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The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the *COMT* Val[158]Met polymorphism

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ABSTRACT

Background: Cannabis use and childhood maltreatment are independent risk factors for the development of psychotic symptoms. These factors have been found to interact in some but not all studies. One of the reasons may be that childhood maltreatment and cannabis primarily induce psychotic symptoms in genetically susceptible individuals. In this context, an extensively studied psychosis vulnerability gene is catechol-methyl-transferase (*COMT*). Therefore, we aimed to examine whether the *COMT* Val[158]Met polymorphism (rs4680) moderates the interaction between childhood maltreatment and cannabis use on psychotic symptoms in the general population.
Method: The discovery sample consisted of 918 individuals from a cross-sectional study. For replication we used an independent sample of 339 individuals from the general population.
Results: A significant three-way interaction was found between childhood maltreatment, cannabis use, and the COMT genotype (rs4680) in the discovery sample ($P = 0.006$). Val-homozygous individuals displayed increased psychotic experiences after exposure to both cannabis use and childhood maltreatment compared to Met-heterozygous and Met-homozygous individuals. Supportive evidence was found in the replication sample with similar effect and direction even though the results did not reach statistical significance ($P = 0.25$).
Conclusions: These findings suggest that a functional polymorphism in the COMT gene may moderate the interaction between childhood maltreatment and cannabis use on psychotic experiences in the general population. In conclusion, the *COMT* Val[158]Met polymorphism may constitute a genetic risk factor for psychotic symptoms in the context of combined exposure to childhood maltreatment and cannabis use.

1. Introduction

A growing body of literature indicates that several environmental risk factors are associated with the occurrence of (sub)clinical psychotic symptoms (Cougnard et al., 2007; van Os et al., 2009). Among these risk factors, childhood trauma has been consistently found to increase the risk for psychotic symptoms, both in psychotic disorders (Read et al., 2005; Bendall et al., 2008) and in the general

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population (Janssen et al., 2004; Lataster et al., 2006; Spauwen et al., 2006; Alemany et al., 2011). In addition, cannabis use is associated with psychosis proneness (Arseneault et al., 2004; Moore et al., 2007; Kuepper et al., 2011b; Large et al., 2011), particularly after early, frequent, and enduring use in adolescence (Henquet et al., 2005; McGrath et al., 2010; Schubart et al., 2010). In light of the established effects of childhood maltreatment and cannabis on psychosis risk, their combination has been suggested to synergistically increase the risk for psychotic symptoms (Compton et al., 2004; Houston et al., 2008; Harley et al., 2010; Konings et al., 2012). However, a relation between childhood trauma, cannabis consumption, and psychosis was not always replicated and contradicting results have been published (Houston et al., 2011; Kuepper et al., 2011a). One of the reasons for these conflicting findings may be that childhood maltreatment and cannabis primarily induce psychotic symptoms in genetically susceptible individuals. In this context, an extensively studied psychosis vulnerability gene is catechol-methyl-transferase (*COMT*) which encodes the prime catecholamine degrading enzyme COMT. A non-synonymous single nucleotide polymorphism (SNP) in the *COMT* gene (rs4680) results in a valine-to-methionine mutation at position 158 (Val^{158}Met). The Val variant possesses increased enzymatic activity compared to the Met variant and directly influences dopamine metabolism with functional impact on the central dopamine system (Mannisto and Kaakkola, 1999). However, the direct effect of this SNP on psychosis and schizophrenia is unconvincing (Fan et al., 2005; Munafo et al., 2005; Okochi et al., 2009). In the context of cannabis use, previous studies investigating the COMT Val^{158}Met genotype as a moderator of the association between cannabis and psychosis found both supportive (Caspi et al., 2005; Henquet et al., 2006; Henquet et al., 2009; Estrada et al., 2011) as well as incongruous results (Costas et al., 2011; van Winkel, 2011; Zammit et al., 2011). Considering the independent effects of cannabis and childhood trauma and their possible interactional effects on (sub)clinical psychotic experiences, we hypothesized that the COMT Val^{158}Met polymorphism moderates the interaction between childhood adversity and cannabis use. More specifically, we hypothesized that Val homozygous individuals are at increased risk for the joint effects of childhood maltreatment and cannabis use on psychotic experiences compared to the other two genotypes. We therefore examined these risk factors and their interaction in a population-based discovery sample and an independent replication sample.

2. Materials and methods

2.1. Samples

2.1.1. Discovery sample

Participants in the discovery sample were recruited using a project website launched in 2006 targeted at Dutch young adults and adolescents from 18 to 25 years (www.cannabisquest.nl) (Schubart et al., 2010). Strategies to generate traffic on the project website included collaboration with over a hundred colleges, universities, and youth centres, as well as the use of online commercial advertisement products (i.e. banners and text links) (Schubart et al., 2010). The chance to win an Apple iPod™ or a Nintendo Wii™ was used as an incentive. Double entries were prevented by exclusion of subjects with an identical e-mail address, surname, and date of birth. Anonymous submission of data was not possible. The online assessment included verification questions to protect against random answers, and participants failing to correctly complete the verification questions were subsequently excluded. From the online data ($N = 17{,}698$), 1259 participants were included for subsequent genetic assessment in two waves. First, in order to increase power for gene × environment interactions (Boks et al., 2007), we prioritized a sample of 719 participants who belonged to the top or bottom quintile of total scores of psychotic experiences as measured by the Community Assessment of Psychic Experiences (CAPE) score (see below) that were either cannabis naïve (i.e. a lifetime cannabis exposure frequency less than 6 times) or were heavy cannabis users (i.e. current expenditure for personal cannabis use exceeded 3€ weekly). Second, an unselected sample of 540 individuals was included. As ascertained with the validated Dutch version of either the Structured Clinical Interview (SCID) (First et al., 1997) or the MINI International Neuropsychiatric Interview (Sheehan et al., 1998), healthy controls had no history of any psychotic disorder. For 84 participants no interview data were available and for these cases, the presence of a psychotic disorder was excluded by the absence of antipsychotic drug use or a history of psychiatric treatment. A significant three-way interaction between childhood maltreatment, cannabis use, and the COMT Val^{158}Met polymorphism remained present after exclusion of the 84 individuals without a diagnostic interview ($P = 0.0064$). The possible concomitant use of recreational drugs was assessed with the substance abuse module of the Composite International Diagnostic Interview (Compton, 1993). Of the 1259 participants that completed comprehensive assessments and provided blood samples for genetic testing, complete data were available for 918 subjects due to a later implementation of the Childhood Trauma Questionnaire (CTQ) assessment in the study, with 525 individuals from the first tier and 393 individuals from the second tier. All participants provided a urine sample to screen for the presence of recreational drugs in order to verify recent self-reported cannabis use. The study was approved by the Ethical Review Board of the University Medical Center Utrecht and all participants gave written informed consent.

2.1.2. Replication sample

Healthy participants were selected from the Genetic Risk and Outcome of Psychosis (GROUP) study, a multisite longitudinal cohort study in The Netherlands and Belgium investigating schizophrenia patients, siblings, and healthy controls (Korver et al., 2012). In selected representative geographical areas in The Netherlands, controls were selected through a system of random mailings in the catchment areas of the cases. The full GROUP sample consists of patients with non-affective psychotic disorder, siblings of these patients, parents of the patients and their siblings, and unrelated controls. General inclusion criteria were: (1) age range of 16–50 years and (2) good command of the Dutch language. Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree or second-degree family member with a history of psychotic disorder as established by the Family Interview for Genetic Studies. Out of 419 healthy controls, we succeeded in obtaining complete data for 339 individuals, of which 285 healthy controls were assessed at two time points and 54 healthy controls only once. Thus, in total, 624 measurements were available for the analysis ($285 \times 2 + (339 - 285)$). Of the 339 healthy controls, 41 individuals were related healthy siblings, i.e. more than one individual from a healthy family. The study protocol was approved centrally by the Ethical Review Board of the University Medical Center Utrecht and subsequently by local review boards of each participating institute. All participants gave written informed consent.

2.2. Measures

2.2.1. Cannabis consumption

In the discovery sample, cannabis use was defined as current use more than an equivalent of 3€ euro per week (roughly equivalent to weekly cannabis use) during the last month or longer. The monetary amount spent on cannabis has been reported as a valid proxy of exposure to Δ^9-tetrahydrocannabinol (THC) (Niesink et al., 2009). In the replication sample, cannabis use was derived from the Composite International Diagnostic Interview (CIDI) with the pattern of cannabis use during the last year as main outcome (hereafter referred to as 'cannabis use') (van Winkel, 2011). Outcomes of cannabis use during

the last year were: none (0), less than weekly (1), weekly (2), and daily (3). Moreover, a dichotomous cannabis measure (cannabis use versus no cannabis use) was analyzed in the replication sample to allow for a direct comparison with the discovery sample with regard to cannabis use.

2.2.2. Childhood maltreatment

In both the discovery and replication samples, childhood maltreatment was assessed using the 25-item version of the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998). The CTQ assesses five types of self-report childhood trauma: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. The validity of the CTQ, including a Dutch translation, has been demonstrated in clinical and community samples (Bernstein and Fink, 1998; Thombs et al., 2009). One translated item ("I believe I was molested") was excluded in the discovery sample as this translation was found to be an invalid indicator of childhood sexual abuse in a previous validation study (Thombs et al., 2009). Childhood maltreatment was used as the continuous sum score divided by the number of completed items. One item of the CTQ in the discovery sample was only available for a subset of the discovery sample ("My family was a source of strength and support"). Additional analyses in which this item was excluded altogether did not affect the results. In the replication sample, all CTQ items were available.

2.2.3. Psychotic experiences

The Community Assessment of Psychic Experiences (CAPE) was used to assess psychotic experiences in both samples. This validated 42-item self-report questionnaire measures the prevalence of psychotic experiences on a frequency scale ranging from 'never' (1), 'sometimes' (2), 'often' (3), to 'nearly always' (4) and displays discriminative validity in assessing psychotic experiences in the general population (Konings et al., 2006). Scores were transposed to zero for absent symptoms and divided by the number of completed items to deal with missingness as previously described (Konings et al., 2006). Thus, total CAPE scores may vary between 0 and 3. From the total CAPE score, dimensions of positive, negative, and depressive symptoms may be extracted which are significantly correlated (Stefanis et al., 2002). Therefore, we also analyzed the effects of childhood maltreatment, cannabis use, and the COMT Val^{158}Met genotype on these three dimensions of psychosis for the discovery sample using multiple analysis of covariance (MANCOVA).

2.3. Genotyping procedures

2.3.1. Discovery sample

All participants were of Dutch ancestry. Genotype data were generated on three different array platforms: the IlluminaHumanOmniExpress (N = 576), the IlluminaHuman610-QuadBeadchip (N = 768), and the IlluminaHumanHap550 array (N = 34). For each SNP platform, quality control procedures were initially performed separately using PLINK V1.07 (Purcell et al., 2007). Subjects were excluded based on >5% missing genotypes and gender errors. We used linkage disequilibrium (LD) based SNP pruning to select the most informative SNPs ($R^2 < 0.2$), only for the subsequent quality control step. This resulted in ~67k SNPs for the sets to assess heterozygosity (F < 3SD), homozygosity (F > 3SD) and relatedness by pairwise IBD values (pihat > 0.15). Datasets were merged with Hapmap Phase 3 individuals to check ethnicity. After these QC procedures on subjects (excluding in total 101 individuals), quality control on SNPs was performed as follows. All SNPs were filtered on missingness (inclusion with <2%) and Hardy Weinberg (inclusion $P > 1e^{-6}$) before merging the three datasets. Four duplicates and three related sample-pairs were detected in the merged datasets (according to criteria described above) and one outlier after clustering the merged dataset. From these data, the COMT Val^{158}Met genotype (rs4680) was extracted.

2.3.2. Replication sample

The COMT Val^{158}Met genotype was determined by Sequenom (Hamburg, Germany) using the Sequenom MassARRAY iPLEX platform at the facilities of the manufacturer, using the SNP array described in the previous work (van Winkel et al., 2011).

2.4. Statistical analysis

To examine the interaction between COMT, cannabis use, and childhood maltreatment on psychotic experiences, the total CAPE score was regressed on cannabis use, childhood maltreatment, COMT rs4680 genotype, their interaction, and covariates using the following model: $CAPE = \beta_0 + (\beta_1 * \text{covariate}) + (\beta_2 * \text{rs4680}) + (\beta_3 * \text{cannabis use}) + (\beta_4 * \text{childhood maltreatment}) + (\beta_5 * \text{rs4680} * \text{cannabis use}) + (\beta_6 * \text{rs4680} * \text{childhood maltreatment}) + (\beta_7 * \text{rs4680} * \text{cannabis use} * \text{childhood maltreatment})$. To enhance the interpretation of the three-way interaction, we also tested the main effects of childhood maltreatment, cannabis use, and the COMT Val^{158}Met genotype on psychotic symptoms as well as the two-way interactions between these variables. Moreover, to facilitate the interpretation of the interaction, we also calculated the zero-order associations between childhood trauma, cannabis use, and the COMT Val^{158}Met genotype in the discovery and replication sample. In the discovery sample, cannabis use was modeled as a dichotomous indicator and included covariates were age and gender. In the replication sample, a mixed model was used to account for family relatedness and repeated measures with age, sex, and ethnic background as covariates. Random effects were unique subject number and family number. Analyses were performed with the nlme package in R (www.r-project.org) (Pinheiro et al., 2012). A priori planned stratified analyses were carried out for cannabis use and the three genotypes of the COMT Val^{158}Met polymorphism.

Genotypes were coded 0, 1, or 2 and modeled as a linear effect (additive genetic model) to account for different genotype distributions because it avoids small subgroup stratification (Cordell and Clayton, 2005). Cannabis use in the replication sample was analyzed as a linear effect as applied in previous papers (van Winkel et al., 2011). Continuous sum scores of the CAPE and the CTQ were used in both the discovery and replication samples. Difference in group characteristics was tested using an independent *t*-test or chi-square test where appropriate.

2.4.1. Effect analysis

To facilitate the interpretation of the three-way interaction between childhood maltreatment, cannabis use, and COMT, we first conducted an effect analysis of this interaction using the effects package in R (Fox, 2003). This allows the study of individual parameters of general and mixed models while adjusting for covariates and other fixed effects. This method is particularly useful to investigate how complex interactions behave for several values. We examined the three-way interaction for five equally spaced levels of the full range of CTQ scores.

3. Results

3.1. Sample characteristics

Table 1 reports the distribution of demographic characteristics, cannabis use, levels of maltreatment, psychotic experiences (CAPE), and the *COMT* Val^{158}Met genotype in the discovery and replication sample. The reported levels of psychotic experiences, cannabis use, and childhood maltreatment are consistent with previous research and representative of young populations (Bernstein and Fink, 1998; Stefanis et al., 2002). Moreover, the characteristics in the discovery sample generalize to the full sample which includes all non-genotyped individuals (Schubart et al., 2010). Genotyping of rs4680 was successful in all subjects and no departure from HWE was detected

Table 1
Characteristics of the discovery sample and the replication sample. P values refer to the comparison between the discovery and replication sample.

Parameter	Discovery sample CannabisQuest (N = 918)	Replication sample GROUP (N = 339)[a]	P value
Female sex, %	53	57	<0.001
Age, mean (range), year	20 (18–40)	32 (16–56)	<0.001
Dutch ethnicity, %	100%	90%	<0.001
CTQ[d] score, mean (range)	1.40 (1.00–4.26)	1.33 (1.0–2.95)	<0.001
Cannabis use in the past year		<0.001	
>3€/week, %	33		
Daily, %		2	
Weekly, %		4	
Less, %		8	
None, %		86	
COMT Val^{158}Met genotype (rs4680)			0.77
G/G (val/val), %	20	24	
A/G (met/val), %	50	49	
A/A (met/met), %	30	27	
HWE[b] P-value	0.88	0.59	N/A
CAPE[c], mean (range)	0.61 (0.02–2.48)	0.38 (0.0–1.29)	P < 0.001

[a] With a total of 624 (repeated) measurements.
[b] Hardy–Weinberg Equilibrium.
[c] Community Assessment of Psychic-like Experiences.
[d] Childhood Trauma Questionnaire.

in both samples (P = 0.61 and P = 0.38, respectively). The COMT genotype minor allele frequency was comparable to previously reported frequencies in a population of European descent (Caspi et al., 2005; Zammit et al., 2011). The discovery and replication sample differed significantly with respect to age (t = 26.8, P < 0.001), gender (χ^2 = 13.98, P < 0.001), the number of cannabis users (χ^2 = 151.32, P < 0.001), and frequency of psychotic experiences (t = 15.87, P < 0.001) (Table 1). In both samples, the COMT Val^{158}Met genotype was not associated with childhood maltreatment (discovery sample: P = 0.94; replication sample: P = 0.15) or cannabis use (discovery sample: P = 0.88; replication sample: P = 0.20). In the discovery sample, cannabis use was associated with increased levels of childhood maltreatment (P < 0.001), but this effect was absent in the replication sample (P = 0.60). Levels of cannabis use and childhood maltreatment in Val/Val-carriers in the discovery sample and the replication sample are reported in Table 2.

3.2. Effect analyses

First, to understand how childhood trauma interacts with cannabis use and the COMT genotype, we completed an effect analysis using five equal parts of the full range of the Childhood Trauma Questionnaire score in the discovery and replication sample. Fig. 1 illustrates that in Val/Val individuals who use cannabis, increased levels of childhood maltreatment are associated with increased self-report levels of the CAPE score. In the replication sample, a similar pattern is apparent, with increasing levels of childhood maltreatment resulting in a marked increase in psychotic experiences in Val/Val individuals who use cannabis (Fig. 1).

Table 2
Cannabis use and levels of childhood maltreatment in Val/Val-carriers in the discovery sample and replication sample.

Discovery sample			
Val/Val-carriers (N = 185)		N	CTQ score (mean)
Cannabis use	Yes	58	1.34
	No	127	1.26
Replication sample			
Val/Val-carriers (N = 84)		Observations	CTQ score (mean)
Cannabis use	Yes	17	1.27
	No	133	1.30

CTQ: Childhood Trauma Questionnaire.

3.3. Main effects and two-way interactions in the discovery and replication sample

In the discovery sample, childhood maltreatment (β = 0.38, P < 0.001), cannabis use (β = 0.14, P < 0.001) but not the COMT Val^{158}Met genotype (β = −0.015, P = 0.35) were significantly associated with psychotic symptoms. In the replication sample, similar results were obtained, with significant main effects of childhood maltreatment (β = 0.29, P < 0.001), cannabis use (β = 0.036, P = 0.033) but not the COMT Val^{158}Met genotype (β = −0.014, P = 0.41). With regard to two-way interactions, the discovery and replication sample showed comparable results. No significant interactions were present between childhood maltreatment and cannabis use (discovery: β = −0.059, P = 0.34; replication: β = −0.024, P = 0.66), as well as cannabis use and the COMT Val^{158}Met genotype (discovery: β = 0.011, P = 0.75; replication: β = 0.019, P = 0.44). In contrast, childhood maltreatment and the COMT Val^{158}Met genotype significantly interacted in the discovery sample (β = 0.14, P = 0.0039) and the replication sample (β = −0.12, P = 0.022). After testing the main and two-way interactions, analyses were carried out for the three-way interaction between childhood maltreatment, cannabis use and the COMT Val^{158}Met genotype in the discovery sample (Section 3.4) and the replication sample (Section 3.5).

3.4. Childhood maltreatment, cannabis use, COMT Val^{158}Met genotype, and psychotic experiences in the discovery sample

Table 3 shows the results of the linear regression model in the discovery sample. Significant effects on psychotic experiences were present for maltreatment (β = 0.27, P = 0.023), cannabis use (β = 0.72, P = 0.008), and their interaction (β = −0.47, P = 0.019). Moreover, there was a significant three-way interaction between cannabis use, childhood maltreatment and the COMT genotype (β = 0.29, P = 0.006). For individuals carrying the Val/Val COMT genotype, cannabis use in combination with increased levels of childhood maltreatment resulted in increased levels of subclinical psychotic experiences (Fig. 2A). Sex, age, and the *COMT* Val^{158}Met genotype were not significantly associated with the presence of psychotic experiences.

Subsequently, we analyzed the positive, negative, and depressive dimensions of the CAPE questionnaire. The interaction between childhood maltreatment, cannabis use, and the COMT Val^{158}Met genotype was significant for negative (P = 0.004) and depressive (P = 0.007) dimensions of the CAPE questionnaire in the discovery sample but not for the positive dimension (P = 0.10).

3.5. Childhood maltreatment, cannabis use, COMT Val^{158}Met genotype, and psychotic experiences in the replication sample

In the replication sample, childhood maltreatment (β = 0.44, P < 0.001) and the *COMT* Val^{158}Met genotype (β = 0.18, P = 0.019) were significantly associated with psychotic experiences (Table 3). Moreover, sex and age were also significantly associated with psychotic experiences. There was no significant effect of cannabis use in predicting psychotic experiences (β = 0.16, P = 0.14). The interaction between cannabis use and childhood maltreatment was not significant (β = −0.11, P = 0.18). In addition, no significant three-way interaction between cannabis use, childhood maltreatment and the COMT genotype was found (β = 0.10, P = 0.25), even though a similar direction of the effect of cannabis use and childhood maltreatment in Val/Val individuals was apparent (Fig. 2B). To allow for comparison between the discovery and replication sample, dichotomized cannabis use (no use vs. any cannabis use) was subsequently analyzed in the

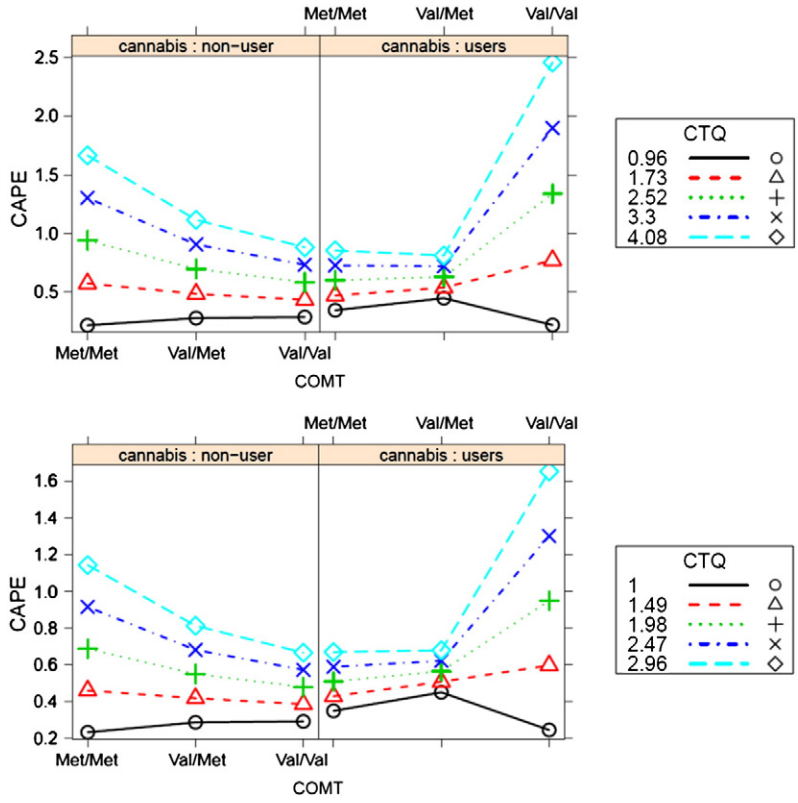

Fig. 1. Effect analyses investigating the interaction between childhood maltreatment, cannabis use, and the COMT Val[158]Met genotype for five equal parts of the full range of the childhood maltreatment questionnaire (CTQ) score. Both in the discovery sample (top panel) and the replication sample (bottom panel), Val-homozygous individuals display increased levels of psychotic symptoms after cannabis use and childhood maltreatment.

replication sample, resulting in a significant main effect of cannabis use ($\beta = 0.43$, $P < 0.001$) and an increased albeit non-significant result of the interaction between cannabis use, childhood maltreatment, and the COMT genotype ($\beta = 0.29$, $P = 0.11$).

Table 3
The effects of cannabis use, childhood maltreatment, and COMT Val[158]Met genotype (rs4680) and their interaction on psychotic experiences in the discovery sample and replication sample.

Sample	Beta	SE	t-Value	P value
Discovery sample: CannabisQuest				
Intercept	0.337	0.183	1.84	0.066
Sex	−0.037	0.023	−1.63	0.104
Age	−0.003	0.004	−0.78	0.435
Childhood maltreatment	0.273	0.120	2.28	0.023*
rs4680	−0.062	0.081	−0.77	0.443
Cannabis	0.721	0.273	2.64	0.008**
Maltreatment × rs4680	0.035	0.062	0.57	0.569
Maltreatment × cannabis	−0.474	0.201	−2.36	0.019*
Cannabis × rs4680	−0.390	0.141	−2.77	0.006**
Maltreatment × cannabis × rs4680	0.290	0.104	2.78	0.006**
Replication sample: GROUP				
Intercept	−0.123	0.092	−1.33	0.18
Sex	0.048	0.023	2.11	0.03*
Age	−0.002	0.001	−2.83	0.005**
Ethnicity	−0.037	0.036	−1.03	0.30
Childhood maltreatment	0.438	0.067	6.59	<0.001***
Cannabis	0.162	0.109	1.49	0.14
rs4680	0.177	0.075	−1.33	0.019*
Maltreatment × rs4680	−0.145	0.056	−2.59	0.010*
Maltreatment × cannabis	−0.113	0.083	−1.35	0.18
Cannabis × rs4680	−0.117	0.115	−1.02	0.31
Maltreatment × cannabis × rs4680	0.102	0.089	1.14	0.25

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

3.6. Stratified analysis of cannabis use and the COMT Val[158]Met genotype in both samples

In the discovery sample, stratified analysis of cannabis users showed that the effect of childhood maltreatment on psychotic symptoms was most pronounced in Val/Val-carriers (childhood maltreatment × COMT Val[158]Met genotype interaction, $\beta = 0.56$, $P < 0.001$). In contrast, no significant interaction was present between the COMT Val[158]Met genotype and childhood maltreatment in individuals who did not use cannabis in the discovery sample ($\beta = 0.066$, $P = 0.52$). In contrast, Val/Val-carriers who did not use cannabis reported lower levels of psychotic symptoms compared to the other genotypes in the replication sample (childhood maltreatment × COMT Val/Met genotype interaction, $\beta = -0.12$, $P = 0.034$). In individuals from the replication sample who used cannabis, no significant interaction was present ($\beta = -0.069$, $P = 0.61$). These stratified analyses suggest that the effect of childhood maltreatment on psychotic symptoms in Val/Val-carriers depends on cannabis use. Additionally, planned stratified analysis of the COMT Val/Met genotypes in the discovery sample resulted in consistent trends for the interaction between cannabis use and childhood maltreatment but did not reach statistical significance (Met/Met: $\beta = -0.39$, $P = 0.08$; Val/Met: $\beta = 0.23$, $P = 0.098$; Val/Val: $\beta = 0.56$, $P = 0.08$). In the replication sample, the interaction between childhood maltreatment and cannabis use did not reach statistical significance in any of the genotypes (Met/Met: $\beta = -0.08$, $P = 0.40$; Val/Met: $\beta = -0.15$, $P = 0.064$; Val/Val: $\beta = 0.20$, $P = 0.30$).

4. Discussion

We examined the effects of childhood maltreatment, cannabis use, the *COMT* Val[158]Met polymorphism (rs4680) on psychotic experiences in the general population. In the discovery sample, we found

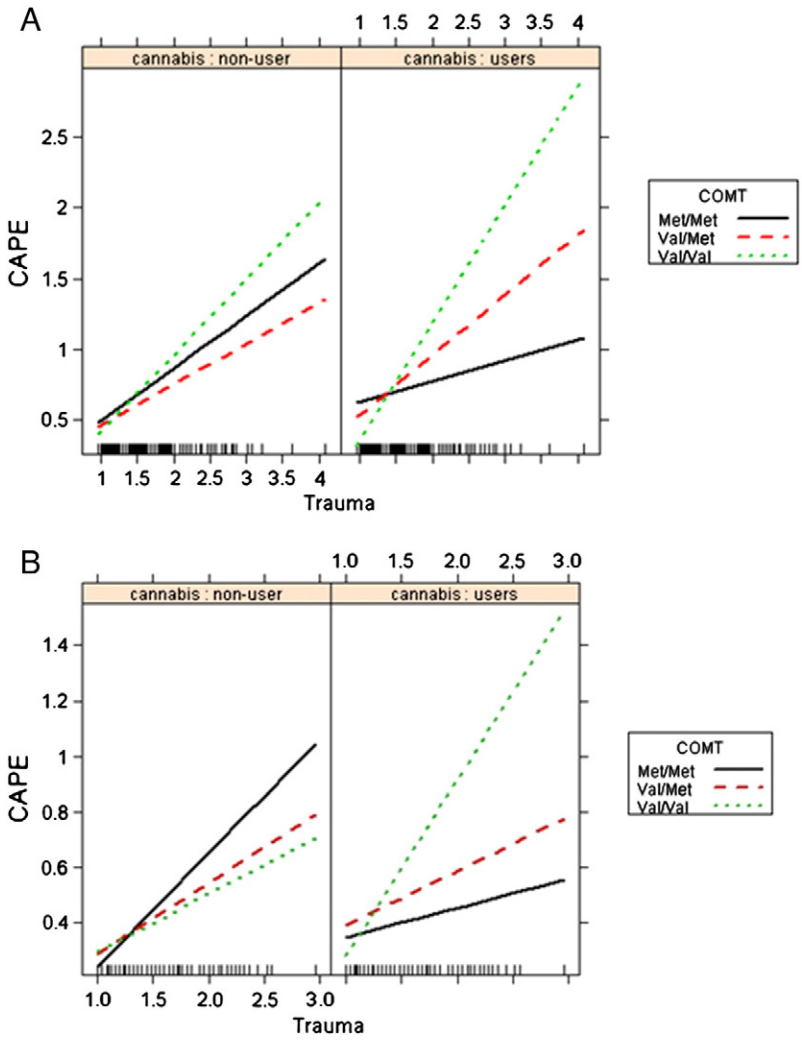

Fig. 2. Interaction between childhood maltreatment, cannabis use, and the COMT Val[158]Met COMT genotype on psychotic experiences (Community Assessment of Psychic Experiences, CAPE) in the discovery sample (A) and the replication sample (B).

a significant three-way interaction between childhood maltreatment, cannabis use, and the common *COMT(Val/Met)* genotype. Consistent with our hypothesis, Val/Val carriers who used cannabis and who had been exposed to higher levels of childhood maltreatment reported increased levels of psychotic experiences (Fig 2A). We attempted to replicate this gene–environment–environment interaction in the healthy individuals of the GROUP sample, a multisite longitudinal cohort study in The Netherlands and Belgium investigating schizophrenia patients, siblings, and healthy controls (Korver et al., 2012). In this sample, the three-way interaction between childhood maltreatment, cannabis use, and COMT had a similar directionality (Fig. 2B) but did not reach statistical significance. Both in the discovery and the replication sample, Val/Val individuals who used cannabis were the most susceptible to the effects of childhood maltreatment (Fig. 1). Considering previous evidence that the functionality of the dopamine system is affected by cannabis use (Bossong et al., 2009; Kuepper et al., 2010) and childhood maltreatment (Lee and Coccaro, 2010; Rodrigues et al., 2011), it may be hypothesized that childhood maltreatment and cannabis use increase psychosis risk in Val/Val carriers as a result of altered dopamine levels (Tunbridge et al., 2006). The more heat-stable Val-variant of the COMT enzyme (encoded by the G allele) possesses a higher intrinsic activity compared to the Met-variant (Mannisto and Kaakkola, 1999). As a result, the functional *COMT(Val/Met)* polymorphism directly influences central dopamine levels and is regarded as a plausible biological risk factor for psychosis in light of the dopamine hypothesis of psychosis (Akil et al., 2003). Our finding that Val/Val carriers are associated with the highest risk for psychotic symptoms after exposure to childhood maltreatment and cannabis is somewhat surprising as Val-allele carriers possess an increased activity of the COMT enzyme and are expected to have relatively decreased prefrontal dopamine levels. Met/Met-carriers may be more vulnerable to stress compared to Val-carriers, but only if no cannabis is consumed (Alemany et al., in press). Moreover, in patients with a non-affective psychotic disorder, the COMT Met/Met genotype was associated with increased negative affect and momentary psychosis in reaction to stress compared to the Val/Met and Val/Val genotypes (Collip et al., 2011). However, this was not the case for healthy controls. Therefore, the role of the COMT genotype may depend on the a priori genetic risk for psychotic symptoms. Another important consideration is that, although COMT is expressed throughout the brain, it is of particular importance in the prefrontal cortex. In the striatum, removal of dopamine from the synaptic cleft is mediated by the highly expressed dopamine transporter (DAT) rather than COMT. COMT knockout mice display major changes in dopamine levels in the prefrontal cortex (Gogos et al., 1998), and the COMT genotype influences D_1 receptor occupation in the cortex but not in the striatum of healthy individuals (Slifstein et al., 2008). Together, these data suggest that the COMT Val[158]Met genotype is differentially involved in cortical vs. subcortical regions. In this light, it is interesting that increased midbrain dopamine synthesis has been found in Val-carriers which may be associated

with an increased risk for subsequent dopaminergic disinhibition in the mesolimbic system (Meyer-Lindenberg et al., 2005). Moreover, differential COMT effects between cortical and limbic regions may be related to differences in phasic and tonic dopaminergic transmission (Bilder et al., 2004). Therefore, the relation between enzymatic activity of COMT and dopaminergic activity in the brain is complex and cannot be directly translated. Moreover, molecular changes due to the interaction between *COMT*, childhood adversity, and cannabis use were not studied in the present study and other neurotransmitter systems other than dopamine may be involved (Behan et al., 2012). Moreover, the *COMT* Val^{158}Met polymorphism exerts pleiotropic effects on behavior and has been implicated in other psychiatric disorders such as mood disorders (Hosak, 2007). Our results confirm and extend the findings that childhood trauma is strongly associated with psychotic symptoms independently of cannabis and the COMT genotype (Read et al., 2005; Bendall et al., 2008; van Os et al., 2010). In support, a significant main effect of childhood maltreatment remained present in both samples after exclusion of the factors cannabis use and COMT Val^{158}Met genotype.

We found a significant interaction between childhood maltreatment, cannabis use, and COMT in the discovery sample but not in the replication sample. Nonetheless, the direction and effect size of the interaction are very similar to the discovery sample. There may be several other reasons why the initial interaction was not unequivocally confirmed. First, the replication sample may have had insufficient statistical power to detect a three-way interaction due to a relative smaller sample size ($n = 339$ vs. $n = 918$ in the discovery sample). Another important factor that may have adversely influenced the power in the replication sample is the fact that only 14% of the individuals in the replication sample used cannabis compared to 33% in the discovery sample. This is relevant because the power to detect gene–environment interactions rapidly decreases with declining exposure rates (Boks et al., 2007; Caspi et al., 2010). Moreover, individuals in the replication sample reported fewer psychotic experiences. Thus, the replication sample may have experienced too few psychotic symptoms to detect an interaction between cannabis use, childhood maltreatment, and *COMT*. Moreover, the overall increased age of the replication sample is of importance as adolescent but not adult-onset cannabis use is associated with an increased risk for both clinical and subclinical psychotic symptoms (Arseneault et al., 2002; Fergusson et al., 2003; Schubart et al., 2010). Therefore, its interaction with genetic and other environmental factors may be more prominent during adolescence. In the discovery sample, no main sex effect was present. In contrast, females reported overall increased psychotic symptoms compared to males in the replication sample.

The interpretation of this study is constrained by several limitations. First, our results do not provide information about the causality of the interaction between childhood maltreatment, cannabis, and *COMT* on psychotic experiences due to the cross-sectional nature of the data. Second, the variable indexing cannabis use was not consistent across the discovery and replication sample. In the discovery sample, a question assessing current cannabis expenditure was used, whereas the Composite International Diagnostic Interview (CIDI) was used in the replication sample. Third, childhood maltreatment was retrospectively assessed and may be subject to recall bias depending on personal characteristics including the level of current psychotic experiences. Nonetheless, CTQ scores are stable over time and have good convergent and divergent validity (Bernstein et al., 1994; Bernstein and Fink, 1998). Moreover, an important limitation of this study is the sample size of both cohorts. The estimation of this gene × environment × environment interaction therefore depends on relatively low numbers of Val/Val carriers in the different conditions, and further independent replication in large cohorts is required. Nevertheless, a very recent study showed an similar interaction between exposure to childhood abuse and cannabis use on psychotic experiences in Val-carriers (Alemany et al., in press).

In conclusion, we provide suggestive evidence that the functional COMT Val^{158}Met polymorphism moderates the interaction between childhood maltreatment and cannabis use on psychotic experiences in the general population. The contributions of cannabis and childhood adversity on psychosis risk may be of particular significance in Val carriers of the *COMT* Val^{158}Met genotype. The present study reports a complex and hypothesis-driven gene–environment interaction between two well-documented environmental psychosis risk factors and genetic variation in the COMT gene. Our results may explain the heterogeneous findings in the existing literature on the psychosis-inducing effects of cannabis use and childhood maltreatment. Moreover, our data demonstrate the large influence of sample selection, environmental factor assessment, and the use of cutoff values. Nevertheless, our comprehensive effect analyses facilitate the interpretation of this complex gene–environment interaction. Overall, the present study provides further insight into the complex interplay between two extensively documented environmental factors and genetic background in shaping the risk for psychotic symptoms.

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Contributors

C. Vinkers and M. Boks developed and designed the study concept and design. W. van Gastel, C. Schubart, and M. Boks were responsible for the acquisition of the data from the discovery sample. GROUP investigators were responsible for the design and acquisition of the data for the GROUP study. C. Vinkers and M. Boks performed the statistical analyses and wrote the manuscript. R. Ophoff and K. van Eijk aided in the genetic analyses. M. Joels, R. Ophoff, R. van Winkel, W. van Gastel, K. van Eijk, J. Luykx, J. van Os, R. Kahn, and C. Schubart provided critical review of the manuscript.

Conflict of interest

Ruud van Winkel was supported by a Dr. Gustave Delport Award of the King Baudouin Foundation and received unrestricted grants from AstraZeneca and Eli Lilly. The remaining authors have no interests to disclose.

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