Nonhuman Primate Models of Neuropsychiatric Disorders: Influences of Early Rearing, Genetics, and Epigenetics

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Abstract

This report reviews the scientific literature from the past several decades that focuses on nonhuman primates (NHPs) as models of neuropsychiatric disorders, including anxiety, and alcoholism. In particular, we highlight the approaches, advantages, and disadvantages of the rearing, genetic, and epigenetic methodologies behind these studies as a means of evaluating the application of these methods in assessing disorders in NHPs as models of human disease. Finally, we describe the contributions the NHP studies have made to neuropsychiatric research and areas for future research.

Key Words: early life adversity; epigenetics; genetics; neuropsychiatric disorders; nonhuman primate; rhesus macaque

Introduction

Nonhuman primates (NHPs), particularly Macaca species, have been utilized as models for neuropsychiatric disorders since the mid-20th century. Macaques, in particular rhesus monkeys (Macaca mulatta), serve as valuable models for human disorders owing to their genetic, physiologic, neuroanatomic, and behavioral similarity to humans (Gibbs et al. 2007). In addition, after humans, rhesus monkeys are the most widely distributed primates on earth (Southwick et al. 1996). From Harlow’s first investigations in the 1960s into behavioral pathologies resulting from maternal deprivation (Arling and Harlow 1967; Harlow 1960; Harlow and Harlow 1961) to studies in the 1990s and 2000s of neurohormones underlying these and other disorders (Barr et al. 2003; Barr, Newman, Shannon et al. 2004; Higley et al. 1992; Higley, Hasert et al. 1991; Winslow et al. 2003) to very recent studies examining genetic and epigenetic influences on the incidence of neuropsychiatric-like disorders (Higham et al. 2011; Provençal et al. 2012), macaque studies have contributed significantly to our understanding of similar disorders in humans. Despite the clear advantages of utilizing the macaque model for human neuropsychiatric disorders, limitations exist and persist in the methodologies and interpretations of such studies. This report highlights the strengths and limitations of the early rearing, genetic, and epigenetic methodologies of macaque neuropsychiatric studies and ends by describing the findings of the past 10 to 15 years that have advanced our knowledge of the underlying mechanisms of neuropsychiatric disorders in humans. In particular, we focus on such NHP studies examining anxiety, impulsive aggression/antisocial behavior, and alcoholism.

NHP Models of Neuropsychiatric Disorders: Assessment of Methodology

Characterizing Neuropsychiatric Disorders in NHPs: Influences of Early Life History

The majority of studies utilizing NHPs as models of neuropsychiatric disorders have relied on young monkeys exposed to early life adversity in the form of experimental rearing conditions, though in recent years more studies have emerged with normally reared monkeys. The rationale for these studies is the strength of attachment that both human and NHP infants form with their mothers or caregivers, a bond that becomes dysfunctional in response to early insult. This section briefly describes the behavioral methodologies of these studies by providing their historical development and applicability to humans.

Anxiety and Behavioral Inhibition

Studies examining anxious behavior and depressive symptoms in rhesus monkeys have historically relied on behavioral assessments that examine monkeys’ reactions to social separations and reunions, social status manipulations, and novel objects or intruders and monkeys’ behaviors in an undisturbed social setting. Though several studies have established that adult monkeys, such as cynomologus macaques (Macaca
fascicularis) and baboons (Papio anubis), serve as reliable models for depressive behavior and physiology (Sapolsky 1989, 1990; Shively et al. 2009), those studies are beyond the scope of this chapter. The majority of studies into anxious/depressive behavior in monkeys have relied on social separations, usually from the mother, in young primates. The earliest studies relied on rhesus monkeys (Macaca mulatta) undergoing extreme separation from conspecifics (e.g., partial- or total isolate-rearing) and compared them to control monkeys that were reared undisturbed with their mothers and peers in social groups (Cross and Harlow 1965; Griffin and Harlow 1966; Harlow et al. 1965; Mitchell et al. 1966; Suomi et al. 1971). These early studies reported excessive fear (in facial and vocal expressions), abnormal behaviors (such as locomotor stereotypies and self-directed behaviors including self-mouthing, self-clasping, huddling, and rocking), and insecure attachments (i.e., reduced physical contact upon reunion) in the experimentally manipulated animals, and many of these behaviors mimicked those that Bowlby observed in his studies with children undergoing maternal separations and exhibiting insecure attachments to their mothers (Bowlby 1958, 1960, 1961).

One major limitation to these early studies is the severity of separation from conspecifics; most humans are not exposed to such extreme deprivation of social contact so early in life. Thus, in the past few decades, experimental rearing conditions have evolved to include more social contact in the form of peer-only rearing (PR), in which monkeys are reared for the first 6 to 12 months of life for up to 24 hours/day with same-aged peers but no adults (Capitanio et al. 2005; Dettmer et al. 2012; Shannon et al. 1998); surrogate-peer-rearing (SPR), in which monkeys are reared alone in single cages for the majority of the day but are provided with up to 2 hours of daily play sessions with agemates (Dettmer et al. 2012; Sackett et al. 2002; Shannon et al. 1998); and repeated brief separations from mothers or social partners versus total separation (Barr, Newman, Shannon et al. 2004; Hennessey 1997; Hoffman et al. 1995; Levine and Mody 2003; Mendoza and Mason 1997; Meyer et al. 1975; Rilling et al. 2001). Even with these less-severe separation paradigms, studies have consistently shown that young monkeys exposed to disruptions in the mother-infant bond or to adverse early rearing exhibit greater behavioral and physiological responsivity to separation; distress vocalizations, freezing behavior, and aggressive behaviors (e.g., cage-biting and cage-shaking) are increased in noncontrol monkeys, whereas object exploration and social contact upon reunion are decreased. Similarly, adrenocortical responses to separation are heightened in manipulated monkeys compared with control monkeys; this is true in both Old World (e.g., rhesus monkeys) and New World species (e.g., squirrel [Mendoza et al. 1978; Wiener et al. 1990] and titi [Hoffman et al. 1995; Hennessey 1997] monkeys; but see Levine and Mody 2003; Parker et al. 2004).

It is now widely accepted that monkeys exposed to early life adversity in the form of experimental social rearing serve as reliable models for the study of anxious and depressive behaviors in children with insecure attachments (Barry et al. 2008; Bretherton 2000; Dettmer et al. 2014; Kalin and Shelton 2003; Kraemer 1997; Passman and Weisberg 1975; Suomi 2005). Two major reasons for this view are (1) the strong similarities between monkeys and humans in social behavior, endocrine function, brain structure, and degree and duration of mother-infant nurturance (Harlow and Zimmerman 1959; Kalin and Shelton 2003; Mendoza and Mason 1997), or, in the unique case of titi monkeys, the extent of biparental care (Hennessey 1997); and (2) the extent to which monkeys fulfill Ainsworth’s criteria of attachment (Ainsworth 1972), namely, unequivocal distress upon complete separation from the attachment figure and alleviation of this distress (both behavioral and physiological) upon reunion/interaction with the attachment figure (Mendoza and Mason 1997). Other assessments used in NHPs to identify anxious individuals include the Human Intruder Test (equivalent to the human Strange Situation assessment developed by Ainsworth; Ainsworth and Bell 1970; Ainsworth et al. 1978; see Coleman et al., this volume), the Novel Object Test (incorporated into the Strange Situation but also studied independently; see Bronson 1972 and Fox 1989), and the transition to new peer group formation (equivalent to the transition to preschool or kindergarten in humans, studied by numerous developmental psychologists and neuroscientists; see Groeneveld et al. 2013; Gunnar et al. 2004; Ladd and Price 1987; Russ et al. 2012; Turner-Cobb et al. 2008). These assessments have repeatedly demonstrated parallels between human and NHPs, namely that more anxious individuals are more inhibited in their exploration and social interactions (Dettmer et al. 2012; Fox et al. 2001; Kagan et al. 1987; Kalin and Shelton 1989; Ladd and Profilet 1996; Williamson et al. 2003).

**Advantages and Disadvantages**

As described above, a major strength in these NHP studies is the degree of similarity between monkeys and humans in their genetics, physiology, and social behavior. A particular strength in the NHP assessments of anxiety and behavioral inhibition is the degree to which the testing paradigms mimic those for humans. The similarity in study designs across species makes interpretation of the NHP data relatively easy, though limitations with the study designs do exist.

One aforementioned limitation is the degree of maternal separation that PR monkeys undergo; it could easily be argued that the majority of children exhibiting behavioral inhibition or anxiety are not separated from their caregivers 24 hours/day, and as such this model is limited in its translatability. One way to address this concern is to implement repeated but short-term mother-infant separations, as has been done with rhesus (Barr et al. 2008; Barr, Newman, Shannon et al. 2004; Spinelli et al. 2007, 2012) and squirrel monkeys (Lyons and Parker 2007; Parker et al. 2004); however, many...
primate facilities are not equipped with the physical space or personnel to conduct such studies. Another limitation to these studies is that infants are typically tested away from their mothers (e.g., the HIT and Novel Object Test), whereas children are tested with their mothers nearby. The major reason for separating the monkey infant from its mother is that, whereas human mothers can be instructed not to restrain or interact with their children in the test setting, rhesus monkeys cannot; thus, separation is required. One way around this limitation would be to lightly sedate the mother, so that she is present for contact comfort but cannot restrict the infant’s responses to the testing situations. This has been accomplished in the Free Play test for rhesus monkeys designed to mimic the similar test in children (Goldsmith and Campos 1990), though to date only two studies have been published showing individual differences in anxious behavioral responses to this assessment (Bethea et al. 2004; Williamson et al. 2003). Future studies should consider the alternative of a sedated mother for the HIT and Novel Object Test in more normative NHP populations so as to even more closely mimic studies in human children.

**Alcoholism**

The majority of studies utilizing an NHP model for alcohol abuse and alcoholism utilize the free-choice drinking paradigm in rhesus monkeys, in which subjects are provided equal access to ethanol/water solutions of varying concentrations in addition to water (Barr, Newman, Lindell et al. 2004; Henningfield and Meisch 1979; Higley, Hasert et al. 1991; Kornet et al. 1990, 1991; Schwandt et al. 2010). This paradigm is easy possible for socially housed animals (Higley, Hasert et al. 1991). Similar to humans, drinking behavior is assessed by quantifying ethanol consumption over some period of time, whereas intoxication is assessed by measuring blood alcohol levels and impaired motor function (Barr et al. 2003, 2007; Heinz et al. 1998; Henningfield and Meisch 1979; Higley, Suomi, Linnoila 1996b; Kornet et al. 1990, 1991). Researchers have also studied alcohol intake and sensitivity with respect to other behavioral measures, namely excessive aggression (Barr et al. 2003; Heinz et al. 1998; Suomi 2006), as these traits are comorbid in humans (Heinz et al. 2011; Miczek et al. 1994). The past several decades of research with NHPs has established the rhesus monkey as a reliable model of alcohol abuse and alcoholism, as they show similar blood alcohol levels, impairment, and withdrawal and relapse symptoms after alcohol consumption (Higley, Mehlman et al. 1996a; Higley, Suomi, Linnoila 1996b; Kornet et al. 1990, 1991; Schwandt et al. 2010). Furthermore, studies with NHPs have repeatedly demonstrated that individuals exposed to adversity (typically in the form of peer-rearing) are more prone to intoxication, alcohol abuse, and excessive aggression than are mother-reared infants (Barr, Schwandt et al. 2004; Fahlke et al. 2000; Heinz et al. 1998; Higley, Hasert et al. 1991), findings that mimic what is known in humans (Caspi and Moffitt 2006; Enoch 2011).

**Advantages and Disadvantages**

The major advantages to the free-choice drinking rhesus monkey model of alcohol abuse and alcoholism are (1) the ability of monkeys to choose which solution to drink, (2) the ability to socially house animals while providing access to alcohol, and (3) the similar physiological and behavioral responses to alcohol consumption as humans. Specifically, in rhesus monkeys as in humans, increased alcohol consumption is correlated with excessive aggression (Barr et al. 2003; Heinz et al. 1998) and early life adversity (Enoch 2011). Furthermore, as with the studies on anxiety in monkeys, researchers can control the environments of their subjects much more readily than can be done with humans, thereby reducing potential confounds in the results. As such, findings from rhesus monkey studies are readily translatable to humans.

One limitation to these studies in rhesus monkeys is the inability to continually monitor their blood ethanol concentration values (Schwandt et al. 2010). Although this problem could be resolved by catheterization and tethering to collect repeated blood samples, these procedures inherently involve risk of infection and, most importantly, restrict the movement of the animal so subjects cannot be socially housed, a major confound to translating the rhesus model to humans.

**Genetic and Epigenetic Approaches**

Because of their close genetic, physiologic, and neuroanatomic similarity to humans, NHP researchers are keen to investigate the underlying mechanisms for neuropsychiatric disorders. In the past few decades, major advances in genetic and epigenetic techniques have illuminated both the origins and the long-term consequences of, in particular, exposure to adversity in NHPs. This section describes the genetic and epigenetic approaches utilized in NHP studies and their relevance to humans.

**Candidate Gene Studies**

Candidate gene studies aim to identify allelic variations of certain genes that may underlie a specific disorder. The genes for study are selected based on a priori knowledge of their biologic function and their impact on a trait or disease and as such assess the validity of an “educated guess” about the genetic basis for a trait (Kwon and Goate 2000; Zhu and Zhao 2007). With respect to early rearing and associated pathologies and vulnerabilities in NHPs, the vast majority of studies have been conducted in rhesus monkeys exposed to peer rearing. In these studies, candidate genes are selected based on what is known in humans so as to establish the rhesus monkey as a reliable model for the study of the trait or pathology of...
interest. The most commonly studied genes in monkeys are those which genetic studies have identified as functionally equivalent genetic single nucleotide polymorphisms (SNPs) in rhesus monkeys to those found in humans, including the serotonin-transporter-linked polymorphic region (5-HTTLPR; Lesch et al. 1997), the μ-opioid receptor (OPRM1; Miller et al. 2004), the monoamine oxidase A (MAOA) gene promoter (Newman et al. 2005), and the corticotropin releasing hormone (CRH) promoter (Barr et al. 2008) and the brain-derived neurotrophic factor (BDNF) gene (Cirulli et al. 2011). Further research has expanded on the identification of these SNPs by genotyping individual subjects using DNA isolated from blood samples and associating particular genotypes with behaviors of interest (see Part II, below).

With respect to 5-HTTLPR and MAOA, only rhesus macaques (but not other NHPs and not even other Macaca species) possess a functional and allelic polymorphic equivalent to the human version of these transporters (Lesch et al. 1997; Wendland et al. 2006). Humans and rhesus monkeys each possess short and long variants of the 5-HTTLPR, which confer differential transcriptional activity of the serotonin transporter (5HTT) gene promoter: cells homozygous for the long variant of 5-HTTLPR produce higher concentrations of 5HTT messenger RNA than cells containing one or two copies of the short variant (Lesch et al. 1996; Lesch and Merschdorf 2000). A similar picture exists for the MAOA gene promoter for both rhesus monkeys and humans (Lesch and Merschdorf 2000; Wendland et al. 2006). Though other SNPs, such as those for CRH, OPRM1, and BDNF, are not identical in the expression of their variants, functional equivalence has been demonstrated between human and NHPs (Barr et al. 2008; Cirulli et al. 2011; Schwandt et al. 2011).

Genome-Wide Association Studies

In contrast to candidate gene studies, genome-wide association studies (GWASs) scan the entire genome for common genetic variation in hundreds or thousands of individuals without any a priori hypotheses or biased knowledge about particular genes and their functions in traits of interest (Kwon and Goate 2000; Manolio 2010; Zhu and Zhao 2007). The goal of GWASs is to determine if any variant is associated with a trait, and similar to candidate gene studies, they focus on associations between SNPs and traits or major diseases. These studies typically compare the DNA of individuals with the disorder and similar individuals without the disorder (Manolio 2010). Unfortunately, GWASs in NHPs are still quite rare, with the few that have been completed aimed at elucidating mechanisms underlying mammalian evolution (Enard et al. 2010; Kosiol et al. 2008; Nielsen et al. 2005; Pollard et al. 2006). However, these studies have laid the foundation for future work to provide a richer understanding of the genetic basis underlying the long-term consequences of early life adversity, including the development of neuropsychiatric disorders (among other health disparities).

Epigenetics

Epigenetics is the study of changes in gene activity (i.e., chemical modifications) that are not caused by changes in the DNA sequence; one primary chemical modification is DNA methylation, which may then limit gene expression by causing enhancement or silencing of a gene (Bird 2007; Szyf et al. 2008). Once thought to occur during gestation and to remain highly stable in somatic tissues (Razin and Riggs 1980), research in the past 10 to 15 years has led to the acceptance of the notion that DNA methylation also occurs postnatally and thus provides “a platform through which the environment could sculpt the genome and affect the phenotype throughout life” (Szyf et al. 2008, p. 46). Since the advent of these types of studies, several investigators have reported gene-environment interactions where different phenotypes related to identical gene variants are dependent on early life experience.

Advantages and Disadvantages

The obvious advantage of candidate gene studies is the existence of functionally equivalent SNPs in both human and NHPs; as such, findings in macaques are readily transferable to humans. Additionally, these studies can be performed relatively rapidly and inexpensively (Kwon and Goate 2000). The major limitation of this approach is its reliance on existing knowledge about the biology and phenotype of the trait in question (Kwon and Goate 2000; Zhu and Zhao 2007). Regarding GWAS, a major advantage is the unbiased nature of exploration and the ability to screen for many conditions at once, but a chief disadvantage is its cost and reliance on large sample sizes (Manolio 2010; Zhu and Zhao 2007). Both candidate gene studies and GWAS point toward functional genetic variants underlying a disorder but do not answer questions about causative mechanisms (Manolio 2010). Epigenetic techniques have several advantages, including the ability to rely on small sample sizes, the provision of information not fully captured by gene expression profiles, the relative ease of the design and interpretation of screening tests for DNA methylation (because methylation occurs in the same region of a gene unlike than mutations which occur at different sites), and the existence of several different techniques that are available to detect epigenetic changes (Diamandis 2010). Disadvantages of epigenetic studies include the fact that epigenetic changes are diverse and may require various materials and assays and that genome-scale techniques for epigenetic analysis are technically difficult (Callinan and Feinberg 2006; Diamandis 2010).

Findings from Genetic and Epigenetic Approaches in Monkeys Exposed to Early Life Adversity

This section describes the findings reported from studies using the methodologies described in Part I. We first review the
findings establishing that early life adversity in the form of maternal (and sometimes paternal) separation puts monkeys at significantly increased risk for developing behavioral pathologies. We then highlight the genetic and epigenetic research that has recently emerged in monkeys exposed to early life adversity, studies which have almost exclusively relied on rhesus monkeys.

Early Rearing Influences on Anxiety and Alcoholism

Anxious Behavior and Alcohol Consumption

The majority of studies examining early rearing influences on anxious/inhibited behavior have been conducted with PR monkeys, comparing their reactivity and development to mother-peer–reared (MPR) monkeys. These studies have consistently found that PR monkeys exhibit more anxious behavior across development (e.g., social withdrawal and self-directed and stereotypical behaviors; see Barr et al. 2003; Dettmer et al. 2012; Stevens et al. 2009; Suomi 1997, 2004) than their MPR counterparts, whether they are housed in their iso-rearing conditions (Clarke and Snipes 1998; Suomi 1997) or in response to new social group formation (Clarke 1993; Dettmer et al. 2012) or other acute stressors (Barr, Newman, Shannon et al. 2004; Nelson et al. 2009). PR monkeys are also more inhibited in their reactions to and explorations of novel situations than are MPR monkeys (Capitanio et al. 2006; Corcoran et al. 2012; Kinally et al. 2010), findings that mimic those from similar tests in behaviorally inhibited children (Fox et al. 2001). The interpretation behind these findings is that PR monkeys are inefficient at reducing fear reactions in each other or in providing a “secure base” for exploration, thus resulting in an anxious attachment (Suomi 2004). The few studies examining SPR monkeys have demonstrated more anxious behavior, especially in the form of self-directed behavior by these monkeys in social settings, than in MPR monkeys but less anxiety than PR monkeys, especially after novel group formation (Dettmer et al. 2012; Strand et al. 2005). Additionally, nursery-reared monkeys collectively exhibit dysregulated hypothalamic-pituitary-adrenal axis activity in response to separation and novel situations compared with MPR monkeys (Capitanio et al. 2005; Clarke 1993; Dettmer et al. 2012; Higley and Suomi 1989; Higley et al. 1992; Higley, Suomi, Linnoila 1991; Shannon et al. 1998).

It should be noted that studies examining the effects of brief and/or repeated separations from the caregiver(s) have yielded different results based on the species being studied. In squirrel monkeys, it appears that repeated brief separations actually induce stress inoculation (Lyons and Parker 2007). In infant titi monkeys, a 1-hour separation from both the mother and the father, but not the mother alone, resulted in surges in cortisol and distress behavior (Hoffman et al. 1995). These differing responses are thought to reflect the reproductive strategies (polygyny in squirrel monkeys vs. monogamy in titi monkeys) and thus the attachment profiles of the two species (Mendoza and Mason 1997).

With regard to alcoholism, studies with PR monkeys have reliably shown that they are more prone to excessive alcohol consumption and greater alcohol sensitivity than their MPR counterparts (Barr et al. 2003; Barr, Newman, Shannon 2004; Higley, Hasert, et al. 1991; Higley, Suomi, Linnoila 1996b; Schwandt et al. 2010). Interestingly, one study showed that this excessive consumption by PR monkeys occurred only in monkeys tested in single cages and was absent in a social setting (Barr et al. 2007). It is possible that PR monkeys may be more sensitive to the social forces behind alcohol consumption (Schwandt et al. 2010), including competition for access to alcohol.

Overall, the picture that emerges from the majority of these early rearing studies is that monkeys exposed to adverse early rearing in the form of some sort of maternal deprivation consistently exhibit more anxious behaviors and behavioral inhibition, whether in social or nonsocial settings, than monkeys reared with their mothers, and they may be at risk for the development for excessive aggression and alcohol consumption. In addition, these monkeys exhibit alterations in their neurochemical repertoires (Dettmer et al. 2014). Thus, early life adversity puts monkeys at a greater risk for the development of behavioral and biological pathologies, findings that mimic what is known about human children and emphasize the utility of the NHP early-adversity model for studying neuropsychopathology.

Figure 1 Differential DNA methylation in the prefrontal cortex (PFC) (A) and T cells (B) between mother-reared (MR) and surrogate-peer-reared (SPR) rhesus monkeys. Figure adapted with permission from Provencal et al. (2012).
Gene x Environment Interactions

Candidate Gene Studies

Similar to humans, rhesus monkeys possessing the less-functional SNPs for 5-HTTLPR, OPRM, MAOA, and CRH exhibit differential expression of the associated neurotransmitters and related behaviors, and this differential expression is exacerbated by early life adversity. Put another way, “maternal buffering” patterns of gene x environment interactions are apparent in young rhesus monkeys, such that PR monkeys with the less functionally efficient alleles of these candidate genes exhibit greater behavioral dysfunction (e.g., more anxiety, aggression, and alcohol consumption) and dysregulated physiological activity (e.g., lower central serotonin) compared with either PR monkeys with the more efficient allele or with MPR monkeys with either allele (see Kinally et al. 2010; Schwandt et al. 2010; and Suomi 2011 for a review).

One interpretation of all of these findings is that the “good genes” somehow confer resiliency to adverse early rearing environments; another explanation is that a secure attachment confers resiliency to individuals carrying the “risky” allele.

GWAS

Although currently no GWASs exist for monkeys exposed to early life adversity (presumably due to the large sample size required for reliable data), the field is wide open for such studies, particularly through a multipronged approach involving several primate centers and laboratories that utilize differential rearing paradigms. The utility of GWASs in such monkeys would not only confirm the existence of previously identified risk genes for neuropsychiatric disorders but could potentially identify several novel genes for further investigation whose effects on these disorders are moderated by maternal care, as has been indicated for human studies of neuropsychiatric disorders (Anney et al. 2010; Reich et al. 1998; Weiss et al. 2009). Thus, researchers could shed light on the causes of anxiety, aggression, and alcoholism, possibly very early in life, and could work toward developing interventions and treatments to reverse or at least mitigate the deleterious consequences of early life adversity in humans.

Epigenetics

Epigenetic studies in NHPs have only recently been conducted, and our laboratory is thus far the only one to examine

Figure 2

Nursery-reared monkeys and mother-reared (MR) monkeys show differential gene expression in leukocytes at 4 months of age. (A, C) Heat map representations of differential expression in peripheral blood mononuclear cells (PBMCs) between surrogate-peer-reared (SPR) and MR monkeys (A) and between peer-reared (PR) and MR monkeys (C). (B, D) Cellular origins of differentially expressed genes within specific PBMCs between SPR and MR monkeys (B) and between PR and MR monkeys (D). Figure adapted with permission from Cole et al. (2012).
postnatal epigenetic changes in monkeys exposed to early life adversity. In one of our recent studies, we found a signature of maternal care in the DNA methylation pattern in T cells and in the brain of adult monkeys that had been randomly assigned to either MPR or SPR at birth. In particular, early life adversity resulted in differential methylation in more than 1000 promoters. Specifically, more than 500 promoters were more methylated in MPR monkeys, whereas more than 800 were more methylated in SPR monkeys (Provencal et al. 2012; Figure 1). Of note, many of these differentially methylated promoters were found in the prefrontal cortex, a brain region known to be an important modulator of the hypothalamic-pituitary-adrenal axis (Dedovic et al. 2009), as well as one of the brain areas known to sustain long-term effects of early life adversity (Miczek et al. 2007; Uekermann and Daum 2008). Additional, though less severe, differential methylation was observed in T cells (Provencal et al. 2012), indicating an interaction between the immune system and the brain that is modulated by early life adversity well into adulthood (Szyf 2013).

Another study from our laboratory revealed differential transcriptional modulation of the developing immune system in 4-month-old monkeys exposed to either nursery-reared or MPR. Both PR and SPR monkeys showed enhanced expression of genes involved in inflammation and T-lymphocyte activation and suppression of genes involved in antimicrobial defenses (Cole et al. 2012; Figure 2). We also have additional preliminary data showing that the epigenetic effects of early life adversity are present as early as 1 month of age: PR monkeys, while still in the nursery, show differential DNA methylation in 5000 lymphocyte genes that MPR monkeys do not. Interestingly, however, it appears that the magnitude of these differences may wane over time, particularly for females, as at 2 years of age PR females show differential methylation in only 750 genes (males show differential methylation in 2500 genes; M. Szyf et al., unpublished data). Thus, by the time monkeys approach puberty, we observe a 50 to 85% reduction in differential DNA methylation in PR monkeys. Because in our laboratory from 7 months of age onward these differentially reared monkeys are housed in mixed-rearing groups and are exposed to the exact same environmental conditions, we may be able to attribute this process of “normalization” to the normative social experiences that PR monkeys receive later in infancy and beyond. Taken together, these first epigenetic findings in monkeys indicate that early life adversity affects the brain and the immune system from very early in life and that it imparts genome-wide effects that may underlie the biological and behavioral effects already known to result from this type of insult.

Conclusions

Experiments with monkey models of neuropsychiatric disorders during the past 15 to 20 years have yielded critical information regarding the underlying mechanisms for these disorders and further underscore the utility of the NHP, and the rhesus macaque in particular, as a model for neuropsychiatric disorders in humans. Though some limitations do exist in the behavioral and physiological methodologies of the NHP studies that may make the interpretation of some studies difficult, these limitations are largely eclipsed by the numerous advantages of the NHP model. As such, the field of neuropsychiatric disorders has benefited greatly from the development of these NHP models, and the future holds great potential for studies to address both the limitations in methodological design and the gaps of knowledge in existing literature.

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