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Genetic influences on response to novel objects and dimensions of personality in Papio baboons

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INTRODUCTION

Researchers in the field of animal behavior have recently placed increasing focus and attention on differences in behavior expressed among individuals within a species. While traditional studies of animal behavior generally sought to characterize typical or modal patterns of behavior within a given species, investigators are now providing detailed empirical descriptions and extensive theoretical analysis of individual variation (Reale et al. 2007; Smith and Blumstein 2008), its potential proximate causes (Rogers et al. 2013; Hopkins et al. 2014; Reale et al. 2010; Barr et al. 2003) and its long-term ecological and evolutionary consequences (Wolf and Weissing 2012; Tung et al. 2012). The concept of personality (sometimes referred to as temperament) provides an important organizing framework for the study of behavioral differences among individuals within a given animal species, as well as differences among species. Personality is often defined as a pattern or consistency of behavior expressed by a specific individual across various situations and contexts (Gosling 2001; Briffa and Weiss 2010). The central finding of this line of research is that these patterns often show stable differences among individuals, and therefore any given animal can be described as displaying one or more consistent personality traits, such as aggressiveness, anxiousness, agreeableness and others (Briffa and Weiss 2010; Morton et al. 2013; Fox et al. 2008; Kinnally et al. 2008; Capitanio 2004).

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Given their cognitive and social complexity, developmental plasticity, and phylogenetic proximity to humans, nonhuman primates are interesting and productive subjects in the study of personality (Rogers et al. 2013; Weiss et al. 2011; Capitanio et al. 1999). Much of the work on personality in nonhuman primates has used observer ratings in which experienced observers having extensive familiarity with a particular set of animals assess their personalities using standardized questionnaires (Morton et al. 2013; Capitanio et al. 1999; Freeman et al. 2013; Hopper et al. 2014; Weiss et al. 2009). The alternative approach, also used in studies of primates and other vertebrate species, is based on structured observation and quantification of expressed behaviors recorded during specific observation periods, either in natural circumstances (Seyfarth et al. 2012; Silk et al. 2009) or during standardized behavioral testing of captive animals (Kalin and Shelton 2003; Fairbanks et al. 2004; Oler et al. 2010). Differences in temperament or personality among animals can have significant correlations with a number of important life-history outcomes, such as predation risk, access to preferred foods, reproductive success or dispersal (Wolf and Weissing 2012; Silk et al. 2009). This means that personality can have meaningful influences on fitness and thus broader evolutionary processes (Smith and Blumstein 2008; Wolf and Weissing 2012).

Personality is of course also a central and fundamental concept in human psychology, and differences in human personality have been studied extensively for many years. Among humans, personality is correlated with the likelihood of developing specific psychiatric disorders such as anxiety disorders (Brandes and Bienvenu 2006; Clark et al. 1994), major depression (Kendler et al. 1993; Hirschfeld et al. 1989) or alcoholism (Cloninger et al. 1988; Wills et al. 1994), as well as with risk for other medical problems (Denollet et al. 1996; Cole et al. 2003). Due to their close genetic, physiological and neurobiological similarities with humans, nonhuman primates are valuable biomedical models for the study of the relationships among personality, underlying neurobiological or genetic causes, and downstream consequences for health (Rogers et al. 2013; Barr et al. 2003; Capitanio et al. 1999; Fawcett et al. 2014; Birn et al. 2014; Roseboom et al. 2013). Thus, two lines of research (ethologically-oriented studies of behavioral variation within animal species and biomedically-focused investigation of behavioral variation and its health-related correlates in model organisms) are providing increasing information about personality within and among nonhuman primate species.

Baboons (genus *Papio*) are one of the most intensively studied nonhuman primate groups. The genus *Papio* is now generally considered to consist of six closely related parapatric species that differ in pelage and other morphological traits, but which often form natural hybrid zones where they come into contact in the wild (Keller et al. 2010; Jolly et al. 2011; Jolly 2001). The behavior of these six species differs in several ways, including aspects of diet and ranging that likely reflect adaptation to local environments. However, baboon species also differ in several aspects of social behavior, resulting in important divergences in social organization and social structure (Henzi and Barrett 2003; Jolly 1993) which generate fascinating complexity within hybrid zones (Jolly 2001; Bergman et al. 2008). Furthermore, researchers find significant differences in social relationships, social interactions and other aspects of behavior among individuals within taxonomically homogeneous (non-hybrid)

baboon populations (Seyfarth et al. 2012; Silk et al. 2010; Gesquiere et al. 2011; Moscovice et al. 2009; Smuts 1985).

One aspect of primate behavior that can be readily quantified and may impact an individual's ability to cope with complex ecological and social challenges is response to novelty, often described as varying from "shy" to "bold." This "shy-bold" continuum has been investigated in many vertebrate species, but may be particularly important for a geographically widespread and omnivorous group such as the baboons, which live successfully in a variety of ecological habitats. "Boldness" and related measures of one type or another has been studied in several other nonhuman primates (Morton et al. 2013; Kinnally et al. 2008; Hopper et al. 2014; Weiss et al. 2009; Fairbanks et al. 2004; Fawcett et al. 2014; Weiss et al. 2006; Weiss et al. 2013; Fairbanks et al. 1999). Previous studies have described individual differences among wild chacma baboons in reaction to novel food items (Carter et al. 2012). Thus baboons, like other nonhuman primates, exhibit personality differences related to boldness and response to novelty.

One fundamental question in animal personality research is the nature of the proximate mechanisms that generate the observed individual variation. Genetic differences among individuals likely account for some proportion of the observed variation within many species. In chimpanzees (Hopkins et al. 2014), rhesus macaques (Oler et al. 2010; Rogers et al. 2008; Fawcett et al. 2014) and vervet monkeys (Fairbanks et al. 2004), additive genetic variation influences response to novelty, anxiety or other cognitive/behavioral traits. Specific genes have been associated with aspects of nonhuman primate personality and particular behaviors in rhesus macaques (Rogers et al. 2013; Barr et al. 2004; Chen et al. 2010; Trefilov et al. 2000) and chimpanzees (Hong et al. 2011; Hopkins et al. 2012). Thus, genetic variation accounts for a proportion of the variation in personality in several primate species. Despite decades of extensive behavioral study, little is known about the genetic basis of behavioral variation among *Papio* baboons. The goals of this study are: a) to explore individual variation in personality, as indexed by response to novel objects and a mirror, among a large pedigreed population of baboons, b) to investigate quantitative genetic differences among individuals as a potential proximate cause of that variation, and c) to attempt to identify specific genes that influence individual behavioral differences.

METHODS

Study Subjects

The study subjects were 578 olive baboons (*P. anubis*), yellow baboons (*P. cynocephalus*) and their offspring maintained at the Southwest National Primate Research Center, San Antonio, Texas. Some of the founding members of the colony were likely trapped in or near a hybrid zone between yellow and olive baboons, so this population consists of olive baboons, yellow baboons and individuals with varying degrees of admixture. Taxonomy is somewhat controversial in *Papio* baboons, but most experts now divide *Papio* baboons into six species (Jolly et al. 2011; Zinner et al. 2013). Regardless of classification scheme, natural populations of olive and yellow baboons hybridize in the wild (Alberts and Altmann 2001; Charpentier et al. 2012), as well as in the captive population at the Southwest National Primate Research Center, producing healthy fertile offspring. All subjects were adult at the

time of testing (mean age of 15.8 years, range 8.0 to 29.8 yrs). At the time of testing, all subjects were living in social groups of 15–40 individuals, in large outdoor cages (27–47 m^2) with heated indoor shelters. All study procedures were approved by the Institutional Animal Care and Use Committee of the Texas Biomedical Research Institute, an AAALAC, Int. accredited institution.

The 578 subjects for which phenotypes were measured can be connected into a single four generation pedigree. This pedigree must also include 87 additional baboons that were not phenotyped but are needed to link the phenotyped animals into a suitable unbroken pedigree configuration. The frequency of pairwise kinship coefficients between the 578 subjects that did undergo phenotyping is presented in Supplemental Table 1. Importantly, a small number of relationship pairs reveal minor levels of inbreeding within the population. These relationship pairs are the result of directed breeding plans designed to facilitate specific unrelated genetic studies. As can be seen in Supplemental Table 1, the overall the population shows little inbreeding.

Assessment of Response to Novelty

To assess response to novelty, sets of eight animals were removed from their home social groups, placed in individual cages (0.75 m^2) in an indoor facility, and a small metal tray was attached to the outside of each cage to habituate the subject to its presence. The next morning two inanimate, novel objects (first a plastic truck and then a plastic bear, Figure S1) were placed separately on the tray for 5 minutes each. After these trials a 0.09 m^2 mirror was placed on the tray facing the animal for two minutes. Only a single observer (investigator) was present during testing, and while there were generally other baboons housed in the same room, none of the other subjects could see the baboon being tested or the toys being used.

Each baboon's behavioral responses to each novel object were recorded using an ethogram. Measures of frequency and duration of 73 individual behaviors related to locomotion, aggression, submission, object interaction, and other relevant variables were scored. Additionally, location information within the cage and the timing of each event were recorded. The ethogram used was based on responses to novel objects observed during a preliminary study employing a separate set of baboons. A laptop computer and Observer™ software were used to record data. Table 1 presents the specific behaviors scored, and the categories used to group them into classes. Several observers were involved in the study, with all achieving at least 85% inter-observer reliability with L.B. prior to performing testing. Analyses presented here are based on data from each of the 578 subjects. Forty-three subjects underwent testing for two of the novel objects (truck and bear) on two occasions, with an average of 2.76 (SD = 0.58) years between tests.

Behavioral Data Summarization

All files were summarized in the Observer™ program (Noldus, Leesburg, VA) as the frequency and duration of each behavior for each subject on each trial (object). Individual behaviors were grouped into exclusive categories for analysis (see Table 1), and more common individual behaviors (e.g., slap cage, vigilance, watch observer, yawn) were also analyzed separately. All variables are listed as frequency or duration per 5-minute or 2-

minute observation. The Systat® statistical program was used for initial evaluation of results. Upon initial inspection of the univariate plots of the data for each trial and each behavior category, significant skewness and nonhomogeneity of variances were apparent in most distributions. A square root transformation was thus applied to all data prior to analysis to reduce skewness.

Measurement of monoamine metabolites

The second morning after novel object testing the animals were sedated with RAAK (rompum, acepromazine, atropine, and ketamine) and a spinal tap into the cisterna magna was performed to obtain a sample of cerebrospinal fluid (CSF) from each study baboon. The CSF sample was collected within 30 minutes of animal sedation and immediately placed on wet ice. The samples were centrifuged to pellet contaminates and placed at -80◦C within 90 minutes of collection. Homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels were measured in each CSF sample by High Performance Liquid Chromatography (HPLC). A measured aliquot of each sample was mixed with an equal volume of cold mobile phase. The mixture was then filtered at centrifugation and part of the filtrate transferred to a 300-FL microinjection insert. This material was then analyzed using HPLC with electrical detection, allowing simultaneous measurement of HVA, 5-HIAA, and MHPG.

Heritability Analysis

Quantitative genetic theory establishes that within a pedigree, total phenotypic variance of a trait (σ^2_p) can be decomposed into an additive genetic component (σ^2_g), an environmental component (σ^2_e), and any number of covariates (σ^2_c) so that $\sigma^2_p = \sigma^2_g + \sigma^2_e + \sigma^2_c$ (Falconer 1981). Using variance components methods implemented in SOLAR (Almasy and Blangero 1998; Blangero et al. 2001), we investigated the statistical significance of additive genetic variation as well as specific co-variates (age, sex and their interaction) as contributing factors to phenotypic variance in behavioral traits.

Genetic Correlations and Factor Analysis

To identify multivariate factors or dimensions of personality, the heritability of each individual behavior was quantified as described above. The estimated heritability of a behavior is the proportion of phenotypic variance explained by additive genetic variation, while the genetic correlation between two behaviors is the proportion of that genetic variance that is shared between the two. Any behavior phenotype without a significant heritability in our initial analysis was discarded from the subsequent factor analysis. Pair-wise phenotypic correlations were calculated for all remaining behaviors with significant estimates of heritability. All highly correlated behaviors and behavior scores that did not have continuous distribution were also discarded. Pair-wise genetic correlations were estimated among the remaining behaviors using SOLAR to measure genetic variance shared by any two behaviors. This analysis of genetic correlations identified 31 behaviors that served as our genetic correlation matrix. Factor analysis using Statistica version 6.1 was performed using both varimax and promax oblique rotation in an attempt to simplify data structure.

Follow-up observations in home cages

After the assessment of response to novelty among the study baboons, we designed a follow-up analysis to test the validity and relevance of our novel object testing for broader aspects of baboon behavior. One of us (J.R.) selected ten individuals that scored high on levels of aggression in response to the truck stimulus, and ten baboons that scored low on this trait. The list of 20 animal IDs was randomized and provided to S.R., who was therefore blinded to the scores of these animals on the previous novel object testing. S.R. conducted 10 hours of observations on each of these 20 animals in their home social groups, 20 observations of 30 minutes each. During these sessions, S.R. recorded both social and non-social behavior, using a standardized ethogram and the Observer program.

QTL scans

To perform whole genome scans for Quantitative Trait Loci (QTL), the following model was used:

$$\boldsymbol{\Omega}=\sum_{i=1}^{n}\boldsymbol{\Pi}_{\mathbf{i}}\boldsymbol{\sigma}_{qi}^{2}+\mathbf{2}\boldsymbol{\Phi}\boldsymbol{\sigma}_{a}^{2}+\boldsymbol{I}\boldsymbol{\sigma}_{e}^{2}$$

where Π_i is a matrix of Identity by Descent (IBD) allele sharing among family members at marker *i*, σ_{qi}^2 is the additive genetic variance at marker *I*, Φ is a matrix of kinship values, σ_a^2 is the residual additive genetic variance, σ_e^2 is the individual-specific environmental variance, and *I* is an identity matrix. A maximum likelihood analysis was used in which σ_{qi}^2 was estimated and the likelihood of that model compared to a model in which σ_{qi}^2 is constrained to zero, thus testing the null hypothesis that σ_{qi}^2 is not significantly greater than zero. The $\log_{10}$ difference between the two models is a LOD score. This analysis was performed using the software suite SOLAR (Almasy and Blangero 1998). Traditionally in human genetics a LOD score of 3.0 is considered strong evidence of linkage and accounts for issues of multiple testing across the genome. However within this baboon pedigree structure, and due to the density and location of markers in this microsatellite linkage map, a LOD score of 2.73 is genome-wide significant and adequately accounts for multiple testing, while a LOD of 1.5 is suggestive evidence of a QTL in this baboon population (Feingold et al. 1993).

Microsatellite design

Following initial QTL scans using the baboon linkage map (Rogers et al. 2000), we conducted additional analyses to refine positive QTL mapping results. New baboon microsatellites were identified through two processes. Baboon and human chromosomes were aligned using the original baboon linkage map, and both the deCODE (Kong et al. 2002) and Marshfield (Broman et al. 1998) human linkage maps were searched for human microsatellite markers predicted to fall in baboon chromosome regions of interest. Each identified microsatellite was tested for amplification and polymorphism in a set of eight male baboons. Microsatellites with four or more alleles and that were heterozygous in at least half of these eight individuals were then genotyped in the full animal set. The second

method employed was to search the rhesus macaque whole genome DNA sequence (Gibbs et al. 2007) to identify microsatellites in that species. The rhesus–baboon relationship in much closer than the human-baboon, so any microsatellites identified in rhesus have a higher probability of being present and polymorphic in baboons than microsatellites identified in humans (Raveendran et al. 2006). Primer pairs were designed using Primer3 software (http://frodo.wi.mit.edu/) to flank these repeats and then tested and genotyped in all study baboons.

Microsatellite genotyping

Genotyping was performed using panels of four to eight microsatellites. Amplification reactions were performed on ABI 9700 thermal cyclers, and PCR product sizes analyzed using an ABI 3730 Genetic Analyzer and Genemapper 4.0 software. The raw genotypes were checked for Mendelian discrepancies with the PEDSYS software package (Dyke 1996). Errors were individually examined, and changes made when appropriate. In cases where discrepancies still existed, allele frequencies and patterns of allele distribution within the pedigree were evaluated using the Preswalk routine within PEDSYS, and the least likely genotypes blanked. The resulting genotype data were then used to generate first pass linkage maps. Recombination distances were determined using MultiMap (Matise et al. 1994) following the method described previously (Rogers et al. 2000; Cox et al. 2006). These data are then checked for double recombinants using Preswalk, and finally mapped again using MultiMap.

Sequencing analysis of candidate gene SNAP25

To discover and investigate variation in the baboon SNAP25 locus, sequencing primers were designed using the whole genome DNA sequence of the rhesus macaque (Gibbs et al. 2007) and Primer3 (http://frodo.wi.mit.edu). A series of study baboons were sequenced across the SNAP25 gene to identify SNPs. PCR was performed using standard amplification reactions on ABI 9700 thermal cyclers, and products sequenced on an ABI 3730. Once identified, each SNP was genotyped in the baboon population using one of three methods: ABI Snplex, Taqman, or Illumina golden gate assays following each respective protocol.

SNP association analysis

To estimate the influence of genetic differences in SNAP25 on phenotypic variance among animals, we performed pedigree-based genetic association analysis. The initial heritability analyses were performed using age, sex and their interaction as covariates with the following model $\sigma^2_p = \sigma^2_{age} + \sigma^2_{sex} + \sigma^2_{age \times sex} + \sigma^2_g + \sigma^2_e$. To measure the effect of any individual SNP on phenotype, we modify this model to $\sigma^2_p = \sigma^2_{age} + \sigma^2_{sex} + \sigma^2_{age \times sex} + \sigma^2_g + \sigma^2_e + \sigma^2_{SNP1}$, where σ^2_{SNP1} is the variance in the phenotype due to the genotype of SNP1. If the variance attributed to SNP1 is statistically significantly different from zero, based on likelihood comparisons as described above, we then conclude that either SNP1, or an unknown polymorphism in linkage disequilibrium with SNP1, is responsible for a portion of the total phenotypic variance of the trait (Rogers et al. 2013; Rogers et al. 1999).

RESULTS

Initial Analysis of Phenotypic Variation

This population of baboons exhibited substantial individual variation in a number of behavioral responses to novelty. Table 1 presents the specific behaviors scored, and the categories used to group them into classes. In response to the toys, study subjects varied in their duration of locomotion, position within the cage relative to the novel object (i.e. front or back), and frequency of specific behaviors such as cage slapping, object contact and aggression. In response to the mirror, the study baboons differed again in levels of aggressive behavior, various locomotor behaviors, location within the cage and arousal reactions. Among 43 randomly chosen subjects tested on two separate occasions using both the truck and bear, we found a high degree of individual consistency in response (Supplemental Table 2). A wide range of individual behaviors, including measures of activity, arousal, object contact and others show significant correlations between exposures over 2 years apart.

Our measures of behavioral response to novelty differ by sex and age of the study subject in several but not all categories. These results are presented in Tables 2 and 3. Females tended to score higher for activity frequency, locomotion duration, submissive frequency and both watch observer frequency and watch observer duration. Females also had a longer latency to touch the novel object than did males. Males spent significantly more time in the front of the cage and had longer durations of self-directed behavior.

Estimates of Heritability

We found that many behaviors expressed in response to the three stimuli exhibit significant individual trait heritabilities (additive genetic heritability). Genetic results are also presented in Tables 2 and 3. The average heritability of individual behaviors in response to the bear was h^2 (mean) = 0.251 for frequency measures and h^2 (mean) = 0.242 for duration measures. For the truck, those two means are $h^2 = 0.227$ and $h^2 = 0.213$ respectively. Average heritability was slightly lower for the mirror test, h^2 (mean) = 0.171 for frequency and h^2 (mean) = 0.184 for duration. Heritability estimates greater than these average values were observed for watch object frequency, locomote frequency and duration, cage slap frequency, vigilance duration and measures of location within the cage (front, back, other) in response to the toys. In response to the mirror, we observed above average heritability for aggression frequency, submission frequency, watch object frequency and duration, and locomote duration.

Factor Analysis

Our subsequent factor analyses identified three orthogonal factors that account for 77.7% of the variation among the 31 individual behaviors included. Factor 1 is composed of 21 individual behaviors (Table 4). These behaviors may reflect generalized arousal and possibly fear- or anxiety-related reactivity. While there are risks in assigning labels to personality factors, because those labels may over-simplify the nature of the behavioral variation, and similar labels assigned to dimensions of personality in different species or research studies can lead to incorrect assumptions about comparability (Carter et al. 2012),

we nevertheless see Factor 1 as reflecting variation similar to what has been called "Boldness" in other studies. Factor 1 (Boldness) accounts for 46.8% of the variation within the population, and has a high heritability ($h^2 = 0.59$, $p = 2.3 \times 10^{-17}$). Factor 2 is composed of 14 behaviors, and those with heaviest loadings are in general related to interaction with the novel object itself (Table 4). Factor 2 (Engagement with Object) accounts for 18.8% of the variation, and has a lower but still substantial heritability ($h^2 = 0.33$, $p = 1 \times 10^{-7}$), which is nevertheless higher than the average values for heritability across the two toys or mirror. The third factor included only a single behavior, accounts for a small proportion of the variance, and therefore was not further analyzed.

Follow-up Validation

Our results indicate that the behavioral reactions of the study baboons to these test stimuli are influenced by age, sex and genetic variation. However, evaluating the significance and implications of these observations for understanding baboon behavior outside the artificial test situation required further analyses. Our follow-up studies showed that the experimental assessments of temperament conducted individually in a novel environment are positively correlated with social behavior exhibited months after the study subjects were returned to their home cages and social groups. Ten baboons that exhibited above average rates of aggression to the truck also displayed higher rates of aggression to their home cage-mates than did the ten animals that scored low on aggression to the truck ($p = 0.008$). In addition, the same highly aggressive animals received more submissive behavior from their cage mates than did the other ten animals ($p = 0.018$). These results extend our findings and suggest that our novel object test exposes individual variation that does have predictive value regarding normal social behavior in an animal's home social environment.

Scan for Quantitative Trait Loci

Whole genome QTL linkage scans for each individual behavior, factor scores and CSF monoamine metabolite levels (HVA, MHPG and 5HIAA) using the available baboon microsatellite linkage map (Rogers et al. 2000; Cox et al. 2006) identified suggestive, but not definitive peak LOD scores on baboon chromosome 10 for temperament factor 2 (TF2, Engagement with Object), CSF level of HVA, CSF levels of 5-HIAA and the behavior labeled "avert." After the identification and genotyping of an additional 11 microsatellite loci in the region, subsequent QTL analyses revealed peak LOD scores of 1.9 for TF2 (Engagement with Object), 1.6 for avert, 1.5 for HVA and 0.8 for 5-HIAA, all within the same area of PHA10. All of these LOD scores are below the genome-wide threshold to establish definitive linkage (LOD = 2.78), but the scores for TF2 (Engagement with Object), HVA and avert are at or above the threshold for suggestive linkage (LOD = 1.5). Locations of peak LOD score can be seen in supplemental table 3.

Candidate Gene SNP analysis

Given the nature of the phenotypes with overlapping QTL results, we hypothesized that differences among animals in monoamine neurotransmitter levels may be partly responsible for differences in observed behavior and derived personality factor scores. Consequently, we evaluated all genes within the QTL interval as potential candidates, and chose SNAP25 as the most likely positional candidate because of its known role in exocytosis and

neurotransmitter function and its suggested role in bipolar depression, neuroticism and attention deficit hyperactivity (Etain et al. 2010; Brophy et al. 2002; Terracciano et al. 2010). Sequencing of founder individuals in the baboon pedigree identified 15 SNPs within the exons, at exon/intron borders, and across the putative promoter region of SNAP25. We genotyped all study animals for the newly discovered SNPs, and tested association between each polymorphism and our phenotypes (TF2, monoamine metabolite levels and avert). Specific polymorphisms are significantly associated with TF2 (Engagement with Object) (p=0.015), avert behavior (p=.024), HVA levels (p=.035), MHPG levels (p=.050). The amount of variation in the respective phenotypes explained by these SNPs is modest: 1.6%, 2.2%, 1.4%, and 0.8% respectively (supplemental table 4).

DISCUSSION

The increasing use of the concept of temperament or personality in animal behavior research is producing several important benefits (Reale et al. 2010; Weiss et al. 2011; Freeman et al. 2013; Nettle and Penke 2010). One of these is the growth of analyses of the proximate causes of individual variation in particular behaviors and broader dimensions of personality. Clearly, researchers have for many years measured and discussed the factors that lead to differences in expressed behavior among individuals within a population or species. But the increasing focus on identifying and probing patterns of correlated behaviors that are stably expressed by specific individuals in various situations, and that differ among conspecifics has encouraged new approaches to behavioral description and new theory (Reale et al. 2010; Briffa and Weiss 2010; Capitanio 2004; Capitanio et al. 1999; Seyfarth et al. 2012).

Our study of baboons was designed to investigate the causes of individual variation in behavioral responses to novel objects and a mirror. The data clearly show that sex is one factor significantly influencing the behavioral responses of these baboons to our test challenge. Females tended to score higher for activity (e.g. more locomotion) and anxiety, fear or withdrawal (indexed by higher frequency of submission and longer latency to touch a novel object). Males exhibited average responses that can be characterized as bolder and less inhibited. This is not unexpected given prior studies. Humans exhibit consistent sex differences in personality (Costa et al. 2001; Del Giudice et al. 2012). Moreover, consistent with field observations, personality ratings of captive chimpanzees score males as more impulsive and more aggressive than females (King et al 2008). Macaque males are scored as more confident and more active than females (Stevenson-Hinde 1978). Like other primates (human and nonhuman), there are consistent behavioral differences among male and female baboons, and this current finding that males and females respond differently to the novel object challenge is concordant with expectations.

The primary focus of our study was the assessment of genetic differences among individuals as a proximate cause for individual variation in behavioral responses and personality. We found significant heritability for multiple behaviors in response to both novel objects and the mirror. In addition, we determined that the estimated heritability for both of the multivariate factor scores we derived was higher than the average heritability of individual behavioral measurements. This is encouraging, suggesting that these factor scores captured the shared information common to multiple individual behaviors. This approach may reduce the

random variation and noise present in scores for individual behaviors in individual animals. Furthermore, we were able to demonstrate that these heritable responses to the experimental procedures were predictive of patterns of social behavior months later in the home social group. These follow-up studies help to establish the broader ecological, ethological and evolutionary relevance of our experimental results.

Recent studies have begun to investigate differences in personality expressed among wild baboons in natural habitats. Silk and colleagues have documented stable individual differences in patterns of social behavior and social interaction among female yellow baboons (Silk et al. 2003) and chacma baboons (Silk et al. 2009; Silk et al. 2010). Seyfarth et al. (2012) examined variation among wild female chacma baboons in the time they spend alone and their rates of affiliative and aggressive interactions. Seyfarth and colleagues identified three dimensions of personality, and found these are predictive of levels of stress and other aspects of behavior (Seyfarth et al. 2012). The social stimulus we used here, a mirror, obviously constitutes a different type of test, and we would not expect the factors we identified to correspond to the factors identified in strictly observational studies of wild baboons. However, our finding of significant heritability for several behaviors expressed by the baboons to the mirror challenge, including rates of affiliative and aggressive behaviors, suggests that the dimensions of personality identified by Seyfarth et al (2012) may also have some degree of heritability. The factors those authors identified were not accounted for by differences in dominance rank or availability of kin, and therefore some additional proximate cause for these stable patterns of behavioral variation is needed.

Individual differences in response to novelty may also have ecological consequences or correlates. Chacma baboons were found to exhibit more interest in and more exploration of a series of novel objects than did phylogenetically close gelada baboons, genus *Theropithecus* (Bergman and Kitchen 2009). These authors suggest this may be related to the generalist diet of *Papio* baboons, as compared to that of geladas, which feed predominantly on grass. As a group, *Papio* baboons may exhibit greater interest in novel objects than geladas, and if so this too would raise the question of evolutionary mechanism. Our results indicate that there is genetic variability among *Papio* baboons (in our case olive and yellow baboons, rather than chacma baboons) accounting for differences in behavioral reaction to novel objects. This type of genetic variation would be required in order for different species to evolve different patterns of reactivity as a result of natural selection.

However, it is critical to remain cautious and conservative when comparing results across studies that investigate different environmental contexts, which use different measures of behavior or different analytical approaches. Of necessity, researchers apply labels to identified dimensions of personality (e.g. “extraversion” or “anxiousness” or “impulsivity”) to convey their interpretation of these analytically derived factors, but *a priori* ideas concerning the equivalence of such patterns of behavior across situations or species, such as the inference that two personality dimensions in different studies have the same underlying proximate causes, may be problematic. Carter et al. (2012) showed that among 57 wild chacma baboons, variation in “boldness” as measured by response to a model snake was not correlated with variation in “boldness” as measured by reaction to a novel food item (Carter et al. 2012). There is tremendous power in the study of personality among nonhuman

primates, but caution in drawing conclusions about the identity of the proximate mechanisms that lead to apparently similar behaviors expressed in diverse circumstances is certainly warranted.

QTL analysis of several independently measured phenotypes including personality factor 2 (Engagement with Object), the avert behavior, and CSF levels of HVA and 5-HIAA identified a single region of baboon chromosome 10 (PHA10) with a suggestive LOD score. While each of these results alone is interesting, their mapping to overlapping locations makes these results more compelling. Furthermore, the region of human chromosome 20 (HSA20) that is homologous to the segment of PHA10 containing this baboon QTL has been implicated in conditions such as restless legs syndrome (Levchenko et al. 2006), migraine (Oedegaard et al. 2010), and bi-polar disorder (Etain et al. 2010). While the connection between these conditions and our baboon personality phenotypes may not be immediately obvious, dysregulation of the dopaminergic system is a suspected influence on each human phenotype. There are numerous protein coding genes in this region of PHA10, but we selected SNAP 25 as the most likely positional candidate gene because of (a) its role in exocytosis and neurotransmitter function and (b) its prior association with bipolar depression, neuroticism and attention deficit hyperactivity (Etain et al. 2010; Brophy et al. 2002; Terracciano et al. 2010). SNAP25 is involved in SNARE complex formation through interaction with snare proteins present on the vesicles (v-snares) and target membranes (t-snares) of neurons (Hodel 1998; Rizo and Sudhof 2002). The interaction of these proteins (v-snares, t-snares and the SNAP25 protein) is thought to localize synaptic vesicles to the plasma membrane in anticipation of exocytosis, with SNAP25 directly involved in triggering that exocytosis (Hodel 1998; Vilinsky et al. 2002). In mice, homozygous knockouts are lethal, but heterozygous deletion of the SNAP25 gene produces a phenotype resembling attention deficit hyperactivity disorder (Feng et al. 2005; Hess et al. 1992). In addition these heterozygous null mice also show decreased extracellular levels of both dopamine and serotonin within the brain, suggesting that SNAP25 expression may be associated with deficiency in neurotransmitter release. Therefore, our association results are supported by independent data suggesting that SNAP25 can influence neurotransmitter release. In that way, sequence variation in SNAP25 among baboons may influence monoamine levels and downstream expressed behavior.

As the study of individual variation in personality within nonhuman primate species develops, efforts will be made to answer fundamental questions, including the nature and relative impact of various proximate causes of variation. Our results provide additional information concerning behavioral reactivity and personality among baboons. The behavior of baboons, like all nonhuman primates, is influenced by a wide array of inputs. These results from controlled studies of response to novelty demonstrate that sex, age and genetic differences exert significant influences on those traits among baboons, and raise the possibly that sequence differences in the SNAP25 locus may also be among the inputs that determine individual variation in those behaviors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Behaviors recorded and behavioral categories analyzed

Category	Data Type	Behavior(s)
Abnormal	Frequency Duration	clasp self, feces paint, head toss, pace, pull/eat hair, regurgitate, rock, self aggression, other stereotyped movement, suck self
Activity	Frequency	changes in position (front sit, front stand, back sit, back stand, other location, shun)
Aggression	Frequency Duration	aversive to object, brow raise, cage slap, lunge, open mouth threat, stare, teeth grind, yawn
Arousal	Frequency	muzzle wipe, piloerection, penis erection, urinate/defectate, scratch self, mantle shake
Avert	Frequency Duration	look intently away from stimulus object (usually upward) with fixed gaze
Front	Duration	time spent in front of cage (front sit and front stand)
Latency to touch	Duration	latency to first touch object
Locomotion	Duration	locomote, including walk, jump, climb
Object contact	Frequency Duration	bite object, manipulate object, smell object, watch object
Self	Frequency Duration	groom self, manipulate self, masturbate, scratch self
Slap cage	Frequency	cage slap
Submissive	Frequency Duration	ambivalent (displaying submissive and other behavior at same time), avert, clasp self, present, ear flatten, fear grimace, jump back from object, lipsmack, present, scream
Vigilance	Frequency Duration	intent monitoring area away from cage, stimulus and observer
Watch Observer	Frequency Duration	watch observer
Yawn	Frequency Duration	open mouth fully to expose teeth

Table 2

Heritabilities for Behaviors: Duration Measures

A) Truck			
Behavior	**Heritability**	**Covariates**	**p value**
Back Stand	0.27	Sex	0.000025
Locomotion	0.25	age/sex	0.000015
Mantle Shake	0.21	Sex	0.0016
Latency to Touch	0.29	Sex	9.4E-06
Other Location	0.28	age/sex	0.000029
Self Scratch	0.13	Sex	0.0082
Cage Slap	0.39	None	7.3×10^{-9}
Watch Object	0.16	age/sex	0.0019
Watch Observer	0.18	age/sex	0.00078

B) Bear			
Behavior	**Heritability**	**Covariates**	**p value**
Aggression	0.19	None	0.00011
Avert	0.33	age/sex	0.000001
Back Stand	0.21	Sex	0.000059
Locomotion	0.51	age/sex	5.0×10^{-12}
Mantle Shake	0.17	age/sex	0.0024
Object Interaction	0.17	Sex	0.000022
Other Location	0.3	age/sex	6E-07
Self Scratch	0.27	age/sex	1E-07
Cage Slap	0.33	age/sex	8.4×10^{-11}

C) Mirror			
Behavior	**Heritability**	**Covariates**	**p value**
Aggression	0.24	age	0.0023
Avert	0.11	age/sex	3.5×10^{-15}
Back Stand	0.12	sex	0.003
Front of cage	0.15	age/sex	0.007
Half Yawn	0.12	Sex	0.011
Lip Smack	0.27	None	0.0012
Locomotion	0.22	age/sex	0.00031
Other Location	0.21	Sex	0.002
Self Scratch	0.16	age/sex	0.018
Cage Slap	0.27	None	0.00027
Watch Observer	0.22	Sex	0.00027
Yawn	0.16	None	0.0031

Table 3

Heritabilities for Behaviors: Frequency Measures

A) Truck			
Behavior	**Heritability**	**Covariates**	**p value**
Aggression	0.24	Sex	0.0000063
Back Stand	0.32	age/sex	0.0000028
Abnormal Behav	0.38	age/sex	4.88×10^{-10}
Front Stand	0.18	Sex	0.002
Locomotion	0.28	age/sex	0.000051
Mantle Shake	0.14	Sex	0.011
Object interaction	0.19	age/sex	0.0018
Other Location	0.30	age/sex	0.000006
Passive	0.29	age/sex	0.0000029
Self Scratch	0.13	age/sex	0.0097
Cage Slap	0.36	Sex	0.000001
Watch Object	0.30	age/sex	0.0000005
Watch Observer	0.38	age/sex	1.00×10^{-9}
Yawn	0.12	Sex	0.011

B) Bear			
Behavior	**Heritability**	**Covariates**	**p value**
Aggression	0.28	age/sex	0.0000001
Avert	0.32	age/sex	0.000009
Back Sit	0.15	None	0.0038
Back Stand	0.30	Sex	0.000006
Abnormal Behav	0.29	None	0.0000011
Locomation	0.50	age/sex	3.54×10^{-12}
Other Location	0.28	age/sex	0.0000013
Passive	0.22	age/sex	0.000033
Self Scratch	0.32	Age	2.19×10^{-8}
Cage Slap	0.37	age/sex	4.19×10^{-10}
Submissive	0.19	None	0.00077
Watch Observer	0.31	age/sex	1.89×10^{-8}

C) Mirror			
Behavior	**Heritability**	**Covariates**	**p value**
Aggression	0.24	None	0.0021
Watch Observer	0.27	None	0.00052
Front Sit	0.20	age/sex	0.0047
Half Yawn	0.24	Sex	0.00037
Lips Smack	0.21	None	0.0058
Locomotion	0.23	age/sex	0.00065

C) Mirror			
Behavior	**Heritability**	**Covariates**	**p value**
Other Location	0.20	Sex	0.00034
Self-Scratch	0.14	age/sex	0.031
Cage Slap	0.27	None	0.00055
Yawn	0.22	Sex	0.000066

Table 4

Factor Loadings

	Factor	1(Boldness)	2(Engagement with Object)
Object	**Behavior**		
Truck	Aggressive Freq	0.57	
	Back Stand	0.53	
	Latency to touch		−0.40
	Locomotion	0.47	−0.31
	Mantle shake	−0.43	0.37
	Other Location	0.51	−0.34
	Passive Freq	0.61	
	Touch Object (Freq)		0.69
	Watch Object (Freq)	0.36	0.58
	Watch Observer (Freq)	0.73	0.30
Bear	Aggressive Freq	0.53	
	Avert		−0.32
	Back Stand	0.47	
	Locomotion	0.48	
	Other Location	0.55	−0.33
	Passive Freq	0.46	0.38
	Watch Observer (Dur)	0.37	
	Watch Observer (Freq)	0.65	0.46
Mirror	Aggressive Freq	0.32	−0.33
	Half Yawn	0.30	
	Locomotion	0.30	
	Other Location	0.37	−0.35
	Watch Observer (Dur)	0.33	
	Watch Observer (Freq)	0.54	0.34
	Yawn	0.30	