur les différences individuelles entre les réponses biologiques et environnementales au stress, tout au long de la vie des individus. **Résultats:** Environ 20% des singes, en captivité ou dans leur environnement naturel, répondaient avec crainte ou anxiété à des situations sociales nouvelles et légèrement stressantes; ils présentaient de symptômes de type dépressif après avoir été séparés à plusieurs reprises des conspécifiques familiaux ou familiaux lorsqu'ils étaient bébés ou jeunes; les symptômes s'accompagnaient d'une activation profonde et durable de l'axe HPA (axe cortico-hypothalamo-hypophysaire) dans les deux cas. Des facteurs génétiques et expérientiels – ainsi que leur interaction – sont impliqués dans ces réactions au stress social. Par exemple, un polymorphisme spécifique du gène transporteur de la sérotonine est lié au déficit du fonctionnement neurocomportemental néonatal et à des réactions comportementales et adrénocorticales extrêmes lors de séparation des bébés singes ou des jeunes singes qui ont un attachement insécure; cela n'est pas le cas des singes qui ont développé un attachement sécuritaire avec leur mère pendant l'enfance (« zone de protection » maternelle). Des cas identiques de « zones de protection » maternelle ont été constatés lors de l'interaction gène-environnement impliquant divers autres polymorphismes de gènes candidats. De plus, le style d'attachement d'une mère singe étant généralement copié par ses filles lorsque celles-ci deviennent mères à leur tour, il est probable que la génération suivante de bébés singes porteurs d'allèles dits « à risque » bénéficiera d'une « zone de protection » similaire. **Conclusions:** Les interactions spécifiques gène-environnement peuvent influencer les réactions comportementales et biologiques au stress social des singes rhésus pendant leur croissance, mais aussi les réactions des générations à venir.

Mots clés: *risque, résilience, gène-environnement, primates*

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Introduction

Primates are inherently social in nature. Most individuals in most primate species spend most of their time as members of distinctive social groups throughout their respective lifetimes. Moreover, most of these individuals have particular behavioral and biological characteristics that emerge early in life and appear to influence the manner in which they typically interact with others not only throughout development but also later in life. Indeed, it can be argued that individual monkeys and apes – like humans – have distinctive *personalities* that help differentiate themselves from one another.

For many years a major research focus of my laboratory at the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, along with that of many colleagues from other institutions, has been on the study of the development of individual differences in personality – and the biological substrates that underlie those individual differences – in rhesus monkeys (*Macaca mulatta*), indisputably the most highly successful and widely dispersed member of the macaque genus (Thierry, 2007). A primary aim of our research has been to characterize how genetic and environmental factors act – and indeed actually *interact* -- to shape the behavioral and biological developmental trajectories of different individuals. We have been especially interested in two subgroups of monkeys in our colony of rhesus monkeys maintained at the National Institute of Health Animal Center (NIHAC), located in the Maryland countryside near the town of Poolesville.

One subgroup, comprising approximately 20% of the Poolesville colony (as well approximately 20% of the rhesus monkey populations living at two different field sites to which we have had long-term access) appear to be excessively fearful or anxious in the face of novel or mildly challenging circumstance. These monkeys tend to avoid stimuli or situations that other monkeys find interesting and readily explore, and if forced to confront those stimuli or situations they typically exhibit excessively fearful and anxious-like behavior, as well as profound arousal of multiple biological systems, most notably the hypothalamic-pituitary-adrenal (HPA) axis, as indexed by heightened and prolonged elevations of cortisol, and activation of the autonomic nervous system (ANS), as indexed by significant elevations of heart rate (HR) and reductions in HR variability. In both their behavioral and biological responses to such environmental challenges they clearly resemble a subgroup of human children labeled as “behaviorally inhibited” (Fox, Henderson, Marshall, Nichols, & Ghera, 2005; Kagan, Resnick, & Snideman, 1988; Kagan, Snidman, Kahn, & Towsley, 2007), who we now know are at risk for developing anxiety and depressive disorders not only in childhood but also during adolescence and even as adults (Biederman et al., 2001).

A second subgroup, comprising approximately 5-10% of the Poolesville population (as well as comparable percentages of monkeys living at the aforementioned field sites), seem overly impulsive and excessively aggressive in their behavior. Biologically, these monkeys appear to have deficits in serotonin metabolism, as indexed by chronically low cerebrospinal fluid (CSF) concentrations of the primary central serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA). In both these behavioral and biological features they resemble a different subgroup of children who appear to be excessively impulsive and aggressive by late infancy and who tend to remain so throughout development (cf. Nagin & Tremblay, 1999).

We have been especially interested in these two subgroups of rhesus monkeys for a variety of reasons in addition to their apparent similarity to the two aforementioned subgroups of children (who are clearly of considerable concern to developmental researchers, clinicians, educators, policy makers, and indeed the general public alike).

First, for both the excessively fearful (we call them “up-tight”) monkeys and the excessively impulsive/aggressive subgroups, the behavioral and biological features that distinguish them from other monkeys initially appear very early in life and, in the absence of major environmental change, remain remarkably stable throughout infancy and the childhood years, are typically maintained during the multifaceted behavioral and biological transitions associated with puberty, and often persist into adulthood. Second, some of these distinctive features, especially the biological ones, appear to be highly heritable using traditional h^2 calculations, i.e., there is clearly a significant genetic component at least in part underlying their differences from other monkeys. For example, individual differences in HPA activity are highly heritable, as are individual differences in CSF 5-HIAA concentrations, throughout development (h^2 for both measures greater than 0.5) (Williamson et al., 2003; Higley et al., 1993).

However, genetic factors are not the only source of inter-individual variability in the behavioral and biological characteristics of our monkeys. Experiences also matter, especially early attachment experiences, e.g., those involving the monkeys’ biological mothers or, in some cases, alternative caregivers, during their initial months of life. Importantly, these early attachment-related experiences become manifest not only in terms of observable behaviors and expressions of emotions but also in terms of neuro-endocrine output, neurotransmitter metabolism, brain structure and function, and even gene expression.

Species-Normative Patterns of Social Organization and Development in Rhesus Monkeys

Many of the rhesus monkeys in the Poolesville colony are born and raised in physical and social settings designed to reproduce, as faithfully as possible, basic features of their natural habitats. Here, as in the wild, these rhesus monkeys live in a complex social group (troops) organized around several multigenerational female-headed families, with females remaining in their natal troop for their entire lifetime, and males emigrating from their natal group around the time of puberty, then trying to join a different troop. This species-normative form of social organization is also characterized by multiple social dominance hierarchies, with separate hierarchies between and within families, among the males who come into the troop, and among the cohort of infants that are born each year (Lindburg, 1971; Sade, 1967).

In natural settings rhesus monkey infants begin life highly dependent upon their biological mother for essentially all of their immediate biological and psychological needs (in this species fathers are not active participants in infant caregiving activities). An infant spends its first month of life in almost continuous physical contact with its biological mother, typically in ventral-ventral contact but otherwise at no more than an arm's length distance from her. Under these conditions, the mother is usually able to shield her infant from most potentially dangerous or otherwise fear-provoking stimuli. During this time a strong and enduring social bond between mother and infant is established (Harlow, 1958). This bond, essentially homologous with Bowlby's (1969) characterization of human mother-infant *attachment*, is unique in terms of its exclusivity, constituent behavioral features, and ultimate duration – it is unlike any other social relationship the infant will ever experience again in its lifetime, except for females (in reciprocal form) when they grow up to have infants of their own (Suomi, 2008).

Rhesus monkey infants are inherently curious (Harlow, 1953), and once an infant has become securely attached to its mother it can use her as a *secure base* (cf. Harlow, 1958; Bowlby, 1988) from which to make exploratory ventures toward stimuli that have caught its curiosity. Most infant monkeys soon learn that if they become frightened or otherwise threatened, they can always run back to their mother for immediate safety and comfort via mutual ventral contact. Secure attachment relationships thus help infants learn to manage the fears they will inevitably experience in the course of exploring their ever-expanding world. On the other hand, if a rhesus monkey infant develops an insecure attachment relationship with its mother, its ability to regulate fear and its willingness to explore may be compromised,

consistent with Bowlby's observations regarding human attachment relationships (Bowlby, 1988; Suomi, 2009).

In their second and third month, rhesus infants begin to interact with monkeys other than their mother, and they soon develop distinctive social relationships with specific individuals outside of their immediate family. Increasingly, these interactions come to involve *peers* -- other infants of like age and comparable physical, cognitive, and social capabilities. Following weaning (usually in the fourth and fifth months) play with peers emerges as a predominant social activity for young monkeys and essentially remains so until puberty (Ruppenthal, Harlow, Eisele, Harlow, & Suomi, 1974). During this time the play interactions become increasingly gender-specific and sex-segregated, i.e., males tend to play more with males, and females with females (Harlow & Lauerdsdorf, 1974). Peer play also becomes more and more behaviorally and socially complex as the monkeys mature, and by the third year the play bouts typically involve patterns of behavior that appear to simulate the full range of adult social activity. By the time they reach puberty, most rhesus monkey juveniles have had ample opportunity to develop, practice, and perfect virtually all of the basic behavioral routines that will be crucial for normal functioning as adults, especially those involving dominance interactions and aggressive exchanges (Suomi, 2008).

The onset of puberty, typically occurring around the end of the third year for females and the beginning of the fourth year for males, is associated with major life transitions for both female and male rhesus monkeys. Adolescence involves not only major hormonal alterations, pronounced growth spurts, and other obvious physical changes, but also major social changes for both sexes. Pubescent female rhesus monkeys almost always stay in their maternal family and natal troop throughout this time of transition. For them, pubertal change is associated with increases in social activities directed toward maternal kin, usually at the expense of interactions with unrelated peers. Within-family interactions are heightened even more when these young females begin to have offspring of their own. Rhesus monkey females remain actively involved in family social affairs for the rest of their lives, even after they cease having infants of their own (Suomi, 1998).

Contrastingly, rhesus monkey males experience much more dramatic and serious social disruptions: when they leave their natal troop they sever all social contact not only with their mother and other kin but also with all other familiar individuals remaining in the troop. Virtually all of these adolescent males soon join all-male "gangs," and after several months most of them then attempt to join a different troop, usually composed entirely of individuals largely unfamiliar to the immigrant males (Berard, 1989). The process of natal troop emigration represents an exceedingly dangerous

transition period -- the mortality rate for these young males from the time they leave their natal troop until they become successfully integrated into another troop may be as high as 40 to 50%, depending on local circumstances (e.g., Dittus, 1979). Recent field studies have identified and characterized striking variability in both the timing of male emigration and the basic strategies followed in attempting to join other established social groups – variability seemingly associated with individual differences in emotional regulation (Suomi, 2009; Howell et al, 2007).

Behavioral and Biological Consequences of Different Early Attachment Relationships

The individual differences in documented behavioral and biological responses to environmental challenges throughout development described above have all been observed in rhesus monkeys growing up in either naturalistic environments or in captive settings at Poolesville that provided unrestricted access to both their biological mothers and same-aged peers (MP-rearing). However, other rhesus monkeys in our Poolesville colony have been experimentally separated from their biological mothers at birth, hand-reared in the lab's neonatal nursery for their first month of life, and then housed with 3-4 other same-aged peers after that initial month of nursery rearing (cf. Harlow, 1969). After six 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 continued together in these large social groups until puberty. Thus, any differences between MP- and PO-reared monkeys can ultimately be traced to their initial 6-7 months of life experiences.

In general, PO-reared monkeys rapidly develop extremely strong attachment-like bonds with one another within days of being placed together following their initial month of nursery rearing. However, these "hyper-attachments" tend to be essentially nonfunctional, if not outright dysfunctional, largely because a peer is not nearly as good as a mother – even a relatively non-responsive or punitive mother – in either providing a secure base for exploration or soothing an infant whenever it becomes frightened or otherwise upset (Suomi, 2009). Perhaps as a result, PO-reared infants tend to explore little and play less than their MP-reared counterparts during their initial six months living together. 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 neuroendocrine (HPA) responses to social separation at six months

of age than do their MO-reared counterparts (Suomi, 1997; Dettmer, Novak, Suomi, & Meyer, in press). All in all, in both their behavioral patterns and their biological functioning, PO-reared monkeys typically look very much like the "naturally occurring" previously described subgroup of excessively fearful individuals comprising 15-20% of rhesus monkey populations observed in the wild.

In addition, most 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 these PO-reared monkeys 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 (Higley, Suomi, & Linnoila, 1996; Higley, King, et al., 1996). Importantly, they also consistently exhibit significantly lower CSF 5-HIAA concentrations than MP-reared monkeys from early infancy to early adulthood (Shannon et al., 2005; Higley & Suomi, in press), and they also exhibit significantly different developmental trajectories of peripheral measures of the neurotrophic factors NGF and BDNF (Cirulli et al., 2009). Additionally, as adolescents and young adults they typically consume significantly more alcohol than MP-reared subjects in a "happy hour" situation (Higley, Hasert, Suomi, & Linnoila, 1991; Fahlke et al., 2000). In sum, PO-reared monkeys exhibit many of the same behavioral and biological patterns of response to environmental challenge and social stress that have been shown by excessively fearful monkeys, as well as those of overly impulsive and aggressive monkeys growing up in naturalistic settings (Higley & Suomi, in press), i.e., they are co-morbid for both these sets of behavioral and biological features (Suomi, 2009).

In addition, neuroimaging studies have demonstrated that PO-reared monkeys differ significantly from their MO-reared counterparts in both brain function and structure. For example, PO-reared adolescent and adult males exhibit significantly higher rates of whole-brain glucose metabolism under mild isoflurane anesthesia, as determined by positron emission tomography (PET) imaging, than do their MP-reared controls (Doudet et al., 1995). Significant differences between MP-reared and PO-reared juveniles in serotonin transporter ligand binding potential and in cerebral blood flow, also as determined by PET, have been detected in raphe, thalamus, striatum, frontal and parietal brain regions, with PO-reared subjects exhibiting significantly lower levels for both measures in each region (Ichise et al., 2006). With respect to overall brain structure, magnetic resonance imaging (MRI) studies have revealed significant differences in brain structure between peer-reared juveniles and their mother-reared counterparts. Specifically, PO-reared

juveniles have an enlarged vermis, as well as larger dorsomedial prefrontal cortical and dorsal anterior cingulate cortical regions than do MP-reared juveniles, but no differences in corpus callosum thickness or hippocampal size (Spinelli, Chefer, Suomi, Barr, & Stein, 2009). Finally, some very recent data indicate major differences in genome-wide expression in leukocytes at as early as four months of age between MP- and PO-reared infants, as determined by microarray analyses of mRNA expression (Cole, Arevalo, Ruggiero, Heckman, & Suomi, under review).

All in all, early PO-rearing has profound consequences for rhesus monkeys, not only at the levels of behavioral expression and emotional regulation, but also in terms of neuroendocrine output, neurotransmitter metabolism, brain structure and function, and even genome-wide expression. At the phenotypic level, the developmental trajectories of PO-reared infants not only resemble those of naturally occurring subgroups of excessively fearful and excessively impulsive/aggressive rhesus monkeys growing up in the wild, but also persist long after the infants' period of exclusive exposure to peers has been completed and they have been living in more diverse social groups.

Gene-Environment (G x E) Interplay

Studies examining the effects of PO-rearing and other variations in early rearing history (e.g., Harlow & Harlow, 1969), along with the previously cited heritability findings, clearly provide compelling evidence that *both* genetic and early experiential factors can affect multiple aspects of rhesus monkey behavioral and biological development. Do these factors operate independently, or do they interact in some fashion in shaping individual developmental trajectories? Recent and currently ongoing research capitalizing on the discovery of genetic polymorphisms in several specific "candidate" genes suggests that extensive G x E interplay not only occur but also can be expressed in multiple forms and at different points during development.

For example, the 5-HTT gene is a candidate gene for impaired serotonergic function (Lesch et al., 1996). Length variation in its promoter region results in allelic variation in 5-HTT expression: the short allele(s) confers low transcriptional efficiency to the 5-HTT promoter relative to the long allele (l), raising the possibility that low 5-HTT expression may result in decreased serotonergic functioning (Heils et al., 1996), although evidence in support of this hypothesis in humans has been decidedly mixed to date (c.f. Rutter, 2008). The 5-HTT polymorphism was first characterized in humans, but it also appears in largely homologous form in rhesus monkeys (Lesch et al., 1997).

We have recently characterized the genotypic status of several entire birth cohorts of monkeys, i.e., all the monkeys

born in our Poolesville colony in particular years, with respect to their 5-HTT polymorphic status. Some of our MP-reared and PO-reared monkeys in these birth cohorts possess the s allele, and almost all of the rest have the l serotonin transporter allele (a few, less than 2% of the cohorts, possess a third allelic type, an extra long allele. It has therefore been possible for us to examine a wide range of behavioral and physiological measures for potential 5-HTT polymorphic main effects and interactions with early rearing history. Analyses completed to date suggest that such interactions are widespread and diverse.

For example, Bennett et al. (2002) reported that CSF 5-HIAA concentrations did not differ as a function of 5-HTT status for MP-reared subjects, whereas among PO-reared monkeys, individuals with the LS allele had significantly lower CSF 5-HIAA concentrations than those with the LL allele. One interpretation of this interaction is that mother-rearing appeared to "buffer" any potentially deleterious effects of the s allele on serotonin metabolism. A similar pattern appeared with respect to aggression: high levels of aggression were shown by PO-reared monkeys with the s allele, whereas MP-reared s monkeys exhibited low levels of aggression that were comparable to those of both mother-reared and peer-reared l monkeys, again suggesting a buffering effect of maternal rearing (Barr et al., 2003b). Other studies examined behavioral and HPA responsiveness among MP- and PO-reared subjects to short-term social separation at seven months of age. Monkeys with the s allele exhibited greater behavioral disturbance and heightened ACTH responsiveness relative to those with the l allele, but only if they had been peer-reared. In contrast, s monkeys reared by their biological mother did not differ in ACTH responsiveness from MP-reared subjects, suggesting a "buffering" effect of maternal rearing (Barr et al., 2004).

Similar patterns of G x E interplay apparently can emerge in the very first days and weeks of life. Champoux et al. (2002) focused on the relationship between early rearing history and serotonin transporter gene polymorphic status for measures of neonatal neurobehavioral development throughout the first month of life and found further evidence of maternal buffering. Specifically, infants possessing the s allele who were being reared in the laboratory neonatal nursery showed significant deficits in measures of attention, activity, and motor maturity relative to nursery-reared infants possessing the l allele, whereas both s and l infants who were being reared by competent mothers exhibited normal values for each of these measures.

An even more dramatic pattern of G x E interplay was revealed by an analysis of alcohol consumption data: whereas PO-reared monkeys with the s allele consumed significantly more alcohol than PO-reared monkeys with the l allele, the reverse was true for mother-reared subjects, with

MP-reared individuals possessing the s allele actually consuming *less* alcohol than their MP-reared l counterparts (Bennett, Lesch, Heils, & Linnoila, 1998). The same pattern was found for relative levels of alcohol intoxication (Barr et al., 2003a). In other words, the s allele appeared to represent a significant *risk* factor for excessive alcohol consumption among PO-reared monkeys but perhaps instead was a *protective* factor for MP-reared subjects.

In sum, PO-reared monkeys with the s allele displayed deficits in measures of neurobehavioral development during their initial weeks of life and reduced serotonin metabolism and high levels of aggression as juveniles, and excessive alcohol consumption as adolescents and young adults, compared with those possessing the l allele. In contrast, MP-reared subjects with the s allele were characterized by normal early neurobehavioral development, levels of aggression and serotonin metabolism, as well as reduced risk for excessive alcohol consumption later in life compared with their MP-reared counterparts with the l allele. It could be argued on the basis of these findings that having the s allele of the 5-HTT gene may well lead to psychopathology among monkeys with adverse early rearing histories but might actually be adaptive for monkeys who develop secure early attachment relationship with their mothers.

A parallel “maternal buffering” pattern of G x E interaction involving a polymorphism in the MAOA gene was found for levels of aggressive behavior exhibited by MP-reared and PO-reared rhesus monkey juveniles (Newman et al., 2005); here, PO-reared subjects with the less functionally efficient MAOA allele had significantly higher levels of aggression than MP-reared subjects carrying the same allele and both MP- and PO-reared subjects carrying the more functionally efficient allele, essentially replicating findings reported for humans (e.g., Caspi et al., 2002). In addition, my colleagues and I have recently identified additional functional polymorphisms in the corticotrophin releasing factor (CRH)_{2A} gene (Barr et al., 2008a), the neuropeptide Y (NPY) gene (Lindell et al., 2010, and the mu opioid receptor gene (Barr et al., 2008b) and characterized specific G x E interactions with respect to behavioral responses to social separation by juvenile rhesus monkeys, as well as in several measures of alcohol preference and consumption among young adult monkeys (Schwandt et al., 2011). For each of these candidate genes, the significant G x E findings basically followed the “maternal buffering” pattern, i.e., PO-reared monkeys carrying the functionally less efficient allele exhibited significant deficits from PO-reared subjects carrying the same allele, whereas PO-reared monkeys carrying the more efficient allele showed levels that were equivalent to or even better than those of MP-reared monkeys for most of the behavioral or biological measures focused on in each study.

In an effort to better understand the basis for “maternal buffering,” we have recently initiated a series of studies investigating rhesus monkey mother-infant interactions during the infants’ first days and weeks of life. In marked contrast to previous reports concerning the normative development of attachment relationships in this species, we found that rhesus monkey mother-infant dyads engaged in frequent and intensive face-to-face interactions throughout their first three weeks of life, after which those patterns largely disappeared (Ferrari, Paukner, Ionica, & Suomi, 2009). Curiously, none of this intense participation in extensive face-to-face interaction in the initial weeks of life has been previously reported in the voluminous literature on rhesus monkey social development accumulated over the past 50 years or, indeed, for any other non-ape species of nonhuman primate (Paukner, Ferrari, & Suomi, in press). One can speculate that most previous investigations had not specifically focused on the infants’ initial days or weeks of life (cf. Ferrari et al., 2009) or, for those that did, mothers living in natural settings typically would not let field investigators close enough to witness such interactions, while most captive situations were not conducive for mothers and infants to engage in such mutual exchanges in the immediate presence of an observer.

In addition to the above findings regarding early mother-infant interactions, other recent studies have demonstrated that some rhesus monkey infants are capable of imitating specific facial patterns displayed by human models (Ferrari et al., 2006) in a manner strikingly similar to that previously reported for some human infants (Metzoff & Moore, 1977), suggesting that face-to-face interactions between infants and their mothers begin essentially at birth and may facilitate the development of mother-infant attachment in both species (Paukner et al. in press). Given these findings, as well as those indicating that there is considerable inter-individual variability (in both monkey and monkey infants) that is predictive of individual differences in subsequent sensory-motor integrative capabilities (Ferrari et al., 2009), we definitely plan to follow up these initial studies with a more extensive program of research in future years. It is the hope of my colleagues and I that these new studies of early infant capabilities and mother-infant face-to-face interactions will provide some insight regarding the factors and mechanisms that might underlie the phenomenon of so-called “maternal buffering.”

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 results from studies of G x E interplay in rhesus monkeys 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. (2005b) 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. fascicularis*) 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 (Thierry, 2007); a recent field study of Tibetan macaques suggests that this species may be even more aggressive than rhesus monkeys (Berman, Ionica, & Li, 2004).

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 (Wendland et al., 2005a). 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 (Richard, Goldstein, & Dewar, 1989), i.e., at the species level they are remarkably

adaptive and resilient, relative to virtually all other primate species. Both rhesus monkeys and humans can survive – indeed thrive – in an extraordinarily wide 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 most other species of primates (Suomi, 2006). 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*. 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*.

Acknowledgements / Conflicts of Interest

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