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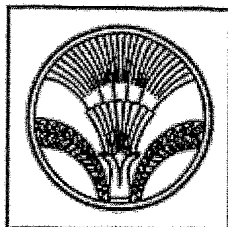
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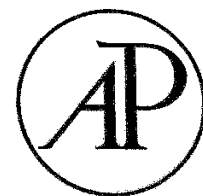
*To the monkeys who, in the service of science, helped
to make the world a better place for children.*

Primate Models of Children's Health and Developmental Disabilities

Thomas M. Burbacher
Gene P. Sackett
Kimberly S. Grant



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Contents

Preface	ix
Abbreviations	xiii
1 <i>Developmental Disabilities and Primate Models Defined</i>	1
Gene P. Sackett	
2 <i>The Origin of Developmental Psychopathologies: Insights from Nonhuman Primate Studies</i>	11
Anne-Pierre Goursaud and Jocelyne Bachevalier	
3 <i>Macaque Models of Visual Development and Disability</i>	45
Lynne Kiorpes	
4 <i>Spontaneous and Experimentally Induced Autoimmune Diseases in Nonhuman Primates</i>	71
Michel Vierboom and Bert A. 't Hart	
5 <i>Self-injurious Behavior: Nonhuman Primate Models for the Human Condition</i>	109
Corrine K. Lutz and Jerrold S. Meyer	
6 <i>Abnormal Behavior in Nonhuman Primates and Models of Development</i>	141
Melinda A. Novak and Stephen J. Suomi	

Abnormal Behavior in Nonhuman Primates and Models of Development

Melinda A. Novak and Stephen J. Suomi

INTRODUCTION

Nonhuman primates raised in captivity can develop a dizzying array of bizarre and unusual patterns of behavior (Bayne and Novak, 1998). These range from stereotypic activities such as pacing, rocking, self-mouthing, eye covering, and excessive self-grooming to more serious behaviors such as self-inflicted wounding. However, captive primates may also display species typical behavior in inappropriate contexts or at levels that are either too high or too low and compromise well-being. Thus, any discussion of abnormal behavior and its relevance for the human condition should consider both kinds of abnormality. The goals of this chapter are first to define and characterize abnormal behavior in nonhuman primates, primarily using macaques as an example; second to identify factors that may contribute to the development of abnormal behavior; and third to explore a functional approach to abnormal behavior in primates and identify parallels between human and nonhuman primates with respect to these phenomena.

TYPES OF ABNORMAL BEHAVIOR IN MACAQUES

Background

Macaques are a genus of Old World monkeys that can be found in a wide range of different environments, including remote forests, agricultural areas, small towns, and even large cities. Rhesus monkeys show arguably the widest range of habitats, and even large cities. Rhesus monkeys show arguably the widest range of habitats, earning the term “weed macaques” because of their ability to thrive in areas of deforestation and human habitation (Teas *et al.*, 1980; Richard *et al.*, 1989). Macaques are highly social and live in large troops that are structured around multigenerational

matrilines consisting of females and their female offspring (Lindburg, 1971; Teas *et al.*, 1980; Berman, 1983; Melnick *et al.*, 1984). This emphasis on females is related to a sex bias in dispersal, in that females remain in their natal troop generally throughout their life whereas males typically emigrate and join new troops (Berard, 1989). Macaques have complex social repertoires that run the gamut from prolonged affiliative responses, as seen in grooming behavior, to highly volatile aggressive altercations that can result in serious injury and even death (e.g. Southwick *et al.*, 1965; Teas *et al.*, 1982). Each troop is essentially a closed society, and troop members typically react to strangers with high levels of aggression (Southwick *et al.*, 1974). Because of their highly complex social nature and their ability to adapt to diverse environments (traits characteristic of humans), macaques may be an ideal model for understanding causes and circumstances surrounding the development of abnormal behavior.

Stereotypic patterns of behavior

Abnormal behavior in nonhuman primates often takes the form of stereotypic behavior, defined as iterative, highly ritualized motor actions which appear to have no identifiable biological function (Berkson, 1968). The word "appear" is important in the definition because it acknowledges that research may ultimately reveal a purpose for various types of stereotypies. Some kinds of abnormal behavior can lead to serious injury (e.g. self-mutilation or head banging). These latter activities are considered in a separate category of pathological behavior because of their potential for self-harm (Bayne and Novak, 1998). Because they are the topic of another chapter in this volume (Chapter 5), they will not be discussed any further here.

In primates, stereotypic behavior is often idiosyncratic (Berkson, 1968; Ridley and Baker, 1982; Bayne and Novak, 1998) and can take many different forms both across and within species of monkeys and apes (Walsh *et al.*, 1982; Bayne *et al.*, 1992). At least two classification schemes have been developed to characterize this variability across primates (Bayne and Novak, 1998). The first scheme emphasizes the form of the motor act, differentiating whole-body, gross motor actions from fine motor movements. Whole-body stereotypies involve repetitive movements through space and time that include pacing, somersaulting, rocking, and bouncing. Fine motor stereotypies consist of activities directed to the animal's own body and include digit sucking, eye saluting, ear covering, claspings, and hair pulling (Berkson, 1968; Bayne *et al.*, 1992).

Because the severity of abnormal behavior can vary substantially across individuals, a second classification scheme is based on the frequency of stereotypic behavior and its potential to disrupt normal activities (Bayne and Novak, 1998). In this scheme stereotypic behavior is divided into two general categories, termed mild and severe. Mild stereotypies can include all of the whole-body and fine motor movements as long as they do not disrupt essential biological processes. However,

any of these patterns can become severe if its frequency of occurrence disrupts basic processes involved in exploration, feeding, reproduction, or parental behavior or if it replaces other species-typical behavior such as grooming or play. A separate category termed "serious or pathological" is reserved for a suite of behavior patterns that can result in tissue damage, such as self-directed biting, head banging, and hair plucking.

Abnormal forms of species-typical behavior

Discussions of abnormal behavior in captive primates should not be limited to stereotypic patterns of behavior but should also include unusual variation in the expression and/or level of species-typical behavior. However, unlike the presence of bizarre behavior which can be recognized with ease, unusual alterations in species-typical behavior may be much more difficult to identify. Here we focus exclusively on two general temperaments or dispositional styles that when expressed in extreme forms may result in unusual variations in species-typical behavior. These two temperaments have been termed high reactivity and impulsive aggressiveness, respectively, and they have clear-cut human counterparts (Suomi, 2000).

Reactivity

It is now well established that there are marked individual differences in reactivity among nonhuman primates when animals are exposed to novel situations or to relatively minor changes in their social or physical environment. Some rhesus monkeys (~20%) respond to relatively mild environmental stressors with unusual behavioral disruption and physiological arousal including prolonged activation of the hypothalamic-pituitary-adrenal (HPA) axis as assessed by plasma cortisol and ACTH, increased cerebrospinal fluid (CSF) levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), heightened sympathetic nervous system activity as reflected in altered heart rate rhythms, and abnormal immune system response (Coe *et al.*, 1989; Higley *et al.*, 1992b; Suomi, 2000). The same stressors elicit only minor behavioral reactions and transient physiological responses in the remainder of the population (Suomi, 1991; see Kagan and Snidman, 1991, for analogous findings in children). Thus, some monkeys can be characterized as highly reactive – having an anxious or fearful temperament – whereas the majority of monkeys show low-moderate reactivity in response to environmental challenges. These differences have proven to be stable and enduring and are thus characteristic of the individual.

Differences in reactivity become even more pronounced with more severe challenges. For example, separation from the mother or from peers elicits a more profound behavioral and physiological response in highly reactive infant and juvenile monkeys. These individuals consistently exhibit marked distress immediately following separation and are more likely to become withdrawn or depressed if the

separation is prolonged or permanent compared to normally reactive monkeys. These patterns are observed in infant monkeys not only under controlled laboratory conditions but also in the wild during times of social disturbance. For example, six-month-old infants frequently experience mother-enforced separations during the breeding season when their mothers form consort relationships with males. Some infants (about 20%) show marked distress responses while the majority of infants show only brief agitation and then seek out their peers and older siblings (Berman *et al.*, 1994). Furthermore, early differences among infants in reactivity are predictive of the timing of later life events, for example the age at which adolescent males emigrate from their troops (Rasmussen and Suomi, 1989).

Impulsive aggression

Another example of unusual variation in species-typical behavior is the presence of impulsive or explosive aggression in a small percentage (5–10%) of the rhesus monkey population, particularly in males. Some male rhesus monkeys living in social groups in the wild or in captivity show heightened levels of aggression in response to relatively innocuous social situations. This aggression is inappropriate not only in terms of its intensity but also with respect to its target (Higley *et al.*, 1990). Furthermore, males with this syndrome often take more risks such as jumping out of trees from a height that sometimes results in injury, show atypical sleep-wakefulness cycles, and have chronically low levels of serotonergic activity as measured by CSF concentrations of the primary central serotonin (5-HT) metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Higley *et al.*, 1992a; Higley *et al.*, 1996b; Zajicek *et al.*, 1997).

FACTORS CONTRIBUTING TO THE DEVELOPMENT OF ABNORMAL BEHAVIOR

Over the last 50 years a variety of factors have been proposed to account for the development of abnormal behavior in monkeys. These factors range from specific environmental situations to neurochemical/cytoarchitectural abnormalities in the brain. A long-standing view is that abnormal behavior in macaques emerges as a result of socially inadequate early rearing experiences (e.g. rearing infants without mothers) or later social separation (e.g. removing animals from social groups and placing them in individual cages). However, abnormal behavior can also be linked to many other factors such as brain damage (Bielefeldt-Ohmann, *et al.*, 2004), painful disorders such as arthritis, and brain neurotransmitter dysfunction (Higley, *et al.*, 1996c). Moreover, some of the behavioral and biological components that characterize both high-reactive and impulsively aggressive monkeys appear to be highly heritable (Higley *et al.*, 1993; Williamson *et al.*, 2003). Recent findings clearly emphasize the need for an integrative model in which abnormal behavior is

viewed as the outcome of environmental exposure, physiological changes, and genetic risk factors (Suomi, 2007).

Early rearing environments

The notion that an animal develops stereotypic behavior because of exposure to adverse housing or inadequate environmental conditions first emerged from the early rearing experience work of Harlow (Harlow and Harlow, 1962, 1965) and subsequently was reinforced with studies of social restriction during different stages of the lifespan. The effects of social restriction were found to vary across the stages of development and by the degree of deprivation. Harlow and his colleagues examined several different kinds of early rearing experiences, each of which produced different amounts and types of abnormal behavior.

In most cases, animals reared in these altered conditions were compared with monkeys that were reared with their mothers in social groups consisting minimally of other adult females and offspring. This form of rearing is variously termed normal rearing or mother-peer rearing.

Isolation rearing from birth

Abnormal behavior

Rhesus monkeys reared alone from birth developed a suite of behavioral characteristics that we now refer to as the "isolation syndrome" (Harlow and Harlow, 1962, 1965; Cross and Harlow, 1965; Sackett, 1968; Capitanio, 1986). Isolate reared monkeys showed high levels of abnormal behavior, excessive emotional responses, and little in the way of normal species typical social behavior (Mason, 1968). At six months of age, most of the isolated monkeys exhibited multiple kinds of stereotypic behavior that included both motor stereotypies and self-directed stereotypies, with the three most common patterns being rocking, huddling, and self-clasping. The time allocated to stereotypic behavior was very high, ranging from 35 to 60% of an observation session, and thus severe in nature. The effects described above could not be traced solely to sensory deprivation inasmuch as isolates reared in sensory-rich environments containing toys and manipulanda and exposed to static pictures and movies fared no better in terms of outcome at six months of age (Sackett *et al.*, 1982).

Some forms of abnormal behavior may have represented normal species-typical behavior that the isolates redirected to themselves (e.g. self-clasping instead of clasping a mother). This hypothesis was tested and confirmed by giving infants access to a warm, terry-cloth mother during the period of isolation. When given inanimate surrogate mothers, infants not only clasped their surrogates rather than themselves, they also developed an attachment to these inanimate mothers, using them as a base of operations when exploring novel stimuli (Harlow, 1958; Harlow and Zimmermann, 1959; Harlow and Suomi, 1970). A subsequent study revealed

that rocking behavior was reduced by adding motion to the surrogate mother (Mason and Berkson, 1975). Despite the reduction in some forms of stereotypic behavior, the addition of an inanimate surrogate mother did not lead to any marked improvements in later social behavior.

Despite the presence of normal developmental milestones with respect to weight gain and hormonal changes associated with puberty, major isolate deficits in social behavior persisted along with high levels of stereotypic behavior. Some developmental changes in stereotypic behavior were noted in that digit sucking and self-clasping decreased with age, whereas other kinds of stereotypies such as somersaults, head bobs, unusual limb manipulations (e.g. leg behind neck, floating limb), and in some cases, self-injurious behavior (SIB) increased (Mitchell *et al.*, 1966; Sackett, 1967; Mitchell, 1968; Fittinghoff *et al.*, 1974).

Considerable interest was focused on reproductive outcomes and maternal behavior in isolate reared monkeys. Males showed deficits in the motor postures associated with copulation, being unable to perform the double foot clasp mount characteristic of normally reared monkeys. Furthermore, most isolate-reared females were indifferent or abusive to their first-born infants. Surprisingly, some isolate-reared mothers showed substantial improvements in their maternal behavior with the birth of a second infant (Ruppenthal *et al.*, 1976).

Physiological effects

Associated with the pronounced behavioral disruption produced by isolation rearing were major changes in central nervous system (CNS) function. As juveniles, isolate-reared monkeys showed significantly higher levels of central serotonin, as measured by CSF concentrations of 5-HIAA, than socially reared controls (Kraemer *et al.*, 1989). Consistent with disruption of the serotonergic system, abnormal behavior was significantly reduced in juvenile isolates by treatment with the 5-HT_{1A} receptor partial agonist buspirone (Kraemer and Clarke, 1990). However, disruption of the serotonergic system could not be detected in adult isolates, who failed to respond to a number of drugs that either enhanced or suppressed serotonergic activity in socially reared animals (Kraemer *et al.*, 1997). These findings suggest that alterations in serotonin may be related to the presence of abnormal behavior in juvenile monkeys, an effect that apparently disappears prior to reaching adulthood.

Catecholaminergic function also appeared to be altered by isolation rearing. For example, isolates showed unusual responses to amphetamine exposure as juveniles. Amphetamine is well known to provoke stereotypic behaviors in normal animals. However, in a comparison of juvenile isolates and socially reared controls, only the controls showed amphetamine induced stereotypy. The isolates, in contrast, displayed high levels of agonistic behavior with occasional wounding of one another (Kraemer *et al.*, 1984). In a later study by Lewis and co-workers (1990), old adult isolates and old social control monkeys displayed a dose-dependent increase in apomorphine-induced stereotypies, but the isolates showed significantly more

whole-body stereotypy than the controls at a dose of 0.3 mg/kg. Together, these studies suggest that early isolation rearing leads to a long-lasting enhancement of catecholaminergic function that is particularly evident following a pharmacologic challenge. This hypothesis is consistent with other studies reporting significant neuroanatomical and physiological changes in the basal ganglia of social isolates (Martin *et al.*, 1991) and reductions in abnormal behavior following treatment of isolates with the dopamine antagonist chlorpromazine (McKinney *et al.*, 1973).

Of considerable interest were possible effects of isolation on stress responsiveness. Juvenile isolate-reared monkeys showed elevated baseline cortisol levels compared to controls (Sackett *et al.* 1973). However, there was no discernable effect of isolation rearing on plasma cortisol levels in adults using a restraint-stress paradigm (Meyer and Bowman, 1972). These results, in combination with the above-reported monoamine results, suggest that the differences from controls may be reduced in adults compared to juveniles. This may have resulted from increased vulnerability during the juvenile period and/or because the long period of time since the isolation period resulted in more nonphysical social exposure to other monkeys.

The studies discussed above suggest that isolation rearing influences some of the major monoamine systems as well as possibly yielding differences in cortisol levels. Although these changes may contribute to the abnormal behavior observed in isolate-reared monkeys, several limitations must be noted. First, relatively few monkeys were actually subjected to the isolation rearing condition, and these animals exhibited wide individual differences in the expression of abnormal behavior. This variation has made it difficult to determine any possible connection of particular abnormal behaviors (e.g. stereotypies) to disruptions in normal species-typical behavior patterns such as maternal behavior. Furthermore, existing data do not permit clear causal explanations to be formulated. For example, although it may be tempting to conclude that the monoaminergic abnormalities discussed above underlie the abnormal behaviors exhibited by social isolates, this relationship is almost entirely correlational.

Peer rearing from birth

The isolation research described above revealed that some kind of social experience was necessary for normal development in rhesus monkey infants. A series of studies were conducted to determine if exposure to young naïve infants was sufficient to induce normal development. This rearing condition was called peer rearing and in all the studies mentioned below, infants were removed from their mothers shortly after birth, reared in a nursery for several weeks or more, and then placed in social groups consisting of other like-reared infants. Although these general procedures were followed, some differences existed across research programs that ultimately may explain some of the inconsistent results reported for some measures. Facilities varied with respect to how long the infants were maintained in the nursery, whether they received any social contact during this period, and the size of the social group into which they were ultimately placed. For example, at the Wisconsin

Primate Center (see Clarke *et al.*, 1996), infants were removed from their mothers at birth, placed in single cages in the nursery for six weeks of life during which they received 30 minutes of contact per day with another infant, and at the end of this period were placed into peer groups of three infants. At the California Primate Center (see Capitanio *et al.*, 2005), infants were removed from their mothers at birth, housed individually in incubators for 30 days during which they had access to a stuffed toy and towels, and at the end of this period, were placed in dyads. At the Laboratory of Comparative Ethology (see Higley *et al.*, 1991; Fahlke *et al.*, 2000; Roma *et al.*, 2006), infants were removed from their mothers at birth, placed in individual cages in a nursery for five weeks where they had access to a surrogate mother. At the end of this period, they were placed in social groups of 4–6 infants. Yet another variant of these procedures was followed at the Yerkes Primate Center (see Winslow *et al.*, 2003). In this facility, infants were separated from their mothers at birth, individually housed in a nursery for the first 45–60 days of life. Each infant was then pair housed most of each day except for a separation period of 4–6 hours per day for feeding and bottle training.

Behavioral effects

In marked contrast to early isolation rearing, infants separated from their mothers at birth and reared in peer groups displayed nearly normal social behavior and showed substantially lower levels of stereotypic behavior (Chamove, 1973). Peer-reared monkeys displayed stereotypic behavior about 4–20% of the time and the more common stereotypic patterns included digit sucking and rocking. However, the development of appropriate social behavior was somewhat delayed in comparison to normally reared monkeys (Chamove *et al.*, 1973).

Despite the appearance of many normal patterns of social behavior, peer-reared monkeys also showed heightened fearfulness. They reacted to minor changes in the environment by vocalizing and clutching other members of their peer group for a prolonged period of time, even to the point where they would continue to cling to one another and move around as a train of monkeys (Harlow and Harlow, 1965). Peer-reared monkeys appeared to have very strong attachments to their peer group as seen by their more prolonged and intense reactions to social separation than normally reared monkeys (Higley *et al.*, 1991). However, despite the appearance of a strong attachment bond in infancy, this bond did not provide much social buffering later in development. For example, Winslow and colleagues (2003) reported that juvenile peer-reared males had lower levels of affiliation (e.g. grooming) and were less likely to have their stress levels alleviated by a companion than mother-peer-reared males. Peer-reared monkeys were much more likely to develop impulsively aggressive patterns of response during their juvenile years than their mother-reared counterparts (Higley *et al.*, 1996c). In addition, peer-reared juvenile monkeys also exhibited greater vulnerability to excessive alcohol consumption than normally reared monkeys (Higley *et al.*, 1991; Fahlke *et al.*, 2000).

Subsequent studies have shown that the effects of early peer rearing can extend into adulthood. Considerable attention has been focused on females to determine whether monkeys reared without a mother but with naive peers can function as normal mothers. A recent study suggests that peer-reared mothers maintained in stable social groups display appropriate maternal behavior and produce infants whose behavior is indistinguishable from the infants of normally reared mothers (Roma *et al.*, 2006).

Physiological effects

As with isolation, the effects of peer rearing extended to various physiological systems, particularly the monoaminergic and neuropeptide systems. Peer-reared infant monkeys showed increased turnover (activity) of the noradrenergic system as indicated by higher CSF levels of the norepinephrine metabolite MHPG compared with normally reared monkeys (Higley *et al.*, 1992b). A subsequent report by Clarke *et al.* (1996) confirmed the increased noradrenergic activity in peer-reared monkey infants. The involvement of the serotonergic system was demonstrated in a comparison of 256 differentially reared infant rhesus monkeys (Shannon *et al.*, 2005). In contrast to isolate-reared monkeys, peer-reared monkeys showed lower central levels of 5-HT across the first year of life than normally reared monkeys as measured by the CSF metabolite 5-HIAA.

A neuroimaging study using positron emission tomography (PET) revealed significantly less serotonin-binding potential and lower rates of cerebral blood flow in many brain regions of juvenile peer-reared monkeys relative to that of mother/peer-reared counterparts (Ichise *et al.*, 2006). Research also suggests that the neuropeptide oxytocin may play a role in peer rearing. Peer-reared juveniles had lower CSF concentrations of oxytocin than normally reared juveniles, and the levels of oxytocin were positively correlated with affiliative social behavior (Winslow *et al.*, 2003). At present, the relationship between these neurotransmitter and neuropeptide alterations and the possible direct effects on stereotypic or other kinds of abnormal behavior remain largely unknown.

Because heightened fearfulness is a key characteristic of peer rearing, the HPA axis has been the focus of a number of studies examining stress responsiveness. Initial studies of cortisol levels were inconclusive in that peer-reared monkeys were reported to have higher concentrations of cortisol (Higley *et al.*, 1992) or lower concentrations of cortisol (Clarke, 1993) compared with mother/peer-reared controls. Peer-reared monkeys also responded to stress with smaller increases in ACTH and cortisol than mother-reared monkeys (Clarke, 1993). A subsequent study was designed to examine infants longitudinally under several different conditions. Mother-reared infants displayed higher concentrations of cortisol than peer-reared monkeys during the first two months of life but showed no difference in their response to 30-minute separation periods (Shannon *et al.*, 1998). In yet another study, neither baseline levels of cortisol or stress levels varied by rearing condition (Winslow *et al.*, 2003). However, a study of 778 infant monkeys provides strong

evidence that peer rearing results in a reduced cortisol set-point for the HPA axis (Capitanio *et al.*, 2005). Peer-reared infants showed lower cortisol levels in the afternoon, lower cortisol rises in response to social separation, and were less responsive to both a dexamethasone suppression test and an ACTH challenge test. It should be noted, however, that these differential findings might in part be the result of differences in peer rearing procedures used at the different facilities.

Peer rearing can also result in long-lasting changes in the immune system. Peer-reared monkeys showed greater lymphocyte proliferation responses than mother-reared monkeys (Coe *et al.*, 1989). This vulnerability was associated with lower proportions of CD8 cells and lower natural killer cell activity (Lubach *et al.*, 1995), and a substantially increased risk of diarrhea (Elmore *et al.*, 1992).

Several general conclusions can be drawn from the work on peer rearing. Peer rearing had less of an impact on behavior than isolation rearing in that normal social behavior was present and abnormal behavior was substantially reduced. However, peer-reared monkeys were unable to regulate or modulate both their fearfulness and their aggressiveness, perhaps a failure of social buffering. These behavioral differences have been associated with alterations in monoamine, neuroendocrine, and immune function. However, as in the case of isolate-reared animals, it is difficult at this time to make direct connections between any of these physiological systems and the abnormal behavior patterns seen in peer-reared monkeys.

Finally, research has indicated that many of the above-reported behavioral and biological consequences of peer-rearing are in part mediated by genetic factors, reflecting gene-environment ($G \times E$) interactions. For example, the behavioral and physiological consequences of functional allelic variation in the serotonin transporter gene (*5-HTT*) are far more pronounced for peer-reared rhesus monkeys than for their mother-reared counterparts. Specifically, peer-reared monkeys carrying the "short" (less transcriptionally efficient) allele of the *5-HTT* gene exhibit significantly more aberrant patterns of early neurobehavioral functioning than peer-reared monkeys carrying the "long" (more transcriptionally efficient) allele (Champoux *et al.*, 2002). This includes higher levels of aggression (Barr *et al.*, 2003), lower CSF concentrations of 5-HIAA (Bennett *et al.*, 2002), greater HPA activation following social separation (Barr *et al.*, 2004a), and higher rates of alcohol consumption (Barr *et al.*, 2004b). Of great importance, there were no significant differences attributable to *5-HTT* allelic variation in any of these behavioral and physiological measures among mother-reared monkeys of comparable age and sex. A comparable pattern of $G \times E$ interaction involving allelic variation in the MAO-A gene and peer versus mother-peer rearing has been reported for various measures of aggressive behavior in rhesus monkey males (Newman *et al.*, 2005).

Surrogate with limited peer rearing from birth

Nursery rearing of infant monkeys occurs for many reasons, including illness of the mother, prematurity or illness of the infant, rejection by the mother, and research

protocol. For many years, peer rearing was the primary way in which nursery-reared monkeys were maintained. In recent years, a second rearing procedure has been examined. The surrogate/peer-rearing condition was instituted in part to overcome the problem of infants serving in the dual role as a mother figure and as playmate. Surrogate/peer-reared monkeys were reared with continuous exposure to an inanimate "terry cloth"-covered mother and were given brief daily exposure to similarly reared peers. Depending on the study, the exposure to peers ranged from 30 minutes to 2 hours a day (Rosenblum, 1961; Hansen, 1966; Meyer *et al.*, 1975). The brief exposure to peers was designed to mimic naturalistic early mother-infant interaction in which infants spend most of their time with their mothers and only interact with other infants for brief periods. The brief exposure was also expected to facilitate play behavior with peers and reduce the risk of developing a primary attachment to peers.

Behavioral effects

In contrast to peer rearing, the surrogate/peer-rearing regimen resulted in the development of normal social behavior without the intense fearful reactions noted in peer-reared monkeys (Hansen, 1966; Ruppenthal *et al.*, 1991). Furthermore, minor differences in vocalization such as geckering and cooing between surrogate/peer-reared and normally reared monkeys disappeared after the first few months of life. Some forms of stereotypic behavior were observed (mostly digit sucking and some rocking against the surrogate surface), occurring about 5–10% of the time. But these patterns declined across age such that surrogate/peer-reared monkeys behaved like normally reared monkeys at one year of age (Hansen, 1966). Surrogate/peer-reared animals continued to develop socially showing adequate skills in grooming, reproduction, and parental care (Novak *et al.*, 1992; Sackett *et al.*, 2002). However, other research has further delineated the differences between the two nursery-rearing regimes. In mixed rearing groups, where monkeys from all three rearing conditions described above were placed together at one year of age, surrogate/peer-reared monkeys were much more likely than peer-reared monkeys to interact with the normally reared monkeys (Strand, 2006). However, a possible emotional deficit was also identified in that surrogate/peer-reared monkeys showed the highest levels of aggression and appeared not to respond readily to the submissive responses of others (Strand and Novak, 2005).

Physiological effects

There are only a few studies of the effect of surrogate/peer rearing on CNS function. To date, the emphasis has been on the HPA axis. Converging evidence suggests that infant surrogate/peer-reared monkeys have significantly lower concentrations of circulating cortisol than mother/peer-reared monkeys (Shannon *et al.*, 2005; Capitanio *et al.*, 2005) and respond significantly less to the stress of brief social separation (Shannon *et al.*, 1998). This difference persisted even after the surrogate/peer-reared

monkeys were housed in a large mixed rearing group containing mother/peer-reared and peer-reared monkeys (Davenport *et al.*, 2003).

The information derived from this rearing condition suggests that infants acquire all species-typical social behaviors and show relatively low levels of abnormal behavior when provided with an inanimate surrogate mother and given brief daily peer interaction. Apart from the HPA system findings, we know little about how surrogate/peer rearing influences neurotransmitter activity. However, in considering both types of peer rearing, it is clear that surrogate/peer rearing generally results in better outcome than continuous peer rearing. Obviously, a number of factors may contribute to this difference but key among these is the excessive clinging behavior observed in peer-only reared monkeys. Infants normally cling to mothers; however, mothers control this activity pushing infants away and encouraging independence. Infants reared continuously with each other develop clinging responses that cannot be easily broken. In turn, clinging behavior suppresses exploration of the environment and promotes emotional responses. In contrast, surrogate/peer-reared infants are free to move away from their surrogate and explore their environment. The brief daily contact with other infants facilitates playful interactions rather than clinging behavior. In essence, peer-reared monkeys have to serve as attachment objects and as playmates at the same time and they end up doing a rather poor job of both (Novak and Sackett, 2006).

Later housing environments

Stereotypic behavior is not limited to animals reared in impoverished circumstances during infancy. It can also arise in monkeys at some later point in development. For example, monkeys placed into individual cages can develop a wide range of whole-body and self-directed stereotypies even if normally reared prior to that time (Lutz *et al.*, 2003; Novak, 2003). Unlike the rearing conditions described above, there is considerable variability both in the age at which monkeys are first placed into individual cage housing and the length of exposure to this environment. This makes it difficult to discern general relationships between the development of stereotypies and alterations in neurotransmitter function, HPA axis, or normal behavior. However, it is clear that the earlier the onset of individual cage housing (15 months compared with 28 months) the greater the risk of developing severely abnormal behavior (Lutz *et al.*, 2003; Novak, 2003).

Environmental/social effects

There are at least three features of the individual cage environment which might be implicated in the development of stereotypies: (1) reductions in cage space leading to restrictions on species-typical patterns of locomotion, (2) the abrupt loss of physical contact with other monkeys after a lengthy period of social housing, and (3) the lack of access to other monkeys, thereby depriving the animal of an appropriate

target for some of its behavioral repertoire. Cage size may play a role in the development of whole-body motor stereotypies such as backflipping and pacing (Draper and Bernstein, 1963; Paulk *et al.*, 1977). However, once such stereotypies become established in individual cages, they are not always reduced. Monkeys showed no reductions in abnormal behavior when their cage size was doubled (Crockett *et al.*, 1993) or increased sixfold (Kaufman *et al.*, 2004). Only large outdoor housing environments reduced motor stereotypies in monkeys (Draper and Bernstein, 1963). Furthermore, exposure to outdoor environments also appeared to reduce self-directed stereotypies in monkeys even though they remained “individually housed” while outdoors (Fontenot *et al.*, 2006).

The loss of companionship and/or the lack thereof may also be relevant determinants of stereotypy in individually housed monkeys. Monkeys that are placed in individual cages after being reared in social groups for varying periods of time face the loss of familiar companions. Social separation is known to have profound effects on infant monkeys, inducing affective changes that can include depression (Suomi, 1991). Whether social loss plays a significant role in the onset of stereotypy is not clear at this time, particularly because the loss of companionship is generally confounded with exposure to a novel situation and unfamiliar animals. However, it should be noted that the reinstatement of social housing appears to mitigate some forms of abnormal behavior (Bayne *et al.*, 1991; Weed *et al.*, 2003).

The lack of an animal with which to interact may also affect the development of stereotypies (Novak *et al.*, 2006). Monkeys spend considerable time in close physical proximity to other monkeys, engaged in contact, grooming, sex, play, and aggression. Monkeys housed in an individual cage are essentially deprived of a target for many of their social activities. Under these conditions, monkeys may direct certain types of social behavior toward themselves, thus becoming the object of their own social motivation. For example, increases in self-grooming and self-sex in individually housed monkeys may represent an accommodation to the lack of social grooming and sexual activity. Similarly, monkeys may direct play gestures to their own limbs and, when provoked, may focus their aggressive responses on the only convenient target, themselves. This hypothesis is also consistent with the early rearing studies of isolate-reared monkeys in that some forms of abnormal behavior were normal behavior patterns that monkeys redirected to themselves (e.g. self-clasping).

Physiological effects

Less is known about the physiological underpinnings of abnormal behavior in monkeys housed alone after infancy because of considerable individual variability in the age of onset and length of individual cage housing. However, an emerging literature on drug exposure and on drug treatment suggests a role for the dopaminergic and serotonergic systems respectively. Administration of amphetamine, a dopamine releasing agent, produced a decrease in whole-body motor movements (Schlemmer *et al.*, 1996), an increased incidence in floating limb (Levin *et al.*, 1990) and prolonged

staring (Ellison *et al.*, 1981). Furthermore, monkeys given repeated low doses of amphetamine showed hallucinatory behavior (complex responses independent of external stimuli) and increases in self-directed stereotypies and other abnormal activities (e.g. mesh weaving) that persisted beyond drug exposure (Castner and Goldman-Rakic, 1999).

Recent research has focused on the role of drugs in alleviating stereotypic behavior. Administration of fluoxetine, a serotonin (5-HT) reuptake inhibitor, markedly reduced self-directed stereotypies in rhesus monkeys (Fontenot *et al.*, 2005) and reduced both whole-body motor stereotypies and self-directed stereotypies in vervet monkeys (Hugo *et al.*, 2003). The use of other drugs such as diazepam has yielded mixed results, working in some monkeys and not others depending on their early history (Tiefenbacher *et al.*, 2005).

THE FUNCTIONS OF ABNORMAL BEHAVIOR IN PRIMATES AND RELATIONSHIP TO MODELS

Considerable effort has been spent characterizing abnormal behavior in monkeys and relating it to early rearing environments. In this regard, monkeys show an amazing array of different kinds of abnormal behavior, much of which can be attributed to impoverished early rearing experiences or later exposure to socially restricted environments. However, less is known about the significance of these behaviors and how they relate to the development of primate models of human health. Are different stereotypies (e.g. pacing, eye poking) indicative of different disorders, do certain stereotypies co-occur with sufficient frequency to form a suite of traits associated with particular disorders, or is the incidence of any stereotypy regardless of its form indicative of the same or similar disorders? There are no clear-cut answers to these questions, and these may be the wrong questions inasmuch as they are focused on form and not function. Increasingly, it may be more important to determine the possible functions of stereotypies rather than to assume that they are functionless. A number of possible functions have actually been proposed ranging from the notion that stereotypies represent maladaptive behavior indicating distress, to the notion that stereotypies represent effective coping strategies, the loss of which might lead to distress. Studies on rodents and farm animals have led to the development of several functional hypotheses for why animals engage in stereotypic behavior (Frith and Done, 1990; Lawrence and Rushen, 1993; Mason and Latham, 2004). Below, we discuss four possible explanations for why animals engage in stereotypic behavior including hypotheses that suggest that stereotypies are beneficial or aversive to well-being.

On the plus side of the equation is the suggestion that stereotypic behavior may be a form of "do it yourself enrichment" (Mason and Latham, 2004). In this context, stereotypies may increase sensory motor stimulation and allow animals to express species-typical behavior in impoverished environments. Are animals that pace or somersault in small cages merely expressing species-typical locomotor

activity? If so, it should be possible to show that pacers and somersaulters are more likely to run and to run for longer periods of time in large outdoor environments than non-pacers. This finding would not fully address the hypothesis proposed above but it would be a starting point.

Another possibility is that stereotypies function to reduce arousal and stress. Indeed, there is evidence that self-directed stereotypies such as self-biting in monkeys may reduce heart rate and raise beta-endorphin levels (Novak, 2003; Tiefenbacher *et al.*, 2005; see also Chapter 5). If stereotypies are adaptive coping responses to anxiety-provoking situations, devising strategies to eliminate them without removing the stressor might actually decrease animal well-being (Mason, 1991). The optimal strategy then is to identify potential stressors and eliminate them from the environment. However, if this strategy is impossible to achieve, then pharmacotherapy with serotonin reuptake inhibitors or with anxiolytic drugs might reduce stereotypic behavior. If stereotypies actually function to reduce arousal in particular environments, it raises two possibilities for the animals that do not show stereotypic behavior in the same environment. Either they are less reactive to stressors (e.g. the low reactivity monkeys described earlier) or intriguingly they may be more distressed because they lack effective coping mechanisms.

A third possible explanation (the habit hypothesis) is that stereotypic behavior initially arose in a stressful context which no longer exists but the stereotypic behavior persists as an ingrained habit (Mason and Turner, 1993; Toates, 2000). Such stereotypies might be considered neutral with respect to animal well-being. However, a corollary of the habit hypothesis is that the stereotypic behavior might eventually be elicited by a greater range of stimuli and performed in more diverse situations. Thus, in terms of time and energy expenditure and potential disruption with other species-typical activities, these habits might come to have a negative impact on well-being. Indeed, there may be interesting parallels between this hypothesis and the development and maintenance of obsessive compulsive disorders in humans.

Finally, stereotypies may be maladaptive responses reflecting underlying states of distress and of poor psychological and/or physical well-being. For this latter interpretation, it is important first to determine any physical causes of stereotypic behavior that might include pain or movement disorders such as arthritis (Bayne and Novak, 1998). Once physical causes have been ruled out, then a variety of psychological disorders can be considered. Currently, there is no well-established link between nonhuman primate stereotypies and models of psychological disease. However, it is reasonable to hypothesize that the presence of stereotypic patterns of behavior may reflect several underlying psychological dysfunctions including anxiety (see the role of anxiety in self-injurious behavior in Chapter 5) and impulse control disorders that are most likely elicited in genetically vulnerable individuals by exposure to stressful environments at crucial periods in development. Further research will be required to understand the significance of stereotypies and determine whether they enable animals to cope better with stressful events or serve as a marker for the presence of psychological distress.

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