# 11 THE ROLE OF THE BRAIN SEROTONERGIC SYSTEM IN THE ORIGIN AND TRANSMISSION OF ADAPTIVE AND MALADAPTIVE VARIATIONS IN MATERNAL BEHAVIOR IN RHESUS MACAQUES

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## INTRODUCTION

The systematic study of maternal behavior in non-human primates, and particularly in rhesus macaques, began in the late 1950s and was driven by the notion that primate research could elucidate the biological mechanisms and functional significance of parent–child attachment (Bowlby, 1969). One influential line of research begun by Harry Harlow at the University of Wisconsin aimed to understand the nature of mother–infant attachment and the extent of maternal influences on infant development. The main experimental paradigm used in this research involved depriving rhesus macaque infants of their mothers early in life and exposing them to different rearing environments (Harlow, 1959). Early studies focused on the behavioral consequences of maternal deprivation for the infants (e.g., Harlow & Harlow, 1962; Kaufman & Rosenblum, 1967), while subsequent research incorporated hormonal responses to separation and artificial rearing (e.g., Champoux *et al.*, 1989; Levine & Wiener, 1988) as well as assessments of brain structure and function in maternally deprived individuals (e.g., Kraemer *et al.*, 1989; Martin *et al.*, 1991; Ginsberg *et al.*, 1993). In the 1960–1980 period, this line of research was pursued in many laboratories around the world and culminated in the development of a psychobiological theory of attachment, in which primate mothers were viewed as playing a fundamental role in the normative neurological, physiological, and sociobehavioral development of their offspring (Kraemer, 1992). This theory, however, was not based on studies of mothers and their behavior but only on the presumed effects of maternal absence on infant development. Although Harlow's early studies of surrogate mothers made a fundamental contribution to our understanding of infant attachment to a caregiver, later research and its extrapolations have been criticized on both conceptual and empirical grounds (see Insel, 1992; Kagan, 1992; Maestripieri, 2003a; Maestripieri & Wallen, 2003).

A different line of research begun by Robert Hinde at the University of Cambridge emphasized the study of rhesus macaque mothers and infants in naturalistic social environments, the quantification of different aspects of maternal behavior with ethological observational methods, and the investigation of naturally occurring interindividual variation in mothering styles (Hinde & Spencer-Booth, 1968, 1971). Hinde's approach had a pervasive influence on the field

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such that virtually every observational study of primate maternal behavior conducted in the last four decades has used some of his concepts or empirical measures. This research has enhanced our knowledge of the causes of naturally occurring interindividual variation in mothering style as well as of its consequences for offspring socio-behavioral development (e.g., see Altmann, 1980; Berman, 1984; Fairbanks, 1996, 2003; Maestripieri, 1999).

Studies of macaques, baboons, and vervet monkeys have shown that most variability in mothering style occurs along the two orthogonal dimensions of maternal protectiveness and rejection (Tanaka, 1989; Schino *et al.*, 1995; Fairbanks, 1996; Maestripieri, 1998a). The maternal protectiveness dimension includes variation in the extent to which the mother physically restrains her infant, initiates proximity and contact, and cradles and grooms her infant. The maternal rejection dimension includes the extent to which the mother limits the timing and duration of contact, suckling, or carrying. Although maternal behavior changes as a function of infant age and the mother's own age and experience, individual differences in mothering style tend to be consistent over time and across infants (Hinde & Spencer-Booth, 1971; Fairbanks, 1996).

There is now a great deal of evidence that variation in mothering style is accounted for by a combination of maternal characteristics (e.g., age, parity, dominance rank, temperament), infant characteristics (e.g., sex, age, baseline activity levels), and those of the surrounding environment (e.g., stress and support from other group members, ecological variables) (Maestripieri, 1999; Fairbanks, 2003). There is also evidence that individual differences in mothering style have long-term effects on the offspring's tendency to respond to challenges or explore the environment. For example, infants reared by highly rejecting (or less responsive) mothers generally develop independence at an earlier age (e.g., spend more time out of contact with their mothers, explore the environment more, and play more with their peers) than infants reared by mothers with low rejection levels (Simpson, 1985; Simpson & Simpson, 1985; Simpson *et al.*, 1989; Simpson & Datta, 1990). In contrast, infants reared by more protective mothers appear to be delayed in the acquisition of their independence and are relatively fearful and cautious when faced with challenging situations (Fairbanks & McGuire, 1987, 1988, 1993; Vochteloo *et al.*, 1993). Effects of mothering style on offspring behavior have been shown to extend into adulthood (Fairbanks & McGuire, 1988; 1993; Schino *et al.*, 2001; Bardi *et al.*, 2005; Bardi & Huffman, 2006; Maestripieri *et al.*, 2006b). These effects have also been demonstrated with experimental manipulations of maternal behavior (Vochteloo *et al.*, 1993) and with infant cross-fostering studies (Maestripieri, 2005a, b; Maestripieri *et al.*, 2006b). Mothering style, and particularly its maternal rejection component, has also been shown to affect the offspring's parenting behavior in adulthood, as there are often significant similarities in maternal behavior between mothers and daughters (Fairbanks, 1989; Berman, 1990; Maestripieri, 2005a; Maestripieri *et al.*, 2007).

Research on naturally occurring variation in primate maternal behavior has recently been revitalized by studies on laboratory rodents, in which the neurobiological and molecular mechanisms underlying the cross-generational effects of naturally occurring individual differences in maternal behavior have been elucidated. These studies have shown that variation in rates of maternal grooming/licking results in dramatic and long-lasting differences in the behavior, responsiveness to stress, and reproduction of the offspring, including the transmission of maternal style across generations (e.g., Meaney, 2001; Champagne & Curley, 2008). These cross-generational effects of maternal behavior are mediated by epigenetic modifications of gene expression (through DNA methylation mechanisms) for glucocorticoid and estrogen receptors in particular areas of the brain, which in turn, trigger a cascade of neuroendocrine effects involving the HPA and HPG axis, and a variety of neuropeptide hormones and neurotransmitters (see Champagne & Curley, 2008, for review). Although research on molecular brain mechanisms in non-human primates is constrained by a number of factors, the success of rodent studies in explaining how variation in maternal behavior affects offspring bio-behavioral development has prompted primate researchers to investigate whether similar or different mechanisms may operate in primates.

## BRAIN SEROTONIN AND NATURALLY OCCURRING VARIATION IN PRIMATE MATERNAL BEHAVIOR

In 1998, I began with my research collaborators a long-term project to investigate the

neurobiological and neuroendocrine mechanisms underlying the cross-generational effects of naturally occurring variation in maternal behavior in rhesus macaques. We focused on individual differences in mothering style along the protectiveness and rejection dimension, as well as on one extreme expression of variable parenting behavior: physical abuse of offspring. The project was conducted at the Field Station of the Yerkes National Primate Research Center in Lawrenceville, Georgia, where previous studies had shown that 5–10% of adult females in the macaque population abuse their offspring and that abusive parenting runs in families, being present in some matrilines for more than 6–7 generations and completely absent in others (Maestripieri *et al.*, 1997; Maestripieri, 1998b; Maestripieri & Carroll, 1998a, b). At the Yerkes Field Station, the rhesus macaque population includes over 1,500 individuals, and monkeys are housed in large outdoor corrals, where they live in social groups of naturalistic size and composition. In our research project, the individuals are studied in their own social groups, where they have the opportunity to express naturally occurring variation in behavioral tendencies. The monkeys are trained for capture and handling, so that procedures involving experimental testing and collection of biological samples are generally brief and the subjects are immediately returned to their groups for observation.

The project involved the longitudinal study, from birth to adulthood, of 16 females that were cross-fostered at birth between abusive and non-abusive mothers, along with the study of 43 males and females that were born and raised by their biological mothers, half of which were abusive and half non-abusive. In addition to studying the social development and behavioral reactivity to stress of offspring exposed to variable maternal behavior in infancy, we assessed the development of hypothalamic–pituitary–adrenal (HPA) function and the functionality of brain monoamine systems such as serotonin, dopamine, and norepinephrine. This was accomplished by measuring the plasma concentrations of ACTH and cortisol in a variety of experimental conditions, and by measuring the CSF concentrations of serotonin, dopamine, and norepinephrine metabolites (5-HIAA, HVA, and MHPG, respectively) at 6-month intervals (see Maestripieri *et al.*, (2006a) for details of the experimental procedures). A subset of infants and their mothers were also genotyped for the polymorphism in the serotonin transporter (SERT) gene (Lesch *et al.*, 1996), which has been shown to modulate the effects of early experience on adult behavior and psychopathology in both humans and rhesus macaques. In particular, individuals with the short (*s*) allele of this gene are more likely to develop anxiety disorders and dysregulation of the HPA axis as a result of early adverse experience than individuals with the long (*l*) allele (Lesch *et al.*, 1996; Bennett *et al.*, 2002; Caspi *et al.*, 2002, 2003; Barr *et al.*, 2004a, b). Analyses of the hormonal data are still in progress, therefore the rest of this chapter will focus on the behavioral and the brain monoamine data, with particular emphasis on serotonin. {AQ1}

We found that abusive mothers were significantly more likely to carry the *s* allele of the SERT gene than non-abusive mothers; however, there was no significant difference in the prevalence of the *l* and *s* alleles between the offspring of abusive and non-abusive mothers (McCormack *et al.* unpublished data). Individual differences in the CSF concentrations of 5-HIAA in the offspring measured at 6, 12, 18, 24, 30, and 36 months of age were highly stable over time (see also Higley *et al.*, 1992). Infants heterozygous (*l/s* genotype) or homozygous for the long or the short allele (*l/l* and *s/s* genotype) of the SERT gene did not differ significantly from each other in their CSF concentrations of 5-HIAA. Moreover, we found no significant variation in CSF concentrations of 5-HIAA in relation to infant abuse experienced in the first 3 months of life (abuse is concentrated in the first month and generally ends by the end of the third month) (Maestripieri *et al.*, 2006b). Therefore, we focused our analysis of offspring development on the effects of exposure to variable mothering style in infancy. We found stable individual differences in many measures of maternal behavior in the first 6 postpartum months and, similar to previous studies, we found that these measures clustered around two factors, or mothering style dimensions: protectiveness (making contact, restraining, cradling, and grooming the infant) and rejection (breaking contact, rejecting the infant's attempt to make contact). We obtained composite measures of these two dimensions and classified all mothers in our sample as being high or low in protectiveness and high or low in rejection depending on whether their scores were above or below the median value for the composite measures.

The individuals exposed to high rates of maternal rejection in infancy had significantly

lower CSF concentrations of 5-HIAA across their first 3 years of life than the individuals exposed to low rates of maternal rejection (Maestripieri *et al.*, 2006a). Data were analyzed separately for cross-fostered and non-cross-fostered individuals and a similar relation between maternal rejection and CSF 5-HIAA was found in both groups, suggesting that this association was not due to genetic similarities between mothers and offspring. In contrast, there were no differences in CSF 5-HIAA between offspring reared by high and low protectiveness mothers. Long-term effects of early experience on the development of the brain serotonergic system have also been reported in other studies of rhesus macaques (Kraemer *et al.*, 1989; Higley *et al.*, 1992; Shannon *et al.*, 2005) as well as rodents (e.g., Ladd *et al.*, 1996; Gardner *et al.*, 2005).

When we examined the development of various social and non-social behaviors prior to the onset of puberty, we found no differences in relation to early maternal protectiveness, and only one difference in relation to maternal rejection: the offspring of high rejection mothers engaged in more solitary play than those of low rejection mothers (Maestripieri *et al.*, 2006b). Thus, exposure to variable maternal behavior early in life had little impact on the offspring's social interactions with other group members prior to puberty. Consistent with this, we found that the general affiliative and aggressive tendencies of cross-fostered females in their first 2 years of life were more similar to those of their biological mothers than to those of their foster mothers (Maestripieri, 2003b). We also found, however, a significant negative correlation between CSF 5-HIAA and rates of scratching (Maestripieri *et al.*, 2006b), suggesting that individuals with low CSF 5-HIAA were more anxious than those with high 5-HIAA (see Schino *et al.* (1991) and Maestripieri *et al.* (1992) for the relation between scratching and anxiety). Differences in anxiety associated with serotonergic function may have contributed to some of the effects of exposure of variable mothering style we observed after our female subjects reached puberty and gave birth for the first time.

Although there were no similarities between the maternal protectiveness scores of mothers and daughters, the maternal rejection rates of daughters closely resembled those of their mothers (Maestripieri *et al.*, 2007). The resemblance was particularly strong for the cross-fostered females and their foster mothers. This finding is consistent with a previously reported intergenerational correlation of maternal rejection rates in another population of rhesus macaques (Berman, 1990) and suggests that this correlation is the result of early experience and not of genetic similarities between mothers and daughters. Although learning through direct experience with one's own mother and/or observations of maternal interactions with siblings may play a role in the intergenerational transmission of maternal rejection in macaques (Berman, 1990), biological mechanisms are also important. In our study, we found that the cross-fostered females' CSF concentrations of 5-HIAA were negatively correlated with their rates of maternal rejection such that the individuals with lower CSF 5-HIAA exhibited higher rates of rejection with their infants (Maestripieri *et al.*, 2007). Therefore, exposure to variable rates of maternal rejection in infancy may affect the development of the brain serotonergic system, and variation in serotonergic function, in turn, may contribute to the expression of maternal rejection with one's own offspring later in life. Interestingly, a preliminary study by Lindell *et al.* (1997) found that the CSF 5-HIAA concentrations of rhesus macaque mothers were significantly correlated with those of their 9-month-old infants, but this study did not assess whether these correlations had a genetic or environmental nature. Evidence of both genetic and environmental effects on CSF concentrations of 5-HIAA and other monoamine metabolites was provided by Rogers *et al.* (2004) in a study of a large pedigreed population of baboons.

In addition to demonstrating the intergenerational transmission of maternal rejection rates, we also found evidence for the intergenerational transmission of infant abuse. Specifically, about half of the females who were abused by their mothers early in life, whether cross-fostered or non-cross-fostered (all cross-fostered females reared by abusive mothers were also abused by them), exhibited abusive parenting toward their first-born offspring, whereas none of the females reared by non-abusive mothers did (including those born to abusive mothers; Maestripieri, 2005a). Moreover, the abused females, both cross-fostered and non-cross-fostered, who became abusive mothers had lower CSF 5-HIAA concentrations than the abused females who did not become abusive mothers (Maestripieri *et al.*, 2006a). This finding suggests

that experience-induced long-term alterations in serotonergic function in females reared by abusive mothers contribute to the manifestation of abusive parenting in adulthood. It is possible that experience-induced reduction in serotonergic function results in elevated anxiety and impaired impulse control, and that high anxiety and impulsivity increase the probability of occurrence of abusive parenting (e.g., Troisi & D'Amato, 1991, 1994), perhaps in conjunction with social learning resulting from direct experience of abuse early in life or observation of abusive parenting displayed by one's own mother with siblings. The intergenerational transmission of infant abuse, however, is likely to be a complex process with multiple determinants and influences. The finding that abusive mothers were more likely to carry the *s* allele of the SERT gene suggests that genetic variation in brain serotonergic function may play a role in the manifestation of abusive parenting and its transmission across generations. In order to understand the complex relationship between serotonin and abusive parenting, one must understand the relation between serotonin and maternal rejection as well as the relationship between maternal rejection and abuse.

## SEROTONIN AND MATERNAL BEHAVIOR

The brain serotonergic system is believed to play an important role in impulse control and in reducing the probability that risky, dangerous, or aggressive behaviors will be expressed in response to internal pressures or external stimuli (e.g., Gollan *et al.*, 2005). Consistent with a large body of human research (e.g., Linnoila & Virkkunen, 1992), studies of rhesus macaques and vervet monkeys have shown that, in adult males, low levels of CSF 5-HIAA are associated with high impulsivity, risk-taking behavior, and propensity to engage in severe forms of aggression (see Higley, 2003, for a review). In young males, low levels of CSF 5-HIAA are associated with earlier age of emigration from the natal group (e.g., Mehlman *et al.*, 1995) and with the attainment of high dominance rank in adulthood (Fairbanks *et al.*, 2004). Similar to the adult males, adult monkey females with low CSF 5-HIAA have been reported to be more likely to be wounded, to engage in violent aggression, and to be lower ranking than females with high CSF 5-HIAA (see Higley, 2003 for review; but see Cleveland *et al.*, 2004). Adult females with low CSF 5-HIAA also appear to be less socially oriented, spending more time alone, grooming less, and having fewer conspecifics in close proximity (Cleveland *et al.*, 2004; rhesus macaque abusive mothers fit this behavioral profile quite well; see Maestripieri, 1998b). Westergaard *et al.* (2003) also reported that the infants born to adult rhesus females with low CSF 5-HIAA concentrations are more likely to die within a year after birth than infants born to females with high CSF 5-HIAA concentrations.

Although serotonin is an obvious candidate neurotransmitter for the regulation of maternal care, there is surprisingly little information about the relationship between serotonin and maternal behavior, not only in non-human primates but in rodents as well (Numan & Insel, 2003). A study of rats found that lesions of the median raphe serotonergic neurons disrupted maternal behavior on day 1 of lactation (Barofsky *et al.*, 1983), but the results of this study have been questioned and the effects on maternal behavior have been ascribed to the surgical procedure rather than to the specific loss of a serotonergic pathway (Numan & Insel, 2003). Other studies of rats involving pharmacological manipulations of the brain serotonergic system reported some effects on maternal aggression but few or no effects on pup retrieval or other aspects of maternal care (reviewed by Numan & Insel, 2003; but see Johns *et al.*, 2005). Studies with knockout mice or with mice with a null mutation for a serotonin receptor gene reported higher fearfulness, impulsivity, and hyperactivity in these individuals but also impaired maternal behavior (Brunner *et al.*, 1999; Gingrich & Hen, 2001; Weller *et al.*, 2003; Jacobs & Emeson, 2006).

Studies involving brain lesions or genetic manipulations in primates are problematic, therefore researchers who have investigated the relationship between serotonin and maternal behavior have relied on measures of the serotonin metabolite 5-HIAA in the CSF. Early studies reported that monkey mothers with low CSF 5-HIAA were more protective and restrictive, and that their infants spent more time in contact with them, than mothers with high CSF 5-HIAA (Lindell *et al.*, 1997; Fairbanks *et al.*, 1998). Cleveland *et al.* (2004) found no relationship between CSF 5-HIAA and maternal behavior in the first few postpartum days, but on postpartum days 15 and 20, females with

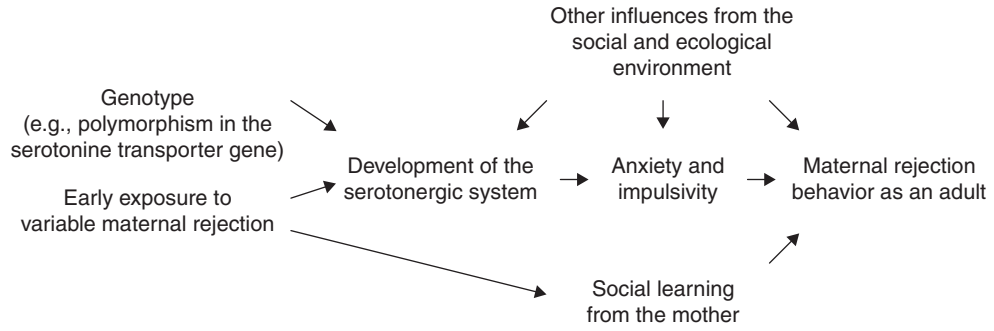


**FIGURE 11.1** A schematic representation of the possible role of genetic and experiential factors in the development and expression of maternal rejection behavior by adult female rhesus monkeys, including the brain serotonergic system and anxiety and impulsivity as important mediating mechanisms.

low CSF 5-HIAA broke contact and left their infants less frequently than females with high CSF 5-HIAA. A preliminary study in our laboratory reported a positive correlation between CSF 5-HIAA concentrations measured during pregnancy and maternal rejection behaviors in the first postpartum month in multiparous females (Maestripieri *et al.*, 2005). Our more recent work involving multiple measurements of CSF 5-HIAA during development, however, reported a negative correlation between CSF 5-HIAA and maternal rejection among first-time mothers (Maestripieri *et al.*, 2007). Taken together, these studies support the notion that variation in serotonergic function can contribute to the expression of differences in maternal behavior, although the relationship between serotonin and primate maternal behavior is not yet fully understood (but see Figure 11.1 for a schematic representation of the possible relationship between genes and early experience, serotonergic function, and maternal rejection).

The relative lack of studies of serotonin and maternal behavior in rodents may reflect the belief that the motivational bases of maternal behaviors such as nest-building, crouching over the pups, licking/grooming, and pup retrieval depend on the direct actions of hormones and peptides such as prolactin and oxytocin in specific regions of the brain (e.g., the medial preoptic area of the hypothalamus; Numan & Insel, 2003). Although serotonin might affect maternal motivation through its actions on oxytocin or prolactin release, serotonin and other monoamines are viewed as having specific effects on emotionality, motivation, or memory rather than specific effects on parentally motivated behaviors (Insel & Winslow, 1998; Numan & Insel, 2003). Research with rodents has established a strong link between anxiety/impulsivity and maternal aggression (e.g., Lonstein & Gammie, 2002), but the emotional substrate of rodent maternal behavior is not well established (but see Weller *et al.*, 2003; Johns *et al.*, 2005).

Emotions, however, play a fundamental role in the regulation of maternal behavior in non-human primates and humans (Dix, 1991; Pryce, 1992; Maestripieri, 1999). Emotions can be powerful elicitors of maternal behavior and play a crucial role in mediating the impact of the surrounding environment on the mother–infant dyad. For example, Pryce (1992) argued that two emotional systems, the attraction–arousal system and the anxiety system, play a central role in the regulation of primate maternal behavior. The attraction–arousal system involves the activation of positive emotions (e.g., excitement or joy) that elicit nurturing maternal behavior, whereas the anxiety system involves the activation of negative emotions (e.g., anxiety and fear) that elicit protective or rejecting maternal behaviors. Whereas the postpartum period is associated with lower reactivity to stress in rodents (Tu *et al.*, 2006; but see Deschamps *et al.*, 2003), pregnancy and the postpartum period in non-human primates and humans are characterized by high emotional instability and reactivity. For example, high cortisol levels and high arousability in the early postpartum period have been associated with greater sensitivity to infant cues and greater maternal responsiveness in humans (Fleming *et al.*, 1987, 1997; see also Maestripieri *et al.*, under review, for rhesus macaques). Interestingly, etiological theories of postpartum

psychosis based on estrogen's interaction with serotonin systems have been proposed (Fink & Sumner, 1996). For example, it has been shown that variation in the SERT genotype affects susceptibility to bipolar affective puerperal psychosis (Coyle *et al.*, 2000).

Motherhood is a psychologically stressful condition in human and non-human primates. In rhesus macaques, the first few months of an infant's life result into a number of anxiety-eliciting situations for the mother (Maestripieri, 1993a). There are marked individual differences in anxiety among rhesus mothers, and such differences translate into differences in maternal style (Maestripieri, 1993b). Maternal anxiety has also been implicated in the etiology of infant abuse (Troisi & D'Amato, 1984, 1991, 1994). Although the role of emotionality, and particularly of impulsivity, in primate maternal behavior is still poorly understood, it is possible that impulsivity affects how primate mothers interact with their infants, and that high impulsivity is expressed as high rejection rates as well as, as other studies suggest, greater maternal protectiveness. Our recent findings suggest that variation in impulsivity and maternal rejection originates, at least in part, from early experience and that there may be causal relationships between these two variables, such that high rates of maternal rejection result in low serotonergic function, which in turn result in high rates of maternal rejection later in life.

Maternal rejection also has a complex relation with infant abuse, perhaps not dissimilar from the relationship between child neglect and abuse in humans. Although abusive parenting in monkeys is probably maladaptive (Maestripieri, 1998b), maternal rejection is a behavior that belongs to the normal maternal repertoire and is used by mothers to limit the amount of time spent by infants in bodily and nipple contact, thus encouraging the infant's social and nutritional independence (e.g., Simpson & Simpson, 1985). Abusive parenting in rhesus macaques co-occurs with high rates of maternal rejection. Abusive mothers begin rejecting their infants shortly after birth (rejection normally begins after 3–4 weeks) and continue to do so at much higher rates than non-abusive mothers (Maestripieri, 1998b; McCormack *et al.*, 2006). Although we found no direct effects of infant abuse on CSF 5-HIAA, the observed significant effects of maternal rejection on CSF 5-HIAA were likely driven by abused infants, who were exposed to much higher levels of rejection than non-abused infants. Rejection occurs more frequently than abuse and although it does not cause physical harm to the infants, it may be even more psychologically traumatic than abuse. Interestingly, human studies have found that child neglect tends to have stronger and more consistent effects on brain structure and function in maltreatment victims than physical abuse does, although both are transmitted across generations (e.g., Glaser, 2000; DeBellis, 2005). Although social learning probably plays an important role in the intergenerational transmission of both maternal rejection and abuse in monkeys, our results suggest that rejection is more likely than abuse to cause long-term alterations in neuroendocrine and emotional functioning, and that these alterations may contribute to the expression of both rejecting and abusive parenting later in life.

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Author Queries

{AQ1} Please confirm the expansion for SERT.
{AQ2} Please update the reference Maestripieri *et al.*