Behavioural Brain Research 292 (2015) 50–55

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Dopamine D4 receptor genotype variation in free-ranging rhesus macaques and its association with juvenile behavior

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HIGHLIGHTS

- We genotyped dopamine receptor D4 (DRD4) for first time in Cayo Santiago macaques.
- We investigated the association of DRD4 with juvenile impulsivity behaviors.
- Individuals with long DRD4 alleles are more restless and independent of mother.
- Individuals with long DRD4 alleles are more avoidant of other monkeys.
- Demonstrate utility of rhesus macaques as a model for ADHD research.

ARTICLE INFO

Article history:
Received 5 May 2015
Received in revised form 3 June 2015
Accepted 7 June 2015
Available online 11 June 2015

Keywords:
DRD4
Rhesus macaque
Juvenile
Social behavior
Impulsivity

ABSTRACT

A polymorphism in the dopamine receptor D4 (*DRD4*) gene has been associated with significant variation in behavioral impulsivity, novelty-seeking, and risk-taking in humans and other animals. Rhesus macaques are an excellent animal model for research on the genetic basis of behavior using the candidate gene approach. Little is known, however, about allelic variation in *DRD4* in large free-ranging populations of rhesus macaques and how this allelic variation relates to emotion regulation and behavior. In this study, we genotyped for the *DRD4* polymorphism 178 individuals of different age and sex categories in the free-ranging rhesus macaque population on the island of Cayo Santiago, PR. Moreover, we examined the possible association between DRD4 allelic variation and three measures of juvenile behavior (time spent in proximity to the mother, avoidance of other individuals, and behavioral restlessness). Five different *DRD4* alleles (5R, 5.5R, 6R, 6.5R, and 7R) were identified in the subject population. The most common allele was the 5R allele (78.5%), followed by the 7R allele (16.1%). Juveniles carrying the long form of the DRD4 allele (7R) spent less time in proximity to their mothers, avoided other individuals more often, and scored higher on behavioral restlessness than juveniles carrying the shorter alleles. Behavioral restlessness was also influenced by maternal *DRD4* genotype. These results highlight both similarities and differences in the relative occurrence of *DRD4* alleles and their association with behavior in this rhesus macaque population, other nonhuman primate species or populations, and humans.

1. Introduction

A large body of literature has shown that individuals who carry different alleles for genes that code for various aspects of monoaminergic (i.e., noradrenergic, serotonergic, and dopaminergic) function often exhibit differences in emotions or behavior (e.g., Gainetdinov and Caron [10]. A gene polymorphism that has received considerable attention involves a particular region (a 48-bp section of exon III, which encodes the third cytoplasmic loop of the receptor) of the gene that codes for the dopamine receptor

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http://dx.doi.org/10.1016/j.bbr.2015.06.014
0166-4328/

D4 (*DRD4*). This polymorphism has a variable number of tandem repeats (VNTR) [24]. In humans, the polymorphism can include anywhere from 2 to 11 repeats (2R–11R) [7], with the 7R being the most derived allele. This *DRD4* polymorphism has been shown to predict individual differences in impulsivity [22], risk-taking [4], and novelty-seeking [8] and has also been linked to clinical conditions such as Attention Deficit and Hyperactivity Disorder (ADHD; [23,17].

Non-human primates (NHPs) are ideal animal models for research on the genetic basis of normal and pathological behavior as they share with humans a variety of similarities in genetics, neuroanatomy, neurochemical and neuroendocrine function, and cognition and behavior (reviewed in Phillips et al [20]. Tandem repeats in the third exon of *DRD4* have already been identified in some NHPs such as vervet monkeys, macaques, and chimpanzees [13,12]. Studies reporting the frequency of occurrence of different *DRD4* alleles, however, have typically been conducted with relatively small captive populations. For example, *DRD4* alleles in rhesus macaques (*Macaca mulatta*) have only been investigated in one captive population housed at the National Institutes of Health Animal Center (NIHAC, [6]). Furthermore, little or no information exists about the potential association between the *DRD4* polymorphism and behavior in rhesus macaques. In fact, the only published studies so far have involved captive vervet monkeys (*Chlorocebus aethiops*). These studies have reported that carriers of low-function *DRD4* alleles are more prone towards novelty-seeking [3] and impulsivity [9].

In this study, we investigated for the first time the *DRD4* polymorphism and its relationship with behavior in the free-ranging rhesus macaque population on the island of Cayo Santiago, PR. This population has been one of most valuable resources for primate behavioral and biomedical research over the past 50 years. Our aims were three-fold. First, we sought to verify that the rhesus macaques in this population display a VTNR polymorphism in exon III of the *DRD4* gene. Second, we investigated the extent to which the different *DRD4* alleles and their distribution in the Cayo Santiago rhesus macaque population are similar or different to those reported for captive rhesus macaques, as well as other nonhuman primates. Finally, we assessed whether the *DRD4* polymorphism in the Cayo Santiago rhesus macaque population shows an association with behaviors related to exploration and risky social responses to other individuals similar to those reported in captive vervet monkeys and in humans.

2. Methods

2.1. Study site and subjects

This study was conducted on Cayo Santiago, a 15.2 ha island located 1 km off the coast of Puerto Rico. A colony of rhesus macaques was established in 1938 with wild individuals captured in India [21]. At the time of the study, the population on Cayo Santiago included approximately 1200 animals split between 9 naturally formed social groups. The subjects of the behavioral study were 46 juveniles ($n = 24$ males) born between August–September 2011 from two of the nine social groups. The behavioral data presented here were collected from June to November 2013, when subjects were aged between 21.32 ± 0.08 and 26.89 ± 0.08 months. In addition to the 46 focal subjects, we were able to collect samples for genotyping from 132 individuals, including the mothers of the focal subjects, for a total of 178 individuals genotyped for the *DRD4* polymorphism.

2.2. Data collection

Behavioral data were collected five days a week from 0700 to 1430 h. Each subject was focally observed for 30 min once a week. Observations were counterbalanced biweekly between morning (0700–1030) and afternoon (1030–1430) observations to control for diurnal effects on behavior. A total of 497.5 h of data were collected on the 46 juvenile subjects across the 24 weeks of observations (on average, 21.6 weekly observations per subject). The following state behaviors were collected on a continuous basis: rest, feed/forage, travel, groom, play, and self-groom. The amount of time the subject was in proximity to the mother (within 3 m) or out of proximity from the mother (more than 3 m) was also recorded continuously. Finally, all agonistic behaviors directed at the subject as well as submissive behaviors initiated by the subject were recorded. Agonistic behaviors included: contact aggression (e.g., bite, slap), non-contact aggression (e.g., chase, lunge), and open-mouth threat. Submissive behaviors included submit-leave (i.e., individual gives submissive posture and moves away from another), submit-stay (i.e., individual gives submissive posture but does not move away from another), and fear-grin [16]. All data were recorded using the Behaviour software on a Psion Workabout. Data were parsed into an Access database (Microsoft Corp., Redmond, WA, USA) and queries were used to obtain frequencies and durations of behaviors.

2.3. Behavioral measures

The three juvenile behaviors studied were chosen due to their relevance to impulsivity or risk-taking. The first, time spent in proximity to the mother, is an indicator of willingness to engage in social and physical exploration. In most NHPs, including rhesus macaques, the mother is essentially the sole provider of resources and protection for the offspring [15]. Therefore, if an individual spends time away from the mother it is able to forge its own social network and explore its environment, but at the risk of being caught in an agonistic interaction without protection. The second variable, avoidant behavior, indicates an individual's risky or bold tendencies to "stand its ground" when approached by an older or more dominant individual. Avoidant behavior is easily and reliably identified and measured in macaques and often correlated with other fearful and submissive behaviors such as the fear grin or bared-teeth display [14,16]. Individual differences in avoidant behavior are relatively stable over time, as they are associated with differences in dominance rank and/or personality [16]. The use of avoidant behavior in our study is similar to the use of "flight initiation distance" (FID) in bird research on boldness. FID is the distance a bird allows a potential predator to approach before it flies away, with shorter distances indicating more risk-prone or bolder birds (e.g., Moller and Garamszegi [18]. Finally, we used a measure of behavioral restlessness, which was operationally defined as the rate at which individuals changed their behavioral state, e.g., from resting to traveling to resting to traveling again. This measure of behavioral restlessness has been used in one of our previous studies of rhesus macaques [11]. In this study, we showed that behavioral restlessness can be reliably measured, that individual differences in restlessness are stable over time, and that they are associated with physiological measures of energetic expenditure. We chose to use a measure of behavioral restlessness over simpler measures of activity levels such as frequency or% of time spent walking or running because our measure has direct parallels with measures of restlessness in human research and because, in humans, restlessness (e.g., fidgeting, being "on the go") is an established diagnostic criterion for ADHD (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition [2]).

Table 1
Allelic frequency of the *DRD4* gene.

Genotype	Population frequency	Male frequency	Female frequency	Adult frequency	Juvenile frequency
5R	0.785	0.791	0.765	0.765	0.778
5.5R	0.011	0.000	0.013	0.005	0.013
6R	0.040	0.036	0.047	0.056	0.025
6.5R	0.003	0.000	0.004	0.005	0.000
7R	0.161	0.155	0.162	0.148	0.184

The distribution of allele frequency in the population and its breakdown between males and females, and adults and juveniles.

Table 2
Allelic frequency of DRD4 among subjects in behavioral observations.

Rank	5R	5.5R	6R	6.5R	7R
Males					
High	0.30	0.00	0.00	0.00	0.04
Middle	0.26	0.00	0.00	0.00	0.09
Low	0.28	0.00	0.00	0.00	0.02
Females					
High	0.14	0.00	0.02	0.00	0.07
Middle	0.30	0.00	0.02	0.00	0.05
Low	0.34	0.00	0.00	0.00	0.07

The distribution of allele frequency among the subjects in the behavioral study. Frequencies are shown only for each sex.

2.4. Genotyping for the 48 bp DRD4 VNTR

Genomic DNA was extracted from whole blood, and *DRD4* genotypes were determined by amplifying a ~300 bp region on chromosome 14 with forward primer of 5′-GTGGTCTACTCGTCCGTGTG and a reverse primer of 3′-CGTACTCCTCCCCTCCTCTC. Applied Biosystem's Amplitaq Gold Fast PCR premix was used with an annealing temperature of 64 °C for 35 cycles: 95 °C, 10 min; 35x(96 °C, 3 s; 64 °C, 3 s; 68 °C, 10 s); 72 °C, 10 sec; 4 °C, hold. Amplicons were separated by electrophoresis on 4–20% TBE gels at 210 V for one hour, and the alleles (5R, 5.5R, 6R, 6.5R, and 7R) were identified by direct visualization following ethidium-bromide staining.

2.5. Data analysis

Two of the three outcome variables were calculated via the combination of several behaviors. The avoidant score is a measure of unprovoked submissions and was calculated by adding together the number of "submit-stay" and "submit-leave" behaviors and subtracting the number of threats, aggressions, and non-contact aggressions directed at the individual. So, for example, if in a focal observation an individual engaged in 8 submit stays and 3 submit leaves, but had 4 threats and 1 non-contact aggression directed at it, its avoidant score would be 6. Finally, the behavioral restlessness score was obtained by computing the number of state behavior changes an individual made per hour. Therefore the behavioral restlessness score was the number of times per hour an individual changed between any of the following activities: rest, feed/forage, travel, groom, play, and self-groom.

Generalized Linear Mixed-effects Models (GLMMs) were used to test for differences in behavior between individuals of different genotypes. Every GLMM used each observation as an individual data point ($n = 995$ observations). For each behavior of interest (i.e., proximity to mother, avoidant score, and behavioral restlessness), the fixed effects were: sex (male or female), juvenile *DRD4* (short 5R-6.5R or long 7R forms), maternal *DRD4* (short 5R-6.5R or long 7R forms), and the interaction of juvenile and maternal *DRD4*. The interaction effect between juvenile and maternal *DRD4* was included as a fixed effect due to previous research in NHPs that has shown this effect to be significant [9]. Animal ID was included in each model as a random factor to account for repeated observations on individuals in order to avoid pseudoreplication; Group ID and Maternal Rank were also included as statistical covariates. In total we ran three models. Model 1 investigated the effects of the fixed factors on time spent in proximity to the mother. Model 2 investigated the effects of the fixed factors on avoidant score. Finally, Model 3 investigated the effects of the fixed factors on behavioral restlessness. In addition to the GLMMs, simultaneous Pearson's correlations were run between all three outcome variables. All statistical analyses were performed in SPSS v.19.0 with the two-tailed alpha level set at $p < 0.05$.

Table 3
Results of GLMM.

Fixed Effects	Numerator df	Denominator df	*F* value	*p* value
Model 1 proximity to mother				
Subject DRD4	1	35.601	4.194	0.048
Subject sex	1	36.549	13.525	0.001
Maternal DRD4	1	35.551	0.885	0.353
Subject × maternal DRD4	1	36.624	1.194	0.262
Model 2 avoidance				
Subject DRD4	1	38.738	5.477	0.025
Subject sex	1	38.857	1.455	0.235
Maternal DRD4	1	38.382	0.85	0.362
Subject × maternal DRD4	1	39.283	4.917	0.032
Model 3 restlessness				
Subject DRD4	1	38.504	6.175	0.017
Subject sex	1	38.999	3.256	0.079
Maternal DRD4	1	38.187	0.648	0.426
Subject × maternal DRD4	1	39.017	1.864	0.18

Full results of the Generalized Linear Mixed Models.

3. Results

3.1. Genotype

In our subject population ($N = 178$), the most common *DRD4* allele was the 5R allele (78.5%), followed by the 7R allele (16.1%). The 5.5R, 6R, and 6.5R alleles occurred with frequencies of 1.1%, 4.0%, and 0.3 %, respectively. There were no differences in the distribution of different alleles between males and females, between adults and juveniles, or in relation to dominance rank (see Tables 1 and 2). For the purposes of data analyses, we clustered genotypes into two groups, a short-allele group (5R, 5.5R, 6R, and 6.5R) and a long-allele group (7R).

3.2. Genotype-behavior associations

Results of data analyses concerning genotype-behavior associations are presented in Tables 3 and 4. Model 1 revealed a significant effect of *DRD4* genotype on time spent in proximity to the mother ($F_{1,35.60} = 4.19$, $p = 0.048$). As predicted, individuals with the long allele spent a smaller proportion of their time in proximity to the mother compared to short-allele individuals (Fig. 1). There was also a significant effect of sex on time spent in proximity ($F_{1,36.55} = 13.53$, $p = 0.001$), with males spending less time in proximity to their mothers ($M = 0.30$, SEM = 0.03) than females ($M = 0.49$, SEM = 0.03). Maternal *DRD4* and the interaction of juvenile and maternal *DRD4*

Table 4
Covariates of GLMM.

Covariance Parameters	Estimate	Std. Error
Model 1 proximity to mother		
Maternal rank	0.0017	0.0036
Group ID	0.002	0.004
Model 2 avoidance		
Maternal rank	0.361	0.566
Group ID	0.315	0.517
Model 3 restlessness		
Maternal rank	4.214	11.066
Group ID	64.798	98.287

Covariate results for the Generalized Linear Mixed Models.

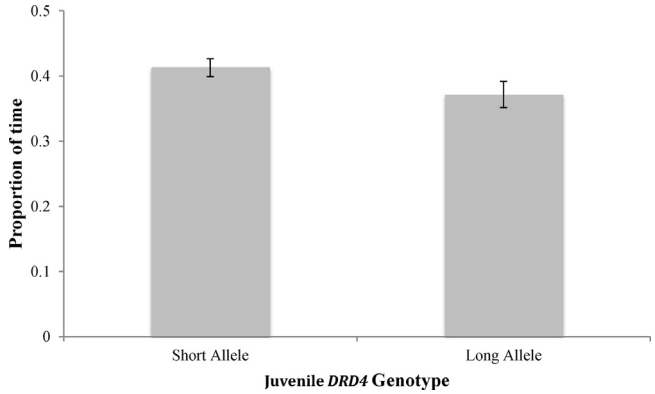

Fig. 1. Mean hourly proportion of time (+/−SEM) that a juvenile spent within 3-m proximity of the mother in relation to the juvenile's DRD4 genotype. Short-allele = 5R–6.5R; long-allele = 7R.

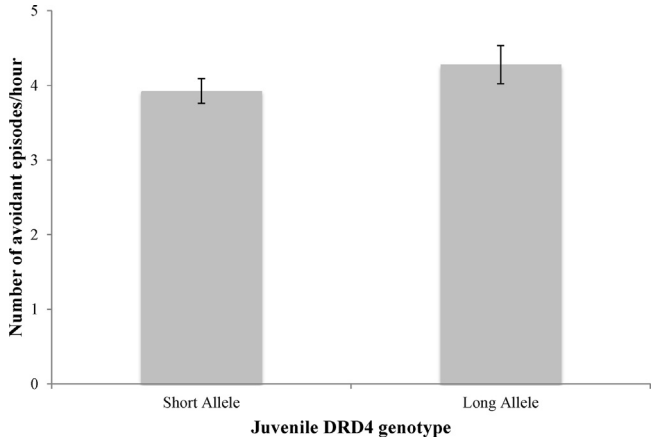

Fig. 2. Average hourly rate of unprovoked avoidance (+/−SEM) by a juvenile in relation to its DRD4 genotype. Short-allele = 5R–6.5R; long-allele = 7R.

had no significant effect on times spent in proximity to the mother (all $ps > 0.05$).

Model 2 revealed a significant effect of longer *DRD4* alleles on avoidant behavior ($F_{1,38.74} = 5.48$, $p = 0.025$). The relationship between genotype and avoidant behavior was, however, opposite of the predicted direction; individuals with the longer allele had higher avoidant scores than their shorter allele counterparts (Fig. 2). There was also an interaction between juvenile and maternal DRD4 genotype ($F_{1,39.28} = 4.92$, $p = 0.032$). An individual's hourly rate of avoidances was lower in offspring raised by mothers of the opposite genotype (5R mother/7R offspring $M = 3.65$, SEM = 0.40; 7R mother/5R offspring $M = 2.62$, SEM = 0.29) than those raised by mothers with the same genotype (5R mother/5R offspring $M = 4.18$, SEM = 0.19, 7R mother/7R offspring $M = 4.65$, SEM = 0.33). Sex and maternal *DRD4* had no effect on avoidant behavior (all $ps > 0.05$).

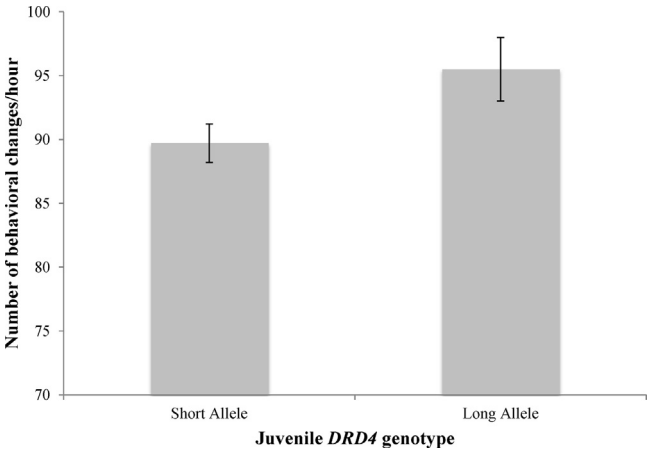

Fig. 3. Average hourly rate (+/−SEM) of behavioral changes (behavioral restlessness) by a juvenile in relation to its DRD4 genotype. Short-allele = 5R–6.5R; long-allele = 7R.

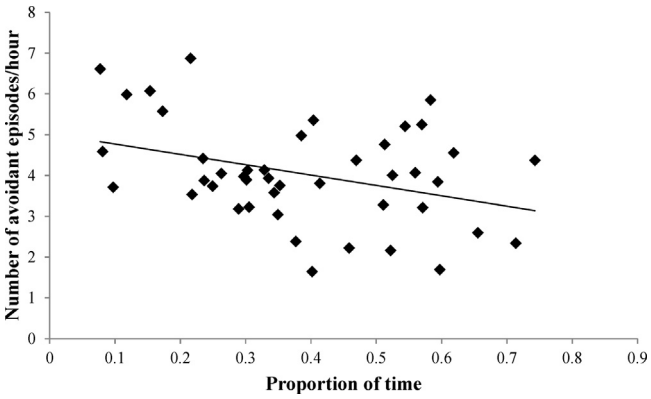

Fig. 4. Correlation between avoidance and time spent within 3-m proximity of the mother.

Finally, Model 3 revealed a positive relationship between having a longer *DRD4* allele and behavioral restlessness ($F_{1,38.50} = 6.175$, $p = 0.017$). Individuals with the longer allele exhibited greater behavioral restlessness than individuals with the shorter alleles (Fig. 3). Sex, maternal *DRD4*, and the interaction of juvenile and maternal *DRD4* had no effect on restlessness (all $ps > 0.05$).

3.3. Correlations between behaviors

There was a significant negative correlation between avoidant behavior and proximity to the mother ($r = -0.314$; $p = 0.034$), such that the less time an individual spent in proximity with its mother, the more avoidant it was (Fig. 4). There was also a significant positive correlation ($r = 0.453$, $p = 0.002$) between behavioral restlessness and avoidant behavior (Fig. 5), such that the more avoidant an individual the higher its behavioral restlessness score. Finally, the correlation between behavioral restlessness and proximity to the mother was not significant ($r = -0.191$; $p = 0.204$).

4. Discussion

One main goal of this study was to document the occurrence of *DRD4* allelic variation in the Cayo Santiago rhesus macaque population and compare the allelic frequencies in this population to those reported in humans, in other species of nonhuman primates (e.g., in

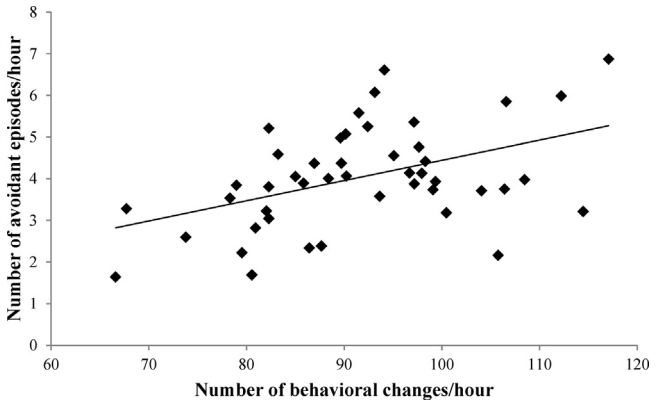

Fig. 5. Correlation between behavioral restlessness and avoidance.

vervet monkeys), and in the only other rhesus macaque population in which the *DRD4* polymorphism was previously investigated. In humans, the frequency of the 7R allele varies greatly among different populations, being high in America and low in Asia [24]. Vervet monkeys have only two *DRD4* alleles, and a 7R allele has not been reported in this species [9,3]. The frequency of the 7R allele in the Cayo Santiago rhesus macaques is 16.1%. This is approximately twice the frequency previously observed in a captive population of rhesus macaques housed at the NIH Animal Center [6]. There are a number of possible explanations for this difference. First, many breeding colonies of rhesus macaques have both Chinese- and Indian-derived individuals. Since the population on Cayo Santiago is Indian-derived only, if Chinese-derived macaques lacked 7R allele the frequency of this allele would be higher on Cayo than in Indian/Chinese mixed populations. However, in the NIHAC population, Chinese-derived rhesus macaques carry the 7R allele, so this is not a likely explanation. Other possible explanations involve differences in breeding dynamics. Since the Cayo Santiago colony is a closed one, there is potential for genetic drift to have occurred. In the captive rhesus population housed the NIHAC, breeding groups are small (they include 8–12 females and 2 males) and the adult males are selected to become breeders by colony managers. On Cayo Santiago, instead, males transfer to new social groups in order to gain access to females, and their social status plays a major role in their ability to mate. Therefore, a genetic variant that influenced either the timing of emigration or the ability to achieve high status in a new group could be under selection in the Cayo Santiago population [6], for preliminary evidence that the 7R allele is linked to aggression). In fact, studies in humans demonstrate similar degrees of variation in frequency of the more derived and loss of function 7R allele across populations, and the extended range of linkage disequilibrium and increased frequency of this allele have led some to hypothesize that this allele has been subject to recent positive selection [24].

In the present study, we did not investigate the possible association between *DRD4* allelic variation and mating-related behavioral traits such as timing of male emigration, aggressiveness or dominance rank in adult rhesus macaques. We did provide evidence, however, that the *DRD4* polymorphism is associated with significant differences in aspects of rhesus juveniles' behavior that may reflect exploration of the environment and risk-taking in social interactions. Juveniles with the longer *DRD4* allele spent significantly less time in proximity to their mother, were more avoidant of other individuals, and were more behaviorally restless than their short-allele peers. One behavioral difference between individuals with longer and shorter *DRD4* alleles was unexpected. Juveniles with the long allele were predicted to be bolder and less avoidant of other individuals than short-allele juveniles, but we found the opposite. This result can be interpreted in light of the negative correlation between time spent in proximity to the mother and avoidance behavior: individuals who spent less time in proximity to their mother were more avoidant of others. This correlation suggests that the juveniles who explore the environment more without their mother's protection do so cautiously, by avoiding other individuals at a high rate. This tendency comes about perhaps because they have learned that by being actively avoidant they can reduce the probability of receiving aggression. More avoidant individuals were also more restless, regardless of the time spent in proximity to the mother. A possible interpretation of these results is that while the tendencies to be away from the mother and to explore the environment as well as to be restless are strongly influenced by genotype, avoidance of other individuals is a learned response that results from receiving aggression from those individuals.

Unlike a previous study on *DRD4* in vervet monkeys [9], in our study maternal *DRD4* genotype had, with one exception, little influence on juvenile behavior. The only significant effect of maternal genotype was an interaction affecting juveniles' avoidant behavior: individuals raised by mothers of the opposite genotype (e.g., 5R mother/7R offspring or 7R mother/5R offspring) were less avoidant than those raised by mothers with the same genotype (e.g., 5R mother/5R offspring or 7R mother/7R offspring). This finding may be due to the fact that a mother's alleles may affect some aspects of her parenting behavior and that this, in turn, influences the development of their offspring's behavior, perhaps because the offspring's alleles may affect how they respond to a specific parenting style [19]. Clearly, variation in juvenile behavior has both genetic and environmental components and the relative role of maternal genotype and offspring genotype needs to be further investigated in future research. One of the main limitations of our study is the relatively small sample size, especially with regard to the number of individuals with the 7R allele. Thus, future studies will have to include larger sample sizes.

5. Conclusions

Our reported association between *DRD4* genotype and time spent away from the mother and behavioral restlessness can potentially impact survival and reproduction. In immature monkeys, time spent away from the mother can be related to vulnerability to predation or aggression from conspecifics but also to the development of foraging skills (e.g. Altmann [1]. A previous study of adult male rhesus macaques has shown that more restless individuals tend to have lower BMIs and lower available energy stores, which in turn relates to their mating strategies and their mating success [11]. Therefore, some forms of *DRD4* allelic variation may be under positive selection pressure because they make positive contributions to survival or reproductive success. It is also possible that other *DRD4* alleles are associated with maladaptive behavior, which hinders survival or reproduction. Future research on *DRD4* variation in rhesus macaques and other nonhuman primates can help us understand the functional significance of this variation in all primates, including the possible evolutionary origins of human pathologies such as ADHD.

Acknowledgements

We would like to thank Christine Fleener, Aneila Hogan, and Michelle Evans for help in the field, John Addicott and James Higham for creating the Access database and queries, and the Caribbean Primate Research Center staff for logistical assistance. We are also grateful to Alex Georgiev and Tara Mandalaywala for thoughtful discussion of analyses. This research was supported by

NIH grant R01-HD067175 to D. Maestripieri and K. J. Parker, the Hinds Fund of the University of Chicago to S.P. Coyne, and grant P40-OD012217-25 from the National Center for Research Resources (NCRR) and the Office of Research Infrastructure Programs of the NIH to the Caribbean Primate Research Center of the University of Puerto Rico. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of NCRR or NIH.

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