



Research report

# Influence of parenting style on the offspring's behaviour and CSF monoamine metabolite levels in crossfostered and noncrossfostered female rhesus macaques

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## Abstract

We investigated the association between variation in parenting style and the offspring's behaviour and CSF monoamine metabolite (5-HIAA, 5-HVA, and MHPG) levels in rhesus monkeys. Study subjects were 25 two-year-old females reared by their biological mothers and 15 same-aged males that were crossfostered at birth and reared by unrelated mothers. Subjects that were rejected more by their mothers in the first 6 months of life engaged in more solitary play and had lower CSF concentrations of 5-HIAA than subjects that were rejected less. The relation between these variables was generally similar in crossfostered and noncrossfostered females. CSF levels of 5-HIAA were negatively correlated with rates of scratching, a behavioural indicator of anxiety. These results suggest that early exposure to high rates of maternal rejection can result in higher anxiety later in life, and that this effect may be mediated by serotonergic mechanisms. Variation in maternal protectiveness did not affect offspring behaviour and neither protectiveness nor rejection affected CSF levels of HVA and MHPG. CSF levels of MHPG, however, were negatively correlated with solitary play behaviour and avoidance of other individuals, suggesting that individuals with lower CSF MHPG were more fearful and socially phobic than those with higher CSF MHPG. Taken together, these findings suggest that individual differences in anxiety and fearfulness in young rhesus monkeys are accounted for, at least in part, by variation in CSF levels of monoamine metabolites, and that the development of brain monoamine systems, particularly serotonin, can be affected by early exposure to variable maternal behaviour.

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## Introduction

Nonhuman primates (hereafter primates) are excellent animal models for investigating the effects of early experience on the development of brain and behaviour [19,21]. Similar to humans, primates have an extended period of post-natal growth and maturation, in which the developing neural systems have ample opportunity to be influenced by experience [18]. Most

of a primate infant's early experience occurs in interaction with its mother and this experience can be highly variable. In cercopithecine monkeys such as macaques (*Macaca* spp.), baboons (*Papio* spp.) and vervet monkeys (*Chlorocebus aethiops*), there is a great deal of interindividual variation in parenting style along the two orthogonal dimensions of maternal protectiveness and rejection [13,22]. The protectiveness dimension includes variation in the extent to which the mother physically restrains infant exploration, initiates proximity and contact, and cradles and grooms her infant. The rejection dimension includes variation in the extent to which the mother limits the timing and duration of contact, suckling, and carrying. Although studies of rodents have demonstrated that offspring reared by mothers

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with different patterns of maternal care exhibit long-lasting differences in their neurobiological, physiological, and behavioural development [3,16], the question of whether variable parenting style affects the development of brain and behaviour in primates is only beginning to be investigated.

Only a few studies to date have longitudinally investigated the effects of exposure to naturally occurring variation in parenting style on behavioural development in cercopithecine monkeys and these studies have produced conflicting results. An early study of rhesus macaques (*Macaca mulatta*) by Simpson [26] showed that exposure to high levels of maternal rejection in the first few months of life was associated with reduced infant's exploration at the end of the first year. In contrast, in vervet monkeys, moderately rejecting mothers appear to produce offspring that are more independent, more sociable, and spend more time exploring the environment, while protective parenting produces offspring that are delayed in the development of independence and are relatively fearful and cautious when faced with challenging situations [5]. Finally, in Japanese macaques (*M. fuscata*), Schino et al. [23] found no significant association between variation in maternal protectiveness or rejection early in life and the offspring's behaviour several years later. They did report, however, a relationship between early maternal rejection and the offspring's responsiveness to stressful situations. Specifically, individuals that were rejected more by their mothers early in life were less likely to respond with submissive signals or with avoidance to an approach from another individual and exhibited lower rates of scratching (an indicator of anxiety) in the 5-min period following the receipt of aggression.

Developmental differences in reactivity to novelty or social responsiveness to other individuals are likely to be accompanied by differences in neurochemical and neuroendocrine substrates regulating emotional and social processes. The brain monoamine systems, norepinephrine, serotonin, and dopamine, would be likely candidates, as these systems play an important role in the regulation of emotional and behavioural processes and their development is sensitive to experimental perturbations of the rearing environment [9,10]. Unfortunately, none of the longitudinal studies of parenting style and offspring development in cercopithecine monkeys conducted to date has reported data on brain monoamine systems or any other physiological variables (but see [4] for hormonal data in a New World primate species, and [6] for human data). Furthermore, none of these studies involved experimental manipulations to tease apart the role of genetic inheritance versus early experience in the development of the offspring's behaviour.

Previous studies have shown that the concentrations of monoamine metabolites in the cerebrospinal fluid (CSF) have a significant heritable component [11,20]. In particular, quantitative genetic analyses of CSF levels of monoamine metabolites in a large baboon population of known pedigree provided evidence for high heritability for each metabolite as well as genetic correlations between metabolites [20]. These analyses also provided evidence for environmental correlations between CSF monoamine metabolites but the source of these correlations was not clear. The authors hypothesized that "social experience during development (e.g. the style of maternal behaviour received

as an infant) might affect these neurotransmitter systems" [20, p. 743].

In this study of rhesus macaques we investigated the potential association between exposure to variable parenting style early in life and individual differences in the behaviour and CSF levels of monoamine metabolites in the offspring's second year of life. Differences in behaviour and CSF levels of monoamine metabolites in female juveniles reared by mothers with different parenting styles might be the result of genetic similarities between mothers and offspring. To control for this possibility, we studied 25 rhesus females that were reared by their biological mothers and 15 females that were crossfostered at birth and reared by unrelated mothers. We hypothesized that if variable parenting style affects the development of offspring behaviour and brain monoamine systems, such effects should be apparent in both noncrossfostered and crossfostered females. In contrast, if the association between variable parenting style and offspring behavioural and neurochemical variables is the result of genetic similarities between mothers and offspring, this association should occur among the noncrossfostered females but not among the crossfostered females.

## 2. Methods

### 2.1. Subjects

This study was conducted with rhesus macaques from a population of over 1500 individuals living at the Field Station of the Yerkes National Primate Research Center in Lawrenceville, GA (USA). Study subjects included 25 juvenile females reared by their biological mothers in their natal groups and 15 juvenile females that were crossfostered at birth and reared by unrelated females living in different groups. Twenty of these juveniles (12 noncrossfostered and 8 crossfostered) were abused by their mothers early in life while 20 of them were not (see [14] for details on the crossfostering procedure and data on infant abuse). The subjects lived in several different social groups and were housed in 38 m × 38 m outdoor compounds with indoor housing areas. The groups consisted of 30–35 adult females with their immature offspring and 2–5 unrelated adult males. All groups had a stable matrilineal structure and a linear dominance hierarchy. Female dominance ranks were assessed using data on unidirectional aggression and submission collected during previous studies.

### 2.2. Procedures

All 40 subjects were observed in their first 6 months of life and their mothers' behaviour was recorded. They were observed again from 12 to 24 months of age and several social and nonsocial behaviours were recorded. Hours of observation ranged from 2 to 5 h per week in the first month of life to 1 h per month in the 4th–6th month and in the second year. All behavioural data were collected with the focal sampling method [15] and converted into mean hourly rates of behaviour per month for the purposes of data analysis. Experienced observers collected the data. For reliability purposes, prior to the beginning of data collection, observers watched and recorded behaviour until percent agreement exceeded 90% and Cohen's kappa exceeded 0.8.

Behavioural data collection in the first 6 months of life focused on the mothers and included the following behaviours: making contact (any physical contact with the infant lasting more than 5 s), breaking contact, cradling (holding one or both arms around the infant), grooming (common definition), restraining (preventing the infant from breaking contact by pulling its leg or tail), and rejection (preventing the infant from making contact by holding the infant at a distance with an arm or forcibly removing the infant from the nipple and pushing infant away). Behavioural data collection in the second year included the following offspring behaviours: aggression (threats, hits, bites, and chases) initiated and received, allogrooming initiated and received, social play (rough-and-tumble or

approach-withdrawal) initiated and received, solitary play (locomotor or object play), avoidance (withdrawal in response to an approach) and self-scratching. Self-scratching was used as an indicator of anxiety [24,28].

### 3. CSF sample collection and assays

All subjects were captured and anesthetized twice in their second year of life, at 18 and 24 months of age, for the collection of CSF samples. All samples were obtained between 1000 and 1200 h. Prior to sample collection, all animals had been trained to run into an indoor capture area, where they were transferred via a transfer box into a standard squeeze cage. CSF samples were obtained as soon as possible following anesthesia induction (with telazol, 5 mg/kg i.m.) and time to obtain the sample was recorded for each subject. One 2–3 ml CSF sample was collected from the cisterna magna using a 5 ml syringe with a 1-in., 22-gauge, level-tipped needle [10]. CSF samples were immediately frozen on dry ice and stored at –80 °C until further analysis. CSF samples were analyzed using liquid chromatography with electrochemical detection [25] and assayed for concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), the dopamine metabolite, homovanillic acid (HVA), and the norepinephrine metabolite, 3-methoxy-4-hydroxyphenylglycol (MHPG). The CSF concentrations of monoamine metabolites of the two samples were not significantly different and their average values were used for data analysis. All inter- and intra-assay variabilities were less than 10%. All experimental procedures were approved by the Institutional Animal Care and Use Committees of Emory University and the University of Chicago and adhere to standards for animal research set forth by the National Institutes of Health.

### 4. Data analyses

The relationship among different measures of maternal behaviour in the first 6 months was assessed with the principal components analysis (PCA; see [22,27] for similar analyses). Other statistical tests included analysis of variance (ANOVA) and Pearson’s correlation coefficients. Whenever the data were non-normally distributed or the variances were non-homogeneous, the data were log transformed. All tests were two-tailed and probabilities ≤0.05 were considered statistically significant.

## Results

### 1. Variation in parenting style and its relation to offspring behaviour

Preliminary analyses indicated that there were no significant differences between abused and nonabused subjects, between crossfostered and noncrossfostered subjects, or between the off-

spring of low ranking and high ranking mothers in any of nine behavioural variables or in the CSF concentrations of the three monoamine metabolites. Therefore, these variables were not considered in subsequent analyses, which focused on parenting style as a potential predictor of offspring measures.

The principal components analysis showed that the maternal behaviours of “making contact” and “restraining” loaded positively onto a first factor, labeled maternal protectiveness, while “breaking contact” and “rejection” loaded positively onto a second factor, labeled maternal rejection. A composite measure of protectiveness was therefore obtained by adding together the average scores of making contact and restraining, while a composite measure of rejection was obtained by adding together the average scores of breaking contact and rejection. The subjects’ mothers were classified as 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.

2 × 2 ANOVAs, with factors being parenting style and rearing condition, were used to assess whether behavioural differences existed between offspring reared by mothers with high and low protectiveness and rejection, and whether these differences occurred in both the noncrossfostered and the crossfostered females. The subjects reared by mothers with high and low protectiveness did not differ significantly in any of the nine behavioural variables measured in their second year of life (Tables 1 and 2). The subjects reared by high rejection mothers engaged in solitary play significantly more than the subjects reared by low rejection mothers ( $p < 0.05$ ; Tables 1 and 2). There was no significant interaction between maternal rejection and rearing condition for any of the nine behavioural variables, including solitary play (Table 1). Therefore, the effect of maternal rejection on solitary play was generally similar in the crossfostered and the noncrossfostered females.

### 3.2. CSF levels of monoamine metabolites in the offspring in relation to early experience and social behaviour

The CSF concentrations of 5-HIAA were significantly positively correlated with those of HVA ( $r = 0.65, n = 40, p < 0.0001$ )

Table 1  
F-values for 2 × 2 ANOVAs (d.f. = 1, 36) assessing the effects of maternal protectiveness and rejection on offspring behavioural and neurochemical variables

	Protectiveness			Rejection		
	Parenting style	Rearing	Interaction	Parenting style	Rearing	Interaction
Aggression I	1.71	0.66	0.33	1.04	0.47	0.04
Aggression R	1.00	0.27	2.78	0.68	0.58	0.60
Avoidance	0.19	1.26	0.02	0.60	1.18	0.43
Scratching	2.53	1.05	1.43	1.33	0.96	0.01
Solitary play	0.04	1.74	0.02	4.63*	0.12	0.21
Social play I	0.13	1.72	0.08	0.30	1.18	0.06
Social play R	0.73	1.04	0.09	0.39	1.32	0.65
Snoring I	0.59	0.11	0.41	0.05	0.17	0.02
Snoring R	0.78	1.34	0.04	1.65	0.90	0.68
5-HIAA	0.08	0.33	1.43	4.12*	0.53	1.13
HVA	0.46	0.07	0.01	1.53	0.04	0.18
MHPG	0.04	0.08	1.61	2.34	0.54	0.15

The two factors are: parenting style (high or low) and rearing condition (noncrossfostered or crossfostered); I: initiated; R: received; \* $p < 0.05$ .

Table 2

Mean ( $\pm$ S.E.) hourly rates of behaviour and CSF concentrations (pmol/ml) of monoamine metabolites in subjects reared by high and low protectiveness (*P*) mothers and high and low rejection (*R*) mothers

	High <i>P</i>	Low <i>P</i>	High <i>R</i>	Low <i>R</i>
Aggression I	0.15 $\pm$ 0.03	0.22 $\pm$ 0.05	0.14 $\pm$ 0.02	0.23 $\pm$ 0.05
Aggression R	0.59 $\pm$ 0.07	0.49 $\pm$ 0.16	0.62 $\pm$ 0.14	0.46 $\pm$ 0.06
Avoidance	2.05 $\pm$ 0.20	1.81 $\pm$ 0.25	2.04 $\pm$ 0.24	1.94 $\pm$ 0.20
Scratching	5.39 $\pm$ 0.39	4.86 $\pm$ 0.55	4.95 $\pm$ 0.41	5.45 $\pm$ 0.47
Solitary play	9.96 $\pm$ 0.72	9.43 $\pm$ 1.08	10.72 $\pm$ 0.89	8.74 $\pm$ 0.74
Social play I	2.86 $\pm$ 0.46	3.39 $\pm$ 0.56	3.31 $\pm$ 0.58	2.83 $\pm$ 0.42
Social play R	1.39 $\pm$ 0.23	1.87 $\pm$ 0.36	1.75 $\pm$ 0.34	1.39 $\pm$ 0.20
Grooming I	0.99 $\pm$ 0.10	1.06 $\pm$ 0.17	1.04 $\pm$ 0.14	0.99 $\pm$ 0.11
Grooming R	0.84 $\pm$ 0.13	0.67 $\pm$ 0.15	0.90 $\pm$ 0.17	0.66 $\pm$ 0.10
5-HIAA	703 $\pm$ 26	678 $\pm$ 29	649 $\pm$ 16	734 $\pm$ 28
HVA	4436 $\pm$ 182	4182 $\pm$ 269	4137 $\pm$ 188	4499 $\pm$ 223
MHPG	172 $\pm$ 5	172 $\pm$ 7	165 $\pm$ 4	178 $\pm$ 5

I: initiated; R: received.

but not with those of MHPG ( $r=0.27$ ,  $p=0.09$ ). The CSF concentrations of HVA and MHPG were positively correlated ( $r=0.39$ ,  $p=0.01$ ). As with the offspring behavioural variables,  $2 \times 2$  ANOVAs were used to assess whether there were differences in CSF levels of monoamine metabolites between offspring reared by mothers with high and low protectiveness and rejection, and whether these differences occurred in both the noncrossfostered and the crossfostered females. The subjects reared by high and low protectiveness mothers did not differ significantly in the CSF concentrations of 5-HIAA, HVA, or MHPG (Tables 1 and 2). In contrast, the subjects reared by high rejection mothers had significantly lower CSF concentrations of 5-HIAA ( $p < 0.05$ ; Tables 1 and 2), while the differences for HVA and MHPG were in the same direction but not statistically significant (HVA:  $p=0.22$ ; MHPG:  $p=0.13$ ; Tables 1 and 2). There was no significant interaction between maternal rejection and rearing condition for any of the three monoamine metabolites, including 5-HIAA (Table 1). Therefore, the effects of rejection were generally similar for crossfostered and noncrossfostered females. Across all infants, 5-HIAA was negatively correlated with scratching ( $p=0.05$ ; Table 3). Individuals with lower CSF 5-HIAA scratched themselves more in their second year of life than individuals with higher CSF 5-HIAA (Fig. 1). HVA was not correlated with any behavioural variable (Table 3). MHPG was negatively correlated with both avoidance ( $p=0.04$ ; Table 3)

and solitary play ( $p=0.03$ ; Table 3). Individuals with lower CSF MHPG avoided other group members more and played by themselves more in their second year of life than individuals with higher CSF MHPG (Fig. 2a and b).

#### 4. Discussion

Exposure to variable parenting style in the first 6 months of life was generally not a good predictor of offspring social behaviour in the second year of life. Variation in maternal protectiveness did not significantly predict variation in any of the nine offspring behavioural variables, while variation in maternal rejection was significantly associated with only one behavioural variable. Females reared by mothers with higher levels of maternal rejection engaged in solitary play more frequently than females reared by mothers with lower levels of maternal rejection. The relation between early maternal rejection and offspring solitary play was generally similar in noncrossfostered and crossfostered females, suggesting that it was unlikely to

Table 3  
Correlations (Pearson's coefficients,  $n=40$ ) between offspring behavioural and neurochemical variables

	5-HIAA	HVA	MHPG
Aggression I	-0.11	-0.21	0.10
Aggression R	-0.16	-0.11	-0.08
Avoidance	-0.06	-0.15	-0.32*
Scratching	-0.31*	-0.04	0.22
Solitary play	-0.08	-0.11	-0.33*
Social play I	-0.16	-0.09	-0.09
Social play R	-0.14	-0.20	0.09
Grooming I	0.01	-0.10	-0.16
Grooming R	0.08	0.06	0.03

I: initiated; R: received; \*  $p < 0.05$ .

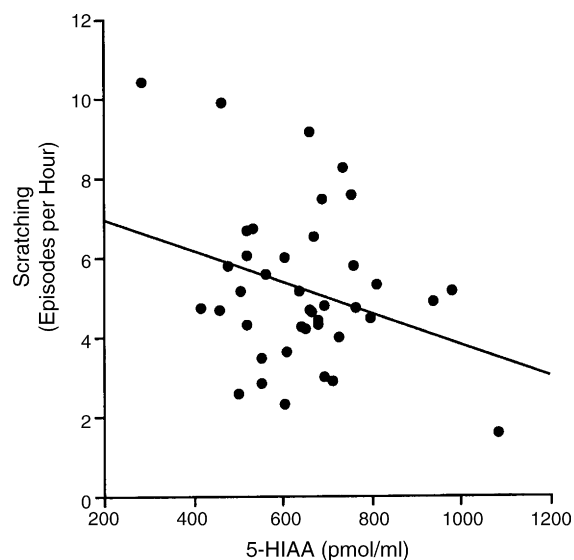


Fig. 1. Correlation between CSF concentrations of 5-HIAA and hourly rates of scratching in the offspring's second year of life.

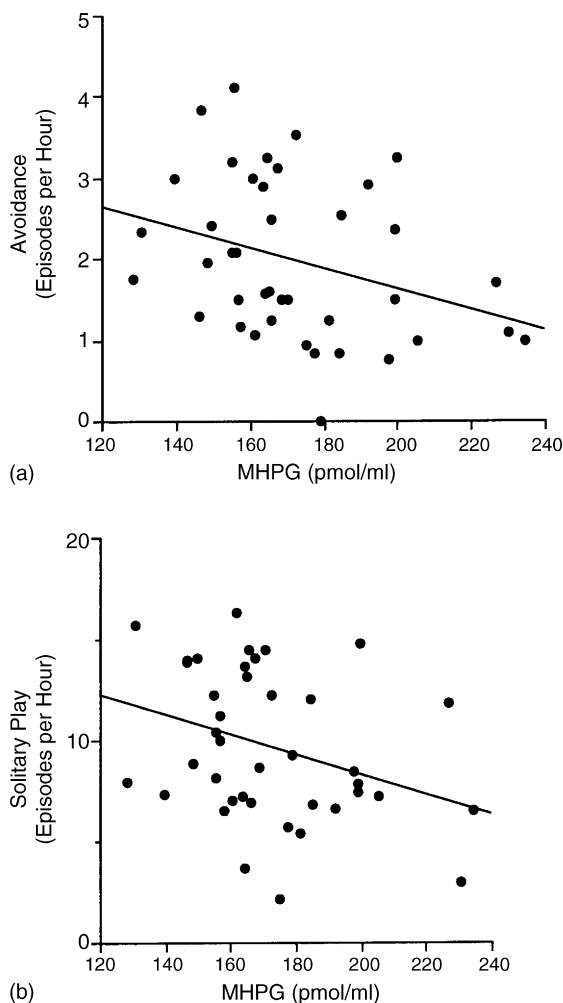


Fig. 2. (a) Correlation between CSF concentrations of MHPG and hourly rates of avoidance of other individuals in the offspring's second year of life. (b) Correlation between CSF concentrations of MHPG and hourly rates of solitary play in the offspring's second year of life.

the result of genetic similarities between mothers and offspring. Although these results suggest that exposure to variable parenting style early in life does not appear to have dramatic effects on the social development of the offspring, caution should be taken in generalizing these conclusions because this study only involved female offspring and social behaviour was only recorded in the second year of life. Early experience through interactions with one's mother could affect the behaviour of male and female offspring differently, and these effects could become more apparent later in life (e.g. in adulthood). Previous studies of macaques and vervet monkeys provided mixed results about the effects of parenting style on the development of offspring behaviour [5,23,26]. Unfortunately, their findings cannot be directly compared to those of this study due to species differences, differences in the subjects' age, and methodological differences in how parenting style and the offspring's behaviour were recorded.

Exposure to variable maternal rejection in the first 6 months of life was associated with significant differences in the offspring's CSF concentrations of the serotonin metabolite, 5-HIAA. This

association was generally similar in noncrossfostered and crossfostered females, suggesting that it was unlikely to be the result of genetic similarities between mothers and offspring. Females reared by mothers with higher rates of maternal rejection had lower CSF levels of 5-HIAA in their second year of life. Although there were no differences in CSF 5-HIAA levels between abused and nonabused infants, infant abuse in rhesus macaques co-occurs with high rates of maternal rejection [13], suggesting that the relation between high maternal rejection and low CSF 5-HIAA may have been, at least in part, driven by abusive mother–infant dyads. The brain serotonergic system plays an important role in impulse control and in reducing the probability that risky, dangerous, or aggressive behaviours will be expressed in response to internal pressures or external stimuli (see [1,7] for reviews). In humans, low CSF 5-HIAA has been associated with impulsive criminal behaviour [1] while monkeys with low CSF 5-HIAA levels are characterized by high impulsivity, risk-taking behaviour, and propensity to engage in severe forms of aggression (see [7] for a review). In this study, individuals with low CSF 5-HIAA had higher scratching rates. Scratching is a reliable indicator of anxiety in primates and, specifically, of anxiety resulting from uncertainty and motivational conflict rather than of fear-related anxiety [24,28]. Uncertainty and motivational conflict may be elevated in individuals with low impulse control, and this may explain the association between high scratching rates and low CSF 5-HIAA. Therefore, the results of this study suggest that exposure to variable maternal rejection early in life may be potentially associated with long-term alterations in anxiety and impulse control and their underlying neurochemical substrates. In this study, neither CSF levels of 5-HIAA nor scratching rates in the second year of life were significantly correlated with any social behaviours during the same period. However, a relation between low CSF 5-HIAA, high anxiety, and particular social behaviours might emerge later in life, e.g. in adulthood.

Although the CSF concentrations of the three monoamine metabolites were generally positively correlated among individuals, individual differences in CSF levels of HVA and MHPG were not significantly associated with exposure to variable parenting style early in life. CSF levels of MHPG in the second year of life, however, were negatively correlated with solitary play and avoidance, so that individuals with lower CSF MHPG avoided others more and played by themselves more than individuals with higher CSF MHPG. The brain noradrenergic system has been associated with the regulation of arousal and an individual's fearful or aggressive responses to novel or threatening stimuli [1]. Some studies have reported a positive correlation between CSF MHPG and aggressive behaviour in primates [8] while human studies have reported lower CSF MHPG in antisocial and violent offenders [29]. In rhesus macaques, avoidance of other individuals and propensity to engage in solitary play may be interpreted as expressions of fearful or socio-phobic behavioural tendencies. Therefore, the observed association between low CSF MHPG, high solitary play behaviour, and high avoidance suggests that the juveniles with low CSF MHPG may be relatively fearful and socially phobic individuals. Since variable parenting style was a predictor of solitary play but not of

avoidance or CSF MHPG levels, these results suggest that fearfulness and social phobia may only weakly be affected by early experience and perhaps, be more dependent on genetic inheritance [30].

The influence of maternal rejection on CSF levels of 5-HIAA and on offspring anxiety and behaviour reported in this study is an example of evolutionary maternal effects, i.e. nongenomic effects of the maternal phenotype on the offspring's phenotype [2]. Maternal effects play an important role in biological evolution and have been reported in plants and in a wide range of animal taxa [2]. Maternal effects can be adaptive or maladaptive. Adaptive maternal effects may be a mechanism through which parents transfer information about the environment to their offspring and facilitate the development of phenotypic adaptation [17]. For example, if parents adaptively modify their phenotype in relation to their environment, they could facilitate the development of similarly adaptive phenotypes in the offspring through maternal effects. On the other hand, maternal effects could also be a mechanism through which behavioural pathologies are transmitted across generations (e.g. infant abuse; [14]). Therefore, the maternal effects on brain monoamine systems and behaviour reported in this study could have important implications for understanding the origins and maintenance of adaptive phenotypes in primate populations as well as for the effects of early experience on developmental psychopathology.

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