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Inheritance of Hormonal Stress Response and Temperament in Infant Rhesus Macaques (*Macaca Mulatta*): Nonadditive and Sex-Specific Effects

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Objective: Early life interindividual variation in hypothalamic-pituitary-adrenal (HPA) reactivity to stress is predictive of later life psychological and physical well-being, including the development of many pathological syndromes that are often sex-biased. A complex and interactive set of environmental and genetic causes for such variation has been implicated by previous studies, though little attention has been paid to nonadditive effects (e.g. dominance, *X*-linked) or sex-specific genetic effects. ***Method:*** We used a large pedigreed sample of captive 3–4 months old infant rhesus macaques (N = 2,661, 54% female) to fit univariate and multivariate linear mixed quantitative genetic models for four longitudinal blood cortisol samples and three reliable ratings of infant temperament (nervousness, gentleness, confidence) during a mother–infant separation protocol. ***Results:*** Each trait had a moderate narrow-sense heritability (h^2, 0.26–0.46), but dominance effects caused the first two cortisol samples to have much larger broad-sense heritabilities (H^2, 0.57 and 0.77). We found no evidence for *X*-linked variance or common maternal environment variance. There was a sex difference in heritability of the first cortisol sample ($h_f^2 < h_m^2$), suggesting differing genetic architecture of perception of maternal separation and relocation during infancy. Otherwise, genetic covariance matrices for the sexes were very similar. Genetic correlations between cortisol levels and temperament were weak (<|0.4|) but stronger than residual or phenotypic correlations. ***Conclusions:*** HPA reactivity and temperament had a primarily additive genetic basis in infant macaques, but there were important complexities to the genetic architecture of including genetic dominance and sex differences in heritability at this early life stage.

Keywords: stress physiology, primate development, sex differences, quantitative genetics, heritability

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The hypothalamic-pituitary-adrenal (HPA) glucocorticoid stress response is a critical pathway coordinating behavioral and additional physiological responses (Kudielka & Kirschbaum, 2005). Early life interindividual variation in HPA reactivity is predictive of later life psychological and physical well-being, including the development of many pathological syndromes such as major depression, social anxiety, post-traumatic stress disorder (PTSD), and schizophrenia (Caspi, 2000; Gillespie et al., 2009). Experimental work on a variety of species and observational studies on humans have shown early life experiences can have long-lasting "programming" effects on HPA function and are often correlated with social behaviors such as gregariousness, aggression, and social memory (Gunnar, 2016; Spencer, 2017).

A complex and interactive set of environmental and genetic causes has been implicated by previous studies of variation in HPA reactivity and associated behavior. The early life environment provided by mammalian mothers is likely to be of particular importance because of the opportunities for mother–offspring interaction through intimate behavioral and chemical channels. Glucocorticoids and other bioactive molecules are secreted in milk and predict infant temperament differences in human and primate samples (Bernstein & Hinde, 2016; Dettmer et al., 2018; Grey et al., 2013; Hinde et al., 2015). Molecular

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genetic work has highlighted the importance of variation in neurotransmitter systems, especially for the serotonin transporter length polymorphism (5-HTTLPR; Kinnally et al., 2010; Maestripieri et al., 2006; McCormack et al., 2009; Oler et al., 2010). Abusive or aggressive primate mothers alter the expression of neurotransmitter receptor genes in their infants regardless of infant genotype. Maternal stress can also lead to methylation of these genes in their offspring suggesting epigenetic transmission of stress (Oberlander et al., 2008; Palma-Gudiel et al., 2015).

Quantitative genetic studies identify additional heritable patterns in HPA response and behaviors by decomposing phenotypic variance (V_P) into genetic and nongenetic components (Fairbanks et al., 2004, 2011a, 2011b; Fawcett et al., 2014; Johnson et al., 2015; Ouellet-Morin et al., 2008, 2009; Rogers et al., 2008; Williamson et al., 2003). These may help explain additional heritable differences in personality or temperament that are widespread in human and animal populations (Carter et al., 2013; Réale et al., 2010).

Prior quantitative genetic work on HPA and temperament has focused almost exclusively on additive genetic variance components (V_A) or narrow-sense heritability estimates ($h^2 = V_A/V_P$). While a primarily additive basis for genetic variance in quantitative traits has been posited (Hill et al., 2008), there is some empirical evidence for greater nonadditive variance for nonmorphological traits like life history, physiology, and behavior. Moreover, theoretical arguments also support a more complex genetic architecture for HPA reactivity and temperament. This includes increased amounts of dominance variance (Crnokrak & Roff, 1995; Merilä & Sheldon, 1999; Wolak & Keller, 2014), maternal effect variance (Hadfield, 2012; Räsänen & Kruuk, 2007), sex chromosomal (*X*-linked) variance (Fairbairn & Roff, 2006; Wolak et al., 2015), and imprinting variance (Santure & Spencer, 2011; Tier & Meyer, 2012). These nonadditive components can have important phenotypic consequences. For example, dominance variance implies possible inbreeding effects including inbreeding depression (Lynch & Walsh, 1998) which is widely documented (Chapman et al., 2009; Charpentier et al., 2007; Larson et al., 2009) and can have sex-specific effects (Ebel & Phillips, 2016). Dominance variance can equal or exceed additive genetic variance in human temperament or anthropometric traits (Boomsma et al., 2018; Herzig et al., 2018).

Further insights may be gained from multivariate analysis of phenotypes where stress response can be measured under differing conditions and these can be related to each other and behavioral metrics of temperament. Such analysis results in increased statistical power and highlights genetic relationships between physiology and behavior (Böhnke et al., 2010; Killen et al., 2013; Oler et al., 2010). For example, HPA-axis response to stress measured through salivary cortisol is predicted by "big five" personality traits (Xin et al., 2017). Sex differences in stress response and their relationship with personality characteristics have also been documented (DeSoto & Salinas, 2015; Oswald et al., 2006). Treating sexes as different phenotypes within a population offers opportunities to identify pathways for the emergence of sexual dimorphism or genetic constraints (Byars et al., 2010; Gosden et al., 2012; Poissant et al., 2016; Walsh & Blows, 2009). A wide range of neuropsychiatric traits were recently shown to have very similar genetic architectures in men and women (Martin et al., 2021). However, several traits were genetically sex-differentiated including risk-taking and educational attainment, which have been associated with HPA function (Finy et al., 2014).

We address these additional complexities of the genetic architecture of HPA response and infant temperament in a large nonhuman primate sample that were reared and assessed under standardized conditions (Camus et al., 2015). Consistent with previous studies of human variation and other laboratory-housed mammals, we predict sizable additive genetic variance for each phenotype. For reasons noted above, we also predict modest dominance variance. In addition, we predict maternal effects will be large due to the early life stage in which phenotypes are measured. Similarly, we hypothesize little difference in the genetic architecture between the sexes which predicts equal sex-specific heritabilities and very strong intersex genetic correlations that limit the evolution of dimorphism.

Materials and Method

Data Collection

We rely on data from 2,817 rhesus macaque infants from the California National Primate Research Center (CNPRC) that were assessed in a standardized biobehavioral assessment (BBA) protocol when they were approximately 3–4 months old. The protocol is described in greater detail elsewhere (Capitanio, 2017; Capitanio et al., 2005; Golub et al., 2009). All procedures were conducted according to the Guidelines for Use and Care of Laboratory Animals of the National Research Council and according to CNPRC Standard Opperating Procedures (SOPs). The CNPRC is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care. Experimental protocols were approved prior to implementation by the University of California, Davis Institutional Animal Use and Care Committee (IACUC).

We only note the essential elements of the BBA protocol here. Prior to measurement, all animals lived in outdoor half-acre field cages with genetic mothers in social groups that ranged in size up to 180 animals of all ages and both sexes. Animals were fed standard monkey chow twice daily, fresh fruit/vegetables once or twice per week, and had water continuously available. Infants were temporarily separated from their mothers at a mean age of 107 days (range = 89–133 days) for 25 hr and relocated to an indoor test room. Four blood samples (0.5 mL each) were drawn under manual restraint from a femoral vein. Samples were transferred to ethylenediamine tetraacetic acid (EDTA) tubes and centrifuged to separate plasma which was frozen (−80 °C) until cortisol concentrations were measured by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA) through the CNPRC Endocrine Core. The samples were taken (a) in the morning approximately 2 hr after relocation (1,100 h) which is 4.5 hr after sunrise, (b) later in the afternoon (1,600 h), (c) the following morning which was approximately 16.5 hr after intramuscular dexamethasone injection (0830 h; 500 μg/kg; American Regent Laboratories, Inc., Shirley, NY), and (d) 30 min after intramuscular ACTH injection (0900 h; 2.5 IU; Amphastar Pharmaceuticals, Inc., Rancho Cucamongo, CA). We treat the four samples as "response to relocation," "adaptation to relocation," "response to suppression," and "response to stimulation." Just prior to the infant's reunion with its mother, they were also rated for overall temperament during the 25-hr test period. A list of 16 adjectives describing affect quality were rated on a Likert-like scale of 1–7, with one reflecting a total absence of the behavior and seven reflecting an extremely large amount of the behavior. Ratings on each adjective were *z*-scored across all subjects

tested within a given birth year, and exploratory and confirmatory factor analyses of the temperament ratings were previously conducted by JPC and are described in Golub et al. (2009). Additional behavioral scales collected on the BBA infants were excluded due to their strongly nonnormal distributions (Beasley et al., 2009).

We log-transformed the cortisol data because it dramatically reduced their skewness and kurtosis (Adam & Kumari, 2009; Keene, 1995) and then screened for any major outliers with visual inspection of points in univariate density plots and bivariate scatter plots (Table 1; Online Supplement). Finally, we removed any cases with *z*-scored residuals from univariate linear models (described below) with an absolute value greater than 3.5, resulting in 2,661 complete cases. Log transformation of the cortisol measurements implies their additive genetic variances are estimates of evolvability on a proportionate scale (Hansen et al., 2011), and their heritabilities are not directly comparable to those of temperament. However, our primary interests were in independently testing each variable for additive and nonadditive effects and exploring correlations among them that will not be affected by these scale issues.

Univariate Quantitative Genetic Models

We used a series of linear mixed models that decompose observable, phenotypic variance in the seven phenotypes described above into one or more nonresidual variance components (Kruuk, 2004; Lynch & Walsh, 1998). In all models each phenotype was also adjusted for a set of covariates we selected from a priori considerations of their potential effects on stress and temperament. These were infant sex, infant inbreeding coefficient, the year of the assessment (2001–2015), membership in the specific pathogen free segment of the colony, maternal dominance rank (high, middle, low, or unknown), infant age (days), infant body mass (g), and the number of conceptions the mother had (gravidity). Because few mothers had 12 or more conceptions we truncated all conceptions greater than or equal to 12 at this value. This variable entered the models as a quadratic covariate to account for nonlinear effects due to primiparity and senescence, and is more flexible than a simple categorization of mothers as nulliparous, primiparous, and multiparous. We used gravidity because it is strongly correlated with parity but may capture physiological changes during pregnancy such as mammary development known to influence HPA axis function (e.g., Dettmer et al., 2018). Infant inbreeding coefficient, age, and mass were linear covariates while all remaining were categorical (Table 1). We used a Covariate × Sex interaction to allow sex differences in each additional covariate. This large set of covariates will tend to reduce phenotypic variance by accounting for nongenetic sources of variation. This will increase heritability estimates or other ratios where phenotypic variance is the denominator. Alternatively, additive genetic variance could be reduced by covariates with similar measurements among closely related individuals (Wilson, 2008). This is unlikely in our study. For example, each infant of a mother in the sample will be in a different birth year. We quantified the amount of total phenotypic variance accounted for by the covariates with R^2 measurements (Nakagawa & Schielzeth, 2013).

We ran univariate models for each phenotype with the full set of covariates and an additive genetic effect linked to the colony pedigree (Table 2). We compared this baseline, additive-only model with others having the additive genetic effect and one additional random effect. These were maternal identity, genetic dominance, and *X*-linked effects. Initial data exploration was carried out in R (R Core Team, 2017) and the quantitative genetic models were fit via restricted maximum likelihood (REML) using the regress package (Clifford & McCullagh, 2006). The baseline model is described as:

$$\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{Z_a a} + \boldsymbol{e} \quad (1)$$

where $\mathbf{y}$ is the vector of phenotypic measurements, $\boldsymbol{\beta}$ is the vector of regression coefficients for covariates with the design matrix $\boldsymbol{X}$, $\boldsymbol{a}$ is the vector of additive genetic or breeding values with the design matrix $\boldsymbol{Z_a}$ and $\boldsymbol{e}$ is the vector of residuals (Lynch & Walsh, 1998). The other models added a new vector of random effect solutions and corresponding design matrix (e.g., $\boldsymbol{Z_d d}$ for dominance). Residuals and maternal identity effects ($\boldsymbol{c}$) were assumed to be normally and independently distributed, but additive genetic, dominance, and *X*-linked ($\boldsymbol{s}$) effects have complex covariances determined by Mendelian rules of allele sharing from the pedigree. The generalized inverses of these covariance matrices for additive genetic ($\boldsymbol{A^{-1}}$), genetic dominance ($\boldsymbol{D^{-1}}$), and *X*-linked effects ($\boldsymbol{S^{-1}}$) were calculated directly or via simulation with the R package nadiv (Wolak, 2012).

Table 1

Descriptive Statistics by Sex for the Four Cortisol Samples, Three Temperament Scales, and Covariates Used in Quantitative Genetic Models

	Female				Male			
Variable	*M*	*SD*	Min	Max	*M*	*SD*	Min	Max
Relocation (μg/dl)	83.936	21.897	38.57	174.21	74.637	18.799	29.78	165.14
Adaptation (μg/dl)	88.648	28.650	36.87	206.00	81.894	24.168	30.50	182.07
Suppression (μg/dl)	68.755	24.285	19.29	234.90	61.027	24.412	17.99	338.75
Stimulation (μg/dl)	99.330	27.471	40.96	257.33	88.069	24.447	39.46	313.49
Gentle (*z*-score)	−0.138	0.996	−2.680	2.972	−0.046	0.958	−2.608	2.448
Confident (*z*-score)	−0.006	0.965	−3.316	2.727	−0.117	0.996	−2.947	2.727
Nervous (*z*-score)	0.003	0.947	−2.792	3.045	−0.067	0.906	−2.407	3.047
Weight (kg)	0.975	0.155	0.51	1.46	1.03	0.159	0.576	1.632
Age (days)	106.703	10.275	89	133	107.172	9.938	90	129
Conceptions	4.102	3.064	1	12[a]	3.823	2.883	1	12[a]
Maternal rank[b]	$h = 455$; $m = 496$; $l = 444$; $u = 48$				$h = 398$; $m = 407$; $l = 374$; $u = 39$			
Year	2001–2015, 64–123/year				2001–2015, 51–120/year			
Pathogen free	No = 1,006; Yes = 437				No = 823; Yes = 395			

[a] Truncated at 12. [b] High, middle, low or unknown.

Table 2
Pedigree Statistics for the Full Pedigree and the Analyzed Infants

Statistics for full pedigree (N = 5,381)			
Founders = 235	Maximum generations = 10		
Full sibs = 623	Maternal ½ sibs = 4,725		Paternal ½ sibs = 29,479
MGM = 4,294	MGF = 3,769	PGM = 4,093	PGF = 4,294

Statistics for analyzed infants (N = 2,661)				
	M	Median	IQR	Range
Kinship (A_{ij})	0.01147	0	0–0.00781	0–0.81250
Inbreeding (F)	0.01822	0	0–0.01465	0–0.29395

Note. MGM = maternal grandmothers; MGF = maternal grandfathers; PGM = paternal grandmothers; PGF = paternal grandfathers.

We compare each model for a phenotype with likelihood ratio tests (LRTs) of the additive-only model against each augmented model with the recommended $\chi^2 p$ value-halving correction (Visscher, 2006).

Multivariate Quantitative Genetic Models

We extended the analysis by exploring the multivariate and sex-specific patterns of additive genetic (co)variance. We fit a single large model for all seven traits separated by sex to be 14 correlated phenotypes in the Bayesian software BESSiE (Boerner & Tier, 2016). All of the same fixed effects from the univariate models were used without the sex interaction, which is subsumed by separation of the phenotypes by sex. A set of five chains were run in parallel having different random number seeds and each retaining 200 iterates that were combined for inference on the posterior distributions (210,000 iterates with 10,000 discarded as burn-in saving only every 1000th iterate from each chain). Effective sample sizes were close to the 1,000 retained (minimum 742) for all variance components, heritabilities, and genetic correlations. Priors for the covariance matrices were multivariate t-distributions with 0 degrees of freedom. Nonadditive effects were not explored due to difficulty fitting such large multivariate models and univariate results identifying a primarily additive basis for these phenotypes (see below). Differences in heritability between the sexes were identified by exclusion of 0 from the 95% credible interval of the male–female heritability posterior distribution. We compared the sex-specific genetic covariance matrices ($\mathbf{G}_m$ and $\mathbf{G}_f$) with principal components and Mantel correlations. To explore the influence of the intersex-covariance matrix ($\boldsymbol{B}$; Gosden et al., 2012) we used random skewers (Cox et al., 2017). Skewers are a vector of randomly generated selection gradients ($\boldsymbol{\beta}$) multiplied by the 14×14 $\boldsymbol{G}$-matrix to produce a simulated response to selection ($\Delta \mathbf{z} = \boldsymbol{G\beta}$). The influence of the intersex-covariance matrix is quantified by the correlation between predicted responses with the observed matrix and that where it was maximally constrained ($\boldsymbol{B_1}$) or set to be all zeros, that is, unconstrained ($\boldsymbol{B_0}$). Data are available from the authors upon request.

Results

Univariate Models

Each cortisol sample and temperament scale had substantial additive genetic variance with a moderate heritability (range: 0.263–0.456) in this infant rhesus macaque sample (Table 3, Figure 1). The heritability estimates were not affected strongly by the inclusion of additional random effects with only slight depression in some cases. This implies little upward bias to heritability estimates when ignoring additional effects such as maternal identity or dominance.

In general, the additive-only model was well-supported with no augmented model declared significant by LRTs (Table 4). There was weak evidence for a maternal identity effect on cortisol after ACTH stimulation (p = .099), a dominance effect on initial cortisol response to relocation and later adaptation (p = .160 and .065), and X-linked effect on cortisol after stimulation (p = .147), and the nervous temperament scale (p = .179). With the exception of the dominance effects on initial cortisol response to relocation and later measurement of adaptation all of the estimated nonadditive effects were very small. Consequently, the broad-sense heritabilities for only these cortisol samples were considerably larger than narrow-sense counterparts (response to relocation $H^2 = 0.571$ vs. $h^2 = 0.347$, adaptation to relocation $H^2 = 0.769$ vs. $h^2 = 0.419$).

Fixed effects of the known infant or maternal characteristics had relatively small influence on the phenotypes (Table 5, Online Supplement). Marginal R^2 were very low for the temperament scales (range: 0.014–0.020) but much larger for the cortisol samples (range: 0.110–0.205). Sex differences were similarly small for the temperament scales but somewhat larger for the cortisol samples with the largest effect size on initial response to relocation ($d = -0.556$). Males were lower on all measures except the gentle temperament scale. Inbreeding coefficients were unimportant in all models.

Multivariate Models

The genetic architecture of cortisol response and temperament was remarkably similar between the sexes for rhesus infants. For almost all phenotypes heritability estimates were nearly identical and similar to the additive-only pooled estimates above (Figure 2, Table 6). The only exception to this was the initial cortisol response to relocation for which the female heritability was lower than male (0.366 vs.0.545), and these are significantly different relying on the credible intervals for the posterior distribution of heritability differences. The heritability difference is caused primarily by greater residual variance in females. There was a weaker indication that female heritability of cortisol after ACTH stimulation may be greater than male (0.539 vs. 0.439). This would be due to greater genetic variance among females. Cross-sex genetic correlations are all strongly positive but are all reliably less than one (posterior mode range: 0.765–0.851).

Table 3

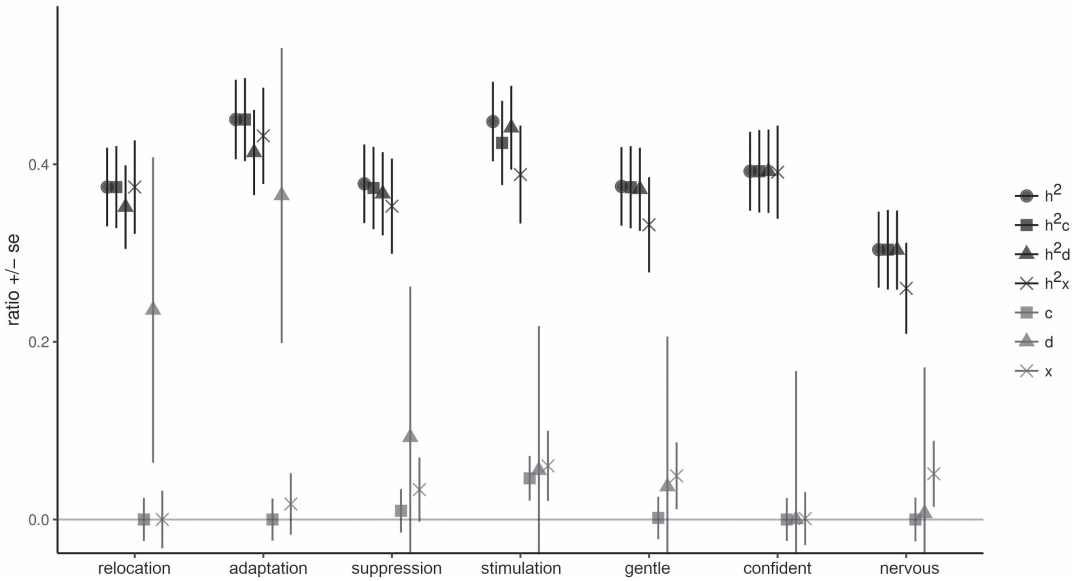
Variance Components and Standard Errors From Each of the Four Quantitative Genetic Models for Seven Infant Macaque Hormonal Stress and Behavioral Phenotypes

	Cortisol samples				Temperament scales		
Variance	Relocation	Adaptation	Suppression	Stimulation	Gentle	Confident	Nervous
Additive-only model							
V_A	2.232 (0.297)	3.418 (0.398)	3.857 (0.510)	2.482 (0.290)	35.073 (4.661)	36.734 (4.730)	25.989 (3.993)
V_R	3.731 (0.241)	4.171 (0.304)	6.347 (0.413)	3.057 (0.222)	58.444 (3.783)	56.947 (3.785)	59.549 (3.460)
Maternal identity model							
V_A	2.232 (0.308)	3.418 (0.412)	3.808 (0.529)	2.345 (0.300)	34.986 (4.839)	36.734 (4.908)	25.989 (4.155)
V_C	0.000 (0.144)	0.000 (0.179)	0.100 (0.249)	0.256 (0.139)	0.169 (2.227)	0.000 (2.253)	0.000 (2.107)
V_R	3.731 (0.251)	4.171 (0.315)	6.294 (0.428)	2.928 (0.227)	58.356 (3.930)	56.947 (3.931)	59.549 (3.615)
Dominance model							
V_A	2.104 (0.308)	3.150 (0.411)	3.745 (0.529)	2.444 (0.300)	34.788 (4.848)	36.732 (4.916)	25.952 (4.176)
V_D	1.412 (1.033)	2.781 (1.276)	0.945 (1.733)	0.307 (0.900)	3.463 (15.814)	0.000 (15.669)	0.589 (14.057)
V_R	2.466 (0.950)	1.691 (1.162)	5.520 (1.615)	2.790 (0.846)	55.318 (14.744)	56.948 (14.607)	59.010 (13.843)
X-linked model							
V_A	2.232 (0.335)	3.289 (0.447)	3.632 (0.580)	2.178 (0.326)	31.388 (5.286)	36.648 (5.322)	22.539 (4.546)
V_X	0.000 (0.192)	0.133 (0.263)	0.346 (0.375)	0.339 (0.224)	4.650 (3.602)	0.095 (2.805)	4.457 (3.260)
V_R	3.731 (0.241)	4.191 (0.304)	6.317 (0.412)	3.090 (0.221)	58.545 (3.770)	56.956 (3.785)	59.575 (3.443)

The moderate heritabilities coupled with genetic correlations <1 could indicate ample independent genetic variance that would facilitate sexual dimorphism in these phenotypes. However, the full multivariate $\boldsymbol{G}$ was more consistent with strong higher-dimension constraints. In particular, the intersex matrix $\boldsymbol{B}$ was a strong constraint on dimorphism. Random skewers comparisons of the observed posterior modal $\boldsymbol{B}$ were very similar to a matrix of maximum constraint ($\boldsymbol{B_1}$, mean $r = 0.973$) and far less similar to one with no intersex constraint ($\boldsymbol{B_0}$, $r = 0.766$). The sex-specific $\boldsymbol{G_m}$ and $\boldsymbol{G_f}$ were oriented very similarly and had very similar hypervolumes (Mantel $r = 0.974$; Figure 3). Within $\boldsymbol{G_m}$ and $\boldsymbol{G_f}$, the genetic correlations between cortisol responses and temperament are very similar for the sexes but often slightly stronger for males. The strongest negative correlations were for adaptation, suppression, and stimulation samples with gentleness and comparable positive correlations were found for those samples with nervousness (range: −0.330–0.355). These indicate a modest ability to predict infant temperament from stress physiology, which is likely mediated by pleiotropic gene action on both sets of traits.

Figure 1

Variance Component Ratios and Standard Errors From Each of the Four Quantitative Genetic Models for Seven Infant Macaque Hormonal Stress And Behavioral Phenotypes



Note. Narrow-sense heritabilities are estimated in all models. Other ratios have single estimates (c = maternal, d = dominance, x = X-linked).

Table 4
Likelihood Ratio Test p Values Against the Additive-Only Model Including the Visscher Halving Correction

	Cortisol samples				Temperament scales		
Model	Relocation	Adaptation	Suppression	Stimulation	Gentle	Confident	Nervous
Maternal identity	0.498	0.500	0.391	0.099	0.478	0.500	0.500
Dominance	0.160	0.065	0.355	0.414	0.430	0.500	0.489
X-linked	0.498	0.373	0.277	0.147	0.216	0.491	0.179

Discussion

The HPA axis is a major biological system associated with significant psychopathology in both children and adults (Buitelaar, 2013). Using the largest sample to-date of nonhuman primates, we examined quantitative genetic contributions to naturally occurring variation in aspects of HPA regulation in infants. Generalizing from laboratory models to humans requires caution, but notably HPA function is deeply conserved among primates (Meyer & Hamel, 2014). Moreover, our results complement recent analyses of polygenic variation in neuropsychiatric and behavioral traits in humans (Martin et al., 2021), by ensuring environmental standardization and additional opportunities for longitudinal studies of later life effects on HPA function emerging in infancy.

Our quantitative genetic analysis describes a primarily additive basis for infant macaque cortisol levels and temperament measures. This contrasted with our predictions from theoretical arguments for a more complex genetic architecture of physiological and behavioral traits. Genetic dominance effects on the initial cortisol response to relocation and later measurement after adaptation were the only traits with sizable nonadditive effects in our models. While they were modest (<0.4), they do combine with additive effects for large broad-sense heritabilities, such that additive and dominance effects together explain 77% of variation in the cortisol measurement of adaptation to the novel environment. With large samples and adequate pedigree structure, dominance effects should be estimated. Extended pedigree designs such as those used here provided many advantages over standard twin model where dominance and common environment variance cannot be distinguished (ACE or ADE models, c.f. Boomsma et al., 2018). Despite some dominance variance, we found no significant influence of inbreeding on these phenotypes. This may be due to captive breeding protocols to avoid high inbreeding levels such that the scope of inbreeding is quite narrow in our sample despite its deep pedigree. Indeed, less than 25% of infants had $F > 1/64$, the coefficient of second-cousin mating often used in clinical genetic literature (Fareed & Afzal, 2017; Romeo & Bittles, 2014).

We were unable to detect any *X*-linked genetic variance. This is somewhat surprising given known variation in neurotransmitter receptors genes on the *X*-chromosome (Kinnally et al., 2010), and some reports of *X*-linked variance in human phenotypes (Ober et al., 2008; Pan et al., 2007). Nevertheless, such *X*-linked variance tends to be a small portion of total phenotypic variance, and it may interact in sex-limited ways with dominance variance (Dean & Mank, 2014). The simplistic univariate variance component estimation we used also cannot capture further complexities such as *X*-inactivation or dosage compensation and imprinting (Griffin et al., 2016; Sidorenko et al., 2019).

Even more surprising was the lack of maternal effects given the young infant ages (3–4 months), as cercopithecine mothers strongly influence the environment in which infants develop (e.g., Maestripieri et al., 2007) and maternal effects generally decline with age (Moore et al., 2019). This cannot be caused by artifacts of the dataset such as many mothers having only a single measured infant. Only 30% of the infants lacked maternal siblings, and rerunning our models limiting the dataset to sibships of two or more infants per mother had no effect on the amount of maternal identity variance. Our results cannot be considered as absence of evidence due to lower power. Standard errors on the estimates were very small, and simulations with the CNPRC pedigree for the measured individuals show adequate power for any maternal effect over 0.06 (Online Supplement, Figure S3). We speculate that the beneficial, standardized environment of captivity might explain the limited scope for variation among mothers thereby reducing maternal variance. However, there is limited empirical support for the argument that maternal effects decline in favorable environments (Charmantier & Garant, 2005; Rowiński & Rogell, 2017).

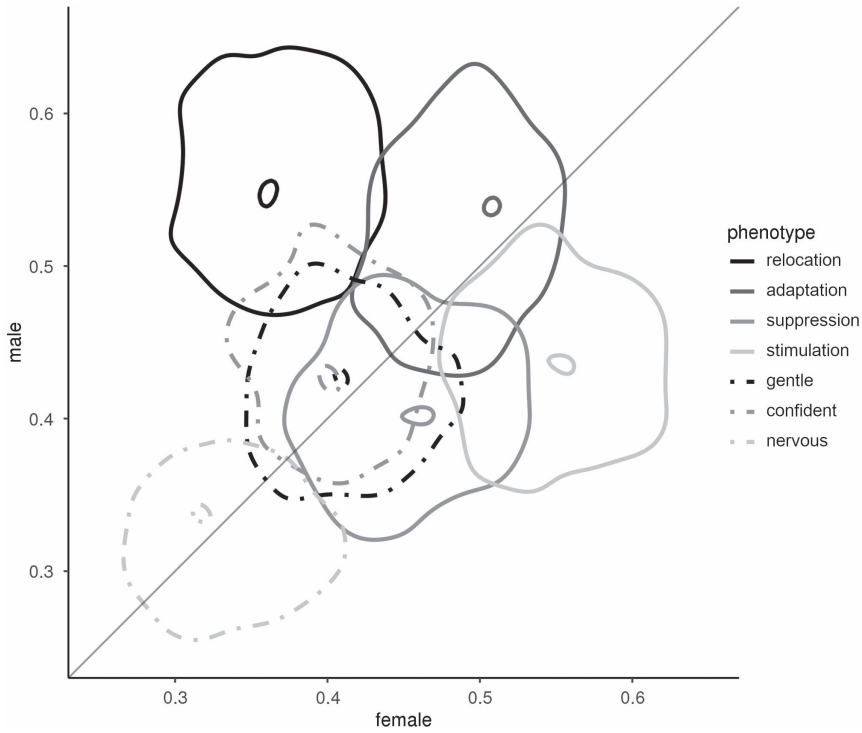
Table 5
Fixed Effect Variance, Marginal R^2_m, Conditional R^2_c, and Sex Main Effect (Maleness) Regression Coefficients and Effect Sizes for Sex Differences From the Additive-Only Models

Variable	V_{fix}	R^2_m	R^2_c	β	*SE* (β)	SD_f	SD_m	*d*
Relocation	0.007	0.109	0.443	−0.140	0.045	0.256	0.247	−0.556
Adaptation	0.011	0.129	0.521	−0.081	0.050	0.301	0.279	−0.279
Suppression	0.019	0.155	0.474	−0.049	0.059	0.329	0.348	−0.146
Stimulation	0.014	0.205	0.561	−0.090	0.043	0.258	0.251	−0.353
Gentle	0.018	0.019	0.387	0.141	0.179	0.996	0.958	0.145
Confident	0.019	0.020	0.404	−0.019	0.179	0.965	0.996	−0.020
Nervous	0.012	0.014	0.314	−0.034	0.174	0.947	0.906	−0.036

Note. Effect size is Cohen's *d* here calculated as $d = \beta/0.5^{*}\ (SD_m + SD_f)$.

Figure 2

Sex-Specific Heritability Posterior Distributions (2% and 50% Credible Interval Contours) for Infant Macaque Hormonal Stress and Temperament Phenotypes From the Multivariate Model



We found limited evidence for sex differences in the genetic architecture of cortisol levels or temperament. Narrow-sense heritabilities for each trait were similar for the sexes and cross-sex genetic correlations were all strongly positive. However, ample opportunity for the sexes to evolve dimorphism in stress response or temperament is implied by the genetic correlations that did not approach +1 and some subtle but significant differences in sex-specific heritabilities. While mean sex differences were small at these infant ages, the initial cortisol sample measuring response to separation and relocation had the largest mean difference, greatest difference in sex-specific heritabilities, and lowest cross-sex genetic correlation. The heritability difference was due to greater additive genetic variance and lower residual variance in males. The higher male genetic variance might reflect the variance depressing effects of *X*-chromosomal dosage compensation in females. However, the cortisol sample following ACTH stimulation had nearly as large a difference in sex-specific heritabilities with females having the greater genetic variance and heritability. While both cortisol measurements reflect HPA-axis function, the first captures infant perception of the stress of separation from their mother and relocation to a novel environment, while the latter is a physiological maximum induced by ACTH stimulation, and has been found in previous work to differentiate the sexes (Capitanio et al., 2005; Kudielka et al., 2004). The greater initial male variance may thus reflect sex differences in psychosocial stress physiology or perception already present in infancy (Kajantie & Phillips, 2006; Sayal et al., 2014).

Table 6

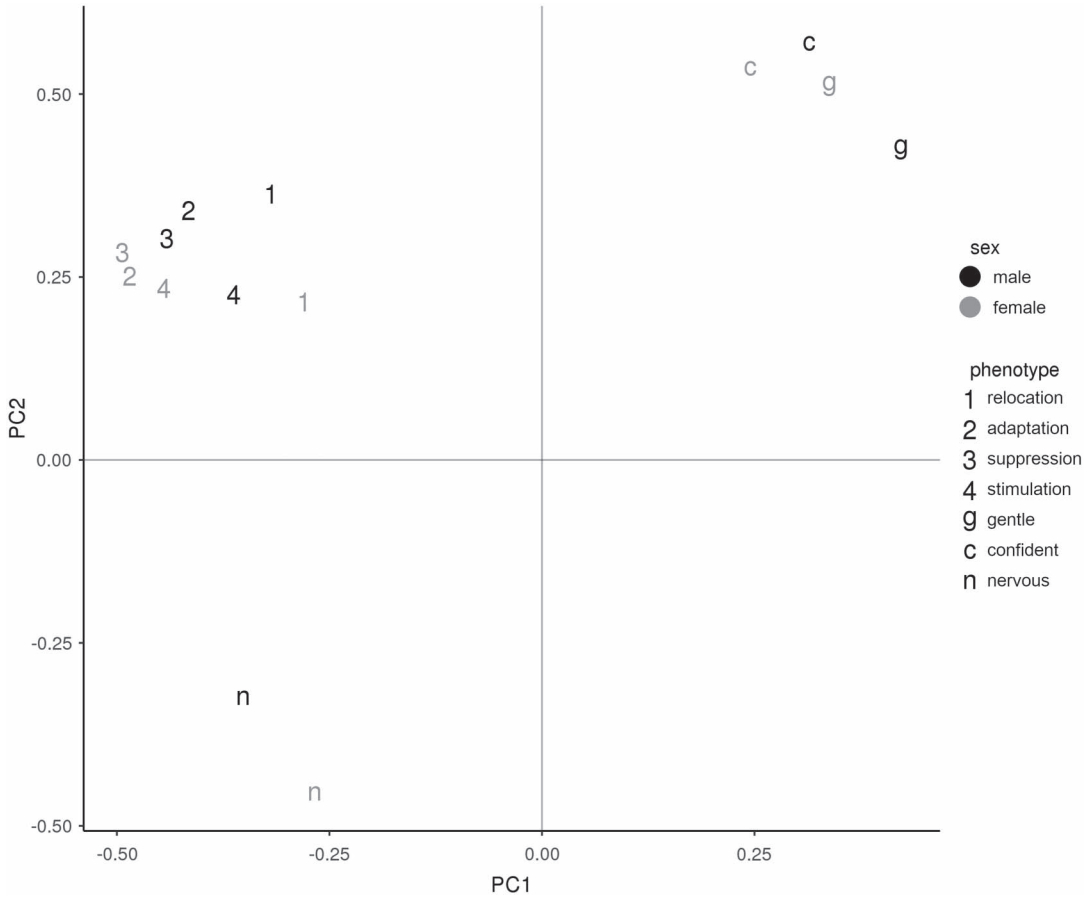
Posterior Modes and Credible Intervals for Sex-Specific Heritabilities and Cross-sex Genetic Correlations ($r_{A(m,\ f)}$) for Infant Cortisol Samples and Temperament Scales

Variable	$r_{A(m,\ f)}$	h_f^2	h_m^2	h_f^2–h_m^2
Relocation	0.780 (0.635, 0.891)	0.366 (0.260, 0.470)	0.545 (0.392, 0.709)	−0.193 (−0.359, −0.004)
Adaptation	0.816 (0.673, 0.913)	0.496 (0.372, 0.606)	0.534 (0.389, 0.682)	−0.036 (−0.215, 0.137)
Suppression	0.822 (0.657, 0.914)	0.439 (0.340, 0.572)	0.401 (0.283, 0.543)	0.058 (−0.124, 0.204)
Stimulation	0.843 (0.722, 0.924)	0.539 (0.421, 0.658)	0.439 (0.302, 0.545)	0.126 (−0.053, 0.275)
Gentle	0.836 (0.664, 0.910)	0.398 (0.314, 0.526)	0.421 (0.296, 0.547)	−0.008 (−0.167, 0.167)
Confident	0.851 (0.719, 0.928)	0.407 (0.294, 0.503)	0.448 (0.323, 0.566)	−0.030 (−0.179, 0.129)
Nervous	0.765 (0.561, 0.882)	0.321 (0.230, 0.455)	0.321 (0.229, 0.457)	0.022 (−0.153, 0.147)

Note. Significant differences between heritabilities are indicated by the exclusion of 0 from the credible interval for h_f^2–h_m^2.

Figure 3

Principal Components (PC) Biplot of Posterior Modal Sex-Specific Genetic Covariance Matrices (G_m and G_f)



Note. PC1 explains 48% and PC2 explains 34% of variance each sex's matrix.

Multivariate assessment of the sex-specific genetic architecture showed little additional opportunity for the evolution of dimorphism. G_m and G_f were very similarly oriented and the cross-sex B was very nearly identical to a matrix of maximum constraint. This contrasts with theoretical arguments and some empirical work showing that constraints on the evolution of dimorphism are *weaker* when rephrased in a multivariate framework (Wyman et al., 2013; Wyman & Rowe, 2014). Genetic correlations across traits were in expected directions—nervous monkeys had high cortisol and were less confident or gentle. The correlations were weak to modest (<|0.4|) suggesting limited ability to predict temperament from cortisol or *vice versa*. However, genetic correlations were much stronger than their phenotypic counterparts. This is likely due to pleiotropic effects meaning the same genetic variants are responsible for this covariation perhaps through the mediating effect of cortisol itself or common physiological triggers in brain and adrenals. Mean sex differences in HPA function become more pronounced with sex steroid secretion later in life and may interact with these subtle differences in genetic architecture present in infancy (Kudielka & Kirschbaum, 2005). A wide array of psychological phenotypes including depression and resilience may be related to such sex differences in HPA function affecting their mean and variance (Boardman et al., 2008; Kendler et al., 2006; Waaktaar & Torgersen, 2012). While greater male variance is a common feature of many traits in humans (Lehre et al., 2009) there was no such bias phenotypically in our measurements. However, the subtle differences in heritabilities we found for some cortisol measurements suggest even when sexes have phenotypically similar distributions there may be hidden differences in genetic variance that are magnified later in life (Badyaev, 2002; Bale & Epperson, 2015; Juster et al., 2011).

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