Cerebral Cortex, March 2016;26: 904–914

doi: 10.1093/cercor/bhu249
Advance Access Publication Date: 19 October 2014
Original Article

ORIGINAL ARTICLE

Evidence for a Sex-Dependent *MAOA* × Childhood Stress Interaction in the Neural Circuitry of Aggression

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Abstract

Converging evidence emphasizes the role of an interaction between monoamine oxidase A (*MAOA*) genotype, environmental adversity, and sex in the pathophysiology of aggression. The present study aimed to clarify the impact of this interaction on neural activity in aggression-related brain systems. Functional magnetic resonance imaging was performed in 125 healthy adults from a high-risk community sample followed since birth. DNA was genotyped for the *MAOA-VNTR* (variable number of tandem repeats). Exposure to childhood life stress (CLS) between the ages of 4 and 11 years was assessed using a standardized parent interview, aggression by the Youth/Young Adult Self-Report between the ages of 15 and 25 years, and the VIRA-R (Vragenlijst Instrumentele En Reactieve Agressie) at the age of 15 years. Significant interactions were obtained between *MAOA* genotype, CLS, and sex relating to amygdala, hippocampus, and anterior cingulate cortex (ACC) response, respectively. Activity in the amygdala and hippocampus during emotional face-matching increased with the level of CLS in male *MAOA-L*, while decreasing in male *MAOA-H*, with the reverse pattern present in females. Findings in the opposite direction in the ACC during a flanker NoGo task suggested that increased emotional activity coincided with decreased inhibitory control. Moreover, increasing amygdala activity was associated with higher Y(A)SR aggression in male *MAOA-L* and female *MAOA-H* carriers. Likewise, a significant association between amygdala activity and reactive aggression was detected in female *MAOA-H* carriers. The results point to a moderating role of sex in the *MAOA* × CLS interaction for intermediate phenotypes of emotional and inhibitory processing, suggesting a possible mechanism in conferring susceptibility to violence-related disorders.

Key words: aggression, amygdala, fMRI, life stress, *MAOA*

Introduction

Aggression is a key feature of various mental disorders such as conduct disorder or antisocial personality disorder. Usually, it is classified into 2 subtypes, with a differentiation being drawn between an impulsive-reactive–hostile-affective form and a controlled-proactive–instrumental-predatory form, both of which show distinct neurobiological features (Dodge 1991; Barratt and Felthous 2003; Meloy 2006; Siever 2008; Blair 2010, 2013; Buitelaar et al. 2013). Heritability estimates of 44–72% (Siever 2008) clearly accentuate the role of genetic factors. Likewise, research emphasizes the importance of sex differences in aggression (e.g., Stephenson et al. 2013). Moreover, like in most complex phenotypes, there is strong evidence that genetic risk is conditional on environmental influences (Frazzetto et al. 2007; Simons et al. 2011; Gallardo-Pujol et al. 2013).

Pharmacological studies have provided ample evidence of low tonic serotonergic activity as being linked to aggression (Brown et al. 1982; Coccaro 1989; Coccaro and Astill 1990; Linnoila and Virkkunen 1992; Virkkunen et al. 1994; Audero et al. 2013). However, this association has been challenged by the finding that 5-HT_{1A} receptor agonist administration, inducing negative feedback on 5-HT release, reduced aggressive behavior (Mos et al. 1993; Olivier et al. 1995; de Boer et al. 1999; Fish et al. 1999; van der Vegt et al. 2003). Monoamine oxidase A (MAOA) is a key enzyme metabolizing serotonin. A common functional variable number of tandem repeats (VNTR) polymorphism has been identified in the promoter region of the *MAOA* gene (chromosome Xp11.23), leading to a lower expression of MAOA in carriers of 3 and 5 repeats (*MAOA-L*) when compared with carriers of 3.5 or 4 repeats (*MAOA-H*; Sabol et al. 1998). Following the seminal work of Caspi et al. (2002) providing the first indication of a gene–environment interaction with regard to antisocial and aggressive behavior in *MAOA-L* males exposed to maltreatment, recent evidence has accumulated, suggesting that this G × E may be extended to females with the high activity allele (*MAOA-H*) who experienced childhood adversity (Wakschlag et al. 2010; Aslund et al. 2011; Verhoeven et al. 2012; Byrd and Manuck 2014).

In recent years, several neuroimaging studies have provided support for an impact of *MAOA-VNTR* on brain function modulating the neural circuits underlying impulsive and aggressive behavior, presumably related to altered inhibition and emotion processing. In the first of such studies, Fan et al. (2003) showed that *MAOA-L* carriers displayed a blunted response of the anterior cingulate cortex (ACC) during the execution of a flanker task involving conflict resolution when compared with *MAOA-H* carriers. In the same vein, the response of the ventromedial prefrontal cortex and the ACC elicited by a Go/NoGo paradigm was found to be decreased in male *MAOA-L* carriers (Passamonti et al. 2006, 2008). Recently, Clemens et al. (2015) reported evidence of the resting-state network of executive control and salience, including the ACC, to be compromised in the *MAOA-L* group, indicative of less action and conflict monitoring. Extending these findings to the emotion circuit, individuals with the *MAOA-L* genotype were found to exhibit increased activity in the amygdala (Meyer-Lindenberg et al. 2006). Sex-specific effects with respect to the hippocampus and the anterior cingulate revealed increased hippocampal activity and decreased ACC response in male *MAOA-L* carriers, while no difference emerged in females (Meyer-Lindenberg et al. 2006). Subsequent studies confirmed the presence of genotype-dependent activity changes in limbic and connected regions in a visual linguistic anger task in males (Alia-Klein et al. 2009) and also extended them to women during passive viewing of negative faces (Lee and Ham 2008). However, so far no study has elucidated the effect of a (sex-dependent) gene–environment interaction on brain endophenotypes.

Evidence from animal and human studies, along with a growing amount of imaging work, has highlighted the profound and long-term impact of environmental adversity on different regions of the brain (Teicher et al. 2003; Fumagalli et al. 2007). Notably, the timing of exposure has been suggested to be particularly crucial for the effects on brain systems, positing that environmental adversity has the highest impact on those brain structures that are developing at the time of exposure (sensitive periods; Andersen et al. 2008; Lupien et al. 2009; Fox et al. 2010; Tottenham and Sheridan 2010; Lenroot and Giedd 2011). As an example, the development of the amygdala already begins early in life and continues until late childhood (Tottenham and Sheridan 2010). Likewise, changes in hippocampal growth rather occur during childhood than in early infancy (Tottenham and Sheridan 2010). Similarly, the prefrontal cortex undergoes its major development during childhood (Giedd 2004) and has been shown to be susceptible to later childhood stress (Baker et al. 2013). Thus, the critical periods of these regions all overlap in middle childhood.

Given the wealth of evidence suggesting a sex-specific gene–environment interaction related to aggressive behavior and the current lack of imaging research on this topic, the present study aimed to clarify a moderating role of sex in the interaction between *MAOA* genotype and life stress during middle childhood (age 4–11 years), which is presumed to be a sensitive period of our regions of interest (ROIs). Therefore, we administered an emotive (face-matching) task and a cognitive (flanker NoGo) task such as previously used by Meyer-Lindenberg et al. (2006), which robustly elicited amygdala as well as hippocampus and ACC activity (Baumeister et al. 2014; Holz, Boecker, et al. 2014; Holz, Buchmann, et al. 2014). These regions have previously been shown to be compromised in antisocial individuals (Yang and Raine 2009) and *MAOA-L* carriers (Meyer-Lindenberg et al. 2006). In detail, we hypothesized that, in *MAOA-L* males and *MAOA-H* females, (1) activity in key regions of affective processing such as the amygdala and the hippocampus increased with the level of exposure to adversity, whereas (2) activity in the ACC, indicative of less inhibitory control, decreased with the level of adversity. Moreover, given the link of *MAOA* (Manuck et al. 2000) and amygdala response (Siever 2008) with aggression as well as the described increased liability to aggression in male *MAOA-L* and female *MAOA-H* carriers, we exploratively investigated the association between amygdala activity and aggressive behavior in these groups using data from a prospective study over 25 years.

Materials and Methods

Sample

The initial sample of the Mannheim Study of Children at Risk consisted of 384 children of predominantly (>99.0%) European descent, born between 1986 and 1988. Infants were recruited from 2 obstetric and 6 children's hospitals in the Rhine-Neckar Region of Germany and were included consecutively into the sample according to a two-factorial design intended to enrich and to control the risk status of the sample [factor 1 varying the degree of obstetric complications, and factor 2, the degree of psychosocial adversity (Laucht et al. 1997; for full details c.f. Laucht et al. 2000)]. To control for confounding effects of family environment and infant medical status, only firstborn children with singleton births and German-speaking parents were

enrolled. Assessments were conducted at the age of 3 months and at regular intervals throughout development, most recently in young adulthood. The present investigation comprised 125 right-handed young adults (72 males) who agreed to participate in the 25-year assessment and who were genotyped for *MAOA*. Owing to possible escape of X-inactivation of this locus (Carrel and Willard 2005), males and homozygous females were included similarly to previous studies (Widom and Brzustowicz 2006; Cicchetti et al. 2007; Derringer et al. 2010; Verhoeven et al. 2012; Hill et al. 2013; Clemens et al. 2015), allowing optimal identification of *MAOA* functionality on brain response. Results changed only marginally when including heterozygous females as an intermediate group (data not shown). Exclusion criteria were usual contraindications for magnetic resonance imaging (MRI), current psychiatric disorder, or psychotropic medication. For the flanker task, 3 subjects had to be excluded due to movement artifacts (>2 mm). The study was approved by the ethics committee of the University of Heidelberg and written informed consent was obtained from all participants.

Psychological Assessments

To assess childhood life stress (CLS), a semistructured parent interview was conducted at the children's age of 4, 8, and 11 years. The interview, a modified and shortened version of the Munich Events List (Maier-Diewald et al. 1983), evaluated the occurrence of adverse life events during a period of 1 year prior to the assessment. A reliability study by Wittchen et al. (1989) provided evidence for a test–retest reliability (during a 6-week interval) of 95.5% ($\kappa = 0.85$) with regard to the life events in the past 8 years. There was a tendency toward a higher indication of the number of life events when the participants were younger. The 26 items covered all relevant areas of children's life stress including family, school, parents, health, legal troubles, and living conditions, such as birth of a sibling, death of a close relative, or parents' separation. A composite score was computed by summing up the *z*-standardized scores of the 4- to 11-year assessments (CLS, range = −3.40–6.21). Unstandardized values for the different assessments are listed in Supplementary Table 1.

At the age of 25 years, the Structured Clinical Interview for DSM-IV [SCID-I German version (Wittchen et al. 1997)] was administered by trained psychologists to assess young adults' psychiatric disorders. To evaluate behavior problems in adolescence and adulthood, the Youth Self-Report (YSR, Achenbach 1991a) and the Young Adult Self-Report (YASR, Achenbach 1991b), respectively, were administered to the participants. Owing to the established association between MAOA and aggression (Manuck et al. 2000), we focused on the subscale "aggressive behavior". Scores (available for $N = 123$) acquired at the ages of 15, 19, 22, 23, and 25 years were z-standardized to form a composite sum score, which is hereafter referred to as aggression during later life (raw and *t*-values for the different assessments are depicted in Supplementary Table 2). To better differentiate between proactive and reactive aggression, we additionally evaluated the triple interaction between *MAOA*, aggression, and sex on amygdala activity using the Vragenlijst Instrumentele En Reactieve Agressie (VIRA-R, Kempes et al. 2006), which was acquired at the age of 15 years (available for $N = 122$). This 22-item questionnaire asks significant others to rate a child on a scale ranging from 1 ("never true") to 3 ("almost always true"). Items load on either a proactive aggression scale, e.g., "uses force to dominate peers, threatens others in order get to his/her own way", or a reactive aggression scale with items like "strikes back when teased, overreacts to accidents". Scales were created by summing the respective item scores. Both the proactive aggression and reactive aggression scales were the sum of 11 items (range of 11–33). Internal consistency was reported to be excellent for both subscales (Cronbach's alpha = 0.89 for reactive aggression and 0.77 for proactive aggression, respectively). In the present study, parent ratings were obtained for a German version of the VIRA-R.

Genotyping

Genomic DNA was extracted from ethylenediaminetetraacetic acid (EDTA) anticoagulated venous blood according to standard procedures. The VNTR polymorphism located approximately 1–1.2 kb upstream of the transcription initiation site of the *MAOA* gene was analyzed using polymerase chain reaction (PCR). In a total volume of 20 μL, 30 ng genomic DNA was amplified with oligonucleotide primers MAOaPT1 5′-ACAGCCT GACCGTGGAGAAG-3′ and MAOaPB1 5′-GAACGGACGCTCCATT CGGA-3′ (Sabol et al. 1998). The 4 alleles, consisting of 3, 3.5, or 4 copies of a 30-bp repeated sequence, were scored according to Sabol et al. (1998), using agarose gel electrophoresis. Individuals with 3 copies were considered *MAOA-L*, while those with 3.5. or 4 copies were considered *MAOA-H* (exact genotype frequencies for males were: 3r: 23, 3.5r: 1, and 4r: 48; for females: 3r/3r: 15; 3r/4r: 53; 3.5r/4r: 1; and 4r/4r: 37). There were no individuals with 5 copies. Genotyping accuracy was assessed by running 15% of the sample in duplicates. Reproducibility was 100%.

fMRI Face-Matching Task

A face-matching task presented in a block design was administered. This task robustly activates the amygdala (Hariri et al. 2002) and has been used extensively in the study of genetic variants linked to the risk of psychiatric disorders (Pezawas et al. 2005; Esslinger et al. 2009). For 12 blocks, sequences of 12 fearful/angry faces were alternated with sequences of 12 shapes. At the beginning of each block, brief instructions ("comparison faces" and "comparison shapes") were shown on the screen for 2 s. In the face blocks, trios of faces derived from the Ekman and Friesen (1979) stimulus set, balanced for sex and emotional expression, were presented. Participants were instructed to indicate which of the 2 faces at the bottom was identical to the target face (at the top) and to press the button on the respective side. According to the same criterion, in the sensorimotor control task, participants had to compare circles and ellipses. Both stimulus sets consisted of 6 different trios of faces or shapes and were presented on average every 2.5 s (slightly jittered in 12 different steps to vary by 0–50 ms around the mean). Finally, an end screen was shown for 8 s. The total task time was 6 min 49 s. Reaction time and accuracy were measured.

Flanker NoGo Task

In the flanker NoGo task (Blasi et al. 2006; Meyer-Lindenberg et al. 2006), subjects saw an array of 5 shapes including a central target arrow pointing either left or right, flanked by 2 shapes (arrows, squares, or Xs) on each side. Subjects were instructed to press a button corresponding to the central arrow when flankers were other arrows or boxes (neutral condition), but not when flankers were Xs (NoGo condition). Flanking arrows were pointing either in the same (congruent) or opposite (incongruent) direction as the central arrow, thus enabling conflict processing and interference to be investigated. A total of 145 stimuli (33 NoGo) were randomly presented for 800 ms with an interstimulus interval (ISI), which varied between 2.2 and 8.1 s. During the

ISI, a fixation cross was presented. The total duration of the task was 10 min 19 s.

fMRI Parameters and Data Analysis

Functional MRI was performed using a 3 T scanner (Magnetom TRIO, Siemens, Erlangen, Germany) with a standard 12-channel head coil. The imaging protocol consisted of a localizer scan followed by a blood oxygen level-dependent (BOLD)-sensitive T_2^*-weighted echo-planar imaging sequence and a structural T_1-weighted sequence. For functional imaging, a total of 183 (face-matching task) and 277 volumes (flanker NoGo task) with 36 slices (matrix 64 × 64, resolution 3.43 × 3.43 × 3 mm with 1 mm gap, repetition time = 2210 ms, echo time = 28 ms, flip angle = 90°) covering the whole brain were acquired. The slices were inclined 20° from the anterior/posterior commissure level to minimize dropout artifacts in orbitofrontal and mediotemporal regions. The first images (4 in the face-matching task and 3 in the flanker NoGo task) were discarded to allow longitudinal magnetization to reach equilibrium. The functional images were analyzed using Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.12. (Mathworks, Inc., Natick, MA, USA). Preprocessing included slice time correction of the volumes to the first slice, realignment to correct for movement artifacts, coregistration of functional and anatomical data, spatial normalization to standard MNI (Montreal Neurological Institute) space, and smoothing with a Gaussian kernel of 8 mm full-width at half-maximum. For the face-matching task, onsets and durations of either shapes or faces were convolved with the SPM8 canonical hemodynamic response function in the context of a general linear model in order to model the BOLD time course. For the flanker task, vectors of the NoGo, incongruent, congruent, and neutral trials as well as a vector comprising the errors, modeled separately for the left and right side, were used. Furthermore, 6 movement parameters were included as regressors of no interest.

First-level contrast images revealing activation to fearful/angry faces compared with shapes and NoGo versus neutral trials, respectively, were entered into a second-level group analysis. To account for genotype, environmental and sex-dependent main effects, *MAOA* genotype (1 = H and 2 = L), the continuous CLS measure, and sex were added separately as covariates. The interaction effect was investigated by calculating the interaction term (*MAOA* × CLS × sex) including all possible two-way interactions and main effects into the multiple regression analysis. The covariates were mean-centered. For exploratory whole-brain analyses, an uncorrected threshold of $P < 0.001$ and a criterion of 5 (20 for task effects) adjacent voxels was set. According to previous research (Meyer-Lindenberg et al. 2006) the amygdala, the hippocampus (face-matching task), and the ACC (flanker NoGo task) were defined as ROIs using the anatomical masks implemented in the WFU PickAtlas v2.4 (Maldjian et al. 2003). Separate masks for the left and right amygdala and hippocampus were defined due to lateralized effects of *MAOA* (Meyer-Lindenberg et al. 2006) as well as evidence for a functional distinction between the 2 hemispheres (Frings et al. 2006; Klur et al. 2009; Schneider et al. 2011; Vrticka et al. 2012). To adjust for multiple comparisons, a $P < 0.05$ family-wise error (FWE) correction was applied in the ROIs. For display reasons, the statistical threshold was set to $P = 0.005$ uncorrected in all figures. To visualize the interaction effects and to perform linear regression analyses to establish the relationship between amygdala activity and aggression dependent on *MAOA* and sex, peak contrast values of each participant were extracted from the significant clusters and exported to PASW Statistics (IBM, Armonk, NY, USA).

Results

Sample Characteristics

Genotypes were unrelated to sex and did not differ with regard to age, education, reaction times, CLS, and aggressive behavior (Table 1). However, the *MAOA-H* group was less accurate in the faces condition. A significant interaction effect between *MAOA*, sex, and CLS was obtained on reactive aggression ($\beta = -2.00$, $P = 0.01$), but not on proactive ($P = 0.23$) and Y(A)SR aggression during later life ($P = 0.27$).

fMRI Face-Matching Task

In accordance with previous research, a strong bilateral amygdala activation due to the emotional task was observed (right: $t_{(124)} = 19.80$, $P_{FWE} < 0.001$; left: $t_{(124)} = 17.24$, $P_{FWE} < 0.001$). For results of whole-brain activation, see Supplementary Table 3. Activity in our ROIs did not survive correction for multiple comparisons with respect to main effects and all possible two-way interactions. More information can be derived from the Supplementary Tables 4–9.

A three-way interaction *MAOA* × CLS × sex emerged in the amygdala (left: $t_{(117)} = 2.85$, $P_{FWE} = .04$; $x = -20$, $y = -10$, $z = -12$; right: $t_{(117)} = 3.42$, $P_{FWE} = 0.008$, $x = 28$, $y = -6$, $z = -22$; Fig. 1A) and the hippocampus (left: $t_{(117)} = 3.10$, $P_{FWE} = 0.03$, $x = -32$, $y = -20$, $z = -18$; right: $t_{(117)} = 4.08$, $P_{FWE} = 0.005$, $x = 30$, $y = -10$, $z = -24$; Fig. 1B). Activity in both areas increased with the number of CLS events in male *MAOA-L*, while decreasing in male *MAOA-H*, whereas the opposite was found in the female *MAOA-H* and *MAOA-L* genotype. Whole-brain results are depicted in Supplementary Table 10.

Association with Aggressive Behavior

A significant sex-dependent interaction between *MAOA* and aggression on amygdala response was detected ($\beta = -0.04$, $P = 0.03$). In detail, activity in both male *MAOA-L* ($\beta = 0.02$, $P = 0.03$) and, at a trend level, in female *MAOA-H* ($\beta = 0.01$, $P = 0.07$) carriers increased with the level of aggressive behavior during adolescence and adulthood (Fig. 2A). No significant association emerged in male *MAOA-H* ($\beta = -0.010$, $P = 0.22$) and female *MAOA-L* carriers

Table 1 Sample characteristics

MAOA genotype	MAOA-H	MAOA-L	P-value
N	87	38	
Males, N (%)	49 (56.3)	23 (60.5)	0.55
Age, M (SEM)	24.61 (0.05)	24.61 (0.07)	0.98
Years in school, M (SEM)	11.62 (0.18)	11.89 (0.25)	0.37
Reaction time faces in ms, M (SEM)	879.56 (16.22)	858.90 (23.41)	0.48
Reaction time shapes in ms, M (SEM)	750.13 (12.24)	739.86 (13.82)	0.62
% correct faces, M (SEM)	97.27 (0.35)	98.28 (0.32)	0.04
% correct shapes, M (SEM)	95.67 (0.35)	96.24 (0.47)	0.36
Errors (NoGo), M (SEM)	1.49 (0.21)	1.46 (0.34)	0.94
CLS, M (SEM)	−0.03 (0.22)	0.06 (0.35)	0.83
Y(A)SR aggressive behavior, M (SEM)	−0.29 (0.36)	0.55 (0.72)	0.24
VIRA-R reactive aggression, M (SEM)	14.76 (0.41)	16.03 (0.81)	0.17

Note: X^2 test and t-test were performed where appropriate. For CLS and Y(A)SR aggressive behavior, z-standardized values are indicated.
M, mean; SEM, standard error of the mean.

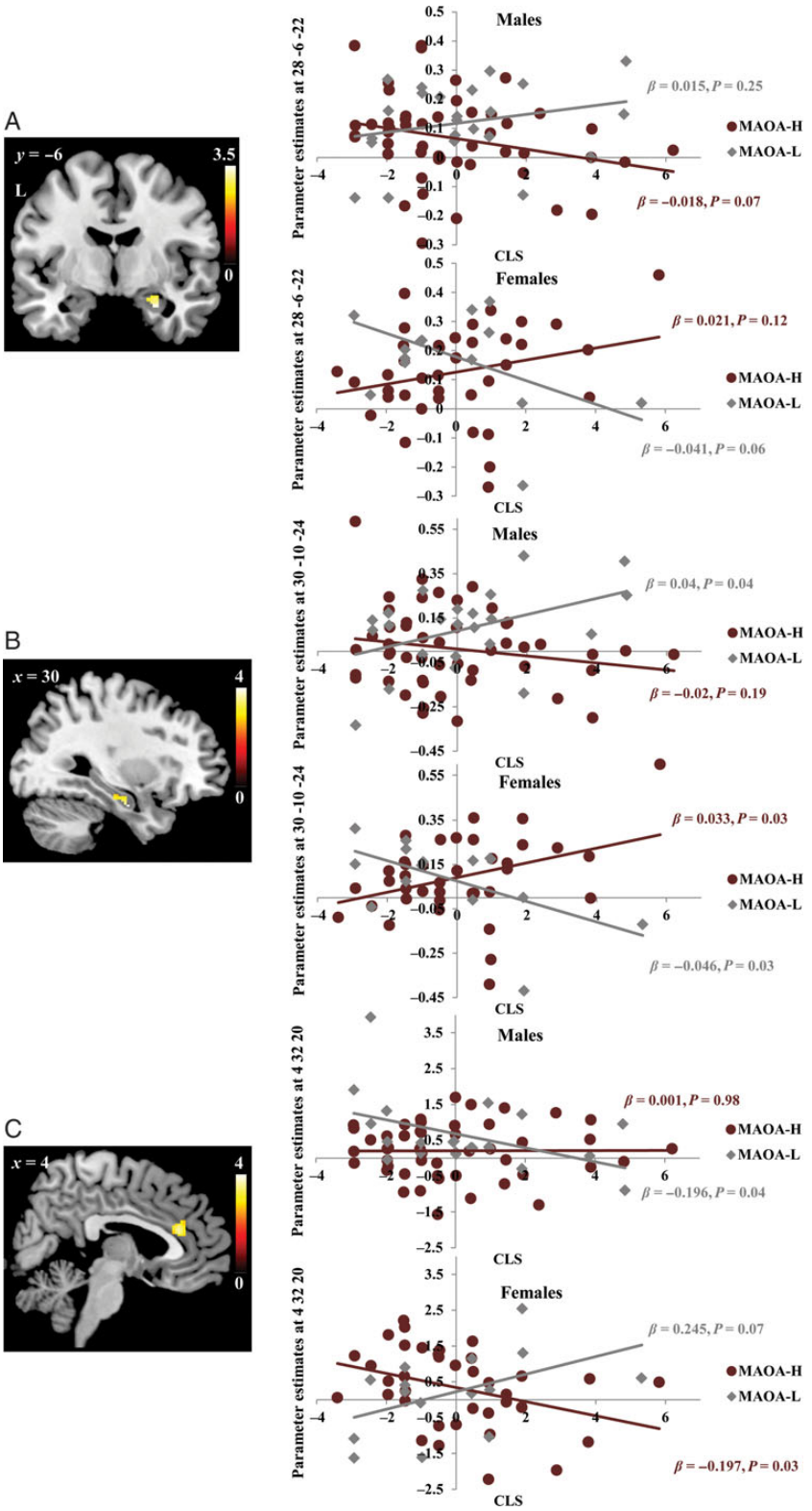

Figure 1. *MAOA* × CLS × sex-dependent amygdala ($P_{FWE} = 0.008$, 25 voxels, *A*) and hippocampus activity ($P_{FWE} = 0.005$, 165 voxels, *B*) during faces versus shapes, and ACC activity ($P_{FWE} = 0.04$, 121 voxels, *C*) during NoGo > neutral with the corresponding parameter estimates at the peak voxel for females and males. Given beta values are for visualization only.

($\beta = 0.006$, $P = 0.47$). Likewise, a significant triple interaction between *MAOA*, sex, and reactive aggression on amygdala activity was obtained ($\beta = -0.34$, $P = 0.02$; Fig. 2*B*), but not with respect to the three-way interaction including proactive aggression ($\beta = -0.004$, $P = 0.93$). Whereas a significant association between reactive aggression and amygdala was found in *MAOA-H* females

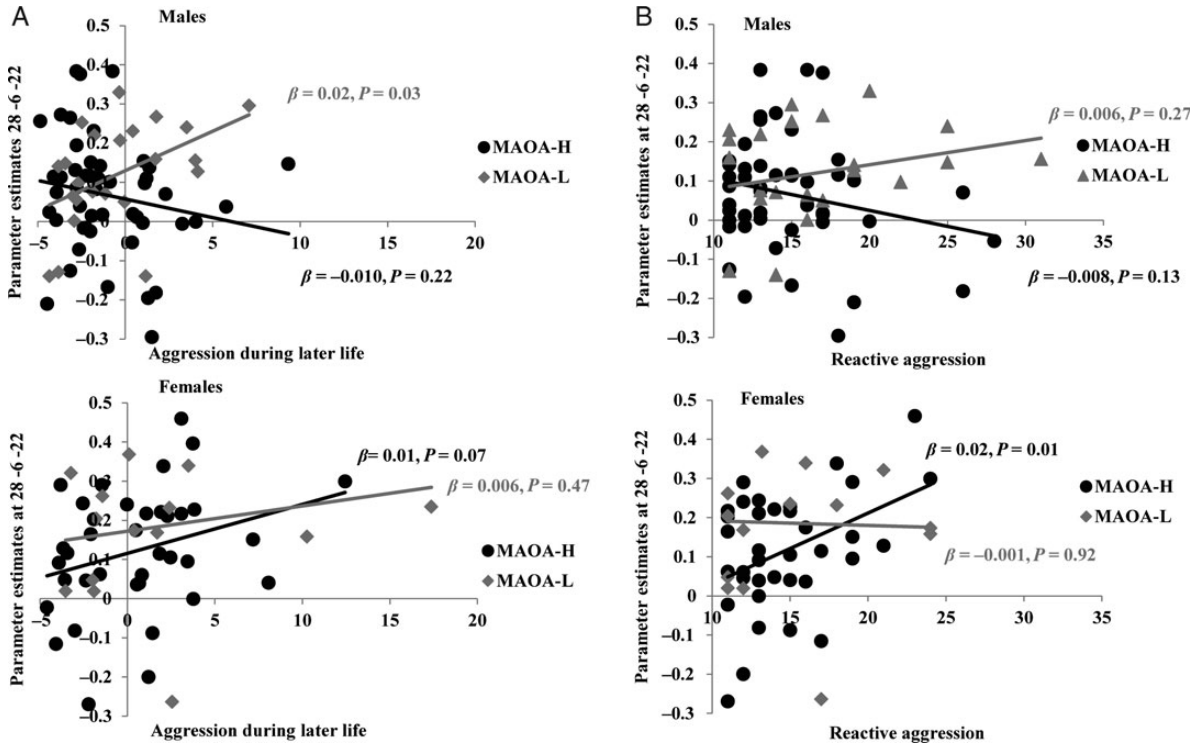

Figure 2. *MAOA* × aggression × sex-dependent amygdala activity for females and males. (*A*) Aggression during later life was assessed by means of the Y(A)SR and (*B*) reactive aggression was assessed by VIRA-R.

($\beta = 0.02$, $P = 0.01$), no significant relationship emerged in the other groups (male *MAOA-L*: $\beta = 0.006$, $P = 0.27$; male *MAOA-H*: $\beta = -0.008$, $P = 0.13$; female *MAOA-L*: $\beta = -0.001$, $P = 0.92$).

fMRI Flanker Task

Robust NoGo versus neutral effects were obtained, with increased activation to NoGo compared with neutral stimuli in an inhibitory network comprising the bilateral insula (right: $t_{(121)} = 14.93$, $P_{FWE} < 0.001$; left: $t_{(121)} = 13.71$, $P_{FWE} < 0.001$) and the ACC (right: $t_{(121)} = 7.99$, $P_{FWE} < 0.001$; left: $t_{(121)} = 6.12$, $P_{FWE} < 0.001$). Whole-brain activation (Supplementary Table 11), main effects of genotype (Supplementary Table 12), CLS (Supplementary Table 13), and sex (Supplementary Table 14) and their two-way interactions (Supplementary Tables 15–17) are listed in Supplementary Tables.

Consistent with the findings reported above, analyses revealed a three-way interaction between *MAOA*, CLS, and sex in the ACC ($t_{(114)} = 3.71$, $P_{FWE} = 0.04$, x = 4, y = 32, z = 20; Fig. 1C). Exclusion of one outlier with a value of >3 standard deviations from mean ACC activity reduced the significance ($t_{(113)} = 3.36$, $P_{FWE} = 0.05$). Specifically, in males with the *MAOA-L* genotype, activity decreased with the level of CLS, while increasing in male *MAOA-H* carriers. In contrast, findings in the opposite direction were observed in females (for whole-brain activation results conditional on the three-way interaction see Supplementary Table 18).

Discussion

The present study provides first evidence of a sex-dependent interaction between *MAOA* genotype and exposure to CLS in terms of predicting functional alterations of neural circuits involved in emotion processing and inhibitory control. In detail, males carrying the *MAOA-L* displayed increasing activity, whereas male *MAOA-H* carriers showed a decreasing response in the amygdala and the hippocampus with the level of stress, with the opposite applying to females. These findings were corroborated by demonstrating (1) a sex- and genotype-dependent association of amygdala activity with (reactive) aggression and (2) a corresponding sex-specific *MAOA* × CLS interaction with regard to ACC activity during response inhibition.

Research on the neural systems underlying emotion has particularly implicated the amygdala in aggression. For example, in animals, stimulation of the amygdala has been demonstrated to elicit aggressive behavior (Adamec 1990; Shaikh et al. 1993). In humans, amygdala responding has been suggested to differ between the 2 subtypes of aggression: whereas callous-unemotional aggression (psychopathy) has been associated with blunted amygdala activity (Kiehl et al. 2001; Birbaumer et al. 2005; Kiehl 2006; Marsh et al. 2008; Jones et al. 2009; Passamonti et al. 2010), impulsive aggression has predominantly been linked to heightened amygdala activity (Meyer-Lindenberg et al. 2006; Coccaro et al. 2007; Siever 2008). Consistent with the notion of *MAOA* as being linked to impulsive violence (Meyer-Lindenberg et al. 2006), a three-way interaction between *MAOA*, sex, and amygdala activity has been observed with regard to reactive, but not proactive aggression. Our finding of a relationship between amygdala activity and aggression during later life and reactive aggression, in particular, male *MAOA-L* and female *MAOA-H* carriers may be interpreted as suggesting that heightened limbic responding following exposure to CLS might represent a possible neurobiological pathway underlying the previously reported increased risk of aggression in these individuals (Kim-Cohen et al. 2006; Verhoeven et al. 2012).

The hippocampus has long since been attributed a crucial role in learning and memory (Squire 1986). Evidence of *MAOA*

involvement in the emotional memory circuit has recently been provided by Meyer-Lindenberg et al. (2006), who demonstrated that male *MAOA-L* carriers exhibited increased hippocampal activity during the retrieval of aversive scenes. Higher hippocampal activation has been related to an enhanced contextualization of fear- and anger-related stimuli, particularly in individuals exposed to environmental adversity (Maheu et al. 2010; Edmiston and Blackford 2013). According to our results, one may speculate that the susceptibility of emotional memory formation to the impact of CLS might differ across sex depending on the *MAOA* genotype, leading to an increased consolidation of emotional material in male *MAOA-L* and female *MAOA-H* carriers. Moreover, higher hippocampal activity has been demonstrated to be related to angry rumination (Denson et al. 2009), thus providing a link to the increased risk of aggression in these subjects. Remarkably, in addition to aggression (Verhoeven et al. 2012), the *MAOA-H* genotype has been associated with anxiety disorders in females (Deckert et al. 1999; Samochowiec et al. 2004; Maron et al. 2005; Reif et al. 2012). Likewise, an emotionally aversive memory has been considered as central in anxiety disorders such as posttraumatic stress disorder (e.g., de Quervain et al. 2012). Notably, aggression and anxiety are likely to share common neural pathways (Neumann et al. 2010).

In line with the enhanced limbic activity in *MAOA-L* males and *MAOA-H* females exposed to high CLS, a decrease in ACC activity during response inhibition emerged. The ACC is one of the major components of executive functions such as attention processes (Allman et al. 2001), response selection (Devinsky et al. 1995), and error monitoring (Bush et al. 2000), but is also critically involved in the mediation of emotional, motivational, and social behavior (Vogt et al. 1992). Evidence suggests that its anatomical maturation develops until early adulthood (Cunningham et al. 2002), with increasing activity from childhood to early adulthood (van Bogaert et al. 1998; Adleman et al. 2002), which is in accordance with the observed impact of childhood stress on ACC in the present study. Here, we extended previous findings by Meyer-Lindenberg et al. (2006) of a synergism between increased emotional liability and decreased cognitive inhibitory control in *MAOA-L* men, by showing that this mechanism may be conditional on CLS and may also apply to *MAOA-H* females. Interestingly, a compromised ACC response and volume has previously been linked to increased aggressive behavior (Birbaumer et al. 2005; Soloff et al. 2008; Yang and Raine 2009; Baird et al. 2010; Ducharme et al. 2011; Pawliczek et al. 2013).

One important finding of the present study concerns the moderating influence of sex on the interaction between *MAOA* genotype and CLS related to neural activity. Consistent with this, previous studies reported a sex-specific effect of *MAOA* on aggression, which is likely due to the X-linked locus of the *MAOA* gene resulting in 2 copies in females and 1 copy in males. Hence, to date, it is unclear whether MAOA expression levels differ as a function of sex, since a possible escape from X-inactivation in females could result in higher MAOA expression. Crucially, moreover, serotonin stimulates cortisol secretion (Deakin et al. 1990; Price et al. 1998), with *MAOA-L* carriers showing increased hypothalamus-pituitary axis reactivity after stress (Jabbi et al. 2007; Bouma et al. 2012). In addition, responses to stressors have been found to differ between males and females, indicating higher cortisol responses after stress in men (Kudielka and Kirschbaum 2005). These findings might explain why *MAOA-L* men exposed to high stress displayed increased limbic activity in response to negative emotional faces. In contrast, *MAOA-H* females have been demonstrated to exhibit higher baseline plasma cortisol (Jabbi et al. 2007), indicative of an increased tonic arousal, suggesting a chronic condition of hypervigilance. Thus, one could speculate that increasing limbic responding with the level of CLS might be a consequence of enhanced phasic activity in *MAOA-L* males, whereas it might be attributed to a higher tonic limbic activity in *MAOA-H* females. Future studies investigating limbic activation at rest should clarify this issue. In this line, it would be interesting to examine whether glucocorticoid levels differ as a function of the interaction between *MAOA*, CLS, and sex. Moreover, sex steroids influence brain development, with receptors being expressed in the amygdala and the ACC (MacLusky et al. 1986) as well as in the hippocampus (MacLusky et al. 1987). Accordingly, emotion-related brain regions show sexual dimorphism regarding their neural development (Suzuki et al. 2005; Tottenham and Sheridan 2010). Importantly, the amygdala, the hippocampus, and the prefrontal cortex are involved in processing psychological stress (Herman et al. 1996; Herman and Cullinan 1997), and additionally, exhibit a high density of glucocorticoid (Teicher et al. 2003) and serotonin receptors (Molodtsova and Il'iuchenok 1990; Varnas et al. 2004; Berumen et al. 2012). This corresponds well with our results, indicating that these areas were neural targets of the interactive effect between *MAOA*, CLS, and sex.

Several limitations of our study have to be considered when evaluating the results. First, the sample size is relatively small for a genetic association study, albeit in accordance with previous estimates of necessary samples for imaging genetic studies of common functional variants (Mier et al. 2010). Second, our sample is enriched with high-risk individuals, reducing the ability to generalize our findings which, therefore, warrant replication. However, probing brain function under conditions of stress inevitably requires a certain level of exposure to adversity. Third, the majority of studies revealing a gene–environment interaction (G × E) related to antisocial disorder pertained to childhood maltreatment. In the current study, we used exposure to adverse life events during childhood as a measure of environmental adversity, which may not be fully comparable with previous research. However, evidence exists that a broader range of adverse environments may moderate the genetic impact on psychopathology (Laucht et al. 2013). Fourth, no significant three-way interaction with regard to Y(A)SR aggression emerged (Table 1). However, endophenotypes are presumed to have a higher penetrance of genetic impact (Meyer-Lindenberg and Weinberger 2006), and associations between aggressive behavior and amygdala activity are present. Fifth, as the CLS measure used in this study assessed stress during a period of 1 year prior to the respective assessment, significant adverse events might have been missed. Sixth, the measurement of epigenetic mechanisms might have been useful in order to explain G × E results by providing a plausible biological underpinning. Likewise, epigenetic data might have contributed to clarifying the sex-specific effects, as the *MAOA* locus has been shown to exhibit sex-dependent methylation patterns (e.g., Philibert et al. 2008; Wong et al. 2010; Domschke et al. 2012). Seventh, in order to test for an interaction with sex, we included females in our study. As Meyer-Lindenberg et al. (2006) previously demonstrated that homozygous females and hemizygous males showed comparable patterns of neural activity and heterozygous females are mosaics due to random inactivation of one X chromosome in the cell (Migeon 2014), we refrained from including the latter group. Given these reasons, problems regarding the pooling of homozygous females and hemizygous males should be minimized in the present study. Finally, we acquired information on aggressive behavior in later life using the Y(A)SR questionnaires, which do not differentiate between impulsive and callous-unemotional aggression. However

we validated our findings using the VIRA-R, which confirmed an association with regard to reactive, but not proactive aggression.

In conclusion, the findings reported here may have important implications for aggression research and prevention. Our results emphasize the importance of childhood as a sensitive period in which accumulating adversity might increase the vulnerability to externalizing psychopathology in *MAOA-L* males and *MAOA-H* females, strengthening the significance of implementing preventive health care programs during childhood in high-risk groups. Our results further highlight the sex-specific nature of this G × E and contribute to a better understanding of sex differences in the pathophysiology of aggression, indicating a possible mechanism as to how susceptibility is increased. Hence, future research on *MAOA* should take into account sex-dependent G × E effects. Moreover, future studies in patient groups are warranted in order to establish the link between different intermediate phenotypes and psychopathology.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Funding

This work was supported by grants from the German Research Foundation (grant number DFG LA 733/1-2) to M.L., D.B., A.M.-L., and T.B. The funding source had no role in study design, in collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Notes

Conflict of Interest: T.B. served in an advisory or consultancy role for Hexal Pharma, Lilly, Medice, Novartis, Otsuka, Oxford outcomes, PCM scientific, Shire, and Viforpharma. He received conference attendance support and conference support or received speaker's fee by Lilly, Medice, Novartis, and Shire. He is/has been involved in clinical trials conducted by Lilly, Shire, and Viforpharma. A.M.-L. receives consultant fees and travel expenses from AstraZeneca, Hoffmann-La Roche, Lundbeck Foundation, speaker's fees from Pfizer Pharma, Lilly Deutschland, Glaxo SmithKline, Janssen Cilag, Bristol-Myers Squibb, Lundbeck, and AstraZeneca. All other authors declare that they have no biomedical financial interest or potential conflicts of interest. The present work is unrelated to the above grants and relationships.

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