Understanding Genetic Risk for Aggression: Clues From the Brain's Response to Social Exclusion

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Background: Although research indicates a relationship between the monoamine oxidase-A (MAOA) gene and aggression, the intervening neural and psychological mechanisms are unknown. Individuals with the low expression allele (MAOA-L) of a functional polymorphism in the MAOA gene might be prone to aggression because they are socially or emotionally hyposensitive and thus care less about harming others or because they are socially or emotionally hypersensitive and thus respond to negative social experiences with defensively aggressive behavior.

Methods: We investigated the relationships between the MAOA polymorphism, trait aggression, trait interpersonal hypersensitivity, and neural responses to social exclusion in 32 healthy men and women.

Results: The MAOA-L individuals (men and women) reported higher trait aggression than individuals with the high expression allele (MAOA-H). The MAOA-L individuals reported higher trait interpersonal hypersensitivity and showed greater dorsal anterior cingulate cortex (dACC) activity (associated with rejection-related distress) to social exclusion compared with MAOA-H individuals, consistent with a social hypersensitivity hypothesis. Moreover, the MAOA–aggression relationship was mediated by greater dACC reactivity to social exclusion, suggesting that MAOA might relate to aggression through socioemotional hypersensitivity.

Conclusions: These data suggest that the relationship between MAOA and aggression might be due to a heightened rather than a reduced sensitivity to negative socioemotional experiences like social rejection.

Key Words: Aggression, dorsal anterior cingulate cortex, fMRI, interpersonal sensitivity, MAOA gene, MAOA-uVNTR, neuroimaging, social exclusion

In both animal and human populations, aggressive behavior has been linked to a genetic deficiency in monoamine oxidase-A (MAOA), an enzyme that degrades serotonin, dopamine, and norepinephrine (Shih *et al.* 1999). Monoamine oxidase-A–deficient male mice were found to be more aggressive as evidenced by a shorter latency to attack and a greater number of skin wounds in a resident-intruder paradigm (Cases *et al.* 1995). Monoamine oxidase-A–deficient men from a single Dutch kindred demonstrated elevated levels of impulsive aggression, arson, and attempted rape (Brunner *et al.* 1993). In line with these findings, when exposed to early adversity, men with the low expression allele (MAOA-L) of the 30-base pair (bp) variable number tandem repeats polymorphism in the MAOA promoter (MAOA-uVNTR) were more likely to develop antisocial behavior than men with the high expression allele (MAOA-H; Caspi *et al.* 2002). Despite mounting evidence suggesting a relationship between the MAOA-uVNTR polymorphism and aggressive behavior, it is unclear how this genetic polymorphism predisposes individuals to aggressive behavior.

Aggression researchers have distinguished between two types of aggressive behavior, one resulting from a lack of emotional sensitivity and one resulting from excessive emotional sensitivity (Blair *et al.* 2006; Crick and Dodge 1996). Instrumental or proactive aggression is pre-meditated, goal-directed aggression that is used to obtain a desired goal. This type of aggression has been associated with psychopathy and often involves diminished emotional sensitivity, empathy, and remorse (Berkowitz 1993; Blair *et al.* 2006; Frick *et al.* 2003). Reactive aggression, in contrast, is triggered by negative experiences and involves exaggerated levels of negative emotion, such as anger or anxiety, in response. This type of aggression is thought to result from a more responsive threat detection system as well as a diminished capacity to regulate the heightened emotional responses (Blair 2004; Blair *et al.* 2006; Grafman *et al.* 1996). Despite the fact that aggressive behavior clearly relates to affective processes, few neuroimaging studies have investigated how the MAOA polymorphism relates to neural activity associated with these affective processes. Instead, neuroimaging studies have focused primarily on how the MAOA polymorphism relates to executive attention or inhibitory control during cognitive tasks, typically observing that the MAOA polymorphism relates to altered activity in neural regions involved in triggering and instantiating cognitive control (Fan *et al.* 2003; Meyer-Lindenberg *et al.* 2006; Passamonti *et al.* 2006).

To date, only one study has examined the relationship between the MAOA polymorphism and affect-related processing. This study examined how the MAOA polymorphism related to individual differences in the gray matter volume of limbic regions and in the responses of these regions to emotional stimuli, specifically negative emotional faces (Meyer-Lindenberg *et al.* 2006). Compared with MAOA-H, MAOA-L individuals showed reduced gray matter volumes in limbic regions such as the amygdala, dorsal anterior cingulate cortex (dACC), and subgenual ACC and greater amygdala and subgenual ACC activity to negative emotional faces. Although this study represents an advance in understanding how the MAOA-uVNTR polymorphism relates to affective processing, the study did not examine self-reports or behavioral assessments of aggression. Moreover, because the affective stimuli used in this study, namely pictures of negative emotional expressions, are not likely to elicit full-blown emotions, it is difficult to know how the MAOA polymor-

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phism relates to actual emotional responses to negative events. Thus, in the present study, we examined how the MAOA polymorphism related to trait aggression as well as how it related to neural responses to a negative socioemotional experience that has been shown to elicit real negative feelings, specifically an experimental episode of social exclusion (Williams *et al.* 2000).

In line with the distinction between aggression due to blunted emotional sensitivity (instrumental) versus aggression due to exaggerated emotional sensitivity (reactive), we examined whether MAOA-L individuals showed evidence of social hyposensitivity, making them more likely to commit violent acts because they care less about harming others, or social hypersensitivity, making them more sensitive to negative social events and more likely to respond with defensively aggressive behavior (Dodge and Pettit 2003; Twenge *et al.* 2001). Although each of these possibilities results in aggressive behavior, the experiential predictors of these acts are quite different and would have different implications for treatment alternatives.

We first examined how the MAOA polymorphism related to self-reported trait aggression (e.g., "having urges to harm someone") in both men and women. We then examined whether MAOA-related aggression was associated with social hypo- or social hyper-sensitivity by examining: 1) how the MAOA polymorphism related to self-reported trait interpersonal hypersensitivity (e.g., "you feel that people are unfriendly or dislike you," "your feelings are easily hurt"), and 2) how the MAOA polymorphism related to neural responses to an experimental episode of social exclusion. Previous work has shown that, in response to an experimental episode of social exclusion, participants show increases in self-reported social distress (e.g., "I felt rejected") (Williams *et al.* 2000) and that these increases in social distress parallel increased activity in the dACC (Eisenberger *et al.* 2003). Thus, if the MAOA–aggression link reflects reduced socioemotional sensitivity, MAOA-L individuals should report less trait interpersonal hypersensitivity and show less dACC activity to social rejection than MAOA-H individuals. Alternatively, if the MAOA–aggression link reflects heightened socioemotional sensitivity, MAOA-L individuals should report greater trait interpersonal hypersensitivity and show greater dACC activity to social rejection than MAOA-H individuals. In either case, MAOA-L individuals should report higher levels of trait aggression than MAOA-H individuals.

Methods and Materials

Subjects

Members of the University of California at Los Angeles (UCLA) community responded to an advertisement offering $60 for participation. Prospective participants with the following conditions were excluded from participation through a structured telephone interview: serious physical or mental health problems (e.g., "Has a doctor ever told you that you have a serious physical/mental health problem?"), current treatment from a mental health professional, current use of mental health-related medication (e.g., Prozac), claustrophobia, and the presence of metals in their bodies (dental fillings were allowed). Thirty-two healthy, right-handed participants (19 female; mean age = 20.59, SD = 3.17) provided written informed consent. The sample was 28.1% European-American, 40.6% Asian, 15.6% Hispanic, 6.3% African-American, and 9.4% "mixed" or other, a pattern that reflects the composition of the UCLA community. Experimental procedures were approved by the UCLA Human Subjects Protection Committee.

Measures

Before completing the neuroimaging task, participants completed several self-report measures related to aggression and interpersonal hypersensitivity. Specifically, participants completed the Brief Symptom Inventory (BSI) (Derogatis and Spencer 1982), which contains a subscale assessing hostility (e.g., "How bothered do you feel about: ". . . having urges to beat, injure, or harm someone?" ". . . feeling easily annoyed or irritated?") and a subscale assessing interpersonal hypersensitivity (e.g., "How bothered do you feel about: ". . . feeling very self-conscious with others?" ". . . your feelings being easily hurt?"). Both of these subscales demonstrated strong reliability (hostility subscale: $\alpha = .76$; interpersonal hypersensitivity subscale: $\alpha = .85$). Participants also completed the Spielberger Trait Anger scale (Spielberger *et al.* 1985; e.g., "When I get frustrated, I feel like hitting someone," "When I get mad, I say nasty things"). This measure also demonstrated strong reliability ($\alpha = .83$). Trait aggression scores were calculated by normalizing and then averaging scores from the hostility subscale of the BSI and the Spielberger Trait Anger scale. Interpersonal hypersensitivity scores were calculated by taking the average of the items in the BSI interpersonal hypersensitivity subscale.

Genotyping

After the completion of the self-report measures, DNA was obtained with the Orasure oral specimen collection device (Orasure Technologies, Bethlehem, Pennsylvania) and extracted with the Puregene DNA purification kit (Gentra Systems, Minneapolis, Minnesota). The MAOA-uVNTR polymorphism was identified using polymerase chain reaction (PCR) with a protocol modified from Sabol *et al.* (1998). The forward primer was 5'-ACA GCC TGA CCG TGG AGA AG-3' (VIC labeled [Applied Biosystems, Foster City, California]) and the reverse primer was 5'-GAA CGG ACG CTC CAT TCG GA-3'. Amplification was performed in a total volume of 8 μL containing 25 ng DNA, 125 μmol/L primers, 200 μmol/L deoxyribonucleotide triphosphate (dNTP), 10% dimethyl sulfoxide (DMSO), 2.5 mmol/L magnesium dichloride, and .8 U of Amplitaq Gold (Applied Biosystems) in the manufacturer's buffer. Samples were denatured at 94°C for 12 min, followed by 35 cycles of 94°C for 30 sec, 55°C for 30 sec, and 72°C for 2 min. The PCR products were separated on an ABI 3700 DNA analyzer (Applied Biosystems). To assess genotyping accuracy, 15 samples were reprocessed, and no errors were detected. Alleles were grouped into either a low expression category that consisted of 2, 3, and 5 repeats of the 30-bp sequence or a high expression category that consisted of a 4-repeat allele as well as 3-repeat allele with an additional 18-bp incomplete repeat, as performed previously (Caspi *et al.* 2002; Meyer-Lindenberg *et al.* 2006; Sabol *et al.* 1998).

Because MAOA is an X-linked gene, men carry only one allele and can thus only be MAOA-L or MAOA-H; however, women carry two alleles and can thus have two MAOA-L alleles, two MAOA-H alleles, or one of each. Thus, there were three genotype categories: 1) the MAOA-L category ($n = 13$), consisting of men with MAOA-L and women with two copies of MAOA-L, 2) the MAOA-LH category ($n = 10$), consisting of women with one copy of MAOA-L and one copy of MAOA-H, and 3) the MAOA-H category ($n = 9$), consisting of men with MAOA-H and women with two copies of MAOA-H. Previous research has shown that female heterozygotes show patterns of neural

activity intermediate between MAOA-L and MAOA-H male hemizygotes and that female homozygotes show patterns of neural activity comparable to male hemizygotes (Meyer-Lindenberg *et al.* 2006).

Functional Magnetic Resonance Imaging Paradigm

To assess neurocognitive reactivity to social rejection, participants were scanned while completing the Cyberball social exclusion task, in a manner similar to previous work (Eisenberger *et al.* 2003; Williams *et al.* 2000). Participants were told that they would be playing a virtual ball-tossing game with two other individuals who were also in functional magnetic resonance imaging (fMRI) scanners. In reality, however, there were no other players; participants were playing with a preset computer program. Each game began with a still picture of the two virtual players in the upper corners of the screen and a hand, representing the participant, in the lower-center portion of the screen. After 9 sec, the cartoon player in the upper left-hand corner started the game by throwing the ball to either the other cartoon player or the participant. The participant could return the ball to one of the players by pressing one of two keys. The Cyberball program was set for 60 throws/game, with the computer players waiting .5–3.0 sec (determined randomly) before making a throw to heighten the sense that the participant was actually playing with other individuals.

During the task, participants completed two scans. In the first scan (inclusion), participants played with the two other players for the entire scanning period, with each virtual player throwing the ball to the participant on approximately 50% of the throws. In the second scan (exclusion), participants only received the ball for a total of seven throws and were then excluded for the rest of the scan when the two players stopped throwing the ball to the participant (60–90 sec) (although it would have been ideal to counterbalance the order of the inclusion and exclusion scans across participants, having the exclusion scan come before the inclusion scan would likely change the meaning of the inclusion scan for participants; thus, participants who were first excluded might subsequently worry about being excluded again or anticipate that another exclusion episode is possible). Immediately after the scanning session, participants completed a measure of self-reported social distress, in which they were asked to rate how socially distressed they felt during the final ball-tossing game (e.g., "I felt rejected," "I felt invisible"; Williams *et al.* 2000).

fMRI Data Acquisition and Data Analysis

Data were acquired on a Siemens Allegra 3T head-only scanner (Siemens, Malvern, Pennsylvania). Head movements were restrained with foam padding and surgical tape placed across each participant's forehead. For each participant, a high-resolution structural T2-weighted echo-planar imaging volume (spin-echo; repetition time [TR] = 5000 msec; echo time [TE] = 33 msec; matrix size 128 × 128; 36 axial slices; field of view [FOV] = 20-cm; 3-mm thick, skip 1-mm) was acquired coplanar with the functional scans. Two functional scans were acquired (echo planar T2*-weighted gradient-echo, TR = 3000 msec, TE = 25 msec, flip angle = 90°, matrix size 64 × 64, 36 axial slices, FOV = 20-cm; 3-mm thick, skip 1-mm), each lasting 2 min and 30 sec.

The imaging data were analyzed with SPM'99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, United Kingdom). Images for each subject were realigned to correct for head motion, normalized into a standard stereotactic space, and smoothed with an 8-mm Gaussian kernel, full width at half maximum, to increase signal-to-noise ratio. The design was modeled with a boxcar function convolved with a canonical hemodynamic response function. For each participant, periods of inclusion and exclusion were modeled as epochs on the basis of the length of that participant's inclusion and exclusion episodes (these varied slightly between participants owing to the random delay assigned to the virtual players when throwing the ball). After the task was modeled for each participant, planned comparisons were computed as linear contrasts to investigate neural activity during the exclusion compared with the inclusion episode. Random effects analyses of the group were computed with the contrast images generated for each participant.

To assess the relationship between the MAOA polymorphism and neural responses to social exclusion, three different analyses were performed. First, measures of self-reported social distress were entered as regressors into a random-effects, whole-brain group analysis, comparing activations during exclusion relative to inclusion ($p < .005$, 20-voxel extent threshold; Forman *et al.* 1995). Regions of the dACC that correlated positively with self-reported social distress were extracted and then examined to see if they varied as a function of the MAOA polymorphism, gender, or the interaction between the two using a two-way analysis of variance (ANOVA). Second, measures of individual differences in the allelic combinations (MAOA-L = 0; MAOA-LH = 1; MAOA-H = 2) were entered as regressors into a random-effects, whole-brain group analysis, comparing neural activity during exclusion relative to inclusion ($p < .005$, 20-voxel extent threshold) to see which neural regions correlated with the MAOA polymorphism in a linear fashion. Last, a one-way ANOVA was conducted in SPM'99 to see which neural regions, during exclusion relative to inclusion, showed significantly different activity for MAOA-L and MAOA-H individuals in whole-brain analyses ($p < .005$, 20-voxel extent threshold). All coordinates are reported in Montreal Neurological Institute (MNI) format. One participant was excluded from genetic analyses, owing to outlier data on neural activity; two participants were excluded from neuroimaging analyses, one owing to excessive motion and one owing to prior experience with the Cyberball task.

Results

MAOA and Self-Reported Trait Aggression

To investigate the relationship between the MAOA polymorphism and trait aggression, a two-way ANOVA was conducted, with the MAOA polymorphism (MAOA-L, MAOA-LH, MAOA-H) and gender (male, female) as independent variables and self-reported trait aggression as the dependent variable. One subject was a multivariate outlier when examining the relationship between MAOA and aggression and was thus removed from this analysis.

Results revealed a main effect of the MAOA polymorphism on self-reported trait aggression [$F(2,29) = 3.68$, $p < .05$] (Figure 1) but no main effect of gender [$F(1,29) = .02$, ns] and no significant interaction between MAOA and gender [$F(1,29) = .10$, ns] in predicting trait aggression. Thus, individual differences in the MAOA polymorphism significantly related to trait aggression scores; however, there were no significant differences between men and women in levels of self-reported trait aggression or in the relationship between the MAOA polymorphism and self-reported aggression. Additional analyses revealed that MAOA-L individuals were significantly higher in self-reported trait aggression than MAOA-H individuals [$t(18) = 2.92$, $p < .01$] and

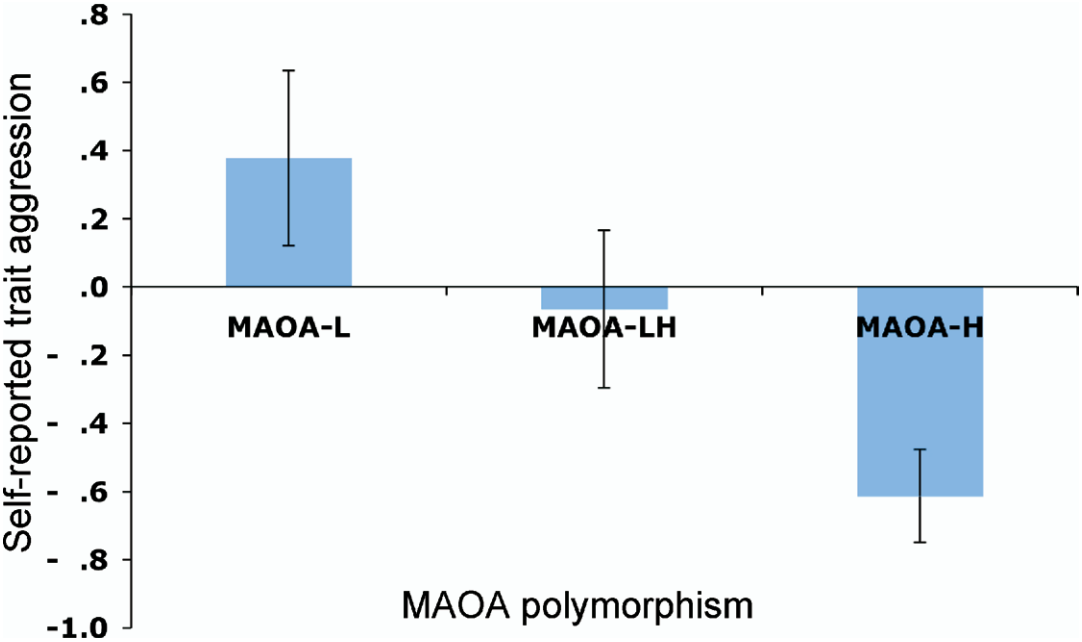

Figure 1. Bar graph showing the relationship between the monoamine oxidase-A (MAOA) polymorphism (x-axis) and self-reported trait aggression scores (y-axis; these have been *Z*-scored).

MAOA-LH individuals were marginally higher in trait aggression than MAOA-H individuals [$t(16) = 1.89$, $p = .08$] (these results should be interpreted with caution given the small sample size; the issue of sample size is addressed more fully in the Discussion section). To further explore the possible experiential mediators of this MAOA–aggression link, we next examined the relationship between the MAOA polymorphism and self-reported trait interpersonal hypersensitivity.

MAOA and Trait Interpersonal Hypersensitivity

To investigate whether the MAOA polymorphism related to trait interpersonal hypersensitivity, a two-way ANOVA was conducted, with the MAOA polymorphism and gender as independent variables and self-reported trait interpersonal hypersensitivity as the dependent variable. Because the interpersonal hypersensitivity variable was not normally distributed, we performed a natural log-transformation on this variable.

There was a marginal main effect of the MAOA polymorphism on trait interpersonal hypersensitivity [$F(2,30) = 2.61$, $p = .09$] (Figure 2), no main effect of gender [$F(1,30) = .50$, ns], and no significant interaction between MAOA and gender [$F(1,30) = .00$, ns] in predicting interpersonal hypersensitivity. Thus, individual differences in the MAOA polymorphism showed a trend in predicting trait interpersonal hypersensitivity; however, there were no significant differences between men and women in levels of self-reported interpersonal hypersensitivity or in the relationship between the MAOA polymorphism and self-reported interpersonal hypersensitivity. Additional analyses revealed that MAOA-L individuals were significantly more interpersonally hypersensitive than MAOA-H individuals [$t(19) = 2.32$, $p < .05$]. There were no significant differences between MAOA-L and MAOA-LH individuals [$t(20) = 1.06$, ns] or between MAOA-LH and MAOA-H individuals [$t(17) = 1.27$, ns].

This finding favors the possibility that MAOA-L individuals might be more prone to reactive rather than instrumental aggression, owing in part to heightened socioemotional sensitivity, which might ultimately result in defensively aggressive behavior. Indeed, higher levels of trait interpersonal hypersensitivity were associated with higher levels of trait aggression [$r(31) = .53$, $p < .005$; see Table 1 for a complete list of intercorrelations among study variables], and the magnitude of these correlations was similar for men and women when analyzed separately [men: $r(13) = .60$, $p < .05$; women: $r(18) = .47$, $p < .05$].

To further examine the possibility that MAOA-L individuals are more interpersonally hypersensitive, we investigated how the MAOA polymorphism related to neural responses to social exclusion. If MAOA-L is related to aggression through heightened sensitivity to negative social experiences (as suggested by the analyses examining trait interpersonal hypersensitivity), MAOA-L, compared with MAOA-H, individuals should show heightened dACC responses to social exclusion.

MAOA and Neural Response to Social Exclusion

The relationship between the MAOA polymorphism and neural responses to social exclusion was investigated in several different ways. The first analysis identified regions of the dACC during the exclusion, compared with the inclusion, episode that correlated with self-reported social distress in whole-brain analyses ($p < .005$, 20-voxels). Values were then extracted from these regions, and ANOVAs were conducted (with standard statistical software) to examine whether the activity in these dACC regions varied as a function of the MAOA polymorphism, gender, or the interaction between the two.

Three regions of the dACC correlated significantly with self-reported social distress in the exclusion versus inclusion contrast in whole-brain analyses (dACC1: 6,36,32, $r = .64$; dACC2: 10,26,18, $r = .59$; dACC3: −14,22,36, $r = .55$). Of these activations, one differed as a function of the MAOA polymorphism (6,36,32). For this activation, there was a main effect of the MAOA polymorphism [$F(2,28) = 4.07$, $p < .05$] (Figures 3A and B), no main effect of gender [$F(1,28) = .74$, ns], and no MAOA × gender interaction [$F(1,28) = .00$, ns] on levels of dACC activity. Thus, individual differences in the MAOA polymorphism significantly related to dACC activity to social exclusion (vs. inclusion);

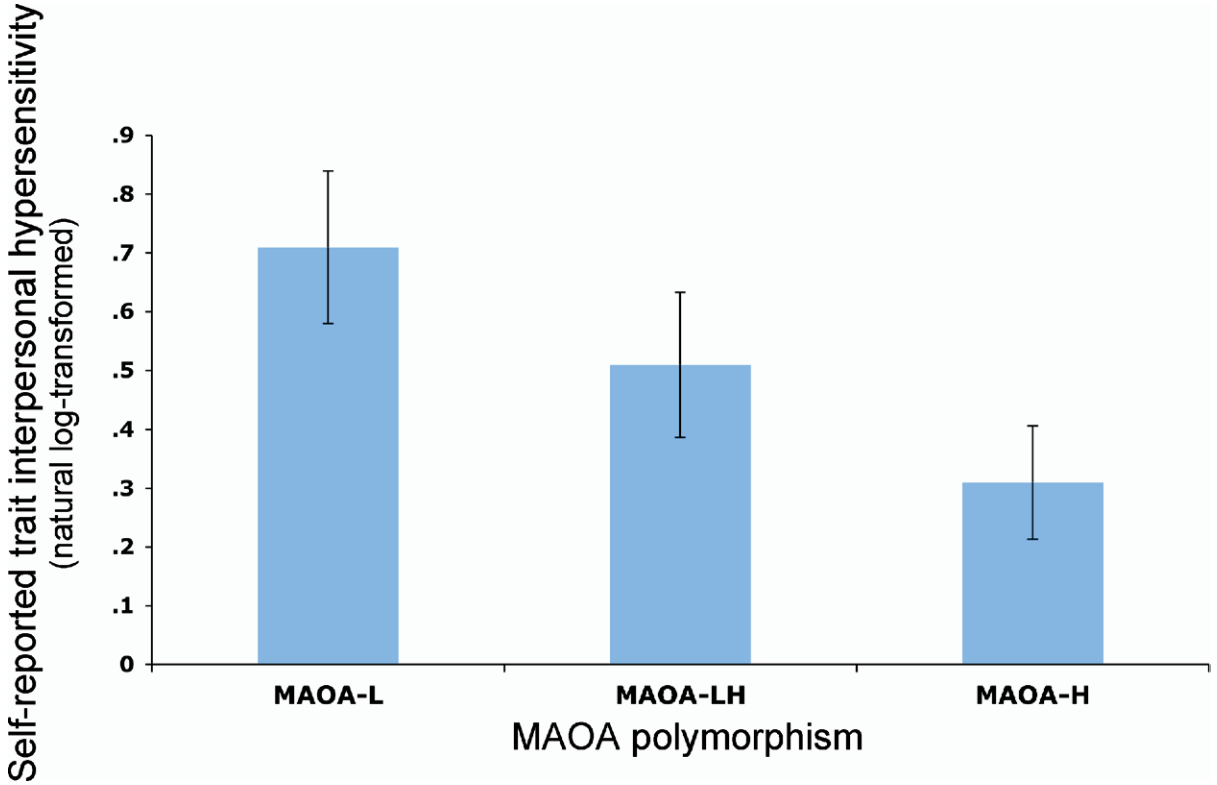

Figure 2. Bar graph showing the relationship between the monoamine oxidase-A (MAOA) polymorphism (x-axis) and self-reported trait interpersonal hypersensitivity scores, which have been natural log-transformed (y-axis).

however, there were no significant differences between men and women in dACC activity or in the relationship between the MAOA polymorphism and dACC activity to social exclusion (vs. inclusion). Additional analyses revealed that MAOA-L individuals showed significantly more dACC activity to social exclusion than MAOA-LH individuals [$t(15) = 2.10$, $p = .05$] or MAOA-H individuals [$t(18) = 2.55$, $p < .05$] (Figure 3B).

The next analysis examined whether there was any neural activity during exclusion compared with inclusion that correlated with the MAOA polymorphism in a linear fashion (MAOA-L > MAOA-LH > MAOA-H or MAOA-H > MAOA-LH > MAOA-L). This analysis is predicated on previous research showing that female heterozygotes (MAOA-LH) show patterns of neural activity intermediate between MAOA-L and MAOA-H male hemizygotes and that female homozygotes show patterns of neural activity comparable to male hemizygotes (Meyer-Lindenberg *et al.* 2006). To perform this analysis, individual differences in the MAOA allelic combinations (MAOA-L = 0, MAOA-LH = 1, MAOA-H = 2) were regressed into whole-brain analyses ($p < .005$, 20-voxels).

Results indicated that the MAOA polymorphism correlated with dACC activity [MNI coordinates: 8,30,36; $t = 3.89$; $r(29) = -.60$, $p < .001$] such that MAOA-L individuals showed greater dACC activity during social exclusion versus inclusion than MAOA-LH or MAOA-H individuals [MAOA-L vs. MAOA-LH: $t(19) = 2.72$, $p < .05$; MAOA-L vs. MAOA-H: $t(18) = 3.57$, $p < .005$] (Figure 4A and B; Table 2A). Moreover, this dACC activation overlapped substantially with the region of the dACC from the previous analysis (6,36,32) that correlated with self-reported social distress and varied as a function of MAOA-uVNTR. Both of these dACC activations were also significantly positively correlated with trait interpersonal hypersensitivity (Table 1). There were no regions that correlated positively with the MAOA polymorphism (MAOA-H > MAOA-LH > MAOA-L).

To examine whether activity in this region of the dACC (8,30,36) varied as a function of gender or as a function of a gender × MAOA interaction, data was extracted from this region and a two-way ANOVA was conducted (with standard statistical software), with MAOA and gender as the independent variables and dACC activity (8,30,36) as the dependent variable. Analyses revealed a main effect of MAOA [$F(2,28) = 10.27$, $p < .005$], consistent with results reported in the preceding text; a marginal main effect of gender [$F(1,28) = 3.38$, $p = .08$], such that women showed marginally more dACC activity than men; and no gender ×

Table 1. Correlations Between the MAOA Polymorphism (MAOA-L = 0, MAOA-LH = 1, MAOA-H = 2), dACC Activity, and Self-Report Measures

	MAOA Polymorphism	dACC (6,36,32)	dACC (8,30,36)	Interpersonal Hypersensitivity
dACC (6,36,32)	−.47[a]			
dACC (8,30,36)	−.60[b]	.75[b]		
Interpersonal Hypersensitivity	−.40[c]	.45[c]	.46[c]	
Aggression	−.49[a]	.48[a]	.34[d]	.53[b]

MAOA, monoamine oxidase-A; MAOA-L, low expression allele; MAOA-H, high expression allele; MAOA-LH, consisting of females with one copy of MAOA-L and one copy of MAOA-H; dACC, dorsal anterior cingulate cortex.
[a] $p < .01$.
[b] $p < .005$.
[c] $p < .05$.
[d] $p < .08$.

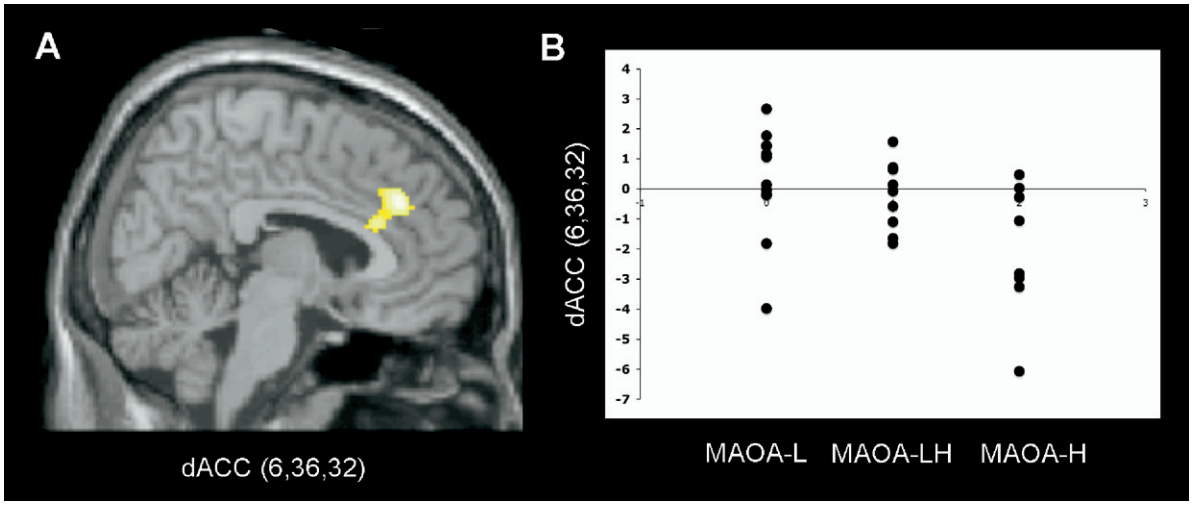

Figure 3. Dorsal anterior cingulate cortex (dACC) activity (6,36,32) that varies as a function of the monoamine oxidase-A (MAOA) polymorphism. **(A)** Activity in the dACC, during social exclusion versus inclusion, that correlates with social distress (maximum activation at 6,36,32) and shows greater activity for low expression allele (MAOA-L) individuals, compared with the high expression allele (MAOA-H) individuals or MAOA-LH individuals, consisting of women with one copy of MAOA-L and one copy of MAOA-H. **(B)** Scatterplot showing the relationship between the MAOA polymorphism and dACC (6,36,32) responses to social exclusion versus inclusion.

MAOA interaction [$F(1,28) = .58$, ns], such that there were no significant differences between men and women in the relationship between the MAOA polymorphism and dACC activity to social exclusion versus inclusion.

In the final analysis, a one-way ANOVA was conducted in SPM'99 to examine which neural regions (during exclusion vs. inclusion) showed differential activity for MAOA-L compared with MAOA-H individuals. When examining which regions were more active for MAOA-L than MAOA-H individuals ($p < .005$, 20-voxels), results showed significant differences in neural activity in the same region of the dACC that was found previously (8,30,36) (Figures 4A and 4B), providing additional confirmatory evidence that MAOA-L individuals showed greater activity in this region in response to rejection than MAOA-H individuals (Table 2B). There were no regions that were significantly more active for MAOA-H than MAOA-L individuals.

Mediation Analyses

To examine whether dACC activity mediated the MAOA–aggression relationship, standard mediation analyses were performed (MacKinnon *et al.* 2002). The MAOA polymorphism (coded as MAOA-L = 0, MAOA-LH = 1, MAOA-H = 2) correlated significantly with self-reported trait aggression [$r(30) = -.49$, $p < .01$] and with both dACC activations [8,30,36: $r(29) = -.60$, $p < .005$; 6,36,32: $r(29) = -.49$, $p < .05$]. Trait aggression correlated significantly with activity in one of the dACC activations [6,36,32: $r(29) = .48$, $p < .01$] and marginally with activity in the other [8,30,36: $r(29) = .34$, $p = .08$]. On the basis of these relationships, we examined whether dACC activity (6,36,32) mediated the relationship between MAOA and trait aggression. Results demonstrated that dACC activity was a significant mediator of the MAOA–aggression relationship, such that the relationship between MAOA-L and aggression was due partly to greater

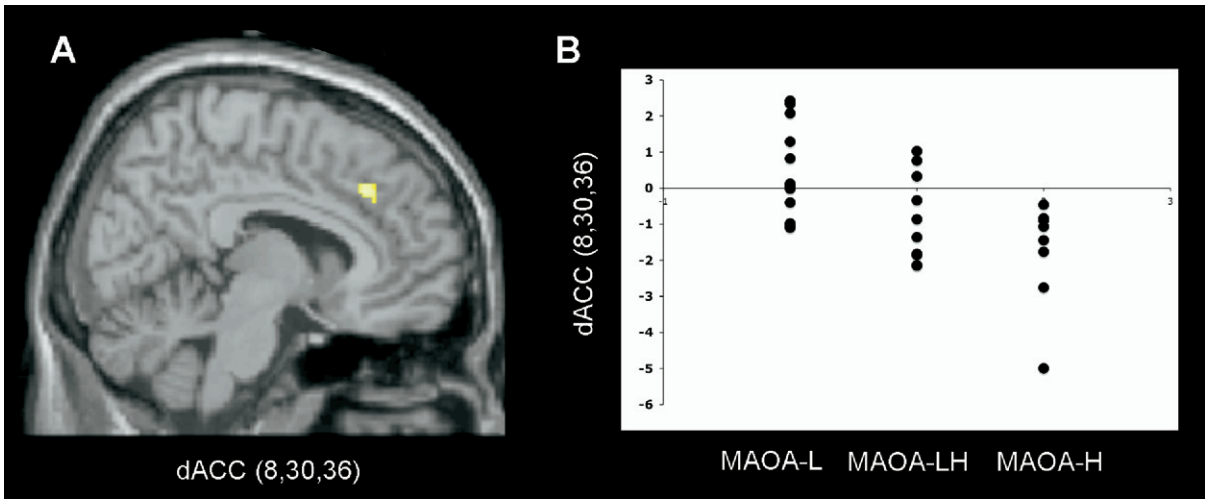

Figure 4. Dorsal anterior cingulate cortex (dACC) activity (8,30,36) that varies as a function of the MAOA polymorphism. **(A)** Activity in the dACC, during social exclusion versus inclusion, that correlates with individual differences in the MAOA polymorphism (maximum activation at 8,30,36) and shows greater activity for MAOA-L, compared with MAOA-H or MAOA-LH, individuals. **(B)** Scatterplot showing the relationship between the MAOA polymorphism and dACC (8,30,36) responses to social exclusion versus inclusion. Abbreviations as in Figure 3.

Table 2. Neural Activations During Social Exclusion Versus Inclusion that: (A) Correlated with Individual Differences in MAOA Allelic Combinations (negative correlations indicate that MAOA-L individuals demonstrated increased neural activity in the listed regions) and (B) Showed Significantly More Activity for MAOA-L than MAOA-H Individuals

(A) Neural Activity that Correlated with the MAOA Polymorphism

Region	Brodmann's Area	MNI Coordinate			k (voxels)	Correlation (*r*)
dACC	32	8	30	36	31	−.60
Posterior Corpus Callosum		6	−40	12	139	−.57
Thalamus		4	−24	12	46	−.55
Cerebellum		−40	−50	−40	69	−.67
		8	−52	−38	22	−.58
		30	−74	−24	38	−.57

(B) Neural Activity that Was Significantly Greater for MAOA-L than MAOA-H Individuals

Region	Brodmann's Area	MNI Coordinate			k (voxels)	T-value
dACC	32	8	30	36	29	3.75
Superior Frontal Gyrus	8	−40	22	52	20	3.89
Posterior Corpus Callosum		2	−42	12	123	3.59
Thalamus		4	−24	12	36	3.26
Cerebellum		−40	−50	−40	66	4.59
		10	−50	−36	29	3.67
		30	−72	−24	34	3.52

All coordinates are in Montreal Neurological Institute (MNI)-coordinate space. Significance was determined with $p < .005$ and a 20-voxel extent threshold. Other abbreviations as in Table 1.

dACC reactivity to social rejection ($Z_\alpha Z_\beta = 4.74$, $p < .05$) (MacKinnon *et al.* 2002). Likewise, trait interpersonal hypersensitivity mediated the relationship between MAOA and trait aggression ($Z_\alpha Z_\beta = 5.71$, $p < .05$) (MacKinnon *et al.* 2002), again suggesting that the relationship between MAOA and aggression is due to interpersonal hypersensitivity (e.g., feeling self-conscious, inferior, disliked by others) rather than interpersonal hyposensitivity.

Discussion

Previous studies have demonstrated a relationship between the MAOA-uVNTR and aggressive behavior, but the underlying neural and psychological mechanisms explaining this relationship are unknown. The goal of the present study was to examine whether MAOA-related aggression was associated with blunted socioemotional sensitivity (leading to aggressive acts due to a lack of social concern) or with heightened socioemotional sensitivity (leading to defensively aggressive behavior). To examine these possibilities, we first investigated the relationship between the MAOA polymorphism and self-reported trait aggression; we then examined whether MAOA-related aggression was associated with blunted or heightened self-reported trait interpersonal hypersensitivity as well as blunted or heightened neural responses to social exclusion.

Results indicated that MAOA-L individuals, both men and women, showed significantly greater levels of trait aggression than MAOA-H individuals, consistent with the notion that the MAOA gene might be an important predictor of risk for aggression. Additionally, MAOA-L, compared with MAOA-H, individuals showed significantly greater levels of trait interpersonal hypersensitivity and significantly greater dACC activity (associated with rejection-related distress) in response to a social exclusion task, consistent with a social hypersensitivity account of MAOA-related aggression. Finally, mediation analyses revealed that both dACC activity and trait interpersonal hypersensitivity mediated the relationship between MAOA and trait aggression, suggesting that the relationship between MAOA and aggression might be due, in part, to a heightened sensitivity to negative socioemotional experience.

The fact that MAOA-L individuals reported higher levels of trait aggression than MAOA-H individuals is consistent with previous findings showing that MAOA-deficient humans and animals are more likely to show aggressive behavior (Brunner *et al.* 1993; Cases *et al.* 1995). However, previous work has typically not shown a main effect of the MAOA polymorphism on aggression but rather a gene × environment interaction, such that MAOA-L men exposed to early maltreatment were more likely to have committed violent crimes than MAOA-H men or MAOA-L men not exposed to early maltreatment (Caspi *et al.* 2002; Manuck *et al.* 2000). In contrast, the present study indicated a main effect of MAOA on aggression. These different findings could be due to several methodological differences between the two studies, including the fact that the present study excluded subjects who were psychologically unhealthy, whereas this previous study did not. Additionally, the present study used continuous self-report measures that can detect levels of aggression present in normal samples, whereas the previous study used a more restrictive measure of aggression, such as the diagnosis of conduct disorder or the number of previous convictions. Differences in the restrictiveness of these aggression assessments (self-reported aggressive feelings vs. number of convictions for violent crimes) as well as the format of these assessments (continuous self-report measures vs. the dichotomous assessment of the presence or absence of a diagnosis of conduct disorder) might have also contributed to the different pattern of results reported here.

The present study advances our understanding of the genetic risk for aggression in several ways. First, this study is one of the first to examine the possible psychological and neurocognitive mediators of MAOA-related aggression. Rather than showing that MAOA-L individuals were insensitive to or unaffected by social situations, the present study demon-

strated that MAOA-L individuals (compared with MAOA-H individuals) were, in fact, more affected by negative social situations, showing higher levels of trait interpersonal hypersensitivity and greater dACC activity to social rejection. This is consistent with previous work showing amygdala hyperresponsivity to negative images among MAOA-L individuals (Meyer-Lindenberg *et al.* 2006). Clarifying the underlying mechanisms that link MAOA to aggression is critical for both understanding the experience of these individuals and for identifying appropriate interventions for treating these aggressive behaviors. Knowing that MAOA-L individuals are more likely to show evidence of reactive rather than instrumental aggression and more likely to show interpersonal hyperrather than hypo-sensitivity can help clinicians devise appropriate treatment alternatives.

Second, the present study focused specifically on affective processes. Despite the important role that affective processes play in aggression, few studies have examined how MAOA-related aggression corresponds with emotional processes. This study is one of the first to investigate how the MAOA polymorphism relates to neural responses to affective stimuli (Meyer-Lindenberg *et al.* 2006) and the only study to investigate how the MAOA polymorphism relates to affective stimuli that have been shown to induce full-blown emotional experiences ("Cyberball task"). Thus, the findings reported here might give a better sense of how the MAOA polymorphism relates to real-world socioemotional sensitivity. Additionally, the present study contributes to our understanding of these processes by examining MAOA-related processes in a psychologically healthy group of young men and women. Thus, these data reveal patterns of behavior that are present in non-disordered populations but that might predict the likelihood of aggression-related clinical disorders as well.

Last, the overlapping relationships between dACC activity, interpersonal hypersensitivity, and aggression are consistent with prior work and suggest a specific role for the dACC in MAOA-related aggression. For example, cingulotomy (a surgery in which part of the cingulate cortex is removed, often the dACC; Richter *et al.* 2004) has been shown to diminish interpersonal shyness, hostility, and anger and has been used in some cases to treat disorders of aggression (Cohen *et al.* 2001; Meyer *et al.* 1973; Ward 1948), suggesting that heightened activity within this region is related to greater socioemotional sensitivity and aggression. Similarly, neuroimaging studies of healthy individuals have shown that both feelings of anger (Dougherty *et al.* 1999) and feelings of social distress (Eisenberger *et al.* 2003) lead to increased dACC activity (for a more complete review of the extended circuitry of the ACC, see Paus 2001). Finally, with regard to a specific relationship between MAOA and dACC activity, it has been shown that the most robust MAOA-related differences in gray matter volume were observed within the anterior cingulate (MAOA-L individuals showed smaller ACC volumes; Meyer-Lindenberg *et al.* 2006) and that this region also possesses a high concentration of the MAOA enzyme (Ginovart *et al.* 2006; for a more complete review of the functional effects of monoamines, such as serotonin, on corticolimbic function, see Hensler 2006).

Study Limitations

This study has several limitations, the first of which is the small sample size. Although previous neuroimaging studies, relating genetic polymorphisms to neural activity, have used comparable sample sizes (Bookheimer *et al.* 2000; Hariri and Weinberger 2003; Hariri *et al.* 2002; Mattay *et al.* 2003), studies relating genetic polymorphisms to behavioral or self-report assessments typically use much larger samples. Thus, the present results should be interpreted with caution until these findings have been replicated in larger samples. One consequence of the small sample size is the limited ability to carefully investigate gender differences. Although the present study revealed no MAOA-uVNTR × gender interactions, it is possible that the relationships between MAOA-uVNTR and the variables reported here vary as a function of gender and that we did not have the power to detect such differences in the current study.

Another limitation is that the present study did not measure aggressive behaviors, thoughts, or feelings after the social exclusion task, and thus it is not possible to determine whether MAOA-related interpersonal hypersensitivity predicts aggression in a causal manner. Future studies would add to our knowledge of MAOA-related aggression by examining aggressive responses to negative social experiences to see whether greater sensitivity to these social experiences (as a function of MAOA) predicts more aggressive responses. Nonetheless, this study is the first to include both an assessment of aggression as well as a measure of neural activity to emotion-inducing stimuli and thus adds to our understanding of the relationships between these measures.

A final limitation of this study concerns the use of genetic association methodology. A criticism of this methodological approach is that it is vulnerable to population stratification bias, wherein variation in allele frequency across certain ethnic subgroups covaries with the dependent variable (Cardon and Palmer 2003). Because the potential for such bias decreases with increasing numbers of ethnic strata (Wacholder *et al.* 2000), the many different ethnic subgroups represented in the present study minimizes this concern. Furthermore, there were no differences between the two largest ethnic sub-samples, Asians ($n = 13$) and Whites ($n = 9$), in terms of MAOA genotype, self-reported aggression or interpersonal hypersensitivity, or neural responses to social exclusion (p values $> .25$). Future work will be needed to determine whether ethnicity and corresponding cultural differences contribute to MAOA-related aggression.

Conclusions

In sum, the present study helps to clarify some of the psychological, affective, and neurocognitive correlates of the MAOA–aggression link in men and women. Showing that the MAOA–aggression relationship is due to a heightened rather than a reduced sensitivity to negative social experience provides a more complete understanding of MAOA-related aggression and suggests that this type of aggression is not due to a lack of social concern but to exaggerated social concern instead. Identifying the mechanisms that underlie gene–behavior relationships provides a clearer picture of the experiences and sensitivities that mediate gene–behavior relationships and might ultimately lead to better and more targeted treatment alternatives.

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