



The role of oxytocin receptor gene variants in appetitive aggression: A study in a South African male sample

Catherine Lohrentz^{1,2}  | Jacqueline S. Womersley^{1,3}  | Patricia C. Swart^{1,3} |
Jessica Sommer⁴ | Martina Hinsberger⁴ | Thomas Elbert⁴ | Roland Weierstall^{4,5} |
Debbie Kaminer⁶ | Soraya Seedat^{1,3} | Sian M. J. Hemmings^{1,3}

¹South African Medical Research Council/
Stellenbosch University Genomics of Brain
Disorders Research Unit, Faculty of Medicine
& Health Sciences, Stellenbosch University,
Cape Town, South Africa

²Division of Molecular Biology and Human
Genetics, Faculty of Medicine & Health
Sciences, Stellenbosch University, Cape Town,
South Africa

³Department of Psychiatry, Faculty of
Medicine & Health Sciences, Stellenbosch
University, Cape Town, South Africa

⁴Department of Psychology, University of
Konstanz, Konstanz, Germany

⁵Clinical Psychology & Psychotherapy,
Medical School Hamburg, Hamburg, Germany

⁶Department of Psychology, University of
Cape Town, Cape Town, South Africa

Correspondence

Sian M. J. Hemmings
Email: smjh@sun.ac.za

Funding information

Harry Crossley Foundation; South African
Medical Research Council; European Research
Council

Abstract

Chronic exposure to trauma and violence can promote aggressive behavior. Oxytocin and variants in the oxytocin receptor (OXTR) gene may play a role in the etiology of proactive, that is, goal-oriented instrumental aggression, or reactive aggression, which typically occurs in response to emotionally triggering situations. The current study builds on previous findings that experienced and witnessed trauma in childhood predicts higher levels of appetitive aggression, a form of proactive aggression characterized by the enjoyment of participating in violent behavior. The current study explores the role of *OXTR* rs2254298 and rs53576 variants in appetitive and reactive aggression. Adult males living in Cape Town, South Africa, and at risk for violent behavior completed the Appetitive Aggression Scale (AAS) and Buss–Perry Aggression Questionnaire (BPAQ). *OXTR* rs2254298 and rs53576 were successfully genotyped via restriction fragment length polymorphism (RFLP) analysis in 238 and 239 participants, respectively. Regression analysis showed that rs2254298 G/G and A/G genotypes and the rs53576 A/G genotype were significantly associated with lower AAS scores ($p < .001$) compared to the A/A genotype. Additionally, genotype interaction analyses conducted in 232 participants, found that the combination of rs2254298 A/G and rs53576 G/G genotypes produced opposite effects on appetitive and reactive aggression. Specifically, this combination was associated with a 0.29-point increase in AAS scores ($p = .032$) and a 0.13-point decrease in BPAQ scores ($p = .037$) when compared to A-allele homozygosity for both variants. These results suggest that genetic variation in a signaling system involved in influencing environmental and social salience may contribute to appetitive aggression.

KEYWORDS

aggression, *OXTR* rs2254298, *OXTR* rs53576, oxytocin, trauma

Konstanzer Online-Publikations-System (KOPS)
URL: <http://nbn-resolving.de/urn:nbn:de:bsz:352-2-1qkp91ywh319b8>

Catherine Lohrentz and Jacqueline S. Womersley authors contributed jointly as first authors.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Authors. *Aggressive Behavior* published by Wiley Periodicals LLC.

1 | INTRODUCTION

Rates of gender-based violence, physical and sexual assault, and murder within low socioeconomic settings in South Africa rank well above the global norm (Seedat et al., 2009). In these settings, trauma exposure is a common occurrence (Hinsberger et al., 2016). Chronic exposure to trauma during critical developmental periods, such as childhood, has been linked to poor psychological functioning and can increase the risk for posttraumatic stress, depression, and anxiety disorders (Hatcher et al., 2019; McKay et al., 2021; Nelson et al., 2020). Increased trauma exposure is also associated with future aggressive behavior (Hecker et al., 2013; Hinsberger et al., 2016), fueling a potential cycle of violence. With enough reinforcement from the social environment, these aggressive tendencies can become entrenched (Hecker et al., 2013).

Aggression is a complex behavior underpinned by the intention to cause harm to a desired target and has been broadly categorized as reactive or proactive, based on the underlying motivation (Elbert et al., 2018; Miller & Lynam, 2006). Reactive aggression typically occurs when an individual is faced with an emotionally triggering situation and is motivated by the desire for relief (Elbert et al., 2018). Conversely, proactive aggression is instrumental, driven by the desire for benefit or reward (Romero-Martínez et al., 2022). Appetitive aggression, a form of proactive aggression, occurs when violent behavior gives rise to a sense of arousal or fascination, resulting in an incentive to participate in acts of violence (Elbert et al., 2018).

Aggressive and violent behavior are influenced by gene-environment interactions (Veroude et al., 2016) with twin and family studies suggesting that genetics accounts for approximately 45% of the variance in aggression (Romero-Martínez et al., 2022). Though most genome-wide association studies of aggression yielded non-significant results (Veroude et al., 2016), a meta-analysis by Romero-Martínez et al. (2022) examining biological contributions to aggression found that 12 of the 14 articles using a candidate gene approach reported significant associations between allelic variation and proactive and/or reactive aggression. Significant associations were found in genes implicated in neuroendocrine and neurotransmitter mechanisms, such as arginine-vasopressin, serotonin, dopamine, oxytocin, and monoamine oxidase. The neuroendocrine system refers to hormones that work in conjunction with the nervous system to elicit reactions required for the maintenance of normal bodily functions, including social behavioral cues (van Donkelaar et al., 2020), as well as long-term behavioral plasticity, which facilitates behavioral shifts to adapt to changing social contexts and interpersonal interactions (Kelly & Vitousek, 2017; Schmid Mast & Hall, 2018). Thus, variants in neuroendocrine genes may moderate the development of aggressive behavior in response to environmental adversity (Kelly & Vitousek, 2017; Veroude et al., 2016).

Oxytocin was originally characterized as a prosocial neuropeptide and plays an important role in affiliative behavior, cooperation, and stress attenuation (Leng et al., 2022). However, the more recent expansion of the oxytocin research field to include different clinical populations and environmental factors, combined with inconsistent results of studies examining the effect of intranasal

oxytocin administration on behavior, have necessitated a shift in understanding, as reviewed by Leng et al. (2022), Zik and Roberts (2015), and Onaka and Takayanagi (2021). The social salience hypothesis proposes a more nuanced role for oxytocin in mediating social interactions, with the valence and chronicity of an environmental factor influencing behavior that is, higher levels of oxytocin may amplify sensitivity to both supportive and harmful contexts, with corresponding effects on behavior (Shamay-Tsoory & Abu-Akel, 2016). Oxytocin exerts its effects by binding to the oxytocin receptor (OXTR), a G-protein-coupled receptor highly concentrated in the central nervous system that plays a key role in oxytocinergic signaling (Vaidyanathan & Hammock, 2017). Experiences, such as social interaction and trauma during developmental years, may influence the distribution of OXTR and expression of the OXTR gene, with downstream effects on behavior via altered oxytocinergic signaling (Onaka & Takayanagi, 2021).

Several previous studies have shown associations between OXTR variants, including single nucleotide polymorphisms (SNPs), such as rs53576, rs2254298, rs4564970, rs7632287, and rs4686302, and poor social behavior, specifically in terms of actively engaging in aggressive behavior (Butovskaya et al., 2020; LoParo et al., 2016; Malik et al., 2012), as well as aggressive phenotypes within neuropsychiatric and neurodevelopmental disorders (Hovey et al., 2016; Kalyoncu et al., 2019; Slane et al., 2014), such as schizophrenia (Montag et al., 2013). Interactions between OXTR variants have also been associated with modulatory effects on neurological development and behavior (Slane et al., 2014). However, even within the studies mentioned, there is inconsistency in the results. This may arise from several factors, including the failure to account for the different motivations (reactive or instrumental) underlying aggressive behavior; nuanced roles of oxytocin in behavior; developmental effects on OXTR distribution and expression; and the influence of environmental context. Importantly to note, the majority of studies investigating the genetic contributions to aggression have been conducted in cohorts of European and Asian ancestry (Hovey et al., 2016; Kalyoncu et al., 2019; LoParo et al., 2016; Montag et al., 2013; Slane et al., 2014), and hence the genetic relations suggested may or may not be valid for other population groups.

While the abovementioned evidence indicates a relationship between variants in OXTR and impaired social behavior, it is unclear as to how these polymorphisms influence OXTR functioning and subsequent adverse psychiatric outcomes. Rodent knockout models show that rodents with a null mutant OXTR display subpar social memory and impaired social behavior (Ferguson et al., 2000; Takayanagi et al., 2005). Furthermore, expression analysis has indicated that the A (minor) allele of the rs53576 A/G genotype is associated with an increase in OXTR messenger RNA expression compared to individuals carrying the rs53576 G/G genotype, suggesting that the A allele corresponds with greater oxytocin signaling capacity (GTEx Consortium et al., 2017). As such, we hypothesized that variants in OXTR may influence the transcription of the receptor, subsequently moderating oxytocin signaling capacity.

This exploratory study aimed to investigate the relationship between OXTR rs2254298 and rs53576 genotypes and aggressive

behavior in adult males of a common South African ancestry. Recruitment was conducted in Khayelitsha and Gugulethu, two relatively homogeneous suburbs that were designated for “Black” South Africans under Apartheid segregationist policy. The legacies of social, educational, and economic discrimination persist and are reflected in high rates of unemployment, poverty, poor service delivery, and crime (Turok et al., 2021). More specifically, the 2011 suburb-level census data indicated that residents are relatively young [45.3% (Gugulethu) and 49.5% (Khayelitsha) are 24 years of age or younger]; overwhelmingly self-identify as belonging to the Black African census group [99% for both suburbs]; have poor housing security [48% (Gugulethu) and 55% (Khayelitsha) reside in informal dwellings], and suffer from high rates of unemployment [39.3% (Gugulethu) and 40.4% (Khayelitsha) of residents of working age are employed] (Policy and Strategy Department, City of Cape Town, City of Cape Town, 2013a, 2013b). The genetic variants, rs22254298 and rs53576, located in introns 2 and 3 of *OXTR*, respectively, have been previously associated with poor social development and aggressive phenotypes in predominantly European population groups (Butovskaya et al., 2020; Montag et al., 2013; Slane et al., 2014). We hypothesized that appetitive and reactive aggression scores, measured by the Appetitive Aggression Scale (AAS) (Weierstall & Elbert, 2011) and Buss–Perry Aggression Questionnaire (BPAQ) (Buss & Perry, 1992), respectively, would be influenced by *OXTR* rs2254298 and rs53576 genotypes.

2 | METHODS

2.1 | Participant recruitment

This study (Figure 1) is nested within a larger parent study that investigated the relationships between trauma exposure and

aggression in young men residing in Khayelitsha and Gugulethu, two low-income suburbs in Cape Town, South Africa, with high levels of violence (Hinsberger et al., 2016). The study recruited 290 male participants, ranging from 14 to 40 years of age, who self-identified as being isiXhosa, a South African population belonging to the Niger–Kordafarian linguistic subgroup (Bryc et al., 2010). Hinsberger et al. (2016) recruited a strictly male cohort based on the findings of a study conducted by Kaminer et al. (2013), which determined that, in a cohort of Xhosa-speaking adolescents, boys were more likely to report more severe trauma experience, including higher reported rates of sexual abuse and physical punishment, compared to their female counterparts. Participants were recruited if they were deemed as being at risk of perpetrating violence, based on either previously committed violent acts or were at increased risk of doing so based on their responses to an appetitive aggression event checklist (Weierstall & Elbert, 2011). Participants were recruited with assistance from the community-based Rebuilding and Life Skill Training Center (REALISTIC) in Gugulethu and provided written informed consent to participate. The center provides a 6-month life skills training program, aimed at reducing recidivism and drug abuse relapse, to support ex-prisoners and at-risk youth. Participation in the REALISTIC program was either voluntary or mandatory, where in mandatory cases participants were referred by police or sent by family members (Hinsberger et al., 2016). The parent study comprised participants who had never participated in a reintegration program (49%), as well as those who had ever been enrolled in the reintegration program (51%). Twenty percent of participants were former offenders currently enrolled in the REALISTIC program (Sommer et al., 2017). This study was approved by the Health Research Ethics Committee of Stellenbosch University, South Africa (REC: N21/01/003_Substudy_N13/01/006).

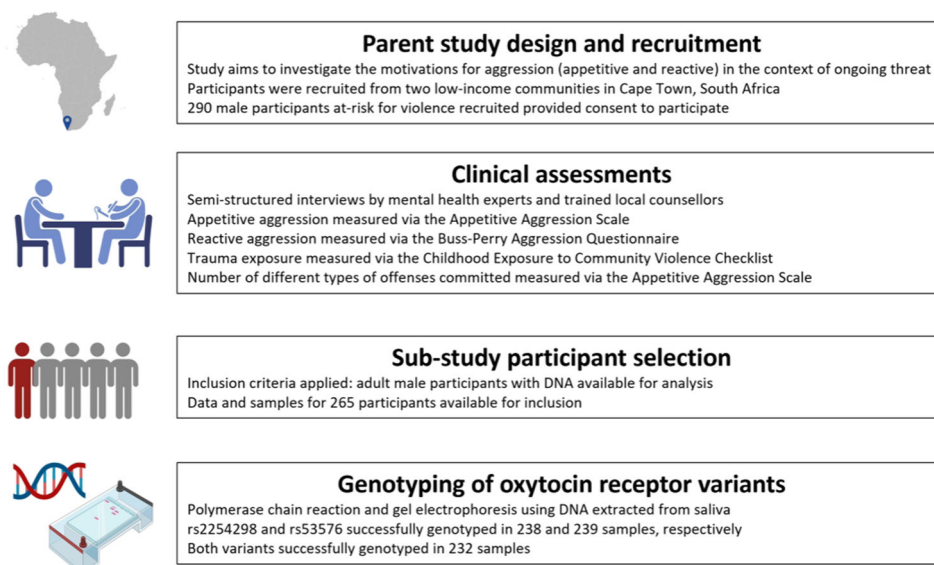


FIGURE 1 Study flow diagram. Figure created using [BioRender.com](https://www.biorender.com). [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

2.2 | Measures of trauma, aggression, and violence

Details of the assessment procedure have been reported in previous publications (Hinsberger et al., 2016; Sommer et al., 2017). Briefly, interviews were conducted between October 2013 and March 2014 and took place on either the REALISTIC premises or at otherwise secluded offices to ensure privacy. The interview team included four German mental-health experts and three local trained counselors, as well as bilingual isiXhosa/English interpreters specifically trained for clinical settings and who were responsible for the translation and back-translation of the assessment instruments (Hinsberger et al., 2016; Sommer et al., 2017).

Trauma exposure was measured using an adapted Childhood Exposure to Community Violence Checklist (CECV) (Amaya-Jackson, 1998), a 33-item self-report checklist measuring an individual's exposure to levels of hearing, witnessing, and experiencing trauma during childhood. The adapted CECV includes violence typically experienced in low-socioeconomic areas within South Africa, such as sexual and physical assault. The total score of 33 indicates the severity of the individual's exposure to traumatic events, subdivided into questions pertaining to witnessed and self-experienced traumatic events. Possible scores range from 0 to 33. The CECV score reliability in the current sample cohort, where internal consistency is measured using the McDonald's coefficient omega, was found to be 0.79 (95% confidence interval [CI]: 0.75–0.82) (Sommer et al., 2017). The interpretation of McDonald's omega is the same as Cronbach's α with the score of .79 indicating acceptable internal consistency ($.7 \leq \omega < .8$).

The AAS was used to measure appetitive aggression (Weierstall & Elbert, 2011). The AAS score was calculated by summing scores determined from 15 questions on instrumental aggression, addiction behavior, and desire to cause harm, rated on a 5-point Likert scale with potential scores ranging from 0 to 60. The McDonald's coefficient omega of 0.87 (95 CI: 0.84–0.89) indicated good internal consistency ($.8 \leq \omega < .9$) (Sommer et al., 2017). The AAS was also used to assess the number of different offenses committed in their lifetime. The number of positive responses to a list of 21 possible offenses, including rape, assault, and murder, was summed to yield a score ranging from 0 to 21. McDonald's coefficient omega for the number of offense types committed was 0.88 (95 CI: 0.86–0.90), indicating good internal consistency (Sommer et al., 2017).

Reactive aggression was measured using the BPAQ, a 29-item inventory scored on a 5-point Likert scale (Buss & Perry, 1992). Scores can range from 29 to 145, with higher scores indicating higher levels of trait aggression.

Thirty-eight of the 290 parent study participants had missing data for one or more variables. In these cases, missing values were estimated using maximum likelihood estimation as reported by Sommer et al. (2017).

2.3 | Sample collection and DNA extraction

Saliva samples were collected in Oragene™ DNA self-collection kits (OG-500, DNA Genotek) at the interview, and genomic DNA was

extracted using the Prep-It L2P reagent (DNA Genotek) according to the manufacturer's instructions. DNA quantity and quality were assessed using a NanoDrop Spectrophotometer (Thermo Fisher Scientific). DNA was stored at -80°C until use in polymerase chain reaction (PCR) RFLP experiments.

2.4 | PCR RFLP

Genotyping experiments were limited to adult participants with DNA available for analysis ($n = 265$). Two OXTR SNPs, rs2254298 and rs53576, were amplified by PCR performed on a MiniAmp Plus Thermal Cycler (Thermo Fisher Scientific) with use of KAPA2G Robust HotStart ReadyMix (Kapa Biosystems) and the following primers (Integrated DNA Technologies): rs2254298—forward: 5'-TGA AAG CAG AGG TTG TGT GGA CAG G-3'; reverse: 5'-AAC GCC CAC CCC AGT TTC TTC-3'; rs53576—forward: 5'-GCC CAC CAT GCT CTC CAC ATC-3'; reverse: 5'-GCT GGA CTC AGG AGG AAT AGG GAC-3' (Wu et al., 2005). Gel electrophoresis (1% agarose (SeaKem LE) gel, 120 V, 60 min) was used to visualize the PCR products, after which the amplified products were subjected to an RFLP to determine the genotype. The full experimental details are provided in the Supporting Information materials, including the PCR components (Supporting Information S1: Table 1), PCR conditions (Supporting Information S1: Table 2), and RFLP components (Supporting Information S1: Table 3). Restriction enzyme digest conditions were as follows. Rs2254298 samples were incubated with *BsrI* restriction enzyme (New England Biolabs) at 65°C for 15 min, followed by 20 min at 80°C to stop the reaction. Results were visualized on a 2% agarose gel (120 V, 60 min). Rs53576 samples were incubated with *Bam*HI restriction enzyme (New England Biolabs) at 37°C for 16 h. Results were visualized on a 1.5% agarose gel (120 V for 60 min). A random selection of 10 samples was sent for Sanger sequencing at the Central Analytical Facility DNA Sequencing Unit (Stellenbosch University) to confirm the OXTR rs2254298 and rs53576 genotype calls determined by RFLP. Genotyping of rs2254298 and rs53576 was successfully performed in 238 and 239 samples, respectively, with genotype data for both variants available for 232 participants. Genotyping results were tested for Hardy-Weinberg Equilibrium (HWE) using the R package *SNPassoc* (R Core Team, 2022). Haplotype analysis was conducted using the R package *LDlinkR* (R Core Team, 2022).

2.5 | Statistical analysis

Continuous data were assessed for normality using the Shapiro–Wilk test. Correlation coefficients between variables were determined using Spearman's rank correlation test. Both appetitive and reactive aggression models made use of continuous scores. AAS scores were distributed as a bounded rare event, similar to that of a Poisson-like distribution. Therefore, a Poisson regression was used to determine the association between AAS/BPAQ scores and rs2254298 and rs53576 genotypes, and to allow for the adjustment of known

covariates within the cohort. Witnessed and experienced trauma, age, education, and participation in the REALISTIC program were considered as potential covariates and were included in regression models when significantly associated with the outcome of interest. Furthermore, as BPAQ and AAS scores were significantly associated with each other, regression models with AAS scores as an outcome variable included BPAQ scores as a covariate and vice versa. Appetitive aggression models were as follows:

$$\text{AAS} \sim \text{genotype} + \text{witnessed trauma} + \text{experienced trauma} + \text{BPAQ} + \text{age} + \text{education} + \text{REALISTIC participation.}$$

BPAQ scores were regressed against genotype and covariates as below:

$$\text{BPAQ} \sim \text{genotype} + \text{witnessed trauma} + \text{experienced trauma} + \text{AAS} + \text{education} + \text{REALISTIC participation.}$$

Finally, we ran models that included the rs2254298–rs53576 interaction. Model sample size was based on the number of participants for whom genotype data were available [rs2254298 $n = 238$; rs53576 $n = 239$; rs2254298 \times rs53576 $n = 232$].

Diagnostic plots were used to assess model fit. All data analysis was performed in R v4.1.1, using packages corrplot, dplyr, epicalc, epiDisplay, ggplot2, ggsignif, Hmisc, LDlinkR, psych, readr, readxl, ResourceSelection, SNPassoc, and skimr (R Core Team, 2022). Results are reported as medians and interquartile range (IQR). Post hoc power calculations were performed using G*Power v3.1.9.7 (Faul et al., 2007). To aid in the interpretation of our results, we drew on the Gene-Tissue Expression (GTEx) project, which combines gene expression analysis along with dense genotyping of multiple different human tissues to provide insight into how genetic variation is related to expression and regulation (GTEx Consortium et al., 2017). The GTEx database was searched for both rs2254298 and rs53576.

3 | RESULTS

3.1 | Cohort data

Descriptive statistics for demographic and clinical data were calculated for the 245 participants for whom rs2254298 and/or rs53576 genotype data were available. The age of participants ranged from 18 to 40 years with a median age of 22 years (IQR: 19–24). The number of years of education ranged from 1 to 16 years with a median value of 11 years (IQR: 10–12). All individuals experienced at least one form of traumatic event as measured by the CECV. Participants experienced a median of 9 (IQR: 6–11) self-experienced traumatic event types and witnessed a median of 10 (IQR: 8–12) traumatic events. The median total trauma score measured by the CECV was 19 (IQR: 15–23). The AAS score ranged

from 0 to 60, with a median score of 12 (IQR: 6–23). The median BPAQ score was 87 (IQR: 72–00). Scores for the number of different types of offenses committed ranged from 1 to 21, with a median value of 12 (IQR: 8–15).

Correlation values between continuous measures were calculated (Supporting Information S1: Table 4). The analyses indicated significant positive correlations between all measures of trauma (witnessed and experienced), aggression (appetitive and reactive), and perpetrated violence (number of different offense types committed) (Figure 2). The strongest correlation was between witnessed and experienced trauma ($r = .60$, $p < .001$). AAS scores were found to be moderately positively correlated with the number of different offense types committed ($r = .50$, $p < .001$) and BPAQ scores ($r = .49$, $p < .001$), and weakly positively correlated with witnessed ($r = .31$, $p < .001$) and experienced trauma ($r = .36$, $p < .001$). BPAQ scores were found to be moderately positively correlated with the number of different offense types committed ($r = .40$, $p < .001$) and weakly correlated with witnessed ($r = .23$, $p < .001$) and experienced trauma ($r = .36$, $p < .001$).

3.2 | OXTR rs2254298 and rs53576 genotype frequencies

Genotyping data for the OXTR SNPs are presented in Supporting Information S1: Table 5. Both rs2254298 and rs53576 were found to be out of HWE. If OXTR variants do play a role in aggression, our targeted selection of previous offenders or those at-risk of violence may have produced an artificial HWE result. Consequently, we

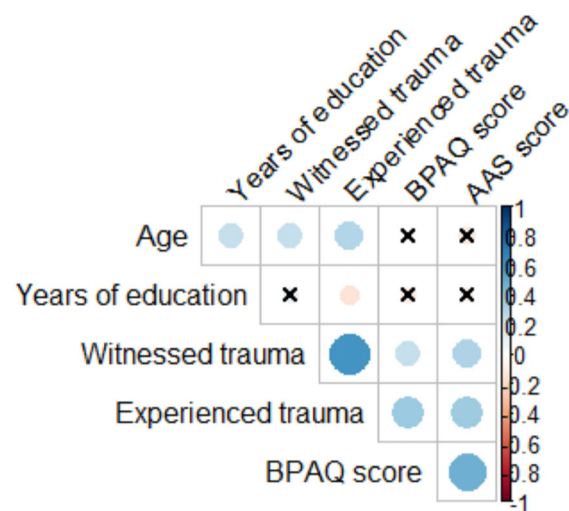


FIGURE 2 Spearman's rank correlation matrix of continuous study variables. The strength of correlations is indicated by the size and color of the circle, with positive and negative correlations indicated in a spectrum spanning from blue to red, respectively. Correlations that did not reach significance are indicated by a cross. AAS, Appetitive Aggression Scale; BPAQ, Buss–Perry Aggression Questionnaire. [Color figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

adopted the approach employed by a previous study in this same cohort, which designated participants with AAS scores ≤ 8 as having low appetitive aggression (Hinsberger et al., 2017). When analyses were repeated in participants with low appetitive aggression, both variants were found to be in HWE.

3.3 | OXTR variants and aggression measures

Median AAS and BPAQ scores per rs2254298 and rs53576 genotype are reported in Table 1. Poisson regression models indicated that participants with rs2254298 A/G and G/G genotypes had 0.22- and 0.31-point lower AAS scores than participants with the A/A genotype ($p < .001$ for both) (Supporting Information S1: Table 6). Participants heterozygous for rs53576 were found to have a 0.15-point lower AAS scores than those carrying the homozygous A/A genotype ($p = .024$). No significant associations were observed in participants with the G/G genotype (Supporting Information S1: Table 7).

Participants with the rs2254298 A/G genotype had a 0.05-point higher BPAQ score compared to individuals with an A/A genotype ($p = .015$). No significant associations between BPAQ score and the G/G genotype were observed (Supporting Information S1: Table 8). Carrying at least one rs53576 G allele was significantly associated with BPAQ score, with the A/G and G/G genotypes associated with 0.13- ($p = .008$) and 0.07-point ($p = .013$) higher BPAQ score, respectively (Supporting Information S1: Table 9).

TABLE 1 Median aggression scores with interquartile range per OXTR SNP genotype.

Aggression score	Genotype	Median	IQR
rs2254298 (n = 238)			
AAS	A/A	15.0	5.5–26.0
	A/G	12.0	6.0–22.0
	G/G	11.5	–5.3 to 20.8
BPAQ	A/A	87.0	70.5–95.0
	A/G	89.0	75.0–105.0
	G/G	85.0	70.0 – 97.8
rs53576 (n = 239)			
AAS	A/A	12.5	5.3–20.2
	A/G	11.5	–7.0 to 22.2
	G/G	13.0	–6.0 to 24.0
BPAQ	A/A	82.5	69.8–95.5
	A/G	89.5	80.0–103.0
	G/G	86.0	70.5–97.5

Abbreviations: AAS, Appetitive Aggression Scale; BPAQ, Buss–Perry Aggression Questionnaire; IQR, interquartile range; SNP, single nucleotide polymorphism.

Genotype interaction analyses found that participants heterozygous for rs2254298 and carrying the rs53576 G/G genotype had 0.29-point higher AAS scores compared to individuals carrying the A/A genotype for both variants ($p = .032$) (Supporting Information S1: Table 10). rs2254298 A/G participants carrying the rs53576 G/G genotype had a 0.13-point lower BPAQ score in comparison to participants with rs53576 and rs225498 A/A genotypes ($p = .037$) (Supporting Information S1: Table 11).

Our search of the GTEx database identified rs53576 as an expression quantitative trait locus, that is, a variant that can influence gene expression. This significant variant–expression relationship was limited to brain tissue and the G/G genotype was associated with lower expression across the regions assessed, though the extent of this effect varied according to region (Figure 3).

4 | DISCUSSION

The present study is an exploratory investigation to determine the association between OXTR rs2254298 and rs53576 genotypes and aggressive behavior in a cohort of South African Xhosa males at high risk for perpetrating violence. We specifically focussed on appetitive aggression as we wanted to understand how fascination with violence and the viewing of such actions as arousing contributes to cycles of violence in nonconflict settings that are nevertheless characterized by high stress and trauma exposure. The characterization of this study group as being at-risk for violence is borne out by the finding that the median value (12) for the number of different types of offenses committed reflects answers in the affirmative to more than half of the 21 different types of offenses listed. The finding that witnessed and experienced trauma were significantly correlated with both appetitive and reactive aggression measures, as well as the number of different types of offenses committed, supports the suggestion that high-trauma contexts may foster aggressive behavior and contribute to a cycle of violence.

When evaluating the influence of OXTR genotypic variation on AAS scores, we found that the rs2254298 G/G and A/G genotypes were associated with lower AAS scores compared to the A/A genotype. As this is the first study to examine rs2254298 in relation to appetitive aggression specifically, we can only interpret this result in comparison to studies investigating other behaviors. Brüne's (2012) finding that early childhood adversity heightened the risk of developing a psychiatric disorder, that is, depression, autism, or anxiety, in rs2254298 A allele carriers suggests that the rs554298-environment interaction may influence behavior. In a study of autism in children, the presence of the rs2254298 A allele was associated with impaired social behavior (Parker et al., 2014). While social impairment is not directly congruent with an aggressive phenotype, a study investigating aggression in children from 24 months to 9 years of age found that children on a high-stable aggression trajectory were more likely to display poor social skills (Campbell et al., 2006). Therefore, OXTR rs2254298 genetic variation may also play a role in abnormal or challenging behavior with aggression-like tendencies in

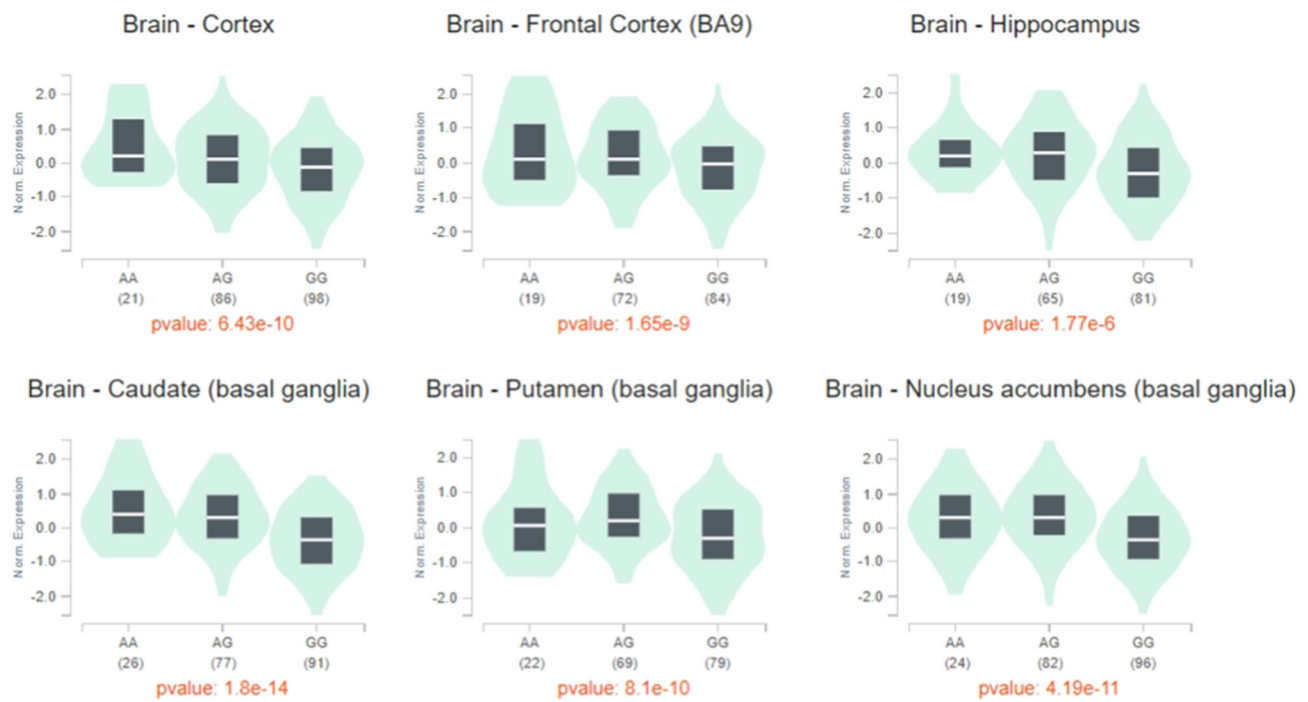


FIGURE 3 Oxytocin receptor (*OXTR*) rs53576 acts as an expression quantitative trait locus in human brain tissue. Violin plots showing *OXTR* expression indicate that rs53576 acts as an expression quantitative trait locus in multiple regions of the human brain, including the cortex, hippocampus, and basal ganglia. [Color figure can be viewed at wileyonlinelibrary.com]

psychiatric disorders such as autism spectrum disorder (Brüne, 2012; Campbell et al., 2006; Parker et al., 2014). Nevertheless, it is unlikely that rs2254298 variation exerts a clinically meaningful influence on appetitive aggression, given that the effect size (0.19–0.28 points) represents a small difference in an instrument with scores ranging from 0 to 60.

Participants carrying the *OXTR* rs53576 A/G genotype had lower AAS scores compared to those with the A/A genotype. This suggests a "Goldilocks effect", that is, a distinct heterozygous phenotype that does not lie intermediate between the two homozygous phenotypes, which though uncommon, has been previously observed in genetic investigations (Craig Cohen et al., 2004). Linkage disequilibrium (LD) may also play a role in this association. Though our haplotype analysis indicated that rs2254298 and rs53576 are not in LD ($r^2 = .02$) in our study group, this does not preclude the possibility that other SNPs in LD could be responsible for this effect. One possibility is the functional *OXTR* SNP rs2268498 (Reuter et al., 2017), which is in LD with rs53576 in participants of Asian ancestry (Koh et al., 2015), and has been previously associated with pro-social behavior (Christ et al., 2016). However, the lack of consistency in haplotypes across population groups, combined with the fact that our results were observed in comparison to a small reference group ($n_{A/A} = 20$), requires studies with a more comprehensive range of *OXTR* SNPs that can investigate haplotype structure and different modes of inheritance in African populations be performed.

In terms of reactive aggression, rs2254298 and rs53576 A-allele homozygosity were both associated with higher BPAQ scores in

comparison to rs2254298 A/G and rs53576 A/G or G/G genotypes, respectively. These findings of an opposite direction of effect on AAS and BPAQ scores were also observed when investigating the role of the serotonergic STin2.12 repeat allele (Hemmings et al., 2018). Divergent effects were also observed in our interaction analyses. We found that the rs53576 G/G genotype, compared to the rs53576 A/A genotype, was associated with higher AAS scores but only in rs2254298 heterozygous participants. The same interaction had an opposite effect on BPAQ score, that is, the rs53576 G/G versus A/A genotype was associated with lower BPAQ scores in participants heterozygous for rs2254298. Previous literature has indicated that the rs2254298–rs53576 interaction may influence neurological development and behavior. More specifically, in a study of typically developing children, Slane et al. (2014) observed that the same rs2254298 A/G x rs52576 GG interaction observed in our study was associated with worse social cognition, including measures addressing social problems, social avoidance, emotion recognition, and interpersonal relatedness. With respect to aggression, a three-loci interaction (rs6133010–rs22542908–rs53576) including our SNPs of interest, was found to predict physical aggression in men (Yang et al., 2017).

In considering our findings of opposite effects on reactive and appetitive aggression, it is important to note that conceptualization of reactive and proactive aggression as dichotomous entities is under debate, with an alternative view being that these represent facets of aggression that are not sufficiently distinct to be clinically meaningful (Polman et al., 2007). The difficulty in reactive versus proactive interpretation can be seen in the results of a meta-analysis, which

found that though the mean correlation between the two measures was strong ($r = .64$), there was considerable variation across studies ($-.10 \leq r \leq .89$), suggesting that other elements, including choice of measurement instrument, and personal and environmental factors may play a role (Polman et al., 2007). From a biological perspective, proactive, and reactive aggression show both common and distinct pathophysiology. Both reactive and proactive aggression are estimated to be approximately 45% heritable, with 60% of this shared by both types of aggression and 10% representing unique contributions. Both reactive and proactive aggression are associated with increased medial prefrontal cortex activity and alterations to amygdala and temporal cortex volumes (Romero-Martínez et al., 2022). However, in comparison to reactive aggression, proactive aggression has been associated with lower sympathetic nervous system fear reactivity (Thomson et al., 2021) and cortisol awakening response (Paré-Ruel et al., 2022). It is, therefore, possible that the biology underlying appetitive aggression and reactive aggression also show common and distinct mechanisms. Our study found a moderate correlation between AAS and BPAQ scores, suggesting that they are representing related constructs rather than the same factor. By controlling for reactive aggression in models assessing appetitive aggression and vice versa, we could better discern *OXTR* contributions to the two different types of aggression. Our findings thus support suggestions that similar pathways may subservise appetitive and reactive aggression but that subtle differences in their mechanisms of action or effects may influence the aggression phenotype (Elbert et al., 2018; Hecker et al., 2013).

It is not possible to discern the mechanisms underlying our findings without conducting a more in-depth study that collects multimodal data. However, GTEX data showed not only that rs53576 genotype may influence *OXTR* expression but that the magnitude and direction of this effect varied across the brain regions assessed (GTEX Consortium et al., 2017). Animal models investigating behavioral responses to threat and fear, have shown that *OXTR* neurotransmission in the central amygdala reduces reactivity to diffuse or distant threats but mediates the transition from passive to active escape behaviors when threat is imminent (as reviewed by Olivera-Pasilio & Dabrowska, 2020). Region-level differences in *OXTR* signaling have also been associated with dominance or offensive aggression behavior. Higher levels of unprovoked aggression have been associated with higher *OXTR* binding in the bed nucleus of the stria terminalis in male rats (Calcagnoli et al., 2014), and lower *OXTR* binding in the ventral and rostral lateral septum of female rats (Oliveira et al., 2021) and male mice, respectively (Lee et al., 2019). If we were to make inferences from these findings, it is possible that the appetitive aggression-associated *OXTR* SNP profile observed in our study group may correspond with brain region-level differences in *OXTR* expression and availability for binding, and thus oxytocinergic signaling. However, this is speculation given that the effects of rs2254298 and rs53575 genotypes on *OXTR* expression in the specific regions mentioned is unknown.

While this exploratory study found associations between two *OXTR* variants and appetitive aggression, certain limitations should be

taken into consideration. First, the study is underpowered to detect small effect sizes, (Cohen's $f^2 = .02$) with the sample size of 232 participants having only 33% power to detect such effects. An *a priori* calculation based on a multiple regression model including a single genetic variant and six covariates would require 725 participants to detect small effect sizes with 80% power. A model including nine predictors (two genotypes plus their interaction, as well as six covariates) would increase the required sample size to 791. However, this is probably a substantial underestimation given that the effect size is likely smaller and the standard error larger for interactions compared to the main effects (Leon & Heo, 2009). Second, the specific genetic ancestry of our study group limits the ability to generalize our results to other population groups, seeing as previous literature indicates differing allele frequencies amongst population groups such as those of European or Asian descent (Butovskaya et al., 2020). Third, our focus on male participants prevents us from making inferences about the role of *OXTR* variants in aggression in females. Fourth, while rodent models have investigated the relationship between *OXTR* variants in relation to behavioral outcomes (Ferguson et al., 2000; Takayanagi et al., 2005), the functionality of *OXTR* rs2254298 and rs53576, either alone or in interaction, has not been investigated. Fifth, we only examined one aspect of aggression pathophysiology, which is known to be multifactorial, with contributions from (epi)genetics, neurotransmission, neuroendocrine systems, and brain structure and function (Slattery & Young, 2019). Finally, our study was not able to account for the broad range of potential psychiatric conditions or adverse mental health states in participants. This limitation is particularly pertinent given the findings of a recent meta-analysis, which included 16,277 cases (defined as having a mental disorder diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders or International Classification of Disease criteria) and 77,586 controls. The analyses indicated that experience of psychological trauma, whether during childhood or adulthood, was a transdiagnostic risk factor for mental disorders (Hogg et al., 2023). Considering the abovementioned limitations, the findings of this study should be interpreted with caution until more extensive and detailed research has been performed.

A strength of our investigation is that aggression studies in the context of trauma exposure are typically investigated in participants who have been exposed to military conflict (Hecker et al., 2013). Whilst war zones are plagued with continuous stressors (Hecker et al., 2013), it is not clear to what degree the findings can be translated to the general population. Stressors resulting from low socioeconomic environments with high levels of violence are globally prevalent, thus allowing for findings of trauma-aggression interactions to be relevant to globally relatable population groups (Atwoli et al., 2015).

This exploratory study is the first to investigate the association between appetitive aggression and the *OXTR* rs2254298 and rs53576 variants in a cohort of South African Xhosa males at high risk for committing aggressive acts. Although these variants have previously been implicated in broader displays of poor social behavior, such as in those with neurodevelopmental disorders, they have not, until now, been investigated in the context of appetitive

aggression. These findings support the hypothesis that appetitive and reactive aggression may arise from opposite effects of a common biological pathway or that the two forms of aggression display differing genetic signatures. Our results add to the limited insight into the genetic etiology of appetitive aggression. Our findings should be replicated in well-powered studies that collect multimodal data from both male and female participants representing a range of genetic ancestries, so that the mechanisms of oxytocin, alone and in interaction with other biological systems, in aggressive phenotypes can be investigated. Such studies could ultimately contribute to better understanding of aggression and inform future studies aimed at identifying risk trajectories, as well as prevention and treatment strategies.

ACKNOWLEDGMENTS

The study was financially supported by the Harry Crossley Foundation. Open access funding was enabled by Stellenbosch University Library. Research reported in this publication was partly supported by the South African Medical Research Council and by the European Research Council (ERC). The work by J. S. W. was made possible through funding by the South African Medical Research Council (SAMRC) through its Division of Research Capacity Development under the Early Investigators Program from funding received from the South African National Treasury. The content hereof is the sole responsibility of the authors and does not necessarily represent the official view of the SAMRC.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets presented in this article are not readily available due to ethical and legal restrictions. Requests to access the data sets should be directed to Sian Hemmings (smjh@sun.ac.za). The authors are open to collaborating and sharing data within the limits of ethical review restrictions and data transfer policies of Stellenbosch University.

ORCID

Catherine Lohrentz  <https://orcid.org/0000-0002-9406-5555>

Jacqueline S. Womersley  <https://orcid.org/0000-0001-9731-4505>

REFERENCES

- Amaya-Jackson, L. (1998). Child's exposure to violence checklist. Adopted from Richter's things i've seen and heard. *Trauma evaluation, treatment and research program*. Center for Child and Family Health.
- Atwoli, L., Stein, D. J., Koenen, K. C., & McLaughlin, K. A. (2015). Epidemiology of posttraumatic stress disorder: Prevalence, correlates and consequences. *Current Opinion in Psychiatry*, 28(4), 307–311. <https://doi.org/10.1097/YCO.0000000000000167>
- Brüne, M. (2012). Does the oxytocin receptor polymorphism (rs2254298) confer 'vulnerability' for psychopathology or 'differential susceptibility'? insights from evolution. *BMC Medicine*, 10, 38. <https://doi.org/10.1186/1741-7015-10-38>
- Bryc, K., Auton, A., Nelson, M. R., Oksenberg, J. R., Hauser, S. L., Williams, S., Froment, A., Bodo, J. M., Wambebe, C., Tishkoff, S. A., & Bustamante, C. D. (2010). Genome-wide patterns of population structure and admixture in West Africans and African Americans. *Proceedings of the National Academy of Sciences of the United States of America*, 107(2), 786–791. <https://doi.org/10.1073/pnas.0909559107>
- Buss, A. H., & Perry, M. (1992). The Aggression Questionnaire. *Journal of Personality and Social Psychology*, 63(3), 452–459. <https://doi.org/10.1037/0022-3514.63.3.452>
- Butovskaya, M., Rostovtseva, V., Butovskaya, P., Burkova, V., Dronova, D., Filatova, V., Sukhodolskaya, E., Vasiliev, V., Mesa, T., Rosa, A., & Lazebny, O. (2020). Oxytocin receptor gene polymorphism (Rs53576) and digit ratio associates with aggression: Comparison in seven ethnic groups. *Journal of Physiological Anthropology*, 39(1), 20. <https://doi.org/10.1186/s40101-020-00232-y>
- Calcagnoli, F., de Boer, S. F., Beiderbeck, D. I., Althaus, M., Koolhaas, J. M., Neumann, I. D. (2014). Local oxytocin expression and oxytocin receptor binding in the male rat brain is associated with aggressiveness. *Behavioural Brain Research*, 261, 315–322. [doi:10.1016/j.bbr.2013.12.050](https://doi.org/10.1016/j.bbr.2013.12.050)
- Campbell, S. B., Spieker, S., Burchinal, M., Poe, M. D., & The NICHD Early Child Care Research Network. (2006). Trajectories of aggression from toddlerhood to age 9 predict academic and social functioning through age 12. *Journal of Child Psychology and Psychiatry*, 47(8), 791–800. <https://doi.org/10.1111/j.1469-7610.2006.01636.x>
- Christ, C. C., Carlo, G., & Stoltenberg, S. F. (2016). Oxytocin receptor (OXTR) single nucleotide polymorphisms indirectly predict prosocial behavior through perspective taking and empathic concern. *Journal of Personality*, 84(2), 204–213. <https://doi.org/10.1111/jopy.12152>
- Craig Cohen, J., Lundblad, L. K., Bates, J. H., Levitzky, M., & Larson, J. E. (2004). The "goldilocks effect" in cystic fibrosis: Identification of a lung phenotype in the cftr knockout and heterozygous mouse. *BMC Genetics*, 5, 21. <https://doi.org/10.1186/1471-2156-5-21>
- van Donkelaar, M. M. J., Hoogman, M., Shumskaya, E., Buitelaar, J. K., Bralten, J., & Franke, B. (2020). Monoamine and neuroendocrine gene-sets associate with frustration-based aggression in a gender-specific manner. *European Neuropsychopharmacology*, 30, 75–86. <https://doi.org/10.1016/j.euroneuro.2017.11.016>
- Elbert, T., Schauer, M., & Moran, J. K. (2018). Two pedals drive the bicycle of violence: Reactive and appetitive aggression. *Current Opinion in Psychology*, 19, 135–138. <https://doi.org/10.1016/j.copsyc.2017.03.016>
- Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, 39(2), 175–191. <https://doi.org/10.3758/BF03193146>
- Ferguson, J. N., Young, L. J., Hearn, E. F., Matzuk, M. M., Insel, T. R., & Winslow, J. T. (2000). Social amnesia in mice lacking the oxytocin gene. *Nature Genetics*, 25(3), 284–288. <https://doi.org/10.1038/77040>
- GTE Consortium, Laboratory, Data Analysis & Coordinating Center (LDACC)—Analysis Working Group, Statistical Methods groups—Analysis Working Group, Enhancing GTE (eGTE) groups, NIH Common Fund, NIH/NCI, NIH/NHGRI, NIH/NIMH, NIH/NIDA, Biospecimen Collection Source Site—NDRI, Biospecimen Collection Source Site—RPCI, Biospecimen Core Resource—VARI, Brain Bank Repository—University of Miami Brain Endowment Bank, Leidos Biomedical—Project Management, ELSI Study, Genome Browser Data Integration & Visualization—EBI, Genome Browser Data Integration & Visualization—UCSC Genomics Institute, University of California Santa Cruz, Lead analysts; Laboratory, Data Analysis & Coordinating Center (LDACC); NIH Program Management; Biospecimen Collection; Pathology; eQTL Manuscript Working Group, Battle, A., Brown, C. D., Engelhardt, B. E., & Montgomery, S. B.

- (2017). Genetic effects on gene expression across human tissues. *Nature*, 550(7675), 204–213. <https://doi.org/10.1038/nature24277>
- Hatcher, A. M., Gibbs, A., Jewkes, R., McBride, R. S., Peacock, D., & Christofides, N. (2019). Effect of childhood poverty and trauma on adult depressive symptoms among young men in peri-urban South African settlements. *Journal of Adolescent Health*, 64(1), 79–85. <https://doi.org/10.1016/j.jadohealth.2018.07.026>
- Hecker, T., Hermenau, K., Maedl, A., Schauer, M., & Elbert, T. (2013). Aggression inoculates against PTSD symptom severity—Insights from armed groups in the Eastern DR Congo. *European Journal of Psychotraumatology*, 4(1), 20070. <https://doi.org/10.3402/ejpt.v4i0.20070>
- Hemmings, S. M. J., Xulu, K., Sommer, J., Hinsberger, M., Malan-Muller, S., Tromp, G., Elbert, T., Weierstall, R., & Seedat, S. (2018). Appetitive and reactive aggression are differentially associated with the STin2 genetic variant in the serotonin transporter gene. *Scientific Reports*, 8(1), 6714. <https://doi.org/10.1038/s41598-018-25066-8>
- Hinsberger, M., Holtzhausen, L., Sommer, J., Kaminer, D., Elbert, T., Seedat, S., Wilker, S., Crombach, A., & Weierstall, R. (2017). Feasibility and effectiveness of narrative exposure therapy and cognitive behavioral therapy in a context of ongoing violence in South Africa. *Psychological Trauma: Theory, Research, Practice and Policy*, 9(3), 282–291. <https://doi.org/10.1037/tra0000197>
- Hinsberger, M., Sommer, J., Kaminer, D., Holtzhausen, L., Weierstall, R., Seedat, S., Madikane, S., & Elbert, T. (2016). Perpetuating the cycle of violence in South African low-income communities: Attraction to violence in young men exposed to continuous threat. *European Journal of Psychotraumatology*, 7(1):29099. <https://doi.org/10.3402/ejpt.v7.29099>
- Hogg, B., Gardoki-Souto, I., Valiente-Gómez, A., Rosa, A. R., Fortea, L., Radua, J., Amann, B. L., & Moreno-Alcázar, A. (2023). Psychological trauma as a transdiagnostic risk factor for mental disorder: An umbrella meta-analysis. *European Archives of Psychiatry and Clinical Neuroscience*, 273(2), 397–410. <https://doi.org/10.1007/s00406-022-01495-5>
- Hovey, D., Lindstedt, M., Zettergren, A., Jonsson, L., Johansson, A., Melke, J., Kerekes, N., Anckarsäter, H., Lichtenstein, P., Lundström, S., & Westberg, L. (2016). Antisocial behavior and polymorphisms in the oxytocin receptor gene: Findings in two independent samples. *Molecular Psychiatry*, 21(7), 983–988. <https://doi.org/10.1038/mp.2015.144>
- Kalyoncu, T., Özbaran, B., Köse, S., and Onay, H. (2019). Variation in the oxytocin receptor gene is associated with social cognition and ADHD. *Journal of Attention Disorders*, 23(7), 702–711. <https://doi.org/10.1177/1087054717706757>
- Kaminer, D., Hardy, A., Heath, K., Mosdell, J., & Bawa, U. (2013). Gender patterns in the contribution of different types of violence to posttraumatic stress symptoms among South African urban youth. *Child Abuse & Neglect*, 37, 320–330. <https://doi.org/10.1016/j.chiabu.2012.12.011>
- Kelly, A. M., & Vitousek, M. N. (2017). Dynamic modulation of sociality and aggression: An examination of plasticity within endocrine and neuroendocrine systems. *Philosophical Transactions of the Royal Society, B: Biological Sciences*, 372(1727), 20160243. <https://doi.org/10.1098/rstb.2016.0243>
- Koh, M. J., Kim, W., Kang, J. I., Namkoong, K., & Kim, S. J. (2015). Lack of association between oxytocin receptor (OXTR) gene polymorphisms and alexithymia: Evidence from patients with obsessive-compulsive disorder. *PLoS One*, 10(11), e0143168. <https://doi.org/10.1371/journal.pone.0143168>
- Lee, W., Hiura, L. C., Yang, E., Broekman, K. A., Ophir, A. G., & Curley, J. P. (2019). Social status in mouse social hierarchies is associated with variation in oxytocin and vasopressin 1a receptor densities. *Hormones and Behavior*, 114, 104551. [doi:10.1016/j.yhbeh.2019.06.015](https://doi.org/10.1016/j.yhbeh.2019.06.015)
- Leng, G., Leng, R. I., & Ludwig, M. (2022). Oxytocin—A social peptide? deconstructing the evidence. *Philosophical Transactions of the Royal Society, B: Biological Sciences*, 377(1858), 20210055. <https://doi.org/10.1098/rstb.2021.0055>
- Leon, A. C., & Heo, M. (2009). Sample sizes required to detect interactions between two binary fixed-effects in a mixed-effects linear regression model. *Computational Statistics & Data Analysis*, 53(3), 603–608. <https://doi.org/10.1016/j.csda.2008.06.010>
- LoParo, D., Johansson, A., Walum, H., Westberg, L., Santtila, P., and Waldman, I. (2016). Rigorous tests of gene-environment interactions in a lab study of the oxytocin receptor gene (OXTR), alcohol exposure, and aggression. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, 171(5), 589–602. <https://doi.org/10.1002/ajmg.b.32359>
- Malik, A. I., Zai, C. C., Abu, Z., Nowrouzi, B., & Beitchman, J. H. (2012). The role of oxytocin and oxytocin receptor gene variants in childhood-onset aggression. *Genes, Brain and Behavior*, 11(5), 545–551. <https://doi.org/10.1111/j.1601-183X.2012.00776.x>
- McKay, M. T., Cannon, M., Chambers, D., Conroy, R. M., Coughlan, H., Dodd, P., Healy, C., O'Donnell, L., & Clarke, M. C. (2021). Childhood trauma and adult mental disorder: A systematic review and meta-analysis of longitudinal cohort studies. *Acta Psychiatrica Scandinavica*, 143(3), 189–205. <https://doi.org/10.1111/acps.13268>
- Miller, J. D., & Lynam, D. R. (2006). Reactive and proactive aggression: Similarities and differences. *Personality and Individual Differences*, 41, 1469–1480. <https://doi.org/10.1016/j.paid.2006.06.004>
- Montag, C., Brockmann, E. M., Bayerl, M., Rujescu, D., Müller, D. J., & Gallinat, J. (2013). Oxytocin and oxytocin receptor gene polymorphisms and risk for schizophrenia: A case-control study. *The World Journal of Biological Psychiatry*, 14(7), 500–508. <https://doi.org/10.3109/15622975.2012.677547>
- Nelson, C. A., Bhutta, Z. A., Burke Harris, N., Danese, A., & Samara, M. (2020). Adversity in childhood is linked to mental and physical health throughout life. *BMJ*, 371, m3048. <https://doi.org/10.1136/bmj.m3048>
- Olivera-Pasilio, V., & Dabrowska, J. (2020). Oxytocin promotes accurate fear discrimination and adaptive defensive behaviors. *Frontiers in Neuroscience*, 14, 583878. <https://doi.org/10.3389/fnins.2020.583878>
- Oliveira, V., DeMoura, E., Lukas, M., Wolf, H. N., Durante, E., Lorenz, A., Mayer, A.-L., Bludau, A., Bosch, O. J., Grinevich, V., Egger, V., De Jong, T. R., & Neumann, I. D. (2021). Oxytocin and vasopressin with in the ventral and dorsal lateral septum modulate aggression in female rats. *Nature Communications*, 12(1), 2900. [doi:10.1038/s41467-021-23064-5](https://doi.org/10.1038/s41467-021-23064-5)
- Onaka, T., & Takayanagi, Y. (2021). The oxytocin system and early-life experience-dependent plastic changes. *Journal of Neuroendocrinology*, 33(11), e13049. <https://doi.org/10.1111/jne.13049>
- Paré-Ruel, M. P., Brendgen, M., Ouellet-Morin, I., Lupien, S., Vitaro, F., Dionne, G., & Boivin, M. (2022). Unique and interactive associations of proactive and reactive aggression with cortisol secretion. *Hormones and Behavior*, 137, 105100. <https://doi.org/10.1016/j.yhbeh.2021.105100>
- Parker, K. J., Garner, J. P., Libove, R. A., Hyde, S. A., Hornbeak, K. B., Carson, D. S., Liao, C. P., Phillips, J. M., Hallmayer, J. F., & Hardan, A. Y. (2014). Plasma oxytocin concentrations and OXTR polymorphisms predict social impairments in children with and without autism spectrum disorder. *Proceedings of the National Academy of Sciences of the United States of America*, 111(33), 12258–12263. <https://doi.org/10.1073/pnas.1402236111>
- Policy and Strategy Department, City of Cape Town. (2013a). *City of Cape Town—2011 census suburb Gugulethu*. Compiled by the Policy and Strategy Department, City of Cape Town, using 2011 Census data supplied by Statistics South Africa.

- Policy and Strategy Department, City of Cape Town. (2013b). *City of Cape Town—2011 census suburb Khayelitsha*. Compiled by the Policy and Strategy Department, City of Cape Town, using 2011 Census data supplied by Statistics South Africa.
- Polman, H., Orobio de Castro, B., Kooops, W., van Boxtel, H. W., & Merk, W. W. (2007). A meta-analysis of the distinction between reactive and proactive aggression in children and adolescents. *Journal of Abnormal Child Psychology*, 35(4), 522–535. <https://doi.org/10.1007/s10802-007-9109-4>
- R Core Team. (2022). *R: A language and environment for statistical computing*.
- Reuter, M., Montag, C., Altmann, S., Bendlow, F., Elger, C., Kirsch, P., Becker, A., Schoch-McGovern, S., Simon, M., Weber, B., & Felten, A. (2017). Functional characterization of an oxytocin receptor gene variant (Rs2268498) previously associated with social cognition by expression analysis in vitro and in human brain biopsy. *Social Neuroscience*, 12(5), 604–611. <https://doi.org/10.1080/17470919.2016.1214174>
- Romero-Martínez, Á., Sarrate-Costa, C., & Moya-Albiol, L. (2022). Reactive vs proactive aggression: A differential psychobiological profile? conclusions derived from a systematic review. *Neuroscience & Biobehavioral Reviews*, 136, 104626. <https://doi.org/10.1016/j.neubiorev.2022.104626>
- Schmid Mast, M., & Hall, J. A. (2018). The impact of interpersonal accuracy on behavioral outcomes. *Current Directions in Psychological Science*, 27(5), 309–314. <https://doi.org/10.1177/0963721418758437>
- Seedat, M., Van Niekerk, A., Jewkes, R., Suffla, S., & Ratele, K. (2009). Violence and injuries in South Africa: Prioritising an agenda for prevention. *The Lancet*, 374(9694), 1011–1022. [https://doi.org/10.1016/S0140-6736\(09\)60948-X](https://doi.org/10.1016/S0140-6736(09)60948-X)
- Shamay-Tsoory, S. G., & Abu-Akel, A. (2016). The social salience hypothesis of oxytocin. *Biological Psychiatry*, 79(3), 194–202. <https://doi.org/10.1016/j.biopsych.2015.07.020>
- Slane, M. M., Lusk, L. G., Boomer, K. B., Hare, A. E., King, M. K., & Evans, D. W. (2014). Social cognition, face processing, and oxytocin receptor single nucleotide polymorphisms in typically developing children. *Developmental Cognitive Neuroscience*, 9, 160–171. <https://doi.org/10.1016/j.dcn.2014.04.001>
- Slattery, D. A., & Young, J. W. (2019). Current status of the neurobiology of aggression and impulsivity. *Neuropharmacology*, 156, 107665. <https://doi.org/10.1016/j.neuropharm.2019.107665>
- Sommer, J., Hinsberger, M., Elbert, T., Holtzhausen, L., Kaminer, D., Seedat, S., Madikane, S., & Weierstall, R. (2017). The interplay between trauma, substance abuse and appetitive aggression and its relation to criminal activity among high-risk males in South Africa. *Addictive Behaviors*, 64, 29–34. <https://doi.org/10.1016/j.addbeh.2016.08.008>
- Takayanagi, Y., Yoshida, M., Bielsky, I. F., Ross, H. E., Kawamata, M., Onaka, T., Yanagisawa, T., Kimura, T., Matzuk, M. M., Young, L. J., & Nishimori, K. (2005). Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. *Proceedings of the National Academy of Sciences of the United States of America*, 102(44), 16096–16101. <https://doi.org/10.1073/pnas.0505312102>
- Thomson, N. D., Kevorkian, S., Blair, J., Farrell, A., West, S. J., & Bjork, J. M. (2021). Psychophysiological underpinnings of proactive and reactive aggression in young men and women. *Physiology & Behavior*, 242, 113601. <https://doi.org/10.1016/j.physbeh.2021.113601>
- Turok, I., Visagie, J., & Scheba, A. (2021). Social inequality and spatial segregation in Cape Town. In M. van Ham, T. Tammaru, R. Ubarevičienė, & H. Janssen (Eds.), *Urban socio-economic segregation and income inequality: A global perspective, the urban book series* (pp. 71–90). Springer International Publishing.
- Vaidyanathan, R., & Hammock, E. A. D. (2017). Oxytocin receptor dynamics in the brain across development and species. *Developmental Neurobiology*, 77(2), 143–157. <https://doi.org/10.1002/dneu.22403>
- Veroude, K., Zhang-James, Y., Fernández-Castillo, N., Bakker, M. J., Cormand, B., & Faraone, S. V. (2016). Genetics of aggressive behavior: An overview. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, 171B(1), 3–43. <https://doi.org/10.1002/ajmg.b.32364>
- Weierstall, R., & Elbert, T. (2011). The Appetitive Aggression Scale—Development of an instrument for the assessment of human's attraction to violence. *European Journal of Psychotraumatology*, 2, 0. <https://doi.org/10.3402/ejpt.v2i0.8430>
- Wu, S., Jia, M., Ruan, Y., Liu, J., Guo, Y., Shuang, M., Gong, X., Zhang, Y., Yang, X., and Zhang, D. (2005). Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han Population. *Biological Psychiatry*, 58(1), 74–77. <https://doi.org/10.1016/j.biopsych.2005.03.013>
- Yang, L., Wang, F., Wang, M., Han, M., Hu, L., Zheng, M., Ma, J., Kang, Y., Wang, P., Sun, H., Zuo, W., Xie, L., Wang, A., Yu, D., & Liu, Y. (2017). Association between oxytocin and receptor genetic polymorphisms and aggression in a Northern Chinese Han Population with alcohol dependence. *Neuroscience Letters*, 636, 140–144. <https://doi.org/10.1016/j.neulet.2016.10.066>
- Zik, J. B., & Roberts, D. L. (2015). The many faces of oxytocin: Implications for psychiatry. *Psychiatry Research*, 226(1), 31–37. <https://doi.org/10.1016/j.psychres.2014.11.048>

SUPPORTING INFORMATION

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

How to cite this article: Lohrentz, C., Womersley, J. S., Swart, P. C., Sommer, J., Hinsberger, M., Elbert, T., Weierstall, R., Kaminer, D., Seedat, S., & Hemmings, S. M. J. (2024). The role of oxytocin receptor gene variants in appetitive aggression: A study in a South African male sample. *Aggressive Behavior*, 50, e22131. <https://doi.org/10.1002/ab.22131>