npg

A Polymorphism of the *MAOA* Gene is Associated with Emotional Brain Markers and Personality Traits on an Antisocial Index

Leanne M Williams*[1,2], Justine M Gatt[1,2], Stacey A Kuan[1,2], Carol Dobson-Stone[3,4], Donna M Palmer[1,5], Robert H Paul[6], Le Song[7,8], Paul T Costa[9], Peter R Schofield[3,4] and Evian Gordon[1,2,6]

[1]The Brain Dynamics Centre, Westmead Millennium Institute, Westmead Hospital and Western Clinical School, University of Sydney, Westmead, NSW, Australia; [2]Psychological Medicine, Western Clinical School, University of Sydney, Sydney, NSW, Australia; [3]Prince of Wales Medical Research Institute, Sydney, NSW, Australia; [4]University of New South Wales, Sydney, NSW, Australia; [5]School of Psychology, University of Sydney, Sydney, NSW, Australia; [6]Department of Psychology, Behavioral Neuroscience, University of Missouri, St Louis, MO, USA; [7]The Brain Resource Company and Brain Resource International Database, Ultimo, NSW, Australia; [8]NICTA and School of Information Technologies, University of Sydney, Sydney, NSW, Australia; [9]Laboratory of Personality and Cognition, National Institute on Aging, National Institutes of Health, Baltimore, MD, USA

Association studies suggest that the low activity variant of the monoamine oxidase A (MAOA)-uVNTR polymorphism confers risk for emotional disturbances associated with antisocial traits, particularly in males. Here, we assessed the low (MAOA-*L*) activity variant in relation to both brain function and a behavioral index of antisocial traits. From an initial sample of 290 healthy participants, 210 had low (MAOA-*L*) or high (MAOA-*H*) activity variants. Participants underwent a brief assessment of personality traits and event-related potential (ERP) recording during an emotion-processing task. Genotype differences in ERPs were localized using LORETA. The MAOA-*L* genotype was distinguished by elevated scores on the index of antisocial traits. These traits were related to altered ERPs elicited 120–280 ms post-stimulus, particularly for negative emotion. Altered neural processing of anger in MAOA-*L* genotypes was localized to medial frontal, parietal, and superior temporo-occipital regions in males, but only to the superior occipital cortex in females. The MAOA low activity variant may increase susceptibility to antisocial traits through alterations to the neural systems for processing threat-related emotion, especially for males. Monoamines such as noradrenalin and serotonin may modulate these relationships, given that their metabolism varies according to MAOA variants, and that they modulate both emotional brain systems and antisocial aggression.
Neuropsychopharmacology (2009) **34,** 1797–1809; doi:10.1038/npp.2009.1; published online 4 February 2009

Keywords: monoamine oxidase A (MAOA) genotype; event-related potentials (ERPs); LORETA; NEO personality factors; antisocial traits

INTRODUCTION

In the INTEGRATE model of brain organization, we consider how genetic variants may modulate brain systems for emotion, feeling and self regulation, and associated temperamental personality traits (Williams *et al*, 2008; Williams and Gordon, 2007). Here, we examined the effect of a functional polymorphism in the monoamine oxidase A (*MAOA*) gene on emotional brain activity and antisocial traits.

*Correspondence: Professor LM Williams, The Brain Dynamics Centre, Westmead Millennium Institute, Westmead Hospital, Westmead 2145, Australia, Tel: +61 2 9845 8195, Fax: +61 2 9845 8190, E-mail: lea_williams@wmi.usyd.edu.au

MAOA is a catabolic enzyme involved in regulating serotonin, noradrenalin, and dopamine (Weyler *et al*, 1990). The variable number of tandem repeats polymorphism (MAOA-uVNTR) of the *MAOA* gene on chromosome Xp11.23, produces genotypes with low (MAOA-*L*) and high (MAOA-*H*) activity (Sabol *et al*, 1998; Huang *et al*, 2004).

Low MAOA activity is implicated in antisocial behavior. A small kindred study has linked MAOA deficiency, because of gene mutation, to impulsive aggression (Brunner *et al*, 1993). In the MAOA-*L* carriers, risk for conduct disorder and antisocial traits is enhanced by environmental stressors such as maltreatment (Caspi *et al*, 2002; Foley *et al*, 2004; Huang *et al*, 2004; Nilsson *et al*, 2006). This interaction has been confirmed in meta-analyses, and is strongest in males (Kim-Cohen *et al*, 2006; Taylor and Kim-Cohen, 2007). The MAOA-environment interaction also confers risk for attention deficit which, in combination with conduct

disorder, predicts antisocial personality disorder in adulthood (Holmes *et al*, 2001).

MAOA-antisocial trait associations may vary with other sample characteristics. In adolescent females, MAOA-*H* (rather than MAOA-*L*) has been related to antisocial behavior in terms of alcohol problems (Nilsson *et al*, 2008). MAOA-*L* has been associated with reduced aggression in older males (Manuck *et al*, 2000), and is unrelated to antisocial behavior in schizophrenia (Zammit *et al*, 2004).

The Revised NEO Personality Inventory (NEO-PI-R, Costa and McCrae, 1992) has been used to derive a profile of antisocial personality disorder, confirmed by expert ratings (Miller *et al*, 2001; Miller *et al*, 2005). This profile has not been examined in relation to MAOA genotype. The standard NEO five factors show elevated neuroticism in MAOA-*L* males (Eley *et al*, 2003), and higher anxiety and depression, particularly in MAOA-*H* females, (Deckert *et al*, 1999; Samochowiec *et al*, 2004; Yu *et al*, 2005), as well as null results (Tochigi *et al*, 2006).

Brain function endophenotypes may help elucidate MAOA associations with these traits (Gottesman and Gould, 2003). Event-related potentials (ERPs) are promising endophenotypes, given they are heritable (eg, Young *et al*, 1996) and index brain function in real time (Rennie *et al*, 2002).

Antisocial traits are a cardinal feature of adult psychopathy. In emotion-discrimination tasks, psychopathic individuals show reduced ERP negativity within 100 ms, and around 300 ms, over fronto-central and occipital cortices (Campanella *et al*, 2005; Munro *et al.*, 2007). These reductions suggest difficulties in automatic appraisal of the arousing properties of emotion stimuli. More controlled emotion tasks (and linguistic ones) elicit later enhancements in negativity (300–800 ms), related to psychopathic and antisocial traits (Howard and McCullagh, 2007; Ishikawa and Raine, 2002; Kiehl *et al*, 1999).

In functional neuroimaging studies, the impact of the MAOA-*L* genotype has also varied with task. MAOA-*L* genotypes show limbic, including amygdala, hyper-reactivity during passive viewing, and simple matching of facial emotion stimuli (Lee and Ham, 2008; Meyer-Lindenberg *et al*, 2006), with concomitant prefrontal hypo-reactivity (Meyer-Lindenberg *et al*, 2006). Reduced subcortical and cortical MAOA levels in the 'resting' brain have been associated with higher trait aggression (Alia-Klein *et al*, 2008). Particularly low anterior cingulate activation has been revealed for the MAOA-*L* carriers, who are also homozygous for the long allele of the serotonin transporter polymorphism (5HTT-LPR), for an impulsivity task (Passamonti *et al*, 2008). In a more controlled social exclusion task, the MAOA-*L* genotype has been associated with hyper- rather than hypo-reactivity of the dorsal anterior cingulate, which mediated higher trait aggression (Eisenberger *et al*, 2007). Taken together, these findings suggest that alterations in sensitivity to emotion cues and experience, depending on task, contribute to MAOA-*L* and antisocial trait associations.

We assessed MAOA variants in relation to a NEO index of antisocial traits, ERPs elicited during automatic and controlled processing of emotion stimuli, and their neural sources. MAOA-*L* genotypes, particularly males, were predicted to show higher antisocial traits, and altered early

ERPs for both conditions, preferentially involving fronto-temporal and occipital networks.

MATERIALS AND METHODS

Study Sample

A total of 290 healthy individuals of European ancestry were recruited in collaboration with the Brain Resource International Database (BRID, http://www.brainresource.com; Gordon, 2003; Gordon *et al*, 2005) and of these, 210 were identified as MAOA-*L* or MAOA-*H* activity genotypes (141 males, mean age = 36.34 ± 12.43 years; 69 females, mean age = 35.87 ± 11.60 years). Inclusion criteria were normal, (or corrected to normal) hearing and vision, and estimated IQ (Baddeley *et al*, 1993) were within the normal range. Exclusion criteria included symptoms of Axis 1 disorder (based on the SPHERE, Hickie *et al*, 1998), family history of psychiatric disorder (defined in terms of severity as requiring medication and/or hospitalization), physical brain injury (causing loss of consciousness for > 10 min), neurological disorder, other serious medical or genetic condition and drug dependence (using the AUDIT (Alcohol Use Disorders Identification Test of the WHO), and the Fagerstrom Tobacco Dependency Questionnaire. For all subjects who reported infrequent alcohol–drug use, the most recent use occurred at least a week prior to testing. In the assessment of demographic factors, we included an earlier established measure of Early Life Stress (Cohen *et al*, 2006; Hoth *et al*, 2006; McFarlane *et al*, 2005; see Supplementary Methods for details). All participants provided written informed consent.

Genotyping

Genomic DNA was extracted from cheek swab samples by standard proteinase K digestion and chloroform extraction. MAOA-uVNTR genotypes were determined by polymerase chain reaction amplification, with fluorescent-labeled primers and capillary electrophoresis on the 3730 DNA Analyzer (Applied Biosystems, Foster City, CA). Here, of the initial 290 participants, 210 were classified as MAOA-*L* (3R, 3R/3R; $n = 73$, 55 males) or MAOA-*H* (3.5R, 4R, 3.5R/4R, 4R/4R; $n = 137$, 86 males). The other 80 participants were excluded as they were classified as other MAOA variants (see Supplementary Methods for additional details). MAOA genotypes were in the Hardy–Weinberg equilibrium ($\chi^2(6) = 4.34$, $p = 0.631$) based on female distribution (as only females have two MAOA alleles because of X-chromosome localization). Allele frequencies did not differ between sexes ($\chi^2(4) = 0.59$, $p = 0.964$).

As shown in Table 1, genotype groups did not differ on demographic characteristics, including the level of exposure to early life stress. MAOA genotype groups were also matched in terms of the catechol-O-methyltransferase Val108/158Met polymorphism (COMT) Met allele and the serotonin transporter promoter polymorphism (5HTT-LPR) Short allele, implicated in emotion-related disorders (Anguelova *et al*, 2003; Caspi *et al*, 2003; Woo *et al*, 2004) (Table 1).

Table 1 Summary Demographic, Genotype Distribution, and FFI-Antisocial Index Means for MAOA-L and MAOA-H Genotype Groups, for the Total Sample and for Males and Females Considered Separately

	Combined		Male		Female	
	MAOA-L	**MAOA-H**	**MAOA-L**	**MAOA-H**	**MAOA-L**	**MAOA-H**
Sample size (n)	73	135	55	85	18	50
Age in years (M ± SD)	36.76 ± 13.12	35.88 ± 11.62	37.32 ± 13.87	35.71 ± 11.46	35.05 ± 10.69	36.16 ± 11.99
Estimated IQ (M ± SD)[a]	104.20 ± 12.60	105.87 ± 10.18	103.69 ± 13.76	105.64 ± 11.70	105.73 ± 8.39	106.22 ± 7.33
Education in years (M ± SD)	14.45 ± 2.57	14.72 ± 2.73	14.53 ± 2.52	14.85 ± 2.69	14.22 ± 2.78	14.51 ± 2.80
Early life stressors (M ± SD)[b]	1.58 ± 1.52	1.92 ± 1.74	1.40 ± 1.33	1.86 ± 1.65	2.18 ± 1.94	2.02 ± 1.91
COMT distribution (% of VV:VM:MM)[c]	22:56:22	18:47:35	24:56:20	19:46:34	18:53:29	16:49:35
5HTT-LPR distribution (% of LL: Short)[d]	22:78	31:69	27:73	32:68	28:72	31:69
FFI-Antisocial Index[e]	70.78 ± 8.10	66.89 ± 7.94	71.96 ± 8.42	68.31 ± 7.43	67.17 ± 5.87	64.48 ± 8.26
DASS depression[f]	3.21 ± 5.06	4.16 ± 6.00	2.57 ± 3.09	4.29 ± 6.44	5.14 ± 8.55	3.95 ± 5.31
DASS anxiety[f]	1.61 ± 2.53	2.07 ± 4.08	1.19 ± 1.80	2.20 ± 4.51	2.86 ± 3.82	1.86 ± 3.32

COMT, catechol-O-methyltransferase; FFI-AI, Five-Factor Inventory Antisocial Index; MAOA, monoamine oxidase A.
[a]Estimated using a Spot-the-Real-Word test, earlier validated against the WAIS-III IQ test (Paul et al, 2005).
[b]MAOA genotypes did not differ on ELS exposure as a full sample ($t = -1.381$, $p = 0.169$), or when split by sex (males: $t = -1.743$, $p = 0.084$; females: $t = 0.290$, $p = 0.772$). The distribution of number of early life stressors was: 0–1, 51%; 2–3, 30%; 4 or more, 19%.
[c]VV, VM, and MM represent the three genotype variants for COMT, defined by distinct valine to methionine substitutions.
[d]LL are those homozygous for the 5HTT-LPR Long allele, and Short are those with either one or two copies of the short allele.
[e]The FFI-AI is derived from NEO-FFI scores. FFI-AI raw scores (and corresponding T scores) followed a normal distribution, with 50% of participants scoring above 68 (T score 50), 25% above 73 (T score 58), 10% above 80 (T score 65), and 2% above 88 (T score 75). Correspondingly, 25% scored below 62 (T score 45), 10% below 57 (T score 38), and 2% below 51 (T score 29). Setting a cutoff of 2 SDs for extreme scores, 4% of the sample in total had extreme high or low scores.
[f]Depression scale categories: Normal 0–9; Mild 10–13; Moderate 14–20; Severe 21–27; Extremely severe 28+; Anxiety scale categories: Normal 0–7; Mild 8–9; Moderate 10–14; Severe 15–19; Extremely severe 20+.

Behavioral Measures and Analysis

NEO-FFI and NEO-PI-R. The NEO Five-Factor Inventory (NEO-FFI) is a 60-item self-report questionnaire that assesses five major factors of personality traits: Neuroticism (N), Extraversion (E), Openness to Experience (O), Agreeableness (A), and Conscientiousness (C) (see Supplementary Methods for additional details).

It is a shortened version of the Revised NEO-PI-R(Costa and McCrae, 1992), and the 240 items of the NEO-PI-R contain the 60 items from the NEO-FFI. The NEO-FFI shows high correlations (0.77–0.91) with the NEO-PI-R for each of the N, E, O, A, and C factors, and has high internal consistency (0.68–0.81) for these factors.

FFI antisocial index (FFI-AI). Each of the five factors of the NEO-PI-R assesses six different facets of personality, making a total of 30 facets for the full measure. Miller et al (2005) developed a NEO-PI-R index based on the sum of 17 facets, which captures the DSM-IV antisocial personality disorder criteria. Prototypes formed by experts have been used to verify the facets that capture core antisocial traits (Miller et al, 2001).

We derived an FFI Antisocial Index (FFI-AI) for equivalent NEO-FFI facets (Supplementary Table S1). First, the 60 NEO-FFI items were extracted from another normative sample, which also had NEO-PI-R data (Baltimore Longitudinal Study of Aging, $n = 1.759$). A stepwise regression analysis was used to regress the NEO-FFI items onto Miller et al's (2005) index from the NEO-PI-R data (A NEO-PI-R dataset from the Baltimore Longitudinal Study of Aging ($n = 1.759$) was used in this

regression analysis. In these results, the reverse-scored NEO-FFI items were reflected by a negative standardized $â$ coefficient.). The resulting model retained 36 NEO-FFI items, with a correlation of 0.86, and adjusted R-squared of 0.73. These 36 items were summed to form the FFI-AI (Supplementary Table S1). Consistent with a dimensional model of personality disorders (Caccaro, 2000), the FFI-AI was intended to assess the aspects of antisocial traits that have a common heritability and neural basis across normal and clinical populations.

The FFI-AI scores were examined using univariate analysis of variance (ANOVA) with MAOA genotype (MAOA-L vs MAOA-H), as the between-subjects factor, and age as a covariate. To test for sex differences, a parallel ANOVA was undertaken with an additional between-subjects factor of sex (male vs female), followed by contrasts within male and female MAOA groups. Levene's test confirmed homogeneity of variance assumption was met. The contribution of MAOA genotype was reported in terms of effect size (eta-squared; η^2).

ERP Recording

Facial emotion perception task. Using the standardized LabNeuro protocols (Gordon et al, 2005), we recorded the EEG data during a previously established the Facial Expression of Emotion for Brain Activation task (Williams et al, 2006, 2007). Gray scale 3D evoked facial expression stimuli (depicting fear, anger, disgust, sadness, and happiness) were selected from a standardized set of stimuli (Gur et al, 2002). A total of 160 stimuli (four repeats of eight different individuals depicting each expression) were

presented pseudo randomly under both overt (to elicit controlled processing) and covert (to elicit non-conscious, automatic processing) conditions. In the overt condition, stimulus duration was 500 ms, with an inter-stimulus interval of 767 ms. In the covert condition, facial expression stimuli were presented for 10 ms, followed immediately by a neutral mask for 150 ms, with an inter-stimulus interval of 1100 ms between target-mask pairs to ensure that the total duration of stimulus plus inter-stimulus interval was equivalent across conditions (1267 ms). Mask stimuli were slightly spatially offset ($\sim 1^\circ$ in each of the diagonals, randomly), to control for the potential effects of perceptual priming because of the mask.

Using functional neuroimaging, we have earlier shown that robust neural activity is still elicited in the absence of an overt 'online' response to facial expression stimuli. Indeed, this evidence suggests that overt identification of expressions during brain function recording may in fact inhibit neural activation (Lange *et al*, 2003). To ensure attention to stimuli, participants were instructed to actively attend to each facial expression in preparation for post-testing assessments. After each condition, participants were shown simultaneously the eight individuals depicting each expression, and asked to select (through mouse click) which expression they found the most intense. χ^2 analysis showed there were no significant differences in the distribution of these selections across individuals, confirming the consistency of stimuli within each expression category.

ERP data acquisition. ERPs were extracted from the EEG data recorded from 26 scalp electrode sites according to the NuAmps International 10–10 system using a Quikcap with sintered Ag–AgCl electrodes, and a sampling rate of 500 Hz (see Supplementary Methods for additional details).

ERP Data Reduction and Analysis

ERP waveform analysis. ERP waveforms comprised a series of negative- and positive-going deflections in electrical brain activity, which defined these components of interest. Component names (eg, N200) indicated their direction ('N', negative-going deflection and 'P', positive-going deflection) and the latency at which they typically peak (eg 200 ms). These components (and the latency window within which the peak was determined) were N120 (80–130 ms), vertex positive potential (VPP) (The VPP is the standard terminology for a positive ERP component elicited by face stimuli, equivalent to a P200 elicited by other stimuli) (130–220 ms), N200 (150–280 ms), and P300 (280–400 ms) over medial fronto-central-parietal (Fz, Cz, Pz) sites, and concomitant N170 (130–220 ms, polarity reversal of VPP) and P230 (150–280 ms) over temporal (left, T5; right, T6) and occipital (left, O1; right, O2) sites (Note that although the latency windows for these components may overlap, this is a consequence of having to allow for temporal variations across electrode sites. At each site, there was a distinctive sequence of positive- and negative-going components.).

Using the Facial Expressions of Emotions for Brain Activation task in 250 healthy individuals, we have earlier shown that these ERP components are modulated by facial emotion in both overt and covert conditions (Williams *et al*, 2006, 2007). To confirm earlier findings, and to provide a

context for MAOA effects, we first analyzed ERPs for the total sample collapsed across genotype. For each component in both overt and covert conditions, we undertook repeated measures ANOVAs with emotion (each expression *vs* neutral) and region (medial fronto-central-parietal, temporal, or occipital), as the within-subjects factors with repeated measures.

ERP waveform analyses of MAOA genotypes focused on the timing of significant effects. Repeated measures ANOVA were undertaken for the representative sites, with MAOA genotype (MAOA-*L vs* MAOA-*H*) as the between-subjects factor, and region (medial fronto-central-parietal: Fz, Cz, Pz; temporal: T5, T6; or occipital: O1, O2) as the within-subjects factor with repeated measures. Dependent measures were ERP components for each emotional expression in overt and covert conditions. Focal effects of interest were those involving MAOA genotype (main effects and genotype by region interactions). Significant interactions with region were explored using contrasts between MAOA groups at each site. The effect size (η^2) of the MAOA genotype contribution was reported for each significant effect.

To test for sex differences, a parallel set of ANOVAs was undertaken with an additional between-subjects factor of sex (male *vs* female), followed by contrasts within male and female MAOA groups to examine the significant effects of sex.

The Greenhouse–Geisser correction (relevant to multivariate models) was applied to ensure the homogeneity of variance assumption was met. As noted under the section, Confirmatory Analyses, below, the issue of multiple testing was addressed using a permutation procedure.

LORETA Source Localization

LORETA was used to identify the neural sources of differences in ERP components because of MAOA genotype, in this case focusing on the spatial localization of effects. The LORETA inverse solution method (Pascual-Marqui, 1999; Pascual-Marqui *et al*, 2002) was applied following our earlier published procedure (Williams *et al*, 2006) (see Supplementary Methods for additional details). LORETA was undertaken for the 130–280 ms time segment, which revealed the most robust genotype effects in waveform analyses. Statistical Nonparametric Mapping (Nichols and Holmes, 2002) was applied at the threshold of $p < 0.05$, corrected for multiple comparisons according to the contiguity of voxels criterion.

Behavior-Brain Relationships

The ERP components that showed a significant MAOA genotype effect were included in linear regression analyses, to examine whether these components predict behavior in terms of the FFI-AI. Regression analyses were undertaken for the MAOA-*L* and MAOA-*H* genotype groups for males and females combined, and considered separately.

To examine whether ERP components may mediate the relationship between MAOA genotype and FFI-AI, we repeated the regression analyses with genotype as a second predictor, controlling for ERPs as the first predictor. In this model, if ERPs mediate the MAOA-FFI-A$_I$ association, then the regression model will not reach significance, when

controlling for ERPs in the prediction of FFI-A$_I$ from the MAOA genotype (Miles and Shevlin, 2001).

Confirmatory Analyses

Three sets of additional analyses were undertaken to confirm the significant MAOA genotype effects, in regard to multiple testing, equal group sizes, and the specificity of these effects in relation to other genotypes (for 5HTT-LPR and COMT), which modulate emotional brain function (see Supplementary Methods for details of subsampling into equal-sized groups, and additional genotyping).

We first undertook permutation testing to confirm that the significant MAOA effects on ERPs were not because of chance discovery, given multiple testing. Dependent measures for the same ERP variables were used in focal ANOVAs. A Monte Carlo procedure was used, with 10 000 random permutations and two-tailed confidence interval of at least 95%. As ERP components are highly inter-correlated, this procedure was considered more appropriate than standard corrections for multiple testing.

A second set of parallel ANOVAs was undertaken with the equal-sized subsamples of MAOA-L and MAOA-H genotypes to confirm that significant results for both the NEO-FFI and the ERP measures were not because of the effects of the unequal size of the genotype groups used in focal analyses. These subsamples were matched on demographic measures, early life stress, and distribution of the COMT and 5HTT-LPR variants.

To further determine the specificity of results to MAOA variants, additional repeated measures ANOVAs were also undertaken to examine whether the COMT (V/V, V/M, M/M) and 5HTT (LL vs Short carriers) genotypes show similar differences in the NEO-FFI indices and ERPs, and interactions between these genotype differences and sex. We used the same statistical procedures to examine the significant effects, as used for focal MAOA analyses.

RESULTS

Behavioral Measures

The missing NEO-FFI data ($<5\%$ of cases) were replaced by mean values according to MAOA genotype and sex.

FFI-antisocial index: MAOA effects. There was a significant MAOA genotype effect for the FFI-AI ($F (1,205) = 14.22$, $p < 0.001$; $\eta^2 = 0.065$), because of higher antisocial traits in MAOA-L relative to MAOA-H genotypes (Table 1 for means). There was no significant MAOA genotype by sex interaction for the FFI-AI. In males, the FFI-AI scores were higher in MAOA-L compared with MAOA-H genotypes ($F (1,137) = 11.12$, $p = 0.001$; $\eta^2 = 0.075$, Table 1). In females, there was no significant difference ($F (1, 65) = 1.41$, $p = 0.239$).

When the NEO-FFI five factors were considered, there was a significant MAOA genotype effect for Conscientiousness ($F (1, 203) = 14.75$, $p < 0.001$; $\eta^2 = 0.082$), such that the MAOA-L group was lower than the MAOA-H group. The genotype by sex interaction was not significant. There were no significant MAOA genotype or genotype by sex interactions for the other factors.

Depression and anxiety: MAOA effects. There were no MAOA effects or interactions between MAOA genotype and sex for DASS depression and anxiety measures (Table 1 for means).

MAOA interactions with early life stress. There were no significant interactions between MAOA genotype and level of early life stress for the FFI-AI, assessed in terms of dichotomous categories (<3 stressful events vs $\geqslant 3$ events) or six finer-grained categories. Similarly, there were no significant interactions between MAOA genotype and early life stress for depression and anxiety.

ERP Waveform Results

Total group emotion effects. For the total group (collapsing across MAOA genotypes), we confirmed earlier findings (Williams et al, 2006) that ERPs of interest are modulated by facial emotion stimuli. In common, emotion stimuli (relative to neutral baseline) enhanced the temporo-occipital N170 and medial VPP components in both overt and covert conditions (Supplementary Table S2). More specific effects for threat-related emotion (anger and fear) were revealed for the earlier (within 120 ms) and the later (150–280 ms) ERPs. The medial fronto-central N120 and concomitant occipital P120 were reduced for overt perception of emotion, whereas the N120 was enhanced distinctively for covert perception of emotion. The medial fronto-central N200 (150–280 ms) was reduced more specifically for fear and anger in both conditions, as well as covert sadness, as was the concomitant temporal P230. Threat-related expressions of fear and anger elicited an increase in the following medial P300 (Supplementary Table S2).

MAOA main effects. A thorough visual inspection of ERP components across sites identified 130–280 ms period as the time segment in which genotype effects were most apparent, and these effects were confirmed with statistical analysis (Table 2). These effects reflected a shift in the direction of positivity (ie, greater VPP positivity with reduced N200 negativity).

Within the 130–220 ms period, there was an enhancement of positivity in MAOA-L (relative to MAOA-H) for the VPP over medial fronto-central-parietal regions, for overt perception of anger and disgust (Table 2). The VPP was enhanced similarly for MAOA-L over the medial parietal site for overt perception of sadness, reflected in a significant MAOA by region interaction (Table 2).

There was a subsequent reduction in negativity for MAOA-L relative to MAOA-H for the N200 over medial fronto-central and parietal sites, elicited by overt perception of each emotional expression: anger, fear, sadness, disgust, and happiness (Table 2). N200 negativity was reduced similarly in MAOA-L genotypes relative to MAOA-H genotypes for covert perception of anger, sadness, and disgust (Table 2).

A complementary increase in positivity for the P230 (150–280 ms) in MAOA-L relative to MAOA-H genotypes was apparent over the left temporal site in particular, reflected in a MAOA by region interaction for overt fear and disgust. However, these interactions were not confirmed by

Table 2 Summary of ANOVA Main Effects of MAOA-L (L) vs MAOA-H (H) Genotype ($df = 1,186$) on ERPs Elicited by Emotion Stimuli within 80–130 ms, 130–280 ms, and 280–400 ms Latency Windows, Across Medial (Fronto-Central-Parietal) and Temporal Brain Regions; with Dark Gray Shading Indicating Increases in ERP Amplitude, and Light Gray Shading Decreases in Amplitude According to L vs H Genotype

Emotion: condition	80–130 ms	130–280 ms		280–400 ms
	Medial N120	Medial VPP	Medial N200	Medial P300
Anger: overt		$F = 5.51^*$: $L > H$; $\eta^2 = 0.029$	$F = 8.88^{**}$: $L < H$; $\eta^2 = 0.054$	
Anger: covert			$F = 12.38^{***}$: $L < H$; $\eta^2 = 0.068$	
Fear: overt			$F = 12.30^{***}$: $L < H$; $\eta^2 = 0.067$	
Sadness: overt		$F = 4.63^{**}$ (Pz)[a]: $L > H$; $\eta^2 = 0.037$	$F = 5.43^*$: $L < H$; $\eta^2 = 0.033$	
Sadness: covert			$F = 5.24^*$: $L < H$; $\eta^2 = 0.030$	
Disgust: overt		$F = 4.28^*$: $L > H$; $\eta^2 = 0.022$	$F = 12.71^{***}$: $L < H$; $\eta^2 = 0.072$	
Disgust: covert			$F = 5.72^*$: $L < H$; $\eta^2 = 0.033$	
Happiness: overt			$F = 8.24^{**}$: $L < H$; $\eta^2 = 0.050$	

ANOVA, univariate analysis of variance; MAOA, monoamine oxidase A; VPP, vertex positive potential.
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
[a]Indicates a significant MAOA by region interaction (and site responsible for the interaction).

permutation analyses (see section, Confirmatory Analyses), and, therefore, not included in focal results.

Sex differences in MAOA effects. Significant interactions between MAOA genotype and sex were also most apparent for the 130–280 ms period (Table 3; Figure 1).

MAOA by sex by region interactions for the VPP (130–220 ms) were apparent over medial fronto-central regions for overt perception of anger and disgust, and over the parietal site for covert perception of anger, fear, and sadness (Table 3; Figure 1). Contrasts confirmed that MAOA-L males showed enhanced fronto-central VPP positivity relative to MAOA-H males for overt anger ($p < 0.05$) and disgust ($p < 0.01$). By contrast, MAOA-L females had enhanced parietal VPP relative to MAOA-H females for covert anger ($p < 0.001$), with non-significant trend effects for covert fear and sadness (Table 3, Figure 1).

For the medial fronto-central-parietal N200 (150–280 ms), significant MAOA by sex interactions were present for overt perception of disgust, and covert perception of anger and sadness (Table 3; Figure 1). These effects were due to reduced N200 in MAOA-L males (but not females) relative to MAOA-H males, for overt disgust ($p < 0.001$), for covert anger ($p < 0.001$), and sadness ($p < 0.01$).

There was a concomitant MAOA by sex interaction for the occipital N170 (130–220 ms) for overt perception of disgust and happiness, because of a non-significant trend for reduced negativity in female MAOA-L relative to MAOA-H-genotypes (Table 3; Figure 1). There was a corresponding MAOA by sex interaction for the occipital P230 (150–280 ms; Table 3) for overt anger, in this case due to a non-significant trend for enhanced positivity in female MAOA-L relative to MAOA-H genotypes (Table 3; Figure 1).

Only isolated MAOA by sex interactions were apparent for components extending outside the 130–280 ms period of the VPP and N200/P230 components. There was a MAOA by

sex by region interaction reflecting enhanced positivity in the medial fronto-central P300 (280–400 ms) in male MAOA-L relative to MAOA-H genotypes for overt disgust ($p < 0.01$) (Table 3). In the earlier period, MAOA by sex interactions for the medial N120 (80–130 ms) were due to enhanced negativity in female (but not male) MAOA-L relative to MAOA-H genotypes for covert fear ($p < 0.05$) and sadness ($p < 0.05$) (Table 3; Figure 1).

MAOA interactions with early life stress. There were no significant interactions between MAOA genotype and level of early life stress for the ERP measures.

LORETA Source Localization

Given that MAOA genotype effects, and their interaction with sex, were most apparent for the VPP–N200 complex in the 130–280 ms period, LORETA source localization focused on this period. LORETA revealed significant MAOA effects on source localization only for overt anger, in males and females considered separately.

For males, anger-related ERP alterations in the MAOA-L (relative to MAOA-H) genotype were localized to the right medial frontal, superior temporal and superior occipital, and left parietal regions for the 130–280 ms period (Table 4; Figure 2).

For females, anger-related ERP alterations for the MAOA-L relative to MAOA-H genotype showed a far more focal localization within 130–280 ms, constrained to the right superior occipital region (Table 4; Figure 2).

Complementing the LORETA findings for overt anger, the topographical distribution of ERP waveforms for MAOA-L and MAOA-H groups for this condition were consistent with the more cortically distributed pattern of differences for male MAOA-L vs MAOA-H genotypes in the 120–280 ms period, compared with the more localized effect for females (Supplementary Figure S1).

Table 3 Summary of the ANOVA Effects for MAOA-*L* (L) *vs* MAOA-*H* (H) Genotype by Sex Interactions ($df = 1,183$) for ERPs Elicited by Emotion Stimuli within 80–130 ms, 130–280 ms, and 280–400 ms Latency Windows, Across Medial (Fronto-Central-Parietal), and Occipital Brain Regions; with Dark gray Shading Indicating Increases in ERP Amplitude, and Light gray Shading Decreases in Amplitude According to Female or Male *L vs H* Genotypes as Indicated

Emotion: condition	80–130 ms	130–280 ms		280–400 ms
	Medial N120	Medial VPP/Occipital N170	Medial N200/Occipital P230	Medial P300
Males				
Anger: overt		VPP $F = 3.72^*$ (Fz): $L > H$; $\eta^2 = 0.022$	N200 $F = 3.78^*$ (Fz)[a]: $L < H$; $\eta^2 = 0.019$	
Anger: covert			N200 $F = 5.01^*$: $L < H$; $\eta^2 = 0.032$	
Sadness: covert			N200 $F = 4.53^*$: $L < H$; $\eta^2 = 0.075$	
Disgust: overt		VPP $F = 6.81^{**}$ (Fz,Cz)[a]: $L > H$; $\eta^2 = 0.052$	N200 $F = 3.37^*$ (Fz,Cz)[a]: $L < H$; $\eta^2 = 0.016$	P300 $F = 5.05^*$ (Fz,Cz)[a]: $L > H$; $\eta^2 = 0.041$
Females				
Anger: overt			P230 $F = 3.92^{*,b}$: $L > H$; $\eta^2 = 0.018$	
Anger: covert		VPP $F = 11.89^{***}$ (Pz)[a,b]: $L > H$; $\eta^2 = 0.068$		
Fear: covert	N120 $F = 6.71^{**}$: $L > H$; $\eta^2 = 0.035$	VPP $F = 6.1^{**}$ (Pz)[a,b]: $L > H$; $\eta^2 = 0.034$		
Sadness: covert	N120 $F = 9.15^{**}$: $L > H$; $\eta^2 = 0.064$	VPP $F = 5.15^*$ (Pz)[a]: $L > H$; $\eta^2 = 0.031$		
Disgust: overt		N170 $F = 4.99^{*,b}$: $L < H$; $\eta^2 = 0.029$		
Happiness: overt		N170 $F = 4.31^{*,b}$: $L < H$; $\eta^2 = 0.025$		

ANOVA, univariate analysis of variance; MAOA, monoamine oxidase A; VPP, vertex positive potential.
$^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.
[a]Indicates a significant MAOA by sex by region interaction (and site(s) responsible for the interaction in parentheses).
[b]The contrast for the significant MAOA by sex interaction showed a mean difference for MAOA-*L vs* MAOA-*H* in females, but this difference did not reach significance.

Behavior-Brain Relationships

ERP components, which showed a MAOA genotype effect in ANOVAs, were found to significantly predict the FFI-AI scores.

Higher FFI-AI scores were predicted by lower medial activity for the medial N200 for overt anger (Cz; $F = 4.58$, $p = 0.034$), covert anger (Cz, $F = 4.05$, $p = 0.046$), overt fear ($F = 3.13$, $p = 0.027$), covert sadness ($F = 3.04$, $p = 0.030$), and overt happiness ($F = 4.06$, $p = 0.008$), consistent with the direction of MAOA-*L*.

In males, higher FFI-AI scores were also predicted by the medial VPP for overt anger ($F = 3.52$, $p = 0.017$), corresponding to the direction of effects for MAOA-*L* males.

When MAOA genotype was included as the second predictor of the FFI-AI in stepwise regression analyses, with each of these ERP components controlled as the first predictor, these ERP components were excluded from the final model in each case. These results are consistent with the role of ERPs as a mediator of the FFI-AI and the MAOA-*L* association.

Confirmatory Analyses

Permutation procedure. The Monte Carlo permutation analyses confirmed the significant MAOA effects revealed in ANOVAs for ERP components, at $p < 0.01$ for combined males/females, and $p < 0.05$ for males and females considered separately. The only exception was for the left temporal P230 for overt fear and disgust, which was not confirmed in permutation analyses.

Equal-sized groups. Confirmatory ANOVAs on the equal-sized subsample confirmed the elevation in FFI-AI for MAOA-*L* genotypes at $p < 0.05$, along with the null effects for the DASS.

Confirmatory ANOVAs of the emotion-related ERPs confirmed the above pattern of genotype main effects and genotype by sex interactions, largely as significant ($p < 0.05$), but at least at trend-level ($p < 0.085$). In each case, the pattern of means followed a similar trend as for the total sample.

Confirmatory LORETA analyses for the equal-sized subsample also largely verified the total sample findings for males and females.

Specificity of MAOA effects. Follow-up analyses of behavioral and ERP measures in relation to the COMT and 5HTT genotypes, which also impact neuromodulation, revealed significant but distinctive effects on these measures (see Supplementary Material for details), and their interaction with MAOA genotype. These findings support the specificity of MAOA genotype effects on the FFI-AI and ERP measures of emotional brain function.

DISCUSSION

This study provides new evidence that the MAOA low activity variant is associated with effects on early, emotion-related brain activity, as well as antisocial personality traits. Consistent with predictions, individuals with the
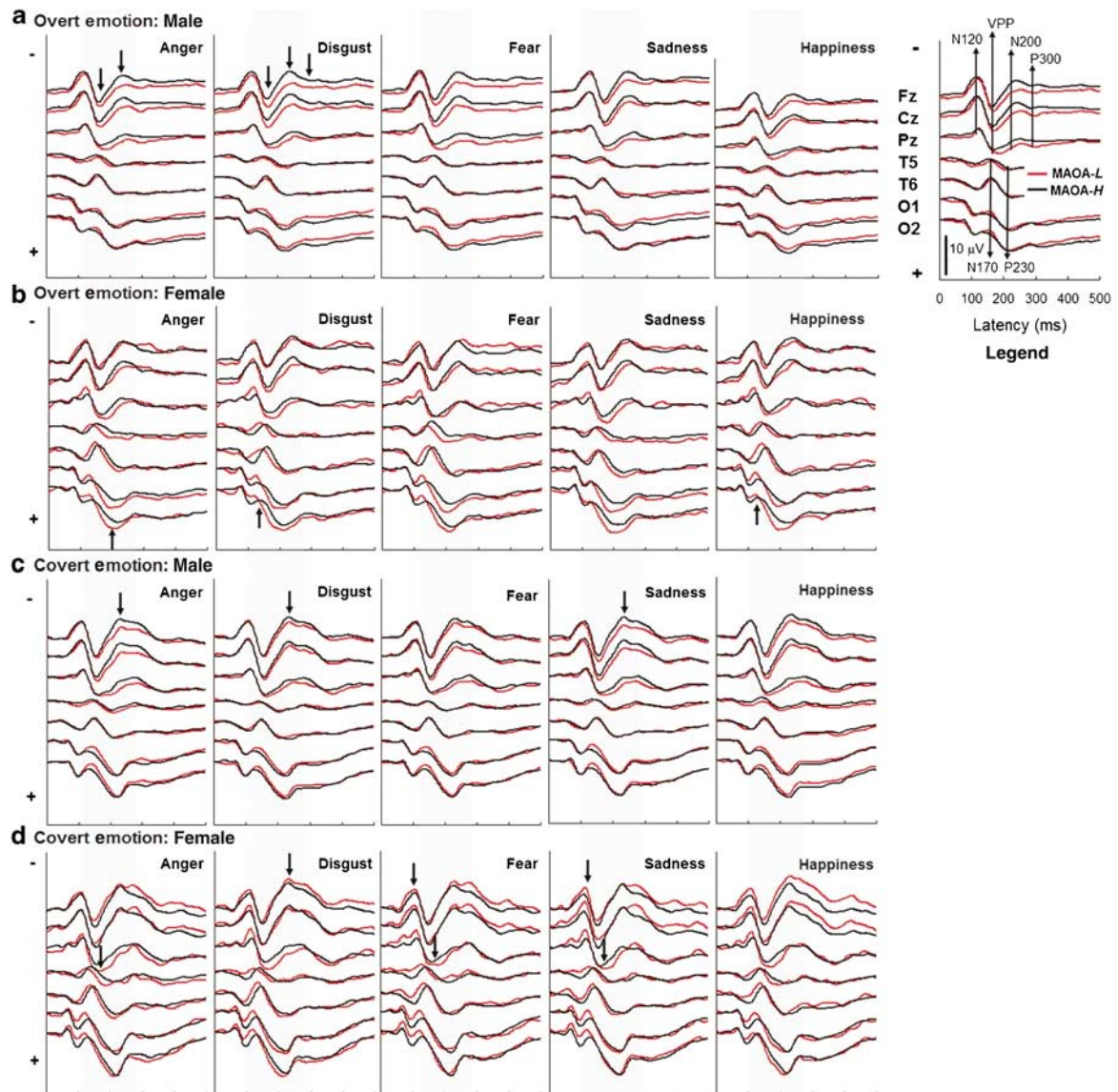
Figure 1 Average ERP waveforms across representative sites in overt and covert emotion processing conditions, for MAOA-*L* (red line) *vs* MAOA-*H* (black line) genotype groups in both males and females. Gray shading indicates the 120–280-ms period, in which the genotype effects on ERP waveforms were most apparent, and interacted with sex differences. Arrows indicate specific effects revealed in statistical analyses (summary of results in Table 3). For the 120–220 ms period, in which the VPP and concomitant N170 ERP components are elicited, MAOA-*L* (*vs* MAOA-*H*) males showed enhanced medial fronto-central positivity for overt anger and disgust. On the other hand, MAOA-*L* (*vs* MAOA-*H*) females showed enhanced parietal VPP for covert anger and (trend level) for fear and sadness. Female MAOA-*L* genotypes showed a corresponding trend level reduction in the N170 (120–220 ms) for overt disgust and happiness. For the 150–280 ms period, in which the N200 and concomitant P230 components are elicited, MAOA-*L* (relative to MAOA-*H*) males showed a reduction in N200 for overt disgust, and for covert anger and sadness (Table 3). In females, the MAOA-*L* (*vs* MAOA-*H*) group showed a trend enhancement in the occipital P230 for overt anger. Extending outside the 120–280 ms period, female MAOA-*L* (*vs* MAOA-*H*) genotypes showed enhanced negativity for the medial fronto-central-parietal N120 (80–180 ms) for covert fear and sadness, and male MAOA-*L* (*vs* MAOA-*H*) genotypes showed enhanced positivity for medial fronto-central P300 (220–450 ms) for overt disgust (Table 3). Abbreviations for sites: medial frontal, Fz-central, Cz-parietal, Pz, temporal (left T5, right T6); occipital (left O1, right O2).

MAOA-*L* genotype showed alterations in ERPs within 130–280 ms post-stimulus that were most apparent for negative emotion, and also related to higher scores on a NEO-FFI index of antisocial traits. These findings extend on the earlier studies reporting MAOA-*L* and antisocial behavior associations, using high spatial resolution imaging techniques (Meyer-Lindenberg *et al*, 2006; Lee and Ham, 2008).

Although the contribution of MAOA genotypes was modest in effect size, it was highly consistent in its impact on the first 130–280 ms of emotional brain function. These findings indicate that the MAOA variants modulate the early, automatic appraisal of emotion cues (Williams *et al*, 2008). The sensitivity of ERPs for capturing the effects of MAOA-*L*, may in part reflect the heritability and stability of electrical brain measures (Anokhin *et al*, 2006).

In MAOA-*L* (relative to MAOA-*H*), the most prominent effect was a reduction in negativity for the medial N200 ERP component (150–280 ms). This reduction occurred for both overt and covert conditions, across emotions. There

Table 4 Summary of LORETA Source Localization for Regions of Activity Elicited by Overt Anger (120–280 ms Post-Stimulus), which Differed Significantly According to MAOA-L vs MAOA-H Genotypes in Males and Females

Region	Side	BA	x,y,z coordinates	t value
Male				
Frontal cortex				
Superior frontal gyrus (medial part)	R	BA8	25, 31, 50	3.11*
Middle frontal gyrus (lateral premotor area)	R	BA6	32, −4, 64	2.92*
Temporal cortex				
Superior temporal gyrus	R	BA6	60, 3, 1	2.84*
Parietal cortex				
Inferior parietal lobule	L	BA40	−59, −39, 50	3.11*
Superior parietal lobule	L	BA7	−45, −74, 43	2.95*
Occipital cortex				
Superior occipital gyrus	R	BA19	25, −88, 36	3.00*
Female				
Occipital cortex				
Superior occipital gyrus	R	BA19	18, −88, 43	−3.12*

MAOA, monoamine oxidase A.
Regions are defined by associated Brodmann Area (BA) and talairach coordinates.
*p < 0.05 corrected for SnPM tests.

was a more specific enhancement in positivity for MAOA-L for the preceding medial VPP component (130–220 ms), for overt perception of negative emotion. As negative emotion processing was associated with enhanced VPP and reduced N200 ERPs in the total group, the findings for MAOA-L suggest an alteration of normal negative emotion processing; specifically a shift towards relatively reduced neural excitation within the first 200 ms post-stimulus. ERP negativity (here, N200) has been associated with excitatory depolarizing potentials, whereas positivity (here, VPP) may reflect hyperpolarizing inhibition of the apical dendrites of pyramidal cells (Allison et al, 2002).

Our observation of an early alteration in ERPs in MAOA-L genotypes, particularly reduced negativity, accords with evidence for similar alterations during automatic emotion-processing tasks in psychopathy, suggesting that these findings reflect the common contribution of antisocial traits (Campanella et al, 2005; Ishikawa and Raine, 2002; Raine et al, 1990; Scarpa and Raine, 1997). Emotion-elicited negativity around 200 ms has been linked to increases in phasic skin conductance arousal (Williams et al, 2004), and antisocial behavior to reductions in skin conductance arousal (Gilbert et al, 1991). These findings suggest that the MAOA-L genotype may contribute to poor initial appraisal of the arousing properties of emotional signals and mobilization of action tendencies, consistent with higher antisocial traits.

In accordance with this proposal, alterations in the VPP and N200 in the MAOA-L genotype group, predicted higher levels on the FFI-AI. In particular, prediction was significant for anger stimuli, compatible with antisocial and aggressive tendencies. Moreover, these ERP components were found to

mediate the association between MAOA genotype and antisocial traits. Exposure to early life stress did not interact with MAOA-L for its impact on both the FFI-AI and ERPs, but such interactions may be apparent in clinical samples, as observed previously (Kim-Cohen et al, 2006; Taylor and Kim-Cohen, 2007).

MAOA-L effects on both emotion-elicited ERPs and FFI-AI were most apparent in males, consistent with association studies (Brunner et al, 1993). The reduction in N200 was due in particular to males with the MAOA-L genotype, and was apparent for both overt and covert anger processing. MAOA-L males also showed a concomitant increase in fronto-central positivity (VPP) for overt anger and disgust.

On the other hand, the earlier enhancement in the VPP was most apparent in females with the MAOA-L variant, for covert processing of negative emotion (anger, fear, and sadness). MAOA-L females also showed earlier enhancements in the medial N120 during covert processing of fear and sadness. The presence of distinctive effects for the covert condition in MAOA-L females suggests that the shift in neural excitation commences earlier in females, which may reflect qualitatively different sex-dependent effects of the MAOA genotype on automatic emotion appraisal.

Altered ERPs for MAOA-L genotypes were localized to neural sources that were more distributed for males than females, consistent with greater prominence of these alterations for males.

In MAOA-L males, alterations in the VPP and N200 (130–280 ms) were localized to right medial frontal and premotor areas, right superior temporo-occipital, and left inferior and superior parietal regions for overt processing of anger. These regions have been implicated in distributed cortical
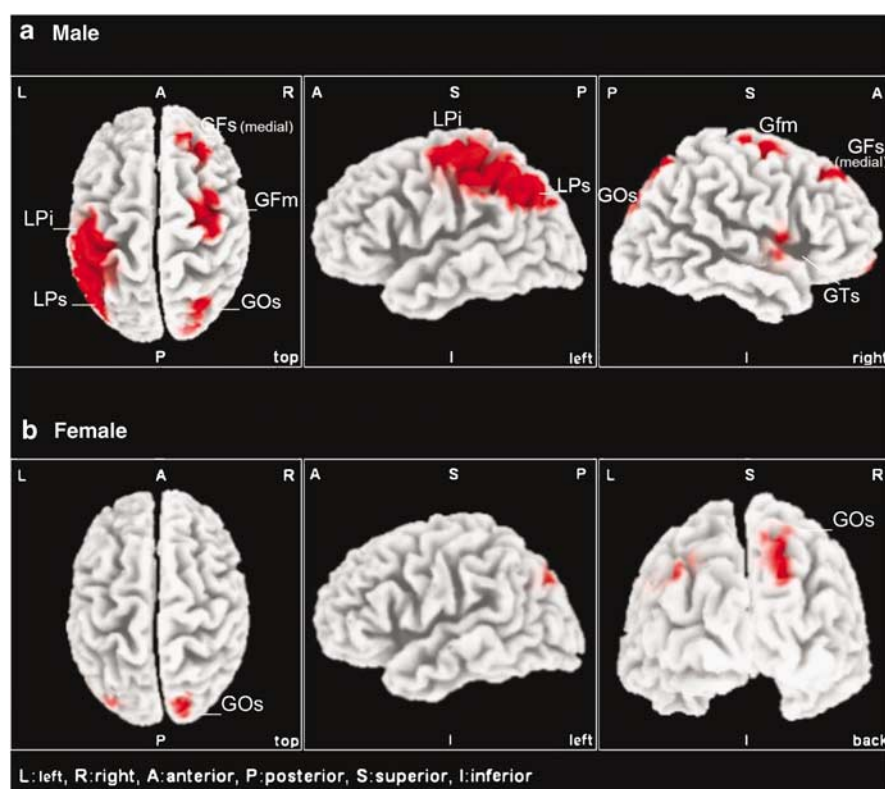
Figure 2 Statistical non-parametric maps from LORETA for localization of the comparison between MAOA-*L* vs MAOA-*H* genotypes in response to overt anger during the time period 120–280 ms, for male and females. Regions of significant (*p* < 0.05) source localization are colored red. In males (a), alterations in MAOA-*L* were localized to right medial frontal, superior temporal and superior occipital, and left parietal regions; and in females (b), to the right superior occipital cortex only. Coordinates for these neural sources are presented in Table 4. Abbreviations: GFs, superior frontal gyrus (medial part); GFm, middle frontal gyrus (lateral premotor area); GTs, superior temporal gyrus; LPs, superior parietal lobule; Lpi, inferior parietal lobule; Gos, superior occipital gyrus.

systems for face and emotion perception (Williams *et al*, 2006). Since ERPs around 200 ms reflect increases in arousal, and associated medial prefrontal-premotor activation (Williams *et al*, 2004; 2008), the present findings suggest difficulties in appraising the arousing properties of salient emotion stimuli within this time frame, in relation to both MAOA-*L* and antisocial traits. Parietal regions have also been implicated in the central representation of arousing signals (Adolphs, 2002). Convergent evidence indicates a preferential role for the superior temporal cortex in perceiving facial signals of threat (Allison *et al*, 2000), and the salience of these signals modulates early visual processing within the temporo-occipital and the fronto-parietal networks (Vuilleumier and Pourtois, 2006).

These source localization findings accord with functional neuroimaging evidence highlighting differences in frontal and temporal cortices during emotion processing in MAOA-*L* males (Lee and Ham, 2008; Meyer-Lindenberg *et al*, 2006). Neural disturbances in MAOA-*L* males may be associated with anger processing in particular, consistent with antisocial characteristics. Alternatively, the absence of significant differences in neural sources for other facial expressions may reflect their reduced salience for MAOA-*L* males.

In contrast, the effect of MAOA-*L* on ERPs within 130–280 ms for overt anger in females was localized specifically to the right superior occipital brain region. In females, the MAOA-*L* variant may preferentially impact neural systems for early visual appraisal of salient emotion, compared with the more distributed neural systems in males.

On the basis of these findings, we speculate that monoamine mechanisms may modulate links between MAOA genotype, neural alterations in early emotion processing, and antisocial personality traits. Monoamine mechanisms, such as a dysregulation in both noradrenaline (norepinephrine) and serotonin, have long been implicated in antisocial aggression. Although contradictory findings exist, psychopathy and associated personality traits have been linked to relatively low serotonin but high noradrenaline (Haden and Scarpa, 2007; Haller *et al*, 1998; Soderstrom *et al*, 2003; Woodman, 1979). Serotonin has also been found to attenuate neural excitation for glutamate-evoked sensory input, including for threat-related signals, whereas noradrenaline may enhance basal glutamate-evoked excitation (Aston-Jones *et al*, 1991) In MAOA-*L* individuals, lower levels of these monoamines may mediate alterations in early neural excitation, as well as contribute to associated antisocial traits. The specificity of these mechanisms to the MAOA variant is suggested by the differential impact of both 5HTT-LPR and COMT genotypes on the measures used in this study. Future research using MAOA inhibitors, and monoamine agonists and antagonists shown to also alter ERPs (Luthringer *et al*, 1996; Turetsky and Fein, 2002), may help elucidate the mechanisms of MAOA genotype effects on ERPs. MAOA might also be examined in relation to other genetic variants, shown to modulate emotion ERPs (Gatt *et al*, 2007).

Sex hormones or sex-linked chromosomes might contribute to the sex differences in MAOA-*L* effects, either through direct influences on gene function or by their role in the sexual differentiation of neural development (Cahill, 2005). For instance, research with rhesus monkeys has shown that estrogen and progesterone significantly reduce MAOA transcription in the brain (Gundlah *et al*, 2002). Testosterone correlates positively with aggression and violent crime (Scerbo and Kolko, 1994; Dabbs *et al*, 1995), and might contribute to the link between MAOA genotype and antisocial behaviors through an influence on the *MAOA* gene transcription (Sjöberg *et al*, 2007). The localization of the *MAOA* gene on the X-chromosome (producing two MAOA alleles in females and one in males) may also contribute to functional differences in emotional brain and behavior.

To validate these associations between the MAOA genotype and the new FFI-AI of antisocial and psychopathic traits, future research with clinical samples of antisocial personality disorder and conduct disorder (with allied ADHD) is warranted. It would also be valuable to consider the contribution of stressors, such as maltreatment, to the effects of MAOA-*L* on emotional brain function in these clinical samples. As the FFI-AI has limitations in the coverage of antisocial traits, future work might also extend our findings to Miller *et al*'s (2005) NEO-PI-R Antisocial Index. In addition, the timing of MAOA-*L* effects on emotional brain function needs to be explored using additional emotion tasks, including those requiring an overt behavioral response and more controlled processing during ERP recording. Although this ERP protocol did not rely on overt responses, we are confident that participants attended to stimuli. The ERP morphology corresponds closely with that of an earlier study, in which responses to an implicit sex classification instruction were recorded (Williams *et al*, 2004).

In conclusion, this study provides new evidence that the MAOA-uVNTR polymorphism alters the neural functions of early automatic emotion processing, especially anger. These alterations may mediate heightened risk for antisocial personality traits, for males in particular. The findings provide a platform for integrative neuroscience research into the linkages between genetic polymorphisms, brain function and behavior in relation to emotional functions (Williams *et al.*, 2008). Specifically, they point to the role of neuromodulators and their interaction with sex differences in the effects of MAOA genotypes on emotion-related brain function and risk for antisocial behavior.

REFERENCES

Adolphs R (2002). Neural systems for recognizing emotion. *Curr Opin Neurobiol* **12**: 169–177.

Alia-Klein N, Goldstein RZ, Kriplani A, Logan J, Tomasi D, Williams B *et al* (2008). Brain monoamine oxidase A activity predicts trait aggressions. *J Neurosci* **28**: 5099–5104.

Allison T, Puce A, McCarthy G (2000). Social perception from visual cues: role of the STS region. *Trends Cogn Sci* **4**: 267–278.

Allison T, Puce A, McCarthy G (2002). Category-sensitive excitatory and inhibitory processes in human extrastriate cortex. *J Neurophysiol* **88**: 2864–2868.

Anguelova M, Benkelfat C, Turecki G (2003). A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. affective disorders. *Mol Psychiatry* **8**: 574–591.

Anokhin AP, Heath AC, Myers E (2006). Genetic and environmental influences on frontal EEG asymmetry: a twin study. *Biol Psychol* **71**: 289–295.

Aston-Jones G, Akaoka H, Charlety P, Chouvet G (1991). Serotonin selectively attenuates glutamate-evoked activation of noradrenergic locus coeruleus neurons. *J Neurosci* **11**: 760–769.

Baddeley A, Emslie H, Nimmo-Smith I (1993). The Spot-the-Word test: a robust estimate of verbal intelligence based on lexical decision. *Br J Clin Psychol* **32**: 55–65.

Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA (1993). Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* **262**: 578–580.

Caccaro E (2000). Is the nature of personality disorder categoric or dimensional? *Curr Psychiatry Rep* **2**: 49–50.

Cahill L (2005). His brain, her brain. *Scientific American* **292**(5): 40–47.

Campanella S, Vanhoolandt ME, Philippot P (2005). Emotional deficit in subjects with psychopathic tendencies as assessed by the Minnesota Multiphasic Personality Inventory-2: an event-related potentials study. *Neurosci Lett* **373**: 26–31.

Caspi A, McClay J, Moffitt TE, Mill J, Martin J, Craig IW *et al* (2002). Role of genotype in the cycle of violence in maltreated children. *Science* **297**: 851–854.

Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H *et al* (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science* **301**: 386–389.

Cohen RA, Grieve SM, Hoth K, Paul RH, Sweet L, Tate D *et al* (2006). Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biol Psychiatry* **59**: 975–982.

Costa PT, McCrae RR (1992). Normal personality assessment in clinical practice: The NEO Personality Inventory. *Psychol Assess* **4**: 5–13.

Dabbs JM, Carr TS, Frady RL, Riad JK (1995). Testosterone, crime, and misbehavior among 692 male prison inmates. *Pers Individ Dif* **18**: 627–633.

Deckert J, Catalano M, Syagailo YV, Bosi M, Okladnova O, Di Bella D et al (1999). Excess of high activity monoamine oxidase A gene promoter alleles in female patients with panic disorder. *Hum Mol Genet* **8**: 621–624.

Eisenberger N, Way B, Taylor S, Welch W, Lieberman M (2007). Understanding genetic risk for aggression: clues from the brain's response to social exclusion. *Biol Psychiatry* **61**: 1100–1108.

Eley TC, Tahir E, Angleitner A, Harriss K, McClay J, Plomin R et al (2003). Association analysis of MAOA and COMT with neuroticism assessed by peers. *Am J Med Genet B Neuropsychiatr Genet* **120**: 90–96.

Foley DL, Eaves LJ, Wormley B, Silberg JL, Maes HH, Kuhn J et al (2004). Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. *Arch Gen Psychiatry* **61**: 738–744.

Gatt JM, Clark CR, Kemp AH, Liddell BJ, Dobson-Stone C, Kuan SA et al (2007). A genotype-endophenotype-phenotype path model of depressed mood: integrating cognitive and emotional markers. *J Integr Neurosci* **6**: 75–104.

Gilbert DG, Gilbert BO, Johnson S, McColloch MA (1991). Electrocortical and electrodermal activity differences between aggressive adolescents and controls. *J Soc Behav Pers* **6**: 403–410.

Gordon E (2003). Integrative neuroscience. *Neuropsychopharmacology* **28**: S2–S8.

Gordon E, Cooper N, Rennie C, Hermens D, Williams LM (2005). Integrative neuroscience: the role of a standardized database. *Clin EEG Neurosci* **36**: 64–75.

Gottesman II, Gould TD (2003). The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* **160**: 636–645.

Gundlah C, Lu NZ, Bethea CL (2002). Ovarian steroid regulation of monoamine oxidase-A and -B mRNAs in the macaque dorsal raphe and hypothalamic nuclei. *Psychopharmacology* **160**: 271–282.

Gur RC, Sara R, Hagendoorn M, Marom O, Hughett P, Macy L et al (2002). A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *J Neurosci Methods* **115**: 137–143.

Haden SC, Srarpa A (2007). The noradrenergic system and its involvement in aggressive behaviours. *Aggress Violent Behav* **12**: 1–15.

Haller J, Makara GB, Kruk MR (1998). Catecholaminergic involvement in the control of aggression: hormones, the peripheral sympathetic, and central noradrenergic systems. *Neurosci Biobehav Rev* **22**: 85–97.

Hickie I, Hadzi-Pavlovic D, Scott E, Davenport T, Koschera A, Naismith S (1998). SPHERE: a national depression project. *Australas Psychiatry* **6**: 248–250.

Holmes SE, Slaughter JR, Kashani J (2001). Risk factors in childhood that lead to the development of conduct disorder and antisocial personality disorder. *Child Psychiatry Hum Dev* **31**: 183–193.

Hoth KF, Paul RH, Williams LM, Dobson-Stone C, Todd E, Schofield PR et al (2006). Associations between the COMT Val/Met polymorphism, early life stress and personality among healthy adults. *Neuropsychiatr Dis Treat* **2**: 219–225.

Howard R, McCullagh P (2007). Neuroaffective processing in criminal psychopaths: brain event-related potentials reveal task-specific anomalies. *J Personal Disord* **21**: 322–339.

Huang YY, Cate SP, Battistuzzi C, Oquendo MA, Brent D, Mann JJ (2004). An association between a functional polymorphism in the monoamine oxidase a gene promoter, impulsive traits and early abuse experiences. *Neuropsychopharmacology* **29**: 1498–1505.

Ishikawa SS, Raine A (2002). Psychophysiological correlates of antisocial behavior: a central control hypothesis. In: Glicksohn J (ed). *The Neurobiology of Criminal Behavior.* Kluwer Academic Publishers: Norwell, pp 187–229.

Kiehl KA, Hare RD, McDonald JJ, Brink J (1999). Semantic and affective processing in psychopaths: an event-related potential (ERP) study. *Psychophysiology* **36**: 765–774.

Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW et al (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: new evidence and meta-analysis. *Mol Psychiatry* **11**: 903–912.

Lange K, Williams LM, Young AW, Bullmore ET, Brammer MJ, Williams SCR et al (2003). Task instructions modulate neural responses to fearful facial expressions. *Biol Psychiatry* **53**: 226–232.

Lee B-T, Ham B-J (2008). Monoamine oxidase A-uVNTR genotype affects limbic brain activity in response to affective facial stimuli. *Neuroreport* **19**: 515–519.

Luthringer R, Dago KT, Patat A, Caille P, Curet O, Durieu G et al (1996). Pharmacoelectroencephalographic profile of befloxatone, a new reversible MAO-A inhibitor, in healthy subjects. *Neuropsychobiology* **34**: 98–105.

Manuck SB, Flory JD, Ferrell RE, Mann JJ, Muldoon MF (2000). A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsivity. *Psychiatry Res* **95**: 9–23.

McFarlane A, Clark CR, Bryant RA, Williams LM, Niaura R, Paul RH et al (2005). The impact of early life stress on psychophysiological, personality and behavioral measures in 740 non-clinical subjects. *J Integr Neurosci* **4**: 27–40.

Meyer-Lindenberg A, Buckholtz JW, Kolachana B, Hariri AR, Pezawas L, Blasi G et al (2006). Neural mechanisms of genetic risk for impulsivity and violence in humans. *Proc Natl Acad Sci USA* **103**: 6269–6274.

Miles J, Shevlin M (2001). *Applying Regression and Correlation: A guide for Students and Researchers.* Sage: York, UK.

Miller JD, Bagby M, Pilkonis PA, Reynolds SK, Lynam DR (2005). A simplified technique for scoring the DSM-IV personality disorders with the Five-Factor Model. *Assessment* **12**: 404–415.

Miller JD, Lynam DR, Widiger TA, Leukefeld C (2001). Personality disorders as extreme variants of common personality dimensions: can the Five-Factor Model adequately represent psychopathy? *J Pers* **69**: 253–276.

Munro GES, Dywan J, Harris GT, Mokee S, Unsal A, Segalowitz SJ. (2007). ERN varies with degree of psychopathy in an emotion discrimination task *Biol. Psychiatry* **76**: 31–42.

Nichols TE, Holmes AP (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* **15**: 1–25.

Nilsson KW, Sjoberg RL, Damberg M, Leppert J, Ohrvik J, Alm PO et al (2006). Role of monoamine oxidase a genotype and psychosocial factors in male adolescent criminal activity. *Biol Psychiatry* **59**: 121–127.

Nilsson KW, Wargelius H-L, Sjoberg RL, Leppert J, Oreland L (2008). The MAO-A gene, platelet MAO-B activity and psychosocial environment in adolescent female alcohol-related problem behavior. *Drug Alcohol Depend* **93**: 51–62.

Pascual-Marqui RD (1999). Review of methods for solving the EEG inverse problem. *Int J Bioelectromagn* **1**: 75–86.

Pascual-Marqui RD, Esslen M, Kochi K, Lehmann D (2002). Functional imaging with low resolution brain electromagnetic tomography (LORETA): a review. *Methods Find Exp Clin Pharmacol* **24C**: 91–95.

Passamonti L, Cerasa A, Gioia MC, Magariello A, Muglia M, Quattrone A et al (2008). Genetically dependent modulation of serotonergic inactivation in the human prefrontal cortex. *Neuroimage* **40**: 1264–1273.

Paul RH, Lawrence J, Williams LM, Clark CR, Cooper N, Gordon E (2005). The validity of 'IntegNeuro': a new computerized and standardized battery of neurocognitive tests. *Int J Neurosci* 115: 1549–1567.

Raine A, Venables PH, Williams M (1990). Relationships between N1, P300 and CNV recorded at age 15 and criminal behavior at age 24. *Psychophysiology* 27: 567–575.

Rennie CJ, Robinson PA, Wright JJ (2002). Unified neurophysical model of EEG spectra and evoked potentials. *Biol Cybern* 86: 457–471.

Sabol SZ, Hu S, Hamer D (1998). A functional polymorphism in the monoamine oxidase A gene promoter. *Hum Genet* 103: 273–279.

Samochowiec J, Hajduk A, Samochowiec A, Horodnicki J, Stepien G, Grzywacz A et al (2004). Association studies of MAO-A, COMT, and 5-HTT genes polymorphisms in patients with anxiety disorders of the phobic spectrum. *Psychiatry Res* 128: 21–26.

Scarpa A, Raine A (1997). Psychophysiology of anger and violent behavior. *Psychiatr Clin North Am* 20: 375–394.

Scerbo AS, Kolko DJ (1994). Salivary testosterone and cortisol in disruptive children: relationship to aggressive, hyperactive, and internalizing behaviors. *J Am Acad Child Adolesc Psychiatry* 33: 1174–1184.

Sjöberg RL, Ducci F, Barr CS, Newman TK, Dell'osso L, Virkkunen M et al (2007). A non-additive interaction of a functional MAO-A VNTR and testosterone predicts antisocial behavior. *Neuropsychopharmacology* print copy in press (originally published online Apr. 11, 2007, at http://dx.doi.org/10.1038/sj.npp.1301417).

Soderstrom H, Blennow K, Sjodin A-K, Forsman A (2003). New evidence for an association between the CSF HVA:5-HIAA ratio and psychopathic traits. *J Neurol Neurosurg Psychiatry* 74: 918–921.

Taylor A, Kim-Cohen J (2007). Meta-analysis of gene-environment interactions in developmental psychopathology. *Dev Psychopathol* 19: 1029–1037.

Tochigi M, Otowa T, Hibino H, Kato C, Otani T, Umekage T et al (2006). Combined analysis of association between personality traits and three functional polymorphisms in the tyrosine hydroxylase, monoamine oxidase A, and catechol-O-methyltransferase genes. *Neurosci Res* 54: 180–185.

Turetsky BI, Fein G (2002). a2-Noradrenergic effects on ERP and behavioral indices of auditory information processing. *Psychophysiology* 39: 147–157.

Vuilleumier P, Pourtois G (2006). Distributed and interactive brain mechanisms during emotion face perception: evidence from functional neuroimaging. *Neuropsychologia* 45: 174–194.

Weyler W, Hsu YP, Breakefield XO (1990). Biochemistry and genetics of monoamine oxidase. *Pharmacol Ther* 47: 391–417.

Williams LM, Gatt JM, Hatch A, Palmer DM, Nagy M, Rennie C et al (2008). The INTEGRATE model of emotion, thinking and self regulation: an application to the 'Paradox of Aging'. *J Integr Neurosci* (in press, Sept. volume) 7: 367–404.

Williams LM, Gordon E (2007). Dynamic organization of the emotional brain: responsivity, stability, and instability. *Neuroscientist* 13: 349–370.

Williams LM, Kemp AH, Felmingham K, Liddell B, Palmer D, Bryant RA (2007). The negativity bias to covert and overt signals of fear: impact of anxiety and depressed mood. *J Cogn Neurosci* 19: 1595–1608.

Williams LM, Liddell BJ, Rathjen J, Brown KJ, Gray J, Phillips M et al (2004). Mapping the time course of nonconscious and conscious perception of fear: an integration of central and peripheral measures. *Hum Brain Mapp* 21: 64–74.

Williams LM, Palmer D, Liddell BJ, Song L, Gordon E (2006). The 'when' and 'where' of perceiving signals of threat versus non-threat. *Neuroimage* 31: 458–467.

Woo JM, Yoon KS, Choi YH, Oh KS, Lee YS, Yu BH (2004). The association between panic disorder and the L/L genotype of catechol-O-methyltransferase. *J Psychiatr Res* 38: 365–370.

Woodman DD (1979). Evidence of a permanent imbalance in catecholamine secretion in violent social deviants. *J Psychosom Res* 23: 155–157.

Young DA, Waldo M, Rutledge JH, Freedman R (1996). Heritability of inhibitory gating of the P50 auditory-evoked potential in monozygotic and dizygotic twins. *Neuropsychobiology* 33: 113–117.

Yu YW, Tsai SJ, Hong CJ, Chen TJ, Chen MC, Yang CW (2005). Association study of a monoamine oxidase a gene promoter polymorphism with major depressive disorder and antidepressant response. *Neuropsychopharmacology* 30: 1719–1723.

Zammit S, Jones G, Jones SJ, Norton N, Sanders RD, Milham C et al (2004). Polymorphisms in the MAOA, MAOB, and COMT genes and aggressive behavior in schizophrenia. *Am J Med Genet* 128B: 19–20.

Supplementary Information accompanies the paper on the Neuropsychopharmacology website (http://www.nature.com/npp)