Molecular Psychiatry (2007), 1–12

www.nature.com/mp

ORIGINAL ARTICLE

Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality

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Little is known about neural mechanisms underlying human personality and temperament, despite their considerable importance as highly heritable risk mediators for somatic and psychiatric disorders. To identify these circuits, we used a combined genetic and imaging approach focused on Monoamine Oxidase A (MAOA), encoding a key enzyme for monoamine metabolism previously associated with temperament and antisocial behavior. Male carriers of a low-expressing genetic variant exhibited dysregulated amygdala activation and increased functional coupling with ventromedial prefrontal cortex (vmPFC). Stronger coupling predicted increased harm avoidance and decreased reward dependence scores, suggesting that this circuitry mediates a part of the association of MAOA with these traits. We utilized path analysis to parse the effective connectivity within this system, and provide evidence that vmPFC regulates amygdala indirectly by influencing rostral cingulate cortex function. Our data implicate a neural circuit for variation in human personality under genetic control, provide an anatomically consistent mechanism for vmPFC–amygdala interactions underlying this variation, and suggest a role for vmPFC as a superordinate regulatory area for emotional arousal and social behavior.
Molecular Psychiatry advance online publication, 22 May 2007; doi:10.1038/sj.mp.4002020

Keywords: fMRI; antisocial; functional connectivity; effective connectivity; amygdala; cingulate; emotion regulation

Introduction

Personality traits are stable stimulus–response patterns that characterize individual behavior. Epidemiological research shows that personality affects stress resilience, psychosocial adaptation and risk for mental and physical disease.[1–4] Considerable interest has therefore been directed at uncovering the biological basis of personality. Cloninger proposed an influential operationalization of personality, a tripartite model based hypothetically on neurotransmitter neurobiology with three basic stimulus–response characteristics: Novelty Seeking, Harm Avoidance and Reward Dependence, measured by the Tridimensional Personality Questionnaire (TPQ) and thought to be related to dopaminergic, serotonergic and noradrenergic neurotransmission, respectively.[5] Other models of personality, such as the Five Factor Model or Eysenck's Extraversion and Neuroticism dimensions, have different theoretical underpinnings but have been shown to access very similar aspects of human behavior.[6]

Neuropsychological and psychopharmacological studies have contributed to our understanding of the neural basis of personality and this work continues apace with new tools. Two recent avenues of inquiry have revealed promising results; first, functional neuroimaging has been used to correlate brain activation during behaviorally relevant tasks with personality scores across individuals. This work has highlighted regions within the limbic system, particularly the amygdala, dorsal anterior cingulate, insula and orbitofrontal cortex.[7–9] A second approach involves assessing the impact of genetic variation on personality measures. The validity of this approach is

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Received 31 October 2006; revised 23 February 2007; accepted 3 April 2007

bolstered by evidence that the majority of personality traits appear to be moderately to highly heritable, with only minor influences of individual environment in twins reared apart.[10,11]

Following the Cloninger model, much of this work has focused on candidate genes affecting monoaminergic neurotransmission and their prediction of variation in temperament ratings on instruments such as the TPQ. However, even for the most widely studied such gene, a promoter variant in the serotonin transporter (5-HTTLPR), a consistent picture has not emerged.[6,12] One likely reason for small effect sizes on the level of behavior is that genetic variation must be mediated by functional alterations on the neural systems level.[13] This suggests that progress can be made by combining these two strategies through studying the impact of genetic variation linked to personality on human brain structure and function.[14]

In the present paper we pursue this approach, focusing on genetic variation in the X-linked Monoamine Oxidase A (*MAOA*) gene (MIM 309850), comprised of 15 exons and located on chromosome Xp11.23,[15] that encodes MAOA. Catabolism by MAOA is the primary enzymatic degradation route for synaptic serotonin and norepinephrine during neurodevelopment,[16] with murine MAOA knockouts demonstrating strongly increased concentrations of both and concomitant decreases in their metabolites.[17] A relatively common functional genetic variant within the MAOA gene region has been identified.[18] Sabol *et al*.[18] described a variable-number tandem repeat (VNTR) polymorphism of 30 bp located in the upstream promoter region (MAOA u-VNTR) that impacted upon transcriptional efficiency in transfected cell lines; the presence of 3.5 or 4 repeat elements was associated with relatively higher MAOA expression (MAOA-H), while the presence 3 or 5 repeats resulted in relatively lower expression (MAOA-L).

According to Cloninger's model, variation in MAOA would be predicted to impact harm avoidance and reward dependence, by virtue of its effect on serotonin and norepinephrine, respectively. Significant effort has been directed at detecting an influence of MAOA on individual differences in temperament. However, clinical associations of the MAOA u-VNTR with personality traits and cerbrospinal fluid monoamine metabolite levels are mixed, with heterogeneity in the personality measures used and inconsistent directionality of effects making interpretation difficult.[19–30] A more consistent picture has emerged showing the relevance of MAOA genetic variation to a complex behavior, impulsive violence. In a large longitudinal study of at-risk children, Caspi *et al*.[31] found evidence for a gene–environment interaction, whereby childhood abuse predicted later life antisocial behavior in men hemizygous for the MAOA-L allele. Several independent replications[32,33] and a positive meta-analysis[19] support this finding, although some groups have reported negative results.[20,21]

Building on these findings, recent work has endeavored to discover the neural pathways by which MAOA variation exerts its effects on temperament and behavior by examining its influence on brain activity and structure in healthy individuals. To date, three studies have found evidence for an impact of the MAOA u-VNTR on brain function during tasks that index inhibitory control. Fan *et al*.[22,23] found decreased dorsal cingulate activation during conflict resolution in MAOA-L subjects, and Passamonti *et al*.[24] showed diminished ventrolateral prefrontal engagement during response inhibition in these individuals. A recent investigation of the effect of this genetic variant on brain structure and function in a large sample of healthy volunteers found a pronounced impact on amygdala and perigenual cingulate cortex, as well as gender-dimorphic (males only) effects on limbic circuitry for emotional arousal, memory and cognitive control, including orbitofrontal cortex and dorsal anterior cingulate.[25] Here, we build on this previous work by examining functional and effective connectivity within this circuitry and its relation to individual differences in temperament. Since the MAOA u-VNTR affected structure and function in key brain regions implicated in emotion regulation and social cognition, we utilized this genetic variant to pursue a combined imaging genetics/trait-association approach to identify neural systems mediating personality traits in humans.

Based on previous work,[25–27] we focused on regions functionally interacting with amygdala. We identified ventromedial prefrontal cortex (vmPFC), a region strongly implicated in higher-order cognitive functions related to social behavior, theory of mind, and empathy,[28] as an area where coupling with amygdala was significantly affected by MAOA genotype in gender-specific fashion; the strength of this coupling predicted TPQ harm avoidance and reward dependence traits in males. Using path analysis, we show that this effect of vmPFC on amygdala may be mediated through supragenual cingulate cortex, and that this neural circuit links genetic variation in MAOA to temperament scores. Thus, these findings converge on the amygdala-cingulate circuitry highlighted in a study of another serotonergic gene variant, the 5-HTTLPR.[27] In that study, we found that the 5-HTTLPR short allele was associated with decreased cingulate gray matter volume and diminished regulation of amygdala by cingulate; the strength of that regulation was tightly linked to TPQ Harm Avoidance scores. Our findings suggest that vmPFC is a superordinate region for emotional regulation that biases an amygdala-perigenual cingulate mood circuit contributing to the neural basis of human temperament.

Materials and methods

Subjects

Subjects were culled from a larger sample after careful screening to ensure they were free of any lifetime

history of psychiatric or neurological illness, psychiatric treatment, or drug or alcohol abuse.[29] Previous results from this ongoing study have been reported in subjects that partially overlap with the group reported here.[25] We used all available subjects meeting clinical inclusion criteria who possessed both functional Magnetic Resonance Imagimg (fMRI) and personality questionnaire data. Of the 142 subjects examined for a previous study of the impact of MAOA genotype on cognitive and emotional regulation, TPQ scores were obtained for 123 individuals. Only Caucasians of European ancestry were studied to avoid stratification artifacts. Subject demographics are shown in Table 1. Sex distribution differed significantly among genotypes in our original fMRI cohort of 142 subjects, which did not influence the analyses, because the genetic situation mandated that main effects and interactions with sex were explicitly included into the statistical model. A slight age difference in the group studied in fMRI was addressed by adding age as a covariate in all analyses. Subjects gave written informed consent and participated in the study according to the guidelines of the National Institute of Mental Health Institutional Review Board.

DNA collection

Our genotyping methods for MAOA and Catechol-O-Methyltransferase (COMT) have been described in detail previously.[25,29] Briefly, we used standard methods to extract DNA from white blood cells with the Puregene DNA purification kit (Gentra Systems, Minneapolis, MN, USA). The 30-bp MAOA VNTR polymorphism was amplified in an Applied Biosystems (Foster City, CA, USA) 9700 thermal cycler by polymerase chain reaction using the primer sequence of Sabol *et al*.[18] The VNTR alleles consist of 3 repeats (209 bp), 3.5 repeats (227 bp), 4 repeats (239 bp) and 5 repeats (269 bp). We did not include in our analysis two individuals who possessed two repeats. Based on previous reports, we dichotomized subjects into high- and low-expression groups on the basis of their repeat number. Individuals possessing 3 or 5 repeats were assigned to the 'low' group (MAOA-L) and those possessing 3.5 and 4 repeats were assigned to the 'high' group (MAOA-H). Genomic control panels were performed to investigate occult genetic stratification between *MAOA* genotype groups: the sample was genotyped with a panel of 100 unlinked single nucleotide polymorphism (SNP) loci (available upon request) to survey for occult genetic stratification and showed no significant differences in frequency at any of these SNPs (omnibus χ^2 (d.f. 200) = 172.5, $P = 0.92$),[30] and, in particular, did not differ in the distribution of *5-HTTLPR* variants of the serotonin transporter – a gene linked previously to structural and functional variation within some of the brain regions studied herein. For our vmPFC–amygdala functional connectivity 'control' experiment using the COMT val158met polymorphism, we used 26 val/val, 63 val/met and 28 met/met subjects from the studied sample that were matched for age and gender across genotypes.

Face matching task

The face-matching task is a simple perceptual task previously described to robustly engage the amygdala.[34] During two blocks of this task, subjects viewed a trio of emotional facial expressions, selecting one of the two faces (bottom) that was identical to the target face (top). Per block, six images were presented sequentially for 5 s, three of each sex and target affect (angry or fearful) derived from a standard set of pictures of facial affect. Emotion blocks alternated with three blocks of a sensorimotor control task, where faces were replaced with simple geometric shapes.

Functional image processing

Blood oxygen level-dependent (BOLD) fMRI was performed on a General Electric Signa 3T (Milwau-

Table 1 Demographics

Group	*MAOA genotype*		*Total*	P-*value*
	Low-activity	*High-activity*		
TPQ				
N	49	74	123	—
Sex (male/female)	18/31	42/32	60/63	0.04[a]
Age	26.89 ± 0.8725	30.77 ± 1.018	29.23 ± 0.7222	0.01
IQ	105.38 ± 1.3882	107.24 ± 1.1344	106.49 ± 0.8787	0.30
Task accuracy, %	99.48 ± 0.2941	98.81 ± 0.4251	99.08 ± 0.2798	0.24
Reaction time, ms	1434.67 ± 54.0163	1491.87 ± 39.7153	1468.61 ± 32.1768	0.39
Harm Avoidance	9.84 ± 0.6982	8.52 ± 0.5494	9.05 ± 0.4340	0.14
Novelty Seeking	16.22 ± 0.6146	15.08 ± 0.4983	15.54 ± 0.3888	0.15
Reward Dependence	19.71 ± 0.4792	19.84 ± 0.4202	19.79 ± 0.3153	0.85

Abbreviations: IQ, intelligence quotient; MAOA, Monoamine Oxidase A; TPQ1, Tridimensional Personality Questionnaire. Mean ± s.e.m.

[a]Result from χ^2 analysis; all other *P*-values obtained from one-way ANOVAs.

kee, WI, USA) by using gradient echo, echo-planar imaging (EPI) (24 axial slices; 4-mm thickness; 1-mm gap; TR = 2000, TE = 28 ms; FOV, 24 cm; matrix, 64_64). Images were processed as described previously[25] using SPM99 (www.fil.ion.ucl.ac.uk/spm). Briefly, images were realigned to the first image of the scan run, spatially normalized into a standard stereotactic space (Montreal Neurological Institute (MNI) template) by using affine and nonlinear ($4 \times 5 \times 4$ basis functions) transformations, smoothed with an 8-mm full-width half-maximum (FWHM) Gaussian filter and ratio normalized to the whole-brain global mean. A statistical image for the contrast of the emotion task versus the sensorimotor control was then obtained for each subject and analyzed in a second-level random effects model (analysis of variance (ANOVA) and one-tailed *t*-test) to identify significant activations within and between genotype groups. Both main effects and interactions with sex were considered in the ANOVA. Age was included as a nuisance covariate.

Functional connectivity analyses

Our methods to measure what we refer to as 'functional connectivity' have been described.[27,35] This technique examines the covariation across the brain with activation in a region (volume) of interest. Functional connectivity is correlational in nature; therefore, it should not be assumed to reflect anatomical connections or a causal link. After mean and drift correction of the time series, median activity within this region of interest (ROI) was calculated (we prefer median as a robust estimator that coincides with the mean under the assumption of normality) for each scan and then correlated across the brain with all voxel time series, resulting in a map that contained, in each voxel, the correlation coefficient of the time series in this voxel with that of the reference regions. These maps, one per subject, were then analyzed in a random effects model in SPM identical to the one described in the previous paragraph. According to our hypothesis, the seed was placed in bilateral amygdala and correlations were studied in the corticolimbic circuit for amygdala regulation defined in our previous two studies.[25,27] The significance threshold was set to $P < 0.05$, corrected for multiple comparisons within ROI defined by using the Wake Forest University PICKATLAS (www.fmri.wfubmc.edu) as described previously.[27] In addition, we report whole-brain significant findings ($P < 0.05$), corrected for multiple comparisons at the cluster ($t > 2.5$) or voxel level.

Further connectivity and path analyses

Since we identified a genetic effect on vmPFC–amygdala connectivity, we conducted further analysis to characterize the underlying functional architecture of this relationship. Given the strong evidence that vmPFC is not directly anatomically connected to amygdala,[36–38] we first identified regions that might mediate this effect by using amygdala–vmPFC connectivity as a covariate in a second-level random effects analysis of brain activation during the fMRI task (methodological and statistical procedures as above). This approach highlighted perigenual cingulate (see Results). Since strong anatomical, physiological and previous imaging evidence shows a direct inhibitory connection between amygdala and this cingulate region[27,36,37,39,40] and anatomical connections between it and vmPFC are also well established,[41] we hypothesized that the observed vmPFC–amygdala connectivity was mediated through perigenual cingulate.

To test this hypothesis, we used path analysis. Our methods for model fitting, selection and evaluation have been described previously.[42] Briefly, models were fitted from eigenvariates[43] using the software package Mx (http://www.vcu.edu/mx/). Activity from vmPFC, perigenual cingulate and bilateral amygdala was extracted from anatomical masks for all male participants. Residual variance was computed from imaging data as described by Bullmore *et al*.[43] Degrees of freedom were estimated from the crosscorrelation function of the eigenvariates assuming an AR(1) model following Kruggel *et al*.[44] We modelled bidirectional interactions between vmPFC and perigenual cingulate, as well as directed paths from both cortical regions to amygdala. Significance of model fit was ascertained by χ^2 test (required to be > 0.05, indicating nonrejection of the null hypothesis that the correlation structure predicted by the model fit the observations), and model parsimony was measured using Akaike's information criterion (AIC). Significance of paths was ascertained by bootstrapping confidence intervals.

Statistical inference: fMRI-personality correlations

Since our analysis identified vmPFC (BA 10) as a region where connectivity with amygdala is influenced by genotype, we examined the hypothesis that this coupling mediates individual variation in personality traits by extracting the average correlation between amygdala and this region for each subject and correlating these parameters (two-tailed, bivariate correlation) with subjects' TPQ scores using SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, USA). For both personality scales, we set α equal to 0.01 to achieve strong control for Type-I error. To minimize the number of statistical tests, we only examined correlations with full-scale scores for TPQ.

Mediation analyses

Finally, we used path analysis to test our hypothesis that vmPFC–amygdala connectivity mediates the relationship between MAOA genotype and personality. Models were fitted from the parameter estimates for vmPFC–amygdala functional connectivity and raw TPQ scores. We modelled mediated (indirect path from MAOA genotype to trait score through vmPFC–amygdala functional connectivity value) and unmediated (direct path from MAOA genotype to trait score) relationships between MAOA and personality.

Significance of model fit was ascertained by χ^2 test (required to be >0.05, indicating nonrejection of the null hypothesis that the correlation structure predicted by the model fit the observations), and model parsimony was measured using AIC. Comparison of mediated and unmediated models was accomplished by contrasting Bollen's relative fit index (RFI) scores. Significance of paths was ascertained by bootstrapping confidence intervals.

Results

Functional connectivity

MAOA genotype predicted the degree of functional coupling between the amygdala and vmPFC (BA 10), such that MAOA-L subjects demonstrated increa sed connectivity between amygdala and this area ($P<0.05$, corrected for multiple comparisons) (Table 2, Figure 1a and b). The sign of the parameter estimates for this connectivity analysis was negative. This may signify a reciprocal relationship between activation in these two regions suggestive of a regulatory influence (vide infra for evidence in direct support of this). However, the key feature of our connectivity analysis is its ability to determine how much variance in one region is explained by another, while the sign is relevant but secondary. *Post hoc* analysis of extracted correlation coefficients by ANOVA revealed a significant genotype-by-gender interaction: ($F(1,119)=9.78$, $P<0.002$). Sex-specific *post hoc* analysis by independent sample *t*-test with MAOA genotype as a grouping variable confirmed that genotype-dependent connectivity differences were significant in men only ($P<0.008$ versus $P<0.646$ in women).

To test whether altered vmPFC–amygdala functional connectivity was affected by genetic variation in other monoaminergic systems, or could be related more specifically to neural physiology linked to MAOA (such as serotonergic neurotransmission), we examined the impact of a well-characterized functional allelic variant affecting the enzymatic efficiency of another monoamine degrading enzyme (COMT) on the functional coupling of these two regions. ANOVA revealed no difference in vmPFC–amygdala functional coupling between COMT val158-met genotypes ($F(1,116)=0.553$, $P>0.6$).

Since direct anatomical connections between vmPFC and amygdala are very sparse,[36–38,41,45] we conducted an additional analysis to characterize the functional architecture underlying our finding of increased vmPFC–amygdala connectivity in MAOA-L subjects. Using the amygdala–vmPFC connectivity parameter estimates as a covariate in a second-level random effects analysis of brain activation during the fMRI task, we found that perigenual cingulate (BA32) activity was significantly ($P<0.05$, corrected for multiple comparisons) correlated with the degree of functional linkage between vmPFC and amygdala (Table 2, Figure 2), suggesting that this area might mediate the observed interaction between vmPFC and amygdala. We then tested this hypothesis using path analysis.

Path analysis

A path model with bidirectional interactions between vmPFC and perigenual cingulate and directional interactions from both vmPFC and cingulate to amygdala fit the observed data well (χ^2 $P=0.43$, AIC -3.29) (Figure 3a). Bootstrapping analysis of individual paths demonstrated significant positive interactions between vmPFC and cingulate and a significant negative path from cingulate to amygdala. In contrast, the path from vmPFC to amygdala was close to zero (0.03) and nonsignificantly different from zero (95% CI, -0.64 to 0.69). This suggested that direct interactions between vmPFC and amygdala did not contribute to the observed functional interactions and that the observed correlation between vmPFC and amygdala was entirely mediated through an effect of vmPFC on cingulate. To verify this conclusion, a second model was tested where the path from vmPFC to amygdala was deleted (Figure 3b). This model did not worsen the fit ($P=0.61$, AIC -5.29) and the more parsimonious model was retained (see Supplementary Table 1).

Connectivity and amygdala activation

These findings suggested that the observed alterations in corticolimbic connectivity might impact temperament and behavior by influencing the regulation of amygdala activation. Indeed, we found a significant negative correlation between amygdala–vmPFC connectivity and amygdala activation in male MAOA-L subjects only ($r=-0.542$, $P<0.01$) (Figure 4).

Table 2 Coordinates and significance for imaging findings

Talairach (x, y, z)	*BA/region*	*Z score*	P-*value*	*Cluster size, voxels*
	Functional connectivity: Amygdala seed (high > low)			
4 56 10	10/vmPFC	3.07	0.001	21
	vmPFC–amygdala connectivity: positive correlation with task-related activation (in male MAOA-L's)			
−11 34 21	32/Rostral anterior cingulate	3.46	0.000	174

Abbreviations: MAOA, Monoamine Oxidase A; vmPFC, ventromedial prefrontal cortex.

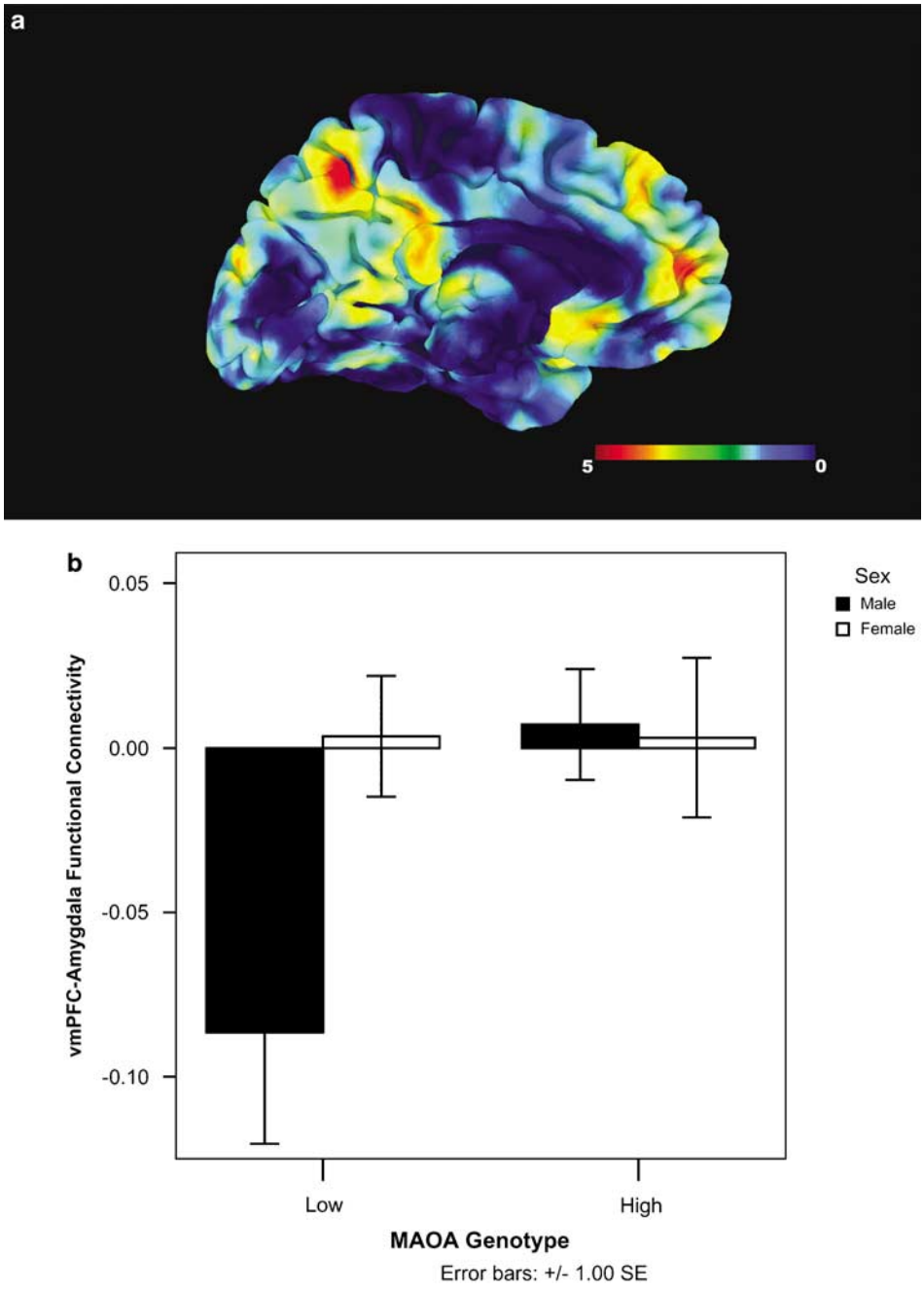

Figure 1 (**a–b**). Statistical parametric map of differential functional connectivity in MAOA-L subjects (MAOA-L > MAOA-H) using bilateral amygdala seed, rendered on single-subject cortical surface (unthresholded image) (**a**). Bar graph demonstrates the influence of MAOA genotype and gender on amygdala–vmPFC connectivity using extracted connectivity parameter estimates (**b**). MAOA, Monoamine Oxidase A; vmPFC, ventromedial prefrontal cortex.

Connectivity and temperament

If these MAOA genotype-dependent changes in limbic reactivity and corticolimbic functional connectivity are relevant for the effect of MAO on personality measures, the parameters of the identified neural circuits should predict trait scores in the study participants. Correlational analysis confirmed this by showing that mPFC–amygdala connectivity predicted TPQ Harm Avoidance ($r = -0.348$, $P < 0.006$ in men; not significant in women) and Reward Dependence ($r = 0.242$, $P < 0.007$; not significant in women) scores. (Figure 5a–b). Thus, MAOA-L-associated functional connectivity was linked to increased Harm Avoidance and decreased Reward Dependence. Effect sizes (Cohen's d) for the correlation of vmPFC–amygdala functional coupling with traits were calculated as 0.37 for Harm Avoidance and 0.25 for Reward Dependence (Table 3).

Test for mediation

Finally, we tested whether the neural circuit properties identified in this study accounted for the linkage between MAOA genotype and personality measures in our data. A path model with directional paths from MAOA genotype to Harm Avoidance and Reward Dependence trait scores and vmPFC–amygdala connectivity, and directional paths from vmPFC–amygdala connectivity to Harm Avoidance and Reward Dependence trait scores fit the observed data (χ^2 $P = 0.29$, AIC 18.436, Bollen's RFI 0.736) (Figure 6a). Bootstrapping analysis of individual paths demonstrated a significant positive path from MAOA genotype to vmPFC–amygdala functional connectivity, a significant positive path from vmPFC–amygdala functional connectivity to Reward Dependence and a

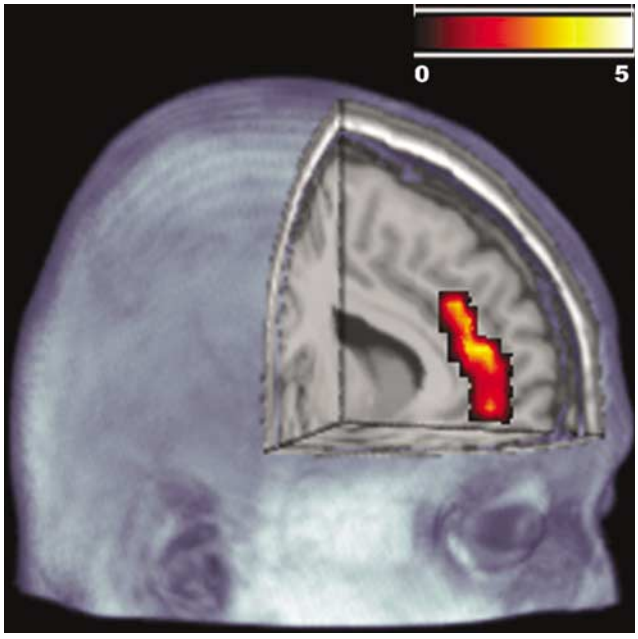

Figure 2 Statistical parametric map depicts regional activation correlated with amygdala–vmPFC functional connectivity ($P < 0.05$, corrected for multiple comparisons in a cingulate ROI). ROI, region of interest; vmPFC, ventromedial prefrontal cortex.

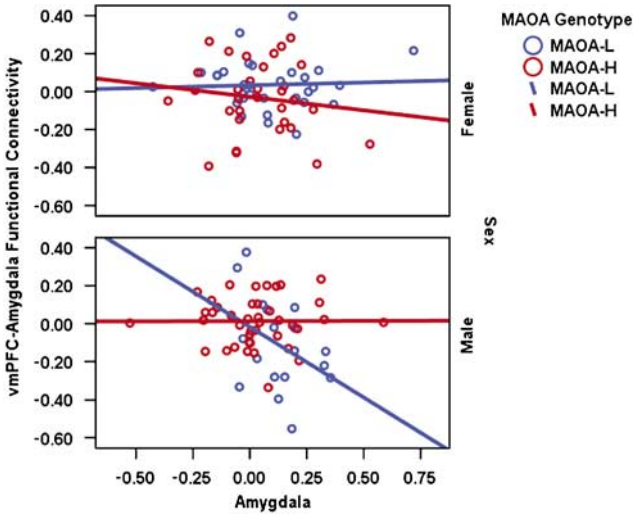

Figure 4 Scatterplot depicts the relationship between amygdala activation and amygdala–vmPFC connectivity in MAOA-L men. MAOA, Monoamine Oxidase A; vmPFC, ventromedial prefrontal cortex.

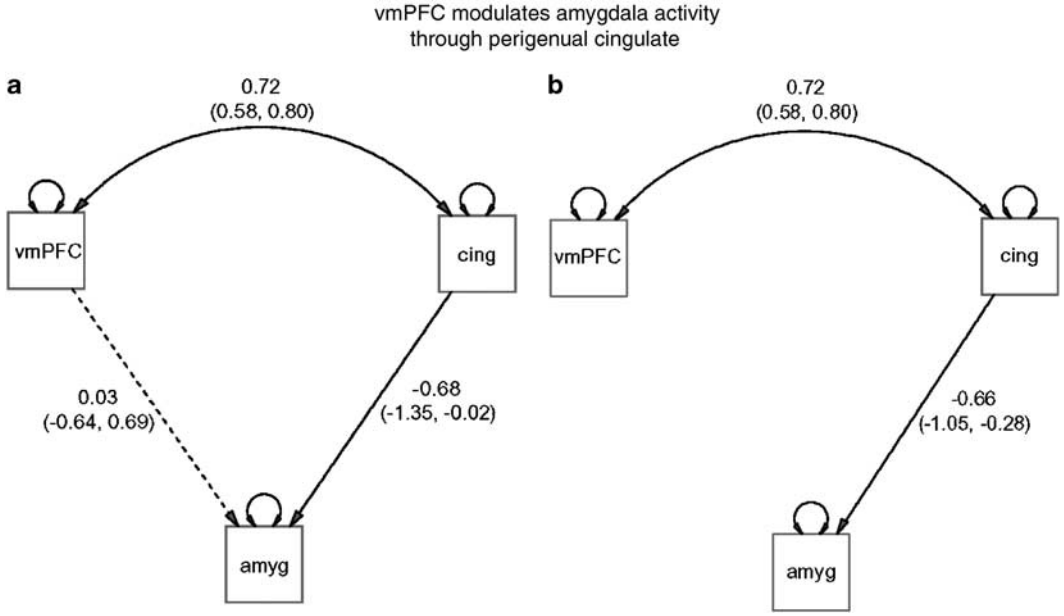

Figure 3 Path analysis of connectivity within a vmPFC-cingulate-amygdala circuit. (**a**) Depicts network with direct (nonsignificant) path from vmPFC to amygdala. (**b**) Depicts network in which vmPFC influences amygdala indirectly via cingulate. VmPFC, ventromedial prefrontal cortex.

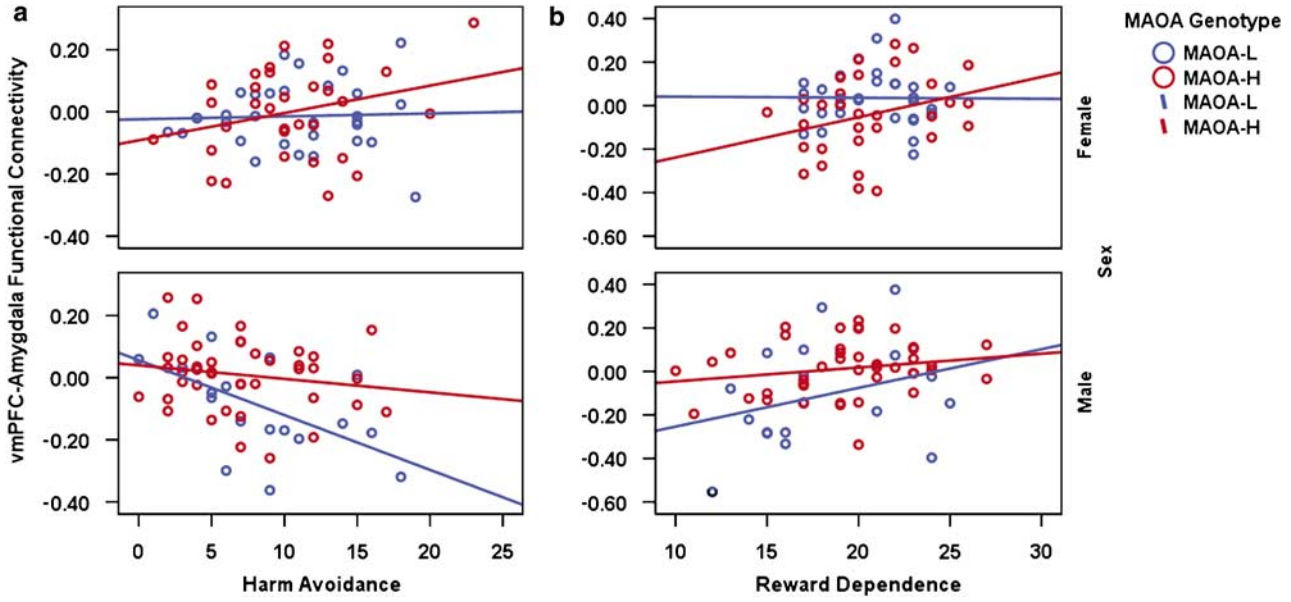

Figure 5 (**a–b**) Scatterplot depicts the relationship between amygdala–vmPFC connectivity and TPQ Harm Avoidance ($r = -0.348$, $P < 0.006$ in men; not significant in women) (**a**) and TPQ Reward Dependence ($r = 0.242$, $P < 0.007$; not significant in women) (**b**) values in MAOA-L men. MAOA, Monoamine Oxidase A; TPQ1, Tridimensional Personality Questionnaire; vmPFC, ventromedial prefrontal cortex.

Table 3 fMRI-trait correlations

Functional connectivity	*Trait*	*Pearson's* r	P-*value*	*Effect size (Cohen's* d)
vmPFC-amygdala	TPQ Harm Avoidance	−0.348	0.006 (men; NS women)	0.37
	TPQ Reward Dependence	0.242	0.007 (NS women)	0.25

Abbreviations: fMRI, functional Magnetic Resonance Imaging; NS, not significant; TPQ, Tridimensional Personality Questionnaire; vmPFC, ventromedial prefrontal cortex.

significant negative path from vmPFC–amygdala functional connectivity to Harm Avoidance. By contrast, the direct paths from MAOA genotype to Harm Avoidance and Reward Dependence were zero and close to zero (0.08), respectively and nonsignificantly different from zero (95% CI, −0.27 to 0.30 and −0.22 to 0.40, respectively). This suggested that the effects of MAOA on temperament in our sample were accounted for by genotype-related variation in vmPFC–amygdala functional connectivity. To verify this conclusion, a second model was tested, where the direct paths from genotype to temperament scores were deleted (Figure 6b). This model did not worsen the fit ($P = 0.57$, AIC 14.9, Bollen's RFI 0.845) and the more parsimonious model was retained.

Discussion

The present data provide evidence for a mediation of individual differences in aspects of human temperament by a corticolimbic circuit, comprised of vmPFC, perigenual anterior cingulate cortex and amygdala. Furthermore, this circuit appears to be under significant genetic control by variation in MAOA, but not by another functional genetic variant in COMT that impacts prefrontal dopamine catabolism, studied as a control. In particular, our findings suggest an anatomically consistent mechanism for the indirect regulation of amygdala function by vmPFC, which has been hypothesized to subserve interindividual variation in emotion regulation and affective style.[46–48] In linking this mechanism to genetic variation in MAOA, our results support a growing body of literature which proposes a key role for the MAOA gene in human trait variation and personality disorder susceptibility,[19,31] and identify neural mechanisms that could underlie these gene-behavior associations. Finally, our findings suggest a strong influence of sex on these effects, consistent with prior research showing a unique neurobiological susceptibility to the impact of the MAOA-L allele in men,[25] as well as the greater prevalence of antisocial behavior in this population.[49]

Our study identified vmPFC (BA 10) as a brain region where functional connectivity with amygdala

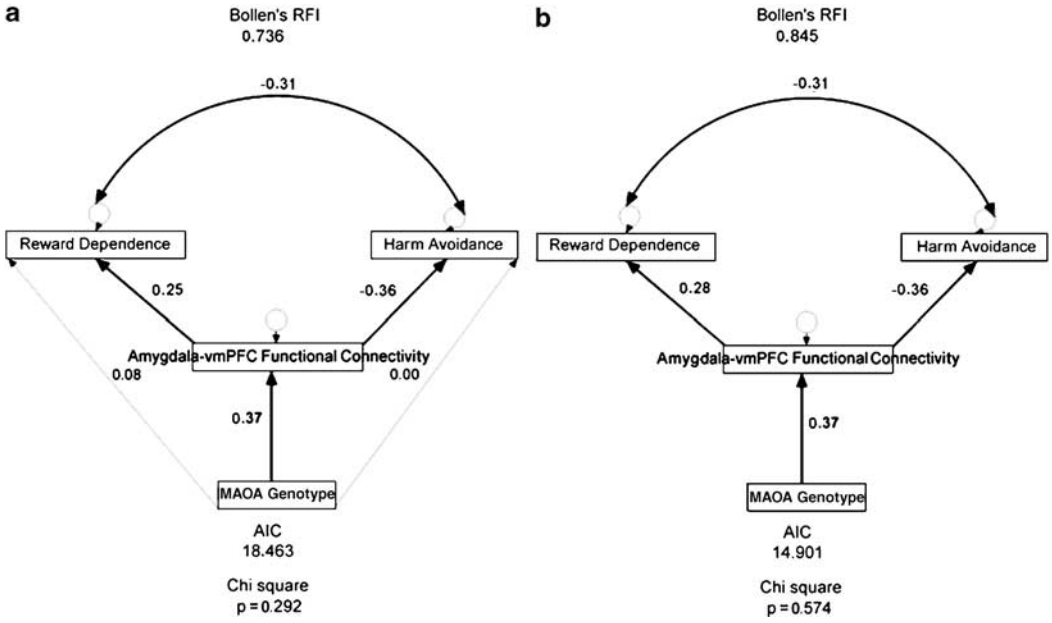

Figure 6 (**a–b**) Path analysis of the relationship between MAOA genotype, amygdala–vmPFC functional connectivity and TPQ trait scores. (**a**) Depicts an unmediated model (direct paths from MAOA genotype to personality scores), while (**b**) depicts a model in which amygdala–vmPFC connectivity mediates the relationship between MAOA genotype and trait scores. MAOA, Monoamine Oxidase A; TPQ1, Tridimensional Personality Questionnaire; vmPFC, ventromedial prefrontal cortex.

was significantly affected by MAOA genotype. A large body of evidence shows a prominent role for this area in social cognitive functions such as theory of mind, empathy, moral reasoning and social decision making.[28,50–52] In addition, vmPFC has been strongly implicated in explicit emotion regulation, particularly when subjects utilize an egocentric strategy.[53] Aberrant serotonin signalling in medial PFC is implicated impulsive decision making,[54] and deleterious changes in reward-based decision making and social behavior, including impulsive violence, are seen following damage to vmPFC in humans.[55–57]

At first glance, the identification of a significant functional linkage between vmPFC and amygdala in the present study seems to be in conflict with the known paucity of connections between amygdala and anterior aspects of the medial prefrontal wall, Brodmann areas 9 and 10,[36–38,41,45] in contrast to the robust reciprocal connectivity between the amygdala and Brodmann areas 24, 25 and 32 (otherwise referred to as rostral anterior cingulate cortex).[27,36–40,58] This anatomical situation makes it likely that vmPFC affects amygdala activity through an intermediary structure. We identified supragenual cingulate cortex – anatomically connected to both vmPFC[38] and amygdala[37] – as a region where activity was significantly related to the degree of vmPFC–amygdala coupling and then analyzed the effective connections of this system using path analysis. Our results recapitulate the known anatomy and indicate that the observed functional data can be accounted for by the input of vmPFC into supragenual cingulate cortex, that in turn does connect directly to the amygdala.

These results suggest the vmPFC exerts its regulatory influence on amygdala indirectly by modulating activity of the supragenual cingulate. The supragenual cingulate is a critical node in an inhibitory feedback loop with amygdala[39,59] that is essential for fear extinction,[40] and has been previously implicated by functional imaging studies of temperament,[27,60,61] affect regulation[53] and mood disorders.[62,63] Taken together, our findings therefore imply a superordinate role for vmPFC as a second-level region for amygdala regulation.

Previous results show that the core cingulate-amygdala regulatory circuit is strongly affected by variation in serotonergic neurotransmission, both in the case of 5-HTTLPR[26,27] and MAOA[25] with genetic variants associated with higher synaptic serotonin predicting increased amygdala reactivity in the context of impaired cingulate regulation. This suggests that the increased functional coupling between vmPFC and amygdala in MAOA-L men observed here could reflect a compensatory response to a primary regulatory deficiency in the core cingulate loop, where vmPFC is engaged as a secondary control mechanism acting through perigenual cingulate (a region where activation is relatively deficient in male carriers of MAO-L[25]). If this regulation is sufficient, as we would suggest is the case in MAOA-H allele individuals, there is no need for vmPFC to come online; hence, there would not be significant coupling between either amygdala or cingulate and vmPFC. However, in the case of MAOA-L hemizygous males, we suspect (based on prior functional and structural evidence in addition to connectivity evidence pre-

sented here) that this primary cingulate-amygdala regulatory circuit is compromised. We argue that only in this instance is vmPFC engaged to provide support to the deficient primary amygdala-anterior cingulate circuit. This is supported by the observed tight correlation between vmPFC–amygdala functional connectivity and amygdala activation in MAOA-L men (where amygdala activation predicts >30% of individual variation in vmPFC–amygdala functional connectivity), suggesting that the magnitude of amygdala dysregulation predicts the degree of vmPFC engagement. If this assumption is correct, increased coupling of vmPFC and amygdala should also be observed in 5-HTTLPR short allele carriers, in whom abnormal neural interactions in the core amygdala-cingulate circuit were found.[27] This is indeed confirmed by the presently available data.[26,27]

Importantly, we found that this indirect effect of vmPFC on amygdala predicted individual differences in human temperament, implicating vmPFC in the neural basis of personality. If the neural system identified through studying the impact of MAOA genetic variation on amygdala interactions is relevant for mediating personality traits associated with this gene, changes in activation and connectivity of this circuit should predict traits associated with the risk allele. This is what we observed, as increased connectivity of vmPFC was associated with higher scores on a measure of sensitivity to threat cues (Harm Avoidance) and lower scores on a measure of sensitivity to cues that elicit and maintain prosocial behavior (Reward Dependence).[64] It is noteworthy that the personality domains affected by MAOA genetic variation (Harm Avoidance, Reward Dependence) correspond, in the Cloninger hypothesis,[5] to those neurotransmitter systems (serotonin, norepinephrine) impacted by MAOA during neurodevelopment.[16] In addition, genetic variation in COMT, previously linked to functional coupling in another neural circuit and associated with TPQ Novelty Seeking,[65] was not linked to functional coupling in the circuit identified here. Taken together, these findings are consistent with Cloninger's predictions regarding the neurochemical underpinnings of TPQ traits: Harm Avoidance (serotonin), Novelty Seeking (dopamine) and Reward Dependence (norepinephrine). MAOA, primarily affecting serotonin and norepinephrine, is associated with Harm Avoidance and Reward Dependence but not Novelty Seeking, and COMT, primarily affecting dopamine, is associated with Novelty Seeking but not Harm Avoidance or Reward Dependence. It should be noted that effect sizes for variation in the identified circuit were small to medium, in accordance with the interpretation that a single genetic variant and the neural circuitry directly impacted by it, while making a significant contribution, do not explain the majority of variance in a complex trait such as personality.[14]

We observed that both genotype effects on vmPFC connectivity and correlations with personality traits were highly gender dimorphic, with carrying an MAOA-L allele affecting mPFC–amygdala connectivity in men only. This is in good agreement with data showing an increased impact of MAOA genetic variation on male behavior and personality traits,[66] but poses the question of the biological mechanism underlying this finding. Since MAOA is an X-chromosomal gene, it is possible that gene dosage differences between men and women due to incomplete X inactivation could underlie the predominant effect on males. However, we observed previously[25] that the effect of the MAOA-L allele on several parameters of neural activation and structure was very similar in both genders, suggesting that different gene dosage is unlikely to be the single underlying cause. This conclusion is strengthened by the finding of a very similar effect on vmPFC predominantly in males as a consequence of genetic variation of 5-HTTLPR, an autosomal gene.[26,27] Further research is necessary to clarify the cellular mechanisms underlying these observations; of note, sex hormone receptors are prominently expressed in amygdala, cingulate and orbitofrontal cortex,[67] where they are able to influence monoamine metabolism by regulating MAOA messenger RNA transcription.[68]

One important aspect of this study is our finding that TPQ-assessed human temperament covaries with connectivity in a critical circuit for emotional arousal and regulation in MAOA-L males. We suggest that elevated serotonin and norepinephrine levels present in these individuals during development may alter the maturation of key nodes within this circuit, consistent with preclinical work linking such changes to elevated anxiety and aberrant social behavior.[69] Thus, MAOA-L status may introduce a less stable developmental framework, reflected in the pattern of connectivity seen here and leading to the promotion of stable stimulus–response biases. This less stable platform for affective response in MAOA-L individuals may render them more susceptible to influence from environmental factors compared with their more robust MAOA-H counterparts.

In summary, we present evidence that vmPFC mediates human personality traits associated with genetic variation in MAOA by influencing amygdala regulation indirectly though interactions with perigenual cingulate cortex. These results extend prior evidence of a mechanism contributing to temperamental risk for impulsive aggression and identify a neural circuit for emotional control in the context of human social behavior and cognition.

Acknowledgments

This work was supported by the NIMH/IRP.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)