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Influence of the catechol-*O*-methyltransferase val158met genotype on amygdala and prefrontal cortex emotional processing in panic disorder

Katharina Domschke[a,1], Patricia Ohrmann[a,1], Miriam Braun[a], Thomas Suslow[a], Jochen Bauer[a], Christa Hohoff[a], Anette Kersting[a], Almut Engelien[a,c], Volker Arolt[a], Walter Heindel[b], Jürgen Deckert[a,d,*], Harald Kugel[b]

[a]*Department of Psychiatry, University of Muenster, Albert-Schweitzer-Str. 11, D-48143 Muenster, Germany*
[b]*Department of Clinical Radiology, University Hospital of Muenster, Muenster, Germany*
[c]*IZKF-Research Group 4, IZKF Muenster, University of Muenster, Germany*
[d]*Department of Psychiatry, University of Wuerzburg, Germany*

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Abstract

Panic disorder is an anxiety disorder with an estimated heritability of up to 48%. The functional val158met polymorphism in the catechol-*O*-methyltransferase (COMT) gene has been found to be associated with panic disorder and to influence limbic and prefrontal brain activation in response to unpleasant stimuli. In the present study, neuronal activation following emotional stimulation was used as an endophenotype and investigated for association with the COMT val158met polymorphism in panic disorder. Twenty patients with panic disorder were scanned by means of functional magnetic resonance imaging at 3 Tesla under visual presentation of emotional faces and genotyped for the COMT val158met polymorphism. In response to fearful faces, increased activation in the right amygdala was observed in patients carrying at least one 158val allele. Increased activation or less deactivation associated with the 158val allele was seen upon presentation of fearful, angry and happy faces in the orbitofrontal and ventromedial prefrontal cortex, respectively. Our data provide preliminary evidence for a role of the functional val158met COMT polymorphism in amygdala and prefrontal activation in response to emotional faces in panic disorder. This COMT variant might increase the vulnerability to panic disorder by modulating dopaminergic tonus in relevant brain regions and thus altering neuronal processing of anxiety-related emotional cues.

Keywords: Anxiety disorder; COMT; fMRI; Emotional faces; Endophenotype

* Corresponding author. Department of Psychiatry, University of Wuerzburg, Füchsleinstrasse 15, D-97080 Wuerzburg, Germany. Tel.: +49 931 20177000; fax: +49 931 20177020.
E-mail address: Deckert_J@klinik.uni-wuerzburg.de (J. Deckert).
[1] This is to indicate that Katharina Domschke and Patricia Ohrmann contributed equally to this work and should therefore both be considered first authors.

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1. Introduction

Panic disorder is an anxiety disorder characterized by sudden attacks of intense fear with a lifetime prevalence of 1–3% (Weissman et al., 1997). Twin studies propose a strong genetic contribution to the pathogenesis of panic disorder with an estimated heritability of up to 48% (Hettema et al., 2001).

Catechol-O-methyltransferase (COMT) is a methylation enzyme metabolizing monoaminergic neurotransmitters including dopamine (Weinshilboum et al., 1999). In patients with anxiety states, significantly elevated erythrocyte COMT activity has been reported (Shulman et al., 1978). COMT inhibitors are effectively used in the treatment of Parkinson's disease, which is associated with panic attacks in up to 40% of patients (Richard et al., 1996). Pharmacological treatment of panic patients with L-dopa and the dopaminergic agent bupropion was shown to result in an improvement in panic symptoms (Vazquez et al., 1993; Simon et al., 2003) and severity of anxiety in Parkinson's patients was correlated with lower dopamine transporter binding, suggesting that anxiety in Parkinson's disease is associated with a specific loss of dopamine in the limbic system (Remy et al., 2005).

A single-nucleotide polymorphism (472G/A) in the COMT gene mapped to chromosome 22q11.2 causes an amino acid change from valine to methionine at position 158 (V158M) with the valine (val) allele (472G) being associated with a three- to four-fold higher COMT activity as compared with the methionine (met) allele (472A) (Lachman et al., 1996; Chen et al., 2004). To date, seven association studies of this polymorphism in panic disorder have been published with contradictory results of association with the valine allele (Hamilton et al., 2002; Domschke et al., 2004; Rothe et al., 2006) in predominantly Caucasian populations and no association or a tentative association with the methionine allele, mostly in Asian populations (Ohara et al., 1998; Woo et al., 2002, 2004; Samochowiec et al., 2004).

Inconsistencies in association findings with panic disorder have been suggested to be in part due to the heterogeneity of the clinically defined panic disorder phenotype. Neuronal activation patterns as measured by functional magnetic resonance imaging (fMRI) following emotional stimulation in brain regions critical for emotional and learning processes might more closely reflect genetic function (Hariri and Weinberger, 2003) and therefore serve as a promising novel endophenotype for genetic studies in panic disorder. With regard to COMT, the val158met polymorphism has been found to be associated with prefrontal executive functions, with prefrontal fMRI response, and with activation in limbic and prefrontal brain areas in response to unpleasant pictures in healthy probands (Egan et al., 2001; Smolka et al., 2005).

Given the probable physiological and genetic influence of COMT on the pathogenesis of panic disorder on the one hand and the role of COMT activity in brain regions critical for emotional and learning processes on the other hand, in the present study we for the first time investigated regional brain activation in response to emotional stimuli using fMRI in relation to the COMT val158met variant in a sample of patients with panic disorder.

2. Methods

2.1. Subjects

A sample of 20 unrelated German patients with panic disorder was investigated in this study (female = 12, male = 8, average age 36.75 ± 9.39). Panic disorder was diagnosed by experienced psychiatrists on the basis of medical records and a structured clinical interview (SKID-I) according to the criteria of DSM-IV (Wittchen et al., 1997). Only patients with primary panic disorder were included; secondary lifetime diagnoses were social phobia in 10 patients and major depression in five patients. Ten patients were treated with a selective serotonin re-uptake inhibitor (SSRI), and the other 10 patients were free of medication. The study was approved by the local ethical committee, and informed consent was obtained from all participating subjects.

2.2. Facial emotion presentation

Facial stimuli consisted of gray-scale normalized fearful (F), angry (A), happy (H) and neutral (N) expressions of 10 individuals (Ekman and Friesen, 1976). Patients were presented with 30-s blocks of alternating emotional (F, A, H or N) faces or a no-face control stimulus (a gray rectangle). Within unmasked blocks, emotional stimuli were presented twice per second in a random sequence for 500 ms. Within masked blocks, emotional faces were shown twice per second for 33 ms followed by a neutral face mask of 467-ms duration. The no-face control stimulus was shown for 450 ms followed by a blank screen for 50 ms. The order of the 30-s blocks containing facial stimuli was counterbalanced across subjects. There were four counterbalanced orders of presentation (Latin square design) [1. c (no-face control epoch), A, c, F, c, H, c, N, c, A, c, F, c, H, c, N; 2. c, F, c, N, c, A, c, H, c, F, c, N, c, A, c, H; 3. c, N, c, H, c, F, c, A, c, N, c, H, c, F, c, A; 4. c, H, c, A, c, N, c, F, c, H, c, A, c, N, c, F]. Thus, each face epoch was preceded by a no-face control