Neural Mechanisms of the Testosterone–Aggression Relation: The Role of Orbitofrontal Cortex

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Abstract

■ Testosterone plays a role in aggressive behavior, but the mechanisms remain unclear. The present study tested the hypothesis that testosterone influences aggression through the OFC, a region implicated in self-regulation and impulse control. In a decision-making paradigm in which people chose between aggression and monetary reward (the ultimatum game), testosterone was associated with increased aggression following social provocation (rejecting unfair offers). The effect of testosterone on aggression was explained by reduced activity in the medial OFC. The findings suggest that testosterone increases the propensity toward aggression because of reduced activation of the neural circuitry of impulse control and self-regulation. ■

INTRODUCTION

Aggression is a complex social behavior that is regulated by multiple social and biological factors. Although these factors likely work together as part of an integrated system, most human studies on aggression to date have investigated the effects of specific biological factors in isolation. Research in behavioral endocrinology, for example, has examined the role of hormones in aggression, and cognitive neuroscience research has investigated how the brain influences aggression (see reviews by Siever, 2008; Strüber, Lück, & Roth, 2008; Bufkin & Luttrell, 2005; Davidson, Putnam, & Larson, 2000). These two literatures on hormone–behavior and brain–behavior associations have contributed greatly to our understanding of the biological underpinnings of aggression. An important next step is research that integrates the two perspectives to understand how hormones and the brain work together to regulate human aggression. The present research implemented this hormone–brain–behavior approach to identify the neural systems that mediate the association between testosterone and aggression in humans.

Naturally occurring and experimentally elevated testosterone levels are positively associated with aggressive behavior in a variety of animal species, especially when the status hierarchy is unstable (Giammanco, Tabacchi, Giammanco, Di Majo, & La Guardia, 2005; Collias, Barfield, & Tarvyd, 2002; Ruiz-de-la-Torre & Manteca, 1999; Oliveira, Almada, & Canario, 1996; Sapolsky, 1991; Wingfield, Hegner, Dufty, & Ball, 1990). Higher testosterone in humans is related to aggression, social dominance, and hyperreactivity to status threats in both men and women (Mehta, Jones, & Josephs, 2008; van Honk & Schutter, 2007; Wirth & Schultheiss, 2007; Josephs, Sellers, Newman, & Mehta, 2006; Archer, Graham-Kevan, & Davies, 2005; Newman, Sellers, & Josephs, 2005; O'Connor, Archer, & Wu, 2004; Grant & France, 2001; van Honk et al., 2001; Pope, Kouri, & Hudson, 2000; Archer, Birring, & Wu, 1998; Mazur & Booth, 1998; Finkelstein et al., 1997). Psychiatric disorders that include symptoms of impulsive aggression, such as antisocial personality disorder and borderline personality disorder, are also associated with high levels of testosterone (Rasanen et al., 1999; Stalenheim, Eriksson, von Knorring, & Wide, 1998; Virkkunen et al., 1994). Testosterone is not related to all forms of aggression but may specifically control impulsive aggression in response to social threat (e.g., dominance threat, Mazur & Booth, 1998). Overall, the evidence suggests that higher testosterone in both sexes is associated with aggressive reactions to social provocation.

What neural mechanisms explain the effect of testosterone on aggressive behavior? Although separate studies in humans have examined the endocrine and neural systems involved in aggression, no research to date has combined measures of hormones, human neural activity, and aggressive behavior in the same study. Therefore, the neural systems through which testosterone levels influence aggression in humans remain largely unknown. One possible mechanism for testosterone's influence on aggression is through the OFC, a region implicated in self-regulation and impulse control (Beer, Shimamura, & Knight, 2004; Blair, 2004; Rahman, Sahakian, Cardinal, Rogers, & Robbins, 2001; Bechara, Damasio, & Damasio, 2000; Tucker, Luu, & Pribram, 1995; Rolls, Hornak, Wade, & McGrath, 1994). Increased OFC activity leads to low levels of reactive aggression, whereas OFC lesions lead to impulsive behavior and hyperaggression (Strüber et al., 2008; Bufkin & Luttrell, 2005; Davidson et al., 2000; Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). Psychiatric disorders characterized by

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high levels of reactive aggression are associated with reduced activity in the OFC (Coccaro, McCloskey, Fitzgerald, & Phan, 2007), and lower gray matter volume in the OFC is linked to low impulse control (Matsuo et al., 2009). Together studies of OFC activation, damage, and disorder all converge on an association between OFC function and regulation of impulsive aggression. Furthermore, receptors for androgens such as testosterone are found in the OFC (Finley & Kritzer, 1999). Following social threat, androgens modulate changes in the OFC such as neurotransmitter turnover (Handa, Hejna, & Lorens, 1997) and activation (van Wingen et al., 2009; Hermans, Ramsey, & van Honk, 2008). Although separate lines of research suggest that (a) aggression is associated with testosterone, (b) aggression is associated with OFC function, and (c) OFC has the capability of mediating the relation between testosterone and aggression, little is understood about how these systems work together to support the regulation of aggressive behavior.

One avenue for testing OFC as a mediator of the relation between testosterone and aggression is the ultimatum game, a laboratory model of social decision making in which people choose between aggression and monetary reward (Crockett, Clark, Tabibnia, Lieberman, & Robbins, 2008; Sanfey, Rilling, Aronson, Nystrom, & Cohen, 2003; Pillutla & Murnighan, 1996; Güth, Schmittberger, & Schwarze, 1982). This game involves two players: a proposer and a responder. The proposer makes an offer as to how to split a sum of money (the stake) with the responder. The responder then decides whether to accept or to reject the offer. If the offer is accepted, the stake is split as proposed. However, if the offer is rejected, then both players receive $0. After the responder makes a decision, the game is over. Although responders almost always accept fair offers (e.g., proposer gets 50% and responder gets 50% of stake), responders often reject unfair offers (e.g., proposer gets 80% and responder gets 20% of the stake). Accepting unfair offers guarantees monetary reward, so why do people ever reject them? Unfair offer rejections are aggressive, aimed at retaliating against the other player in the face of perceived social provocation (unfair treatment) (Crockett et al., 2008; Sanfey et al., 2003; Pillutla & Murnighan, 1996). Responders report feeling insulted and angry after receiving unfair offers (van't Wout, Kahn, Sanfey, & Aleman, 2006; Pillutla & Murnighan, 1996). Responders are also less likely to reject unfair offers from computer partners, indicating that unfair offer rejections are driven by the motivation to inflict harm upon other humans (Sanfey et al., 2003). In addition, high trait aggression is associated with an increased tendency to reject unfair offers (Mehta, 2007), further indicating that these rejections are a form of social aggression.

If testosterone and OFC are indeed involved in aggressive reactions to provocation, then they should both influence behavior in the ultimatum game. One recent study examined the association between testosterone and ultimatum game decision making in male economics students (Burnham, 2007). Consistent with an association between testosterone and aggressive behavior, individuals with high testosterone levels were more likely to reject unfair offers. Two studies examined the association between OFC damage and ultimatum game decision making (Moretti, Dragone, & di Pellegrino, 2008; Koenigs & Tranel, 2007). Both studies found that patients with medial OFC lesions were more likely to reject unfair offers than were control participants. Taken together, research on the ultimatum game is consistent with the larger literature on aggression in showing that testosterone levels and OFC function both influence aggressive reactions to social provocation.

To sum up, separate lines of research in the fields of behavioral endocrinology and cognitive neuroscience indicate that testosterone influences aggression (Archer, 2006), OFC activity influences aggression (Strüber et al., 2008), and testosterone influences OFC activity (Hermans et al., 2008; Handa et al., 1997). The findings from these disparate literatures suggest that reduced OFC activity may be a mechanism through which testosterone influences aggressive behavior. This hypothesis, however, has yet to be empirically tested.

The present research combined measurements of testosterone, neural activity, and aggressive behavior in the same study to identify the neural mechanisms through which testosterone influences aggressive behavioral reactions to social provocation. Participants provided saliva samples for hormone measurement and then were scanned with fMRI while playing the ultimatum game in the role of responder. Participants believed they were playing with other players in one-shot interactions. In reality, offers were experimentally manipulated with a computer program such that participants received equal numbers of fair offers and unfair offers. It was hypothesized that (a) higher testosterone would predict aggressive behavioral reactions to unfairness and (b) decreased activity in the OFC would mediate the association between testosterone and aggression.

METHODS

Participants

Thirty-four participants were recruited through posted advertisements. All participants were screened for medications and psychological or neurological conditions that might influence the measurement of CBF as well as minimal exposure to economic theory. One participant was excluded because of excessive motion (>3 mm), and another participant was excluded because testosterone levels were out of range (three standard deviations above the mean), most likely due to blood contamination of saliva. The final analysis included 32 right-handed participants (17 men, 15 women; mean age = 23.3 years, *SD* = 3.2 years).

Procedure

Participants refrained from eating or drinking anything besides water for at least 30 min prior to the study. Experimental sessions began between 12:30 and 3:30 p.m.

to minimize the effect of circadian fluctuations in testosterone levels (Touitou & Haus, 2000).

Saliva Collection

Standard salivary hormone collections procedures were used (Schultheiss & Stanton, 2009). Before providing saliva samples, participants rinsed their mouths and chewed on a piece of Trident sugar-free gum for 3 min to stimulate salivation. Then participants drooled 3 mL of saliva into a sterile polypropylene microtubule and spit out their gum. Saliva samples were immediately brought to a freezer in an adjacent lab room to avoid hormone degradation and to precipitate mucins.

Ultimatum Game

Neural activity was measured with fMRI while participants played the ultimatum game (Güth et al., 1982). Participants believed that that they would play the ultimatum game with 40 players in one-shot interactions. In each round, participants had to split $10 with another player. The other player (the proposer) made an offer as to how to split the $10. Participants (responders) decided whether to accept or to reject the offer with a button press. If they accepted the offer, the $10 was split as proposed. If they rejected the offer, then both players received nothing. Participants were informed that they would be paid a percentage of their final bank total. In each round, participants saw the proposer's user name (e.g., "mbc42 is making an offer"), followed by the offer (see Figure 1). In reality, offers were determined by a computer program. All participants received the same 40 offers presented in random order: 20 fair offers ($5 or $4) and 20 unfair offers ($3, $2, or $1) (Koenigs & Tranel, 2007). Participants were debriefed and paid a percentage of their total earnings (M = $24.60, SD = $1.23).

Hormone Assays

Saliva was thawed and separated from residuals (e.g., mucins) by mixing by vortex followed by centrifugation at 3000 rpm for 15 min. Saliva samples were then analyzed for testosterone concentrations with enzyme immunoassay kits purchased from Salimetrics (State College, PA, USA). Samples were assayed twice. Two control samples (one low and one high) were run in every assay. Intra-assay coefficient of variation was 4.21%, and interassay coefficient of variation averaged across low and high controls was 7.71%. The lower limit of detection (B_0 + 3 SD) was 2 pg/mL.

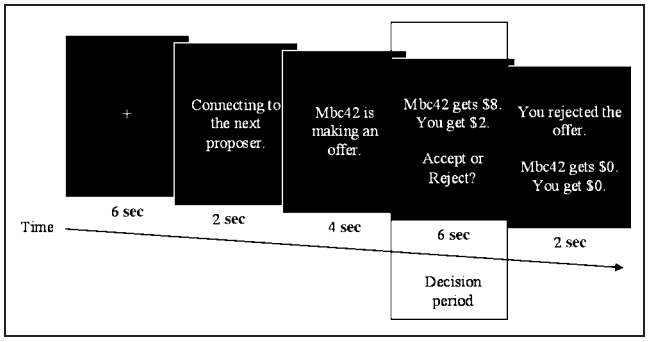

Figure 1. Ultimatum game paradigm. Participants were presented with 20 fair offers ($5:$5 or $6:$4) and 20 unfair offers ($7:$3, $8:$2, or $9:$1) and decided to accept or to reject the offers. Neural mediators of the relation between testosterone and aggression (unfair offer rejection) were drawn from the decision period.

Imaging Acquisition

Data were acquired on the GE Signa EXCITE 3.0-T scanner at the University of Texas at Austin Imaging Research Center. Functional EPI images were collected using a multiecho GRAPPA parallel imaging EPI sequence developed at Stanford that optimizes BOLD signal in regions of OFC that are typically vulnerable to susceptibility artifact (repetition time = 2 sec, 3 shot, echo time = 30 msec, field of view = 240, 64 × 64 matrix, 35 axial slices oriented to the AC–PC line, voxel size = 3.3 × 3.3 × 3.3 mm). The first four EPI volumes were discarded to allow scans to reach equilibrium. In all cases, stimuli were viewed through a back projection screen and a mirror mounted on the top of the head coil. In addition to functional EPI images, a high-resolution anatomical T1 SPGR scan empirically optimized for high contrast between gray matter and white matter and gray matter and cerebrospinal fluid was acquired. The images were acquired in the sagittal plane using a 1.3-mm slice thickness with 1 cubic mm in plane resolution.

Imaging Data Analysis

All statistical analyses were conducted using SPM2 (Wellcome Department of Cognitive Neurology). Structural and functional volumes were normalized to T1 and EPI templates, respectively. The normalization algorithm used a 12-parameter affine transformation together with a nonlinear transformation involving cosine basis functions and resampled the volumes to 2-mm cubic voxels. Templates were based on the MNI305 stereotaxic space (Cosoco, Kollokian, Kwan, & Evans, 1997), an approximation of Talairach space (Talairach & Tournoux, 1988). Image volumes were corrected for slice-timing skew using temporal sinc interpolation and corrected for movement using rigid-body transformation parameters. Images were then smoothed with an 8-mm FWHM Gaussian kernel. To remove drifts within sessions, a high-pass filter with a cutoff period of 128 sec was applied.

A fixed-effects analysis was used to model event-related responses for each participant. BOLD responses related to unfair offers ($7:$3, $8:$2, or $9:$1) and fair offers ($5:$5 or $6:$4) were modeled with a canonical hemodynamic response function with a duration of 4 sec. These fair and unfair categories have been used in previous research on the ultimatum game (Koenigs & Tranel, 2007). A duration of 4 sec was chosen because the RT data indicated that

decisions were most often made within a span of 4 sec (see section on RTs). A general linear model analysis was used to create contrast images for each participant summarizing differences of interest. Contrasts from each participant were used in a second-level analysis treating participants as a random effect to create group average SPM{t} maps for the unfair offer condition and the fair offer condition.

On the basis of previous research associating OFC activation with inhibition of aggression (Strüber et al., 2008; Bufkin & Luttrell, 2005; Davidson et al., 2000), we hypothesized that inhibition of aggression (e.g., acceptance of unfair offers) would be positively associated with OFC activation whereas aggressive responses would be negatively associated with OFC activation. In addition, we expected that although the unfair condition would be associated with more aggressive responses than the fair condition, there would be individual variation in the frequency of aggressive behavior within the unfair condition. In this case, a direct contrast between the unfair and the fair conditions would obscure OFC activity (e.g., individuals with high levels of aggression and individuals with low levels of aggression within the unfair condition might cancel each other out). Therefore, the appropriate analysis to identify neural regions that track aggressive responding is a regression analysis. The interpretation of the results was restricted to regions identified in previous research on aggression (Strüber et al., 2008; Bufkin & Luttrell, 2005; Davidson et al., 2000) and decision making (e.g., Lee, 2008; Moretti et al., 2008; Tabibnia, Satpute, & Lieberman, 2008; Koenigs & Tranel, 2007; De Martino, Kumaran, Seymour, & Dolan, 2006; Sanfey et al., 2003). The group maps of the regression analysis ($p < .005$ uncorrected, $k = 10$) were inclusively masked for the hypothesized regions of OFC, dorsolateral prefrontal cortex (DLPFC), ACC, caudate, and insula according to the automated anatomical labeling (AAL) map (Tzourio-Mazoyer et al., 2002).

Potential OFC region mediators of the relation between testosterone and behavior were identified by regressing unfair offer acceptance rate on the unfair > fair contrast, regressing testosterone level on the unfair > fair contrast, and testing for significant conjunction within the medial and the lateral OFC (corrected $p < .05$ FWE threshold, minimum 10 face-to-face contiguous 2-mm^3 resampled voxels; search volumes: lOFC (23 mm^3) and mOFC (17 mm^3) according to the AAL map). Parameter estimates were extracted from the OFC regions surviving the conjunction analysis for further use in the mediation analyses using Marsbar (Brett, Anton, Valabregue, & Poline, 2002).

RESULTS

Behavior Analyses

Consistent with previous studies on the ultimatum game (Koenigs & Tranel, 2007; Sanfey et al., 2003; Güth et al., 1982), unfair offers ($M = 54.06\%$, $SE = 5.68\%$) were more likely to be rejected than fair offers ($M = 0.94\%$, $SE = 0.42\%$), $t(31) = 9.52$, $p < .001$. Offer fairness also predicted RTs, $t(31) = 6.09$, $p < .001$. Decisions were made more quickly for fair offers ($M = 1352$ msec, $SE = 60$ msec) than for unfair offers ($M = 1727$ msec, $SE = 68$ msec). Previous neural research on the ultimatum game typically groups offers into fair and unfair categories (Moretti et al., 2008; Koenigs & Tranel, 2007; Sanfey et al., 2003); our results are reported in that manner for comparison purposes. As a secondary check that this was an appropriate representation of the current study's results, we examined acceptance rates for each type of offer. The ceiling effect for acceptance of the \$5:\$5 and \$6:\$4 offers confirmed that these offers were in a different category than the others. Average rejection rates were 0.59% for \$5:\$5 offers, 2.34% for \$6:\$4 offers, 23.44% for \$7:\$3 offers, 50.39% for \$8:\$2 offers, and 73.05% for \$9:\$1 offers.

Hormone–Behavior Analyses

The mean testosterone level for men was 72.14 pg/mL ($SD = 42.64$), and the mean testosterone level for women was 25.74 pg/mL ($SD = 19.15$). Testosterone scores were standardized separately for men and women by converting the raw scores for every participant to z scores. High scores indicated high testosterone levels relative to other individuals of the same sex. This standardization procedure maximizes statistical power in mixed-sex samples and allows for the test of sex differences in the magnitude of testosterone–behavior relationships (e.g., Mehta et al., 2008; Wirth & Schultheiss, 2007; Josephs et al., 2006).

The first goal in the present research was to test the hypothesis that testosterone is associated with aggressive reactions to unfair treatment. Consistent with this hypothesis and with previous research (Burnham, 2007), a regression analysis showed that testosterone was positively related to unfair offer rejection ($\beta = .35$, $p < .05$). The magnitude of the testosterone–behavior relationship was similar in men ($\beta = .35$) and in women ($\beta = .36$). Participant sex ($\beta = .01$, $p = .97$) and Participant Sex × Testosterone interaction were not significantly related to unfair offer rejection ($\beta = .02$, $p = .93$). Together, these analyses indicate that higher testosterone levels predict an increased rejection of unfair offers.

Neuroimaging Analyses

The second goal in the present research was to identify the neural systems through testosterone influences aggressive behavioral reactions to unfairness. It was hypothesized that decreased OFC activity would mediate the association between testosterone and increased aggressive behavior. Regression analyses were conducted to identify neural ROIs that track individual differences in aggressive behavior. Mediation analyses were conducted to test statistical mediation of the testosterone–aggression relation.

Identifying Neural Regions of Interest that Track Individual Differences in Aggressive Behavior

As expected on the basis of previous research, there was almost no variation in behavioral responses to fair offers (approximately 100% of fair offers were accepted across all participants), but there was individual variation in behavioral reactions to unfairness, with some individuals rejecting a greater number of unfair offers than others. A regression analysis was used to test whether the hypothesized neural regions tracked individual differences in behavioral responses to unfairness (aggressive behavior). Regression was chosen instead of a direct contrast because it was expected that individuals who tended to accept unfair offers would show increased OFC activity in the unfair condition compared with the fair condition, whereas individuals who tended to reject unfair offers would show decreased OFC activity in the unfair condition compared with the fair condition; in that case, OFC would not be detected by a direct contrast between the unfair and the fair conditions because individuals who tend to accept unfair offers and individuals who tend to reject unfair offers would cancel each other out. A regression analysis was conducted in which unfair offer rejection rate was regressed on the unfair > fair contrast map. As hypothesized, the tendency to reject unfair offers (i.e., behave more aggressively) was associated with less activity in the medial and lateral OFC, ACC, caudate, and DLPFC (see Table 1).

Statistical Tests for Neural Mediation of the Testosterone–Aggression Relation

The hormone–behavior analyses reported above indicate that higher testosterone levels are associated with aggressive behavior. Did reduced OFC activity explain the association between testosterone and aggression (i.e., unfair offer rejection)? To address this question, a conjunction analysis was conducted on the independent regressions of unfair offer rejection on the unfair > fair contrast and testosterone on the unfair > fair contrast. As described in the Methods section, small volume correction was used for this conjunction analysis. This conjunction analysis identified two medial OFC regions (left medial OFC (Brodmann's area [BA] 11): −16, 56, −8 and right medial OFC (BA 11): 16, 50, −6) that were significantly related to both unfair offer rejection and testosterone (see Table 2 and Figure 2). Furthermore, these regions overlapped with the OFC clusters identified in the broader regression of unfair offer rejection on the unfair > fair contrast reported in Table 1. The relation between each of the OFC regions that survived the conjunction analysis with (a) unfair offer rejection and (b) testosterone is depicted in Figure 2. As shown, decreased medial OFC activity was associated with high levels of aggression, whereas increased medial OFC activity was associated with low levels of aggression. Similarly, decreased medial OFC activity was associated with high levels of testosterone, whereas increased medial OFC activity was associated with low levels of testosterone.

There were no significant correlations between lateral OFC and testosterone ($p > .05$). Exploratory analyses were also conducted to examine whether neural regions outside of the OFC that were associated with unfair offer rejection (see Table 1) might show significant conjunction with a regression of testosterone on the unfair > fair contrast. Although a region within the ACC did negatively correlate with testosterone (peak 6, 40, 0; $t = 5.13$, $k = 47$), this region did not show significant activation in the conjunction analysis ($p > .05$ FWE for the AAL map VOI of bilateral ACC). The remaining regions (caudate and DLPFC) were not significantly correlated with testosterone (all ps $> .05$) and therefore did not qualify for conjunction analysis.

Parameter estimates were extracted from the OFC regions surviving the conjunction analysis. The parameter estimates were used in a series of analyses that test for statistical mediation (Preacher & Hayes, 2004; Shrout & Bolger, 2002; Baron & Kenny, 1986; see Table 2 and Figure 3).

Table 1. Neural Activation Negatively Modulated by Unfair Offer Rejection Rate (Unfair > Fair Contrast Map)

		MNI Coordinates				
Region (BA)	*Laterality*	*x*	*y*	*z*	*Cluster Size*	*t Statistics*
Medial orbitofrontal cortex (11)[a]	L	−22	40	−16	264	4.54
Medial orbitofrontal cortex (10/11)[b]	R	14	52	−4	30	3.04
Insula/lateral orbitofrontal cortex (47)	R	28	24	−14	40	3.38
Anterior cingulate cortex (32)	LR	2	44	16	50	3.75
Caudate nucleus	L	−8	4	16	24	3.16
DLPFC (46)	R	24	56	26	11	2.99

L = left; R = right.

[a]This activation cluster is on the medial orbitofrontal gyrus as indicated in Duvernoy's atlas rather than the lateral orbital gyrus.

[b]This activation cluster is anterior to the cingulate gyrus and is right at the juncture of BA 11 and BA 10 according to the AAL map.

Table 2. Statistical Tests for Neural Activity Mediation of Testosterone and Unfair Offer Rejection

Region (BA)	*A*	*B*	*C*	*C′*	*Indirect Effect (Lower Limit 95% CI, Upper Limit 95% CI)*
Medial orbitofrontal cortex (11) (−16, 56, −8, t = 3.65, k = 153)	−0.55*	−0.42*	0.35*	0.12	7.79* (1.23, 15.71)
Medial orbitofrontal cortex (11) (16, 50, −6, t = 3.34, k = 56)	−0.45*	−0.41*	0.35*	0.17	6.00* (.40, 12.89)

Parameter estimates were extracted from a conjunction analysis in which unfair offer rejection rate and testosterone were independently regressed on the unfair > fair contrast map. Testosterone levels were standardized within sex. Mediation tests are based on Shrout and Bolger (2002) and Baron and Kenny (1986). (A) Regression slope of testosterone predicting neural activity; (B) regression slope of neural activity predicting rejection of unfair offers, controlling for testosterone; (C) regression slope of testosterone predicting rejection of unfair offers; (C′) regression slope of testosterone predicting rejection of unfair offers, controlling for neural activity. Bootstrapping was used to estimate indirect effects (Shrout & Bolger, 2002; see also Preacher & Hayes, 2004). A confidence interval that does not overlap with zero indicates statistically significant mediation. CI = confidence interval.

*Indicates statistically different from zero, $p < .05$.

According to Baron and Kenny (1986), four steps are required to establish that neural activity in a particular region mediates the relation between testosterone and aggression (see Table 2 and Figure 3): (1) show that testosterone is associated with aggression (this association was reported in the section on Hormone–Behavior Analyses section but is rereported in Table 2, column C); (2) show that testosterone is associated with neural activity in the region (Table 2, column A and Figure 2); (3) show that neural activity in the region predicts aggression when controlling for testosterone (Table 2, column B); and (4) show that the relation between testosterone and aggression is reduced when controlling for neural activity in the region (Table 2, column C′). For a sample of 20–80 participants, statisticians recommend the use of bootstrapping methods for testing the statistical significance of mediation (rather than the Sobel test, which is appropriate for larger samples; see Shrout & Bolger, 2002; Preacher & Hayes, 2004; Efron & Tibshirani, 1993). The current study used the bootstrapping approach outlined by Shrout and Bolger (2002), which provides a mean estimate of the indirect effect (i.e., the path through the mediator) and the associated 95% confidence interval. A confidence interval that does not contain zero indicates statistically significant mediation ($p < .05$).

As shown in Table 2 and Figure 3, OFC activation (BA 11) mediated the relation between testosterone and unfair offer rejection. Testosterone and unfair offer rejection were negatively associated with activity in the left medial OFC (peak in MNI space: −16 56 −8, t = 3.65, $p < .05$ FWE; testosterone: $\beta = -.55$; unfair offer rejection controlling for testosterone: $\beta = -.42$). The relationship between testosterone and unfair offer rejection ($\beta = .35$) was reduced when controlling for activity in the left medial OFC ($\beta = .12$). Bootstrapping revealed that the left medial OFC significantly mediated the relation between testosterone and unfair offer rejection (mean indirect effect = 7.79, 95% confidence interval ranging from 1.23 to 15.71). Similarly, testosterone and unfair offer rejection were negatively associated with activation in the right medial OFC (BA 11; peak in MNI space: 16 50 −6, t = 3.34, $p < .05$ FWE; testosterone: $\beta = -.45$; unfair offer rejection controlling for testosterone: $\beta = -.41$). The relationship between testosterone and unfair offer rejection ($\beta = .35$) was reduced when controlling for activity in the right medial OFC ($\beta = .17$). Bootstrapping revealed that the right medial OFC significantly mediated the relation between testosterone and unfair offer rejection (mean indirect effect = 6.00, 95% confidence interval ranging from 0.40 to 12.89). Finally, these findings could not be explained by RT differences. Unfair offer RTs, fair offer RTs, and unfair minus fair offer RTs were uncorrelated with testosterone ($p > .05$), uncorrelated with parameter estimates for each of the neural regions (ps > .05), and did not significantly change the results of the mediation analyses when included in the regression models.

DISCUSSION

The current research integrated theories and methods from behavioral endocrinology and cognitive neuroscience to examine how endocrine and neural systems work together to influence aggressive behavior. Two main findings emerged. First, higher testosterone levels predicted subsequent aggressive behavioral reactions to unfairness (rejection of unfair offers in the ultimatum game). This finding conceptually replicates a previous study on testosterone and aggressive behavior following unfair treatment that was restricted to participants who were eononomics experts (Burnham, 2007). Second, the present investigation extends disparate lines of research that have associated aggression with either testosterone or reduced OFC activity; the association between testosterone and aggressive behavior is explained by reduced activity in the medial OFC. Previous experimental studies have shown that testosterone influences aggression (Archer, 2006), testosterone influences medial OFC activity (Handa et al., 1997), and medial OFC activity influences aggression (Moretti et al., 2008; Koenigs & Tranel, 2007; Pietrini, Guazzelli, Basso, Jaffe, & Grafman, 2000), but the current research provides the first empirical support for the claim that testosterone regulates aggressive behavior because of reduced medial OFC engagement following social provocation.

Medial OFC activity is strongly associated with impulse control and self-regulation systems that integrate emotion, motivation, and cognition to guide context-appropriate behavior (Beer et al., 2004; Blair, 2004; Rahman et al., 2001; Bechara et al., 2000; Tucker et al., 1995; Rolls et al., 1994). Indeed, not only do patients with medial OFC lesions show increases in reactive aggression (Blair, 2004; Rolls et al., 1994), but they also show increases in impulsive behavior, socially inappropriate behavior, and impaired decision making (Beer, John, Scabini, & Knight, 2006; Beer, Heerey, Keltner, Scabini, & Knight, 2003; Rahman et al., 2001; Bechara et al., 2000; Tucker et al., 1995). These behavioral deficits have been theorized to occur because of a failure to monitor behavior such as failing to consider longer term rewards (Moretti et al., 2008; Beer et al., 2006; De Martino et al., 2006; Bechara et al., 2000). Thus, the present findings suggest that higher testosterone is associated with aggressive reactions to social provocation because of impairments in self-regulation and impulse control systems. Furthermore, these findings suggest a specific neurobiological

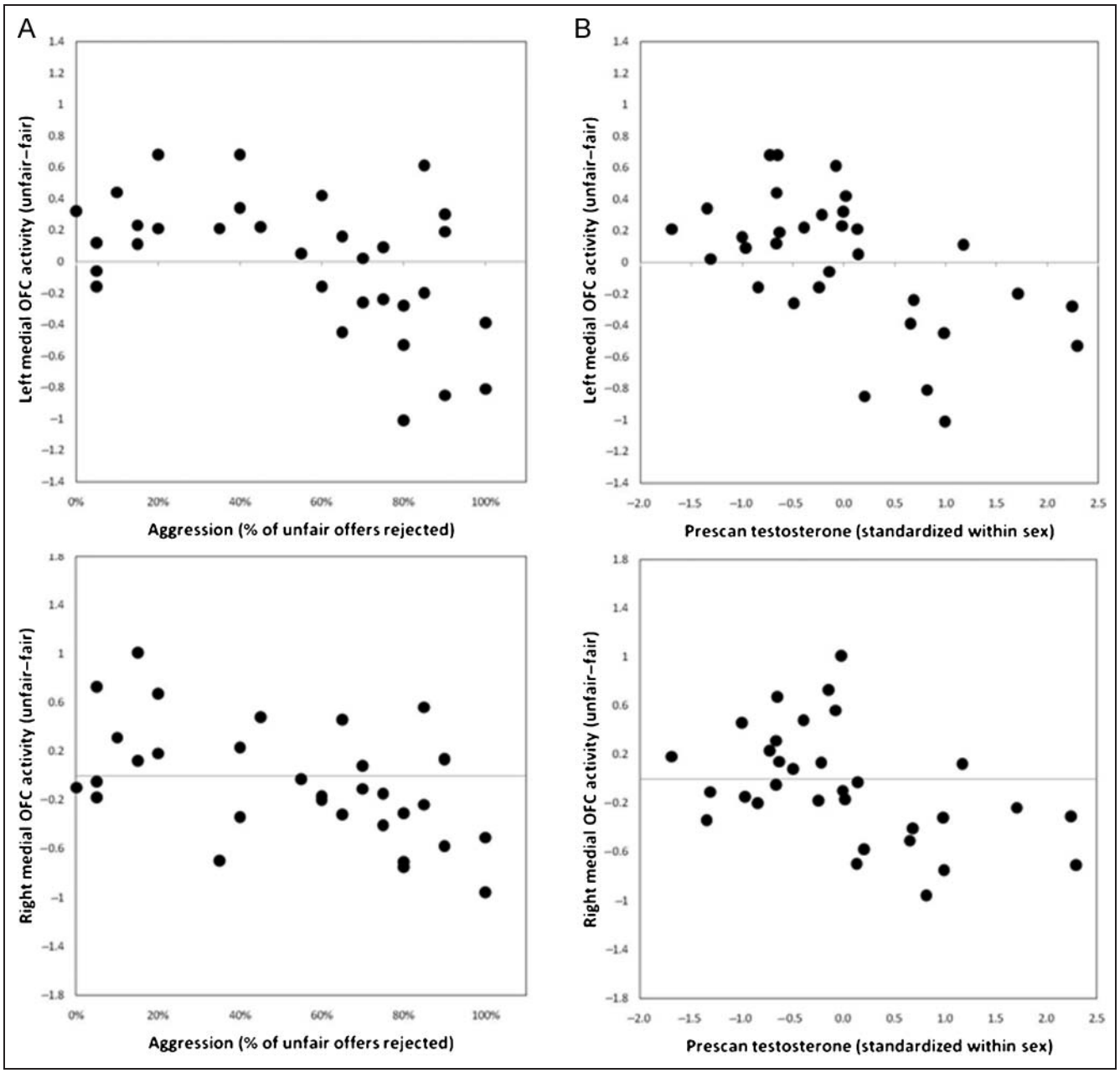

Figure 2. Scatterplots of associations between medial OFC activity and aggressive behavior (percentage of unfair offers rejected) for the peaks of the clusters surviving conjunction analysis with an independent regression of testosterone. (A) Association between aggression and left medial OFC activity (BA 11, peak in MNI space: −16 56 −8; $r = -.49$, $p < .05$) and right medial OFC activity (BA 11, peak in MNI space: 16 50 −6; $r = -.48$, $p < .05$). (B) Association between testosterone and left medial OFC activity (BA 11, peak in MNI space: −16 56 −8; $r = -.55$, $p < .05$) and right medial OFC activity (BA 11, peak in MNI space: 16 50 −6; $r = -.45$, $p < .05$).

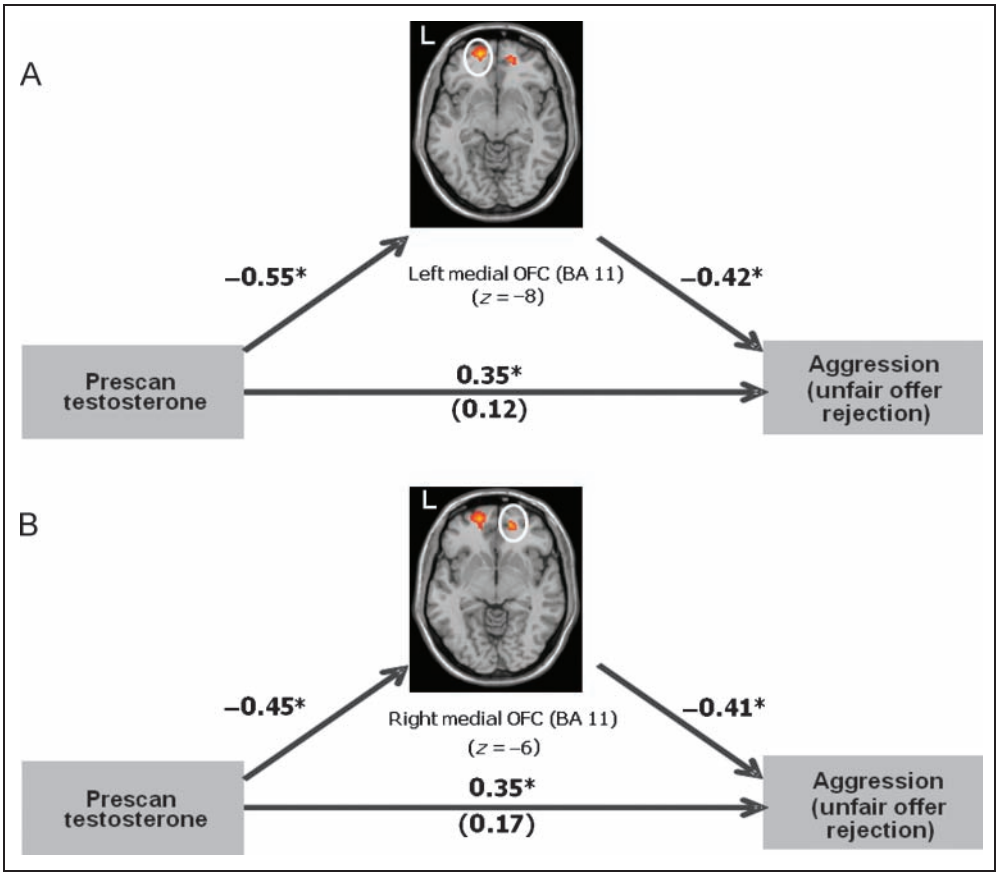

Figure 3. Brain regions that mediated the relationship between prescan testosterone (standardized within sex) and aggressive behavior (unfair offer rejection). Regression slopes in parentheses indicate the relation between testosterone and behavior after controlling for neural activity. Coordinates are in MNI space. (A) Left medial OFC ($z = -8$); (B) right medial OFC ($z = -6$).

avenue, the OFC, for understanding decreased impulse control as a key risk factor in reactive aggression (MacDonald, 2008; Strüber et al., 2008; Anderson & Bushman, 2002).

The present findings also suggest that the function of testosterone in behavior may be broader than currently theorized. Studies to date have concentrated on testosterone's relationships with aggression and dominance (Archer, 2006; Mazur & Booth, 1998), but an association between testosterone and medial OFC activity suggests that testosterone may be involved in broader aspects of self-regulation and impulse control. If that is the case, then testosterone may influence self-regulation and impulse control (Baumeister & Heatherton, 1996) by modulating OFC activation in some other domains. Aggression may be just one example of a domain in which testosterone and medial OFC work together to affect impulse control. For example, testosterone has been associated with drug abuse (Reynolds et al., 2007), a disorder associated with poor impulse control and abnormal OFC volume and function (Volkow & Li, 2004; Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001; Liu, Matochik, Cadet, & London, 1998). This raises the possibility that high testosterone individuals are at risk for disorders associated with poor impulse control such as drug abuse because they either do not engage the OFC in situations requiring impulse control or have abnormal OFC function.

Previous research provides strong evidence that OFC is involved in self-regulation and impulse control, but OFC also plays a role in reward and punishment processing. Specifically, the left OFC region in Figure 3 (in BA 11, but portions of the cluster extend to a region that is considered part of the lateral OFC in some models of OFC function; Kringelbach, 2005; Kringelbach & Rolls, 2004) is activated by abstract punishment (e.g., monetary loss), whereas the right OFC region that is more circumscribed to the medial portion of BA 11 is activated by abstract reward (e.g., monetary gain; Kringelbach, 2005; Kringelbach & Rolls, 2004, O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Thus, an alternative psychological interpretation of the present results is that high testosterone individuals may react aggressively to unfairness because they are less attuned to future punishments (both financial and social) that may result from their aggressive behavior, such as losing money or being disliked by others, and because they are less attuned to future rewards that may result from nonaggressive behavior, such as monetary reward or social cooperation. In other words, high testosterone people may respond aggressively to social provocation because they are less attuned to the potential costs of aggression and the potential benefits of nonaggression. This interpretation fits with evidence that the perceived costs and benefits of aggression predict aggressive behavior above and beyond impulse control (Archer & Southhall, 2009). It also fits initial evidence that testosterone decreases sensitivity to abstract punishment (van Honk et al., 2004).

Other psychological mechanisms for aggression include cognitive appraisals (e.g., perceived unfairness) and negative affect (e.g., anger) (Anderson & Bushman, 2002), but these mechanisms are unlikely to explain the current findings. For example, although patients with medial OFC damage exhibit hyperaggressive behavioral reactions to unfairness, patients do not report more anger or perceived unfairness than control participants (Moretti et al., 2008). These results suggest that negative affect and perceived unfairness do not critically rely on medial OFC activity. Nevertheless, follow-up studies are needed to examine the precise psychological function of OFC in explaining the testosterone–aggression relation (e.g., future neuroimaging research that includes jittering in the design may help clarify the psychological function of OFC in the inhibition of aggressive behavior).

The present findings suggest that testosterone influences aggression through reduced activity in the medial OFC, but how might testosterone affect medial OFC function? One likely pathway is through serotonin. Low serotonin has long been implicated in impulsivity and aggression (Siever, 2008), including aggressive behavioral reactions to unfairness in the ultimatum game (Crockett et al., 2008). Testosterone may influence serotonin function in the medial OFC. Androgens downregulate serotonin receptor mRNA expression and serotonin turnover in the medial pFC (Ambar & Chiavegatto, 2009; Handa et al., 1997), and lower serotonin leads to hypometabolism in the medial OFC (New et al., 2004). These findings suggest that testosterone may increase aggression through serotonin deficits in the medial OFC, a hypothesis that warrants future research.

The current study examined baseline levels of testosterone; future research should consider neural mediators of task-induced changes in testosterone. Research suggests that aggressive behavior can feed back to induce short-term changes in testosterone levels (Archer, 2006; Mazur & Booth, 1998). These fluctuations in testosterone can reinforce or discourage further acts of aggression and dominance (Carre, Putnam, & McCormick, 2009; Mehta & Josephs, 2006). Future research is needed to investigate whether OFC also mediates associations among short-term testosterone fluctuations and aggressive behavior.

Future research should also consider different manipulations of testosterone, aggression, and OFC function to provide convergent evidence of the causal relations found in the present study. For example, additional experiments might exogenously manipulate testosterone levels (e.g., Hermans et al., 2008) and/or involve other paradigms to model aggression. Furthermore, if the OFC is a critical mechanism for the relation between testosterone and aggression, then exogenous manipulations of testosterone should only affect the aggressive behavior of individuals with intact OFC function (although the likelihood of a large enough human sample is low; Beer, 2009).

The present study represents an important integrative step in understanding the hormonal and neural systems that influence aggression, but it is not intended as establishing a complete model. Previous research suggests a number of additional mechanisms and moderators of the testosterone–aggression relation. For example, animal studies indicate that (i) testosterone is converted to estradiol by the aromatase enzyme—estradiol can influence aggressive behavior, perhaps in part because of estradiol's effects on the mesolimbic dopamine system (Marsh, Creutz, Hawkins, & Godwin, 2006; Trainor, Kyomen, & Marler, 2006; Bless, McGinnis, Mitchell, Hartwell, & Mitchell, 1997), and (ii) testosterone facilitates aggression by modulating vasopressin systems in the hypothalamus (Delville, Mansour, & Ferris, 1996). Initial human studies show that testosterone enhances amygdala reactivity to social threat cues (anger faces), which may be a marker of aggressive motivation (van Wingen et al., 2009; Hermans et al., 2008). Finally, other hormones and gene polymorphisms are associated with aggressive behavior (e.g., dehydroepiandrosterone sulphate, cortisol, Vermeersch, T'Sjoen, Kaufman, & Vincke, 2008; Popma et al., 2007; Pajer et al., 2006; *MAOA* gene, Caspi et al., 2002; *TPH* gene, Hennig, Reuter, Netter, Burk, & Landt, 2005). Testosterone can interact with some of these genes and hormones to influence aggression and dominance (e.g., *MAOA* polymorphisms, Sjöberg et al., 2008; cortisol, Mehta & Josephs, 2008; Popma et al., 2007), potentially by modulating neural activity in the OFC (Hermans et al., 2008). Future research should consider these other factors along with testosterone and OFC to gain a broader understanding of the neurobiology of aggression.

In conclusion, the present research integrated approaches from behavioral endocrinology and cognitive neuroscience to elucidate the neural mechanisms through which testosterone influences aggression in humans. The findings suggest that the relation between testosterone and aggressive behavior is explained by decreased activity in the medial OFC. These results are consistent with neurobiological models of aggression, which implicate testosterone in aggression and dominance (Archer, 2006; Mazur & Booth, 1998) and the OFC in the inhibition of aggressive behavior (Siever, 2008; Strüber et al., 2008; Bufkin & Luttrell, 2005; Davidson et al., 2000).

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