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ORIGINAL RESEARCH ARTICLE

# Serotonin transporter gene polymorphism, differential early rearing, and behavior in rhesus monkey neonates

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**A polymorphism in the serotonin (5-HT) transporter gene regulatory region (5-HTTLPR) is associated with measures of 5-HT transporter (5-HTT) expression and 5-HT-mediated behaviors in humans. An analogous length variation of the 5-HTTLPR has been reported in rhesus monkeys (rh5-HTTLPR). A retrospective association study was conducted on 115 rhesus macaque infants either homozygous for the long 5HTTLPR variant (*l/l*) or heterozygous for the short and long form (*l/s*). To assess contributions of genotype and early rearing environment, 36 mother-reared monkeys (*l/l* = 26, *l/s* = 10) and 79 nursery-reared monkeys (*l/l* = 54, *l/s* = 25) were assessed on days 7, 14, 21, and 30 of life on a standardized primate neurobehavioral test designed to measure orienting, motor maturity, reflex functioning, and temperament. Both mother-reared and nursery-reared heterozygote animals demonstrated increased affective responding relative to *l/l* homozygotes. Nursery-reared, but not mother-reared, l/s infants exhibited lower orientation scores than their *l/l* counterparts. These results demonstrate the contributions of rearing environment and genetic background, and their interaction, in a nonhuman primate model of behavioral development.**
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## Introduction

Accumulating evidence supports the role of heritable factors in the determination of temperament characteristics.[1] Traits such as activity level, task persistence, behavioral intensity, and inhibition have been shown to demonstrate substantial heritability (ie, proportion of variation accounted for by genetic factors). It is likely that multiple genes, each contributing a small amount of variance, underlie much of the phenotypic variation in temperament traits. Recently several polymorphisms have been identified that are associated with temperament and personality variables. One of these polymorphisms, the human serotonin transporter promoter polymorphism (5-HTTLPR), is associated with measures of 5-HT transporter (5-HTT) expression, 5-HT-mediated behaviors, and personality traits in adults[2,3] and with temperament characteristics in infants.[4,5]

Nonhuman primate models of temperament confer great promise for the study of biobehavioral development.[6] Because of their similarity to humans in temperamental traits, nonhuman primates are widely used as subjects in developmental studies designed to investigate psychopathology and developmental outcomes. Additional benefits of studying nonhuman primate infants for assessment of temperament characteristics include similarity of physiological and basic behavioral traits to those of human infants, ease of access to subjects for repeated testing, and, relative to humans, accelerated development. A length variation of the 5-HTTLPR that is basically homologous with the human polymorphism (rh5-HTTLPR) has been identified in the rhesus monkey,[7] providing the opportunity to assess genotype effects as well as genotype/environment interactions on temperament in this species. The purpose of the present study was to assess the association between the rh5-HTTLPR and behavioral characteristics potentially influenced by 5-HT functioning in a large sample of infant rhesus monkeys with well-characterized environmental histories. Our test instrument was a standardized primate neonatal assessment, derived from measures utilized in human infant clinical research, which is uniformly administered to rhesus neonates in our laboratory. This assessment, designed to measure orienting ability, motor maturity, reflex functioning, and temperament, captures emerging behavioral capabilities across the first month of life. Based on previous findings in

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humans,[4,5] we hypothesized that rhesus neonates carrying the *l/s* genotype would exhibit diminished orientation abilities relative to *l/l* homozygotes. We also hypothesized that animals carrying the *l/s* genotype would evince higher levels of behavioral manifestations of anxiety or distress during the examination, than infants carrying the *l/l* genotype.

## Methods

*Subjects*

One hundred and fifteen rhesus macaque infants (*Macaca mulatta*) served as study subjects. All infants were laboratory-born in the Laboratory of Comparative Ethology, National Institute of Child Health and Human Development colony. Infants were either mother-reared (MR) or nursery-reared (NR) according to previously published procedures.[8] Genotyping was accomplished as described by Bennett *et al*.[9] The sample consisted of 36 MR infants (12 *l/l* males, 14 *l/l* females, 5 *l/l* males, and 5 *l/s* females) and 79 NR infants (22 *l/l* males, 32 *l/l* females, 16 *l/s* males, and 9 *l/s* females). Only two infants in the colony were homozygous for the *s* allele, and one infant carried an *xl/l* genotype; these infants were not included in the analyses. All infants belonged to one pedigree structure that extended back several generations to the colony founders. Hence all infants were related to each other to a greater or lesser extent. Twenty infants were Chinese/Indian hybrid (ie, one Chinese-origin parent and one Indian-origin parent) and 95 infants were solely Indian-origin.

At the beginning of each birth season all interested investigators met to determine guidelines for assignment of infants to rearing condition and to specific studies. There were several basic criteria regarding assignment:

(1) The long-term goal, over the lifespan of the study, was to have equal representation by sire in each of three rearing conditions—peer-reared (nursery infants who on day 37 would enter social groups containing four infants permanently housed together), surrogate/peer-reared (nursery infants who on day 37 would enter groups of four infants living in individual cages containing surrogates, and with 2 h daily peer socialization), and mother-reared. In addition, some infants were opportunistically foster-mother reared (fostered to unrelated lactating females).
(2) Infants from primiparous mothers were to be left with the mother if possible.
(3) The age difference between the oldest and the youngest infant in peer and surrogate/peer groups could not exceed 30 days.
(4) Some investigators wished for sex balance within nursery groups, others were concerned with diversity of sire.

Because of the relative unpredictability of timing of monkey births (we did not use timed mating procedures), the occasional rejection or inability of a mother to care for her infant, and the uncertainty of success of foster rearing, assignment of infants was therefore most typically made on a case-by-case basis with each infant being placed in the most 'useful' rearing condition as it was born.

*Neonatal assessment*

A 30-minute developmental assessment battery was administered on days 7, 14, 21, and 30 of life. This test was derived from the Brazelton Neonatal Assessment Scale used in human newborns[10]and has been described in detail elsewhere.[11,12] Raters were trained to a reliability criterion of 0.90 before collecting data (Pearson product-moment correlation) according to a rigorous training protocol.[13] Because the analysis reported here was conducted retrospectively, all testers were unaware of the genotypes of the animals being tested.

*Statistical analysis*

Following the procedure previously described,[12] several individual test items were condensed into four clusters: Orienting, State Control, Motor Maturity, and Activity. Historically, few sex differences have been noted on these neonatal measures. However, because there have been reports of sex differences in Motor Maturity and Activity Cluster data on day 30 of life,[14] initial analyses were conducted as follows: four-way multivariate analyses of variance with Rearing Condition (NR, MR), Genotype (*l/l*, *l/s*), and Sex (male, female) as between-group factors, and Day of Test (Days 7, 14, 21, or 30) as a within-groups factor. As expected, there were no significant main effects of Sex or interactions of Sex with any other factor for the Orientation, State Control, or Motor Maturity Clusters. For the Activity Cluster, there was a significant Rearing Condition × Sex interaction—mother-reared males were more active than females; this finding was reversed for nursery-reared infants. However, there were no interactions of Sex with any other factor for this cluster. Thus Sex was removed as a variable and all cluster data were reanalyzed by three-way multivariate analyses of variance with Rearing Condition (NR, MR) and Genotype (*l/l*, *l/s*) as between-group factors, and Day of Test (Days 7, 14, 21, or 30) as a within-groups factor. Table 1 lists the components of each cluster. The statistical program SuperANOVA (Abacus Concepts, Berkeley, CA, USA) was used for all analyses. Note that degrees of freedom differ across identical analyses; in case of missing data for a cluster (eg, due to experimenter inadvertently not recording the test items), the animals with missing data were eliminated from the statistical analysis of that cluster.

## Results

Analyses detected a significant main effect of Genotype on the State Control Cluster. Although there was also a statistically significant effect of Rearing on the State Control cluster (MR animals obtained higher scores,

**Table 1** Neonatal test items

| | |
|---|---|
| **Orientation cluster** | |
| Visual orientation | Eyes oriented toward toy (Mickey Mouse face) held in four positions in infant's periphery |
| Visual following | Eyes following moving toy (same as above) in horizontal and vertical directions |
| Duration of looking | Examiner rating of length of looks on orienting items |
| Attention | Examiner rating of attention on orienting items |
| **State control cluster** | |
| Irritability | Amount of distress noted during the entire examination |
| Consolability | Ease of consoling infant following distress |
| Predominant state | State of infant during examination |
| Struggle | Amount of squirming during examination |
| **Motor maturity cluster** | |
| Coordination | Quality of motor activity rated during the 5-min observation period |
| Head posture prone | Ability to hold head up when held in air prone |
| Head posture supine | Ability to hold head up when held in air supine |
| Labyrinthian righting | Realignment of head when body is tilted 45 sideways |
| Response speed | Examiner rating of speed of responding |
| **Activity cluster** | |
| Passive | Duration of time spent inactive during the 5-min observation period |
| Coordination | Quality of motor activity rated during the 5-min observation period |
| Motor activity | Observation of amount of motor activity during the 5-min observation period |
| Spontaneous locomotion | Quality of locomotion rated during the 5-min observation period |

indicative of more emotionality), regardless of rearing condition, monkeys with the *l/s* genotype demonstrated higher scores (ie, exhibited more struggling, were less easy to console, and manifested higher amounts of, and more frequent, emotional distress) than the *l/l* homozygotic infants. A significant Rearing by Test Day interaction indicated that the differences between MR and NR infants increased over successive test days. A significant interaction of genotype and rearing condition was detected for the Orientation Cluster. Although NR animals obtained higher average scores on this cluster than did MR animals, indicating better visual orientation, visual tracking, and attentional capabilities, the effect of the *l/s* genotype was to

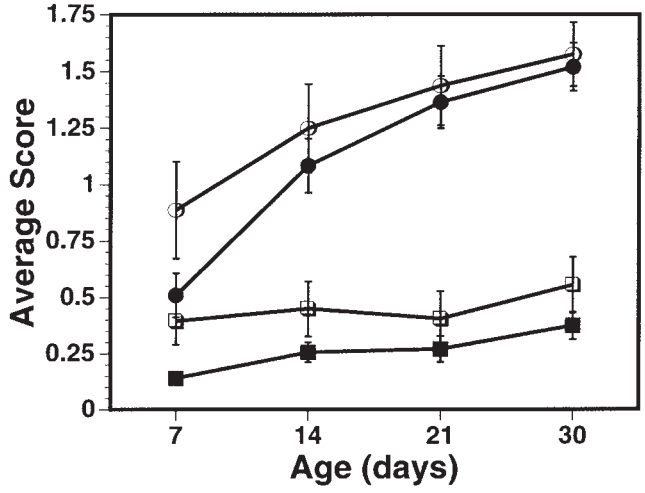


**Figure 1** State Control Cluster on days 7, 14, 21, and 30 (mean ± SE). Closed circles = MR l/l infants; closed squares = NR l/l infants; open circles = MR l/s infants; open squares = NR l/s infants.

substantially lower orientation scores in NR animals but not MR infants. An additional interaction was detected between Genotype and Test Day, with differences between *l/l* and *l/s* animals most pronounced on later test days. MR infants exhibited higher scores overall on the Activity Cluster than did NR animals; no other main effects or interactions were observed. As expected, scores on all four clusters increased over time, indicating maturation of visual, attention, and motor abilities, as well as increased emotionality in response to the examination. Figures 1–4 depict the State Control, Orientation, Activity, and Motor Maturity cluster data. ANOVA results for these clusters are provided in Table 2.

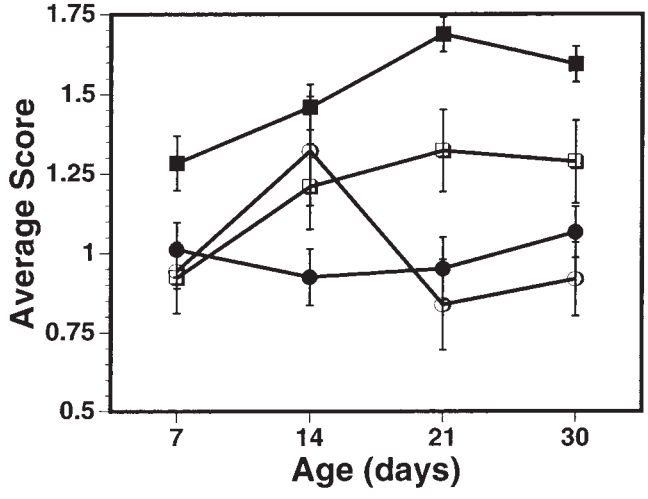


**Figure 2** Orientation Cluster on days 7, 14, 21, and 30 (mean ± SE). Closed circles = MR l/l infants; closed squares = NR l/l infants; open circles = MR l/s infants; open squares = NR l/s infants.

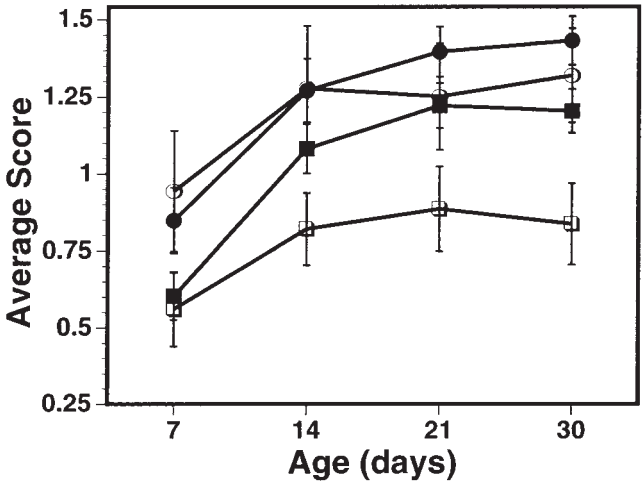


**Figure 3** Activity Cluster on days 7, 14, 21, and 30 (mean ± SE). Closed circles = MR l/l infants; closed squares = NR l/l infants; open circles = MR l/s infants; open squares = NR l/s infants.

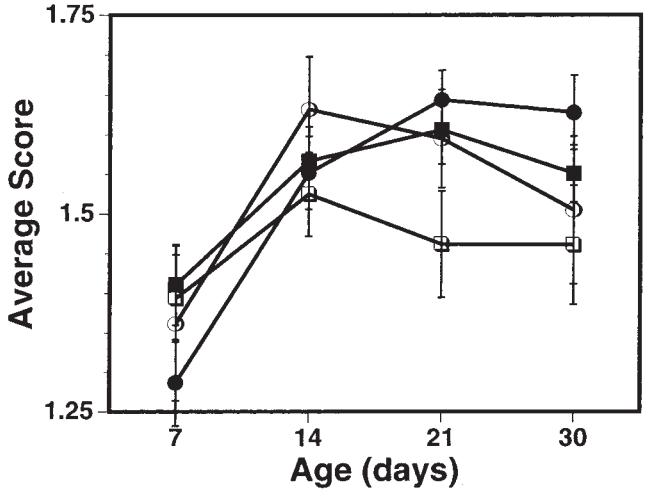


**Figure 4** Motor Maturity Cluster on days 7, 14, 21, and 30 (mean ± SE). Closed circles = MR l/l infants; closed squares = NR l/l infants; open circles = MR l/s infants; open squares = NR l/s infants.

## Discussion

This study demonstrates both main effects of rh-5HTTLPR genotype as well as early rearing and genotype/environment interaction effects on orientation, attentional, and affective capacities of neonatal rhesus monkeys. Development of the brain, including the neocortex, involves a complex series of rigorously timed stages that are subdivided into generation, migration, and differentiation of neurons and glia.[15] Components of monoaminergic neurotransmitter systems such as receptors, transporters, and modifying enzymes participate in brain development and thus set the stage for brain (dys)function. There is an increasing body of evidence indicating that 5HT system homeostasis is critical in the genesis, differentiation, and maturation of neuronal cells and networks in brain regions controlling sensory inputs, stimulus processing, and motor output.[16–20] Given the intricacy of these processes that will eventually be regulated by these circuitries, it is conceivable that neurodevelopment is exquisitely prone to allelic variation in functional gene expression. Based on the notion that serotonergic gene expression is involved in a myriad of processes during brain development, complex behavior is likely to be influenced by genetically driven variability of 5HT function.

Our results are comparable to those observed in human infants. Rhesus infants carrying the *s* allele were more distressed during the examination, as indexed by higher State Control cluster scores. In human infants, similar results were noted at 2 months of age on the Negative Emotionality dimension of the Infant Behavior Questionnaire.[4] In human infants undergoing similar assessments,[4,5] possession of an *s* allele results in decreased orientation scores.* We noted similar results, but for nursery-reared infants only. Attentional and orienting deficits can be attributable to distractibility during the examination, and can also be caused by extreme emotional arousal, as was observed in a comparison of rhesus neonates from different countries of origin.[22] Given the differences in distractibility and temperament scores between the *l/l* and *l/s* genotypes, it is most likely that affective arousal and distractibility are interfering with optimal attention in the nursery-reared *l/s* neonates. There are several explanations as to why genotype did not influence orientation capabilities in MR rhesus infants. It is possible that there is a 'floor effect', inasmuch as MR infants already exhibit low orientation scores in this context. It is also possible that mothers provide a 'buffer' by exerting protective or compensatory effects for their offspring, thereby mitigating or eliminating phenotypic expression of genotypic characteristics. Although there is abundant evidence that macaque mothers can tailor their behavior as a function of infant sex, age, and physical handicap[23,24] and in response to variations in environmental conditions,[25,26] direct evidence for differential maternal treatment based on offspring genotype is lacking at present. Because one advantage of the nursery-rearing environment is the ability to exert maximal control over environmental conditions, it is also possible that the limited amount of environmental variance engendered by the nursery environment allows expression of genetic variance that would not be as readily apparent in mother-reared infants. Finally, one must also consider the possibility of differential validity of the test instrument for monkeys in the two rearing conditions; perhaps the assessment provided a more valid test for nursery-reared infants. This speculation is weakened somewhat by our findings of

* In human infants, the 5HTTLPR and DRD4 genotypes interacted to produce phenotypic effects on orientation. Rhesus monkeys do not possess the equivalent DRD4 polymorphisms,[21] which suggests that in monkeys the effects of 5HTTLPR are more 'purely' expressed than in humans.

**Table 2** ANOVA results for neonatal clusters

| *Source* | *df* | *SS* | *MS* | *F* | *P* |
|---|---|---|---|---|---|
| **State Control Cluster** | | | | | |
| Genotype | 1 | 2.561 | 2.561 | 4.355 | 0.0392 |
| Rearing | 1 | 57.431 | 57.431 | 97.671 | 0.0001 |
| Genotype × rearing | 1 | 0.010 | 0.010 | 0.017 | 0.8961 |
| Subject (group) | 109 | 64.093 | 0.588 | | |
| Test day | 3 | 11.796 | 3.932 | 34.998 | 0.0001 |
| Test day × genotype | 3 | 0.564 | 0.188 | 1.675 | 0.1723 |
| Test day × rear | 3 | 5.524 | 1.841 | 16.388 | 0.0001 |
| Test day × genotype × rearing | 3 | 0.165 | 0.055 | 0.491 | 0.6890 |
| Test day × subject (group) | 327 | 36.739 | 0.112 | | |
| **Orientation Cluster** | | | | | |
| Genotype | 1 | 1.874 | 1.874 | 3.470 | 0.0652 |
| Rearing | 1 | 9.894 | 9.894 | 18.316 | 0.0001 |
| Genotype × rearing | 1 | 2.313 | 2.313 | 4.282 | 0.0408 |
| Subject (group) | 111 | 59.957 | 0.540 | | |
| Test day | 3 | 1.903 | 0.634 | 3.624 | 0.0134 |
| Test day × genotype | 3 | 1.392 | 0.464 | 2.650 | 0.0488 |
| Test day × rear | 3 | 2.986 | 0.995 | 5.687 | 0.0008 |
| Test day × genotype × rearing | 3 | 0.696 | 0.232 | 1.325 | 0.2660 |
| Test day × subject (group) | 333 | 58.291 | 0.175 | | |
| **Activity Cluster** | | | | | |
| Genotype | 1 | 1.570 | 1.570 | 2.951 | 0.0888 |
| Rearing | 1 | 7.406 | 7.406 | 13.921 | 0.0003 |
| Genotype × rearing | 1 | 0.841 | 0.841 | 1.580 | 0.2115 |
| Subject (group) | 105 | 55.860 | 0.532 | | |
| Test day | 3 | 10.501 | 3.500 | 16.346 | 0.0001 |
| Test day × genotype | 3 | 0.893 | 0.298 | 1.390 | 0.2458 |
| Test day × rear | 3 | 0.069 | 0.023 | 0.108 | 0.9554 |
| Test day × genotype × rearing | 3 | 0.052 | 0.017 | 0.081 | 0.9705 |
| Test day × subject (group) | 315 | 67.453 | 0.214 | | |
| **Motor Maturity Cluster** | | | | | |
| Genotype | 1 | 0.121 | 0.121 | 0.755 | 0.3866 |
| Rearing | 1 | 0.066 | 0.066 | 0.414 | 0.5212 |
| Genotype × rearing | 1 | 0.098 | 0.098 | 0.611 | 0.4362 |
| Subject (group) | 111 | 17.791 | 0.160 | | |
| Test day | 3 | 2.445 | 0.815 | 12.549 | 0.0001 |
| Test day × genotype | 3 | 0.326 | 0.109 | 1.671 | 0.1731 |
| Test day × rear | 3 | 0.323 | 0.108 | 1.660 | 0.1755 |
| Test day × genotype × rearing | 3 | 0.074 | 0.025 | 0.378 | 0.7687 |
| Test day × subject (group) | 333 | 21.629 | 0.065 | | |

persistent genotype/rearing environment interactions in CSF 5-HIAA concentration later in life.[9]

The neonatal assessment was conducted at four time points to capture the developmental progression of visual and motor abilities. Although there were no differences between *l/l* and *l/s* infants in the development of motor maturity or activity levels, differences between the two groups in orientation scores were especially evident on days 21 and 30. In previous studies[27] we have noted a 'ceiling effect' for the Orientation Cluster, such that by days 21 and 30 most infants can achieve high scores on these items. Although it is possible that there is a maturational lag in orientation ability in the *l/s* infants resulting in lower scores, it is more likely that the infants' emotionality is inhibiting optimal attention at these later ages.

Although provocative, these results bear replication in other rhesus colonies, and in other macaque species. In particular, it would be instructive to conduct similar assessments on unrelated individuals to control for possible influences of population structure. Examination of alternative polymorphisms homologous to those observed in humans (eg, DAT) should also be conducted. In summary, these results demonstrate the contributions of rearing environment and genetic background, and their interaction, in a nonhuman primate model of behavioral development.

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