A Non-Additive Interaction of a Functional *MAO*-A VNTR and Testosterone Predicts Antisocial Behavior

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Abstract

A functional VNTR polymorphism in the promoter of the monoamine oxidase A gene (*MAOA-LPR*) has previously been shown to be an important predictor of antisocial behavior in men. Testosterone analogues are known to interact with the *MAOA* promoter *in vitro* to influence gene transcription as well as *in vivo* to influence CSF levels of the MAO metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in human males. We examined the possible joint effects of testosterone (measured in CSF) and *MAOA-LPR* genotype on antisocial personality disorder and scores on the Brown–Goodwin Aggression scale in 95 unrelated male criminal alcoholics and 45 controls. The results confirm that *MAOA* genotype and CSF testosterone interact to predict antisocial behaviors. The *MAOA*/testosterone interaction also predicted low levels of CSF MHPG, which tentatively suggests the possibility that the interaction may be mediated by a direct effect on gene transcription. If replicated these findings offer plausible explanations for previous inconsistencies in studies of the relationship between testosterone and male human aggression, as well as for how *MAOA* genotype may influence aggressive behavior in human males.

Keywords

antisocial personality disorder; antisocial behavior; *MAO-A* gene; testosterone; gene by hormone interaction; MHPG

INTRODUCTION

Antisocial personality disorder (ASPD) and aggression are phenomena that are likely to be caused by a complex interplay of environmental and hereditary factor, and also include behaviors that can be situationally appropriate. ASPD is a diagnosis defined clinically rather than etiologically and includes socially influenced factors such as employment. Nevertheless, ASPD is moderately heritable and cross-transmitted with other dyscontrol disorders (Rhee and Waldman, 2002). ASPD has several well-defined biological correlates

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including impaired frontal lobe function leading to diminished capacity to inhibit behavior (Dolan and Park, 2002) and decreased levels of the serotonin metabolite 5-HIAA in cerebrospinal fluid (Brown *et al*, 1979; Roy *et al*, 1988), reflecting decreased turnover of this inhibitory neurotransmitter in the frontal lobe (Stanley *et al*, 1985). Aggression is an important manifestation of ASPD, which also displays moderate heritability (Rhee and Waldman, 2002), yet aggression can occur in many healthy individuals and in a manner that falls within the range of normal behavior in certain social situations.

The joint importance of environmental and genetic influences on ASPD is illustrated by the finding that a functional VNTR polymorphism in the *monoamine oxidase A (MAOA)* gene (Deckert *et al*, 1999; Sabol *et al*, 1998) interacts with childhood adversity to predict antisocial personality and antisocial behavior in men (Caspi *et al*, 2002). The childhood adversity and *MAOA* interaction has been replicated in at least four studies (Foley *et al*, 2004; Kim-Cohen *et al*, 2006; Nilsson *et al*, 2006; Widom and Brzustowicz, 2006); one study reported a non-significant trend in the same direction (Haberstick *et al*, 2005) and one study based on a clinical sample has failed to replicate (Young *et al*, 2006). These studies were all conducted on human males, except Widom and Brzustowicz (2006) which included men and women as will be discussed.

The effect of *MAOA* genotype on aggressive and antisocial behavior in women appears to be less consistent. In their longitudinal study, Widom and Brzustowicz (2006) found that the combination of childhood abuse and the low activity allele predicted juvenile, but not lifetime violent and antisocial behavior in Caucasian females. Sjoberg *et al* (2006), studying a sample of 119 adolescent girls (16 and 19 year olds), failed to replicate the effect of *MAOA* on antisocial behavior visible in the boys they studied (Nilsson *et al*, 2006) and even described a modest interaction effect in the opposite direction.

There are several reasons why there may be sex differences in the way the *MAOA* genotype influences antisocial behavior and aggression. One reason is that there are considerable sex differences in the prevalence of antisocial personality disorder, with a male preponderance of some 10 : 1 for the early onset-life course persistent variant (Rutter *et al*, 2003). Such differences may suggest the operation of sexual selection (Darwin, 1871) leading to differences in the behavioral expression of the same *MAOA* genotype in males and females. In addition, cultural expectations may reinforce innate differences between the sexes or even create them, leading to differential effects of *MAOA* genotype.

One possible source of sexual divergence with regard to the *MAOA* gene is effects of sex hormones such as testosterone. There are several ways in which testosterone may interact with effects of the *MAOA* gene. First, there is evidence suggesting that both the *MAOA* gene (Meyer-Lindenberg *et al*, 2006)and testosterone (Nef and Parada, 2000) have effects on brain structure and function. Second, and as we explored in the present study, *MAOA* genotype and testosterone may have an additive or interactive effect on adolescent and adult antisocial behavior. Testosterone has consistently been shown to influence aggression in animal studies and some evidence suggests that it may have similar effects in humans (Archer, 1991; Book *et al*, 2001). In the sample used in the present study, CSF testosterone levels were higher in individuals with antisocial personality disorder as compared to controls (Virkkunen *et al*, 1994).

A particular reason to explore *MAOA*/testosterone interaction is the possibility of direct action of testosterone on the *MAOA* promoter. The *MAOA* promoter contains three glucocorticoid/androgen response elements (GRE/ARE) and four binding sites for the Sp1 and R1 transcription factors. Androgens have recently been shown to interact directly with the third GRE/ARE and it also appears to act indirectly with Sp1 (Ou *et al*, 2006). Although

androgens activated *MAOA* transcription this effect was not as strong as that of glucocorticoids. Since glucocorticoids and testosterone compete for the same sites this may actually mean that high testosterone levels may lead to lower transcription of *MAOA* and lower MAOA levels. Such an interaction could augment differences between *MAOA*-VNTR alleles.

In vivo studies on human males have furthermore shown that administration of methyl-testosterone negatively influences levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) in cerebrospinal fluid (Daly *et al*, 2001). Since MHPG is a degradation product of norepinephrine by MAO-A, this finding is consistent with the idea of a direct effect of MAO activity on testosterone. Other recent findings suggesting that cortisol moderates the relationship between testosterone and aggression in delinquent male adolescents (Popma *et al*, 2006) are also consistent with the molecular mechanisms outlined above. The purpose of the present study was thus to investigate the combined effects of *MAOA* genotype and testosterone measured in CSF on male ASPD and antisocial behavior.

MATERIALS AND METHODS

Human Subjects

The protocol was approved by the Institutional Review Board of the National Institute of Mental Health, the Office for Protection from Research Risks, the University of Helsinki Department of Psychiatry Institutional Review Board, and the University of Helsinki Central Hospital Institutional Review Board. All subjects provided informed consent before entering the study.

A total of 165 unrelated male criminal alcoholics and controls were collected from the relatively homogeneous Finnish source population. The index cases were 95 criminal alcoholics who, because of the extreme nature of their crimes, were remanded to forensic psychiatric examination at the time of initial incarceration. These subjects spent an average of 1 month on the research ward and were drug- and alcohol-free during this period, and maintained on a low monoamine diet.

The control population consisted of 45 psychiatrically interviewed healthy Finnish male volunteers recruited by advertisements in local newspapers and paid for their participation. They were asked to refrain from use of any alcohol or other drugs and medications for a week before admission, and were then housed on the research ward for 3 days and nights. Both cases and controls were in good general health, as established by physical examination, normal erythrocyte and lymphocyte indexes and thyroid hormone levels, and serum electrolyte and creatinine concentrations. Among cases, γg–glutamyltransferase levels were also measured in the 48 h before the start of the study to ascertain alcohol abstinence.

Psychiatric Assessment

Lifetime psychiatric disorders were diagnosed using the Structured Clinical Interview for DSM (SCID) according to DSM-III-R criteria. Diagnoses were independently blind-rated from interview data by two research psychiatrists under the supervision of a senior research psychiatrist. Inter-rater reliability was very high between the two psychiatrists who blindly rated the interviews. Differences were resolved by the senior psychiatrist, who was also blind to the biochemical data. All cases had either alcohol abuse or alcohol dependence and most (82%) were alcohol dependent. Forty eight percent of cases ($N = 50$) met criteria for ASPD. All controls were free from both ASPD and alcohol use disorders.

The Brown–Goodwin Lifetime Aggression Scale was used as a continuous measure of aggression and antisocial behaviors (Brown *et al*, 1979). This self-report instrument consists

of nine questions quantifying, on a four-point scale, aggression towards others (physical as well as verbal), and antisocial behaviors involving disciplinary actions at school or work, with and without police contact.

Cerebrospinal Fluid (CSF) Testosterone

CSF samples were obtained by lumbar puncture at 0800 h after bed rest for one night with only water permitted after 2000 h. The samples were collected into a large polypropylene tube on wet ice. After the first 12 ml had been drawn, the tube was capped, inverted, and the CSF sample was aliquoted into 1 ml tubes on dry ice. CSF concentration of free testosterone was measured by radioimmunoassay (Virkkunen *et al*, 1994).

MAOA (MAOALPR) Genotype

Genomic DNA was purified from lymphoblastoid cell lines using standard methods from 140 participants, including 95 alcoholics (among whom 43 also had ASPD), and 45 controls. The *MAOA* promoter region that contains the *MAOALPR* VNTR was amplified from 25 ng genomic DNA using the primer sequences: Forward 5′ CCCAGGCTGCTCCAGAAACATG 3′ and Reverse 5′ GTTCGGGACCTGGGCAGTTGTG-3′. Because of the high GC content in the VNTR region, amplification was performed using Invitrogen's PlatinumTaq and PCRX Enhancer System kits (Invitrogen, Carlsbad, CA), according to the manufacturer's protocol with 5 μM of each primer and 25mM dNTPs in a total reaction volume of 15 μl. Amplifications were performed on a Perkin Elmer 9700 thermocycler (Applied Biosystems, Foster City, CA) with one cycle at 96°C for 10 min followed by 30 cycles of 94°C for 15 s, 60°C for 15 s, 72°C for 30s, and a final 3min extension at 72°C. The forward primer was labeled with the fluorescent dye 6-FAM, and amplicons were visualized on an ABI 3100 capillary sequencer. Allele sizes (allele 3, 263 bp; allele 3.5, 278 bp; allele 4, 293 bp; allele 5, 323 bp) were determined using Genotyper 2.5 software (Applied Biosystems). The overall success rate for genotyping was 99% (140/ 141). No discrepancies in the duplicates (*N*=14) were found.

Because the study sample was composed of men only, genotypes were grouped by relative transcriptional activity into two categories: high expression (3.5 or 4 repeats) versus low expression (3 or 5 repeats) (Sabol *et al*, 1998). Because the effect of the five-repeat allele on transcription was inconsistent across studies (Deckert *et al*, 1999; Sabol *et al*, 1998) analyses were repeated excluding the four participants who had the five-repeat genotype.

As reported previously (Ducci *et al*, 2006) there were no significant differences in *MAOA* allele frequencies between cases and controls.

Statistical Analyses

A multiple regression analysis was conducted to test for the effect of three independent variables (*MAOALPR* genotype, CSF testosterone levels, and the interaction between these two variables (*MAOALPR* × testosterone) on the Brown–Goodwin Lifetime Aggression Scale total score. The regression analysis was conducted first by assigning *MAOALPR* genotype and CSF testosterone levels as independent variables and then as an interaction element. Because main effects in multiple regression models including interaction variables may be influenced by various statistical artefacts, these are not displayed in the results section. Instead we present the main effects from the model that did not include the interaction. Logistic regression was used in a similar way to test the effect of the same independent variables on ASPD diagnosis. CSF testosterone and CSF MPHG levels were compared between ASPD patients and controls using the *t*-test.

A multiple regression analysis was also conducted to test for effect on CSF MHPG of *MAOA-LPR*, CSF Testosterone and *MAOALPR* × testosterone. Also in this case, main effects of *MAOA-LPR* and testosterone reported refer to those computed before entering the interaction elements.

Other variables that are known to influence CSF monoamine metabolites levels (namely height, BMI, smoking) were entered into the model as independent variables to test for their potential confounding effects. As has been reported elsewhere, the effects of these confounding variables in this sample were significant (Ducci *et al*, 2006). The correlation between smoking and MHPG was negative and the correlations between BMI and height and MHPG were positive. Since MAOA also oxidizes serotonine and dopamine, CSF metabolites for these substances (5-HIAA and HVA) were also analyzed in similar ways.

All analyses were conducted using JMP software v5.1 (SAS Institute, Cary, NC). Criterion for statistical significance was set at 0.05.

RESULTS

Effect of MAOA Genotype and Testosterone Levels on Antisocial Behavior

The effects of CSF testosterone and *MAOALPR* genotype on Brown–Goodwin Lifetime Aggression and ASPD diagnosis are shown in Table 1. As reported previously in this sample (Virkkunen *et al*, 1994), higher CSF testosterone is significantly associated with an increase in risk of having ASPD (logistic regression, d.f.=1, χ^2=6.9, *P*=0.008). CSF testosterone level also tended to be positively correlated with Brown–Goodwin Lifetime Aggression, although this trend was non-significant (linear regression, *β*=1.27, *P*=0.09). As reported previously (Ducci *et al*, 2006), *MAOA* genotype itself does not predict ASPD in this population (see Table 1).

Interaction of *MAOA* Genotype and CSF Testosterone on Brown–Goodwin Aggression and ASPD

Significant interaction effects between *MAOALPR* and CSF testosterone were found on both Brown–Goodwin Lifetime Aggression (*β*=2.21, *P*=0.002) and ASPD (χ^2=4.5, *P*=0.02) (see Table 1). As shown in Figure 1, higher levels of testosterone were associated with increased Brown–Goodwin scores among individuals with the low activity *MAOA* genotype (Figure 1a) but not among individuals with the genotype conferring higher levels of *MAOA* transcription (Figure 1b). Among individuals with the low activity *MAOA* genotype,a one SD increase in testosterone led to a 3.49 unit increase in aggression score. Consistently, it is only among ASPD patients and controls with the reduction-of-function *MAOA* genotype that there is a case–control difference in CSF testosterone levels. As shown in Figure 2, the case–control comparison for CSF testosterone in individuals with the reduction of function genotype is significant (*t*-test: d.f.=1, t=3.43; *P*=0.001). However, there is no difference in CSF testosterone between cases and controls with high *MAOA* activity genotype (*t*-test: d.f.=1; t=0.63, *P*=0.52).

Interaction of *MAOA* Genotype and CSF Testosterone on CSF MHPG

As reported previously (Lappalainen *et al*, 1999), mean CSF MHPG levels were significantly lower in ASPD (mean (SE)=35.11 (12.43) pmol/ml) as compared to controls (mean (SE)=45.17 (12.14) pmol/ml; t=5.79, *P*<0.0001). *MAOA*-LPR genotype were negatively correlated with CSF MHPG *β*=−0.64; *P*=0.03), whereas CSF testosterone did not show any main effect on CSF MHPG (Table 1). Testosterone and *MAOA-LPR* genotype displayed a significant interaction effect on CSF MHPG (*β*=1.88; *P*=0.01).

As shown in Figure 1, higher levels of testosterone were associated with decreased CSF MHPG among individuals with the reduction-of-function *MAOA* genotype (Figure 1c) but not among individuals with the genotype conferring higher levels of *MAOA* transcription (Figure 1d).

The interaction effect between *MAO-LPR* and testosterone on CSF MHPG remained significant, although it was slightly reduced, after taking into account the effects of BMI, smoking, and height ($\beta=-1.40$; $P=0.05$).

The *MAOA* × testosterone interaction did not predict levels of other CSF metabolites of other MAO substrates (5-HIAA and HVA).

DISCUSSION

We investigated the joint effects of the functional *MAOA* VNTR (*MAOALPR*) and CSF testosterone on ASPD and aggression in human males. As reported previously in this same sample (Virkkunen *et al*, 1994), individuals with ASPD had higher levels of CSF testosterone but there was no significant predictive effect of *MAOALPR* genotype alone (Ducci *et al*, 2006). The main finding of the present study is that testosterone (assessed in CSF) and *MAOA* genotype interact to predict ASPD as well as lifetime aggression and antisocial behavior measured on the Brown–Goodwin Scale.

There are two possible explanations for our findings. First the *MAOA*/testosterone interaction may reflect the direct action of testosterone on the *MAOA* promoter paralleling recently reported *in vitro* findings (Ou *et al*, 2006).

The second possibility arises from the functional relationship between brain systems modulated by both *MAOA* and testosterone, or by either. One recent study positron emission tomography study of brain MAOA activity in relation to *MAOA*-LPR genotype suggests that genotype does not have a direct effect on transcriptional activity (Fowler *et al*, 2006). This finding may possibly be explained by the fact that the study did not take hormonal and/or environmental factors into account. However, it has been reported that the low-activity *MAOA* allele predicts amygdala hyperactivity and frontal hypoactivity after an emotional stimulus. Substantial male/female differences in aggression and emotional response are known. For reasons unknown, metabolic responses to emotional stimuli of amygdala and other brain regions differ between men and women (Canli *et al*, 2002), who apparently have different patterns of emotional modulation. The MAOA enzyme metabolizes dopamine and other monoamine neurotransmitters such as serotonin that are critical in emotional responses and behavioral inhibition. *MAO* knockout mice exhibit increased aggression and stress reactivity (Shih, 2004), and the low activity *MAOA-LPR* allele is associated with behavioral dyscontrol and increased aggression. In addition, in one Dutch family, a rare *MAOA* stop-codon variant leads to behavioral dyscontrol and aggression, further illustrating the power of genetic variation at *MAOA* to influence this domain of neurobiology (Brunner *et al*, 1993). The rare *MAOA* stop-codon variant has been genotyped in the present dataset, but it was not detected (D Goldman *et al*, unpublished data).

Across studies, testosterone does not consistently increase human aggression despite meta-analyses suggesting that aggression is a behavioral consequence of testosterone. Indeed studies in animal models fairly, consistently show that higher endogenous and administered levels of testosterone predict aggressive behavior (Albert *et al*, 1993; Archer, 1991; Book *et al*, 2001). In the human, there are multiple sources of factors that contribute to the variance in aggressive behavior, including differences in previous environmental exposures, variation in testosterone exposure, learning and adaptation, and measurement. However, genetic variation almost certainly plays a role, as established in numerous animal studies. The

results of the present study suggest that testosterone response may in part depend on *MAOA* genotype.

The results also suggests a possible explanation to the fact that previous studies (Sjoberg *et al*, 2006; Widom and Brzustowicz, 2006) have had difficulties in replicating findings of interactions between environmental adversity and *MAOA* genotype in females. However, it should be noted that there may be other explanations for this such as a lack of power in these studies. *MAOA* is an X-linked gene such that about 30% of men are hemizygous for the low expressing *MAOA* allele, but only about 9% of women are homozygous with two copies of the low expressing allele. This suggests that there may have been a relative lack of power to detect effects of *MAOA* genotype in females. Furthermore the possibility that the *MAOA*-gene escapes X-inactivation in females as suggested by some (Carrel and Willard, 2005) but not all (Nordquist and Oreland, 2006) studies also suggest other possible mechanisms of molecular differences between males and females with respect to this gene.

This study has several strengths including the relative extremity and uniformity of this sample of Finnish offenders and Finnish controls, the fact that our sample consisted entirely of men thus dramatically increasing power to detect effects of the X-linked *MAOA* gene as well as effects of testosterone found at much higher levels in men, the assessment of ASPD via extensive psychiatric interviews, and the availability of CSF testosterone measures which are more relevant to brain testosterone levels than measures from blood or saliva. However, it should be noted that cause-and-effect inferences for testosterone and behavior in these ASPD subjects are tentative. Although we view this as unlikely, higher testosterone levels could be a consequence of the development of ASPD in the context of the low-expressing *MAOA* genotype. It should also be noted that the results reported in this study were derived from only one, relatively small sample. It is thus important to replicate our findings in other populations before definite conclusions are drawn.

In summary, common, functional *MAOA* alleles and testosterone interact to predict antisocial behaviors defined as a continuous trait on the Brown–Goodwin scale or categorically via the DSM diagnosis of ASPD. The *MAOA*/testosterone interaction also predicted low levels of CSF MHPG, suggesting that the interaction may be mediated by a direct effect on gene transcription. If replicated these findings offer a plausible explanation for previous inconsistencies in studies of the relationship between testosterone and male human aggression, as well as for the understanding of how *MAOA* genotype may influence behavior.

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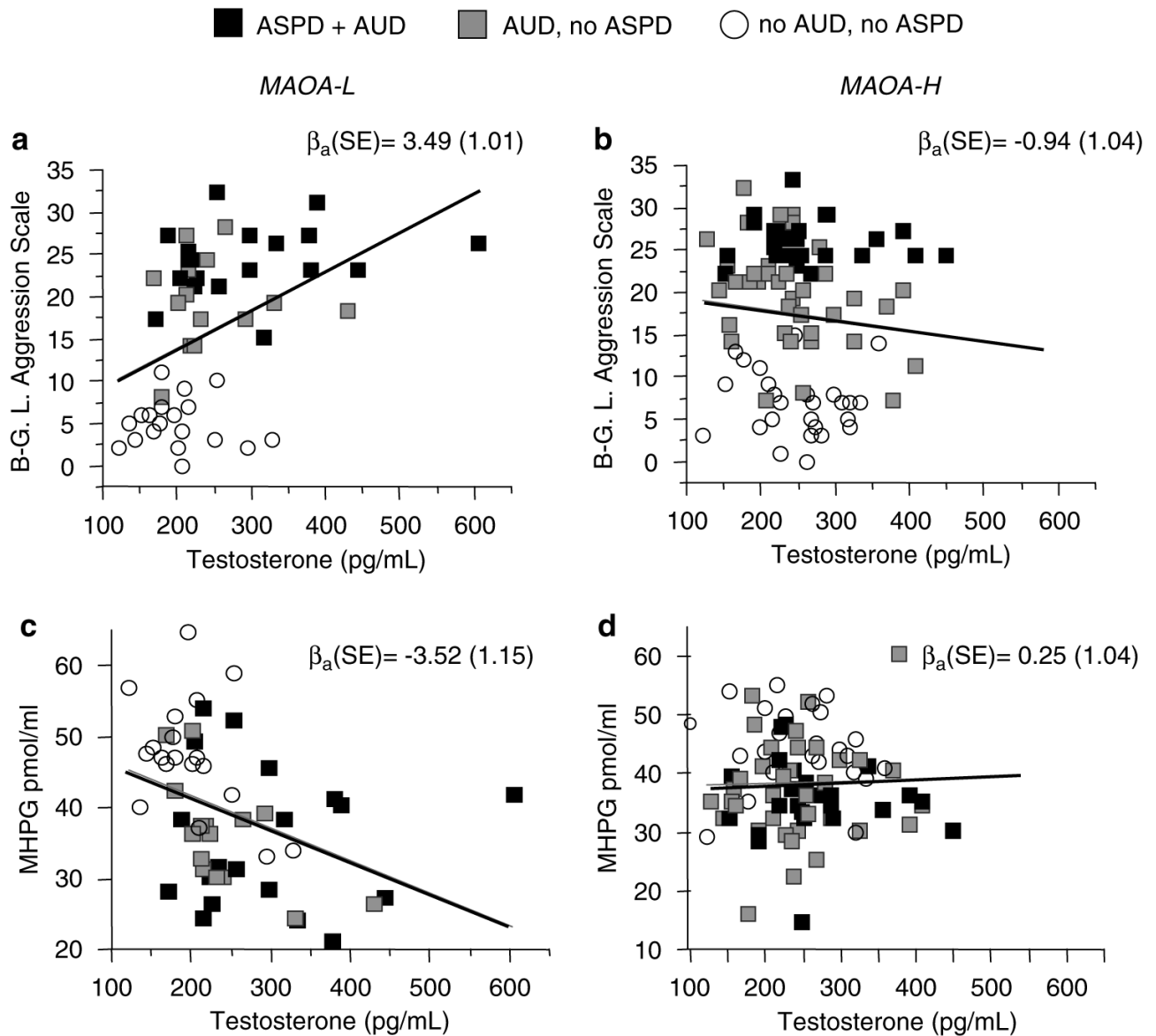
Figure 1.
Correlation between CSF testosterone and aggression in subjects with different *MAOA-LPR* genotype. MAOA-L=Low activity (a); MAOA-H=High activity (b). Correlation between CSF testosterone and CSF MHPG in subjects with different *MAOA-LPR* genotype. MAOA-L=Low activity (c); MAOA-H=High activity (d). ASPD=antisocial personality disorder; AUD: alcohol use disorder; B-G. L. Aggression Scale=*Brown–Goodwin lifetime Aggression scale*.
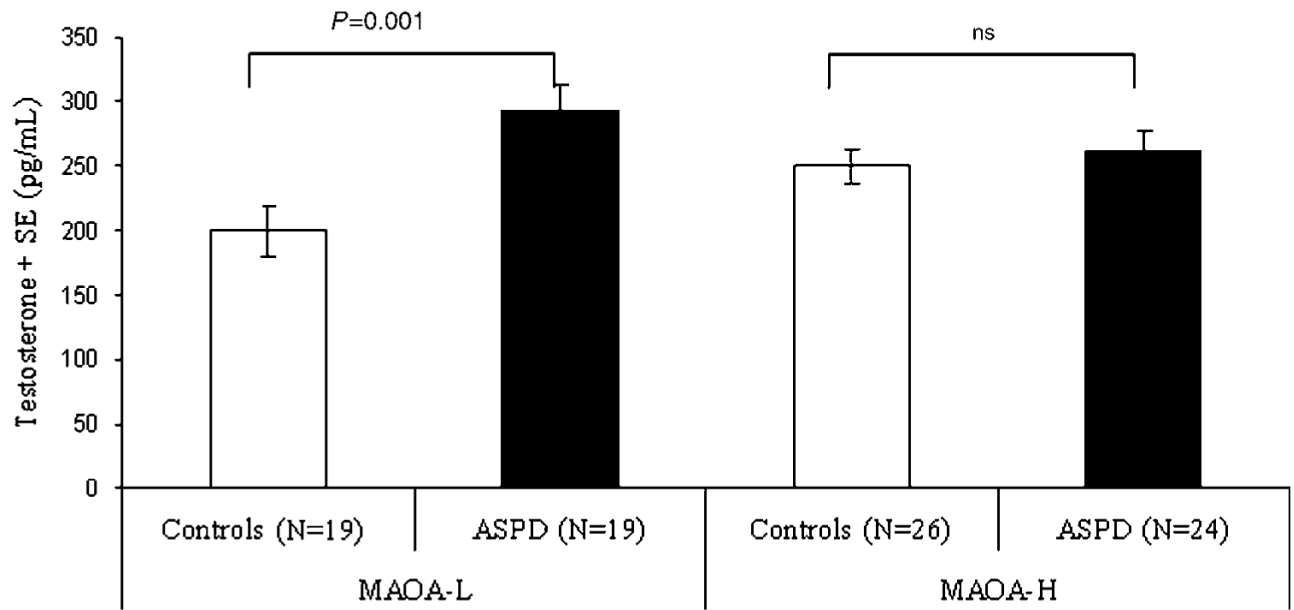
Figure 2.
Mean testosterone levels are compared (*t*-test) between controls (in white) and ASPD patients (in black) among participants with different *MAOA-LPR* genotypes. *MAOA*-H=high activity; *MAOA*-L=low activity. ns=non significant. ASPD=antisocial personality disorder; AUD=alcohol use disorder; MHPG=3-methoxy-4-hydroxyphenylglycol.

Table 1

Relationship of CSF Testosterone and *MAOALPR* Genotype on Aggression (Brown–Goodwin Lifetime Aggression Scale Total Score), ASPD and CSF MHPG

Predictors	Aggression		
	β (SE)	t	P
MAOA	0.74 (0.77)	0.96	0.33
Testosterone[a]	1.27 (0.75)	1.7	0.09
MAOA*testosterone	2.21 (0.73)	3.04	0.002
	ASPD		
	β (SE)	χ^2	P
MAOA	0.10 (0.23)	0.21	0.64
Testosterone[a]	0.67 (0.25)	6.9	0.008
MAOA*testosterone	0.61 (0.21)	4.5	0.04
	CSF MHPG		
	β (SE)	t	P
MAOA	−0.64 (0.79)	−0.81	0.03
Testosterone[a]	−1.62 (0.77)	−2.09	0.42
MAOA*testosterone[a]	1.88 (0.76)	2.47	0.01

ASPD, antisocial personality disorder; β, regression coefficient; SE, standard error.

[a]CSF testosterone levels have been transformed into z scores (mean of zero and SD of one) before entry into the model. Therefore, the corresponding β-value indicates the effect on the outcome variable (eg increase in aggression score or increase in risk of ASPD) for each SD increase in CSF testosterone.