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Disadvantage of Social Sensitivity: Interaction of Oxytocin Receptor Genotype and Child Maltreatment on Brain Structure

Udo Dannlowski, Harald Kugel, Dominik Grotegerd, Ronny Redlich, Nils Opel, Katharina Dohm, Dario Zaremba, Anne Grögler, Juliane Schwieren, Thomas Suslow, Patricia Ohrmann, Jochen Bauer, Axel Krug, Tilo Kircher, Andreas Jansen, Katharina Domschke, Christa Hohoff, Pienie Zwitserlood, Markus Heinrichs, Volker Arolt, Walter Heindel, and Bernhard T. Baune

ABSTRACT

BACKGROUND: Oxytocin has received much attention as a prosocial and anxiolytic neuropeptide. In human studies, the G-allele of a common variant (rs53576) in the oxytocin receptor gene (*OXTR*) has been associated with protective properties such as reduced stress response and higher receptiveness for social support. In contrast, recent studies suggest a detrimental role of the rs53576 G-allele in the context of childhood maltreatment. To further elucidate the role of *OXTR,* gene by maltreatment interactions on brain structure and function were investigated.

METHODS: Three hundred nine healthy participants genotyped for *OXTR* rs53576 underwent structural as well as functional magnetic resonance imaging during a common emotional face-matching task. Childhood maltreatment was assessed with the Childhood Trauma Questionnaire (CTQ). Gray matter volumes were investigated by means of voxel-based morphometry across the entire brain.

RESULTS: Structural magnetic resonance imaging data revealed a strong interaction of rs53576 genotype and CTQ scores, mapping specifically to the bilateral ventral striatum. GG homozygotes but not A-allele carriers showed strong gray matter reduction with increasing CTQ scores. In turn, lower ventral striatum gray matter volumes were associated with lower reward dependence, a prosocial trait. Furthermore, the G-allele was associated with increased amygdala responsiveness to emotional facial expressions.

CONCLUSIONS: The findings suggest that the G-allele constitutes a vulnerability factor for specific alterations of limbic brain structure in individuals with adverse childhood experiences, complemented by increased limbic responsiveness to emotional interpersonal stimuli. While oxytocinergic signaling facilitates attachment and bonding in supportive social environments, this attunement for social cues may turn disadvantageous under early adverse conditions.

Keywords: Amygdala, fMRI, Oxytocin, Reward dependence, VBM, Ventral striatum

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During the past decade, the neuropeptide oxytocin has attracted substantial attention in human neuroscience due to its fundamental role in social behavior and cognition (1). Oxytocin and its receptor have been implicated in several psychiatric disorders such as autism (2), borderline personality disorder (3), or social anxiety disorder (4). A wealth of studies has investigated the association of oxytocin levels and/or intranasal oxytocin application in experimental designs, revealing its role in trust and trustworthiness, social attachment, empathy, and maternal bonding, as well as anxiety, fear conditioning, stress response, and amygdala responsiveness to emotional stimuli (1,5).

On a genetic level, a common variant (rs53576) in the oxytocin receptor gene (*OXTR*), located on chromosome 3p25.3, has been implicated regarding several prosocial traits on phenomenological, behavioral, clinical, and neurobiological levels (6). While the G-allele has been associated with beneficial and protective social traits such as higher empathy (7), prosocial behavior (8), optimism and self-esteem (9), reward dependence (10), and sensitive parenting (11), A-allele carriers, in turn, have been shown to display less positive affect (12), higher levels of loneliness (13), and harm avoidance (14). Furthermore, the A-allele has been associated with higher levels of physiological and dispositional stress reactivity (7), whereas only G-allele carriers were reported to show benefit from social support regarding subjective and endocrine responses to social stress (15).

However, despite strong evidence for beneficial properties of the *OXTR* rs53576 G-allele, at least three recent studies have challenged this. These studies included environmental factors into the equation and consistently reported gene × environment (G × E) interactions, suggesting that the protective

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G-allele paradoxically increased susceptibility to detrimental effects of childhood adversities. McQuaid *et al.* (16) reported that G-allele carriers with high levels of childhood maltreatment showed increased symptoms of depression, whereas AA homozygotes did not show this association. Bradley *et al.* (17) showed that G-allele carriers who lacked a warm or stable family environment showed less resilient coping style and positive affect than G-allele carriers raised in a warm and stable environment, whereas childhood adversities did not significantly affect AA homozygotes. Finally, Hostinar *et al.* (18) reported that in adolescents with objectively documented maltreatment histories, GG homozygotes showed higher levels of internalizing symptoms such as anxiety, depression, or social withdrawal than nonmaltreated GG homozygotes, whereas A-allele carriers revealed no such effects.

This G × E interaction indicates that prosocial, trust-enhancing traits associated with the G-allele might be beneficial in the context of stable, supportive environments but might also increase the vulnerability for social harm, such as childhood maltreatment, or as McQuaid *et al.* (16) phrased it: "Thus, a breach in trust (i.e., in the case of early-life abuse or neglect) may have a more deleterious effect among G carriers, who have been characterized as more prosocial and attuned to social cues."

In the present study, we sought to shed more light on these G × E findings by investigating the interaction of *OXTR* rs53576 genotype and childhood maltreatment on the level of brain structure and function, using structural and functional magnetic resonance imaging (MRI) during emotion processing in a large sample of healthy volunteers. Based on previous findings that 1) *OXTR* is strongly expressed in limbic areas, particularly in the ventral striatum (nucleus accumbens) and the amygdala (19); 2) *OXTR* rs53576 has already been shown to modulate amygdala responsiveness to aversive facial expressions (10); and 3) that childhood maltreatment has been associated with decreased gray matter (GM) volumes of limbic structures (20-23) and with increased amygdala responsiveness to negative facial emotions (21,24-27), we made the following assumptions:

- The previously described detrimental effect of childhood maltreatment on gray matter volumes in limbic areas (particularly hippocampus, amygdala, and ventral striatum) is stronger in GG homozygotes than in A-allele carriers.
- Maltreatment-related amygdala responsiveness to emotional facial expressions is stronger in G-allele than in A-allele carriers.

Areas showing significant structural or functional effects of *OXTR* genotype or genotype × maltreatment interaction were further tested for associations with reward dependence (RD) (28), a prosocial trait already associated with *OXTR* rs53576-related imaging phenotypes as published previously (10).

METHODS AND MATERIALS

Sample Characteristics

A sample of $N = 309$ healthy adult subjects (mean age 34.3 ± 11.2, range 18–59) of European ancestry for whom structural MRI scans and complete childhood maltreatment data were available participated in the study. All subjects were thoroughly investigated by experienced clinical psychologists and were free from any lifetime history of psychiatric disorders according to DSM-IV criteria (29), diagnosed with the Structured Clinical Interview for DSM Disorders interview (30). Exclusion criteria were any neurological abnormalities including stroke, epilepsy, multiple sclerosis, Parkinson's disease or dementia, head trauma or unconsciousness, intake of any psychotropic medication, and the usual MRI contraindications. The study was approved by the Ethics Committee of the University of Münster. After complete description of the study to the participants, written informed consent was obtained.

Verbal intelligence was estimated by the Multiple-Choice Vocabulary Test-B (31). Depression level and trait anxiety were assessed by means of the Beck Depression Inventory (32) and State-Trait Anxiety Inventory trait (33) questionnaires. The Childhood Trauma Questionnaire (CTQ) was administered to assess maltreatment during childhood. The CTQ is a 25-item retrospective self-report questionnaire designed to assess five types of negative childhood experiences (34). Reliability was high in the present sample (Cronbach's $\alpha = .91$). Reward dependence, a prosocial trait, was assessed by means of the Tridimensional Personality Questionnaire (35), an inventory assessing three temperament dimensions of personality according to Cloninger (28).

DNA Extraction and Genotyping

DNA was isolated from ethylenediaminetetraacetic acid anticoagulated venous blood samples using FlexiGene DNA Kit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Genotyping of the *OXTR* single nucleotide polymorphism rs53576 was carried out following published protocols, applying the multiplex genotyping assay iPLEX (Agena Bioscience, San Diego, California) for use with the MassARRAY platform (36). Genotyping was done by investigators blinded for results on maltreatment and structural and functional imaging.

Structural MRI Acquisition and Morphometry Methods

Our MRI methods and statistical approach followed published protocols (21,37-42). Briefly, T1-weighted high-resolution anatomical images were acquired on a 3T-MRI scanner (Gyroscan Intera 3T; Philips Medical Systems, Best, Netherlands) with a three-dimensional fast gradient echo sequence (turbo field echo), repetition time = 7.4 ms, echo time = 3.4 ms, flip angle = 9°, two signal averages, inversion prepulse every 814.5 ms, acquired over a field of view of 256 mm (foot-head) × 204 mm (anterior-posterior) × 160 mm (right-left, nominal slice selection direction) with 1 mm resolution in all directions, frequency encoding in foot-head direction, phase encoding in anterior-posterior and right-left directions, reconstructed to cubic voxels of .5 mm × .5 mm × .5 mm.

The VBM toolbox (http://dbm.neuro.uni-jena.de/vbm) was used for preprocessing the structural images with default parameters. Images were bias-corrected, tissue classified, and normalized to Montreal Neurological Institute space using linear (12-parameter affine) and nonlinear transformations, within a unified model (43) including high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie normalization. Gray matter segments were modulated

only by the nonlinear components to preserve actual gray matter values locally (modulated GM volumes). Using these procedures, no further correction for total brain volume was required. The modulated gray matter images were smoothed with a Gaussian kernel of 8-mm full width at half maximum.

Group statistics were calculated using SPM8. The individual modulated GM images were entered into one single full factorial model, with genotype group as between-subjects factor (A-carrier vs. GG homozygotes). CTQ scores were entered as covariate (dimensional model), including the crucial interaction term of CTQ scores and genotype group. Age and gender were added as nuisance regressors.

Due to the skewed distribution of CTQ scores, which were not normally distributed (Kolmogorov-Smirnov $Z = 3.26$, $p < .001$), a second model (categorical model) was conducted. Subjects were grouped into maltreated and not maltreated based on CTQ data: subjects were considered maltreated if at least one of the five CTQ subscales exceeded a published threshold, indicating maltreatment (21,44,45). For the categorical model, maltreatment (yes vs. no) and genotype group (A-carrier vs. GG) were entered as between-subjects factors, including their interaction term. Age and gender were nuisance regressors.

To control for multiple statistical testing for the entire brain volume, we maintained a cluster-level corrected false-positive detection rate at $p < .05$ using a conservative voxel-level threshold of $p < .001$ as recommended (46) with a cluster extent (k) empirically determined by Monte Carlo simulations ($n = 5000$ iterations). This was performed by means of the AlphaSim procedure that accounted for spatial correlations between GM values in neighboring voxels, implemented in the REST toolbox (http://restfmri.net/forum/index.php). The resulting cluster threshold was k = 458 voxels.

Emotional Face-Matching Task

This paradigm elicits robust amygdala responses to fearful and angry facial expressions and has been frequently used in imaging genetics studies (21,47-50), including a previous report on amygdala responsiveness dependent on *OXTR* rs53576 (10). The task consisted of four blocks with a face-processing task, alternating with five blocks with a sensorimotor control task. During the face-processing task, participants viewed a trio of faces (expressing either anger or fear) from the Ekman and Friesen stimulus set (51). Subjects were instructed to select one of two faces (bottom) that was identical to a target face (top). Each face-processing block consisted of six face trios, balanced for gender and emotion (angry or fearful). During the sensorimotor control blocks, participants viewed a trio of geometric shapes (circles and ellipses) and selected one of two shapes (bottom) that was identical to a target shape (top). Each sensorimotor control block consisted of six different shape trios. All blocks were preceded by an instruction (match faces or match shapes, in German) that lasted 2 seconds. In the face-processing blocks, each of the six face trios was presented for 4 seconds, with a variable interstimulus interval of 2 to 6 seconds (mean, 4 seconds) and a total block length of 48 seconds. In the sensorimotor control blocks, each of the six shape trios was presented for 4 seconds with a fixed interstimulus interval of 2 seconds and a total block length of 36 seconds. Total task time was 390 seconds. Participants' performances (accuracy and reaction time) were recorded.

Functional MRI Methods

Images were projected to the rear end of the scanner (Sharp XG-PC10XE with additional high-frequency shielding; Sharp, Ōsaka, Japan). T2* functional data were acquired at a 3T scanner (Gyroscan Intera 3T; Philips Medical Systems, Best, Netherlands), using a single-shot echo planar sequence with parameters selected to minimize distortion in the region of central interest, while retaining adequate signal to noise ratio and T2* sensitivity. Volumes consisting of 34 slices were acquired (matrix 64 × 64, resolution 3.6 × 3.6 × 3.6 mm; repetition time = 2.1 seconds, echo time = 30 ms, flip angle = 90°). The slices were tilted 25° from the anterior commissure/posterior commissure line to minimize dropout artifacts in the orbitofrontal and mediotemporal regions.

Functional imaging data were realigned and unwarped, spatially normalized to standard Montreal Neurological Institute space and smoothed (Gaussian kernel, 6-mm full width at half maximum) using statistical parametric mapping (SPM8; http://www.fil.ion.ucl.ac.uk/spm). For the functional MRI (fMRI) analyses, $n = 45$ subjects had to be excluded due to failure to acquire fMRI data, technical problems, fMRI-related artifacts, or excessive head movement (exclusion criterion > 2 mm and/or 2°), leaving $n = 264$ complete datasets for fMRI analyses.

Onsets and durations of the two experimental conditions (faces and shapes) were modeled with a canonical hemodynamic response function in the context of the general linear model, and the model was corrected for serial correlations. For each participant, one contrast image was generated in each individual fixed-effects first-level analysis, comparing activation in response to aversive faces with the shapes baseline. The resulting contrast images were then entered into a second-level random-effects group analysis.

As described for the morphometric analyses, a single full-factorial model was conducted with genotype group (GG vs. A-carriers) as between-subjects factor and CTQ scores as covariate, including the interaction term of genotype and CTQ, and with age and gender as nuisance regressors.

Given our hypotheses, fMRI analysis was restricted to the bilateral amygdala, as defined by the automated anatomical labeling atlas (52). The statistical threshold was set to $p < .05$ on the voxel level, again employing a cluster threshold empirically determined with Monte Carlo simulations, yielding k = 38 voxels for the region of interest. However, supplementary whole-brain analyses have been conducted (see Supplementary Results).

Association of Functional and Structural MRI Data With Reward Dependence

To explore the potential relevance of structural or functional correlates of genotype or G × E for the prosocial trait-reward dependence, gray matter values and fMRI contrast values were extracted from a 5-mm sphere centered at the peak coordinates of the respective clusters (ventral striatum and amygdala, respectively), using the first eigenvariate. Since a Kolmogorov-Smirnov test indicated that normal distribution

did not hold for RD scores ($Z = 1.45$, $p = .029$), Spearman's rho was used for correlating MRI measures with RD scores.

RESULTS

Genotyping Results

Genotyping for rs53576 yielded $n = 170$ A-allele carriers (28 AA homozygotes, 142 AG heterozygotes) versus $n = 139$ GG homozygotes. Given the rather small number of AA homozygotes that had to be further subdivided according to CTQ scores, these subjects were grouped together with the AG carriers. However, when using all three genotype groups, similar results were obtained, indicating G × E in an allele-dose fashion (Supplemental Figure S1). Allele frequencies did not deviate from Hardy Weinberg equilibrium, exact test: $p = .36$. Table 1 presents sociodemographic and questionnaire data dependent on *OXTR* rs53576 genotype.

Morphometry Results

No main effect of childhood maltreatment (independent of genotype) was detected at our rigorous threshold, corrected for the entire brain volume. However, at an exploratory threshold ($p < .001$, k = 10), several regions emerged showing decreased gray matter volume associated with increasing maltreatment scores, including the caudate nucleus, hippocampus/parahippocampal gyrus, and prefrontal and occipital areas, which parallel and replicate previous findings (see Supplemental Table S1 for details).

No significant main effects of genotype were detected independent of CTQ scores. However, a highly robust interaction of genotype and maltreatment emerged, mapping to the bilateral ventral striatum (left: x = −9, y = 16, z = −8, $Z = 5.01$, k = 2336, $p_{corrected} < .001$; right: x = 12, y = 18, z = −6, $Z = 5.01$, k = 1143, $p_{corrected} < .001$). The interaction was driven by detrimental effects of maltreatment on ventral striatum gray matter volume in GG homozygotes ($r = -.31$, $p = .00014$, extracted at x = −9, y = 16, z = −8), whereas A-allele carriers did not show significant maltreatment effects ($p = .23$) (Figure 1). Adding five more nuisance regressors to the model (second-degree polynomial expansion of age, verbal IQ, education years, Beck Depression Inventory, and State-Trait Anxiety Inventory trait) did not diminish (but even slightly strengthened) the effects.

Interestingly, highly similar effects were obtained using all three genotype groups (AA vs. AG vs. GG), pointing to allele-dose effects of the interaction term (Supplemental Figure S1).

Using the categorical model (maltreated vs. nonmaltreated) yielded almost identical results. Only one cluster showing an interaction of rs53576 genotype and maltreatment survived whole-brain correction, encompassing the bilateral ventral striatum (left: x = −12, y = 18, z = −8, $Z = 4.19$, k = 1285, $p_{corrected} < .001$; extending to x = 16, y = 24, z = 1, $Z = 3.25$) (Figure 1).

To explore whether the interaction of maltreatment and rs53576 was moderated by gender, gray matter values within the left ventral striatum were extracted at x = −9, y = 16, z = −8 and further analyzed using SPSS 22.0 (IBM Corp., Armonk, NY). The factors genotype and gender, with CTQ scores as covariate, were entered into an analysis of covariance model, including the three-way interaction term of genotype × gender × CTQ scores. The three-way interaction was not significant ($p = .49$), indicating no influence of gender on the observed G × E effect.

For an analysis of different CTQ subscales, see the Supplement.

Table 1. Sample Characteristics ($N = 309$) Stratified According to *OXTR* rs53576

	AA/AG ($n = 170$)	GG ($n = 139$)	p Value[a]
Age	34.6 ± 11.2	33.9 ± 11.2	.57
Sex (M/F)	73/97	65/74	.50
Verbal IQ[b]	114.6 ± 11.9	115.6 ± 13.0	.47
Education, Years	15.2 ± 2.1	14.9 ± 2.1	.25
STAI-Trait	31.8 ± 7.0	31.8 ± 6.9	.98
BDI	2.4 ± 3.4	1.9 ± 2.9	.16
TPQ Reward Dependence[c]	17.5 ± 4.3	17.1 ± 3.9	.48
CTQ	33.4 ± 9.0	33.3 ± 9.0	.91

Values are mean ± SD or *n*.

BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire; F, female; M, male; STAI, State-Trait Anxiety Inventory; TPQ, Tridimensional Personality Questionnaire.

[a]According to *t* tests or χ^2 tests.

[b]Assessed with the Mehrfachwahl-Wortschatz-Test [Multiple-Choice Vocabulary Test (31)]. The Multiple-Choice Word Test-B shows high correlations with Wechsler Adult Intelligence Scale verbal IQ scores but was reported to overestimate intelligence by up to 15 IQ points (72).

[c]Data available for $n = 119$ A-allele carriers vs. $n = 102$ GG homozygotes.

fMRI Results

In line with previous studies, a main effect of maltreatment emerged mapping to the right amygdala, x = 30, y = 0, z = −20, $Z = 2.42$, k = 56, $p_{corrected} = .021$. A main effect of genotype was also found. Replicating Tost *et al.* (10), GG homozygotes showed increased amygdala responsiveness to angry and fearful faces, relative to A-allele carriers (x = 34, y = 0, z = −24, $Z = 2.48$, k = 71, $p_{corrected} = .012$) (Figure 2). However, no significant interaction of genotype and maltreatment emerged ($p = .23$). For whole-brain fMRI data, see the Supplement.

Association of Brain Structure and Function With Reward Dependence

RD scores from the Tridimensional Personality Questionnaire were available from $n = 221$ subjects. A significant positive association of RD and ventral striatum gray matter volume was observed ($r_S = .253$, $p = .003$). For visualization purposes, we also conducted a voxelwise regression of RD scores on gray matter volume that yielded a large spatial overlap with the ventral striatum cluster that showed G × E effects (Supplemental Figure S2).

There was no significant association of reward dependence and amygdala responsiveness to aversive facial expressions ($p = .602$).

DISCUSSION

In this study, we investigated the neurostructural and functional underpinnings of a recently reported gene (*OXTR* rs53576) × environment (maltreatment) interaction that has been described on the phenotype level in previous studies

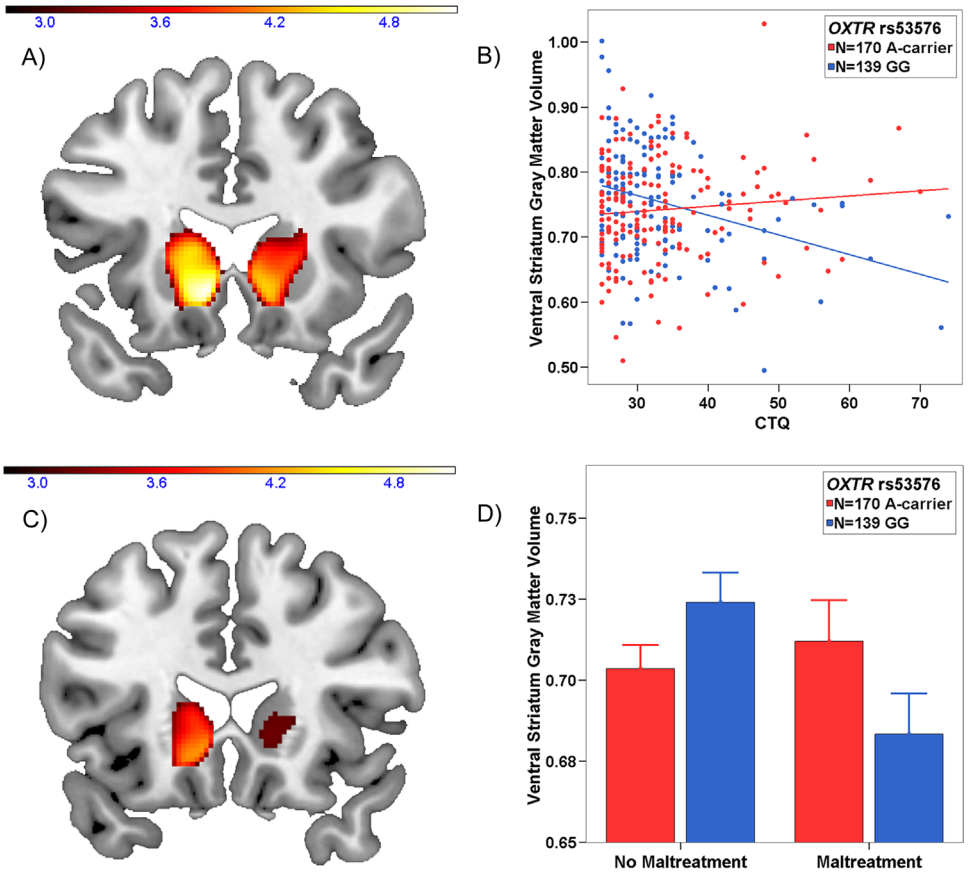

Figure 1. Interaction of *OXTR* rs53576 and childhood maltreatment on gray matter structure. Coronal views **(A, C)** through the ventral striatum showing the effect of childhood maltreatment (Childhood Trauma Questionnaire [CTQ] scores) on gray matter volume as a function of *OXTR* rs53576 genotype (n = 170 A-carriers vs. n = 139 GG homozygotes). Analysis depicts the interaction term (color bar = Z value). For both analyses, voxel threshold was set to $p <$ .001, with an empirically determined cluster threshold of k = 458. Top panels **(A, B)**: Analysis using Childhood Trauma Questionnaire scores as dimensional measure. Bottom panels **(C, D)**: Analysis using dichotomized groups (maltreatment history: yes vs. no). Error bars = SEM.

(16-18). On a neurostructural level, we observed a strong and highly significant interaction of *OXTR* rs53576 genotype and childhood maltreatment, mapping to the bilateral ventral striatum. GG homozygotes revealed a negative correlation of gray matter volume and the degree of childhood maltreatment, whereas A-allele carriers did not show this detrimental maltreatment effect. These results fit with three previous G × E studies in which G-allele carriers showed increased symptoms of depression, less resilient coping style, and positive affect but higher levels of internalizing symptoms such as anxiety, depression, or social withdrawal only when exposed to higher levels of early stressful experiences. In contrast, A-allele carriers appeared to be protected from these maltreatment-associated consequences (16-18). Furthermore, as a potential correlate on the phenotypical level in our study, gray matter volume of the ventral striatum was positively associated with reward dependence, a personality trait associated with sociability, improved learning from interpersonal feedback, and dependence on social approval, whereas low reward dependence is characterized by cold and socially detached traits.

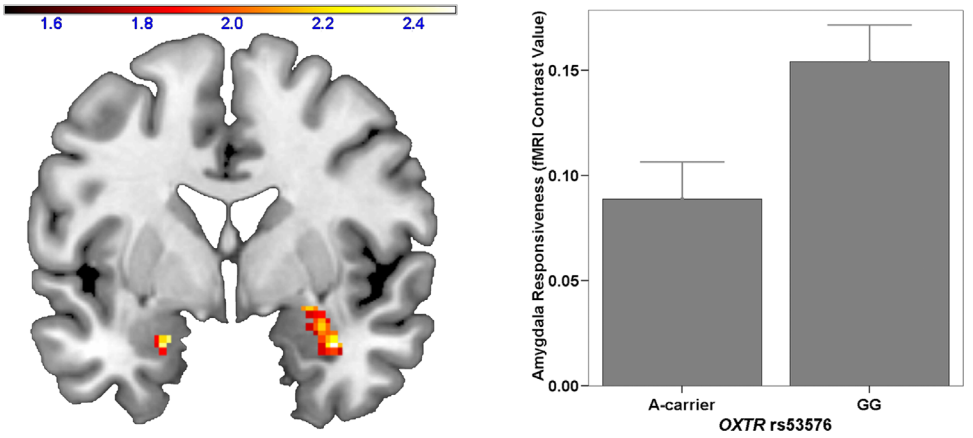

Figure 2. Main effect of *OXTR* rs53576 genotype on amygdala responsiveness to angry and fearful facial expressions. Left: Coronal view through the amygdala depicting genotype-dependent amygdala responsiveness (n = 144 A-carriers vs. n = 120 GG homozygotes), thresholded at $p <$ .05, k = 38 voxels (the cluster depicted in the left amygdala did not survive this cluster threshold). Color bar = t value (df = 262). Right: Bar graph depicting functional magnetic resonance imaging (fMRI) contrast value at x = 30, y = 0, z = −20, as a function of genotype group. Error bars = SEM.

The ventral striatum is a key structure of the reward circuitry (53), which has been implicated in the etiology of several psychiatric disorders, particularly major depression (54-56) and addiction (57). Hence, impairment of striatal gray matter structure with increasing levels of experienced childhood maltreatment observed in our GG homozygotes might correspond with epidemiological findings demonstrating that early maltreatment experiences increase the risk, particularly for these disorders in later life (58).

A second finding is that GG homozygotes revealed stronger amygdala responsiveness to emotional cues than A-allele carriers. This is a direct replication of Tost *et al.* (10), who obtained the same results in the same direction with the same paradigm. This paradigm is one of the most frequently used tasks for activating limbic structures in fMRI studies, particularly the amygdala; it employs images of angry and fearful facial expressions but not positive facial affect.

At first sight, both our findings seem to contradict many earlier studies that showed that the *OXTR* rs53576 G-allele carriers are more empathetic, prosocial, optimistic, and self-confident (7–9) and show higher levels of reward dependence (10) and positive affect (12) but lower levels of loneliness (13) and harm avoidance (14) than A-allele carriers. Furthermore, G-allele carriers appear to benefit more from social support when facing stressful situations (15) and show less physiological and dispositional stress reactivity (7).

However, given our own findings and the recent G × E studies cited above, the notion of a protective or beneficial G-allele has to be reconsidered. Our data suggest that *OXTR* genotype might not influence beneficial or unfavorable traits directly but might modulate receptiveness for (or the salience of) the social environment. This would also explain the increased limbic responsiveness to emotional social cues observed in G-allele carriers. In G-allele carriers, increased amygdala responsiveness to emotional signals might correspond with enhanced processing of these cues. This increased responsiveness might also be observed for positive facial expressions, which neither our study nor the previous studies can prove because such stimuli were not used in the paradigm. However, since the degree of amygdala responsiveness to negative facial expressions has been associated with unfavorable traits such as anxiety (47,48,59), clinical depression (60,61), and evaluative bias for negative stimuli (62,63), while the degree of amygdala responsiveness to positive facial expressions has been associated with emotional awareness (64), extraversion (65), trait happiness (66), and lack of anxiety (67), it seems that the dominating valence of social-environmental stimuli in individuals with high amygdala responsiveness also dominates their trait characteristics later in life. In other words, if G-allele carriers show increased amygdala responsiveness to emotional signals in general, the resulting phenotype would indeed depend much on the environment. A warm and stable environment, mainly providing emotionally positive signals, would lead to a beneficial development, whereas a harmful environment containing a critical mass of aversive, threatening cues would result in detrimental effects on the emotional development and the vulnerability for psychiatric disorders. This receptiveness for environmental cues appears to be less pronounced in A-allele carriers, who therefore might profit less from beneficial environments but are more resilient to the detrimental effects of childhood maltreatment.

This explanation fits well with the differential susceptibility model (68), which argues that it is evolutionary plausible that the same genetic variant could be associated with favorable traits in beneficial environmental settings but at the same time convey higher risk for psychiatric disorders in adverse environments.

As a secondary finding, several brain areas showed a negative association of gray matter volumes and maltreatment severity, irrespective of genotype (Supplemental Table S1), albeit not at a significance level corrected for the entire brain. Among the areas showing reduced gray matter volumes with increasing levels of maltreatment are the hippocampal formation and caudate nucleus, as well as temporal, occipital, and frontal cortex areas already shown to be impaired in maltreated subjects in several previous studies (58).

In sum, the present study sheds new light on the role of genetic variation in the *OXTR* gene that seems to alter limbic brain structure and function dependent on early environmental influences. Strengths of our study are the large and well-characterized sample, particularly for an imaging study, the multimodal imaging approach, and the statistically strong and regionally specific findings matching the expression pattern of *OXTR*.

Limitations include the retrospective nature of questionnaire assessment of maltreatment experiences and the fMRI paradigm lacking positive emotional stimuli. Given recent studies showing that oxytocin administration modulates and partly reverses altered resting state amygdala-prefrontal connectivity patterns associated with emotional abuse in childhood (69,70), analyses of connectivity measures might have complemented the present findings. Unfortunately, we did not employ a resting state sequence, which should be included in future studies. Furthermore, future studies could study epigenetic variation in the *OXTR* gene (4,71), investigate specific groups of highly maltreated participants and/or clinical samples, and assess family history for major psychoses, ideally in a longitudinal design during critical periods of brain development.

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ARTICLE INFORMATION

From the Department of Psychiatry (UD, DG, RR, NO, KD, DZ, AG, JS, PO, JB, CH, VA), University of Münster, Münster; Department of Psychiatry (UD, AK, TK, AJ), University of Marburg, Marburg; Department of Clinical Radiology (HK, WH), University of Münster, Münster; Department of

Psychosomatics and Psychotherapy (TS), University of Leipzig, Leipzig; Department of Psychiatry (KD), University of Würzburg, Würzburg; Department of Psychology (PZ), University of Münster, Münster; and Department of Psychology (MH) and Freiburg Brain Imaging Center (MH), University Medical Center, University of Freiburg, Freiburg, Germany; and Discipline of Psychiatry (BTB), School of Medicine, University of Adelaide, Adelaide, Australia.

UD and HK contributed equally to this work.

Address correspondence to Udo Dannlowski, M.D., Ph.D., University of Münster, Department of Psychiatry, Albert-Schweitzer-Str. 11, Münster 48149, Germany; E-mail: dannlow@uni-muenster.de.

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