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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