Oxytocin receptor gene polymorphism (rs53576) and digit ratio associates with aggression: comparison in seven ethnic groups

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Abstract

Background: The specific role of the oxytocin receptor (OXTR) gene polymorphisms in emotional support seeking, related to social norms and culturally normative behavior, has been discussed in several studies. Evidence on the association between aggression and OXTR polymorphisms has also been reported. The goal of the current study was to analyze the effect of the OXTR rs53576 polymorphism, prenatal testosterone effect (second-to-fourth digit ratio, or 2D:4D), and culture on aggression assessed with the Buss-Perry Aggression Questionnaire (BPAQ).

Methods: The data were collected in Russia and Tanzania and included seven ethnic groups of European, Asian, and African origin. The total sample included 1705 adults (837 males, 868 females). All the subjects were evaluated with the BPAQ. As a measure of prenatal androgenization, the second and fourth digits were measured directly from hand, and the digit ratios were calculated. All the participants provided buccal samples, from which genomic DNA was extracted, and the OXTR gene rs53576 polymorphism was genotyped. Statistical analysis was performed using SPSS version 23.0; the alpha level for all analyses was set at 0.05.

Results: The ethnic group factor was the most significant predictor of ratings on BPAQ (medium effect size for physical aggression, anger and hostility scales, and low for verbal aggression). To study the effect of sex, the OXTR polymorphism, and prenatal androgenization, we conducted the z-score transformation for BPAQ scales and 2D:4D for each ethnic group and pooled these data into new z-score variables. According to the GLM analysis after leveling the effects of culture (z-transformation), all four scales of BPAQ demonstrated association with sex (main effects), with men scoring higher on physical and verbal aggression and women scoring higher on anger and hostility. Anger and hostility scales were also associated with OXTR polymorphism and 2D:4D of the right hand. The lowest levels of anger and hostility were observed in individuals with the AA genotype, especially in men.

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Conclusions: Our data suggest that both oxytocin (OXTR gene polymorphism) and fetal testosterone (2D:4D) may significantly affect emotional (anger) and cognitive (hostility) aggression in humans, given the leveling the role of culture.

Keywords: OXTR rs53576, Digit ratio, 2D:4D, Buss-Perry Aggression Questionnaire, Ethnic groups, Men, Women, Europeans, Asians, Africans

Background
As the capacity to form social bonds and parental behavior, general sociality is a cornerstone of human society, deeply rooted in human evolution [1, 2]. The way how prosocial behavior develops through interactions between culturally varying norms, social cognition, emotions, and, potentially, genes, is at the center of attention for numerous theoretical and empirical studies [3]. Through social norms, humans are intrinsically motivated to enforce rules of social co-existence and cooperation, as well as rules of punishment in the direction of those who do not behave prosocially [4], and do not punish violators [5]. Strong tendency to follow and enforce social norms in our species turns these norms into a powerful tool for enforcing cooperation at a large scale [6]. “Culturally constructed environments create powerful – and often autocatalytic – selection pressures on genes” [7]. Currently accumulated data suggest that human culture has impacted the modern human genome and its variation [8, 9].

It may be useful to keep in mind this perspective while discussing the gene-environmental interactions in the expression of human aggression. Human aggression is multi-dimensional and may be expressed physically, verbally, emotionally (e.g., anger), or cognitively (e.g., impulsivity, hostility) [10]. There are multiple risk factors that directly or indirectly influence aggression, including age, sex, genetics, and psychopathological and environmental factors [11, 12]. Men are exhibiting more violent (physical) same-sex aggression than women in most cultures [13–17], which may be attributed to the higher impulsiveness of men and a stronger fear of physical danger in women. On the other hand, the critical finding in this respect is that cultural and religious norms affect the personal potential for aggressive behavior, regulating physical or verbal expression, reducing or reinforcing their level, and regulating emotional and cognitive potential.

The role of oxytocin in human social integration, as well as aggression, deviant, and antisocial behavior, has been at the focus of attention during recent years. Oxytocin neuropeptide, produced by the hypothalamus and secreted by the pituitary gland, has been frequently mentioned as an essential regulator of mother-child attachment, social affiliation, and social bonding [18, 19]. Oxytocin’s secretion decreases anxiety and protects against stress [18], increases empathy and trust [20, 21], and positively affects generosity in the context of perspective-taking [22]. Some authors also report on its role in group-serving dishonesty/deception, by promoting dishonesty when the outcome favored the group to which an individual belonged [23]. Oxytocin produces its effects through oxytocin receptor (OXTR) [24], which is present both in the brain and other body tissues and is involved in the development of the social brain [25]. Since the discovery of the OXTR gene structure [26], numerous studies have focused on the association between OXTR gene polymorphisms and different aspects of human physiology and behavior. The genetic variation of the OXTR affects the influence of deviant peer affiliation on antisocial behavior and is associated with proactive aggression, but not with reactive aggression [27]. Variation in the OXTR gene is commonly assessed through single nucleotide polymorphisms (SNPs). The interaction effect of the two OXTR SNPs, rs1488467 and rs4564970, with alcohol consumption on trait anger was reported for the Finnish sample of men and women [28]. The A allele at rs53576 of the OXTR gene was associated with prior suicide attempts, and neither abuse history nor attachment style moderated this relationship [29]. Data on Chinese Han adolescent highlight the compound effect of stressful life events on aggression and provided evidence of the relationship between the oxytocin system and aggressive behavior [30]. High life stress during the past 12 months was associated with high levels of physical aggression and hostility in OXTR rs53576 AA carriers, but not in G carrier boys, but this association was not significant for girls. The relevance of OXTR rs237885 to aggression was also demonstrated. Mainly, rs237885 TT carriers with a history of childhood abuse had a higher risk of aggression [31]. The specific role of OXTR gene polymorphisms in emotional support seeking, related to social norms and culturally normative behavior, has been discussed in several studies [32–37], with OXTR rs53576 being one of the main focuses of attention. OXTR rs53576 has been related to attachment security and marital satisfaction, and GG carriers rated higher compared A carriers [38]. Li and colleagues reported a positive association between the rs53576 polymorphism and general sociality and concluded that the
G allele homozygotes had higher general sociality than the A allele carriers [39]. Kim and colleagues [32] found that emotional support seeking was more evident in distressed North Americans having the G allele at the OXTR rs53576 than in those with the AA genotype, but not in Koreans, whose emotional support seeking is not a culturally normative behavior. Later, the same authors reported that Koreans with the GG genotype were more likely to use emotional suppression than those with the AA genotype and hesitated to seek emotional support in response to stress, which is more in line with normative behavior in Korea [32]. Individuals carrying the G allele of the OXTR rs53576 appeared to be more sensitive to the cultural environment [37]. The general conclusion might be that certain people regulate emotions according to cultural norms because they are biologically susceptible to be sensitive to the socio-emotional cues in a culture [36]. However, the only previous cross-sectional study, analyzing the association between rs53576 and a wide variety of emotional traits and states in a sample of young adults of various ethnicities (European, Asian, Maori/Pacific Islander, others), did not find any significant associations [40].

Another focus of the current study is the impact of prenatal androgen exposure on the aggressive behavior and its possible association with OXTR effects. Digit ratio (2D:4D), as a possible proxy to fetal androgenization, has been discussed in numerous studies [41–44]. Sexual dimorphism of the digit ratios is found across the majority of species starting from amphibians [45, 46], although it is not unidirectional in all species [47, 48]. In humans, 2D:4D is also known to be sexually dimorphic, with males having lower ratios than females in the majority of studied populations [15, 16, 49–51] (although see [52–54] for criticism). For today, the direct evidence on the association between digit ratios and prenatal androgen concentrations in humans is still quite scarce and somewhat contradictory [55–57]. However, a part of the mechanisms underlying the impact of prenatal androgen/estrogen exposure on the formation of differences in the 2nd and 4th finger lengths has been revealed in mice [58]. The genetic basis linking gonads’ and digits’ development has also been investigated during recent years [59–61]. It is well-known that in men, testosterone concentrations have two peaks during the lifespan: (1) in the period of early prenatal development (peak at ~ 24th week of gestation) [62] and (2) in puberty. The fetal and postnatal Leydig cells, which are responsible for testosterone production during prenatal and pubertal periods respectively, most likely represent morphologically and functionally different cell generations with different origins [63, 64]. This is also supported by a well-known lack of association between the 2D:4D ratio and adult testosterone levels in humans [65–67]. The latter suggests an existence of a relatively independent path for basic masculinization through exposure to androgens in utero. The period of the prenatal testosterone peak takes place at the time of the early brain maturation, which may play an important role in the formation of the sexual dimorphism of human brain structures [68–71] and concomitant behavior. Of particular interest, within the scope of the current study, are findings on associations between the digit ratio and personality traits [72], including aggression at various stages of life history [73–77], risk-taking [78–81], higher physical aggression in adult men, but not women [73, 82], as well as adolescent boys but not girls [15, 17]. Data from various studies pointed on the mutual influence of oxytocin and testosterone systems on the development of social cognition in humans [83]. In experiments with oxytocin administration versus placebo, conducted on men, individuals with a higher digit ratio (low fetal testosterone) preferred to include low-threat, rather than high-threat targets, into their groups [84]. On the contrary, men with high testosterone exposure in the uterus, after intranasal oxytocin treatment, preferred to select high-threat targets more than controls. According to other studies [85], the administration of oxytocin increased plasma testosterone in young men. Many studies currently are taking efforts to reveal the magnitude of environmental and genetic effects on aggression [86–93], as well as antisocial behavior [94].

It seems clear that genes may shape psychological predispositions, but also that culture might influence how these predispositions are behaviorally manifested, and culture provides particular contexts that afford opportunities and constraints for the development of psychological tendencies by presenting cultural, social norms, and limitations [34, 75, 89, 95]. Given that genes and culture may interact to produce different outcomes, we tested the three-way interaction of genes, culture, and sex in predicting direct aggression, such as physical and verbal aggression; aggressive emotional feelings, such as anger; and cognitive component, such as hostility. To this aim, we investigated the association between culture (ethnic group, religion), sex, OXTR gene SNP rs53576, digit ratio, and self-ratings on aggression assessed with the Buss-Perry Aggression Questionnaire (BPAQ) [10].

The following hypotheses were tested: (1) self-ratings on aggression in men and women are significantly influenced by cultural norms and prescriptions (socialization); (2) the OXTR rs53576 polymorphism may cause differences in BPAQ self-ratings, especially in emotional dimension of aggressive manifestations; (3) the OXTR rs53576 effect on BPAQ ratings is sex-specific; and (4) the digit ratio associations with self-ratings on BPAQ may be different in A-carriers, compared to GG OXTR rs53576 genotypes.
Methods
Participants and procedure
The sample included 1705 adults from seven ethnic groups of European, Asian, and African origin. Four ethnic groups were from Russia (Russians [89], Tatars [75], O–Ugric [96, 97], and Buryats [75, 98]) with the mean age of 21 years. These samples were collected between 2010 and 2019. Three ethnic groups were sampled from Tanzania between 2006 and 2014 (Hadza [16, 74, 87–89, 97, 99–102], Datoga [16, 88, 89, 97, 99–103], and Isanzu), with a mean age of 36 years. These groups are representatives of traditional African cultures. More information about these cultures may be found elsewhere [15, 16, 74, 87–89, 96–105].

All the Russian participants gave written informed consents, while in Tanzania, as most of the participants were illiterate there, the oral informed consents were provided, following the Declaration of Helsinki. The study was approved by the Institute of Ethnology and Anthropology of the Russian Academy of Sciences (RAS) and the Commission for Science and Technology of Tanzania (COSTECH).

Laboratory methods
All the participants provided buccal samples. Genomic DNA was isolated using Diatech DNA Prep 200 (Isogen Lab, Moscow, Russia). DNA quality from all the samples was assessed by spectrophotometer readings (A260/280) using NanoDrop.

The polymorphism of the OXTR gene (rs53576) was genotyped using Taqman 5′ exorulase assay (Applied Biosystems). The probes for genotyping were ordered through the TaqMan SNP genotyping assays (ID: C___3290335_10) Applied Biosystems assay-on-demand service. The final volume was 5 μl, which contained 5 ng of genomic DNA, 2.5 μl of Taqman Master Mix, and 0.25 μl of 40 genotyping assays. Polymerase chain reaction plates were read on an ABI PRISM 7900HT instrument, and SDS v2.3 software (Applied Biosystems) was used for the genotype analysis of data.

All population statistical data processing was carried out using GenAIEx software v6.5 [106, 107]: genotype and allele frequencies, Hardy-Weinberg equilibrium (HWE) test, test of homogeneity, linkage disequilibrium test, estimations of heterozygosity, and fixation index (FST) and their significances.

Assessment of aggression
Self-reported aggression was assessed with the Buss-Perry Aggression Questionnaire (BPAQ) [10]. The BPAQ includes 29 statements, grouped into four scales—physical aggression (9 items), verbal aggression (5 items), anger (7 items), and hostility (8 items)—answered on a Likert scale anchored by 1 (extremely uncharacteristic of me) and 5 (extremely characteristic of me). The translation of the BPAQ into Russian and Swahili was done, following accepted standards (translations and back translations by four bilingual assistants [108, 109]), and translated versions have been already used in several previous studies [15–17, 74, 75, 78, 87–89, 96].

In Russia, all the participants filled out the forms by themselves. In Tanzania, almost all respondents were illiterate; thus, they were personally interviewed in Swahili by the first author or a trained local assistant. Consequently, for Tanzanian respondents, all questions were read aloud in one-to-one dialogs, and further explanations were provided, if necessary. In Tanzania, the local assistant provided examples of actions related to the trait common in the culture to ensure that participants understood the questions. Scores on individual scales and total BPAQ scores were calculated only for respondents who answered all items. Cronbach’s alpha for the total scores was 0.77 for the Russian sample, and 0.79 for the Tanzanian, and ranged between 0.60 and 0.70 for separate scales in both samples.

Anthropometrical assessment
The second and fourth digits of the participants were measured twice with a Vernier caliper, measuring to 0.01 mm, from the basal crease to the tip of the finger. Mean values of the two measurements were used to calculate the 2D:4D ratios. In this study, we provide the data on the right-hand digit ratio (R2D:4D), given the general information that the right-hand digit ratio usually is more sexually dimorphic compared to the left hand [110]. In the cases where there was a band of creases at the base of the digit, the most proximal crease was used [111]. Participants who reported injuries or deformities of the second or fourth digits were excluded from the statistical analysis. All measurements were done by experienced anthropologists.

The 2D:4D ratios were calculated following the procedure described earlier [112]. The repeated measures of the first and second digits for the whole sample gave an intra-class correlation of 0.94. Hence, it was assumed that the differences in between-individual measurements of the 2D:4D were significantly higher than the within-individual measurement error.

Statistical analyses
Mean and standard deviation (SD) for continuous variables was used to describe the sample’s characteristics. T-test was used to estimate the sex differences in ratings on BPAQ scales in each of the studied groups, as well as for estimating differences in aggression between AA and G-allele carriers. The main and interaction effects of ethnic group, sex, and OXTR genotypes on four scales of the BPAQ were calculated using multivariate analysis of
variance (MANOVA). Due to the contradictory results obtained in MAN(C)OVA, the effect of the OXTR gene rs53576 on the z-transformed self-ratings on the BPAQ scales was tested with one-way analysis of variance (ANOVA), followed by the use of the Dunnett’s T3 post hoc test [113, 114]. This approach allowed to solve the problems related to unequal sample sizes and unequal SDs and to test for differences among OXTR genotype groups separately in men and women. One-way ANOVA was used for analysis of the z-transformed scales of BPAQ for male and female samples to estimate the effect of OXTR genotypes. Univariate analysis of covariance (ANCOVA) was used to assess the impact of sex, digit ratio, and OXTR rs53576 on the BPAQ aggression scales after leveling the cultural effects. Linear regression was used to test the effects of the right-hand 2D:4D and rs53576 polymorphism on the BPAQ scales. Statistical analysis was performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The alpha level for all analyses was set at 0.05.

Results
Genotype distribution
The OXTR rs53576 genotype and allele frequencies are presented in Table 1. The genotype distributions by sex are presented in Fig. 1. As seen from Table 1, the frequencies of the alleles A and G are gradually changing from east of Asia (Buryats) to Europe (Russians and Tatars) and Africa. In the Asian populations, allele A prevails over allele G and vice versa in the rest of populations. Accordingly, genotypes AA and AG are prevailing in Buryats and Ob-Ugric people, while AG and GG genotypes in Russians, Tatars, and African populations. As χ² test was applied for HWE several times, the Benjamini-Hochberg approach was used, and the corrected level of significance (p < 0.05) was obtained, q = 0.007. Examining the individual p values justified HWE for all samples, including the Buryat sample, accepting its null hypothesis rejection as accidental.

Ethnic group, sex, OXTR genotype, and 2D:4D as predictors of aggression
Mean scores for physical aggression (PA), verbal aggression (VA), anger (AN), and hostility (HT), assessed with the BPAQ and the 2D:4D ratio in the seven ethnic

Table 1 Genotype and allele frequencies of the OXTR rs53576 and HWE in the samples studied

| Population | N   | Frequency | Genotype | Allele | HWE   |
|------------|-----|-----------|----------|--------|-------|
|            |     |           | AA AG GG | A G    |       |
| Buryats    | 172 | 0.407 0.372 0.221 | 0.593 0.407 | 9.030 0.003 |
| Ob Ugric   | 248 | 0.363 0.427 0.210 | 0.577 0.423 | 3.851 0.05 |
| Tatars     | 203 | 0.167 0.453 0.379 | 0.394 0.606 | 0.528 0.467 |
| Russians   | 218 | 0.083 0.431 0.486 | 0.298 0.702 | 0.226 0.634 |
| Hadza      | 317 | 0.129 0.539 0.331 | 0.399 0.601 | 4.930 0.05 |
| Datoga     | 345 | 0.072 0.475 0.452 | 0.310 0.690 | 4.243 0.05 |
| Isanzu     | 202 | 0.020 0.317 0.663 | 0.178 0.822 | 1.347 0.246 |

HWE: Hardy-Weinberg equilibrium

Fig. 1 Distributions of the OXTR rs53576 genotypes by sex in the seven studied populations. The steady increase in proportion of GG genotypes in tested populations from east (Asia) to west (Europe and Africa)
groups and by sex, are shown in Table 2. Sexual differences were found almost in all four aggression scales and for the 2D:4D ratio (Fig. 2).

The MANOVA two-way analysis with ratings on four aggression scales as dependent variables; the ethnic group factor was the most significant predictor (the medium effect sizes for physical aggression, anger and hostility scales, and low for verbal aggression). Post hoc Bonferroni tests revealed highly significant differences between seven tested groups on physical aggression, anger, and hostility (p ranges from 4.217E–25 to 0.001).

The main effect of sex was significant for all scales, however, with small effect sizes. The effect of OXTR rs53576 polymorphism on aggression was not significant under such conditions. However, we found that the interaction effect of ethnic group × OXTR was significant for the anger scale, and the OXTR × sex interaction for the hostility scale. In both of these cases, the effect sizes were small (Table 3). The interaction effect of ethnic group × sex was significant for all scales but verbal aggression (again, the effect sizes were small) (Table 3).

Given the prevailing impacts of the ethnic origin and sex on the studied aggression parameters, possible effects of the OXTR gene polymorphism on aggression could appear to be masked by such a strong population-specific and sex-specific effects. Hence, to reveal the possible impact of the OXTR on aggression independently of culture and sex, we have leveled the aggression measures for all studied ethnic groups and analyzed males and females separately. Leveling the population effects was achieved through the procedure of z-transformation of the BPAQ scales for each of the ethnic groups with subsequent pooling of these data into new z-transformed variables (z-BPAQ scales). They were later tested separately for males and females using one-way ANOVA with OXTR as an independent factor. In men, the ANOVA revealed a significant effect of OXTR genotypes on BPAQ anger ($F = 3.06, df1 = 2, df2 = 834, p = 0.047$) and hostility ($F = 3.68, df1 = 2, df2 = 834, p = 0.026$) scales. The post hoc Dunnett’s T3 test (for unequal variances) has revealed that the contrasting genotypes were AA and GG for the hostility scale only ($F = 3.096, df1 = 2, df2 = 865, p = 0.046$), but the differences were not significant according to the Dunnett T3 test. To sum up, the lowest levels of anger and hostility were observed in individuals with AA genotype of the OXTR rs53576 irrespective of their ethnic identity, and such association was especially pronounced in men (Fig. 3).

Some previous findings suggested the influence of the oxytocin and testosterone systems on shaping human

| Table 2 Descriptive statistics and sex differences in aggression scales (BPAQ) and right-hand 2D:4D ratio |
|-----------------|-----------------|-------------|-------------|--------|-----------|
| BPAQ scale      | Population      | N      | Men       | Women     | t     | p (sig.) |
| PA              | Buryats         | 172    | 28.4     | 6.1       | 21.0   | 5.3      | 4.339    | <0.001 |
| Ob-Ugric        | 248             | 23.9   | 6.5       | 21.0     | 5.8    | 3.494    | 0.001    |
| Tatars          | 203             | 21.3   | 4.5       | 15.6     | 4.1    | 9.440    | <0.001   |
| Russians        | 217             | 21.9   | 6.7       | 19.9     | 7.1    | 1.957    | 0.052    |
| Hadza           | 317             | 25.9   | 5.1       | 24.1     | 5.4    | 3.048    | 0.002    |
| Yagulans        | 248             | 28.7   | 5.2       | 28.0     | 6.0    | 1.246    | 0.214    |
| Isanzu          | 203             | 16.6   | 4.4       | 17.3     | 5.3    | 0.962    | 0.337    |
| VA              | Buryats         | 172    | 14.1     | 3.2       | 13.3   | 3.2      | 1.517    | 0.131    |
| Ob-Ugric        | 248             | 13.6   | 4.0       | 13.8     | 4.1    | 0.991    | 0.374    |
| Tatars          | 203             | 13.3   | 3.3       | 12.2     | 3.5    | 2.328    | 0.021    |
| Russians        | 217             | 16.7   | 4.2       | 15.4     | 3.5    | 2.393    | 0.018    |
| Datoga          | 317             | 15.8   | 4.1       | 14.7     | 4.2    | 2.727    | 0.024    |
| Dagestan        | 345             | 18.3   | 3.9       | 17.2     | 4.6    | 2.333    | 0.020    |
| Isanzu          | 203             | 13.1   | 3.5       | 13.5     | 4.3    | 0.778    | 0.438    |
| AN              | Buryats         | 172    | 15.5     | 4.3       | 18.1   | 4.8      | 3.749    | <0.001   |
| Ob-Ugric        | 248             | 15.3   | 5.5       | 16.3     | 5.4    | 1.223    | 0.223    |
| Tatars          | 203             | 11.5   | 3.3       | 11.5     | 3.7    | 0.991    | 0.374    |
| Russians        | 217             | 16.9   | 7.0       | 18.7     | 6.3    | 1.964    | 0.051    |
| Hadza           | 317             | 19.4   | 4.6       | 20.2     | 5.3    | 1.424    | 0.155    |
| Yagulans        | 248             | 23.1   | 4.2       | 22.3     | 4.6    | 1.721    | 0.086    |
| Isanzu          | 203             | 15.4   | 3.7       | 17.1     | 4.1    | 2.675    | 0.008    |
| HT              | Buryats         | 172    | 23.5     | 5.1       | 26.0   | 4.7      | 3.362    | <0.001   |
| Ob-Ugric        | 248             | 21.6   | 4.6       | 22.4     | 4.9    | 1.176    | 0.241    |
| Tatars          | 203             | 19.5   | 4.2       | 20.2     | 4.6    | 1.168    | 0.237    |
| Russians        | 217             | 23.5   | 5.3       | 25.1     | 5.8    | 1.945    | 0.053    |
| Hadza           | 317             | 23.2   | 6.0       | 22.7     | 6.3    | 0.699    | 0.485    |
| Datoga          | 345             | 29.0   | 5.3       | 28.6     | 6.3    | 0.686    | 0.493    |
| Isanzu          | 203             | 21.5   | 5.7       | 22.4     | 6.1    | 0.884    | 0.378    |
| R2D:4D          | Buryats         | 172    | 0.95     | 0.03      | 0.96    | 0.03     | 0.329    | 0.743    |
| Ob-Ugric        | 248             | 0.96   | 0.03      | 0.97     | 0.03   | 2.397    | 0.017    |
| Tatars          | 203             | 0.97   | 0.03      | 0.98     | 0.03   | 2.152    | 0.033    |
| Russians        | 217             | 0.97   | 0.03      | 1.00     | 0.03   | 5.132    | <0.001   |
| Hadza           | 317             | 0.97   | 0.04      | 0.98     | 0.04   | 2.365    | 0.019    |
| Datoga          | 345             | 0.96   | 0.04      | 0.97     | 0.04   | 4.075    | <0.001   |
| Isanzu          | 203             | 0.95   | 0.03      | 0.96     | 0.04   | 2.297    | 0.023    |

Sex differences presented according to Student’s T test (t—test statistics, p — statistical significance)
PA Physical aggression, VA Verbal aggression, AN Anger, HT Hostility, R2D:4D Digit ratio of the right hand
social cognition during early development and mutual contributions of these systems to hypo- or hyper-socio-cognitive manifestations [83]. Consequently, we tested the possible interplay between effects of the OXTR polymorphism and the right-hand 2D:4D ratio (as a proxy for prenatal androgenization) after leveling the population differences in aggression ratings and digit ratio (within-population z-score standardization) (Table 4). According to the ANCOVA analysis, and corresponding to what has been previously mentioned above (Table 3), all four scales of BPAQ demonstrated association with sex (main effects): men, in comparison with women, generally scored higher on physical and verbal aggression, whereas women scored higher on anger and hostility (sex differences are statistically significant in all cases; Fig. 4).

Physical and verbal aggression, however, were predicted only by sex, with no significant impacts of other predictors (OXTR (rs53576), R2D:4D²), and their interactions. However, the main effect of the R2D:4D ratio on anger was significant only at the level of trend, which occurred due to previously mentioned significant interaction effect between R2D:4D and OXTR gene polymorphism (Table 4). To see how these two factors interacted in determining the level of anger, we divided the general sample into three parts according to the type of the OXTR rs53576 (AA, AG, GG) and ran linear regression analysis within each type, setting anger (z-score) as a response variable, and R2D:4D (z-score) with sex as predictors.

According to the results of the regression analysis, significant association between anger and 2D:4D ratio of the right hand, when controlling for sex, occurred only in carriers of the AA genotype of the OXTR gene rs53576 ($N = 282$, beta = 0.190, $t = 3.232$, $p = 0.001$; model $R^2 = 0.051$), whereas for the G allele carriers, there were no significant associations. The partial regression plots with control for sex are presented in Fig. 5.

To sum up, these results demonstrate that OXTR rs53576 polymorphism is associated with emotional aggressive manifestations irrespective of individual's population background. G allele carriers of the OXTR were more predisposed to express anger and hostility than individuals with AA genotype, and this tendency was especially pronounced in men (Fig. 3). At the same time, low prenatal androgen levels (high 2D:4D ratio) also led to higher levels of anger and hostility in both sexes. This result fully corresponds to the sex differences in BPAQ subscales' ratings, which demonstrate that high levels of anger and hostility are female-specific (Fig. 4). However, the OXTR effects on aggression even overweighed those of the prenatal androgens exposure (2D:4D) effects. We
came to this conclusion, since the 2D:4D effects were evident only in those individuals who did not have a genetic predisposition to high levels of anger (AA carriers) (Fig. 5).

**Discussion**

In this study, we present the data on the role of cultural (ethnic-group), sex, and genetic (OXTR rs53576 genotypes) factors in human aggression. According to our knowledge, this is the first study confirming the role of the OXTR rs53576 in aggression on the individual level in adult representatives from industrial and traditional ethnic groups.

Our findings supported the hypothesis that (1) self-ratings on aggression are significantly influenced by cultural norms and prescriptions. We demonstrate that ratings on direct (physical and verbal aggression) as well as emotional (anger) and cognitive (hostility) aggression scales were highly culture-specific. To this extent, culture is a “cluster of cognitions, emotions, and practices” [115]. Gender differences in the BPAQ ratings were registered both for industrial and traditional groups. The effect of sex was in the expected direction for physical aggression [13, 15, 17, 116–121]. In Russians, Tatars, Ob-Ugric, Buryats, and Hadza, men rated higher on physical aggression. However, in other traditional African cultures, Datoga and Isanzu, the gender differences in physical aggression were not significant. These findings are important, given the general consensus that universally, this trait is more male-specific as the outcome of sexual selection and social learning [10, 118, 119, 122–126]. In most ethnic groups, gender differences were not found for anger and hostility, with exceptions of anger in Isanzu (higher in women), as well as anger and hostility in Buryats (higher in women). We suggest that the difference obtained in our study reflect cultural norms and socio-cultural network structure. Particularly, relatively high level of ratings on physical aggression in Datoga women may be attributed to the polygynous marriage system and cultural beliefs about individual self-esteem, along with the absence of taboo for the use

| Table 3 The impact of sex, ethnicity, and rs53576 OXTR polymorphism on individual aggression ratings |
|-----------------|-----------------|-----------------|-----------------|
| Predictor       | Dependent variable | F (df) | p (sig.) | Partial eta² |
| Sex             | Physical aggression | 51.78 (1) | < 0.001 | 0.030 |
|                 | Verbal aggression   | 7.73 (1) | 0.005 | 0.005 |
|                 | Anger               | 14.49 (1) | < 0.001 | 0.009 |
|                 | Hostility           | 7.94 (1) | 0.005 | 0.005 |
| Ethnic group    | Physical aggression | 53.48 (6) | < 0.001 | 0.161 |
|                 | Verbal aggression   | 26.28 (6) | < 0.001 | 0.086 |
|                 | Anger               | 80.83 (6) | < 0.001 | 0.225 |
|                 | Hostility           | 42.48 (6) | < 0.001 | 0.132 |
| OXTR rs53576    | Physical aggression | 1.43 (2) | 0.240 | 0.002 |
|                 | Verbal aggression   | 1.44 (2) | 0.236 | 0.002 |
|                 | Anger               | 0.92 (2) | 0.399 | 0.001 |
|                 | Hostility           | 1.77 (2) | 0.171 | 0.002 |
| Sex × ethnic group | Physical aggression | 6.12 (6) | < 0.001 | 0.021 |
|                 | Verbal aggression   | 1.61 (6) | 0.140 | 0.006 |
|                 | Anger               | 3.89 (6) | 0.001 | 0.014 |
|                 | Hostility           | 2.45 (6) | 0.023 | 0.009 |
| OXTR rs53576 × sex | Physical aggression | 0.43 (2) | 0.649 | 0.001 |
|                 | Verbal aggression   | 0.22 (2) | 0.800 | < 0.001 |
|                 | Anger               | 1.43 (2) | 0.240 | 0.002 |
|                 | Hostility           | 3.06 (2) | 0.047 | 0.004 |
| OXTR rs53576 × ethnic group | Physical aggression | 0.90 (12) | 0.547 | 0.006 |
|                 | Verbal aggression   | 0.92 (12) | 0.521 | 0.007 |
|                 | Anger               | 2.50 (12) | 0.003 | 0.018 |
|                 | Hostility           | 0.93 (12) | 0.519 | 0.007 |

MANOVA two-way analysis with the BPAQ scales ratings as dependent variables; ethnic group, sex, and OXTR gene polymorphism (rs53576) as independent factors; and the two-way interaction effects of these factors are presented.

F test statistics, df Degrees of freedom, p statistical significance, partial eta² effect size.
of physical aggression in conflicts among women, which is especially evident in non-kin interactions [127]. The prevalence of physical aggression in men in most still be due to gender differences in motivational sphere. Men are more motivated to revenge physically, and contra to women, such aggression may be mainly proactive, but not reactive (emotional) [125].

Our data demonstrated that groups of European, African, and Asian origin differ in the distribution of OXTR rs53576 genotypes. Buryats and Ob-Ugric, being the most distanced from the rest of our sample, demonstrated a significantly higher prevalence of the AA genotype compared to European and African samples, which is generally in line with previous findings [97]. These differences may suggest certain specific benefits for carriers of the OXTR AA genotype in populations with Asian origin as opposed to Europeans and Africans. Earlier, Kim and colleagues hypothesized that the culturally normative behavior might be subjected to genetic influence [128, 129]. According to their findings, the emotional support seeking in distress was typical for the G allele carriers North Americans, compared to AA genotype carriers, but this was not the case for Koreans [32]. At the same time, Koreans having the GG genotype were more likely to use emotional suppression compared to the AA genotype carriers [34]. Supposedly, the G carriers may be more environmentally sensitive. The question then remained whether positive selection in the direction of the AA genotype in Asian populations makes these populations generally more resistant to social-environmental pressure.

Because of cultural-specific differences in social norms and morality, obviously visible in ratings on BPAQ, we conducted the standardization procedure separately for each study sample and used these z-transformed data in further analysis. Given the general sex differences obtained, the effect of the OXTR gene polymorphism was tested separately for men and women.

Our findings fully support the hypotheses that (2) the OXTR rs53576 polymorphism may cause differences in BPAQ ratings, especially in emotional dimension of aggressive manifestations, and that (3) such effects are sex-specific. We demonstrated that the OXTR rs53576 was a significant predictor for ratings on anger and hostility scales, which was more evident for men. The GG carriers rated higher on anger (emotional aggression) and hostility (cognitive aggression) than the AA carriers. Mind that those differences were obtained after minimizing the effect of culture, by z-transformation procedure; hence, higher anger and hostility ratings reveal genetic-associated patterns, rather than cultural-specific differences. Our findings may be of special interest in light of the results, reported on the relationships between the OXTR rs53576 polymorphism and general sociality and empathetic abilities, with GG carriers being more empathetic [39, 130]. The association between sensitivity to stressful events with the rs53576 genotypes may be gender-specific. Windle and Mrug reported that young adult female (but not males) carriers of the GG genotype, who previously experienced psychological trauma in adolescence due to parental divorce, had significantly more depressive symptoms, compared to
females with AA and AG genotypes [131]. The GG OXTR rs53576 genotype carriers were slower in the recognition of emotion of fear compared to the GA genotype [132]. Our findings that GG carriers rated higher on anger and hostility (this tendency was more expressed in men) extend the previous conclusion about higher threshold on emotional sensitivity and lower stress resistance of this OXTR rs53576 genotype. Assuming GG genotype carriers are less competent in recognizing of fear in others, they may be more emotionally aggressive (anger) and more hostile to others.

According to our knowledge, this is the first study reporting the interaction effect of oxytocin and prenatal androgenization (assessed through 2D:4D ratio) on the BPAQ anger and hostility ratings. The significant positive effects of the right-hand 2D:4D on anger and hostility were found only for AA carriers and were more evident for men than women. Earlier, Weisman with co-authors suggested that women are doing better in Baron-Cohen’s “Reading the Mind in the Eyes” test (RMET), compared to men due to sex differences in testosterone and oxytocin levels [83]. However, in the study, the main differences were obtained for GG carriers. Particularly, men with higher 2D:4D ratio (low fetal testosterone), performed better on the RMET, possibly because they were better at understanding the emotional state of others than individuals with lower 2D:4D [83]. Our current findings do not support the hypothesis that (4) the presence of the A allele of the OXTR plays a crucial role in determining behavioral predispositions, which in turn would distinguish the GG genotype against other variants. A number of studies by other authors have previously reported that AA homozygotes have weaker functional connectivity of the hypothalamus and increased right amygdala activation [130, 133], which most likely affect pro-social behavior and perception. This may suggest that the effects of the A and G alleles could have more or less uniform gradients, with the AA and GG genotypes representing more or less

| N | Trait Predictors | F       | P (sig.) | Partial eta² | Model R² |
|---|------------------|---------|----------|--------------|----------|
| 1 | Physical aggression | Sex     | 53.958   | < 0.001      | 0.031    | 0.039   |
|   |                  | OXTR rs53576 | 2.401   | 0.091      | 0.003    |
|   |                  | R2D:4D² | 2.312   | 0.129      | 0.001    |
|   |                  | OXTR rs53576 * R2D:4D² | 0.543   | 0.581      | 0.001    |
|   |                  | Sex * OXTR rs53576 | 1.591   | 0.204      | 0.002    |
|   |                  | Sex * R2D:4D | 1.180   | 0.277      | 0.001    |
| 2 | Verbal aggression | Sex     | 10.991   | 0.001      | 0.006    | 0.014   |
|   |                  | OXTR rs53576 | 2.587   | 0.076      | 0.003    |
|   |                  | R2D:4D² | 0.407   | 0.524      | < 0.001  |
|   |                  | OXTR rs53576 * R2D:4D² | 2.011   | 0.134      | 0.002    |
|   |                  | Sex * OXTR rs53576 | 0.151   | 0.859      | < 0.001  |
|   |                  | Sex * R2D:4D | 0.090   | 0.764      | < 0.001  |
| 3 | Anger | Sex     | 6.767    | 0.009      | 0.004    | 0.018   |
|   |      | OXTR rs53576 | 3.502   | 0.030      | 0.004    |
|   |      | R2D:4D² | 7.109   | 0.008      | 0.004    |
|   |      | OXTR rs53576 * R2D:4D² | 4.270   | 0.014      | 0.005    |
|   |      | Sex * OXTR rs53576 | 0.675   | 0.509      | 0.001    |
|   |      | Sex * R2D:4D | 2.470   | 0.116      | 0.001    |
| 4 | Hostility | Sex     | 4.427    | 0.036      | 0.003    | 0.015   |
|   |      | OXTR rs53576 | 4.239   | 0.015      | 0.005    |
|   |      | R2D:4D² | 3.900   | 0.048      | 0.002    |
|   |      | OXTR rs53576 * R2D:4D² | 0.986   | 0.373      | 0.001    |
|   |      | Sex * OXTR rs53576 | 2.228   | 0.108      | 0.003    |
|   |      | Sex * R2D:4D | 0.581   | 0.446      | < 0.001  |

Four univariate general linear models (ANCOVA) with multiple predictors are presented.

OXTR (rs53576): AA (N = 282), AG (N = 755), GG (N = 668); sex: male (N = 837), female (N = 868)

N model number; Trait dependent variable, one of the four subscales of BPAQ per each model; Predictors independent variables, * interactions; F test statistics; P level of statistical significance (bold: p < 0.05); partial eta² effect size; Model R² model R-squared

Variable after z-score standardization
equivalent functional polarities. The physiological processes related to the functioning of the \textit{OXTR} \textmd{rs53576} locus still need to be investigated in the future.

It is important to consider these results in light of some limitations. The currently accumulated data are inconsistent, obviously demanding replication in other samples with higher power, keeping in mind the small effect sizes, usually reported. Along with testing the gene-environment interaction factor, the gene-gene interaction effect should be considered; hence, the genome-wide association studies may provide much more profound information on the genetic effect on behavior. Currently, the functionality of the \textit{OXTR} \textmd{rs53576} polymorphism is not clear, as it is located in an untranslated region [134]. At the moment, only associative evidence for the role of \textit{OXTR} in the regulation of brain activity exists. Despite the fact that neuroimaging research has revealed specific brain differences associated with \textmd{rs53576}, such as reduced volumes in hypothalamic gray matter and amygdala for A allele carriers [130, 133, 135], the particular functional role of this very locus remained to be proved in the future studies.

\section*{Conclusions}

The ethnic group factor was the most significant predictor of ratings on all four BPAQ scales. All four scales of the BPAQ demonstrated association with sex (main effects), with men scoring higher on physical and verbal aggression and women scoring higher on anger and hostility. After leveling the effects of culture (z-transformation), all four scales of the BPAQ demonstrated association with sex, with men being higher on physical and verbal aggression and women scoring higher on anger and hostility. Anger and hostility scales were also associated with \textit{OXTR} polymorphism and 2D:4D of the right hand. The lowest levels of anger and hostility were observed in individuals with the AA genotype; this effect was especially obvious in men. Both oxytocin (\textit{OXTR} \textmd{rs53576} polymorphism) and fetal testosterone (2D:4D) significantly affected emotional (anger) and cognitive (hostility) aggression in humans, given the leveling the role of culture.
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Authors’ contributions

Conceptualization: MB, OL, and AR. Project administration: MB. Formal analysis: MB, VR, PB, and OL. Funding acquisition: ML and AR. Data collection: MB, VB, DD, and VR. Laboratory analysis: PB, VV, JS, TM, VF, OL, and AR. Writing—original draft preparation: MB, VR, PB. Writing—review and editing: all the authors. The author(s) read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available in the Figgshare repository, by doi:10.6084/m9.figshare.12442475

Ethics approval and consent to participate

The study was approved by the Institute of Ethnology and Anthropology, RAS, and Commission for Science and Technology of Tanzania (COSTECH). All the Russian participants gave written informed consent, while in Tanzania, as most of the participants there were illiterate, oral informed consent was provided, following the Declaration of Helsinki.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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