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RESEARCH ARTICLE

Early social rearing, the V1A arginine vasopressin receptor genotype, and autistic traits in chimpanzees

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Abstract

Previous studies found associations between autism-related phenotypes and both rearing and V1A arginine vasopressin receptor (AVPR1A) genotypes. We tested whether these exposures as well as their interaction were associated with autism-related phenotypes in 121 laboratory-housed chimpanzees. We used expert-derived weights to obtain autism scores from ratings on the 43-item Chimpanzee Personality Questionnaire; higher scores indicated more autistic-like traits. The first model included fixed effects for sex, age, and rearing, and a random effect that addressed the relatedness of subjects. The second model was the same except that it also included the rearing × AVPR1A genotype interaction as a fixed effect. Both models indicated that the phenotype was moderately heritable and that chimpanzees reared by their mothers had lower scores on the scale. The effect of genotype in both models indicated that chimpanzees with an indel deletion had higher scores on the scale, although the credible interval included zero. Moreover, the rearing × genotype interaction in the second model indicated that chimpanzees who possessed the non-deletion genotype and who were reared by their mother were at even greater risk. The credible interval for this effect did not include zero, but fit statistics indicated that the model without the interaction was marginally better, and the interaction was in the opposite direction than we expected based on previous work. These findings highlight the importance of rearing effects in the typical social development of our closet-living nonhuman relative.

Lay summary

We tested whether, in chimpanzees, scores on a scale comprising traits that resembled aspects of autism were related to a gene associated with autism in prior research and/or early rearing. Human-reared chimpanzees had higher scores (indicating more autistic-like traits). Chimpanzees that possessed the gene also had higher scores, but we could not exclude the possibility that there was no effect of genotype. These findings suggest that we can measure autism-like characteristics in chimpanzees, and so study it in this species.

KEYWORDS
autism, AVPR1A, development, mother, primate, vasopressin

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by difficulties with communication, reciprocal social interactions, and repetitive behaviors (American Psychiatric Association, 2013). Behavioral and neurodevelopmental indicators of ASD, such as difficulty in maintaining eye contact, initiating and responding to joint attention cues, or in tolerating sensory stimuli or environmental change, manifest in infants and in children under the age of 4 years who are at risk of, or who have been diagnosed with, ASD (Courchesne et al., 2007; Hazlett et al., 2017; Zwaigenbaum et al., 2005).

Some ASD phenotypes are increasingly being viewed as the tail end of a normal distribution (Baron-Cohen et al., 2001; Losh et al., 2009). This notion is supported by studies showing that these traits are associated with atypical sensory functioning (Mayer, 2017) and that, in the neurotypical population, they are associated with decreased brain response to gentle touch (Voos et al., 2013).

The causes and mechanisms underlying ASD may be multiplicative (Landrigan et al., 2012). ASD is highly heritable and candidate genes have been identified in studies of people with ASD and neurotypical individuals (Melke, 2008) and in gene knock-out studies (Kazdoba et al., 2015). Studies have also identified nongenetic factors that may moderate the association between ASD candidate genes and ASD-related behaviors. Studies in rodents and nonhuman primates, for instance, have shown that early adverse rearing is associated with impaired development of species-typical social behaviors and the onset of stereotypical or repetitive behaviors in some individuals (Brett et al., 2015; Dettmer & Suomi, 2014; Nelson & Winslow, 2009).

We sought to build on this literature by testing whether chimpanzees' scores on a species-specific autism rating scale (Wilson & Weiss, 2015) were associated with V1A arginine vasopressin receptor gene (*AVPR1A*) polymorphisms, early rearing, or a gene × environment interaction. Our study was motivated by several considerations. First, studies of autism-like traits in nonhuman primates may offer better translation possibilities compared with studies in more distantly related species (Bauman & Schumann, 2018; Watson & Platt, 2012). Second, arginine vasopressin is a neuropeptide that is related to social behaviors, including cooperation, competition, social recognition, and mating behavior in mammals (Caldwell, 2017; Johnson & Young, 2017). Third, there is evidence that *AVPR1A* and a related neuropeptide (oxytocin) are implicated in the expression of ASD (Anagnostou et al., 2014; Donaldson et al., 2008; Hammock & Young, 2006; LoParo & Waldman, 2015; Young et al., 2002). For example, studies of humans have found associations between polymorphisms of the RS3 microsatellite located in the DupB region of *AVPR1A* (Thibonnier et al., 2000) and social appropriateness, sibling conflict, and, in males, prosocial behavior toward one's partner (Bachner-Melman et al., 2005; Walum et al., 2008). Fourth, the long form of the RS3 allele has been associated with altruistic behavior as measured by the dictator game and higher *AVPR1A* mRNA levels in the hippocampus (Knafo et al., 2008), and various microsatellites, including RS1, RS3, and AVR have been associated with externalizing behaviors (Landefeld et al., 2018) and with communication and social skills in humans (Yirmiya et al., 2006). Finally, cerebrospinal fluid vasopressin levels were higher in rhesus macaques that were classified as being more social (Parker et al., 2018).

Chimpanzees are also polymorphic at the DupB region of *AVPR1A*. This polymorphism is an indel deletion (Donaldson et al., 2008; Hammock & Young, 2005). In Western chimpanzees (*Pan troglodytes verus*), the deletion ($DupB^{-}$) is more prevalent than the non-deletion ($DupB^{+}$), that is, it is the major allele; in Eastern chimpanzees (*P. t. schweinfurthii*), $DupB^{-}$ is the minor allele (Anestis et al., 2014; Donaldson et al., 2008; Hammock & Young, 2005; Staes et al., 2014).

Studies of chimpanzees have also examined associations between $DupB^{-}$ and behavioral traits believed to be associated with autism. Hopkins et al. (2014) found that $DupB^{+/-}$ males scored higher than $DupB^{-/-}$ males on a receptive joint attention task—a measure that children with or at risk for ASD perform more poorly on than children who have had developmental delays (Dawson et al., 2002; Mundy, 2018; Mundy et al., 2007). Staes et al. (2015) found that $DupB^{+/+}$ males were significantly higher in "sociability"—a behaviorally-based personality dimension comprised of grooming others and receiving grooming from others—than $DupB^{+/-}$ and $DupB^{-/-}$ males; there was no evidence that $DupB^{+/-}$ and $DupB^{-/-}$ males differed. In the same study, Staes et al. (2015) found that that $DupB^{+/-}$ females were significantly higher in sociability than $DupB^{-/-}$ females and that, contrary to what one might expect from their results based on the male data, $DupB^{+/-}$ females were significantly *higher* than $DupB^{+/+}$ females; they found no significant difference between females who were $DupB^{+/+}$ and $DupB^{-/-}$. Another study (Anestis et al., 2014) found that chimpanzees who possessed the non-deletion allele were higher in a behaviorally based personality dimension ("smart"), which was characterized by prosocial behaviors, than chimpanzees who did not possess the allele. However, the association found was only significant in a model that did not include other covariates, and not in an adjusted model that displayed the best balance of model fit and parsimony. Finally, two studies of chimpanzees, one involving videos designed to provoke anxiety (Latzman et al., 2016) and another involving a mirror self-recognition task (Mahovetz et al., 2016) found that males with the $DupB^{+/-}$ genotype engaged in more self-scratching behavior than males with the $DupB^{-/-}$ genotype and females with either genotype.

These findings have been corroborated by studies of chimpanzee personality in which personality was measured using ratings. $DupB^{+/-}$ males were significantly higher in Dominance and lower in Conscientiousness than $DupB^{+/-}$ females; $DupB^{-/-}$ males and females did not differ significantly in these personality dimensions (Hopkins et al., 2012). A further study of this population found that, among $DupB^{-/-}$ chimpanzees, males scored significantly higher than females on a higher-order personality dimension related to Dominance and low Conscientiousness (Latzman et al., 2014). This study also found that, among $DupB^{+/-}$ chimpanzees, males scored significantly higher than females on a higher-order

personality dimension related to low Conscientiousness and low Agreeableness. Adding to this evidence, a rating-based study of another population found that chimpanzees that possessed the long form of the allele (Dup $B^{+/-}$ and Dup $B^{+/+}$) were significantly higher on Conscientiousness, but only in an unadjusted model, and lower on Extraversion, but only in the fully adjusted model that included sex and sex × genotype, than Dup $B^{-/-}$ chimpanzees (Wilson et al., 2017).

To enhance the translational value of neurogenomic investigations of social behavior in nonhuman primates to ASD, scientists have recently adapted an instrument to assess an autistic trait, social responsiveness, in neurotypical populations, for use in nonhuman primates, including chimpanzees and rhesus monkeys (Faughn et al., 2015; Feczko et al., 2016; Marrus et al., 2011). Building on this approach, Wilson and Weiss (2015) devised a scoring algorithm for a personality inventory deployed across several large samples of nonhuman primates to assess autistic traits. The resulting scale included traits, such as "solitary," "unperceptive," and "individualistic," that were positively weighted, and traits, such as "predictable," "playful," and "unemotional," that were weighted negatively.

For the present study, we built upon the previous work that showed an association between phenotypes related to autism and *AVPR1A* genotype by testing for associations between this genotype and scores on Wilson and Weiss's scale. We also tested for a possible association between early rearing and the gene × rearing interaction. We expected that adverse rearing and the DupB deletion would be independently associated with higher scores, that is, a significant, positive interaction between these effects.

Our interest in the latter two questions, and our predictions, were based on earlier work including reports, consistent with those in rodents and monkeys (Bodden et al., 2017; Brett et al., 2015; French & Carp, 2016; Latham & Mason, 2008), that adverse early rearing is associated with later social behavior, stereotypies, and brain structure in chimpanzees (Bard & Hopkins, 2018; Bogart et al., 2014; Clay et al., 2018; Davenport et al., 1973; Davenport & Rogers, 1970; Latzman, Hecht, et al., 2015; Morimura & Mori, 2010; Turner et al., 1969), and work showing that early rearing interacts with genes to influence behavior in rhesus monkeys (Barr et al., 2004; Bennett et al., 2002; Newman et al., 2005).

METHOD

Subjects

The subjects were 121 (75 females and 46 males) chimpanzees with data on all the variables. The age in years of all subjects ranged from 1.9 to 44.4 (mean = 19.1, SD = 11.4). Age in years ranged from 1.9 to 44.4 (mean = 20.5, SD = 12.8) in females and from 4.6 to 39.0 (mean = 16.8, SD = 8.4) in males. All subjects were drawn from a larger sample of 180 chimpanzees housed at the Yerkes National Primate Research Center of Emory University. Chimpanzees from the larger sample served as subjects in other studies of the *AVPR1A* genotype (Donaldson et al., 2008; Hopkins et al., 2012; Hopkins et al., 2014; Latzman et al., 2014; Latzman et al., 2016; Latzman, Freeman, et al., 2015; Mahovetz et al., 2016; Mulholland et al., 2020).

The subjects had varying backgrounds. Forty-eight subjects (34 females and 14 males) were reared by their mothers. The mother-reared subjects were not separated from their mother for at least 2.5 years of life and were raised in nuclear family groups ranging from 4 to 20 individuals. Fifty-four subjects (25 females and 29 males) were reared by humans. The human-reared subjects were separated from their mothers—usually in response to unresponsive care, injury, or illness—within the first 30 days of life (Bard, 1994; Bard et al., 1992). Human-reared subjects were placed in incubators, fed standard human infant formula (non-supplemented), and cared for by humans until they could sufficiently care for themselves, at which time they were placed with other infants of the same age until they were 3 years old (Bard, 1994; Bard et al., 1992). At 3 years of age, human-reared chimpanzees were integrated into larger social groups of adult and sub-adult chimpanzees. These larger social groups ranged from 2 to 16 individuals and there was always an effort made to integrate nursery-reared individuals with those who were mother-reared and wild-caught. Thus, any given group could have a mixture of wild-caught, mother-reared, and human-reared chimpanzees. Finally, 19 subjects (16 females and 3 males) were wild-caught. Wild-caught chimpanzees had been captured in the wild and subsequently brought to research facilities within the United States before 1974, when the importation of chimpanzees was banned.

Ratings

We used ratings to measure traits related to autism. There were 14 raters who were research assistants with more than 3 years of experience working with and observing each subject, naive to the hypotheses of this study, and blind to the subjects' genotypes. Sixty subjects were rated by one rater and 61 subjects were rated by two raters. Of the 117 subjects for whom we had raw rating data,[1] and so knew who rated them, each rater rated between 1 and 40[2] individuals (mean = 10.1, SD = 13.1).

Although previous studies of *AVPR1A* in chimpanzees housed at Yerkes National Primate Research Center

[1]Only aggregate ratings could be located for four of the chimpanzees.
[2]Only one rater (the third author) rated 40 chimpanzees.

relied on measures derived from the same questionnaire used in the present study (Hopkins et al., 2012; Latzman et al., 2014; Latzman, Freeman, et al., 2015), the scales or domains investigated in those studies were derived from an exploratory factor analysis (Weiss et al., 2007). The scale used in the present study was derived using a different approach, which was described by Wilson and Weiss (2015). In their study, Wilson and Weiss asked six experts with between 3 and 10 years of experience working with autism, and who came from positions of care, education, or academia, to indicate for each of the 54 items on the Hominoid Personality Questionnaire[3] (Weiss, 2017; Weiss et al., 2009) whether the item was associated with autism (+1), neurotypicality (−1), or neither (0). Wilson and Weiss computed the mean of the six judgments for each of the 54 items. They then used these means as weights with which to compute an "autism score" for a sample of 176 chimpanzees from facilities other than Yerkes National Primate Research Center. They found that these scores were normally distributed and the interrater reliability of individual ratings as indicated by Shrout and Fleiss's (1979) *ICC*(3,1) was 0.35.

The chimpanzees in the present study were rated on the Chimpanzee Personality Questionnaire (King & Figueredo, 1997), an earlier version of what was to become the Hominoid Personality Questionnaire (Weiss et al., 2009). The Chimpanzee Personality Questionnaire consists of 43 items, which are included in the Hominoid Personality Questionnaire (see Weiss, 2017 for a history of these questionnaires). Each item consists of a personality descriptive adjective and one to three sentences (King & Figueredo, 1997). These sentences serve to clarify the meaning of the item by providing a behavioral description. For example, the clarifying sentence for the item fearful was "Subject reacts excessively to real or imagined threats by displaying behaviors such as screaming, grimacing, running away or other signs of anxiety or distress." Raters were instructed to not discuss their ratings with others and to answer each question using a seven-point scale with a 1 indicating *Displays either total absence or negligible amounts of the trait* and a 7 indicating *Displays extremely large amounts of the trait*.

For the present study, except for "disorganized," which we assigned a weight of zero because this item's reliability was below 0 in this sample (Weiss et al., 2007), we used the weights derived by Wilson and Weiss to compute scores on the autism scale (see Table 1). This involved, for each subject, multiplying the rating on the items by the weight and then summing these values. Consistent with (Wilson and Weiss 2015), the distribution of the scale's scores in our sample was normal. The interrater reliability (Shrout & Fleiss, 1979) of individual ratings, that is, *ICC*(3,1), based on the 57 chimpanzees that had been rated twice and for whom we had raw data, was 0.27, and so was comparable to that reported by Wilson and Weiss (2015) and to studies of personality traits in humans (Connelly & Ones, 2010). The *ICC*(3,*k*) for this scale, for these subjects, was 0.42. This reliability coefficient indicates how reliable the mean score across raters is (Shrout & Fleiss, 1979) and so is relevant for our subsequent analyses.

[3]The Hominoid Personality Questionnaire can be downloaded at https://extras.springer.com/2011/978-1-4614-0176-6.zip.

Genotyping

The methods and primers used for genotyping the chimpanzees for the V1a receptor gene *AVPR1A* have been described in detail in previous publications (Donaldson et al., 2008; Hopkins et al., 2012).

Analyses

We conducted our analyses using R (R Core Team, 2019). The dependent variable was the autism score, which for subjects rated twice was the mean score across raters. Independent variables included sex, age, rearing, and *AVPR1A* genotype. We standardized the dependent variable and the continuous age variable so that each had a mean of 0 and *SD* of 1, and coded sex as equal to 0 for females and 1 for males. For rearing, we assigned a value of 1 if the subject was nursery reared and a value of −1 if the subject was mother-reared or wild-caught and reared presumably by its mother. For genotype, we assigned a value of 1 if the individual had the $DupB^{-/-}$ genotype and a value of −1 if the individual had the $DupB^{+/-}$ genotype.

To test for the effects of rearing, genotype, and their interaction, we fitted animal models, which can accommodate pedigrees with incomplete information and animals that do not have phenotype data (Kruuk, 2004). In addition, for our purposes it was important to fit animal models because, by doing so, we were able to determine the heritability of our phenotype (the scale score) and ensure that the association between the phenotype and genotype was not confounded by relatedness.

We fitted two models using Hadfield's (2010) MCMCglmm package. The first model tested for the fixed effects of sex, age, rearing, and genotype. The second model tested for these fixed effects and for the rearing × genotype interaction. Both models included subject identity, which was fitted as a random effect conditioned upon a relatedness matrix. The relatedness matrix was based on the subjects' pedigree and was generated by MCMCglmm. The pedigree spanned seven generations and consisted of 121 subjects and 487 other chimpanzees. Both sire and dam were known for 96 subjects, the sire but not the dam was unknown for 6 subjects, and both the sire and the dam were unknown for the 19 wild-caught subjects. We computed the degree of relatedness among all possible 7260 pairs of subjects for

TABLE 1 Items' judged relationships to autism

Item	Judge						Weight
	A	B	C	D	E	F	
Fearful	0	−1	1	1	1	1	0.5
Dominant	−1	−1	1	−1	1	−1	$-0.\overline{3}$
Persistent	1	−1	1	1	1	1	$0.\overline{6}$
Cautious	1	0	−1	0	−1	1	0.0
Stable	0	0	−1	0	−1	−1	−0.5
Autistic	−1	−1	1	1	1	1	$0.\overline{3}$
Curious	1	1	−1	1	0	−1	$0.1\overline{6}$
Thoughtless	0	0	0	1	0	0	$0.1\overline{6}$
Stingy/greedy	−1	−1	1	0	1	1	$0.1\overline{6}$
Jealous	0	−1	0	−1	0	1	$-0.1\overline{6}$
Individualistic	1	1	1	0	missing	1	0.8
Reckless	1	−1	1	1	1	0	0.5
Sociable	0	0	−1	−1	−1	−1	$-0.\overline{6}$
Distractible	1	−1	1	0	1	0	$0.\overline{3}$
Timid	0	−1	1	0	1	0	$0.1\overline{6}$
Sympathetic	1	0	−1	−1	0	−1	$-0.\overline{3}$
Playful	0	1	1	−1	0	0	$0.1\overline{6}$
Solitary	1	−1	1	1	1	1	$0.\overline{6}$
Vulnerable	0	−1	1	0	1	0	$0.1\overline{6}$
Innovative	1	1	−1	0	−1	0	0.0
Active	0	1	1	0	1	0	0.5
Helpful	1	0	−1	0	−1	0	$-0.1\overline{6}$
Bullying	0	−1	0	0	0	0	$-0.1\overline{6}$
Aggressive	−1	−1	1	0	0	1	0.0
Manipulative	0	0	−1	−1	0	−1	−0.5
Gentle	1	0	−1	0	0	−1	$-0.1\overline{6}$
Affectionate	1	0	−1	−1	0	−1	$-0.\overline{3}$
Excitable	1	1	1	0	1	1	$0.8\overline{3}$
Impulsive	1	−1	1	0	1	1	0.5
Inquisitive	1	1	−1	0	0	0	$0.1\overline{6}$
Submissive	0	0	−1	1	0	0	0.0
Cool	−1	0	−1	1	0	0	$-0.1\overline{6}$
Dependent/follower	−1	0	1	0	1	−1	0.0
Irritable	−1	0	1	0	1	1	$0.\overline{3}$
Unperceptive	1	−1	1	1	1	1	$0.\overline{6}$
Predictable	0	0	1	1	−1	1	$0.\overline{3}$
Decisive	0	1	1	0	0	1	0.5
Depressed	−1	−1	1	0	1	1	$0.1\overline{6}$
Conventional	1	0	−1	−1	1	0	0.0
Sensitive	−1	0	−1	−1	1	−1	−0.5
Defiant	−1	−1	1	0	0	1	0.0
Intelligent	1	1	−1	0	−1	−1	$-0.1\overline{6}$
Protective	1	0	−1	−1	0	−1	$-0.\overline{3}$
Quitting	1	−1	−1	0	−1	0	$-0.\overline{3}$
Inventive	0	0	1	−1	−1	0	$-0.1\overline{6}$

(Continues)

TABLE 1 (Continued)

Item	Judge						Weight
	A	B	C	D	E	F	
Clumsy	1	0	−1	1	1	1	0.5
Erratic	−1	−1	1	0	−1	0	$-0.\overline{3}$
Friendly	1	0	−1	0	−1	−1	$-0.\overline{3}$
Anxious	0	−1	1	0	1	1	$0.\overline{3}$
Lazy	0	0	1	0	1	0	$0.\overline{3}$
Disorganized	0	−1	0	−1	1	0	$-0.1\overline{6}$
Unemotional	0	0	−1	0	−1	0	$-0.\overline{3}$
Imitative	1	0	1	−1	1	1	0.5
Independent	1	1	−1	0	0	1	$0.\overline{3}$

Note: Items presented in the order in which they appear in the Hominoid Personality Questionnaire. The 11 items in italics are present in the Hominoid Personality Questionnaire, but not the Chimpanzee Personality Questionnaire. Disorganized, while present in the Chimpanzee Personality Questionnaire, was assigned a weight of 0 in the present study. The mean weight for the item with a missing judgment (individualistic) was based on the five responses.

whom we have phenotype data (see Table 2) using the CalcRped function from the sequoia package (Huisman, 2017).

MCMCglmm uses Markov Chain Monte Carlo estimation to determine the fixed and random effects parameters of a posterior distribution; for the prior of variance components, it uses an inverse-Gamma distribution (Hadfield, 2010). For our analyses, we specified priors because our sample size is relatively small. Our priors were based on the observation across studies that personality traits in humans (Dochtermann et al., 2015) and animals (Dochtermann et al., 2015) are ~40% and 50% heritable, respectively. We, therefore, specified priors with a belief parameter (ν) equal to 0.75 and a covariance matrix (**V**) equal to 0.5 for both the genetic and residual variances. We ran the models for 50,000,000 iterations, had a burn-in period of 10,000,000, and thinned samples from the posterior to 4000.

Ethics statement

The present study complied with the American Psychological Association's (2012) Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research and complied with the Institute of Medicine guidelines for research with chimpanzees. Approval was granted by Emory University Institutional Care and Use Committee (YER-2002189-012916GA).

RESULTS

An R object that can be used to generate the trace and density plots for the parameter estimates in our models is available in supplementary materials. Inspection of the trace plots revealed no evidence of autocorrelations. Inspection of the density plots revealed that the parameter estimates were normally distributed.

The Deviance Information Criterion for the model that did not include the rearing × genotype interaction was only slightly smaller than that of the model with the interaction term (0.361), suggesting that, although it had a better balance of model fit, and model parsimony, that there was no strong reason to it over the model with the interaction term. The parameter estimates for the model that only estimated main effects are presented in the left panel of Table 3. In Model 1, the heritability of autism scale scores and the 95% credible interval (*CI*) of this estimate was 0.28 (95% CI = 0.04 to 0.56). Moreover, males, older subjects, subjects that possessed the $DupB^{-/-}$ genotype, and subjects reared by humans were rated as higher on the autism scale; rearing was the only effect with a 95% credible interval that did not include zero. The parameter estimates from the model that included rearing × genotype were similar to those from the model without the interaction term (see the right panel of Table 3). The heritability of autism scale scores in that model was 0.25 (95% CI = 0.05 to 0.51). Of the main effects, males, older subjects, subjects that possessed the $DupB^{-/-}$ genotype, and subjects reared by humans were rated as higher on the autism scale; rearing was the only effect with a 95% credible interval that did not include zero. The parameter estimate for the interaction term was negative, suggesting that subjects reared by humans who had the $DupB^{-/-}$ genotype had lower scores on the autistic scale than nursery reared subjects who had the $DupB^{+/-}$. The 95% credible interval for the interaction term did not include zero.

DISCUSSION

Approximately one-quarter of the variance in autism scale scores was attributable to additive genetic differences between individuals. Although, subjects with the $DupB^{-/-}$ genotype were approximately one-fifth of a *SD* higher on the autism scale than subjects with the $DupB^{+/-}$ genotype, the credible interval for this

TABLE 2 Degrees of relatedness among all possible pairs of 121 phenotyped subjects

Coefficient of relatedness	*n*
0	5513
0.00390625	9
0.0078125	47
0.01171875	32
0.015625	114
0.01953125	9
0.0234375	53
0.02734375	12
0.03125	158
0.033203125	6
0.0390625	36
0.046875	38
0.0546875	22
0.0625	183
0.06640625	8
0.0703125	13
0.07421875	2
0.078125	35
0.08203125	2
0.0859375	1
0.09375	29
0.109375	14
0.125	344
0.1328125	15
0.13671875	2
0.140625	18
0.14453125	1
0.1484375	3
0.15625	20
0.1640625	3
0.1875	26
0.1953125	2
0.21875	2
0.25	345
0.25390625	1
0.2578125	1
0.26171875	2
0.265625	4
0.28125	6
0.3046875	1
0.3125	8
0.375	12
0.3828125	2
0.5	101
0.5078125	2
0.515625	3

Note: Mean relatedness among pairs was 0.03 ($SD = 0.09$). Mean relatedness among pairs excluding the 5513 that were unrelated was 0.14 ($SD = 0.13$).

difference included zero. The credible interval for the effect of rearing, however, did not include zero: compared with subjects reared by their mothers or subjects who were wild-caught, human-reared subjects were approximately one-third of a *SD* higher in the autism scale score. The credible interval for the interaction term did not include zero, but its direction was opposite to what we expected it would be and the model that included the interaction performed slightly more poorly than the model that excluded it.

Our findings are consistent with data that has demonstrated that early adverse rearing, broadly defined, can have a negative impact on species-typical behavioral development in nonhuman primates (Bodden et al., 2017; Brett et al., 2015; French & Carp, 2016). For example, socially deprived rhesus monkeys displayed inappropriate aggression towards conspecifics (Mitchell et al., 1966) and did not display appropriate maternal care when they reached sexual maturity (Ruppenthal et al., 1976). Later experimental studies of macaques yielded similar findings. For example, 3- to 4-day-old mother-reared rhesus macaque infants exhibited increased lip-smacking toward an experimenter compared with their nursery-reared counterparts (Vanderwert et al., 2015).

Observational studies of chimpanzees have also revealed social detriments in individuals that were reared without their mothers (Davenport & Rogers, 1970). Among former laboratory chimpanzees, for instance, males deprived of biological maternal care early in life exhibited lower levels of affiliative behavior and dominance than males who had been deprived of maternal care later in life (Reimers et al., 2007). Likewise, chimpanzees who were separated from their mothers at less than 2 years old exhibited higher levels of abnormal behavior than those who were separated from their mothers after they turned three (Kalcher-Sommersguter et al., 2015).

The present study builds on these studies, those noted in our introduction, and studies on the effects of atypical rearing on personality (Freeman et al., 2016). In short, it demonstrates that adverse early rearing in chimpanzees is associated with being higher in traits associated with autism, and that these results hold even when controlling for relatedness.

This study is not without limitations. In particular, because the human-reared chimpanzees were a 'self-selected' sample (Bard, 1994; Bard et al., 1992; Losh et al., 2009) and not randomly assigned to their rearing group, such as in experiments reported by Davenport and Rogers (1970), we cannot yet rule out the possibility of reverse causation. To do so will require determining whether these autism-related phenotypes and/or other, related traits, manifest early in life, that is, before human-rearing takes place, or identifying reasons why mothers reject some of their infants.

Another possible limitation is that the level of inter-rater reliability of the measure or missing pedigree

TABLE 3 Parameters from multivariate generalized mixed models

Effect	Model 1					Model 2				
	Mean of posterior distribution	$l_{95\%}$	$u_{95\%}$	$n_{effective}$	*p*MCMC	Mean of posterior distribution	$l_{95\%}$	$u_{95\%}$	$n_{effective}$	*p*MCMC
Fixed effects										
Intercept	−0.10	−0.380	0.179	10000.000	0.4744	−0.09	−0.355	0.180	10000.000	0.4910
Male sex	0.21	−0.181	0.563	9683.675	0.2812	0.15	−0.220	0.512	10000.000	0.4222
Age	0.10	−0.074	0.275	9714.498	0.2454	0.09	−0.079	0.267	10000.000	0.2730
Genotype	0.18	−0.003	0.365	10000.000	0.0570	0.18	−0.004	0.354	9698.145	0.0564
Rearing	0.31	0.123	0.511	9701.972	0.0024	0.37	0.173	0.562	10000.000	0.0004
Genotype × Rearing	—	—	—	—	—	−0.18	−0.352	−0.001	10000.000	0.0490
Random effects										
Animal ID	0.26	0.042	0.561	9549.550		0.22	0.036	0.488	10000.000	
Residual	0.65	0.377	0.960	10000.000		0.66	0.400	0.934	9595.940	

Note: The Deviance Information Criteria for Models 1 and 2 were 320.1973 and 320.5581, respectively. $l_{95\%}$ and $u_{95\%}$ indicate the lower and upper bounds of the 95% credible interval, respectively. $n_{effective}$ = effective sample size. Reference categories for sex, genotype, and rearing are females, dup$B^{+/-}$, and wild-caught/mother-reared, respectively.

information, including whether the founders were related, may have biased the heritability estimates. To address these limitations in future research, efforts should be made to determine relatedness using genomic data (Stanton-Geddes et al., 2013) and by combining measures of autistic traits that differ in how they were collected (Campbell & Fiske, 1959; Riemann & Kandler, 2010).

Despite these limitations, this study demonstrates the potential translational value of a scale used to assess autistic-like traits in chimpanzees. It also shows the versatility of broad personality questionnaires that assess large numbers of traits in nonhuman primates in that these questionnaires can be leveraged to assess autism phenotypes in chimpanzees and probably in other primates, including humans.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Study concept and design: Alexander Weiss, Vanessa A. D. Wilson, and William D. Hopkins. *Statistical analyses*: Alexander Weiss. *Interpretation of results*: Alexander Weiss, Vanessa A. D. Wilson, and William D. Hopkins. *Drafting of and critical revision of the manuscript for important intellectual content*: Alexander Weiss, Vanessa A. D. Wilson, and William D. Hopkins. *Obtained funding*: William D. Hopkins. Study supervision: William D. Hopkins

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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