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Using a Psychopharmacogenetic Approach To Identify the Pathways Through Which—and the People for Whom—Testosterone Promotes Aggression

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Abstract

Little is known about the neurobiological pathways through which testosterone promotes aggression or about the people in whom this effect is observed. Using a psychopharmacogenetic approach, we found that testosterone increases aggression in men ($N = 308$) with select personality profiles and that these effects are further enhanced among those with fewer cytosine-adenine-guanine (CAG) repeats in exon 1 of the androgen receptor (AR) gene, a polymorphism associated with increased AR efficiency. Testosterone's effects were rapid (~30 min after administration) and mediated, in part, by subjective reward associated with aggression. Testosterone thus appears to promote human aggression through an AR-related mechanism and to have stronger effects in men with the select personality profiles because it more strongly upregulates the subjective pleasure they derive from aggression. Given other evidence that testosterone regulates reward through dopaminergic pathways, and that the sensitivity of such pathways is enhanced among individuals with the personality profiles we identified, our findings may also implicate dopaminergic processes in testosterone's heterogeneous effects on aggression.

Keywords

testosterone, aggression, androgen receptor, reward, dopamine, nongenomic, open data

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Despite lay beliefs (Eisenegger, Naef, Snozzi, Heinrichs, & Fehr, 2010) and animal models supporting the role of testosterone in modulating aggression (reviewed in Nelson & Trainor, 2007), there is little experimental evidence for this cause-and-effect relationship in humans. Pharmacological-challenge paradigms that have been developed to establish the causal effects of testosterone on physiology, cognition, and behavior (reviewed in Bos, Panksepp, Bluthé, & van Honk, 2012) have suffered from some key methodological limitations (e.g., exclusively female participants, relatively small sample sizes, and supraphysiological doses of testosterone). These limitations reduce generalizability to men—who are at a greater risk of physical aggression and violence (Daly & Wilson, 1988/2017)—and to real-world situations in which endogenous testosterone fluctuates within a more natural physiological range. Recent studies employing more ecologically relevant doses, which better mimic naturally occurring

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testosterone surges, have shown that a single dose of testosterone can rapidly increase amygdala, hypothalamus, and periaqueductal gray responses to angry facial expressions in men (Goetz et al., 2014) and also increase men's perceptions of their own masculinity—an effect that could lead to overestimations of physical formidability (Welling, Moreau, Bird, Hansen, & Carré, 2016). The first study to use such a dose and measure aggression in healthy young men showed that testosterone's effects were highly variable, increasing aggression only among men high in dominance, low in self-control, or both (Carré et al., 2017). Critical to advancing our understanding of the complex linkage between testosterone and aggression is the identification of biological mechanisms that can both account for this heterogeneity and shed light on the pathways through which testosterone exerts its effects.

In primates, testosterone typically influences behavior via binding to androgen receptors (ARs) and modulating downstream physiological processes (reviewed in McCarthy, 2013). If testosterone-induced aggression is AR dependent, polymorphisms that influence the efficiency of this androgenic pathway—through impairing or bolstering gene transcription or other, nongenomic effects—should directly moderate the effects of testosterone (and also testosterone-personality interactions) on aggression. One functional polymorphism is the number of CAG repeats in exon 1 of the AR gene: Each triplet encodes the amino acid glutamine such that a greater number of cytosine-adenine-guanine (CAG) repeats leads to the production of ARs with longer stretches of glutamine in the N-terminal domain. In vitro experimental work suggests that increasing the number of CAG repeats within the AR gene (or increasing the length of the polyglutamine tract of the AR protein) reduces the receptor's transcriptional potential (Chamberlain, Driver, & Miesfeldi, 1994). In vivo work shows that the correlation between endogenous testosterone and both threat-related amygdala function (Manuck et al., 2010) and self-reported aggression (Vermeersch, T'Sjoen, Kaufman, Vincke, & Van Houtte, 2010) are enhanced among men with relatively fewer CAG repeats. No studies to date, however, have determined whether testosterone's causal effects on behavior are enhanced among men with fewer CAG repeats.

Here, we tested the prediction that testosterone's potentiation of aggressive behavior among men with high-risk personality traits for testosterone-induced aggression—high dominance (Carré et al., 2017), low self-control (Carré et al., 2017), and relatively independent self-construal (Welker et al., 2017)—would be enhanced if the men had relatively efficient ARs (i.e., fewer CAG repeats) but reduced or nonexistent if they had relatively inefficient ARs (i.e., more CAG repeats). To test this prediction, we first created and validated, using an archival data set (N = 114), our measure of personality risk for testosterone-induced aggression. We then validated, for the first time in healthy eugonadal men, a pharmacological-challenge paradigm (N = 13, within subjects) that rapidly modulated testosterone concentrations (within 15 min). We then conducted the largest study to date that has examined the effects of testosterone administration on behavioral aggression (or any other social behavior; N = 308), allowing for a well-powered test of the hypothesized interaction among testosterone, personality, and CAG repeat length.

Method

Participants

Four hundred participants, including students and nonstudents, were recruited through online advertisements and an online participant-recruitment pool.[1] Participants were screened over the phone for eligibility; we excluded those younger than 18 or older than 40, members of sports teams that ban testosterone, those on any prescription medication known to interfere with steroid hormone concentrations, those who were drug or alcohol dependent, and anyone currently diagnosed with any developmental or psychological disorders or with heart conditions. Given that CAG repeat length varied across ethnicity, $F(7, 384) = 5.956$, $p < .001$ (see the Supplemental Material available online), which could introduce confounds associated with ethnicity, we restricted our sample to self-identified White participants (n = 322). An additional 14 participants were excluded from the final analysis because we were unable to determine their CAG repeat length (n = 8) or because they did not complete the measure of aggression (because of technical errors; n = 6). Therefore, 308 men were included in the final sample (see Table 1 for descriptive statistics). All participants provided informed consent to the procedures of the study, which were approved by the Nipissing University Research Ethics Board and consistent with the provisions of Canada's Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans.

Procedure

The procedural timeline is displayed in Figure 1. Each participant was tested in a separate room at one of three testing times (10:00 a.m., 12:30 p.m., or 2:30 p.m.).[2] On arrival, participants completed a consent form, a demographics questionnaire, and personality questionnaires, which took approximately 25 min. Afterward, participants provided the first saliva sample

Table 1. Descriptive Statistics for the Two Drug Groups (Testosterone vs. Placebo)

	Testosterone		Placebo	
Variable	*M*	*SD*	*M*	*SD*
Age (years)	22.747	4.799	22.468	4.322
CAG repeat length	18.539	2.810	18.805	3.016
Personality-risk score	−0.038	0.616	0.038	0.656
Standardized dominance composite	−0.038	0.956	0.038	1.044
Standardized self-control composite	0.041	0.962	−0.041	1.038
Standardized self-construal	−0.036	0.966	0.036	1.035

Note: There were no significant differences between the testosterone and placebo groups on traits, $ts \leq 1.06$, $ps \geq .29$; $n = 154$ for both groups. CAG = cytosine-adenine-guanine.

to assay baseline hormone concentrations and then provided a mouthwash sample for DNA extraction. Next, using a double-blind administration procedure, we randomly assigned each participant to receive a nasal gel containing 11 mg of either testosterone (Natesto) or placebo (the testosterone and placebo gels were administered through two doses of 5.5 mg each, one dose per nostril).

Participants were photographed and then videotaped answering "getting-acquainted" interview questions, which they were told would be shown to another participant in an adjacent testing room. After participants finished the interview questions, they viewed an instructional video for the aggression task (the point-subtraction aggression paradigm, or PSAP), which was disguised as an online decision-making game, and answered several comprehension-check questions. Next, participants watched an interview video featuring a participant being tested in another room, with whom they were told they would be paired during the computer task. In reality, the other player was fictitious; the video was of a White research confederate providing scripted responses to the interview questions (that he was always White further supports our decision to

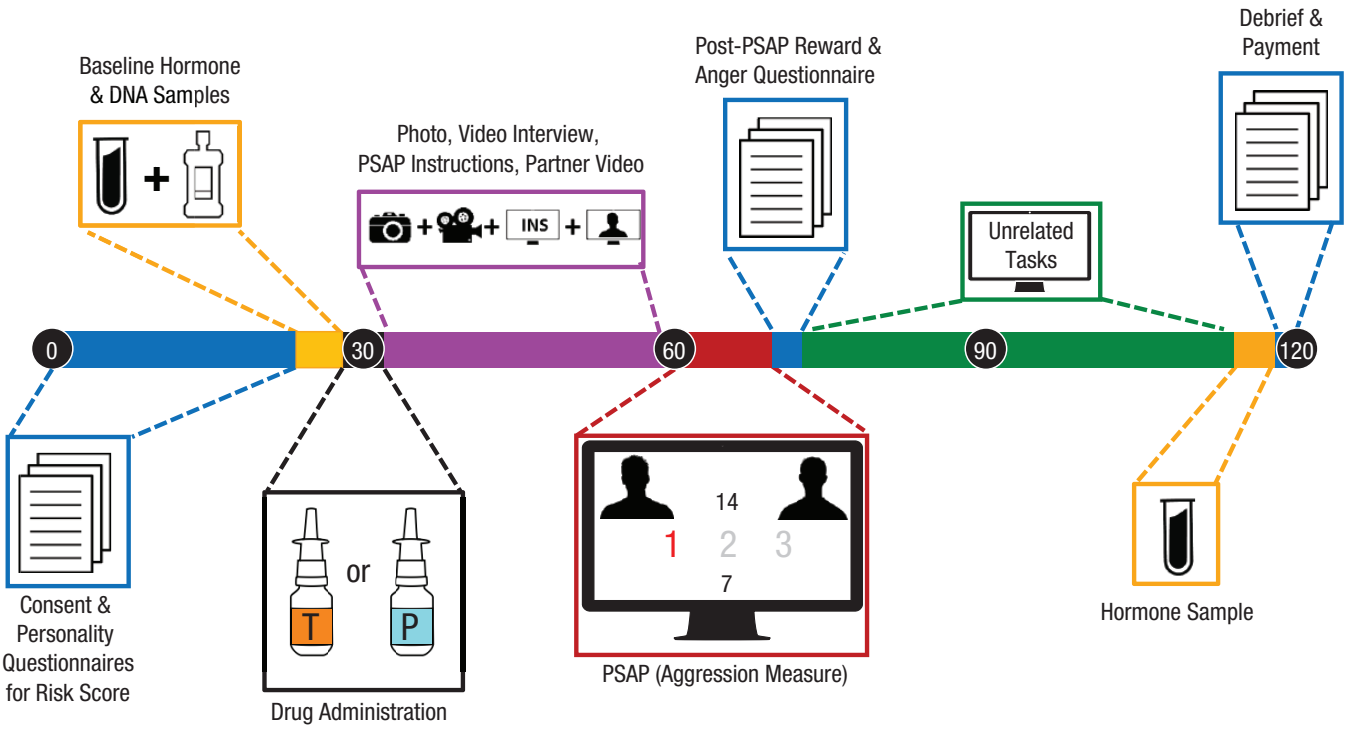

Fig. 1. Procedural timeline. White numbers on the timeline indicate minutes from the beginning of the study. PSAP = point-subtraction aggression paradigm.

include only self-reported White participants in the current study, so as to avoid biases related to playing against an other-ethnicity vs. same-ethnicity opponent). All participants viewed the same video, which was used to enhance the believability of the other player during the PSAP. Participants then completed a brief questionnaire regarding their impressions of the other player and began the PSAP, which started approximately 30 min after participants received the testosterone or placebo gel.

After the PSAP, which lasted 10 min, participants completed a posttask questionnaire, which asked about their impressions of the game and the other player. Participants then completed a battery of other tasks as part of a larger study protocol to answer additional questions unrelated to the current hypotheses (the public-goods game, the Reading the Mind in the Eyes test, the cognitive-reflection test, and the grip-strength test). At the end of the study, participants provided a second, final saliva sample (~80 min after administration of the testosterone or placebo gel) and were debriefed and paid.

Personality questionnaires and the creation of an individual-differences, personality-risk score for testosterone-induced aggression

In previous studies, the effects of testosterone on aggression and competition were stronger among participants higher in dominance (Carré et al., 2017; Mehta et al., 2015) and independent self-construal (Welker et al., 2017) and lower in self-control (Carré et al., 2017; for similar moderator effects involving a genetic polymorphism linked to self-control, see Sjöberg et al., 2008). Because these traits do not, individually, explain a large amount of heterogeneity in the effects of testosterone on aggression, using them as individual moderators within a single model may sacrifice statistical power (by wasting degrees of freedom on their individual interactions and main effects) and overly inflate Type I error rates (Wallace, Frank, & Kraemer, 2013). To circumvent this problem, researchers have combined multiple moderators into single and more powerful risk indices (Wallace et al., 2013). Here, we did so for these personality traits by standardizing the scores on each of the dominance variables (scored as in Carré et al., 2017), self-construal variables (scored as in Welker et al., 2017), and self-control variables (scored as in Carré et al., 2017); reverse-coding the standardized self-control values; and then averaging the three scores to create a single risk index. Higher scores on this index indicated greater risk for testosterone-induced aggression (greater dominance, independent self-construal, and less self-control; see the Supplemental Material for additional information).We first validated this variable as a measure of personality risk for testosterone-induced aggression in an independent, archival data set (Carré et al., 2017) and then used it in the current data set.

Genotyping of AR CAG repeat polymorphism

DNA was collected in mouthwash (Heath et al., 2001) and extracted using the standard phenol-chloroform method. DNA concentrations were determined using a NanoDrop ND-1000 Spectrophotometer (ThermoFisher Scientific, Waltham, MA) and standardized to 10 ng/μL for the polymerase-chain-reaction (PCR) protocol. To investigate CAG repeat length, we amplified an approximately 228-bp fragment of the AR gene using the PCR primers 5′-TCCAGAATCTGTTCCAGAGCGTGC-3′ (forward) and 5′-GCTGTGAAGGTTGCTGTTCCTCAT-3′ (reverse). PCR primers are artificial DNA strands designed to correspond to the start (forward primer) and end (reverse primer) of the DNA fragment of interest. During PCR, the DNA sequence that lies between the two primers is copied thousands of times, resulting in amplification of the fragment of interest. Next, the amplified AR gene fragments were visualized by gel electrophoresis on a LI-COR 4300 DNA analyzer (LI-COR, Lincoln, NE). The AR fragments were compared with DNA markers of known size using Gene ImagIR software (Scanalytics, Milwaukee, WI), which allowed the number of CAG repeats to be determined. CAG repeat numbers ranged between 10 and 30 for our sample, which is consistent with prior studies of CAG repeat numbers in healthy populations (Maney, 2017).

Drug administration

Each participant was randomly assigned, in a double-blind procedure, to receive two syringes containing either testosterone (Natesto) or placebo. The syringes held 5.5 mg of gel each (11 mg total). Under the supervision of a research assistant, participants were asked to apply the gel to the lateral sides of their left and right nostrils (using one syringe per nostril) and to then pinch their nostrils shut to evenly distribute the gel around the nostril walls, where it remained for absorption. After self-administration, participants were instructed to thoroughly sanitize their hands before touching any surfaces to reduce the chance of unintentional contamination of the testing area.

Because this study was the first to employ this drug-administration methodology in healthy, eugonadal men, we first validated the administration procedure in an

independent sample of men (N = 13), using a within-subjects (drug: testosterone vs. placebo) crossover design with a 1-week washout period between the testing days. We used five blood draws to establish the time-course effects of testosterone versus placebo administration on serum hormone concentrations, with blood draws occurring at baseline (preadministration) and at four postadministration sampling times (15, 30, 60, and 180 min after administration). Blood samples (10 ml per sample) were drawn by a phlebotomist, allowed to clot, and then centrifuged at 3,000 rpm to allow for the extraction of serum. The serum was then stored at −20 °C until assayed, in duplicate, using commercial enzyme immunoassay kits from DRG International (Springfield Township, NJ). Intra- and interassay coefficients of variation were 5.89% and 5.91%, respectively.

A 2 (drug: testosterone vs. placebo) × 5 (time: baseline, 15 min, 30 min, 60 min, and 180 min after administration) repeated measures analysis of variance (ANOVA) revealed a significant Drug × Time interaction, $F(4, 48) = 6.515$, $p < .001$, $\eta_p^2 = .352$; specifically, the groups did not differ at baseline, $t(12) = 0.533$, $p = .604$, Cohen's $d = 0.118$, but did significantly differ at each of the postadministration time points, $t(12) > 3.573$, ps < .005 (Fig. 2). The drug caused a sharp increase in serum testosterone within 15 min, and testosterone concentrations remained significantly elevated (compared with placebo) throughout the duration of the study until 180 min after administration (see Fig. 2)—15 min: $t(12) = 3.725$, $p = .003$; 30 min: $t(12) = 3.629$, $p = .003$; 60 min: $t(12) = 3.573$, $p = .004$; 180 min: $t(12) = 4.943$, $p < .001$; Cohen's d was 0.884, 1.020, 1.090, and 0.673 at 15, 30, 60, and 180 min after administration, respectively. Therefore, we decided to begin behavioral testing in the main experiment at 30 min after administration, which is well within the time window during which concentrations of serum testosterone were significantly elevated using this administration procedure. Participants were not more accurate than chance at guessing the condition to which they were assigned (see the Supplemental Material for this and further analyses involving participants' guesses), suggesting that there were no consciously detectible symptoms or signs associated with testosterone versus placebo administration.

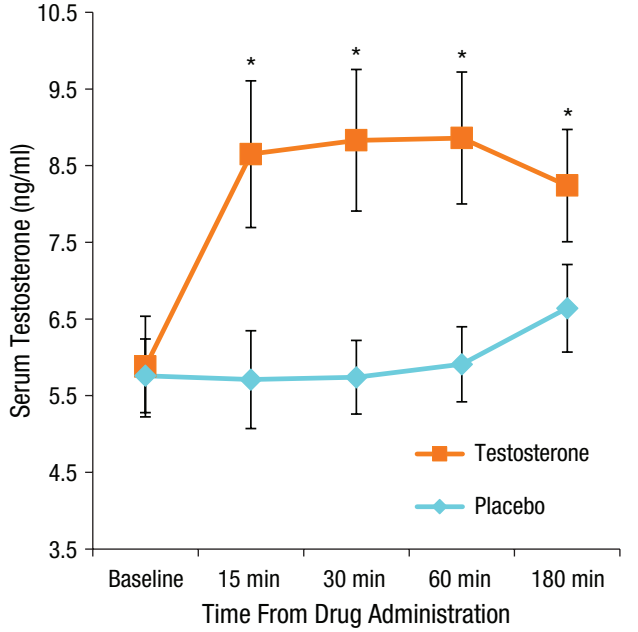

Fig. 2. Pharmacokinetic data showing the time-course effects of drug (testosterone vs. placebo) on serum testosterone concentrations in an independent sample (N = 13, within-subjects crossover design). Blood samples were drawn immediately preceding administration (baseline) and at several times (15, 30, 60, 180 min) after administration. Error bars represent standard errors of the mean. Asterisks indicate significant differences between drug ($p < .005$).

Behavioral measure of aggression

The PSAP is a well-validated laboratory measure of behavioral aggression (see Geniole, MacDonell, & McCormick, 2017, for a review). Here, we used the same version and scoring of the task described in previous work (Carré et al., 2017). In the PSAP, participants are told they will be playing a computer game with another participant, and their goal is to earn points exchangeable for money at the end of the study (here, participants were paid $0.50 per point). To earn points, the participants must repeatedly press a key on the keyboard that is designated for earning points, with 100 consecutive presses required to receive each point. Once they press the earn key 100 consecutive times, "+" signs surround their point counter, which flashes several times and displays a 1-point increase. Throughout the task, however, participants are told that they might notice their point counter flash several times in a red font with "-" signs around it and decrease by 1 point, indicating that the other player has stolen a point from them. They can respond in one of three ways: continue earning points by pressing the earn key, press a different "protect" key to protect their points for a variable amount of time (with 10 consecutive presses initiating a provocation-free period in which the other player's attempts to steal points will be blocked), or press a third "steal" key to steal a point from the other player (with 10 consecutive presses stealing a single point from the other player). However, participants are told that—unlike the other player—they have been randomly assigned to a condition in which they do not get to keep the points they steal. In other words, stealing from the other player reduces the other player's points but does not increase the participant's points.

Because stealing reduces the earnings of the other player but comes at no financial benefit to the

participant, such behavior is consistent with aggression, which is defined as causing harm to other individuals who would rather avoid such treatment, with the harm not necessarily being physical (e.g., it can be emotional or financial; Baron & Richardson, 1994). Consistent with the idea that stealing in the PSAP represents a form of behavioral aggression, results show that individuals who self-report being more aggressive, and populations known for their elevated levels of aggression and hostility (e.g., violent criminals, individuals with intermittent explosive disorder) steal more points on average in the PSAP than do control groups and individuals who report being less aggressive (see Geniole et al., 2017, for a review). Therefore, we used the number of steal presses as our measure of aggression. Because the provocation schedule throughout the PSAP varied across participants, we used the number of steal presses divided by the number of times the participant was provoked in our analysis, consistent with previous work (Carré et al., 2017). Further, aggression can be either proactive, occurring in the absence of provocation, or reactive, occurring in response to provocation. Given that participants were provoked throughout the task, with the first provocation occurring just 45 s into the task, their steal presses (and, thus, our measure of aggression) primarily reflect reactive aggression.

Feelings of pleasure and anger during the PSAP

To determine whether drug effects on PSAP aggression can be explained, in part, by variation in feelings of pleasure or anger during the PSAP, we administered a posttask questionnaire that asked two questions: "Did it make you feel good when you stole points from your game partner?" and "To what extent did you become angry when your game partner stole points from you?" Participants responded using 7-point Likert scales ranging from 1 (*not at all*) to 7 (*very much so*). Because participants' responses to the first question regarding reward were conditional on stealing, participants who did not steal, or who wrongly reported that they did not steal, were not included in the reward analyses (leaving a subsample of 224; $M = 2.81$, $SD = 1.38$). The question about anger was applicable to all participants, but 2 participants failed to provide a response (leaving a subsample of 306; $M = 2.49$, $SD = 1.22$).

Saliva collection and hormone determination

To verify that the drug administration boosted testosterone concentrations in the larger sample (as it did in the independent pharmacokinetic study described previously), we collected a 1- to 2-ml saliva sample from participants after they completed the personality questionnaires but before they received the testosterone or placebo gel (baseline sample). Saliva was collected by asking participants to passively drool into a 5-ml polystyrene tube. Approximately 80 min after administration of the testosterone or placebo gel (and after the PSAP), participants provided a second and final 1- to 2-ml saliva sample. Samples were stored at −20 °C until the time of hormone determination, at which point samples were thawed and centrifuged. The supernatant was then extracted and analyzed (in duplicate) using commercial enzyme immunoassay kits from DRG International (mean coefficients of variation: intra-assay = 8.45%; interassay = 12.46%).

A 2 (drug group: testosterone vs. placebo) × 2 (time: preadministration vs. postadministration) mixed factorial ANOVA revealed a significant interaction between drug group and time, $n = 305$, $F(1, 303) = 27.397$, $p < .001$, $\eta_p^2 = .083$, confirming that the drug elevated postadministration testosterone concentrations compared with the placebo, $t(303) = 5.220$, $p < .001$, Cohen's $d = 0.598$, but the groups did not differ at baseline, before administration, $t(303) = 0.158$, $p = .875$, Cohen's $d = 0.018$. Three participants' samples were not included in these analyses because they either were outside the range of the standard curve of the kits ($n = 1$) or did not provide enough saliva for analyses ($n = 2$).

Statistical analyses

In our initial analysis of the three-way interaction between drug group (testosterone vs. placebo), personality-risk score, and CAG repeat length, we identified some ($n = 19$, 6% of sample) highly influential participants in the model (Cook's Ds $> 4/n$; Fox, 1991).[3] To account for this high level of influence but maintain statistical power, we conducted our analyses using a form of robust regression (lmrob command in the *robustbase* package; Maechler et al., 2016) in the R programming environment (Version 3.4.1; R Core Team, 2017). This robust regression down-weights the influence of participants in the model depending on their degree of deviance from the model's predicted values; participants who are more deviant are down-weighted to a greater extent than are those who are less deviant. This robust analysis approach is preferred to excluding cases because it better preserves power and limits Type I error rates (Field & Wilcox, 2017). Robust regression was also preferred to nonrobust regression given that our data violated some key assumptions of linear regression. Specifically, the errors from the main model were heteroskedastic (nonconstant variance score test: $p = .03$) and also nonnormal (positively skewed and leptokurtic; Kolmogorov-Smirnov and Shapiro-Wilk tests of normality: ps $< .001$). Such violations can

severely bias the standard errors, confidence intervals (CIs), and *p* values and ultimately inflate Type I error rates or reduce statistical power. Researchers thus recommend robust variants of linear regression when such assumptions are violated (Field & Wilcox, 2017). Therefore, robust regression was used to account for both the influential cases and the violations of assumptions mentioned above.

To test our main prediction that the effect of testosterone (both alone and in combination with personality) on aggression is exaggerated among men with fewer versus more CAG repeats, we entered drug group (testosterone vs. placebo), personality-risk score, CAG repeat length, and their interactions as predictors of aggression in a robust regression analysis. Follow-up conditional effects were conducted at relatively low and high levels (±1 *SD*) of personality-risk score and CAG repeat length. To ease interpretation of regression coefficients and results, we standardized CAG repeat length and the personality-risk score so they were centered at zero, and the unstandardized regression coefficients (*b* weights) for these variables represent the extent to which aggression changes with a 1-standard-deviaton increase in CAG repeat length or in personality-risk score. We also coded drug group so it was centered at zero but with a 1-unit distance between the testosterone and placebo conditions, so that the *b* weights corresponding to this variable represent the difference in aggression between participants who received testosterone and those who received the placebo. For effect sizes, we report Cohen's *d* and *r* values (note that these values represent the effect sizes controlling statistically for other predictors in the model). Two-tailed tests were used for all analyses. No statistical corrections (e.g., adjustments for multiple comparisons) were made.

Open practices statement

Although the current study was not preregistered, our decision to investigate the described personality traits and CAG repeat length was well grounded in previous research showing a clear role of these personality traits (e.g., Carré et al., 2017; Welker et al., 2017) and of CAG repeat length (both from in vivo and in vitro work; e.g., Chamberlain et al., 1994; Choong, Kemppainen, Zhou, & Wilson, 1996; Manuck et al., 2010; Vermeersch et al., 2010) in moderating the effects of testosterone. The work regarding personality came directly from the labs of the authors of this article. Following open science practices, we have posted our anonymized data set and analysis code to allow for replication of our results on the Open Science Framework (osf.io/3jhr7).

Results

Archival data set (N = 114)

As predicted, men with higher personality-risk scores were more vulnerable to the aggression-inducing effects of testosterone than were men with lower personality-risk scores (see Fig. 3 and Table 2).

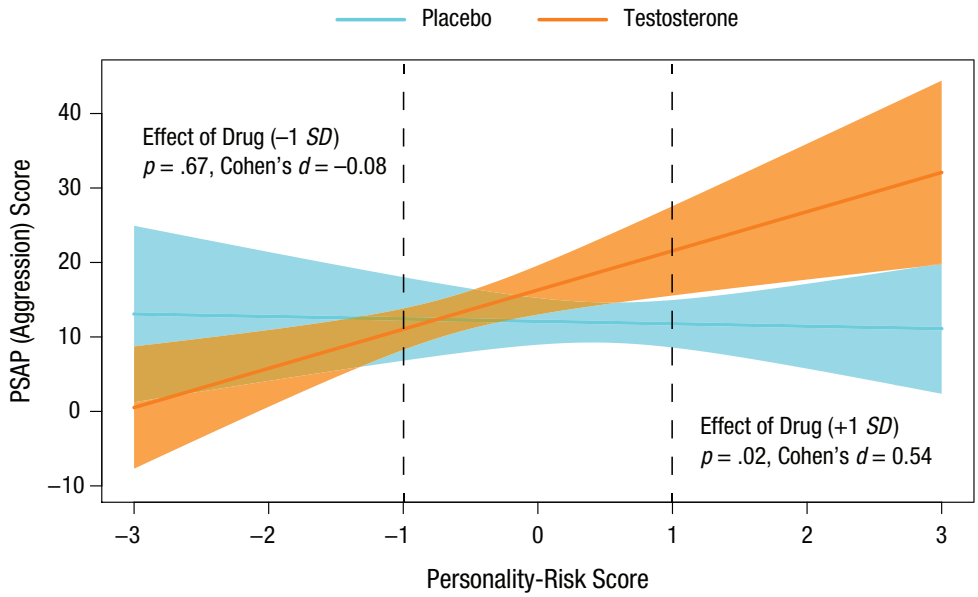

Fig. 3. Aggression (measured using the point-subtraction aggression paradigm, or PSAP) as a function of standardized personality-risk score and drug group (testosterone vs. placebo) in an archival data set (N = 114). Shaded bands represent 95% confidence intervals. Conditional effects of drug group were tested at low (–1 *SD*) and high (+1 *SD*) personality-risk scores (indicated by the dashed lines).

Table 2. Results of Robust Regression Analysis Involving Personality-Risk Score, Drug Group, and Their Interaction as Predictors of Behavioral Aggression in the Archival Data Set ($N = 114$)

Analysis and predictor of aggression	*b*	*SE*	*t*(110)	*p*	*r*	*d*	95% CI (*d*)
Analysis A							
Personality-risk score	2.467	1.210	2.038	.044	.191	0.389	[0.007, 0.771]
Drug group	4.205	2.371	1.774	.079	.167	0.338	[–0.042, 0.719]
Drug Group × Personality-Risk Score	5.589	2.360	2.368	.020	.220	0.452	[0.069, 0.835]
Analysis B							
Drug group's conditional effect at low personality-risk score	–1.384	3.200	–0.432	.666	.041	0.082	[–0.296, 0.460]
Drug group's conditional effect at high personality-risk score	9.793	3.484	2.811	.006	.259	0.536	[0.151, 0.921]

Note: In Analysis A, the personality-risk score was standardized prior to its entry into the model, so its *b* weight represents the extent to which aggression differs with a 1-standard-deviation increase in personality-risk score when drug group is at the average of the testosterone and placebo groups and controlled statistically. Drug group was coded and centered so its *b* weight reflects the difference in aggression between the two groups when personality-risk score was at the mean and controlled statistically. Pearson's *r* and Cohen's *d* values represent the corresponding variable's effect size when all other variables in the model were at their mean and controlled statistically. In Analysis B, the same model was run, but risk was transformed to test the conditional effects of drug group at low risk (–1 *SD*) and high risk (+1 *SD*). CI = confidence interval.

Current data set

Are the effects of testosterone (both alone and in combination with personality-risk scores) exaggerated for men with fewer CAG repeats? Testosterone promoted aggression among participants with high personality-risk scores (see Table 3), replicating findings from the archival data set. This conditional effect was further enhanced among men with fewer CAG repeats (i.e., more efficient ARs; Fig. 4, Table 4). For a simpler model involving only CAG repeat length, drug group, and their interaction, see Table 5.

Are testosterone's effects at high personality risk and low CAG repeat length explained, in part, by variation in feelings of reward or anger? In a secondary set of analyses (involving subsets of participants for whom we had available data; see Method), we also found that testosterone (among high-personality-risk, low-CAG-repeat men) upregulated the pleasure derived from demonstrating aggression, $n = 224$, $b = 0.889$, $SE = 0.361$, $t(216) = 2.463$, $p = .015$, $r = .165$, Cohen's $d = 0.335$, 95% CI = [0.065, 0.605], but not anger experienced in response to provocation, $n = 306$, $b = 0.207$, $SE = 0.362$, $t(298) = 0.572$, $p = .568$, $r = .033$, Cohen's $d = 0.066$, 95%

Table 3. Results of Robust Regression Involving Personality-Risk Score, Drug Group, and Their Interaction as Predictors of Behavioral Aggression in the Current Data Set ($N = 308$)

Analysis and predictor of aggression	*b*	*SE*	*t*(304)	*p*	*r*	*d*	95% CI (*d*)
Analysis A							
Personality-risk score	1.733	0.631	2.745	.006	.156	0.315	[0.088, 0.542]
Drug group	2.059	1.095	1.880	.061	.107	0.216	[–0.010, 0.442]
Drug Group × Personality-Risk Score	2.535	1.249	2.029	.043	.116	0.233	[0.007, 0.459]
Analysis B							
Drug group's conditional effect at low personality-risk score	–0.476	1.295	–0.368	.713	.021	–0.042	[–0.268, 0.184]
Drug group's conditional effect at high personality-risk score	4.594	1.960	2.343	.020	.133	0.269	[0.042, 0.496]

Note: In Analysis A, the personality-risk score was standardized prior to its entry into the model, so its *b* weight represents the extent to which aggression differs with a 1-standard-deviation increase in personality-risk score when drug group is at the average of the testosterone and placebo groups and controlled statistically. Drug group was coded and centered so its *b* weight reflects the difference in aggression between the two groups when personality-risk score was at the mean and controlled statistically. Pearson's *r* and Cohen's *d* values represent the corresponding variable's effect size when all other variables in the model were at their mean and controlled statistically. In Analysis B, the same model was run, but risk was transformed to test the conditional effects of drug group at low risk (–1 *SD*) and high risk (+1 *SD*). CI = confidence interval.

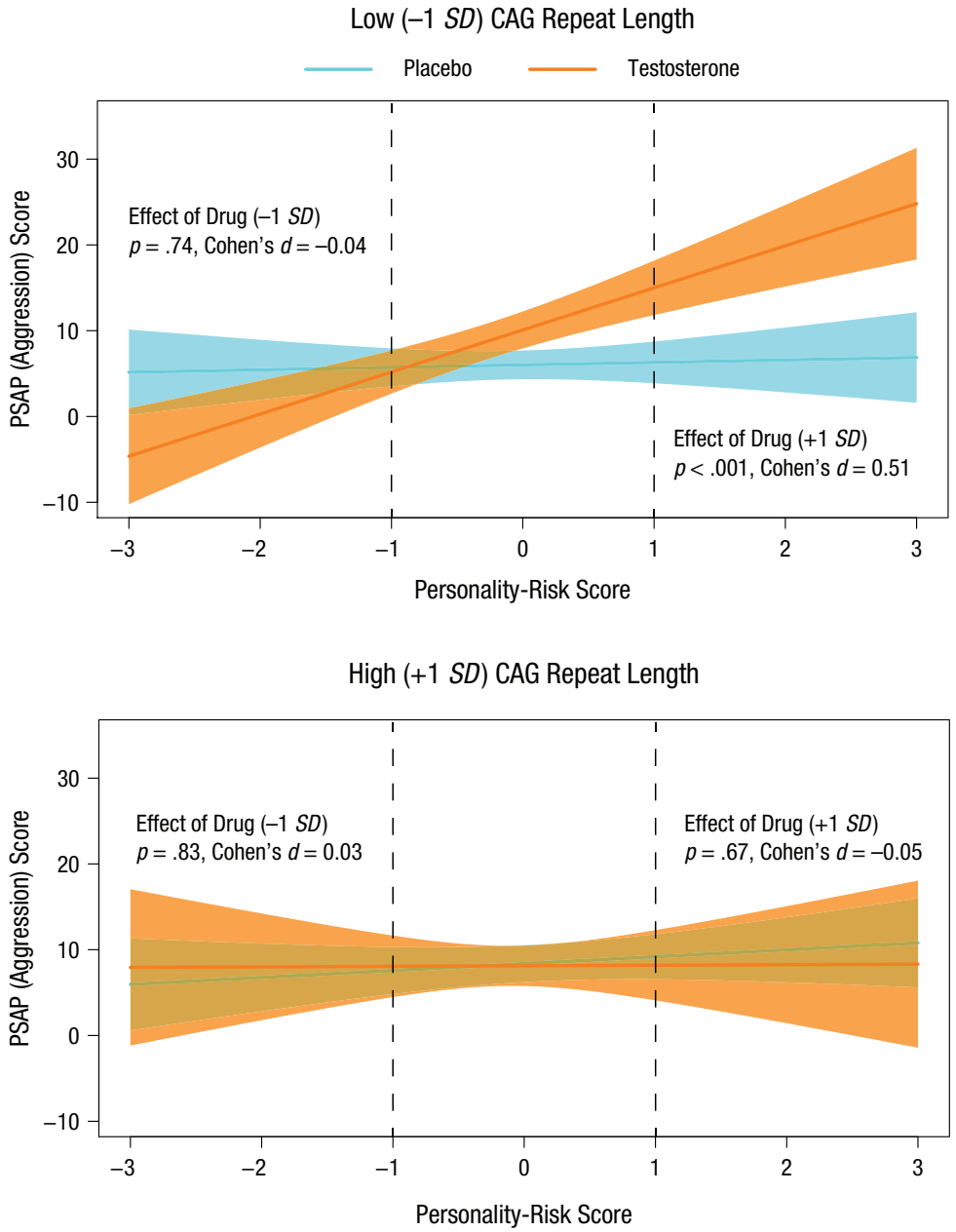

Fig. 4. Aggression (measured using the point-subtraction aggression paradigm, or PSAP) as a function of standardized personality-risk score and drug group (testosterone vs. placebo) in the current data set ($N = 308$). Results are shown separately for participants with low (–1 *SD*) and high (+1 *SD*) cytosine-adenine-guanine (CAG) repeat length. Shaded bands represent 95% confidence intervals. Conditional effects of drug group were tested at low (–1 *SD*) and high (+1 *SD*) personality-risk scores (indicated by the dashed lines).

CI = [–0.162, 0.294].[4] Further, the conditional effect of testosterone on aggression among high-risk, low-CAG-repeat men within this subset of participants, $n = 224$, $b = 7.960$, $SE = 2.201$, $t(216) = 3.617$, $p < .001$, $r = .239$, Cohen's $d = 0.492$, 95% CI = [0.220, 0.764], was weaker and nonsignificant, $b = 3.940$, $SE = 2.396$, $t(212) = 1.644$, $p = .102$, $r = .112$, Cohen's $d = 0.226$, 95% CI = [–0.046, 0.498], when pleasure (and its interactions with personality-risk score and CAG repeat length) was included in the model. Conversely, within this model, higher pleasure (among high-personality-risk, low-CAG-repeat men) was associated with greater aggression during the task, $n = 224$, $b = 4.031$,

Table 4. Results of Robust Regression Involving CAG Repeat Length, Personality-Risk Score, Drug Group, and Their Interactions as Predictors of Behavioral Aggression in the Current Data Set ($N = 308$)

Analysis and predictor of aggression	*b*	*SE*	*t*(300)	*p*	*r*	*d*	95% CI (*d*)
Analysis A							
CAG repeat length	0.100	0.472	0.212	.832	.012	0.024	[–0.203, 0.251]
Personality-risk score	1.515	0.582	2.603	.010	.149	0.301	[0.072, 0.530]
Drug group	1.910	1.023	1.868	.063	.107	0.216	[–0.012, 0.444]
Personality-Risk Score × CAG Repeat Length	–1.081	0.500	–2.165	.031	.124	–0.250	[–0.478, –0.022]
Drug Group × CAG Repeat Length	–2.161	0.927	–2.332	.020	.133	–0.269	[–0.497, –0.041]
Drug Group × Personality-Risk Score	1.938	1.154	1.679	.094	.096	0.194	[–0.034, 0.422]
Drug Group × Personality-Risk Score × CAG Repeat Length	–2.681	1.005	–2.667	.008	.152	–0.308	[–0.537, –0.079]
Analysis B							
Drug Group × Personality-Risk Score at Low CAG Repeat Length	4.619	1.266	3.649	< .001	.206	0.421	[0.191, 0.651]
Drug Group × Personality-Risk Score at High CAG Repeat Length	–0.743	1.756	–0.423	.673	.024	–0.049	[–0.276, 0.178]
Analysis C							
Drug group's conditional effect at low CAG repeat length, low personality-risk score	–0.548	1.668	–0.328	.743	.019	–0.038	[–0.265, 0.189]
Drug group's conditional effect at low CAG repeat length, high personality-risk score	8.691	1.966	4.420	< .001	.247	0.510	[0.279, 0.741]
Drug group's conditional effect at high CAG repeat length, low personality-risk score	0.481	2.211	0.218	.828	.013	0.025	[–0.202, 0.252]
Drug group's conditional effect at high CAG repeat length, high personality-risk score	–0.994	2.333	–0.426	.670	.025	–0.049	[–0.276, 0.178]

Note: In Analysis A, cytosine-adenine-guanine (CAG) repeat length and the personality-risk score were standardized prior to their entry into the model, so their *b* weights represent the extent to which aggression differs with a 1-standard-deviation increase in the variable when other variables in the model are at the mean (or in the case of drug group, at the average of the testosterone and placebo groups) and controlled statistically. Drug group was coded and centered so its *b* weight reflects the difference in aggression between the two groups when the other variables in the model are at the mean and controlled statistically. Pearson's *r* and Cohen's *d* values represent the corresponding variable's effect size when all other variables in the model are at their mean and controlled statistically. In Analysis B, the same models were run, but the values on CAG repeat length were changed to test the Drug Group × Personality-Risk Score interaction at low (–1 *SD*) and high (+1 *SD*) CAG repeat length. In Analysis C, personality-risk score was also changed to test the conditional effects of drug group at low risk (–1 *SD*) and high risk (+1 *SD*) while CAG repeat length was low or high. CI = confidence interval.

SE = 0.946, $t(212) = 4.260$, $p < .001$, $r = .281$, Cohen's $d = 0.585$, 95% CI = [0.308, 0.862]. Therefore, testosterone appears to increase aggression in high-personality-risk, low-CAG-repeat men, in part, by upregulating the pleasure they derive from such behavior.

Discussion

Testosterone promoted aggression in men with high-risk personality profiles consisting of high dominance, relatively independent self-construal, and low self-control, and these effects on behavior were enhanced among men with fewer CAG repeats (i.e., more efficient ARs). The moderation by CAG repeat length provides the clearest, albeit correlational, evidence to date that testosterone's effects on human aggression are likely AR dependent. Further, the rapidity with which testosterone affected behavior (within 30 min), the quickest effects of testosterone on human social behavior reported to date, suggests a nongenomic mechanism of action. Genomic effects are expected to peak hours after steroid hormone exposure, although changes in transcriptional activity have been observed within 10 min in rodent models (see Foradori, Weiser, & Handa, 2008, for a review).

These potentially nongenomic effects may have been enhanced among men with fewer CAG repeats because of this polymorphism's association with AR protein expression and binding-site availability (Choong et al., 1996). Evidence for nongenomic, binding-dependent actions of the AR on neural tissue comes primarily from rodent studies: Testosterone enhanced spatial memory in male rats within 30 min (Jacome et al., 2016) and also modulated spine density in hippocampal tissue, which is critical for memory formation (Hatanaka et al., 2015)—an effect that was abolished by AR antagonists but not by translational and transcriptional inhibitors (Hatanaka et al., 2015). These neural-tissue effects also

Table 5. Results of Robust Regression Analysis Involving CAG Repeat Length, Drug Group, and Their Interaction as Predictors of Behavioral Aggression in the Current Data Set ($N = 308$)

Analysis and predictor of aggression	*b*	*SE*	*t*(304)	*p*	*r*	*d*	95% CI (*d*)
Analysis A							
CAG repeat length	0.171	0.493	0.346	.730	.020	0.040	[–0.186, 0.266]
Drug group	1.361	1.070	1.272	.204	.073	0.146	[–0.080, 0.372]
Drug Group × CAG Repeat Length	–1.982	0.990	–2.002	.046	.114	–0.230	[–0.456, –0.004]
Analysis B							
Drug group's conditional effect at low CAG repeat length	3.343	1.459	2.291	.023	.130	0.263	[0.036, 0.490]
Drug group's conditional effect at high CAG repeat length	–0.622	1.456	–0.427	.670	.024	–0.049	[–0.275, 0.177]

Note: In Analysis A, cytosine-adenine-guanine (CAG) repeat length was standardized prior to its entry into the model, so its *b* weight represents the extent to which aggression differs with a 1-standard-deviation increase in CAG repeat length when drug group is at the average of the testosterone and placebo groups and controlled statistically. Drug group was coded and centered so its *b* weight reflects the difference in aggression between the two groups when CAG repeat length was at the mean and controlled statistically. Pearson's *r* and Cohen's *d* values represent the corresponding variable's effect size when all other variables in the model were at their mean and controlled statistically. In Analysis B, the same model was run, but CAG repeat length was transformed to test the conditional effects of drug group at low (–1 *SD*) and high (+1 *SD*) CAG repeat length. CI = confidence interval.

persisted when testosterone administration was paired with aromatase and 5-α-reductase inhibitors (Hatanaka et al., 2015), indicating that testosterone acted directly rather than indirectly through its conversion to estradiol or dihydrotestosterone metabolites. Our findings thus represent a critical extension of this work, suggesting that such rapid (30-min) effects may also influence human social behavior.

In addition to shedding light on a potential neurobiological pathway, we aimed to tease apart two psychological processes through which testosterone may influence aggression: the modulation of anger and reward. We found that testosterone's conditional effects on aggression were partly explained by increases in feelings of reward associated with aggression, rather than by increases in anger associated with provocation. This finding extends previous work showing (a) that testosterone increases sensitivity to reward (van Honk et al., 2004) and activity in reward-related brain regions (e.g., nucleus accumbens; Hermans et al., 2010) and (b) that people regulate the severity of aggression on the basis of how rewarding they consider it to be and the extent to which they show activation in reward-related brain regions during the decision to demonstrate aggression (see Chester, 2017, for a review).

If testosterone does regulate aggression by modulating reward, the dopaminergic system may be involved. In rodents, testosterone administration enhances dopaminergic activity in reward regions of the brain within 30 min (de Souza Silva, Mattern, Topic, Buddenberg, & Huston, 2009), and testosterone's rewarding effects are abolished when dopamine receptor antagonists are administered to the nucleus accumbens (Packard, Schroeder, & Alexander, 1998). Additionally, the *winner effect*—an increased likelihood of winning an agonistic contest if it is preceded by previous victories rather than losses—is dependent on postcontest testosterone surges that occur after each of the preceding victories; bigger surges lead to greater upregulation of AR expression in the nucleus accumbens and ventral tegmental area, which in turn is associated with more aggressive behavior during the bouts (for a recent review, see Fuxjager, Trainor, & Marler, 2017). Critically, the winner effect is abolished with dopamine receptor antagonists (Becker & Marler, 2015), highlighting dopamine and reward as mediating mechanisms. Therefore, if testosterone modulates aggression by upregulating the pleasure derived from—or anticipated in response to—aggression, these effects may be mediated by the rapid regulation of dopamine.

Dopaminergic mediation could also account for the high-risk personality traits we identified, as each of the traits has been linked to reward-related, dopaminergic function (dominance: see Qu, Ligneul, Van der Henst, & Dreher, 2017, for a review; high independence among European Americans: Kitayama et al., 2014; low self-control: Buckholtz et al., 2010). If dopamine-mediated, testosterone may more strongly promote aggression among individuals with this personality profile because the profile may be indicative of an underlying hypersensitive dopaminergic system. It will be important to test this possibility in future studies. It is also possible, however, that individuals with this profile previously engaged in more conflicts—and experienced greater success in those conflicts—than did other men and that this differential success rate exaggerated the effects of testosterone on aggression reported here.

There are limitations to the current study that warrant some discussion. First, we indexed participants' feelings of reward (and anger) using single-item measures obtained only after they performed the PSAP. Thus, although we speculate that testosterone increases

aggression through a reward-related mechanism, the temporal sequence of data collection does not permit strong conclusions about the causal psychological mechanisms underlying testosterone's effect on aggression. It will be important for future research to consider using more broad and dynamic indices of reward and anger (e.g., assessment of facial affect or reward- and anger-related neural responses while participants perform the PSAP). Such dynamic indices may permit researchers to examine more effectively the prediction that testosterone increases the extent to which participants anticipate reward in response to aggression and that such anticipation of reward promotes the expression of aggression. Another limitation is that we did not manipulate AR availability and thus cannot be certain that testosterone's effects on aggression occur through an AR-dependent mechanism. Future testosterone-administration work involving pharmacological manipulation of AR availability (e.g., through the use of an AR blocker) will be required to determine whether testosterone's effects (and interactions with personality-risk score) on aggression occur through an AR-dependent mechanism.

We conclude, then, that testosterone's effects on aggression depend on personality, with the strongest effects among men high in dominance and independent self-construal and low in self-control. Further, we provide novel evidence that these effects may be AR dependent and nongenomic and that they may function by upregulating subjective reward associated with aggression. Although these reward-related effects highlight the potential involvement of the dopaminergic system, future work is needed to more directly establish the involvement of this pathway and to rule out alternative, nonandrogenic and genomic mechanisms of action. The use of multiple testing times to capture both rapid (5–60 min) and more delayed effects (4 hr or more) of testosterone would be beneficial; indeed, studies involving longer delays (4 hr: Eisenegger et al., 2010; 17.5 hr: Dreher, Dunne, Pazderska, Frodl, & Nolan, 2016) have identified prosocial effects of testosterone, highlighting the possibility that this hormone exerts different (and potentially opposite) slow versus rapid effects. It will also be important to employ behavioral measures that tap into both prosocial and antisocial behavior simultaneously (Dreher et al., 2016). One possibility is that the personality-risk score developed here also accounts for heterogeneity in testosterone's prosocial effects, with exaggerated prosocial behavior among individuals with lower personality-risk scores. Additionally, some work suggests that testosterone administration has similar effects on threat-related neural processing in men and women but that competition-induced surges in salivary testosterone better predict male than female aggression (see Geniole & Carré, 2018, for a review). Nevertheless, it will be important to use a pharmacological-challenge approach and manipulate testosterone to determine whether its causal effects on aggression are similar in women as they were here for men. Finally, because of the rapid rise of testosterone-replacement therapy (e.g., a 3-fold increase in the last decade; Baillargeon, Urban, Ottenbacher, Pierson, & Goodwin, 2013), it will also be important to determine whether these interactive personality-risk effects extend to more chronic doses of testosterone, such as those used in the treatment of hypogonadism.

Action Editor

Steven W. Gangestad served as action editor for this article.

Author Contributions

J. M. Carré and N. V. Watson designed the study; T. L. Ortiz and N. Marley performed the experiments. P. L. Bonin and B. Goldfarb provided medical supervision for testosterone administration. T. L. Procyshyn, N. Marley, and A. L. Marcellus conducted the genotype and hormone analyses. S. N. Geniole and J. M. Carré analyzed the data and wrote the manuscript; S. N. Geniole and B. M. Bird prepared the figures. All authors provided edits and conceptual advice for the final manuscript.

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Declaration of Conflicting Interests

The author(s) declared that there were no conflicts of interest with respect to the authorship or the publication of this article.

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Supplemental Material

Additional supporting information can be found at http://journals.sagepub.com/doi/suppl/10.1177/0956797619826970

Open Practices

The complete anonymized data set and analysis code have been made publicly available via the Open Science Framework and can be accessed at osf.io/3jhr7. Materials have not been made publicly available, and the design and analysis plans were not preregistered. The complete Open Practices Disclosure for this article can be found at http://journals.sagepub.com/doi/suppl/10.1177/0956797619826970. This article has received the badge for Open Data. More information about the Open Practices badges can be found at http://www.psychologicalscience.org/publications/badges.

Notes

1. Our goal for sample-size selection was to ensure we had enough power to detect the anticipated effects and to provide the most precise estimate of testosterone's effects on human aggression. We therefore aimed to conduct the largest single-dose testosterone-administration study to date. Our anticipated main effect of testosterone was based on a previous report (d = 0.30; Carré et al., 2017). To detect this effect with 80% power, one-tailed, and an α of .05, we needed 278 participants. Our estimated Personality-Risk Score × Drug Group interaction was also based on this same report (R^2 = 5.2%, or f^2 = .055; Carré et al., 2017). To detect an interaction of this size with 80% power and an α of .05, we needed 145 participants. We estimated that the three-way interaction between CAG repeat length, personality-risk score, and drug group would be smaller and therefore used an estimate that was half of the size of the estimate for the two-way interaction (f^2 = .0275). To detect this effect with 80% power and an α of .05, we needed 288 participants. Because genetic analyses are typically conducted in ethnically homogenous samples, we wanted to ensure that we could restrict this analysis to White participants and still have adequate power. We therefore estimated, on the basis of recruitment patterns in our previous studies, that approximately 80% of the sample would be White and thus tested 400 men total (expecting 320 to be White). This sample size would give us 84% power to detect the effect (f^2) of .0275. After exclusions, our final sample contained 308 participants, the largest sample to date compared with previous, high-profile testosterone-administration studies (N = 40, Dreher et al., 2016; N = 121, Eisenegger et al., 2010). With this sample size, we had 83% power to detect the estimated effect (f^2) of .0275.
2. Including time of testing (morning vs. afternoon) as a covariate in our analysis did not change the results.
3. Of these 19 influential cases, 6 were outliers on aggression (> 3 *SD* from the mean); 3 were outliers on risk (> 3 *SD*); 1 was an outlier on CAG repeat length (> 3 *SD*); 7 had high leverage values, leverage > $2(k + 1)/n$; and 6 were outliers in the model (standardized residual ≥ 3).
4. When we restricted the same analysis to the subset of participants for whom we had reward data (n = 224), we again found no significant conditional effect of drug group (p = .537).

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