RESEARCH

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COMT Val158Met–Stress Interaction in Psychosis: Role of Background Psychosis Risk

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SUMMARY

Background: The interplay between the catechol-*O*-methyltransferase (COMT) Val158Met polymorphism and environmental stress may have etiological relevance for psychosis, but differential effects have been reported in healthy control and patient groups, suggesting that COMT Val158Met interactions with stress may be conditional on background genetic risk for psychotic disorder. **Methods:** Patients with a nonaffective psychotic disorder (n = 86) and control participants (n = 109) were studied with the experience sampling method (a structured diary technique) in order to assess stress, negative affect and momentary psychotic symptoms in the flow of daily life. **Results:** Multilevel analyses revealed significant three-way interactions between group status (patient or control), COMT genotype and stress in the model of negative affect ($\chi^2(2) = 13.26$, $P < 0.01$) as well as in the model of momentary psychotic symptoms ($\chi^2(2) = 6.92$, $P < 0.05$). Exploration of the three-way interaction revealed that in patients, COMT genotype moderated the association between stress and negative affect ($\chi^2(4) = 11.50$, $P < 0.005$), as well as the association between stress and momentary psychosis ($\chi^2(4) = 12.79$, $P < 0.005$). Met/Met genotype patients showed significantly increased psychotic and affective reactivity to stress in comparison to the Val/Met and Val/Val genotypes. In contrast, healthy controls did not display large or significant COMT Val158Met X stress interactions. **Conclusions:** Important differences exist in the effect of COMT Val158Met on stress reactivity, which may depend on background risk for psychotic disorder. Differential sensitivity to environmental stress occasioned by COMT Val158Met may be contingent on higher order interactions with genetic variation underlying psychotic disorder.

Introduction

There is evidence that interplay between genes and environment constitutes a sufficient cause for the development of psychotic disorder [1]. Studies that have examined molecular genetic variation associated with differential sensitivity to environmental pathogens remain rare, however, emphasizing the need for further investigation of gene–environment interactions and their neurobiological underpinnings [2].

Environmental stress exposure likely represents an important factor in the developmental trajectory towards psychosis [3]. One area of genetic variation that has been extensively explored as possible moderator of environmental influences in psychosis is the Val158Met functional polymorphism of the catechol-*O*-methyltransferase (COMT) gene. While the Val-allele carriers have been found to be more sensitive to the psychotogenic effects of cannabis [4,5], results of some COMT–stress interaction studies point towards exaggerated sensitivity to stress in Met-carriers. In animal research, transgenic mice overexpressing human COMT-Val polymorphism showed a blunted stress response, while COMT knock-out, "Met-like" mice exhibited increased stress response [6]. Likewise, in an experimental human study, COMT Met158 homozygotes exhibited a markedly potentiated startle reflex in reaction to aversive stimuli compared with Val-carriers, suggesting increased emotional dysregulation in Met-carriers [7]. This heightened emotional reactivity in Met-carriers might also contribute to a higher risk for psychopathology in individuals exposed to stress [8]. The first study evaluating the effect of COMT

Val158Met on stress-reactivity in daily life in patients with a psychotic disorder, in comparison with healthy controls, reported that COMT Val158Met moderated psychotic and emotional reactivity to stress in patients, the Met/Met genotype displaying greatest reactivity to stress [9]. Interestingly, this effect was not found in the healthy controls, suggesting that the COMT Val158Met interactions with stress may be contingent on background of genetic risk for psychotic disorder. Given the fact that the findings reported by van Winkel and colleagues (2008) were based on a relatively small sample of patients and controls who were all daily cannabis users, replication of these findings in a larger sample of patients and healthy controls, with adequate control for cannabis use is necessary.

The experience sampling method (ESM) is a structured diary technique that captures mental states and small stressors in the flow of daily life [10]. ESM allows for a prospective, repeated measure of proximal environmental stress and when combined with genetic information, offers an elegant way to test gene–environment interactions [10,11]. Thus, in an independent sample from that of van Winkel and colleagues (2008) ESM was used to investigate how changes in emotional and psychotic experiences may vary with naturally occurring stressors and molecular genetic variation in COMT. Specifically, it was investigated (i) whether group (patient vs. control) moderated the association between (affective and psychotic) reactivity to stress and the COMT Val158Met polymorphism and (ii) how, in case of a significant interaction, the COMT Val158Met polymorphism moderated affective and psychotic reactivity to daily stress within the two groups.

We hypothesized that heightened affective and psychotic stress reactivity would be evident in patients with the Met/Met genotype, but not in the control sample.

Materials and Methods

Sample

The sample consisted of control subjects and patients diagnosed with a nonaffective psychotic disorder. Prior to entering the study, all subjects were screened. Inclusion criteria were: (1) age 18–65 years; (2) sufficient command of the Dutch language. Exclusion criteria were: (1) brain disease; (2) history of head injury with loss of consciousness. Exclusion criteria for control participants were (3) lifetime history of psychotic disorder or mood disorder; and (4) family history of psychotic disorder. In selected representative geographical areas in the South of the Netherlands and the Dutch-speaking part of Belgium, patients were identified through representative clinicians working in regional psychotic disorder services, whose caseload was screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services either as out-patients or in-patients were recruited for the study. Interview data and clinical record data assessing affective and psychotic symptoms were used in patients and controls to complete the Comprehensive Assessment of Symptoms and History (CASH; [12]) or the Operational Criteria Checklist for Psychotic Illness (OCCPI) yielding DSM-IV diagnoses through the OPCRIT computer program [13]. Controls were selected through a system of random mailings to addresses in the catchment areas of the cases. All participants were derived from two earlier studies [for more information on sample, see 14,15]. The original sample comprised a total number of 316 participants (controls and patients with a nonaffective psychotic disorder). Written informed consent, conforming to the local ethics committee's guidelines, was obtained from all participants.

COMT Val158Met Genotyping

DNA was collected either by buccal mucosa or by blood. Buccal cell samples were collected with sterile swabs (Omniswab, Whatman®). DNA was extracted using QIAamp DNA Mini Kits (Qiagen). DNA of the blood samples was isolated either manually according to the Promega protocol or with the Autogenflex3000.

A single SNP was genotyped using the following TaqMan® SNP Genotyping assay (Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands): rs4680 (assay ID C_25746809_50). The assay was run on a 7900HT Fast Real-Time PCR System (Applied Biosystems).

ESM

The ESM is a structured random time-sampling self-assessment technique to assess mental states and contexts in daily living environments. It is a valid and reliable way to study immediate effects of the environment, reducing biases in recall [10]. Participants received a pre-programmed digital wristwatch and ESM self-assessment forms collated in a booklet for each day. Ten times a day on 6 consecutive days, the watch emitted a signal at unpredictable moments between 7.30 a.m. and 10.30 p.m. After each "beep," subjects were asked to fill out the ESM self-assessment forms previously handed to them, collecting reports of thoughts, current context (activity, persons present and location), appraisals of the current situation, mood and psychotic experiences. All self-assessments were rated on 7-point Likert scales. Participants were instructed to complete their reports immediately after the beep, in order to minimize memory distortions, and to record the time at which they completed the form. During the sampling period, research staff contacted subjects by phone to assess whether they were complying with the instructions. Reports are assumed valid when subjects respond to the beep within 15 min. This was ascertained by comparing the actual beep time with the reported time of completion of the reports. All reports completed more than 15 min after the signal were excluded from the analyses. Participants were only included in the analyses, when they provided valid responses to at least one-third of the emitted beeps [16]. Previous studies have demonstrated the feasibility, validity, and reliability of ESM in general and patient populations [10,17,18].

Measures

Stress reactivity, as described in previous work [9,19], was conceptualized as affective and psychotic reactivity to daily life events and minor disturbances in daily life. Measures of stress, mood, and psychotic symptoms were derived from the experience sampling reports as described below.

Assessment of Momentary Stress

In accordance with previous work, stress was conceptualized as the subjectively appraised stressfulness of distinctive events (event stress) [20]. In order to measure event stress, the subject was asked to report, after each beep, the most important event that had happened between the current and the previous report. This event was subsequently rated on a bipolar Likert scale (−3 = very unpleasant, 0 = neutral, 3 = very pleasant). The responses were recoded to allow high scores to reflect stress (−3 = very pleasant, 0 = neutral, 3 = very unpleasant).

Assessment of ESM Psychosis

Momentary psychosis was defined as the sum score of six ESM items *I feel suspicious*, *I cannot get rid of my thoughts, I am afraid of loosing control*, *I feel unreal*, and *I hear voices, I see phenomena.* All items were rated on 7-point Likert scales (ranging from *not at all* to *very)* (Cronbachs $\alpha = 0.72$).

ESM Hallucinations

Momentary hallucinations were defined as the mean score of 2 ESM items *I hear voices* and *I see phenomena.* Both items were rated on 7-point Likert scales (ranging from *not at all* to *very*) (Cronbachs $\alpha = 0.77$).

ESM Delusions

Momentary delusions were defined as the mean score of four ESM items *I feel suspicious*, *I cannot get rid of my thoughts, I am afraid of loosing control*, and *I feel unreal.* All items were rated on 7-point Likert scales (ranging from *not at all* to *very)* (Cronbachs $\alpha = 0.68$).

Assessment of Negative Affect

After each beep, participants were asked to answer questions regarding their mood, on 7-point Likert scales (1 = not at all, 7 = very). In line with previous reports [19] ESM negative affect was assessed with six mood-related adjectives (down, guilty, insecure, lonely, anxious, and angry/irritated) and were reduced to one measure of the mean Negative Affect (NA) (Cronbach's $\alpha = 0.83$).

Cannabis Measures

We assessed use of cannabis using the L-section of the M-CIDI [21], which includes a variety of other substances. A variable for current cannabis use and cannabis use of the last 12 months was constructed. Drug use information was available for 144 participants.

Statistical Analyses

Multilevel linear regression analysis, which is ideally suited for analyses of clustered data [22], was used since ESM data have a hierarchical structure with repeated momentary measurements per subject. Analyses were carried out with the XTREGAR module in STATA/MP version 10.1 [23]. XTREGAR takes into account clustering of data at the level of the beep (moment of the day, level 1) within individuals (level 2), as well as clustering of observations directly following one another (i.e., autocorrelation).

Outcome variables included in the analyses were standardized by dividing the variables by the group standard deviation of this variable, yielding standardized effect sizes.

In order to test the hypothesis that COMT Val158Met genotype moderates psychotic and affective responses to daily life stress, and whether any moderation differs between patients and controls, a three-way interaction between COMT Val158Met genotype, group and event stress was tested with ESM psychosis (delusions, hallucinations) and ESM NA as the respective dependent variables. The independent variables were COMT Val158Met genotype (0 = Val/Val; 1 = Val/Met; 2 = Met/Met), event stress (–3 = very pleasant, 0 = neutral, 3 = very unpleasant), and group (0 = controls; 1 = patients). Main effects and interactions were assessed by Wald test. Stratified effects were calculated by applying and testing the appropriate linear combinations using the STATA LINCOM command.

Results

Sample

Of the 316 participants (171 patients and 145 controls) who entered the study, 216 provided DNA (98 patients and 118 control participants). Genotyping failed in 13 participants. Two control participants were excluded due to failure to complete the protocol (missing information regarding the time of the beep and completion of questionnaires). An additional five patients and one control were excluded from the analyses as they had an insufficient number of valid ESM observations (<20).

The final sample for analysis thus comprised 195 participants (86 patients and 109 control participants). These participants had each completed an average of 44 valid ESM reports (SD = 9) (control group: 47 (SD = 8) and patients: 40 (SD = 9); β[SE] = −3.5 [.61]; $P < 0.001$). The patients were all diagnosed with a nonaffective psychotic disorder (41 with schizophrenia; 10 with schizoaffective disorder; 26 with psychotic disorder NOS; 1 with schizophreniform disorder; 3 with delusional disorder; 5 with a brief psychotic disorder). Patients with a diagnosis of schizoaffective disorder were retained in the sample since (i) all included patients, including the schizoaffective patients, were not in an acute psychotic or affective episode, and (ii) there is no evidence that affective disorders such as (current) major depressive disorder or bipolar disorder are associated with greater reactivity to stress compared to schizophrenia patients [24].

Additional information regarding number of valid reports and sociodemographic and clinical characteristics of the sample are depicted in Table 1.

COMT Val158Met Genotype

The frequencies of the three COMT genotypes were 24.6% (n = 48) Val/Val, 47.2% (n = 92) Val/Met and 28.2% (n = 55)

Table 1 Demographic characteristics and descriptives

	Patients (n = 86)	Controls (n = 109)	
Age, mean (SD)	32.26 (10.60)	40.17 (13.44)	$\beta = -3.96$, $P < 0.001$
Sex (M/F)	58/28 (67%/33%)	35/74 (32%/68%)	χ^2 (1) = 24.06, $P < 0.001$
Education, n (%)			χ^2 (2) = 23.08, $P < 0.001$
Elementary school	1 (1.22%)	0 (0%)	
Secondary school	63 (76.83%)	48 (44.04%)	
Higher education	18 (21.95%)	61 (55.96%)	
Living situation, n (%)			χ^2 (4) = 58.37, $P < 0.001$
Alone	19 (22.62%)	12 (11.01%)	
With partner	19 (22.62%)	80 (73.39%)	
With parents or family	18 (21.43%)	14 (12.84%)	
Protected housing	21 (25.00%)	1 (0.92%)	
Others	7 (8.33%)	2 (1.83%)	
ESM psychosis, mean (SD)	1.59 (0.79)	1.18 (0.29)	$\beta = 0.21$, $P < 0.001$
ESM delusions, mean (SD)	1.73 (0.92)	1.27 (0.44)	$\beta = 0.23$, $P < 0.001$
ESM hallucinations, mean (SD)	1.32 (0.84)	1.0 (0.02)	$\beta = 0.16$, $P < 0.001$
ESM stress, mean (SD)	−1.34 (0.87)	−1.52 (0.62)	$\beta = 0.092$, $P = 0.085$
ESM negative affect, mean (SD)	1.92 (0.95)	1.34 (0.36)	$\beta = 0.29$, $P < 0.001$
Cannabis use, current (y/n)	37/35 (51.4%/48.6%)	7/65 (90.3%/9.7%)	χ^2 (1) = 29.5, $P < 0.001$
Cannabis use, last 12 months (y/n)	31/26 (54.4%/45.6%)	7/13 (35%/65%)	χ^2 (1) = 2.23, $P = 0.14$
DSM IV diagnosis, No. (%)			
Schizophrenia/psychotic Disorder	41 (47.8%)	–	
Schizoaffective disorder	10 (11.6%)	–	
Other psychotic disorders	35 (40.7%)	–	
No diagnosis	–	109 (100%)	

Note: Cannabis use, measured by the CIDI was available for 144 participants.

Met/Met, and were in Hardy-Weinberg equilibrium (χ^2 (1) = 0.59, $P = 0.44$). Genotype was not associated with age, sex, ESM psychosis, ESM hallucinations, ESM delusions, ESM stress, or NA (Table 2). Also, COMT genotype did not predict current cannabis use or cannabis use in the past 12 months. Moreover, there was no main effect of group on COMT genotype (χ^2(df = 2) = 2.75, $P = 0.25$).

Models for NA

A significant main effect was found for event stress on NA (β[SE] = 0.09 [0.01]; $P < 0.001$). Thus, independent of group or genotype, the more subjective stress participants reported, the more NA they experienced. Furthermore, multilevel analyses revealed a significant three-way interaction between COMT

Table 2 Sociodemographic characteristics and Experience Sampling Method (ESM) measures by genotype

	Patients				Controls			
	Val/Val	Val/Met	Met/Met	*P*	Val/Val	Val/Met	Met/Met	*P*
Group (controls/patients)	20	46	20	0.25	28	46	35	0.25
Age (SD)	31.1 (8.2)	33.4 (11.5)	30.9 (10.7)	0.97	39.8 (14.3)	41.7 (13.6)	38.4 (12.7)	0.64
Sex (M/F)	13/7	30/16	15/5	0.71	8/20	15/31	12/23	0.89
Number of ESM reports (SD)	42.1 (10.1)	39.4 (8.6)	39.3 (9.2)	0.33	47.2 (8.3)	47.8 (7.5)	45.9 (8.7)	0.48
ESM psychosis (SD)	7.8 (3.5)	10.3 (5.5)	9.5 (3.7)	0.26	7.2 (2.1)	6.9 (1.7)	7.1 (1.5)	0.79
ESM delusions (SD)	1.4 (0.7)	1.9 (1.0)	1.8 (0.8)	0.22	1.3 (0.5)	1.2 (0.4)	1.3 (0.4)	0.80
ESM hallucinations (SD)	1.1 (0.3)	1.4 (1.0)	1.3 (0.7)	0.64	1.0 (0.01)	1.0 (0.02)	1.0 (0.01)	0.85
ESM stress (SD)	−1.7 (0.8)	−1.3 (0.8)	−1.0 (1.0)	0.02	−1.4 (0.7)	−1.5 (0.6)	−1.6 (0.6)	0.24
ESM negative affect (SD)	1.6 (0.8)	2.1 (1.0)	1.9 (0.7)	0.39	1.4 (0.4)	1.3 (0.4)	1.3(0.4)	0.37
Cannabis use, current (yes/no)	7/7	18/14	9/10	0.81	0/17	1/28	5/17	0.02
Cannabis use, last 12 months (yes/no)	6/6	14/11	8/8	0.91	0/4	1/5	5/4	0.09

Note: Cannabis use, measured by the CIDI was available for 144 participants.

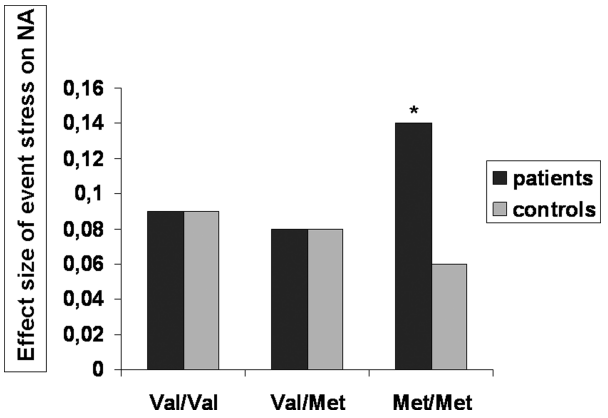

Figure 1 Effect sizes of event stress on NA: effect sizes of the NA response to event stress levels, stratified by COMTVal158Met genotype. *$P < 0.001$ indicates that the difference between COMT Met/Met and COMT Val/Val & Val/Met is significant.

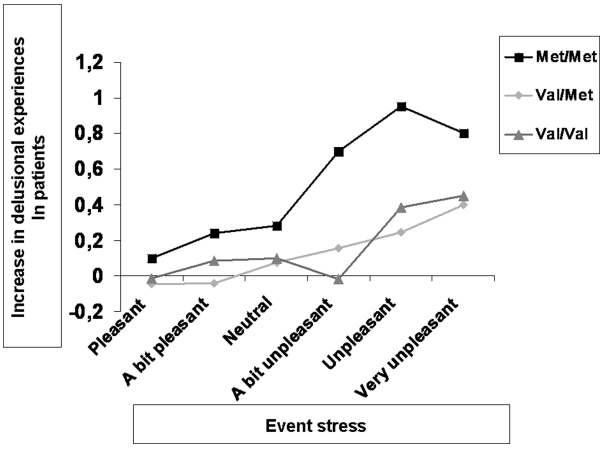

Figure 2 Effect sizes of event stress on momentary delusions in patients: effect sizes of the delusional responses of event stress levels 'pleasant' to 'very unpleasant', stratified by COMT Val158Met genotype. There was a significant two-way interaction in the patient group ($\chi^2(4) = 23.07$, $P < 0.001$).

Val158Met, event stress and group in the model of NA ($\chi^2(\text{df} = 2) = 13.26$, $P < 0.01$), suggesting that the association between stress and NA is moderated by COMT genotype, dependent on group status (patient or control).

Further exploration of the group X COMT Val158Met X ESM stress interaction revealed a strong two-way interaction between COMT Val158Met genotype and ESM stress in the model of NA in patients ($\chi^2(\text{df} = 2) = 11.50$, $P < 0.005$), but not in controls ($\chi^2(\text{df} = 2) = 3.38$, $P = 0.19$). Met/Met genotype patients reported a larger increase in NA after event stress than did Val/Met or Val/Val genotypes (Figure 1; Table 3).

Models for ESM Psychosis

No main effect was found for event stress on ESM psychosis (β[SE] = 0.01 [0.01]; $P = 0.26$). However, a significant three-way interaction between COMT Val158Met genotype, event stress and group in the model of ESM psychosis ($\chi^2(\text{df} = 2) = 6.92$, $P < 0.05$) suggested that the association between event stress and psychosis is not only moderated by COMT Val158Met genotype but is also dependent on group status.

Again, a significant two-way interaction between COMT Val158Met genotype and event stress in the model of ESM psychosis was apparent in the patient group ($\chi^2(\text{df} = 2) = 12.79$, $P < 0.005$), but not in the control group ($\chi^2(\text{df} = 2) = 0.99$, $P = 0.61$). Met/Met genotype patients showed significantly increased psychotic reactivity to stress in comparison to the Val/Met and Val/Val genotypes (Table 3).

Comparable results were found for ESM delusions ($\chi^2(\text{df} = 2) = 13.63$, $P < 0.005$) (see Figure 2 for effect sizes of stratified effects). For ESM hallucinations, neither a significant three-way nor a significant two-way interaction was found.

Sensitivity Analysis in NonCannabis Users

Additional analyses were carried out, investigating whether cannabis use impacted the results. All analyses were repeated with

Table 3 Stratified effects of the interaction between COMT genotype and stress on affective and psychotic reactivity in psychosis patients and healthy controls

		COMT Val158Met genotype					
		Patients			Controls		
		Val/Val	Val/Met	Met/Met	Val/Val	Val/Met	Met/Met
NA	β^a (95% CI; *P*)	0.09 (0.05,0.13; $P < 0.001$)	0.08 (0.06, 0.10; $P < 0.001$)	0.15 (0.11, 0.18; $P < 0.001$)	0.09 (0.06,0.12; $P < 0.001$)	0.08 (0.06, 0.10; $P < 0.001$)	0.06 (0.04, 0.08; $P < 0.001$)
Psychosis	β^b (95% CI; *P*)	0.04 (0.01, 0.07; $P < 0.05$)	0.04 (0.02, 0.05; $P < 0.001$)	0.09 (0.07, 0.12; $P < 0.001$)	0.01 (−0.01, 0.03; $P = 0.3$)	0.02 (0.01, 0.04; $P < 0.05$)	0.03 (0.01, 0.04; $P < 0.05$)

Note: The two-way interactions in the control group were not significant.

[a]Regression coefficient indicates change in negative affect associated with changes in subjectively appraised stress.

[b]Regression coefficient indicates change in ESM psychosis associated with changes in subjectively appraised stress.

exclusion of participants who were current cannabis users or used cannabis in the last 12 months. Apart from some small effect size alterations, results were comparable.

The three-way interaction between COMT Val158Met genotype, event stress and group in the model of NA (χ^2(df = 2) = 15.43, $P < 0.001$), ESM psychosis (χ^2(df = 2) = 15.06, $P < 0.001$) and ESM delusions (χ^2(df = 2) = 20.6, $P < 0.001$) remained significant. Similarly, the two-way interaction between COMT Val158Met genotype and ESM stress in the model of NA, ESM psychosis and ESM delusions was significant in patients (χ^2(df = 2) = 15.50, $P < 0.001$; χ^2(df = 2) = 23.67, $P < 0.001$; χ^2(df = 2) = 31.6, $P < 0.001$, respectively), but not in controls (χ^2(df = 2) = 3.04, $P = 0.22$; χ^2(df = 2) = 1.25, $P = 0.53$; χ^2(df = 2) = 0.39, $P = 0.83$, respectively). Met/Met genotype patients reported a larger increase in NA, ESM psychosis and ESM delusions after event stress than did Val/Met or Val/Val genotypes. Again, for ESM hallucinations, neither a significant three-way nor a significant two-way interaction was found.

Models of Mediated Moderation

Since NA and ESM psychosis were significantly associated (β[SE] = .40 [.01]; $P < 0.001$), models of mediated moderation were also examined. There was no evidence that ESM psychosis was a mediator of the interactive effects of ESM stress and COMT genotype in the model of NA (three-way interaction χ^2(df = 2) = 8.2, $P < 0.05$). The COMT X ESM stress interaction was no longer significant in the model of ESM psychosis after covarying for NA (three-way interaction χ^2(df = 2) = 2.62, $P = 0.27$), however, the interaction did remain significant in the model of ESM delusions (χ^2(df = 2) = 6.31, $P < 0.05$) although with lower effect sizes, suggesting partial mediation by NA in models of psychosis.

Discussion

This study investigated the moderating effect of COMT Val158Met on the association between real-life stress and psychosis as well as on the association between real-life stress and negative affect. It was shown that the immediate effect of daily stress on psychosis and negative affect is not only conditional on COMT Val158Met genotype, but also on group, supporting the hypothesis that this specific instance of gene–environment interaction may be contingent on higher-order interactions with other background genetic risk variants associated with psychotic disorder. COMT Val158Met genotype contributed to differential sensitivity to environmental stress only in the patient group. More specifically, Met/Met genotype patients reported a larger increase in NA and in momentary psychosis (particularly delusions) in reaction to stress than patients with the Val/Met or Val/Val genotype. In addition, no main effects of COMT Val158Met on momentary psychosis or NA were found.

COMT Val158Met and Psychosis

The absence of COMT main effects are in support of earlier case-control studies and meta-analyses examining its association with schizophrenia [25,26], suggesting that the harmful or beneficial effects of COMT Val158Met may be conditional on type, timing and level of environmental exposure, consistent with pleiotropic behavioral effects of COMT genetic variation [27]. Thus, the present results are in support of a recent study by van Winkel and colleagues (2008), reporting that Met/Met genotypes in the patient group were most stress reactive, showing more psychotic symptoms and negative affect in reaction to stress, while no such effect was found in the control sample. However, their study sample consisted exclusively of cannabis users. This study confirmed these initial findings in a much larger sample, with adequate control for the possible confounding effects of cannabis use. Two earlier studies examining psychotic stress response as a function of COMT Val158Met in nonpatient healthy controls are in agreement with the current finding that psychotic stress response in the control group was not contingent on Met/Met genotype [28,29]. However, these two studies also differed in relation to the current results, in that an amplified psychotic stress-response in healthy subjects did show association with Val/Val genotype relative to Met carriers. These studies, however, either used a stress exposure distal to the examined phenotype (army induction) or used a fairly limited assessment of psychotic-like experiences.

COMT Val158Met, Emotional Reactivity and Background Risk for Psychotic Disorder

The finding that COMT Val158Met plays a role in emotional reactivity to stress corresponds with other studies reporting increased sensitivity to stress, anxiety and pain in Met allele carriers [30–32]. Furthermore, a meta-analysis of neuro-imaging studies was in agreement with these findings, showing an increased prefrontal activation in Met-carriers in emotional paradigms [27]. Most of these studies, however, were conducted in general population samples, while the current results only showed increased reactivity for Met/Met genotype patients but not Met/Met genotype controls. A lack of statistical power, given lower variability associated with behavioral measurements of psychopathology in healthy individuals, or demographic differences between the groups may explain absence of COMT X stress interaction in the healthy control group. Another possibility, however, would be that COMT Val158Met interactions with stress may be dependent on background genetic risk for psychotic disorder. Several studies have indeed reported epistatic interactions between COMT Val158Met and other candidate polymorphisms impacting on psychosis risk [33–35].

Association Emotional and Psychotic Reactivity

Models of mediation showed that ESM psychosis was not a mediator of the ESM stress X COMT interaction in the model of NA, whereas NA did have a mediating effect in the model of ESM psychosis. This suggests that the effect on affective outcomes is primary, which may be consistent with the proposed role of stress-reactivity in what has been named the "affective pathway to psychosis" [18]. In the model of momentary delusions, however, NA only partially mediated the interaction between COMT and ESM stress. Thus, while we found a major interactive effect of COMT and ESM stress on negative effect, there also was evidence for

a specific role of the COMT X stress interaction on delusional ideation independent from the association with negative affect.

Strengths and Limitations

Some methodological limitations are apparent. Measurements of momentary psychosis (delusions, hallucinations), NA, and event stress were based on subjective reports. Although it is sometimes assumed that subjective reports are less reliable than objective measures, they can be valid, whereas the validity of objective approaches should not be taken for granted [36]. Another issue in this regard is whether patients with a psychotic disorder were able to provide reliable and valid self-reports. Although, the prospective and real-time nature of ESM makes ESM assessments less prone to recall biases. This might be especially important in patients with psychosis as many of them display cognitive deficits [17]. Second, the current study used a daily life assessment technique in which participants had to comply with a paper-and-pencil diary protocol without the researcher being present. Recently, some authors have cast doubt on the reliability and subject compliance in paper-and-pencil ESM studies, favoring the use of electronic devices [37]. However, in a comparative study, Green et al. concluded that both methods yielded similar results [38]. Third, all analyses were cross-sectional, making it impossible to infer causality. Momentary psychosis and NA may be a reaction to daily stress or daily stress may result in an increase of momentary psychosis and NA. Nevertheless, the effect of COMT genotype on the association between stress and psychosis/NA holds in either case. The use of ESM is also a major strength of the current study, as it provides optimal measures of environmental factors for gene–environment interaction studies. ESM provides a prospective collection of cumulative, repeated measures of proximal environmental risk factors [10,11]. Another strength of the current study is that we included a general population as well as a patient sample and in this way were able to disentangle differential genetic effects between groups. Furthermore, cannabis users as well as no cannabis users were included in the study, thereby providing the possibility to test for the effect of cannabis use on the COMT–stress interaction. The relatively small sample size could have lead to undetected stratification biases. Amongst others, the uneven distribution of males and females between the patient and control sample may be an alternative explanation for the differences between patients and controls. In addition, undetected stratification for variables such as treatment duration, current treatment or symptom profile at intake could have influenced the results. However, since this study is a replication of a previous study in an independent sample, it is unlikely that stratification for any one of these factors can account for the reported results.

Conclusions

Contingent on background liability for psychotic disorder, important differences may exist in the effect of COMT Val158Met on stress reactivity. Therefore, differential sensitivity to environmental stress occasioned by COMT Val158Met may be indicative of higher order interactions with genetic variation predisposing for psychotic disorder.

Conflicts of Interest

The authors have no conflict of interest.

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