Non-Human Primates: Model Animals for Developmental Psychopathology

Eric E Nelson¹ and James T Winslow^{*1,2}

¹Mood and Anxiety Disorders Program, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA; ²Non-Human Primate Neurobiology Research Core, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA

Non-human primates have been used to model psychiatric disease for several decades. The success of this paradigm has issued from comparable cognitive skills, brain morphology, and social complexity in adult monkeys and humans. Recently, interest in biological psychiatry has focused on similar brain, social, and emotional developmental processes in monkeys. In part, this is related to evidence that early postnatal experiences in human development may have profound implications for subsequent mental health. Non-human primate studies of postnatal phenomenon have generally fallen into three basic categories: experiential manipulation (largely manipulations of rearing), pharmacological manipulation (eg drug-induced psychosis), and anatomical localization (defined by strategic surgical damage). Although these efforts have been very informative each of them has certain limitations. In this review we highlight general findings from the non-human primate postnatal developmental literature and their implications for primate models in psychiatry. We argue that primates are uniquely capable of uncovering interactions between genes, environmental challenges, and development resulting in altered risk for psychopathology.

Neuropsychopharmacology Reviews (2009) **34**, 90–105; doi:10.1038/npp.2008.150; published online 17 September 2008

Keywords: rearing; mood; anxiety; social; depression; amygdala

INTRODUCTION

Recent advances in genetic technology hold great potential for advancing our understanding and treatment of psychiatric conditions. It is also clear that many non-genomic factors interact with genotype in the progress of psychopathology (Tsankova *et al*, 2007). A reductionist approach based on genotype alone will likely not suffice to explain the development of much mental illness (Eichler and Zimmerman, 2008). Non-human primate models are poised to provide unique access to highly complex interactions between genes and early developmental experiences, and to the subsequent emergence and expression of mental illness in adulthood. A major challenge for the future will be to identify how a specific genotype or combination of genes might interact differently with a specific environment or life history to increase or decrease the likelihood of subsequent psychopathology.

We assert that a critical window for this interaction occurs during postnatal development. This is distinct from intriguing evidence of prenatal sensitivities to environment that we will not address here due to space limits (Coe and Crispin, 2000; Coe *et al*, 2002, 2003; Francis *et al*, 2003). Although postnatal development had at one point been considered a time of nervous-system plasticity with a broad capacity to ‘absorb’ significant injury (Bower, 1990), it has also become evident that adverse postnatal experiences can both confer significant risk for as well as protection against the subsequent emergence of psychopathology (Nemeroff, 2004; Pine and Cohen, 2002). We believe that the non-human primate provides a unique opportunity to examine the different mechanisms that confer either risk or resilience during development and a method of harnessing these sensitivities to protect individuals against the emergence of mental illness throughout life. A growing number of studies have now begun to look at the persistent effects of early experience on emotional development and the interaction of experience with candidate genes (Barr *et al*, 2004b,c, 2008; Dempster *et al*, 2007; Newman *et al*, 2005; Spinelli *et al*, 2007; Strauss *et al*, 2005). Although predominantly association (*vs* linkage) studies, these provide a broad arsenal of candidate genes for considera-

*Correspondence: Dr JT Winslow, Non-Human Primate Neurobiology Research Core, 16701 Elmer School Road, NIHAC 110/121, Dickerson, MD 20842, USA, Tel: +301 451 2198, Fax: +301 480 4626, E-mail: jameswinslow@mail.nih.gov

Received 19 March 2008; revised 11 July 2008; accepted 2 August 2008

tion including serotonin transporter polymorphisms, opioid, dopamine, and peptide mutations.

In this review we will focus on efforts to understand the consequence of postnatal experiences that have been used to model developmental aspects of psychopathology in non-human primates.

Why are Primate Models Important to Biological Psychiatry?

Primate models of mental processes have served psychiatry for decades particularly in the domains of higher cognitive processes, and auditory and visual image processing. These models have focused on primates to further the understanding of complex neurocognitive processes due to the similar complexities of the adult human and monkey brains. Advances *in vivo* imaging technologies continue to inform these comparisons (Logothetis, 2008; Orban *et al*, 2004). As with complex neurophysiological processes, the similarity between human and non-human primates is evident in many features that are particularly relevant for psychiatric evaluation. Humans share a great deal of evolutionary history with non-human primates. Most non-human primate species live in complex social environments, which require sophisticated social cognition and behavior to recruit social support, alliance formation, and recognition of emotional displays (see for example, Maestripieri, 2007). Many psychiatric diseases are defined by their interference with normal social interactions, associated with impaired social and cognitive skills, and are in turn exacerbated when social support is inadequate or unreliable (Lam and Rosenheck, 1999; McCorkle *et al*, 2008; McManus, 1996).

To understand how psychiatric illnesses are affected by and expressed in a complex social development, non-human primates are uniquely appropriate model animals. Many non-human primates share with humans a prolonged developmental period between birth and adulthood in which socialization is progressively focused from parental care to adolescent independence and peer politics. This protracted period of development provides an opportunity for environment and experience to redirect, exacerbate, or attenuate gene-dependent pathologic tendencies. Understanding how and when these interactions are most influential in primates will likely inform the search for similar relationships in humans.

Practical Limitations and Constraints

For reasons discussed above non-human primate models of psychopathology have been important to psychiatric research for many years (Ellinwood *et al*, 1973; Thorne, 1972). However, relative to both rodent-based models and direct human studies, psychiatric research using primates remains comparatively underrepresented in the literature. There are several reasons for this: (1) primates are much more expensive to recruit, care for, and house than rodents (and perhaps humans); (2) primates are difficult and labor

intensive to handle safely; (3) the prolonged period of development for many primates, although attractive for some applications, can be daunting for others; for example, a developmental study which takes several days to complete in rodents can take several years in primates; (4) there are important ethical and legal concerns and constraints which must be addressed to initiate non-human primate studies (Swiss Committee on Animal Experiments, 2006; Eudey, 1981; Quigley, 2007).

Species Selection and Species Differences

Efforts to develop non-human primate models of developmental processes in psychiatry have focused in large part on studies of old world primate species, primarily Macaque species (eg rhesus) and to a lesser extent *Papio* (eg baboon), or *Cercopithecus* (eg vervet). However, there have been, and continue to be, elegant and very productive efforts to examine similar questions in several new world species, particularly *Callithrix* (marmoset; Pryce *et al*, 2004), *Cebus* (capuchin; Weaver and de Waal, 2003), and *Saimiri* (squirrel monkeys; Parker *et al*, 2007). These latter species offer some distinct practical advantages in terms of husbandry and handling. Furthermore, they offer unique behavioral, endocrinological, and neuroanatomical features, which make them quite attractive for specific research questions. For example, marmoset monkeys form monogamous, biparental social relationships and frequently birth twins. This latter feature, along with a relatively short gestation and rapid maturation make the marmoset an attractive candidate for gene-environment interaction studies and conceivably for genetic manipulation. Caution must nevertheless be taken to appreciate that significant species differences do exist both between humans and non-human primates (Pryce, 2008) and among the many non-human primate species studied.

However, the cost of new world monkeys is that they are one step further away from humans than old world species. These differences are likely to influence the generalizability of findings between species—certainly between new world and old world monkeys—but even between more closely related old world species such as bonnet and rhesus macaques and ultimately between non-human and human species. For example (Pryce, 2008) compared the ontogeny of expression of corticosteroid genes in several new world and old world monkey species and described significant species differences. Pryce suggests that unique expression levels of genes for corticosteroid receptors at the time of an early-life stress will determine what that experience's effect will be on the long-term development of the individual. This will depend on its species, what brain-region was expressing the gene, and the receptor-type specificity. There is also evidence that some genetic polymorphisms (eg 5HTTPR) with demonstrated effect on emotionality and behavior in humans are unique to old world monkey species and may not occur spontaneously in new world monkeys. Conse-

quently their role in development may not be well modeled in new world monkeys (Lesch *et al*, 1997).

Nevertheless, induction of mutations in new world monkeys, for example using lentiviral delivery techniques would likely be very instructive—much like strategic mutations in transgenic mice and rats have been for several decades. Furthermore these mutations would be expressed in species capable of highly complex social relationships. Efforts already initiated in rhesus monkeys have demonstrated both the promise as well as the constraints of this approach in old world monkeys (Yang *et al*, 2008).

Any animal model of a psychopathology must be viewed as an approximation whose value depends on its capacity to ‘reconstruct’ the etiology and pathophysiology of a disease (Lipska and Weinberger, 2000). Although non-human primates display, under specific circumstances, behavioral syndromes comparable to human depression and anxiety, other disorders such as schizophrenia and autism do not appear to occur spontaneously and may depend on the expressions of species-specific behaviors. Furthermore, even when some aspects of a psychopathologic syndrome are present in a primate model, certain aspects—especially those that rely on linguistic processes—may not be present at all. Thus these models are at best only a proxy for a human disease state.

ADVERSE REARING AND SOCIAL EXPERIENCE MODELS

The pioneering studies of Harry Harlow demonstrated that early life stress can have profound and long lasting effects on the behavior, affect, and physiology of non-human primates (Harlow *et al*, 1965). These studies typically involved manipulating the early social environment of an infant monkey and we will refer to these and related methods collectively as adverse rearing. Early applications of these models incorporated rather extreme environmental deprivations (eg total social isolation at birth) in an effort to elicit a fully developed psychopathology such as psychosis, autistic syndrome, or anaclitic depression (Harlow *et al*, 1965; Harlow and Mc Kinney, 1971; Seay and Harlow, 1965).

Accumulating basic, clinical, and epidemiological evidence support assertions that far more modest early adverse experience (compared to social isolation) may alter risk for subsequent psychopathology and medical illnesses both independent of and in interaction with heritable factors (Barr *et al*, 2003; Sanchez, 2006). Animal models have provided evidence that the experience of an early traumatic event such as maternal stress or illness, as well as postnatal neglect or abuse can alter behavioral and neuroendocrine responsiveness, brain morphology, central levels of gene expression, and neurochemical markers. These experiences may also alter normal developmental processes that have been implicated in the etiology of psychiatric disorders (Sanchez, 2006).

Naturalistic Rearing Environments and Infant Emotionality

Studies of spontaneous differences in mothering styles in rats and the consequent alterations in behavioral and neural systems of offspring have recently yielded fascinating insights not only about the effects of experience on developmental outcomes but also on the interaction of experience with genotype through epigenetic processes (Szyf *et al*, 2007; Weaver *et al*, 2004).

Efforts to examine spontaneous variation in infant monkey emotional development as a function of natural differences in mothering style or rearing experience have also begun to reveal important relationships. These efforts are however constrained by relatively small effect sizes requiring very large population samples for detection in the absence of provocative stimuli (such as maternal loss). These efforts have further demonstrated that significant research costs and unique research environments are necessary for studies in naturalistic populations (Capitanio *et al*, 2005; Kinnally *et al*, 2008; Maestripieri *et al*, 2006).

Empirical, *naturalistic* studies of *adverse rearing* in monkeys are relatively recent and have been limited to a preliminary examination of the causes and consequences of abusive or neglectful mothering styles. These are observed to occur at a low but persistent rate in macaque species and appear to be in part heritable (Maestripieri, 1998, 2005; Maestripieri *et al*, 2005).

Evidence of persistent changes in brain systems including reduced corticospinal fluid 5HIAA (5-hydroxy-indoleacetic acid) levels well after weaning suggest that primate maternal abuse might offer some important insights about subsequent risk for pathology in affected offspring (Maestripieri *et al*, 2006; Sanchez *et al*, 2007). This approach, however, suffers from the difficulties of operationally defining or quantifying both severity and the critical timing of abuse (Carroll and Maestripieri, 1998).

Efforts to examine individual differences in emotionality and neural processes associated with variations in maternal care comparable to the methods used successfully by Michael Meaney and his colleagues (Szyf *et al*, 2007; Zhang *et al*, 2006) in rodents are nevertheless being adopted in primate studies (Lyons *et al*, 2000; Parker *et al*, 2006; Sanchez, 2006) and are likely to reveal important relationships between the physiology of neonatal development and mental health.

Experimental Models of Adverse Rearing

Like human infants, most primate species used in models of maternal manipulation such as the old world rhesus and the new world marmoset and squirrel monkeys engage in a great deal of intense infant–parental interaction in early infancy. This typically involves extensive physical contact (eg ventral–ventral contact) and buffering juvenile and adult social interchanges during early maturation. Separating infants from their parents initially elicits an intense,

acute distress and protest response in both infants and mothers. This reaction typically includes psychomotor agitation, vocalization, and elevated secretion of cortisol (Detting *et al*, 2007; Rilling *et al*, 2001) and the behavioral agitation is quickly resolved when mother and infant are reunited.

Reunion is often associated with compensatory mother–infant ventral–ventral contact and heightened protectiveness. The unrelieved protest response typically progresses to a ‘despair’ profile including loss of motivation, psychomotor retardation, and persistent alterations of homeostatic processes with protracted separation (Kaufman and Rosenblum, 1967a,b). The emotional progression in infant monkeys following maternal separation has been described as acute distress followed by chronic despair and in many ways models the emergence of mood and anxiety disorders in humans (Bowlby, 1973; Emde *et al*, 1965; Gilmer and McKinney, 2003; Pryce *et al*, 2005; Spitz, 1952) and rodents (Bush *et al*, 2002; Hofer, 1996; Kirsch *et al*, 2005). Remarkably, behavioral compensation during reunion may yet have potent effects on subsequent adaptation to stress and reunion (Sanchez, 2006).

Parental loss/orphanage rearing—These paradigms represent variations on protocols originally described by Harry Harlow (Seay and Harlow, 1965) and developed by Stephen Suomi (Suomi, 1991, 1997). Typically, infants are removed from their mother shortly after birth, hand raised in a nursery for a few weeks after removal and then housed in small groups or pairs of similarly reared peers. These paradigms are typically referred to as peer rearing or nursery rearing. A variation on this procedure includes a period of ‘surrogate-rearing’ with an inanimate attachment object in place of peers. Although this orphanage-type rearing is clearly abnormal, it is not at all clear what aspect of the experience produces the persistent alterations in behavior and physiology. Indeed, in some ways the nursery-rearing environment is potentially more predictable and possibly less stressful than life with mom in a complex social group. A recent variation on this paradigm has begun to examine maternal loss at different postnatal ages and preliminary reports suggest that the consequent deficits in behavioral development are qualitatively different depending on the age of loss and fostering (Cameron, 2004). These studies ultimately may help clarify when and what aspect of parental loss is significant and what treatments are most successful (Rutter and O’Connor, 2004).

Repeated separation—These paradigms typically involve repeatedly separating infants from their natal group for relatively short periods (few hours, several days, and up to 3–4 weeks) of time followed by repeated reunions (Clarke *et al*, 1998; Higley *et al*, 1991; Sanchez *et al*, 2005). These paradigms are distinguished by more provocative disruptions of parent–infant contact associated with repeated incidents of the protest, despair, and reunion. The impact of these procedures appears to be further intensified if the schedule of the experiences is unpredictable (Levine, 2000; Sanchez *et al*, 2005).

Maternal neglect—These paradigms include a protocol described by Leonard Rosenblum and co-workers (Andrews and Rosenblum, 1991; Rosenblum and Andrews, 1994) that involved systematically varying the foraging demands on bonnet monkey mothers, which then required them to spend less time in close contact with their infants to obtain their daily access to food. As with repeated separation, the most provocative foraging demand schedules contained an element of unpredictability (Andrews and Rosenblum, 1991). This latter protocol offered a systematic, naturalistic method to address some of the same questions sought by Maestripieri and co-workers (Maestripieri, 1998) in natural populations. It has the added advantage of being able to stage the neglect in selected animals rather than relying on a low-rate emergence of spontaneous maternal neglect in large social groups.

Several themes have emerged in studies of infants that have been reared under conditions of suboptimal parental care. Complex behavioral abnormalities have consistently been observed in adversely reared monkeys, with the most notable deficits being in social and emotional behaviors. Intriguingly, with some caveats these behavioral outcomes appear to be similar for each of the different types of adverse rearing paradigms, particularly when the experience occurs within the first 6 months of life.

BEHAVIORAL ABNORMALITIES

Adversely reared monkeys display more aggressive and less affiliative behaviors with peers (Suomi, 1997; Winslow, 2005) and reduced competence in both reproductive and parental behavior (Champoux, 2002b; Suomi, 1997). In spite of the fact that they are more aggressive, adversely reared monkeys are also consistently subordinate in the dominance hierarchy than normally reared monkeys (Bastian *et al*, 2003). The low dominance status is likely to derive from an inability to form alliances with peers (Winslow, 2005). These socioemotional deficits are likely the result of dysfunction in at least two domains. First, adversely reared monkeys generally appear to respond abnormally to emotionally provocative stimuli. In the social domain this has been characterized as blunted or aberrant affective response to social solicitations or social disengagement (Parr *et al*, 2002; Wallen, 1996; Wallen *et al*, 1981; Winslow *et al*, 2003). These emotional alterations typically emerge during early development and persist, and sometimes intensify, as animals mature (Lutz *et al*, 2003). In addition to the deficit in systems related to general affective tone, there also appear to be specific deficits in social cognition. These social deficits likely have cumulative effects as animals develop progressively more abnormal social repertoires and associated withdrawal or isolation.

Infants who have not engaged in normal social modeling and dominance related processes from the protected embrace of their mothers’ ventrum may not acquire the necessary skills to negotiate social politics or the cognitive

information required for the appropriate processing of complex social signals (Suomi, 1997; Sanchez, 2006).

This deficit in social cognition may lead to incompetent and provocative social behavior—for example, being inappropriately aggressive, submissive, or affiliative in response to conspecific social solicitations (Anderson *et al*, 1977). Interestingly, a similar pattern of deficits in social cognitive processes may underlie non-selective hyper-affiliative behaviors often observed in human children who were subjected to institutional privation in early life (Rutter and O'Connor, 2004).

In addition to these marked deficits in social behavior, adversely reared monkeys display several other abnormal behavioral features. Adversely reared monkeys display many more atypical behaviors, including both self-injurious behaviors and motor stereotypies, have a heightened behavioral response to mild stressors, and are much more timid and reticent when faced with novel stimuli (Fahlke *et al*, 2000; Kraemer *et al*, 1997; Suomi, 1997; Winslow, 2005). A number of studies have also shown that adversely reared monkeys will consume more alcohol as juveniles and young adults than their normally reared peers (Fahlke *et al*, 2000; Higley *et al*, 1998). Interestingly, the alcohol consumption of

adversely reared monkeys can be attenuated with antidepressant drug administration (Higley *et al*, 1998) suggesting that increased alcohol consumption of the adversely reared monkeys may be related to an affective disturbance.

Research on adverse rearing in the past decade has focused in large part on alterations in functioning of the hypothalamic-pituitary-adrenal axis. The goal of these studies has been to identify a reliable change in HPA function, which might serve as a risk factor for adult onset mood or anxiety disorder.

Table 1 is a representative bibliography of three common outcomes observed in juvenile and adult non-human primates after experimental disruptions of the mother–infant relationship in early life. These outcomes include both vulnerability and resilience to psychopathological states and also describe deficits in social competence. Experimental manipulations included (1) peer rearing, (2) repeated brief separations from the mother, and (3) both variable foraging and demand and high foraging demand placed on the mother. The species studied included the old world rhesus and bonnet macaques and the new world squirrel and marmoset monkeys.

TABLE 1: Summarizing behavioral and endocrine reactivity findings in mother–infant separation models

PHENOTYPE	PHYSIOLOGY	TREATMENT	SPECIES	CITATION
Psychologically vulnerable	Amygdala ↑ CRF receptors	Brief repeated separation	Rhesus	Sanchez 2006
	CRF ↑ in CSF	VFD	Bonnet	Coplan <i>et al</i> . 1996
	Cort ↑ in infancy, ↓ in juvenile	Brief repeated separation	Marmoset	Coplan <i>et al</i> . 1998
	↑ NE in juvenile ↓ reversal learning			Dettling <i>et al</i> . 2002a; b; Pryce <i>et al</i> . 2005
	Cort in infancy, blunted diurnal in juvenile	Brief repeated separation	Rhesus	Sanchez <i>et al</i> . 2005
	↑ insulin resistance and obesity	VFD	Bonnett	Kaufman and Rosenblum 1967a
	Cort in infancy, ↑ juvenile	Peer rearing	Rhesus	Higley <i>et al</i> . 1992
	↑ TGF-β to stress	VFD	Bonnett	Smith <i>et al</i> . 2001
	↑ NE ↓ 5-HIAA in CSF	Peer rearing	Rhesus	Clarke <i>et al</i> . 1996
				Higley <i>et al</i> . 1992
Psychologically resilient	↑ acoustic startle	Brief repeated separation	Rhesus	Sanchez <i>et al</i> . 2005
	↑ alcohol intake	Peer rearing	Rhesus	Barr <i>et al</i> . 2004a
	↑ HPA negative feedback (↓ ACTH to cort)	Brief repeated separation	Squirrel	Lyons <i>et al</i> . 2000
		HFD		Parker <i>et al</i> . 2006
	↓ cort set point	Peer rearing	Rhesus	Capitanio <i>et al</i> . 2005
	↑ prefrontal inhibitory control	Brief repeated separation	Squirrel	Parker <i>et al</i> . 2005
	Cort in infancy, no change in stress	Peer rearing		Shannon <i>et al</i> . 2005
	↓ Cort to stress	Brief repeated separation	Squirrel	Levine and Mody 2003
				Parker <i>et al</i> . 2006
Socially dysfunctional	↓ social competence	Peer rearing	Rhesus	Champoux 2002
				Suomi 1997
	↓ social reward	Brief repeated separation	Marmoset	Pryce <i>et al</i> . 2005
	↓ dominance	Peer rearing	Rhesus	Bastian <i>et al</i> . 2003
	↑ aggression, ↓ affiliative	Peer rearing	Rhesus	Winslow 2005
	↓ oxytocin	Peer rearing	Rhesus	Winslow <i>et al</i> . 2003

Abbrev: Corticotropin releasing factor (CRF); norepinephrine (NE); cortisol (CORT); transforming growth factor beta (TGF-β); 5HIAA (5-hydroxyindoleacetic acid); adrenocorticotrophic hormone (ACTH); corticospinal Fluid (CSF); hypothalamic pituitary adrenal axis (HPA)

Although a number of promising leads have been identified, it remains unclear what (if any) aspect of altered HPA axis or central CRF control of HPA activity represents a strong risk factor for adult mental illness. Also unclear is the cumulative role of altered emotional and social deficits in the emergence of adult pathology. It is likely that both behavioral and physiological processes are important and that integration of these outcomes with information about candidate genotypes represents an important new direction for these studies (Sanchez, 2006).

Can Early Adversity Result in Resilience?

In contrast to the literature cited above indicating an adverse effect of mother–infant separation on stress reactivity, some early studies of infant–mother separation in rodents reported that experimenter handling and brief bouts of maternal separation may actually be protective for the developing animal (Levine, 2000; Meaney *et al.*, 1996; Parker *et al.*, 2006; Pryce *et al.*, 2005).

In particular, limited handling of infants resulted in increased exploration, reduced anxiety levels, and a blunted HPA response to stress in adult animals. This effect may have been in part due to an increased level of licking and grooming by the mother after reunion (Denenberg, 1999). However, it may also be attributed to a benefit of experiencing mild adversity during early development (Levine, 2000). Intriguingly, this behavioral resilience may be associated with neurogenesis in specific brain areas that have also been implicated in the efficacy of antidepressant treatment (Kozorovitskiy and Gould, 2004; Sahay and Hen, 2008; Thompson *et al.*, 2008).

There is similar evidence that mild developmental adversity may have comparable benefits for some non-human primates (Lyons and Parker, 2007). Young squirrel monkeys who are subjected to a mild separation stress at the developmental junction of infancy and adolescence, develop better cognitive flexibility skills, have blunted HPA response to stress, and are more curious and exploratory as young adults than monkeys who have not had this experience (Lyons and Parker, 2007; Parker *et al.*, 2005, 2006). This may be a result of learning to overcome a mild challenge during an important period of developmental transition (Lyons and Parker, 2007).

These particular effects have so far been described primarily in new world monkeys—so the possibility of species differences seems possible. However, it is noteworthy that differences which may be characterized as resilient have also been described in the physiological baselines and alterations in HPA activity of both new world and old world monkey species (Lyons *et al.*, 2000).

Understanding the specifics of whether a stressful experience early in development will lead to susceptibility or resilience remains a challenge for future investigations.

ADVERSE REARING INTERACTS WITH GENOTYPE

Until recently most studies of the effects of adverse rearing have been conducted without the knowledge of the subjects' genotype, and generally separation from the mother is a robust enough manipulation to alter development across a wide variety of genotypes. However, genotype clearly plays an important role in the role of social support in human psychopathology (Arseneault *et al.*, 2008; Caspi *et al.*, 2003). The interaction between genotype and environment in the ultimate expression of psychopathology is very complex, and is an area where non-human primate research may be uniquely able to make important contributions, especially in the three-way interaction between genotype, environment, and development (Champoux *et al.*, 2002a, b; Kinnally *et al.*, 2008; Newman *et al.*, 2005; Reif *et al.*, 2007).

Hereditary factors appear to play a role in monkey's affect, temperament, and response to early adversity. A recent study in marmosets which takes advantage of the fact that marmosets naturally give birth to twins found that hereditary factors contributed substantially to both the acute and long-term changes in cortisol secretion, social behavior, and response to novelty in monkeys that underwent bouts of maternal separation (Dettling *et al.*, 2007). These hereditary responses may be attributed in part to monoamines. Clarke *et al.*, 1995 demonstrated that levels of the biogenic amines and their metabolites in CSF are highly heritable in rhesus monkeys. This is particularly important for affective disorders because of the role that biogenic amines play in mood regulation and the extensive literature indicating dysfunction in these neuronal systems in adversely reared monkeys. Rhesus monkeys contain a polymorphism in the serotonin transporter gene (Barr *et al.*, 2004c), which is homologous to the serotonin transporter polymorphism in humans and affects bioavailability of serotonin. Infant and juvenile rhesus monkeys that were homozygous for the short form of the (s) allele in the promoter region of the 5-hydroxytryptamine (5-HT) transporter gene (5HTTLPR) were found to consistently show a pattern of anxiety and inhibition in a battery of emotional tests (Bethea *et al.*, 2004; McCorkle *et al.*, 2008). Likewise, cynomolgus monkeys who were categorized as being more stress reactive by ceasing to ovulate in response to mild stressors displayed hypofunctioning of the serotonergic system in response to a pharmacological challenge (Bethea *et al.*, 2005). In monkeys, as in humans, hereditary factors not only contribute to the acute stress response but also affect the long-term developmental consequences of stress. A series of studies has now shown that rhesus monkeys who inherit the short form of the 5HTTLPR and are exposed to adverse rearing exhibit chronically lower levels of serotonin in CSF (Bennett *et al.*, 2002), have a potentiated HPA response to stress (Barr *et al.*, 2004c), and consume more alcohol in a preference test (Barr *et al.*, 2004a) than monkeys who were either homozygous for the long form of 5HTTLPR and underwent adverse rearing or who inherited the short form and did not undergo early adversity. For some of these effects, this interaction may be particularly important for

TABLE 2: Candidate gene polymorphisms interact with rearing experience in monkeys

REFERENCE	POLYMORPHISMS	SPECIES	FINDING
Bailey et al. 2007	DRD4 gene	Vervet	The association of DRD4 and novelty seeking is found in a nonhuman primate model.
Barr et al. 2003	rh-5HTTLPR	Rhesus	Serotonin transporter gene variation is associated with alcohol sensitivity in rhesus macaques exposed to early-life stress.
Barr et al. 2004b	rh-5HTTLPR	Rhesus	Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates.
Barr et al. 2004c	rh-5HTTLPR	Rhesus	Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques.
Barr et al. 2004c	rh-5HTTLPR	Rhesus	Sexual dichotomy of an interaction between early adversity and the serotonin transporter gene promoter variant in rhesus macaques.
Barr et al. 2007	OPRM1 C77G	Rhesus	Association of a functional polymorphism in the mu-opioid receptor gene with alcohol response and consumption in male rhesus macaques.
Barr et al. 2008	OPRM1 C77G	Rhesus	Variation at the mu-opioid receptor gene (OPRM1) influences attachment behavior in infant primates.
Bennett et al. 2002	rh-5HTTLPR	Rhesus	Early experience and serotonin transporter gene variation interact to influence primate CNS function.
Bethea et al. 2004	rh-5HTTLPR	Rhesus	Anxious behavior and fenfluramine-induced prolactin secretion in young rhesus macaques with different alleles of the serotonin reuptake transporter polymorphism
Bethea et al. 2005	rh-5HTTLPR	Rhesus	Serotonin-related gene expression in female monkeys with individual sensitivity to stress.
Champoux et al. 2002	rh-5HTTLPR	Rhesus	Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates.
Donaldson et al. 2008	AVPR1A gene	Apes (2 rpts) Monkeys (1 rpt)	Evolution of a behavior-linked microsatellite-containing element in the 5' flanking region of the primate AVPR1A gene.
Giorgiand Rouquier 2002	V1RL1 pseudogene	Marmoset	Identification of V1R-like putative pheromone receptor sequences in non-human primates. Characterization of V1R pseudogenes in marmoset, a primate species that possesses an intact vomeronasal organ.
Heinz et al. 2003	rh-5HTTLPR	Rhesus	Serotonin transporter availability correlates with alcohol intake in non-human primates.
Heinz et al. 1998	rh-5HTTLPR	Rhesus	In vivo association between alcohol intoxication, aggression, and serotonin transporter availability in nonhuman primates.
Izquierdo et al. 2007	rh-5HTTLPR	Rhesus	Genetic modulation of cognitive flexibility and socio-emotional behavior in rhesus monkeys.
Kinnally et al. 2008	rh-5HTTLPR	Rhesus	Effects of early experience and genotype on serotonin transporter regulation in infant rhesus macaques.
Kraemer et al. 2008	rh-5HTTLPR	Rhesus	Moderate level fetal alcohol exposure and serotonin transporter gene promoter polymorphism affect neonatal temperament and limbic-hypothalamic-pituitary-adrenal axis regulation in monkeys.
Miller et al. 2004	OPRM1 C77G	Rhesus	A mu-opioid receptor single nucleotide polymorphism in rhesus monkey: association with stress response and aggression.
Miller et al. 2001	DAT - VNTR	Rhesus	Single nucleotide polymorphisms distinguish multiple dopamine transporter alleles in primates: implications for association with attention deficit hyperactivity disorder and other neuropsychiatric disorders.
Miller-Butterworth et al. 2007	rh5-HTTLPR	Fascicularis	The serotonin transporter: sequence variation in Macaca fascicularis and its relationship to dominance.
Newman et al. 2005	rhMAOA-LPR	Rhesus	Monoamine oxidase A gene promoter variation and rearing experience influences aggressive behavior in rhesus monkeys.
Putzhammer et al. 2005	5HTTLPR	Rhesus	Evidence of a role for the 5-HTTLPR genotype in the modulation of motor response to antidepressant treatment.
Wendland et al. 2006	rh5-HTTLPR rhMAOA-LPR	Rhesus	Differential functional variability of serotonin transporter and monoamine oxidase A genes in macaque species displaying contrasting levels of aggression-related behavior.

females (Barr *et al.*, 2004a, b), which is an important observation because of the female predominance of affective disorders in humans. Table 2 summarizes numerous studies of the interaction of candidate gene mutations or polymorphisms.

Gene Expression and Gene Regulation Studies

In addition to understanding the contribution that genotype makes to individual differences in emotional responsiveness, a key, recent question is how the expression of specific genes is affected by the timing of exposure to different

stimuli (Levitt, 2003; Sabatini *et al.*, 2007). Studies have shown that at a structural level and even at a neurochemical level human and non-human primate brains continue to undergo regulated developmental changes at least through puberty and likely much longer (Gogtay *et al.*, 2006; Levitt, 2003; Lewis, 1997). At a molecular level developmental changes are occurring in gene expression. Although a tremendously complex problem, some of the normative patterns of postnatal gene expression in non-human primate brain are beginning to be mapped out (Miska *et al.*, 2004; Sabatini *et al.*, 2007). As demonstrated in the

recent study by Sabatini *et al* (2007) the developmental pattern of gene expression occurs as an interaction with environmental factors. Therefore studies like this, which focus on mapping developmental gene expression in targeted regions such as the amygdala, may offer important clues as to what aspects of CNS function are particularly sensitive to adverse or potentially therapeutic innervations at specific developmental periods. Sabatini *et al* (2007) showed that the normative timing of the expression of a gene within the amygdala coincided with a differential behavioral effect induced by removing an infant from the mother at different periods of development. Hence the authors concluded that interaction with the mother during this sensitive period was essential for normal expression of this gene within the amygdala. This study is important not only for the specific results but also because it represents a new approach for describing sensitive or critical periods for gene environment interactions.

BRAIN INJURY MODELS

Although manipulation of the mother–infant relationship has been the most extensively employed method of studying developmental perturbations in primates, it is not the only one. To understand how different brain systems interact across development, studies using lesions, neuroimaging, and gene expression have been performed at different developmental time points.

Brain injury models in primates seek to examine the potential role of specific brain regions or connections between regions in the expression of emotional or cognitive behavior. This is accomplished by examining loss and/or recovery of function following targeted destruction of selected brain structures of affected animals. This can be an awkward experimental approach. Each animal can be used for only one experiment, the lesion is typically irreversible, and the results are based on loss of function and often difficult to interpret. Interpretation is further confounded by the fact that evaluation often occurs months, sometimes years, after the lesion was produced, during which significant neural and behavioral adaptations likely occur.

Early brain injury studies used relatively nonspecific techniques such as aspiration or electrolytic probes to remove small amounts of tissue in targeted areas. The resulting ablations necessarily affect not only the cell bodies but also fibers of passage and consequently reduce the capacity to describe selective and specific relationships between brain loci and behavioral outcomes (Goulet *et al*, 1998). Nevertheless, for some questions this approach continues to yield important insights about the pivotal role of limbic and cortical structures in the modulation of emotion, cognition, and social competence (Felger *et al*, 2007; Machado and Bachevalier, 2003).

A complementary technique involves the application of minute quantities of excitotoxins such as ibotenic acid to target areas. Excitotoxins are selectively taken up into and

destroy cell bodies, leaving fibers of passage intact. The precision of both techniques has been significantly enhanced in recent years by use of *in vivo* brain imaging to guide placement of injections or electrodes (Saunders *et al*, 1990).

Of particular relevance to psychiatry are efforts to examine the role of damaged cortical and limbic structures in monkeys in the emergence of cognitive and social deficits associated with schizophrenia and autism. These include elegant studies of lesions in the prefrontal cortex, orbitofrontal cortex, hippocampus, and amygdala in both adult (for reviews see Bast, 2007; Chudasama and Robbins, 2006; Murray *et al*, 2007) and neonatal monkeys (to be detailed below). Not surprisingly, evidence indicates that the same lesion may have very different effects depending on when the lesion occurs, in infancy versus adulthood or different stages of adolescence (Bachevalier and Malkova, 2006).

Early developmental brain lesion research focused on the rapid recovery of function and the remarkable plasticity of the infant frontocortical structures (Goldman, 1976, 1978; Miller *et al*, 1973). More recently, several investigators have begun to examine persistent alterations in cognitive, social, and emotional behavior associated with neonatal lesions in medial temporal regions including amygdala and hippocampus, or frontocortical structures (Bachevalier *et al*, 1999; Beauregard *et al*, 1995; Goursaud and Bachevalier, 2007). These efforts have generally focused on one of two broad psychiatric syndromes: cognitive deficits assessed as models of symptoms for schizophrenia or social deficits comparable to symptoms of autism.

Neurodevelopmental Model of Schizophrenia: Neonatal Hippocampal Lesions

Informed by persistent and reliable evidence of altered cell biology in the hippocampus and associated prefrontal cortical structures of schizophrenic patients (Heinz *et al*, 1999), numerous investigators have examined animal models of hippocampal damage (Carr and Sesack, 1996; Jay *et al*, 1989). Interest has focused on the hypothesis that neonatal disturbances in the development of the hippocampus along with projections to the prefrontal cortex may underlie deficits in cortical functioning in schizophrenia. Findings in rat models demonstrated that early lesions produced relatively modest deficits in juvenile rats but deficits appear to intensify as subjects mature, particularly around the time of puberty. This mimics to some extent the typical ontogeny of the schizophrenia. The range of deficits appears across both cognitive and social behaviors and many appear related to dopaminergic processes and are sensitive to dopamine-based therapeutic treatment (Lipska *et al*, 1995).

Efforts to translate the rodent model to a primate model have also been productive. Similar to rodents, a neonatal lesion of the hippocampus is associated with relatively modest changes in behavior in the young monkey but with more intense deficits emerging as the animal matures

(Bachevalier *et al*, 1990). Also consistent are findings that neonatal hippocampal lesions produce persistent changes in dopaminergic systems, particularly in the striatum as well as evidence of a broader pattern of altered neuronal development in the prefrontal cortex (Bertolino *et al*, 1997; Heinz *et al*, 1999; Saunders *et al*, 1998). Subsequent studies have described rather specific social and emotional deficits characterized by elevated aggression. Cognitive deficits also emerged, typically related to recognition memory whereas other functions appeared to be spared (Bachevalier *et al*, 1990; Goursaud *et al*, 2006; Kaldy and Sigala, 2004; Lavenex *et al*, 2007a,b). These studies have generally demonstrated that early hippocampal damage results in reliable and persistent alterations in frontocortical development and that at least some of these alterations can be moderated by damage to the prefrontal cortex or with dopamine-based treatments of schizophrenia. Consequently, these models have relatively strong face and predictive validity for some symptoms of schizophrenia. Conversely, there is little evidence of comparable brain damage in schizophrenia and strong evidence of a genetic transmission of risk, which together indicates that a brain injury model is not likely to attain strong construct validity for the cause of disease.

Neurodevelopmental Model of Socioemotional Deficit: Neonatal Amygdala Lesions

Interest in the role of the amygdala in the development of social behavior has a long history (Kling, 1974; Kling and Green, 1967), and studies have detailed a reliable relationship between a damaged amygdala and abnormal adult social behavior. Additional studies suggest that these social deficits are related to difficulties assessing and responding to threatening stimuli. (Thompson, 1981; Thompson *et al*, 1969, 1977; Thompson and Towfighi, 1976) Evidence of a progressive deficit in social and emotional behavior after selective neonatal injuries to the amygdala was replicated by Beauregard *et al* (1995), who examined the development of social interactions of monkeys amygdalectomized during the first postnatal month. Their findings indicated that early damage to the amygdala results in progressively profound changes in affective responses and social behavior, and these changes persisted into adulthood.

Based in part on these studies as well as human post-mortem and *in vivo* MRI findings, several clinical investigators have proposed that the amygdala may be a critical component to normal social development and that defects in the amygdala may underlie some symptoms of autism (Baron-Cohen *et al*, 2000; Brothers, 1990). Subsequent studies have revealed that the development of social behavior does not appear to be specifically impaired in animals with selective, neurotoxin-induced lesions of the amygdala (Bauman *et al*, 2004a,b). Interestingly, one of the factors which may contribute to different outcomes of early lesion is the postnatal rearing environment. Early studies combined neonatal lesion with peer rearing (ie rearing with

age-matched peers without adult animals) wherein social deficits associated with abnormal rearing appeared to be aggravated by brain injury (Amaral *et al*, 2003). Lesioned neonates who are returned to their mothers and for whom the dyad is then provided additional conspecific socialization opportunities until weaning appear to develop normal social repertoires (Bauman *et al*, 2004b). Additional analysis suggests that the neonatal lesion does not specifically affect social behavior but does significantly affect processing and interpretation of threatening stimuli including threatening social stimuli (Bauman *et al*, 2004b). In view of the findings related to the persistent effects of adverse rearing, it seems likely that altered social cognition (ie. misinterpretation of threatening social stimuli) involves the amygdala as well as other cortical structures, and injury results in cumulative effects on social competence. This accumulated deficit in appropriate social experience could also result in altered risk for the emergence of psychopathology (see for example Meyer-Lindenberg *et al*, 2005).

Reversible Inactivation

There has been increasing interest in methods that permit reversible inactivation of localized brain regions. These techniques involve infusion of minute quantities of substances that temporarily suppress neural activity from several hours up to much longer, experimenter-determined intervals depending on the mechanism of action. Such methods represent particularly attractive technologies for examining the potential role of targeted areas during specific periods of development.

The most common of these techniques uses the inhibitory properties of the GABA agonist muscimol and has been optimized in studies of visual information processing, (eg Ono and Mustari, 2007) and motor control (eg Desmurget and Turner, 2008) in non-human primates. Recently, this method has been applied to studies of neural systems related to psychological constructs in adult monkeys including reward pathways (Amiez *et al*, 2006; Wellman *et al*, 2005) and species-specific vocal behavior (Siebert and Jurgens, 2003).

The feasibility of using reversible inactivation techniques to examine developmental models of psychopathology has been demonstrated in rats by Lipska *et al* (2002), who described emergence of dopamine hypersensitivity in adult rats whose ventral hippocampus was transiently inactivated as neonates. Similar approaches have not as yet translated to applications in non-human primate social and emotional development. In part, this may be related to the relatively short duration of inactivation provided by acute application of these agents (on the order of several hours) and the likelihood that repeated administration produces permanent damage to sites of interest (Heiss *et al*, 2005). This may limit their usefulness in an organism whose development is measured in months and years compared to a few days. Nevertheless these techniques may be very useful for examining the progress of functional brain-behavior

relationships over the course of development using limited repeated testing designs (Bay *et al*, 2007; Chen *et al*, 2006). Importantly, new gene-silencing technologies developed in rodents offer an intriguing opportunity in the future to examine localized inactivation over more protracted intervals with exquisite control over timing and targeting of the inactivation (Cryan *et al*, 2007; Kappel *et al*, 2007; Kumar *et al*, 2007; Salahpour *et al*, 2007).

PHARMACOLOGICAL MODELS

A number of pharmacological models of psychopathology have been advanced in adult rodents, monkeys and humans. Remarkably, few of these models have been translated into developmental models in either rodents or non-human primates. We define such models by efforts to reproduce symptoms of unique psychiatric conditions by administering drugs, either acutely or chronically.

The most prominent among these models are psychostimulant-induced psychosis and amphetamine sensitization paradigms (Castner and Williams, 2007). Various regimes of amphetamine treatment elicit behaviors that have been variously referred to as psychotomimetic (Sams-Dodd and Newman, 1997), psychotic like (Machiyama, 1992), abnormal (Schlemmer and Davis, 1986), and hallucinatory like (Ellison and Eison, 1983). These behaviors include hyper-vigilance, abnormal eye tracking, grasping, and checking.

A vigorous research effort has demonstrated that this model shows excellent face validity not only for positive symptoms of schizophrenia but also for persistent cognitive deficits such as altered working memory and social deficits. Similarly, the model successfully predicts the therapeutic efficacies of both conventional dopamine-based and novel antipsychotic treatment. Recent studies have also demonstrated that sensitization treatment strategies depend on the integrity of the prefrontal cortex and produce schizophrenia-like alterations in prefrontal cortical cell morphology (Selemon *et al*, 2007).

A number of studies have also examined the anxiogenic properties of selected drugs in non-human primates, such as β -carboline (Weerts *et al*, 1993; Insel *et al*, 1988; Vellucci *et al*, 1986) or pentylenetetrazol (Palit *et al*, 1998) or adrenergic receptor agonists (Rosenblum *et al*, 1991, 1994; Coplan *et al*, 1992), to describe good face validity for aspects of anxiety and predictive validity for sensitivity to anxiolytic drugs. Indeed, studies by Rosenblum (Rosenblum *et al*, 1994) demonstrated that early adverse rearing experience was an important determinant of the sensitivity of individual animals to the anxiogenic properties of drugs. Similarly, Miller and his colleagues (Felger *et al*, 2007) have recently begun to characterize the depressogenic effects of the cytokine drug interferon A in monkeys.

These pharmacological techniques have, to our knowledge not yet been translated into developmental models of psychopathology in non-human primates. This is not to say that developmental pharmacological methods have not been

applied to other disease models in both rodents and primates. Indeed, there is a well-developed descriptive literature detailing potential brain injury, emotional and cognitive deficits associated with pre- and postnatal exposure environmental toxins, pollutants and drugs of abuse in non-human primates (Buse *et al*, 2003; Haberny *et al*, 2002; Paule, 2005; Rice, 2000; Wu *et al*, 2008). These efforts have demonstrated that developmental pharmacological challenges might be well suited to providing discreet, quantifiable stimulation of critical pathways during development, particularly in validated risk models, to examine the potential role of unique neurotransmitter systems in subsequent pathology.

FUTURE DIRECTIONS IN PRIMATE DEVELOPMENTAL PSYCHIATRY

We see several critically important needs and opportunities for advancing the utility of non-human primates as model organisms for psychiatric research.

A Developmental Neurobiology of Key Non-Human Primate Species

Studies of normative non-human primate postnatal brain development lag far behind efforts in rodents, resulting in significant gaps in information about progressive changes in structure and neurochemistry (Levitt, 2003; Pryce, 2008). Similarly, efforts to characterize gene expression patterns in primate brain are in relatively early stages (Pryce, 2008; Sabatini *et al*, 2007). Further research in the developmental neurobiology of the non-human primate is critically important to progress in efforts to examine the interaction of environment, developmental stage, and genes for modeling psychopathology.

Standardization of Behavioral Testing

Rodent behavioral research has made significant strides in developing standardized testing to ensure generalizability of findings across different species, strains, and laboratories (eg Crawley, 2003). Current primate developmental behavioral research often employs somewhat more idiosyncratic methods with little standardization between investigators. For example, what constitutes nursery rearing varies significantly between primate facilities and likely contributes to some of the variability in the literature. This is amplified by the protracted duration of infancy in primates compared to rodents, which provides many opportunities for unexpected environmental intrusions. Different adverse rearing protocols focus on different aspects of the rearing experience. It is difficult to differentiate post-separation rearing experience from the early distress of parental loss. Furthermore, as these experiences are often sustained for a long period of time it is often difficult to know if there are specific developmental periods that are more sensitive to manipulations than others. The brain lesion literature also

suffers from a similar lack of specificity. Non-human primate developmental research would be well served by an effort to systematically operationalize adverse rearing experiences.

Although studies that focus on broadly defined social behavior are useful in that they allow maximal flexibility in identifying abnormal behavioral responses, they are limited in the extent to which they inform understanding of specific brain pathology. Experimental paradigms such as startle or attention-orienting tasks which focus on behavioral and cognitive processes mapped onto specific neural structures are much more likely to add to our understanding of the specific pathology that underlies emotional dysregulation in primate models.

To date, such paradigms are relatively sparse but non-human primates are capable of performing many of the specific tasks on which humans with disorders typically show deviant responses. Many of these paradigms are both repeatable and stable so probes could be carried out on the same individuals longitudinally. This would enable a better description at a behavioral level as to how pathologic processes emerge; it might also inform how specific brain structures interact across development to sustain behavioral abnormalities.

Gene–Environment Interactions

A second area where future non-human primate studies will likely make an important contribution is a greater understanding of the gene–environment link. The striking recent findings of the differential susceptibility that is conferred by variations in the serotonin transporter gene to early adversity (Barr *et al*, 2004a) emphasizes the importance of genetic–environment interaction in the emergence of psychiatric disease. Human-based studies have identified many other polymorphic genes as potential candidates for psychiatric vulnerability including the μ -opioid receptor (Wand *et al*, 2002), brain-derived neurotrophic factor (Strauss *et al*, 2005), serotonin-1a receptor (Lemondé *et al*, 2003), vasopressin-1b receptor (Dempster *et al*, 2007), and various dopamine receptors such as COMT and DRD4 (Munafo *et al*, 2008; Williams *et al*, 2007) among many others. The genetic profile of non-human primates is easily obtainable but only rarely incorporated into study designs.

The combination of small sample sizes in most primate studies and low base rates of many of these variations often make it difficult to assess the impact of specific polymorphisms on primate behavior. However, routine screening at breeding facilities of select polymorphic genotypes has begun to facilitate the selection of appropriate samples. The three-way interaction between genotype, environment, and developmental timing is likely to have important implications for psychiatry (Barr *et al*, 2008; Kinnally *et al*, 2008; Reif *et al*, 2007). As key structures increasingly become the focus of psychopathology (such as amygdala and ventral prefrontal cortex), developing normative maps of not only

genetic expression but the *timing* of genetic expression—when specific genes are turned on and off—might provide important clues as to the sensitivity to different types of environmental input. Furthermore, advances in molecular techniques may soon make it possible to apply genetic knockout technology to non-human primate models (Yang *et al*, 2008). This would enable activating or deactivating specific genes at different periods of development. This kind of technique will provide important information regarding the physiological cascade of events that takes place within the central nervous system over the course of development.

Finally, the rapidly advancing field of neuroimaging is increasingly incorporated into non-human primate-based studies of developmental psychopathology (Fox *et al*, 2008; Rilling *et al*, 2001). Although ethical considerations have constrained PET and MRI studies in developing humans, fewer restrictions apply to non-human primates. Indeed, there has been a rapid advance in techniques developed to permit imaging in awake animals. Consequently, both structural neuroimaging techniques, such as morphometric assessment and diffusion tensor imaging, and functional techniques such as fMRI are becoming increasingly common in primates (Hadj-Bouziiane *et al*, 2008; Leopold and Maier, 2006; Logothetis *et al*, 1999; Petkov *et al*, 2008). Thus important information regarding developmental trajectories of specific neurochemical systems is remarkably accessible in monkeys. Novel contrast agents, such as manganese, which may signal functional activity and functional connectivity, are also on the horizon (Bock *et al*, 2008; Koretsky and Silva, 2004). Although performing neuroimaging in non-human primates presents a variety of challenges, it also affords the opportunity for much more control and better assessment than is typically available in human studies. This approach in particular opens remarkable opportunities to examine repeatedly the interaction of brain development and genotype over the course of an individual's development (Rogers *et al*, 2008).

SUMMARY

Non-human primate studies have made tremendous contributions to our understanding of the brain basis of behavior and biological underpinnings of psychiatric disease. Although there are clearly limitations to the scope of disease that non-human primate studies can model there is a niche that only primate-based studies can fill. Many experimental questions that focus on intricate social interactions, long-term development, and complex cognitive-affective interactions are best suited for primate studies. Non-human primate studies of emotional behavior have made tremendous contributions to our understanding of psychobiology and will certainly continue to inform future generations for many years to come.

ACKNOWLEDGEMENTS

This work was supported by the NIMH Intramural Research Program.

DISCLOSURE

The authors have no conflicts of interest. Also, JTW declares that in the last 5 years he has received no support for activities other than those provided by the NIMH Intramural Research Program.

REFERENCES

- Amaral DG, Bauman MD, Schumann CM (2003). The amygdala and autism: implications from non-human primate studies. *Genes Brain Behav* **2**: 295–302.
- Amiez C, Joseph JP, Procyk E (2006). Reward encoding in the monkey anterior cingulate cortex. *Cereb Cortex* **16**: 1040–1055.
- Anderson CO, Kenney AM, Mason WA (1977). Effects of maternal mobility, partner, and endocrine state on social responsiveness of adolescent rhesus monkeys. *Dev Psychobiol* **10**: 421–434.
- Andrews MW, Rosenblum LA (1991). Attachment in monkey infants raised in variable- and low-demand environments. *Child Dev* **62**: 686–693.
- Arseneault L, Milne BJ, Taylor A, Adams F, Delgado K, Caspi A *et al* (2008). Being bullied as an environmentally mediated contributing factor to children's internalizing problems: a study of twins discordant for victimization. *Arch Pediatr Adolesc Med* **162**: 145–150.
- Bachevalier J, Beauregard M, Alvarado MC (1999). Long-term effects of neonatal damage to the hippocampal formation and amygdaloid complex on object discrimination and object recognition in rhesus monkeys (*Macaca mulatta*). *Behav Neurosci* **113**: 1127–1151.
- Bachevalier J, Brickson M, Hagger C, Mishkin M (1990). Age and sex differences in the effects of selective temporal lobe lesion on the formation of visual discrimination habits in rhesus monkeys (*Macaca mulatta*). *Behav Neurosci* **104**: 885–899.
- Bachevalier J, Malkova L (2006). The amygdala and development of social cognition: theoretical comment on Bauman, Toscano, Mason, Lavenex, and Amaral (2006). *Behav Neurosci* **120**: 989–991.
- Bailey JN, Breidenthal SE, Jorgensen MJ, McCracken JT, Fairbanks LA (2007). The association of DRD4 and novelty seeking is found in a nonhuman primate model. *Psychiatr Genet* **17**: 23–27.
- Beauregard M, Malkova L, Bachevalier J (1995). Stereotypes and loss of social affiliation after early hippocampectomy in primates. *Neuroreport* **6**: 2521–2526.
- Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SC (2000). The amygdala theory of autism. *Neurosci Biobehav Rev* **24**: 355–364.
- Barr CS, Newman TK, Becker ML, Parker CC, Champoux M, Lesch KP *et al* (2003). The utility of the non-human primate; model for studying gene by environment interactions in behavioral research. *Genes Brain Behav* **2**: 336–340.
- Barr CS, Newman TK, Lindell S, Shannon C, Champoux M, Lesch KP *et al* (2004a). Interaction between serotonin transporter gene variation and rearing condition in alcohol preference and consumption in female primates. *Arch Gen Psychiatry* **61**: 1146–1152.
- Barr CS, Newman TK, Schwandt M, Shannon C, Dvoskin RL, Lindell SG *et al* (2004b). Sexual dichotomy of an interaction between early adversity and the serotonin transporter gene promoter variant in rhesus macaques. *Proc Natl Acad Sci USA* **101**: 12358–12363.
- Barr CS, Newman TK, Shannon C, Parker C, Dvoskin RL, Becker ML *et al* (2004c). Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. *Biol Psychiatry* **55**: 733–738.
- Barr CS, Schwandt M, Lindell SG, Chen SA, Goldman D, Suomi SJ *et al* (2007). Association of a functional polymorphism in the mu-opioid receptor gene with alcohol response and consumption in male rhesus macaques. *Arch Gen Psychiatry* **64**: 369–376.
- Barr CS, Schwandt ML, Lindell SG, Higley JD, Maestripietri D, Goldman D *et al* (2008). Variation at the mu-opioid receptor gene (OPRM1) influences attachment behavior in infant primates. *Proc Natl Acad Sci USA* **105**: 5277–5281.
- Bast T (2007). Toward an integrative perspective on hippocampal function: from the rapid encoding of experience to adaptive behavior. *Rev Neurosci* **18**: 253–281.
- Bastian ML, Sponberg AC, Sponberg AC, Suomi SJ, Higley JD (2003). Long-term effects of infant rearing condition on the acquisition of dominance rank in juvenile and adult rhesus macaques (*Macaca mulatta*). *Dev Psychobiol* **42**: 44–51.
- Bauman MD, Lavenex P, Mason WA, Capitanio JP, Amaral DG (2004a). The development of mother-infant interactions after neonatal amygdala lesions in rhesus monkeys. *J Neurosci* **24**: 711–721.
- Bauman MD, Lavenex P, Mason WA, Capitanio JP, Amaral DG (2004b). The development of social behavior following neonatal amygdala lesions in rhesus monkeys. *J Cogn Neurosci* **16**: 1388–1411.
- Bay KD, Beck P, Skinner RD, Garcia-Rill E (2007). GABAergic modulation of developing pedunculopontine nucleus. *Neuroreport* **18**: 249–253.
- Beauregard M, Malkova L, Bachevalier J (1995). Stereotypes and loss of social affiliation after early hippocampectomy in primates. *Neuroreport* **6**: 2521–2526.
- Bennett AJ, Lesch KP, Heils A, Long JC, Lorenz JG, Shoaf SE *et al* (2002). Early experience and serotonin transporter gene variation interact to influence primate CNS function. *Mol Psychiatry* **7**: 118–122.
- Bertolino A, Saunders RC, Mattay VS, Bachevalier J, Frank JA, Weinberger DR (1997). Altered development of prefrontal neurons in rhesus monkeys with neonatal mesial temporo-limbic lesions: a proton magnetic resonance spectroscopic imaging study. *Cereb Cortex* **7**: 740–748.
- Bethea CL, Pau FK, Fox S, Hess DL, Berga SL, Cameron JL (2005). Sensitivity to stress-induced reproductive dysfunction linked to activity of the serotonin system. *Fertil Steril* **83**: 148–155.
- Bethea CL, Streicher JM, Coleman K, Pau FK, Moessner R, Cameron JL (2004). Anxious behavior and fenfluramine-induced prolactin secretion in young rhesus macaques with different alleles of the serotonin reuptake transporter polymorphism (5HTTLPR). *Behav Genet* **34**: 295–307.
- Bock NA, Paiva FF, Nascimento GC, Newman JD, Silva AC (2008). Cerebrospinal fluid to brain transport of manganese in a non-human primate revealed by MRI. *Brain Res* **1198**: 160–170.
- Bower AJ (1990). Plasticity in the adult and neonatal central nervous system. *Br J Neurosurg* **4**: 253–264.
- Bowlby J (1973). *Attachment and loss. Vol 3: Loss: Sadness and depression*. Basic Books: New York. (reissued, 1999).
- Brothers L (1990). The social brain: a project for integrating primate behaviour and neurophysiology in a new domain. *Concepts Neurosci* **1**: 27–51.
- Buse E, Habermann G, Osterburg I, Korte R, Weinbauer GF (2003). Reproductive/developmental toxicity and immunotoxicity assessment in the nonhuman primate model. *Toxicology* **185**: 221–227.
- Bush WW, Barr CS, Darrin EW, Shofer FS, Vite CH, Steinberg SA (2002). Results of cerebrospinal fluid analysis, neurologic examination findings, and age at the onset of seizures as predictors for results of magnetic resonance imaging of the brain in dogs examined because of seizures: 115 cases (1992–2000). *J Am Vet Med Assoc* **220**: 781–784.
- Cameron JL (2004). Interrelationships between hormones, behavior, and affect during adolescence: complex relationships exist between reproductive hormones, stress-related hormones, and the activity of neural systems that regulate behavioral affect. Comments on part III. *Ann NY Acad Sci* **1021**: 134–142.
- Capitanio JP, Mendoza SP, Mason WA, Maninger N (2005). Rearing environment and hypothalamic-pituitary-adrenal regulation in young rhesus monkeys (*Macaca mulatta*). *Dev Psychobiol* **46**: 318–330.
- Carr D, Sesack S (1996). Hippocampal afferents to the rat prefrontal cortex: synaptic targets and relation to dopaminergic terminals. *J Comp Neurol* **369**: 1–15.
- Carroll KA, Maestripietri D (1998). Infant abuse and neglect in monkeys—a discussion of definitions, epidemiology, etiology, and implications for child maltreatment: reply to Cicchetti (1998) and Mason (1998). *Psychol Bull* **123**: 234–237.
- Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H *et al* (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**: 386–389.
- Castner SA, Williams GV (2007). From vice to virtue: insights from sensitization in the nonhuman primate. *Prog Neuropsychopharmacol Biol Psychiatry* **31**: 1572–1592.
- Champoux M, Bennett A, Shannon C, Higley JD, Lesch KP, Suomi SJ (2002a). Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates. *Mol Psychiatry* **7**: 1058–1063.
- Champoux M, Byrne E, DeLizio R, Suomi SJ (2002b). Motherless mothers revisited: rhesus maternal behavior and rearing history. *Primates* **33**: 251–255.
- Chen SW, Shemyakin A, Wiedenmayer CP (2006). The role of the amygdala and olfaction in unconditioned fear in developing rats. *J Neurosci* **26**: 233–240.
- Chudasama Y, Robbins TW (2006). Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biol Psychol* **73**: 19–38.
- Clarke AS, Hedeker DR, Ebert MH, Schmidt DE, McKinney WT, Kraemer GW (1996). Rearing experience and biogenic amine activity in infant rhesus monkeys. *Biol Psychiatry* **40**: 338–352.

- Clarke AS, Kammerer CM, George KP, Kupfer DJ, McKinney WT, Spence MA *et al* (1995). Evidence for heritability of biogenic amine levels in the cerebrospinal fluid of rhesus monkeys. *Biol Psychiatry* **38**: 572–577.
- Clarke AS, Kraemer GW, Kupfer DJ (1998). Effects of rearing condition on HPA axis response to fluoxetine and desipramine treatment over repeated social separations in young rhesus monkeys. *Psychiatry Res* **79**: 91–104.
- Coe CL, Crispin HR (2000). Social stress in pregnant squirrel monkeys (*Saimiri boliviensis peruviansis*) differentially affects placental transfer of maternal antibody to male and female infants. *Health Psychol* **19**: 554–559.
- Coe CL, Kramer M, Czeh B, Gould E, Reeves AJ, Kirschbaum C *et al* (2003). Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biol Psychiatry* **54**: 1025–1034.
- Coe CL, Lulbach GR, Schneider ML (2002). Prenatal disturbance alters the size of the corpus callosum in young monkeys. *Dev Psychobiol* **41**: 178–185.
- Coplan JD, Andrews MW, Rosenblum LA, Owens MJ, Friedman S, Gorman JM *et al* (1996). Persistent elevations of cerebrospinal fluid concentrations of corticotropin-releasing factor in adult nonhuman primates exposed to early-life stressors: implications for the pathophysiology of mood and anxiety disorders. *Proc Natl Acad Sci USA* **93**: 1619–1623.
- Coplan JD, Rosenblum LA, Friedman S, Bassoff TB, Gorman JM (1992). Behavioral effects of oral yohimbine in differentially reared nonhuman primates. *Neuropsychopharmacology* **6**: 31–37.
- Coplan JD, Trost RC, Owens MJ, Cooper TB, Gorman JM, Nemeroff CB *et al* (1998). Cerebrospinal fluid concentrations of somatostatin and biogenic amines in grown primates reared by mothers exposed to manipulated foraging conditions. *Arch Gen Psychiatry* **55**: 473–477.
- Crawley JN (2003). Behavioral phenotyping of rodents. *Comp Med* **53**: 140–146.
- Cryan JF, Thakker DR, Hoyer D (2007). Emerging use of non-viral RNA interference in the brain. *Biochem Soc Trans* **35**: 411–415.
- Dempster EL, Burcescu I, Wigg K, Kiss E, Bajji I, Gadoros J *et al* (2007). Evidence of an association between the vasopressin V1b receptor gene (AVPR1B) and childhood-onset mood disorders. *Arch Gen Psychiatry* **64**: 1189–1195.
- Denenberg VH (1999). Commentary: is maternal stimulation the mediator of the handling effect in infancy? *Dev Psychobiol* **34**: 1–3.
- Desmurget M, Turner RS (2008). Testing basal ganglia motor functions through reversible inactivations in the posterior internal globus pallidus. *J Neurophysiol* **99**: 1057–1076.
- Detting AC, Feldon J, Pryce CR (2002a). Early deprivation and behavioral and physiological responses to social separation/novelty in the marmoset. *Pharmacol Biochem Behav* **73**: 259–269.
- Detting AC, Feldon J, Pryce CR (2002b). Repeated parental deprivation in the infant common marmoset (*Callithrix jacchus*, primates) and analysis of its effects on early development. *Biol Psychiatry* **52**: 1037–1046.
- Detting AC, Schnell CR, Maier C, Feldon J, Pryce CR (2007). Behavioral and physiological effects of an infant-neglect manipulation in a bi-parental, twinning primate: impact is dependent on familial factors. *Psychoneuroendocrinology* **32**: 331–349.
- Donaldson ZR, Kondrashov FA, Putnam A, Bai Y, Stoinski TL, Hammock EA *et al* (2008). Evolution of a behavior-linked microsatellite-containing element in the 5' flanking region of the primate AVPR1A gene. *BMC Evol Biol* **8**: 180.
- Eichler EE, Zimmerman AW (2008). A hot spot of genetic instability in autism. *N Engl J Med* **358**: 737–739.
- Ellinwood Jr EH, Sudilovsky A, Nelson LM (1973). Evolving behavior in the clinical and experimental amphetamine (model) psychosis. *Am J Psychiatry* **130**: 1088–1093.
- Ellison GD, Eison MS (1983). Continuous amphetamine intoxication: an animal model of the acute psychotic episode. *Psychol Med* **13**: 751–761.
- Emde RN, Polak PR, Spitz RA (1965). Anaclitic depression in an infant raised in an institution. *J Am Acad Child Psychiatry* **4**: 545–553.
- Eudey AA (1981). Ethical concerns in primate use and husbandry. *Int J Study Anim Probl* **2**: 96–102.
- Fahlke C, Lorenz JG, Long J, Champoux M, Suomi SJ, Higley JD (2000). Rearing experiences and stress-induced plasma cortisol as early risk factors for excessive alcohol consumption in nonhuman primates. *Alcohol Clin Exp Res* **24**: 644–650.
- Felger JC, Alagbe O, Hu F, Mook D, Freeman AA, Sanchez MM *et al* (2007). Effects of interferon-alpha on rhesus monkeys: a nonhuman primate model of cytokine-induced depression. *Biol Psychiatry* **62**: 1324–1333.
- Fox AS, Shelton SE, Oakes TR, Davidson RJ, Kalin NH (2008). Trait-like brain activity during adolescence predicts anxious temperament in primates. *PLoS ONE* **3**: e2570.
- Francis DD, Szegda K, Campbell G, Martin WD, Insel TR (2003). Epigenetic sources of behavioral differences in mice. *Nat Neurosci* **6**: 445–446.
- Glimer WS, McKinney WT (2003). Early experience and depressive disorders: human and non-human primate studies. *J Affect Disord* **75**: 97–113.
- Giorgi D, Rouquier S (2002). Identification of V1R-like putative pheromone receptor sequences in non-human primates. Characterization of V1R pseudogenes in marmoset, a primate species that possesses an intact vomeronasal organ. *Chem Senses* **27**: 529–537.
- Gogtay N, Nugent III TF, Herman DH, Ordonez A, Greenstein D, Hayashi KM *et al* (2006). Dynamic mapping of normal human hippocampal development. *Hippocampus* **16**: 664–672.
- Goldman PS (1976). The role of experience in recovery of function following orbital prefrontal lesions in infant monkeys. *Neuropsychologia* **14**: 401–412.
- Goldman PS (1978). Neuronal plasticity in primate telencephalon: anomalous projections induced by prenatal removal of frontal cortex. *Science* **202**: 768–770.
- Goulet S, Dore FY, Murray EA (1998). Aspiration lesions of the amygdala disrupt the rhinal corticothalamic projection system in rhesus monkeys. *Exp Brain Res* **119**: 131–140.
- Goursaud AP, Bachevalier J (2007). Social attachment in juvenile monkeys with neonatal lesion of the hippocampus, amygdala and orbital frontal cortex. *Behav Brain Res* **176**: 75–93.
- Goursaud AP, Mendoza SP, Capitanio JP (2006). Do neonatal bilateral ibotenic acid lesions of the hippocampal formation or of the amygdala impair HPA axis responsiveness and regulation in infant rhesus macaques (*Macaca mulatta*)? *Brain Res* **1071**: 97–104.
- Habermay KA, Paule MG, Scallet AC, Sistare FD, Lester DS, Hanig JP *et al* (2002). Ontogeny of the N-methyl-D-aspartate (NMDA) receptor system and susceptibility to neurotoxicity. *Toxicol Sci* **68**: 9–17.
- Hadj-Bouziane F, Bell AH, Knusten TA, Ungerleider LG, Tootell RB (2008). Perception of emotional expressions is independent of face selectivity in monkey inferior temporal cortex. *Proc Natl Acad Sci USA* **105**: 5591–5596.
- Harlow HF, Dodsworth RO, Harlow MK (1965). Total social isolation in monkeys. *Proc Natl Acad Sci USA* **54**: 90–97.
- Harlow HF, Mc Kinney Jr WT (1971). Nonhuman primates and psychoses. *J Autism Child Schizophr* **1**: 368–375.
- Heinz A, Higley JD, Gorey JG, Saunders RC, Jones DW, Hommer D *et al* (1998). *In vivo* association between alcohol intoxication, aggression, and serotonin transporter availability in nonhuman primates. *Am J Psychiatry* **155**: 1023–1028.
- Heinz A, Jones DW, Gorey JG, Bennet A, Suomi SJ, Weinberger DR *et al* (2003). Serotonin transporter availability correlates with alcohol intake in non-human primates. *Mol Psychiatry* **8**: 231–234.
- Heinz A, Saunders RC, Kolachana BS, Jones DW, Gorey JG, Bachevalier J *et al* (1999). Striatal dopamine receptors and transporters in monkeys with neonatal temporal limbic damage. *Synapse* **32**: 71–79.
- Heiss JD, Walbridge S, Morrison P, Hampton RR, Sato S, Vortmeyer A *et al* (2005). Local distribution and toxicity of prolonged hippocampal infusion of muscimol. *J Neurosurg* **103**: 1035–1045.
- Higley J, Hasert M, Suomi S, Linnoila M (1998). The serotonin reuptake inhibitor sertraline reduces excessive alcohol consumption in nonhuman primates: effect of stress. *Neuropsychopharmacology* **18**: 431–443.
- Higley JD, Suomi SJ, Linnoila M (1991). CSF monoamine metabolite concentrations vary according to age, rearing, and sex, and are influenced by the stressor of social separation in rhesus monkeys. *Psychopharmacology (Berl)* **103**: 551–556.
- Higley JD, Suomi SJ, Linnoila M (1992). A longitudinal assessment of CSF monoamine metabolite and plasma cortisol concentrations in young rhesus monkeys. *Biol Psychiatry* **32**: 127–145.
- Hofer MA (1996). On the nature and consequences of early loss. *Psychosom Med* **58**: 570–581.
- Insel TR, Scanlan J, Champoux M, Suomi SJ (1988). Rearing paradigm in a nonhuman primate affects response to beta-CCE challenge. *Psychopharmacology (Berl)* **96**: 81–86.
- Izquierdo A, Newman TK, Higley JD, Murray EA (2007). Genetic modulation of cognitive flexibility and socioemotional behavior in rhesus monkeys. *Proc Natl Acad Sci USA* **104**: 14128–14133.
- Jay T, Glowinski J, Thierry A (1989). Selectivity of the hippocampal projection to the prelimbic area of the prefrontal cortex in the rat. *Brain Res* **505**: 337–340.
- Kaldy Z, Sigala N (2004). The neural mechanisms of object working memory: what is where in the infant brain? *Neurosci Biobehav Rev* **28**: 113–121.
- Kappel S, Matthess Y, Kaufmann M, Strebhardt K (2007). Silencing of mammalian genes by tetracycline-inducible shRNA expression. *Nat Protoc* **2**: 3257–3269.
- Kaufman IC, Rosenblum LA (1967a). Depression in infant monkeys separated from their mothers. *Science* **155**: 1030–1031.
- Kaufman IC, Rosenblum LA (1967b). The reaction to separation in infant monkeys: anaclitic depression and conservation-withdrawal. *Psychosom Med* **29**: 648–675.

- Kinnally EL, Lyons LA, Abel K, Mendoza S, Capitanio JP (2008). Effects of early experience and genotype on serotonin transporter regulation in infant rhesus macaques. *Genes Brain Behav* **7**: 481–486.
- Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S *et al* (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *J Neurosci* **25**: 11489–11493.
- Kling A (1974). Differential effects of amygdectomy in male and female nonhuman primates. *Arch Sex Behav* **3**: 129–134.
- Kling A, Green PC (1967). Effects of neonatal amygdectomy in the maternally reared and maternally deprived monkey. *Nature* **213**: 742–743.
- Koretsky AP, Silva AC (2004). Manganese-enhanced magnetic resonance imaging (MEMRI). *NMR Biomed* **17**: 527–531.
- Kozorovitskiy Y, Gould E (2004). Dominance hierarchy influences adult neurogenesis in the dentate gyrus. *J Neurosci* **24**: 6755–6759.
- Kraemer GW, Moore CF, Newman TK, Barr CS, Schneider ML (2008). Moderate level fetal alcohol exposure and serotonin transporter gene promoter polymorphism affect neonatal temperament and limbic-hypothalamic-pituitary-adrenal axis regulation in monkeys. *Biol Psychiatry* **63**: 317–324.
- Kraemer GW, Schmidt DE, Ebert MH (1997). The behavioral neurobiology of self-injurious behavior in rhesus monkeys. Current concepts and relations to impulsive behavior in humans. *Ann NY Acad Sci* **836**: 12–38.
- Kumar P, Wu H, McBride JL, Jung KE, Kim MH, Davidson BL *et al* (2007). Transvascular delivery of small interfering RNA to the central nervous system. *Nature* **448**: 39–43.
- Lam JA, Rosenheck R (1999). Social support and service use among homeless persons with serious mental illness. *Int J Soc Psychiatry* **45**: 13–28.
- Lavenex P, Banta Lavenex P, Amaral DG (2007a). Postnatal development of the primate hippocampal formation. *Dev Neurosci* **29**: 179–192.
- Lavenex P, Lavenex PB, Amaral DG (2007b). Spatial relational learning persists following neonatal hippocampal lesions in macaque monkeys. *Nat Neurosci* **10**: 234–239.
- Lemond S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD *et al* (2003). Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosci* **23**: 8788–8799.
- Leopold DA, Maier A (2006). Neuroimaging: perception at the brain's core. *Curr Biol* **16**: R95–R98.
- Lesch KP, Meyer J, Glatz K, Flugge G, Hinney A, Hebebrand J *et al* (1997). The 5-HT transporter gene-linked polymorphic region (5-HTTLPR) in evolutionary perspective: alternative biallelic variation in rhesus monkeys. Rapid communication. *J Neural Transm* **104**: 1259–1266.
- Levine S (2000). Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. *Eur J Pharmacol* **405**: 149–160.
- Levine S, Mody T (2003). The long-term psychobiological consequences of intermittent postnatal separation in the squirrel monkey. *Neurosci Biobehav Rev* **27**: 83–89.
- Levitt P (2003). Structural and functional maturation of the developing primate brain. *J Pediatr* **143**: S35–S45.
- Lewis DA (1997). Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology* **16**: 385–398.
- Lipska B, Chrapusta S, Egan M, Weinberger D (1995). Neonatal excitotoxic ventral hippocampal damage alters dopamine response to mild chronic stress and haloperidol treatment. *Synapse* **20**: 125–130.
- Lipska BK, Halim ND, Segal PN, Weinberger DR (2002). Effects of reversible inactivation of the neonatal ventral hippocampus on behavior in the adult rat. *J Neurosci* **22**: 2835–2842.
- Lipska BK, Weinberger DR (2000). To model a psychiatric disorder in animals: schizophrenia as a reality test. *Neuropsychopharmacology* **23**: 223–239.
- Logothetis NK (2008). What we can do and what we cannot do with fMRI. *Nature* **453**: 869–878.
- Logothetis NK, Guggenberger H, Peled S, Pauls J (1999). Functional imaging of the monkey brain. *Nat Neurosci* **2**: 555–562.
- Lutz C, Well A, Novak M (2003). Stereotypic and self-injurious behavior in rhesus macaques: a survey and retrospective analysis of environment and early experience. *Am J Primatol* **60**: 1–15.
- Lyons DM, Parker KJ (2007). Stress inoculation-induced indications of resilience in monkeys. *J Trauma Stress* **20**: 423–433.
- Lyons DM, Yang C, Mobley BV, Nickerson JT, Schatzberg AF (2000). Early environmental regulation of glucocorticoid feedback sensitivity in young adult monkeys. *J Neuroendocrinol* **12**: 723–728.
- Machado CJ, Bachevalier J (2003). Non-human primate models of childhood psychopathology: the promise and the limitations. *J Child Psychol Psychiatry* **44**: 64–87.
- Machiyma Y (1992). Chronic methamphetamine intoxication model of schizophrenia in animals. *Schizophr Bull* **18**: 107–113.
- Maestriperi D (1998). Parenting styles of abusive mothers in group-living rhesus macaques. *Anim Behav* **55**: 1–11.
- Maestriperi D (2005). Early experience affects the intergenerational transmission of infant abuse in rhesus monkeys. *Proc Natl Acad Sci USA* **102**: 9726–9729.
- Maestriperi D (2007). *Macachiavellian Intelligence. How Rhesus Macaques and Humans have Conquered the World*. University of Chicago Press: London.
- Maestriperi D, Lindell SG, Ayala A, Gold PW, Higley JD (2005). Neurobiological characteristics of rhesus macaque abusive mothers and their relation to social and maternal behavior. *Neurosci Biobehav Rev* **29**: 51–57.
- Maestriperi D, McCormack K, Lindell SG, Higley JD, Sanchez MM (2006). Influence of parenting style on the offspring's behaviour and CSF monoamine metabolite levels in crossfostered and noncrossfostered female rhesus macaques. *Behav Brain Res* **175**: 90–95.
- McCorkle BH, Rogers ES, Dunn EC, Lyass A, Wan YM (2008). Increasing social support for individuals with serious mental illness: evaluating the compeer model of intentional friendship. *Community Ment Health J* [E-pub ahead of print].
- McManus EM (1996). Health promotion and social support for community-based clients with chronic mental illness. *Nursingconnections* **9**: 49–55.
- Meaney MJ, Diorio J, Francis D, Widdowson J, LaPlante P, Caldji C *et al* (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. *Dev Neurosci* **18**: 49–72.
- Meyer-Lindenberg A, Hariri AR, Munoz KE, Mervis CB, Mattay VS, Morris CA *et al* (2005). Neural correlates of genetically abnormal social cognition in Williams syndrome. *Nat Neurosci* **8**: 991–993.
- Miller EA, Goldman PS, Rosvold HE (1973). Delayed recovery of function following orbital prefrontal lesions in infant monkeys. *Science* **182**: 304–306.
- Miller-Butterworth CM, Kaplan JR, Barmada MM, Manuck SB, Ferrell RE (2007). The serotonin transporter: sequence variation in *Macaca fascicularis* and its relationship to dominance. *Behav Genet* **37**: 678–696.
- Miska EA, Alvarez-Saavedra E, Townsend M, Yoshii A, Sestan N, Rakic P *et al* (2004). Microarray analysis of microRNA expression in the developing mammalian brain. *Genome Biol* **5**: R68.
- Munafò MR, Yalcin B, Willis-Owen SA, Flint J (2008). Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: meta-analysis and new data. *Biol Psychiatry* **63**: 197–206.
- Murray EA, O'Doherty JP, Schoenbaum G (2007). What we know and do not know about the functions of the orbitofrontal cortex after 20 years of cross-species studies. *J Neurosci* **27**: 8166–8169.
- Nemeroff CB (2004). Neurobiological consequences of childhood trauma. *J Clin Psychiatry* **65**(Suppl 1): 18–28.
- Newman TK, Syagailo YV, Barr CS, Wendland JR, Champoux M, Graessle M *et al* (2005). Monoamine oxidase A gene promoter variation and rearing experience influences aggressive behavior in rhesus monkeys. *Biol Psychiatry* **57**: 167–172.
- Ono S, Mustari MJ (2007). Horizontal smooth pursuit adaptation in macaques after muscimol inactivation of the dorsolateral pontine nucleus (DLPN). *J Neurophysiol* **98**: 2918–2932.
- Orban GA, Van Essen D, Vanduffel W (2004). Comparative mapping of higher visual areas in monkeys and humans. *Trends Cogn Sci* **8**: 315–324.
- Palit G, Kumar R, Chowdhury SR, Gupta MB, Saxena RC, Srimal RC *et al* (1998). A primate model of anxiety. *Eur Neuropsychopharmacol* **8**: 195–201.
- Parker KJ, Buckmaster CL, Justus KR, Schatzberg AF, Lyons DM (2005). Mild early life stress enhances prefrontal-dependent response inhibition in monkeys. *Biol Psychiatry* **57**: 848–855.
- Parker KJ, Buckmaster CL, Sundlass K, Schatzberg AF, Lyons DM (2006). Maternal mediation, stress inoculation, and the development of neuroendocrine stress resistance in primates. *Proc Natl Acad Sci USA* **103**: 3000–3005.
- Parker KJ, Rainwater KL, Buckmaster CL, Schatzberg AF, Lindley SE, Lyons DM (2007). Early life stress and novelty seeking behavior in adolescent monkeys. *Psychoneuroendocrinology* **32**: 785–792.
- Parr LA, Winslow JT, Davis M (2002). Rearing experience differentially affects somatic and cardiac startle responses in rhesus monkeys (*Macaca mulatta*). *Behav Neurosci* **116**: 378–386.
- Paule MG (2005). Chronic drug exposures during development in nonhuman primates: models of brain dysfunction in humans. *Front Biosci* **10**: 2240–2249.
- Petkov CI, Kayser C, Steudel T, Whittingstall K, Augath M, Logothetis NK (2008). A voice region in the monkey brain. *Nat Neurosci* **11**: 367–374.
- Pine DS, Cohen JA (2002). Trauma in children and adolescents: risk and treatment of psychiatric sequelae. *Biol Psychiatry* **51**: 519–531.
- Pryce CR (2008). Postnatal ontogeny of expression of the corticosteroid receptor genes in mammalian brains: inter-species and intra-species differences. *Brain Res Rev* **57**: 596–605.
- Pryce CR, Dettling AC, Spengler M, Schnell CR, Feldon J (2004). Deprivation of parenting disrupts development of homeostatic and reward systems in marmoset monkey offspring. *Biol Psychiatry* **56**: 72–79.

- Pryce CR, Ruedi-Bettschen D, Dettling AC, Weston A, Russig H, Ferger B *et al* (2005). Long-term effects of early-life environmental manipulations in rodents and primates: potential animal models in depression research. *Neurosci Biobehav Rev* **29**: 649–674.
- Putzhammer A, Schoeler A, Rohrmeier T, Sand P, Hajak G, Eichhammer P (2005). Evidence of a role for the 5-HTTLPR genotype in the modulation of motor response to antidepressant treatment. *Psychopharmacology (Berl)* **178**: 303–308.
- Quigley M (2007). Non-human primates: the appropriate subjects of biomedical research? *J Med Ethics* **33**: 655–658.
- Reif A, Rosler M, Freitag CM, Schneider M, Eujen A, Kissling C *et al* (2007). Nature and nurture predispose to violent behavior: serotonergic genes and adverse childhood environment. *Neuropsychopharmacology* **32**: 2375–2383.
- Rice DC (2000). Parallels between attention deficit hyperactivity disorder and behavioral deficits produced by neurotoxic exposure in monkeys. *Environ Health Perspect* **108**(Suppl 3): 405–408.
- Rilling JK, Winslow JT, O'Brien D, Gutman DA, Hoffman JM, Kilts CD (2001). Neural correlates of maternal separation in rhesus monkeys. *Biol Psychiatry* **49**: 146–157.
- Rogers J, Shelton SE, Shelledy W, Garcia R, Kalin NH (2008). Genetic influences on behavioral inhibition and anxiety in juvenile rhesus macaques. *Genes Brain Behav* **7**: 463–469.
- Rosenblum LA, Andrews MW (1994). Influences of environmental demand on maternal behavior and infant development. *Acta Paediatr Suppl* **397**: 57–63.
- Rosenblum LA, Coplan JD, Friedman S, Bassoff T (1991). Dose-response effects of oral yohimbine in unrestrained primates. *Biol Psychiatry* **29**: 647–657.
- Rosenblum LA, Coplan JD, Friedman S, Bassoff T, Gorman JM, Andrews MW (1994). Adverse early experiences affect noradrenergic and serotonergic functioning in adult primates. *Biol Psychiatry* **35**: 221–227.
- Rutter M, O'Connor TG (2004). Are there biological programming effects for psychological development? Findings from a study of Romanian adoptees. *Dev Psychol* **40**: 81–94.
- Sabatini MJ, Ebert P, Lewis DA, Levitt P, Cameron JL, Mirnics K (2007). Amygdala gene expression correlates of social behavior in monkeys experiencing maternal separation. *J Neurosci* **27**: 3295–3304.
- Sahay A, Hen R (2008). Hippocampal neurogenesis and depression. *Novartis Found Symp* **289**: 152–160; discussion 160–164, 193–195.
- Salahpour A, Medvedev IO, Beaulieu JM, Gainetdinov RR, Caron MG (2007). Local knockdown of genes in the brain using small interfering RNA: a phenotypic comparison with knockout animals. *Biol Psychiatry* **61**: 65–69.
- Sams-Dodd F, Newman JD (1997). Effects of administration regime on the psychotomimetic properties of d-amphetamine in the squirrel monkey (*Saimiri sciureus*). *Pharmacol Biochem Behav* **56**: 471–480.
- Sanchez MM (2006). The impact of early adverse care on HPA axis development: nonhuman primate models. *Horm Behav* **50**: 623–631.
- Sanchez MM, Alagbe O, Felger JC, Zhang J, Graff AE, Grand AP *et al* (2007). Activated p38 MAPK is associated with decreased CSF 5-HIAA and increased maternal rejection during infancy in rhesus monkeys. *Mol Psychiatry* **12**: 895–897.
- Sanchez MM, Noble PM, Lyon CK, Plotsky PM, Davis M, Nemeroff CB *et al* (2005). Alterations in diurnal cortisol rhythm and acoustic startle response in nonhuman primates with adverse rearing. *Biol Psychiatry* **57**: 373–381.
- Saunders RC, Aigner TG, Frank JA (1990). Magnetic resonance imaging of the rhesus monkey brain: use for stereotactic neurosurgery. *Exp Brain Res* **81**: 443–446.
- Saunders RC, Kolachana BS, Bachevalier J, Weinberger DR (1998). Neonatal lesions of the medial temporal lobe disrupt prefrontal cortical regulation of striatal dopamine. *Nature* **393**: 169–171.
- Schlemmer RF, Davis JM (1986). A primate model for the study of hallucinogens. *Pharmacol Biochem Behav* **24**: 381–392.
- Seay B, Harlow HF (1965). Maternal separation in the rhesus monkey. *J Nerv Ment Dis* **140**: 434–441.
- Selemon LD, Begovic A, Goldman-Rakic PS, Castner SA (2007). Amphetamine sensitization alters dendritic morphology in prefrontal cortical pyramidal neurons in the non-human primate. *Neuropsychopharmacology* **32**: 919–931.
- Shannon C, Schwandt ML, Champoux M, Shoaf SE, Suomi SJ, Linnoila M *et al* (2005). Maternal absence and stability of individual differences in CSF 5-HIAA concentrations in rhesus monkey infants. *Am J Psychiatry* **162**: 1658–1664.
- Siebert S, Jurgens U (2003). Vocalization after periaqueductal grey inactivation with the GABA agonist muscimol in the squirrel monkey. *Neurosci Lett* **340**: 111–114.
- Smith EL, Batuman OA, Coplan JD, Rosenblum LA (2001). Stress, peer affiliation, and transforming growth factor-beta1 in differentially reared primates. *CNS Spectr* **6**: 573–578.
- Spinelli S, Schwandt ML, Lindell SG, Newman TK, Heilig M, Suomi SJ *et al* (2007). Association between the recombinant human serotonin transporter linked promoter region polymorphism and behavior in rhesus macaques during a separation paradigm. *Dev Psychopathol* **19**: 977–987.
- Spitz RA (1952). Infantile depression and the general adaptation syndrome; on the relation between physiologic model and psychoanalytic conceptualization. *Proc Annu Meet Am Psychopathol Assoc* **12**: 93–108.
- Strauss J, Barr CL, George CJ, Devlin B, Vetro A, Kiss E *et al* (2005). Brain-derived neurotrophic factor variants are associated with childhood-onset mood disorder: confirmation in a Hungarian sample. *Mol Psychiatry* **10**: 861–867.
- Suomi SJ (1991). Early stress and adult emotional reactivity in rhesus monkeys. *Ciba Found Symp* **156**: 171–183; discussion 183–188.
- Suomi SJ (1997). Early determinants of behaviour: evidence from primate studies. *Br Med Bull* **53**: 170–184.
- Swiss Committee on Animal Experiments (2006). 'Research on primates—an ethical evaluation'. *Altex* **23**: 169–178, 159–168.
- Szyf M, Weaver I, Meaney M (2007). Maternal care, the epigenome and phenotypic differences in behavior. *Reprod Toxicol* **24**: 9–19.
- Thompson A, Boekhoorn K, Van Dam AM, Lucassen PJ (2008). Changes in adult neurogenesis in neurodegenerative diseases: cause or consequence? *Genes Brain Behav* **7**(Suppl 1): 28–42.
- Thompson CI (1981). Learning in rhesus monkeys after amygdectomy in infancy or adulthood. *Behav Brain Res* **2**: 81–101.
- Thompson CI, Bergland RM, Towfighi JT (1977). Social and nonsocial behaviors of adult rhesus monkeys after amygdectomy in infancy or adulthood. *J Comp Physiol Psychol* **91**: 533–548.
- Thompson CI, Schwartzbaum JS, Harlow HF (1969). Development of social fear after amygdectomy in infant rhesus monkeys. *Physiol Behav* **4**: 249–254.
- Thompson CI, Towfighi JT (1976). Social behavior of juvenile rhesus monkeys after amygdectomy in infancy. *Physiol Behav* **17**: 831–836.
- Thorne BM (1972). Brain lesions and affective behavior in primates: a selected review. *J Gen Psychol* **86**: 153–162.
- Tsankova N, Renthal W, Kumar A, Nestler EJ (2007). Epigenetic regulation in psychiatric disorders. *Nat Rev Neurosci* **8**: 355–367.
- Vellucci SV, Herbert J, Keverne EB (1986). The effect of midazolam and beta-carboline carboxylic acid ethyl ester on behaviour, steroid hormones and central monoamine metabolites in social groups of talapoin monkeys. *Psychopharmacology (Berl)* **90**: 367–372.
- Vallen K (1996). Nature needs nurture: the interaction of hormonal and social influences on the development of behavioral sex differences in rhesus monkeys. *Horm Behav* **30**: 364–378.
- Wallen K, Goldfoot DA, Goy RW (1981). Peer and maternal influences on the expression of foot-clasp mounting by juvenile male rhesus monkeys. *Dev Psychobiol* **14**: 299–309.
- Wand GS, McCaul M, Yang X, Reynolds J, Gotjen D, Lee S *et al* (2002). The mu-opioid receptor gene polymorphism (A118G) alters HPA axis activation induced by opioid receptor blockade. *Neuropsychopharmacology* **26**: 106–114.
- Weaver A, de Waal FB (2003). The mother-offspring relationship as a template in social development: reconciliation in captive brown capuchins (*Cebus apella*). *J Comp Psychol* **117**: 101–110.
- Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR *et al* (2004). Epigenetic programming by maternal behavior. *Nat Neurosci* **7**: 847–854.
- Weerts EM, Tomatzky W, Miczek KA (1993). 'Anxiolytic' and 'anxiogenic' benzodiazepines and beta-carbolines: effects on aggressive and social behavior in rats and squirrel monkeys. *Psychopharmacology (Berl)* **110**: 451–459.
- Wellman LL, Gale K, Malkova L (2005). GABAA-mediated inhibition of basolateral amygdala blocks reward devaluation in macaques. *J Neurosci* **25**: 4577–4586.
- Wendland JR, Lesch KP, Newman TK, Timme A, Gachot-Neveu H, Thierry B *et al* (2006). Differential functional variability of serotonin transporter and monoamine oxidase a genes in macaque species displaying contrasting levels of aggression-related behavior. *Behav Genet* **36**: 163–172.
- Williams HJ, Owen MJ, O'Donovan MC (2007). Is COMT a susceptibility gene for schizophrenia? *Schizophr Bull* **33**: 635–641.
- Winslow JT (2005). Neuropeptides and non-human primate social deficits associated with pathogenic rearing experience. *Int J Dev Neurosci* **23**: 245–251.
- Winslow JT, Noble PL, Lyons CK, Sterk SM, Insel TR (2003). Rearing effects on cerebrospinal fluid oxytocin concentration and social buffering in rhesus monkeys. *Neuropsychopharmacology* **28**: 910–918.
- Wu J, Basha MR, Brock B, Cox DP, Cardozo-Pelaez F, McPherson CA *et al* (2008). Alzheimer's disease (AD)-like pathology in aged monkeys after infantile exposure to environmental metal lead (Pb): evidence for a developmental origin and environmental link for AD. *J Neurosci* **28**: 3–9.
- Yang SH, Cheng PH, Banta H, Piotrowska-Nitsche K, Yang JJ, Cheng EC *et al* (2008). Towards a transgenic model of Huntington's disease in a non-human primate. *Nature* **453**: 921–924.
- Zhang TY, Bagot R, Parent C, Nesbitt C, Bredy TW, Caldi C *et al* (2006). Maternal programming of defensive responses through sustained effects on gene expression. *Biol Psychol* **73**: 72–89.

APPENDIX 1

Old World Rhesus Macaque

Suborder: Haplorrhini; Infraorder: Simiiformes; Superfamily: Cercopithecoidea; Family: Cercopithecidae; Subfamily: Cercopithecinae; Genus: *Macaca*; Species: *mulatta*.

Rhesus macaques live in large, multi-male/multi-female groups.

Females remain in their natal groups and form dominance hierarchies according to their matrilineal kinship; males emigrate from their natal groups at the beginning of the breeding shortly before puberty, and may transfer groups throughout their lives.

Gestation lasts 164 days in rhesus macaques and the inter-birth interval is between 12 and 24 months.

Although the majority of parental care is the responsibility of the mother, rhesus infants are also handled by close female relatives and protected by adult males. In the first few days, the infant is carried ventrally and protected from other group members by the mother. Rhesus infants begin to ride dorsally for short periods during the second week. By 6 weeks of age, locomotor skills are developed enough for the infant to move independently. Young rhesus macaques are fully weaned by the birth of their next sibling. Exploration off of the mother begins as early as five days old and continues to increase so that by the third week, the infant breaks physical contact with the mother as frequently as possible.

Females reach puberty around age of 3 years whereas males are sexually mature by age of 4 years. The ovarian cycle lasts for 28 days. Estrus lasts for 8–12 days, with the day of ovulation occurring at the midpoint of the estrus period. Females reproduce from 3 years until about 20 years of age. During this time between becoming sexually mature and when they begin to mate, young rhesus macaques are learning the social skills, including fighting ability, which will influence their success throughout their lives. Adapted from: Cawthon Lang KA. 2005 July 20. Primate fact sheets: Rhesus macaque (*Macaca mulatta*) Taxonomy, Morphology, and Ecology.

<http://pin.primate.wisc.edu/factsheets/entry/rhesus_macaque>. Accessed on 16 March 2008.

APPENDIX 2

Common Marmoset

Suborder: Haplorrhini; Infraorder: Simiiformes; Family: Cebidae; Subfamily: Callitrichinae; Genus: *Callithrix*; Subgenus: *Callithrix*; Species: *jacchus*.

Groups of common marmosets range in size from 3 to 15 animals. Members of this group have a tendency to give birth to nonidentical twins. The average lifespan of a wild common marmoset is 12 years.

Social structure revolves around a stable, extended family unit with a few dominant breeding individuals and flexible mating behavior. Within the group, three generations are often encompassed including one or two breeding females with one breeding male and related adults (possibly parents or siblings) and the breeding pairs' offspring. One of the defining social behaviors of common marmosets is their system of cooperative breeding and infant care.

Menarche occurs between 9 and 14 months of age but common marmosets do not menstruate. The ovarian cycle lasts between 24 and 30 days, but averages 28 days. Gestation lasts about 5 months, and soon after parturition (within 10 days) female marmosets begin to cycle again and shortly thereafter become pregnant. From birth, common marmosets have a very strong cling reflex and do not voluntarily leave their carrier's back for the first 2 weeks of life. They are very active starting in the second week and investigating their surroundings.

Immediately after birth, the breeding male and presumptive father of the infants begins to carry the twins and care giving is offered by the father, mother, or other members of the group.

Over the following weeks, time off the backs of carriers gradually increases and the infants develop locomotor behaviors and coordination and begin to exhibit play behavior. By about 3 months of age, the infants are almost completely weaned and are capable of self-feeding.

By 15 months, common marmosets have reached their adult weight and are capable of reproduction but do not reproduce until social conditions are adequate. Adapted from: Cawthon Lang KA, 20 July 2005. Primate fact sheets: Rhesus macaque (*Macaca mulatta*) Taxonomy, Morphology, and Ecology.

<http://pin.primate.wisc.edu/factsheets/entry/rhesus_macaque>. Accessed on 16 March 2008.