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Research paper

# Interplay between *COMT* Val158Met, childhood adversities and sex in predicting panic pathology: Findings from a general population sample

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ABSTRACT

*Background:* The single nucleotide polymorphism rs4680 of the catechol-O-methyltransferase (*COMT*) gene has been implicated to be involved in the etiopathogenesis of panic. However, it remains unresolved whether rs4680 modifies the risk-association between early life stress and subsequent development of panic pathology.
*Methods:* The genotype of rs4680 was determined for n = 2242 adults with European ancestry from the Study of Health in Pomerania (SHIP, a regional longitudinal cohort study from northeastern Germany). Lifetime fearful spells, panic attacks and panic disorder were assessed according to DSM-IV in 2007–2010 (when participants were aged 29–89) using the Munich Composite International Diagnostic Interview (DIA-X/M-CIDI). Childhood adversities were assessed with the Childhood Trauma Questionnaire (CTQ).
*Results:* Logistic regressions with interaction terms (adjusted for sex and age) revealed that rs4680 interacted with total childhood adversity, emotional abuse and physical abuse in predicting panic disorder: Respective childhood adversities predicted panic disorder in carriers of the Val/Met or Met/Met genotype, but not Val/Val genotype. Moreover, a 3-way interaction was found between rs4680, emotional abuse and sex in predicting panic attacks: Emotional abuse predicted panic attacks among male carriers of the Val/Val genotype and female carriers of the Val/Met or Met/Met genotype, but not among male carriers of the Val/Met or Met/Met genotype or female carriers of the Val/Val genotype.
*Limitations:* Genotype data were derived by imputation. Childhood adversities and panic were assessed retrospectively.
*Conclusions:* Especially (female) carriers of the Val/Met or Met/Met genotype of rs4680 might profit from targeted early interventions to prevent the onset of panic after childhood adversities.

## 1. Introduction

*COMT* is located on chromosome 22q11.2 and encodes catechol-O-methyltransferase, which catalyzes the inactivation of mono-aminergic neurotransmitters by an extra-neuronal transfer of a methyl group to catechol compounds (Domschke et al., 2004). Its coding sequence contains the non-synonymous single-nucleotide polymorphism (nsSNP) rs4680 (472 G/A), which causes the substitution of valine (Val) by methionine (Met) at codon 158 (Val158Met). The Met allele - as compared to the Val allele - is associated with lower *COMT* enzyme activity, slower dopamine catabolism and higher cortical dopamine levels (Chen et al., 2004; Domschke et al., 2004; Lachman et al., 1996; Lee and Prescott, 2014). rs4680 has been implicated to be involved in the etiopathogenesis of a range of mental disorders including panic pathology (Domschke et al., 2007; Howe et al., 2016).

Previous studies on associations between rs4680 and panic disorder were characterized by inconsistent findings: Either the Val allele (Domschke et al., 2007, 2004; Howe et al., 2016; Rothe et al., 2006) or

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the Met allele (Woo et al., 2004, 2002) were identified as the risk variant or no significant associations with panic disorder were found (Gatt et al., 2015; Hettema et al., 2008; Konishi et al., 2014; Watanabe et al., 2017; Wray et al., 2008). Moreover, patients with panic pathology carrying the Val allele showed increased amygdala activation in response to fearful faces (Domschke et al., 2008). In non-clinical samples, carriers of the Met allele demonstrated increased defensive mobilization (as, for instance, indicated by an heightened fear-potentiated startle reflex to unpleasant pictures as well as deficient fear inhibition and extinction) (Lonsdorf et al., 2009; Montag et al., 2008; Wendt et al., 2015), which has been associated particularly with panic pathology (Duits et al., 2015).

Additional evidence suggests rs4680 to be differentially involved in panic pathology in females vs. males (Domschke et al., 2007, 2004; Olsson et al., 2005; Rothe et al., 2006). However, findings were inconclusive and showed either the Val allele (Domschke et al., 2004; Rothe et al., 2006) or the Met allele (Olsson et al., 2005) to be more strongly associated with panic or closely associated anxiety phenotypes in females vs. males. Moreover, it might be conceivable that rs4680 interacts with other genes with sex-specific effects in predicting panic pathology, which could further explain differential associations in females vs. males (McGregor et al., 2016; Reif et al., 2012).

Moreover, there is some (albeit inconsistent) evidence for rs4680 to alter the risk of developing panic in response to environmental adversities: Baumann et al. (2013) demonstrated that childhood adversities were more strongly associated with anxiety sensitivity (an endophenotype closely related to panic pathology (McNally, 2002; Schmidt et al., 2006)) in carriers of the Met/Met vs. Val/Val or Val/Met genotype. Hettema et al. (2015), however, found that rs4680 did not interact significantly with chronic stress in predicting panic or agoraphobic symptoms. Research on interactive effects between rs4680 and different types of childhood adversities in predicting differently severe forms of sub-threshold and full-threshold panic pathology, however, is lacking so far.

Previous research suggests that early life stress might induce prolonged unfavorable changes in psychobiological stress responsivity, associated with an increased long-term risk for mental disorders (Asselmann et al., 2018; Frodl and O'Keane, 2013; Hanson et al., 2015; Heim and Binder, 2012; Lupien et al., 2009). Such unfavorable changes might, for instance, lead to heightened defensive mobilization, which might trigger the development of panic pathology after exposure to subsequent adversity (Asselmann et al., 2018; Duits et al., 2015; Grillon et al., 2008; Lissek et al., 2009). Therefore, interactive effects between rs4680 and childhood adversities in predicting panic pathology seem to be of particular importance.

Epidemiological findings further indicate that fearful spells (milder forms of panic attacks associated with no or fewer panic symptoms and/or lacking crescendo in symptom onset) and panic attacks temporally often precede the onset of full-threshold panic disorder (Asselmann et al., 2014a, 2016, 2014b). Considering fearful spells and panic attacks in addition to panic disorders thus promises to gain further insights into the early developmental pathways into panic pathology.

In summary, although rs4680 as well as interactive effects between rs4680 and environmental adversities have been associated with anxiety, panic or closely associated outcomes, previous findings are inconclusive. It remains unresolved whether rs4680 alters the risk of developing differently severe forms of sub-threshold and full-threshold panic pathology in response to different types of childhood adversities and whether respective GxE interactions vary by sex.

Using epidemiological data from an adult general population sample with European ancestry, this study aims to examine interactive effects between rs4680, different types of childhood adversities and sex in predicting differently severe forms of lifetime panic pathology (fearful spells, panic attacks and panic disorder). Based on previous findings (Baumann et al., 2013), we expect that rs4680 and childhood adversities interact in predicting lifetime panic pathology in a way that childhood adversities are associated with panic pathology more strongly among carriers of the Val/Met or Met/Met (vs. Val/Val) genotype. Respective GxE interactive effects should be more pronounced in females vs. males (3-way interaction between rs4680, childhood adversities and sex).

## 2. Materials and methods

### 2.1. Sample

Data come from the Study of Health in Pomerania (SHIP) (Grabe et al., 2005; Volzke et al., 2011). SHIP is a cohort study based on a two-stage stratified cluster sample with European ancestry randomly drawn from the adult German general population with European ancestry (aged 20–79 years at baseline/ SHIP-0) in northeastern Germany (comprising 3 cities and 29 communities; total population: n = 212,157 individuals; net sample: n = 6267 individuals). Participants were examined in up to 4 assessment waves over up to 17 years (baseline: SHIP-0, 1997–2001, n = 4308; 5-year follow-up: SHIP-1, 2002–2006, n = 3300; 11-year follow-up: SHIP-2, 2008–2012, n = 2333; 17-year follow-up: SHIP-3, 2014–2016, n = 1718). Information on health- and disease-related conditions was collected using various types of assessment.

From 2007–2010, SHIP-LEGEND (Life-Events and Gene-Environment-Interaction in Depression) was conducted among n = 2400 individuals from SHIP-0 (response rate 67%). In June 2007, n = 383 individuals from SHIP-0 were deceased and n = 256 refused further study participation, resulting in n = 3669 individuals invited for study participation. n = 92 individuals deceased over the study course, n = 1011 refused to participate, n = 132 did not respond to repeated efforts of contact and n = 35 individuals did not show up repeatedly or were not able to arrange an appointment. The overall response rate in SHIP-LEGEND was 67% (of those who were invited and not deceased until investigation).

Written informed consent was obtained from all participants. SHIP was approved by the ethics committee of the University of Greifswald and complies with the Helsinki Declaration of 1975, as revised in 2013.

### 2.2. Diagnostic assessment

Lifetime information on symptoms, syndromes and diagnoses of mental disorders including additional data on onset, duration, and severity was assessed face-to-face at SHIP-LEGEND using the fully standardized and computerized Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen and Pfister, 1997). The DIA-X/M-CIDI is an updated version of the World Health Organization's CIDI version 1.2 (World Health Organization, 1990) with additional questions to cover DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1991) criteria. Reliability and validity of the DIA-X/M-CIDI have been shown to be high; more detailed information on the DIA-X/M-CIDI including its psychometric properties has been presented previously (Reed et al., 1998; Wittchen et al., 1998). Clinical interviewers were initially trained and closely supervised throughout the trial.

Information on panic pathology including the non-exclusive categories fearful spells, panic attacks and panic disorder was assessed in the M-CIDI section for panic disorder. The category of fearful spells refers to individuals who affirmed the M-CIDI stem question for panic disorder (“Have you ever had an attack when all of a sudden you felt frightened, anxious or very uneasy?”) meeting or not meeting criteria for panic attacks or panic disorder. The category of panic attacks refers to individuals who met DSM-IV criteria for panic attacks, meeting or not meeting criteria for panic disorder. The category of panic disorder refers to individuals who met criteria for panic disorder.