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ARTICLE

# Reduced amygdala–prefrontal coupling in major depression: association with MAOA genotype and illness severity

**Udo Dannlowski[1,2], Patricia Ohrmann[1], Carsten Konrad[1,2], Katharina Domschke[1], Jochen Bauer[1], Harald Kugel[3], Christa Hohoff[1], Sonja Schöning[1,2], Anette Kersting[1], Bernhard T. Baune[1,4], Lena S. Mortensen[1], Volker Arolt[1], Pienie Zwitserlood[5], Jürgen Deckert[1,6], Walter Heindel[3] and Thomas Suslow[1]**

[1] *Department of Psychiatry, University of Münster, Germany*
[2] *IZKF-Research Group 4, IZKF Münster, University of Münster, Germany*
[3] *Department of Clinical Radiology, University of Münster, Germany*
[4] *Department of Psychiatry, James Cook University, Townsville, Australia*
[5] *Department of Psychology, University of Münster, Germany*
[6] *Department of Psychiatry, University of Würzburg, Germany*

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**Abstract**

The amygdala plays a pivotal role in a cortico-limbic circuitry implicated in emotion processing and regulation. In the present study, functional connectivity of the amygdala with prefrontal areas involved in emotion regulation was investigated during a facial expression processing task in a sample of 34 depressed inpatients and 31 healthy controls. All patients were genotyped for a common functional variable number tandem repeat (VNTR) polymorphism in the promoter region of the monoamine oxidase A gene (MAOA u-VNTR) which has been previously associated with major depression as well as reduced cortico-limbic connectivity in healthy subjects. In our control group, we observed tight coupling of the amygdala and dorsal prefrontal areas comprising the dorsolateral prefrontal cortex (DLPFC), dorsal parts of the anterior cingulate cortex (dACC), and lateral orbitofrontal cortex. Amygdala–prefrontal connectivity was significantly reduced in depressed patients and carriers of the higher active MAOA risk alleles (MAOA-H). Hence, depressed MAOA-H carriers showed the weakest amygdala–prefrontal coupling of the investigated subgroups. Furthermore, reduced coupling of this circuitry predicted more than 40% variance of clinical variables characterizing a longer and more severe course of disease. We conclude that genetic variation in the MAOA gene may affect the course of major depression by disrupting cortico-limbic connectivity.

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**Key words**: Amygdala, fMRI, genetics, major depression, monoamine oxidase A.

## Introduction

Major depression is regarded as the leading global cause of years of life lived with disability (WHO, 2001) and ranks among the top three health conditions in terms of burden of disease (Evans and Charney, 2003). Converging lines of research suggest that monoaminergic signal transduction plays a crucial role in the aetiology of major depression (Wong and Licinio, 2001). Monoamine oxidase A (MAOA) has an important function in the regulation of monoamine neurotransmitter levels in the brain and furthermore, MAOA inhibitors are effective drugs for the treatment of major depression. In depressed patients, highly increased MAOA levels have been observed in several brain areas including the anterior cingulate and prefrontal cortex (Meyer et al., 2006). The MAOA gene mapping to chromosome Xp11.23 contains a well characterized functional polymorphism, consisting of

Address for correspondence: Prof. Dr. T. Suslow, Department of Psychiatry, University of Münster, Albert-Schweitzer-Str. 11, 48149 Münster, Germany.
*Tel.*: +49-251-8356601 *Fax*: +49-251-8356612
*E-mail*: suslow@uni-muenster.de

a variable number of tandem repeats in the upstream promoter region (u-VNTR), with different length variants that influence the protein transcription and hence the enzymatic activity (Sabol et al., 1998). The higher active alleles (MAOA-H, 3.5 and 4 repeats) seem to play a role in the pathogenesis of emotional disorders including borderline personality disorder (Ni et al., 2007), panic disorder (Deckert et al., 1999), complicated grief (Kersting et al., 2008), major depression (Schulze et al., 2000; Yu et al., 2005), and reduced response to antidepressant treatment (Domschke et al., 2007; Yu et al., 2005), although conflicting findings have been reported (e.g. Brummett et al., 2007). However, association studies suffer from methodological difficulties (Malhotra and Goldman, 1999) and such inconsistencies in association findings with depression could be in part due to the heterogeneity and complexity of the clinically defined phenotype. A strategy to circumvent such methodological problems is the endophenotype approach (Hasler et al., 2004). Hariri et al. (2006) suggested that neurobiological activation patterns during emotion processing represent a more promising target for association studies since this might bridge the gap between genes that are likely to be involved in the pathogenesis of depression and the clinical phenotype with effect sizes 10–20 times larger than in classical association studies.

Neurobiological correlates of emotion processing in major depression have been reviewed by Phillips et al. (2003). They suggested that a ventral system, with the amygdala being the core structure, is responsible for the generation of affective states, whereas a dorsal network comprising the dorsal anterior cingulate cortex (dACC) and the dorsolateral prefrontal cortex (DLPFC) is critically engaged during emotion regulation. They proposed that major depression is characterized by functional impairments in these dorsal prefrontal areas and correspondingly with impaired regulation of negative emotions. In support of this notion, dysfunctional dACC activation during a sad emotion suppression task (Beauregard et al., 2006) as well as abnormal DLPFC activity [corresponding to Brodmann's area (BA) 9 and BA 46; Siegle et al., 2002, 2007] have been reported in depressed patients. Utilizing a different approach, recent studies investigated the functional integration of the amygdala–prefrontal emotion regulation network by means of functional connectivity analyses. It was reported that the tight prefrontal-limbic connectivity during emotion-processing tasks observed in healthy subjects is considerably reduced in depressed patients (Anand et al., 2005a; Johnstone et al., 2007) and increases after antidepressant therapy (Anand et al., 2005b, 2007; Chen et al., 2007), hence providing direct support for a disrupted amygdala–prefrontal emotion regulation circuitry in depression.

Thus, amygdala–prefrontal connectivity could represent a promising endophenotype for genetic association studies in the emerging research field called 'imaging genetics'. In healthy subjects, it was repeatedly shown that amygdala reactivity (e.g. Bertolino et al., 2005; Brown et al., 2005; Hariri et al., 2002, 2005; Smolka et al., 2007) and amygdala–prefrontal connectivity (Heinz et al., 2005; Pezawas et al., 2005) are critically modulated by genetic polymorphisms involved in monoaminergic signal transduction. First results in depressed patients support these findings (Dannlowski et al., 2007, 2008). Recently, two studies reported that the MAOA u-VNTR polymorphism also impacts structure and function of limbic and prefrontal areas (Buckholtz et al., 2008; Meyer-Lindenberg et al., 2006). In particular, a reduction of amygdala–prefrontal connectivity (mapping to BA 10) was observed during emotion processing in healthy MAOA-H carriers (Buckholtz et al., 2008). Thus, relative uncoupling of the amygdala as a core neural structure implicated in the production of (negative) affective states from prefrontal cortical areas known to be involved in mood regulation could be a neurobiological endophenotype for the depressogenic effect of the MAOA genotype. Therefore, it could be speculated that the genetic susceptibility for depression and depression persistence reported for the MAOA-H alleles could be mediated via a disruption of an amygdala–prefrontal mood-regulating circuitry. However, no data on amygdala–prefrontal connectivity dependent on genotype in depressed patients have been reported hitherto.

In the present study, we tested the following hypotheses:

(a) Depressed patients show decreased functional connectivity of the amygdala with prefrontal areas implicated in the regulation of emotion (dACC and DLPFC corresponding to BA 46 and BA 9) during emotion processing compared to healthy subjects.
(b) Healthy as well as depressed carriers of MAOA-H alleles show decreased amygdala–prefrontal connectivity in the same areas.
(c) Reduced amygdala–prefrontal connectivity is associated with a severe and chronic course of disease in depressed patients.

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**Table 1.** MAOA allele activity group, clinical and affective characteristics of study participants

| | Patients ($n=34$) | Controls ($n=31$) | Test statistic (two-tailed) |
|---|---|---|---|
| Age (yr) | 36.9 (12.6) | 37.0 (11.5) | $t(63)=0.19$, $p=0.99$ |
| Sex (M/F) | 11/23 | 13/18 | $\chi^2(1)=0.64$, $p=0.42$ |
| Verbal Intelligence (MWT-B) | 115.4 (14.1) | 119.6 (12.6) | $t(63)=1.22$, $p=0.23$ |
| Genotype (MAOA-L/MAOA-H) | 19/15 | 19/12 | $\chi^2(1)=0.20$, $p=0.66$ |
| HAMD | 22.4 (3.6) | 0.9 (1.2) | $t(63)=32.0$, $p<0.001$ |
| BDI | 23.7 (10.1) | 2.6 (2.8) | $t(63)=11.2$, $p<0.001$ |
| Number of episodes | 4.1 (4.2) | n.a. | |
| Duration of illness (months) | 113.5 (118.4) | n.a. | |
| Time since first treatment (months) | 55.5 (62.9) | n.a. | |
| Time since first hospitalization (months) | 29.7 (54.1) | n.a. | |
| Lifetime hospitalization (wk) | 7.0 (9.8) | n.a. | |

MWT-B, Mehrfachwahl-Wortschatz-Intelligenztest (Multiple-choice Verbal Intelligence test; Lehrl, 1995); HAMD, Hamilton Rating Scale for Depression (Hamilton, 1960); BDI, Beck Depression Inventory (Beck and Steer, 1987).

## Patients and methods

### *Subjects*

Datasets of 35 in-patients with major depression, diagnosed by the use of the SCID-I interview (Wittchen et al., 1997), and 32 healthy subjects were obtained. Only patients with primary major depression were included (indicated by earlier onset and predominant symptoms). Secondary lifetime diagnoses were social phobia ($n=3$), agoraphobia ($n=2$), panic disorder ($n=7$), pain disorder ($n=1$), generalized anxiety disorder ($n=1$), anorexia nervosa ($n=1$), and obsessive–compulsive disorder ($n=1$). Given the medium to large effect sizes calculated from previously reported studies concerning genetic effects on amygdala–prefrontal connectivity [Cohen's $d=1.41$ (Heinz et al., 2005); $d=0.68$ (Pezawas et al., 2005); $d=0.61$ (Buckholtz et al., 2008)], the present sample size and genotype distribution provided acceptable statistical power to detect genotype effects ($1-\beta=77.4\%$ for $d=0.61$, 84.8% for $d=0.68$, 98.9% for $d>1.0$, calculated with G*POWER 3.0.4; Faul et al., 2007). Data of one patient were excluded because of missing images due to technical difficulties. One healthy subject who developed a medicated depressive episode within a year of participation was removed from the analysis. All subjects were unrelated and Caucasians of European origin, except for one German patient of Asian descent. However, excluding this patient would not alter the overall results. Sociodemographic and clinical details of the study groups are shown in Table 1. Exclusion criteria were neurological abnormalities, substance abuse, former electroconvulsive therapy, age $\geqslant 60$ yr, benzodiazepine treatment, and the usual magnetic resonance imaging contraindications. Healthy subjects had no history of psychiatric disorders or psychotropic medication. All patients were under antidepressant medication. No patient received MAOA inhibitors, lithium, or anti-epileptic drugs. Two female patients (3/3 and 4/5 MAOA u-VNTR genotype) received additional antipsychotic drugs (amisulprid and quetiapine). Excluding these two patients would rather strengthen the pattern of results. The experiments were conducted in accordance with the Declaration of Helsinki. Approval was obtained from the ethics committee of the University of Münster. After a comprehensive description of the study to the subjects, written informed consent was obtained.

### *Genotyping*

All subjects were genotyped for the MAOA VNTR polymorphism according to a previously published protocol (Deckert et al., 1999) with minor modifications. Genomic DNA was amplified by PCR using primers F: 5′-CCCAGGCTGCTCCAGAAAC and R: 5′-GGACCTGGGCAGTTGTGC, which flank the polymorphic promoter region located ~1.1 kb upstream of the ATG translation start site. PCR (60 s at 94 °C, 60 s at 52 °C, 120 s at 72 °C for 35 cycles after an initial 15-min denaturation step at 95 °C) was performed in a final volume of 20 $\mu$l containing 50 ng DNA, 10 pmol of each primer, 200 $\mu$M dNTPs, $H_2O$ and 0.5 U HotStar *Taq* polymerase with 1.5 mM $MgCl_2$, 1× Q solution and 1× buffer (Qiagen, Hilden, Germany). PCR products were separated by electrophoresis on 15% polyacrylamide gels (1× TBE, 230 V/cm) for 3.5 h and visualized by silver staining, which resulted in fragments between 212 bp and 272 bp

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length allowing differentiation and assignment of all MAOA VNTR alleles (short allele 3: 212 bp; longer alleles 3.5, 4 and 5: 227, 242 and 272 bp, respectively). For genotyping quality control about 10% of subjects were additionally genotyped by direct automated sequencing (only homozygous carriers of MAOA alleles 3, 3.5, 4 and 5) or gene scan analysis (5′ FAM labelling of forward primer), both on an ABI 3730 DNA analyser with software SeqScanner version 1.0 or Peak Scanner version 1.0 (Applied Biosystems, Darmstadt, Germany), which resulted in concordance rates of 100%. Genotypes were determined by investigators blinded for clinical diagnoses.

Subjects were dichotomized into a 'low-allele activity group' (MAOA-L, 3 and 5 repeats) or 'high-allele activity group' (MAOA-H, 3.5 and 4 repeats). Heterozygous women were coded MAOA-L if one or two lower active alleles were present (Buckholtz et al., 2008; Meyer-Lindenberg et al., 2006). We chose this dichotomization proposed by Sabol et al. (1998) for comparability reasons, since it has been frequently used in previous imaging genetics investigations. Deckert et al. (1999) classified the 5-repeat allele as being a higher active allele and grouped the 5-repeat allele together with the 3.5- and 4-repeat allele. In our sample, only two 5-repeat alleles were found. Using the dichotomization suggested by Deckert et al. (1999), one male healthy control subject and one female patient would have to be considered MAOA-H carriers instead of MAOA-L. However, recalculating the data did not change the observed effects.

According to $t$ tests or $\chi^2$ tests, the MAOA-H and MAOA-L groups did not significantly differ concerning age, education, verbal intelligence, and, for patients: medication level, medication type, depression severity, duration of illness, number of episodes, or total hospitalization time (all $p>0.4$). There was a non-significant trend for a higher frequency of MAOA-H alleles in men [$\chi^2(1)=2.5, p=0.11$]. Therefore, and also due to the X-chromosomal location of the MAOA gene, we investigated possible gender × allele activity group interactions on functional connectivity measures.

Since recent – albeit partly contradictive – studies reported that amygdala–prefrontal coupling is influenced by a common functional promoter polymorphism in the serotonin transporter gene (5-HTTLPR; Heinz et al., 2005; Pezawas et al., 2005; Surguladze et al., in press), all subjects were additionally genotyped for the 5-HTTLPR polymorphism, including the newly described SNP rs25531 (A/G) as reported previously (Dannlowski et al., 2008). However, there was no significant association of the MAOA u-VNTR allele activity group and 5-HTTLPR/rs25541 risk alleles [$\chi^2(2)=1.02, p=0.6$].

#### *Functional magnetic resonance imaging (fMRI) methods*

Technical details of the fMRI data acquisition and processing have been reported (Dannlowski et al., 2007; Domschke et al., 2006). Briefly, facial stimuli consisted of sad, angry, happy, and neutral expressions (Ekman and Friesen, 1976). Subjects were presented with alternating 30-s epochs of a face category or a no-face stimulus (a grey rectangle). In a passive viewing task, facial stimuli were presented twice per second for 500 ms in a random sequence. Each emotion epoch was preceded by a no-face epoch and was presented twice, resulting in a total presentation time of 8 min. The order of blocks was counterbalanced across subjects. T2* functional data were acquired at a 3 T scanner (Gyroscan Intera 3.0T, Philips Medical Systems, Best, The Netherlands) using a single-shot echoplanar sequence with parameters selected to minimize distortion in the amygdala while retaining adequate S/N and T2* sensitivity according to suggestions made by Robinson et al. (2004). Volumes consisting of 25 axial slices were acquired (matrix $128\times128$, resolution $1.75\times1.75\times3.5$ mm; TR = 3 s, TE = 30 ms, FA = 90°) 160 times in blocked design, 10 times per condition. To optimize the following normalization procedures, the same sequence parameters were used to cover the whole brain with 43 slices. Additionally, two anatomical datasets were acquired: T1-weighted inversion recovery and a high-resolution T1-weighted 3D sequence (isotropic voxel, 0.5 mm edge length). Functional imaging data were motion corrected, using a set of six rigid-body transformations determined for each image, spatially normalized to standard MNI space (Montreal Neurological Institute) with a voxel size of $2\times2\times2$ mm, and smoothed (Gaussian kernel, 6 mm FWHM) using Statistical Parametric Mapping (SPM2, Wellcome Department of Cognitive Neurology, London, UK).

#### *Effects of task on amygdala and prefrontal neural activity*

In order to demonstrate that the selected regions of interest (ROI) were robustly activated by the experimental procedure, a conventional fMRI analysis was performed. The first (individual) level analysis was performed by modelling the different experimental conditions as variables within the general linear model (modelled with a standard haemodynamic response function). For the purpose of demonstrating task

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effects, individual contrast images of negative (angry and sad) emotional faces contrasted with the baseline condition were created. The first-level contrast images were then included in a second-level group analysis of the whole sample ($n=65$). An anatomical mask encompassing the bilateral amygdala and the whole prefrontal cortex (see below) was constructed using the WFU PickAtlas Toolbox (Maldjian et al., 2003), applying a rigorous $\alpha$-correction [0.05, family-wise entry (FWE) corrected].

### *Functional connectivity analyses*

'Functional connectivity' is an estimate of functional integration of two neuro-anatomical regions derived from blood oxygen level-dependent data. It reflects the covariation of activity in a volume of interest with one or more other brain areas over time and is a widely used measure in the imaging literature (Friston, 1994). For the two prefrontal areas with strong a-priori hypotheses, a mean ROI approach was selected as previously described (Rauch et al., 2007). The ROIs were defined by means of the WFU PickAtlas Toolbox (Maldjian et al., 2003). The bilateral amygdala ROI was defined according to Tzourio-Mazoyer et al. (2002). The DLPFC was defined as BA 46 and BA 9, and the dACC was defined as a sphere with a radius of 8 mm placed in the most dorsal/posterior part of the ACC boundary at $x=0$, $y=2$, $z=30$. The MaRsBar Toolbox (Brett et al., 2002) was used to extract the mean voxel time series (160 time-points) of the amygdala, dACC, and DLPFC ROI for each subject separately. Pearson's product-moment correlation coefficients were calculated between the amygdala and dACC time-series and between the amygdala and DLPFC time-series. Fisher Z-transformations of the correlation coefficients were used as measure for connectivity for the group comparisons, since these better conform to the normality assumption required for parametric testing. However, recalculation with untransformed correlation coefficients, variance-shared (Rauch et al., 2007), or $t$ values (Anand et al., 2005a) yielded almost identical results. Since this ROI approach uses averaged time-series for all voxels in the investigated ROIs, no $\alpha$-correction was required.

Subsequently, exploratory voxel-based functional connectivity analyses were conducted investigating the whole prefrontal cortex for study group (patients vs. controls) and allele activity group (MAOA-L vs. MAOA-H) effects concerning amygdala connectivity. Therefore, the time-course of bilateral amygdala activity was extracted for each participant as described above and then entered as a regressor ('seed') in a subsequent fixed-effects first-(individual) level analysis of the same subject. The presentation conditions and movement parameters were also modelled as nuisance variables to control movement and co-activation by the task. Thus, potential differences in (co-)activations due to the different presentation conditions were regressed out by this procedure. The resulting contrast images containing individual brain-wide connectivity of the amygdala were then entered into random-effects group comparisons. The WFU PickAtlas Toolbox (Maldjian et al., 2003) was used to create a mask for the prefrontal cortex (including all parts of the inferior, middle, and superior frontal gyrus, anterior cingulate gyrus, gyrus rectus, encompassing all parts of BA 9, 10, 11, 24, 25, 32, and 44–47). To maximize sensitivity of this additional exploratory analysis, main effects of study group and allele activity group on amygdala–prefrontal connectivity were investigated with a lenient statistical threshold of $p<0.005$, uncorrected with a cluster threshold of $k=5$ voxels (cf. Anand et al., 2005a).

### *Association with illness severity*

Five variables characterizing illness history were assessed (duration of illness, number of episodes, total hospitalization time, time since first in-patient treatment, time since first outpatient treatment; see Table 1). All variables were entered into a factor analysis using principal component extraction yielding a clear single component solution that extracted 61.3% variance and obtained high loadings ($>0.72$). Component values were calculated for each subject in order to obtain a 'severity index' using the Anderson–Rubin method. Thus, patients with a high severity index had a longer history of depression, more episodes, and spent more cumulative time in hospital. The severity index was used in a second-level random-effects correlation analysis with amygdala–prefrontal connectivity.

## Results

### *Effects of task on amygdala and prefrontal neural activity*

The whole-group task effect analysis yielded robust activations of bilateral amygdala [left amygdala: $k$ (cluster size)$=96$ voxels, peak voxel at $x=-20$, $y=-4$, $z=-20$, $t(64)=8.6$, $p_{\text{corrected}}<0.001$; right amygdala: $k=144$, $x=32$, $y=-4$, $z=-20$, $t(64)=8.4$, $p_{\text{corrected}}<0.001$]. In the whole ACC, only the dorsal part was activated on this level of significance [$k=60$, $x=6$, $y=8$, $z=26$, $t(64)=6.9$, $p_{\text{corrected}}<0.001$].

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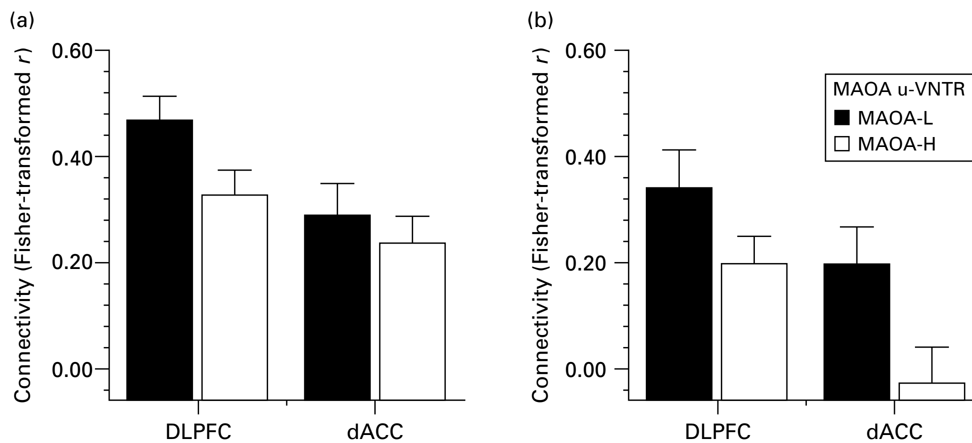


**Figure 1.** Bar graphs depicting functional connectivity of the amygdala with the dorsal anterior cingulate cortex (dACC) and the dorsolateral prefrontal cortex (DLPFC) in (a) controls ($n=31$) and (b) patients ($n=34$) dependent on allele activity group.

Furthermore, large and highly significant clusters in the lateral prefrontal cortex were observed with peak activity in the dorsolateral parts (left DLPFC: $k=3729$, $x=-42$, $y=10$, $z=26$, $t(64)=13.2$, $p_{corrected}<0.001$; right DLPFC: $k=5064$, $x=40$, $y=14$, $z=26$, $t(64)=15.25$, $p_{corrected}<0.001$; see Supplementary Figure 1, available online).

*Functional connectivity*

Healthy controls demonstrated tight functional amygdala connectivity with several prefrontal areas (see Supplementary Figure 2, online). The strongest coupling peaks were observed in the dorsal anterior cingulate gyrus ($x=0$, $y=18$, $z=30$, $r=0.899$, BA 32) and bilateral dorsolateral ($x=-52$, $y=26$, $z=28$, $r=0.853$, BA 46 and BA 9; $x=58$, $y=32$, $z=18$, $r=0.815$, BA 46 and BA 9) and ventrolateral PFC ($x=-38$, $y=32$, $z=-16$, $r=0.848$, BA 47 and BA 11; $x=48$, $y=26$, $z=-12$, $r=0.806$, BA 47).

For each hypothesized area (dACC and DLPFC) a 2 (study group: patients vs. controls) × 2 (allele activity group: MAOA-L vs. MAOA-H) ANOVA was conducted on the functional connectivity parameters. In both cases, Levene tests indicated homogeneity of variances [$F(3,61)<1.3$, $p>0.3$]. For the dACC, a strong main effect of study group [$F(1,61)=7.42$, $p=0.008$, $\eta_p^2=0.11$], and allele activity group [$F(1,61)=4.6$, $p=0.036$, $\eta_p^2=0.07$] emerged. No study group × allele activity group interaction was detected [$F(1,61)=1.7$, $p=0.2$, $\eta_p^2=0.027$]. In line with our hypotheses, depressed patients and MAOA-H carriers had reduced amygdala–dACC connectivity. For the DLPFC, a similar pattern was found with a main effect of study group [$F(1,61)=5.1$, $p=0.027$, $\eta_p^2=0.08$], and allele activity group [$F(1,61)=6.3$, $p=0.015$, $\eta_p^2=0.09$]. Again, no study group × allele activity group interaction was detected [$F(1,61)=0.0$, $p=1.0$], suggesting independent, additive effects of patient status and MAOA-H genotype on amygdala–prefrontal connectivity reduction (Figure 1).

In order to investigate gender effects, we conducted two 2 (allele activity group) × 2 (gender) ANOVAs. The main effects of allele activity group remained stable for the dACC and DLPFC [$F(1,61)=5.1$, $p=0.027$, $\eta_p^2=0.08$ and $F(1,61)=4.0$, $p=0.049$, $\eta_p^2=0.06$, respectively]. No main effect or interaction of gender was found for amygdala–dACC connectivity [both $F(1,61)<1$]. For the DLPFC, also no main effect of gender was observed [$F(1,61)<1$]. However, a gender × allele activity group interaction only just failed to reach significance [$F(1,61)=4.0$, $p=0.051$, $\eta_p^2=0.06$]. The genotype effect on amygdala–DLPFC connectivity appeared to be present in women but not in men (Figure 2).

The exploratory voxel-based analyses confirmed the effects of diagnostic group and genotype on amygdala–dACC and amygdala–DLPFC connectivity. Furthermore, other prefrontal areas demonstrated effects of group and genotype. Depressed patients had reduced amygdala connectivity in dorsolateral and ventrolateral prefrontal areas, particularly in the inferior frontal gyrus (Table 2). Partially overlapping areas showed connectivity reductions in MAOA-H carriers (Table 3), including a ventromedial cluster (at $x=2$, $y=44$, $z=-4$). The genotype effect was maximal in the dACC ($x=0$, $y=14$, $z=30$), almost identical to the location of maximal amygdala–prefrontal coupling in healthy subjects (Figure 3).

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**Table 2.** Main effect of study group (controls >patients) on functional connectivity of the amygdala and the prefrontal cortex

| Anatomical region | BA | Cluster size | x | y | z | Z score | *p* value |
|---|---|---|---|---|---|---|---|
| IFG (orbital part), extending to MFG (orbital part) | 47, 10 | 75 | 40 | 44 | −4 | 4.20 | <0.0001 |
| MFG (orbital part), extending to SFG | 10 | 69 | −26 | −6 | −18 | 3.87 | <0.0001 |
| IFG (orbital part, extending to triangular part) | 47 | 172 | −52 | 24 | −8 | 3.79 | <0.0001 |
| IFG (opercular part) | 9 | 30 | 36 | 2 | 26 | 3.70 | 0.0001 |
| MFG | 46 | 34 | 46 | 46 | 24 | 3.58 | 0.0002 |
| ACG (supragenual) | 24, 32 | 10 | −4 | 14 | 34 | 3.15 | 0.0008 |
| ACG (supragenual) | 24 | 12 | −6 | 2 | 30 | 3.09 | 0.0010 |
| IFG (orbital part) | 47, 11 | 10 | −48 | 44 | −14 | 3.06 | 0.0011 |
| ACG (supragenual) | 32, 24 | 29 | 0 | 28 | 18 | 2.99 | 0.0014 |
| MFG | 10 | 8 | 46 | 56 | 0 | 2.97 | 0.0015 |
| ACG (pregenual) | 24 | 7 | 0 | 28 | −2 | 2.96 | 0.0015 |
| SFG (medial part) | 10 | 9 | −2 | 54 | 2 | 2.84 | 0.0023 |

BA, Brodmann area; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; ACG, anterior cingulate gyrus.
Coordinates are given in MNI space.

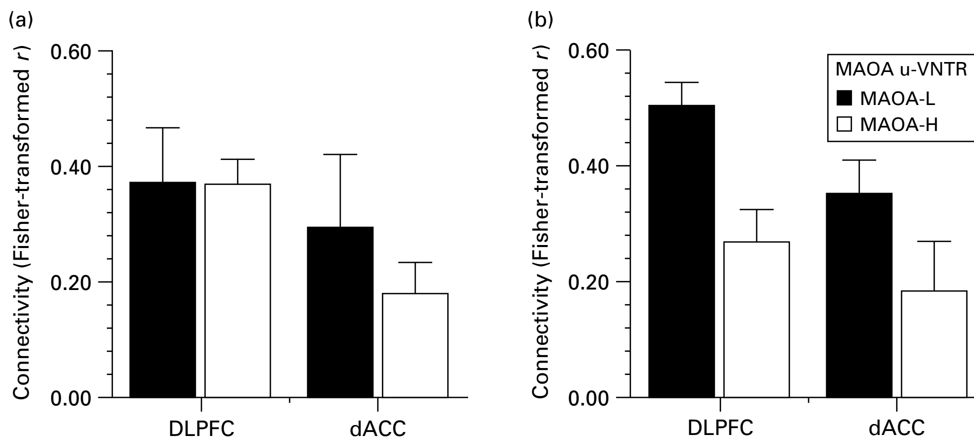


**Figure 2.** Bar graphs depicting functional connectivity of the amygdala with the dorsal anterior cingulate cortex (dACC) and the dorsolateral prefrontal cortex (DLPFC) in (a) males ($n=24$) and (b) women ($n=41$) dependent on allele activity group.

### *Association with illness severity*

Correlating the severity index with amygdala–dACC connectivity yielded no significant association ($r=-0.22$, $p=0.11$, one-tailed). However, in accordance with our third hypothesis, amygdala–DLPFC connectivity correlated significantly with illness severity ($r=-0.45$, $p=0.004$), suggesting that patients with reduced amygdala–DLPFC had a longer and more severe course of disease. This correlation was almost unaffected if medication level (see below) was controlled ($r_p=-0.45$, $p=0.005$). We performed an exploratory voxel-wise analysis for the prefrontal cortex at the same threshold that was used in the group analyses ($p=0.005$, corresponding to $r=-0.44$, $k=5$). Large clusters of prefrontal areas in which lower amygdala connectivity predicted a higher severity index were obtained (see Figure 4). Cluster maxima were found in the bilateral DLPFC (x=−54, y=34, z=18, $k=499$, $r=-0.65$, BA 46 and BA 10; x=52, y=38, z=14, $k=425$, $r=-0.63$, BA 46 and BA 10), in the supragenual anterior cingulate cortex somewhat anterior to our dACC ROI (x=−2, y=38, z=20, $k=183$, $r=-0.56$, BA 24 and BA 32), and also in the medial prefrontal cortex (x=6, y=62, z=6, $k=71$, $r=-0.62$, BA 10).

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**Table 3.** Main effect of allele activity group (MAOA-L >MAOA-H) on functional connectivity of the amygdala and the prefrontal cortex

| Anatomical region | BA | Cluster size | x | y | z | Z score | *p* value |
|---|---|---|---|---|---|---|---|
| ACG (supragenual), extending to MCG | 24 | 301 | 2 | 14 | 30 | 3.91 | <0.0001 |
| SFG (medial part) | 10 | 22 | 4 | 68 | 18 | 3.65 | 0.0001 |
| Rolandic operculum extending to IFG (opercular part) | 44 | 33 | 60 | 8 | 10 | 3.47 | 0.0003 |
| IFG (orbital part) | 47, 11 | 18 | 40 | 34 | −16 | 3.33 | 0.0004 |
| IFG (orbital part) | 47 | 12 | −40 | 14 | −14 | 3.16 | 0.0008 |
| IFG (opercular part) | 44, 45 | 49 | −60 | 10 | 16 | 3.16 | 0.0008 |
| SFG | 9 | 34 | −14 | 44 | 20 | 3.15 | 0.0008 |
| IFG (triangular part) | 46 | 20 | 42 | 28 | 24 | 3.11 | 0.0009 |
| SFG (orbital part), MFG (orbital part) | 11, 10 | 13 | −26 | 48 | −6 | 3.07 | 0.0011 |
| IFG (triangular part) extending to insula | 47 | 19 | −42 | 24 | 0 | 3.07 | 0.0011 |
| ACG (pregenual) extending to MFG (orbital part) | 32 | 28 | 2 | 44 | −4 | 2.99 | 0.0014 |
| IFG (triangular part) | 46 | 11 | 54 | 32 | 28 | 2.99 | 0.0014 |
| ACG (supragenual) | 32 | 16 | 14 | 36 | 20 | 2.98 | 0.0014 |
| IFG (orbital part) extending to insula | 47 | 26 | −30 | 26 | −10 | 2.94 | 0.0016 |
| IFG (triangular part), MFG | 46 | 17 | 46 | 38 | 8 | 2.74 | 0.0031 |
| SFG (medial part) | 10 | 5 | 12 | 54 | 2 | 2.69 | 0.0036 |

BA, Brodmann area; IFG, inferior frontal gyrus; MFG, middle frontal gyrus; SFG, superior frontal gyrus; ACG, anterior cingulate gyrus; MCG, medial cingulate gyrus.
Coordinates are given in MNI space.

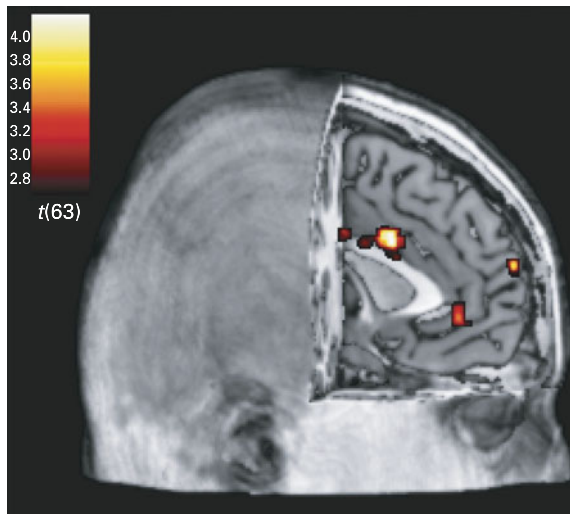


**Figure 3.** Effect of allele activity group on amygdala–prefrontal connectivity. Saggital view (x=0) depicting the cingulate gyrus and the medial prefrontal cortex. A maximal connectivity reduction in MAOA-H carriers was observed in the dorsal anterior cingulate gyrus [x=2, y=14, z=30, $t(63)=4.18$, Cohen's $d=1.05$].

### *Role of medication*

To assess a potential role of antidepressant medication, all medications were coded in terms of treatment duration and dose into medication levels from 1 to 4 following the suggestions of Sackeim (2001). Patients were grouped into low-dose group (medication level 1–2, $n=13$) and high-dose group (medication level 3–4, $n=21$; cf. Surguladze et al., 2005). The low-dose group showed significantly higher Beck Depression Inventory (BDI) scores than the high-dose group [$t(32)=2.26$, $p=0.038$]. However, no effect of medication on other clinical characteristics, or functional connectivity reached a trend level of significance (all $p$ values$>0.3$). A voxel-wise analysis of dose group differences concerning amygdala–prefrontal connectivity yielded no significant activation (at the threshold used in the previous analyses).

## Discussion

The present data suggest that amygdala–DLPFC and amygdala–dACC connectivity is significantly reduced in depressed patients during emotion processing, a finding replicating and extending previous reports of reduced cortico-limbic connectivity in acute major depression. Thus, we provide further evidence for the notion that major depression is characterized by impairments in a neural circuitry which has been shown to be relevant for mood regulation. As an important extension of these previous findings, our data show

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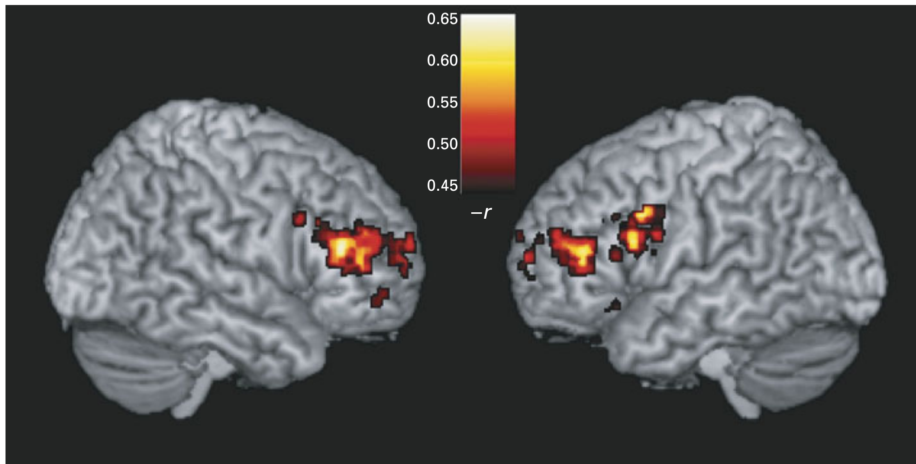


**Figure 4.** Prefrontal areas in which reduced amygdala connectivity is significantly associated with a higher severity index. Correlated activity is displayed at a threshold of $p<0.005$, cluster size $k=5$, rendered on the cortical surface of a template brain.

that this reduced amygdala–prefrontal connectivity predicts about 40% variance of clinical variables characterizing a more severe course of disease (i.e. a longer illness history, more episodes, and more cumulative hospitalization time), indicating a potential relevance of cortico-limbic connectivity for the long-term course of depression.

For carriers of higher active MAOA u-VNTR alleles, a similar pattern of amygdala–prefrontal connectivity reduction was observed in patients and controls, particularly in women. Again, this finding is in line with previous studies reporting that the MAOA gene appears to modulate connectivity between amygdala and prefrontal areas in healthy subjects (Buckholtz et al., 2008). Given the strong association of a reduced cortico-limbic connectivity with illness severity, the present findings suggest that genetic variations in the MAOA gene might affect the course of major depression by substantially reducing the functional integration of a fronto-limbic circuitry involved in emotion regulation. This notion fits well with previous genetic association studies reporting worse therapy response in depressed patients carrying MAOA-H alleles (Domschke et al., 2007; Yu et al., 2005).

An almost significant gender × allele activity group interaction found for amygdala–DLPFC connectivity – the area, where connectivity reduction predicted illness severity best – might correspond to previous reports that the association of MAOA-H alleles with emotional disorders is more pronounced in women (Deckert et al., 1999; Ni et al., 2007; Schulze et al., 2000). These data complement a recent study conducted by our research group, reporting a reduced response to antidepressant therapy in depressed women but not men carrying MAOA-H risk alleles (Domschke et al., 2007).

Main effects of study group and genotype on amygdala connectivity were found in the dorsal anterior cingulate gyrus ('cognitive division') as well as dorsolateral and ventrolateral areas, all of them previously associated with voluntary regulation of emotions. A large number of imaging studies consistently reported engagement of these prefrontal structures during emotion regulation, accompanied by attenuation of the amygdala throughout a variety of tasks and stimulus material (Kim and Hamann, 2007; Lévesque et al., 2003; Ochsner et al., 2004; Ochsner and Gross, 2005; Ohira et al., 2006; Phan et al., 2005). Our results suggest connectivity reductions in patients and MAOA-H carriers largely in lateral parts of the prefrontal cortex and the supragenual/dorsal anterior cingulate gyrus, thus fitting well with various neuroimaging findings in major depression reporting dysfunctions particularly in these lateral prefrontal areas (Baxter et al., 1989; Bench et al., 1993; Drevets, 1999; Mayberg et al., 1999; Siegle et al., 2002, 2007) and the anterior cingulate cortex (reviewed by Fitzgerald et al., 2007), which seems to play a major role in therapy response (Mayberg et al., 2000).

However, certain limitations should be acknowledged. Functional connectivity is correlational in nature. Thus, it should not be regarded as directly reflecting anatomical or causal relations. However, converging lines of research show that functional connectivity is well suited to measure anatomically and functionally relevant connectivity in neural circuitries (Ramnani et al., 2004). Our sample size was relatively small, albeit in the range of other previously

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published studies. In contrast to other highly powered imaging genetics studies among healthy subjects, it is not possible to study gene–gene interactions, haplotype effects or to employ multivariate methods like structural equation modelling in our patient sample without producing statistically fragile results. Nonetheless, it should be stated that to the best of our knowledge, our sample is the largest of acutely depressed patients studied with emotional fMRI paradigms. Furthermore, we cannot rule out the possibility that medication contributed to the group effects since all patients received antidepressant drugs. However, dose level had no significant impact on functional connectivity in the DLPFC and dACC and no patient received MAOA inhibitors. More importantly, previous studies investigating the effect of antidepressant treatment on neural activity and connectivity during emotion processing reported a normalization of pathological activation patterns after therapy, including an increase in cortico-limbic functional connectivity (Anand et al., 2005b, 2007; Chen et al., 2007). Therefore, it seems unlikely that the connectivity reduction reported in our depressed sample is a result of medication effects since these would rather counteract the group differences reported here. However, the present results should not be generalized to unmedicated patients. Finally, the relationship between amygdala–prefrontal connectivity reduction and illness severity is correlational, and therefore it is impossible to clarify whether functional connectivity reduction is a predictor for or the result of a longer and severer course of disease. Longitudinal studies with larger sample sizes could resolve this problem.

With these caveats, the present study contributes to the emerging field of imaging genetics in mood disorders. A disrupted amygdala–prefrontal mood-regulating network appears to be associated with major depression and among these patients with a tendency for a more chronic course of disease. Reduced amygdala–prefrontal connectivity was especially pronounced in carriers of MAOA-H alleles, which represent potential risk alleles for depression. In sum, we conclude that genetic variation in the MAOA gene affects cortico-limbic connectivity, relevant for the functional neuropathology of major depression.

## Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org).

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## Statement of Interest

None.

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