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Genetic moderation of the effects of cannabis: Catechol-O-methyltransferase (COMT) affects the impact of Δ^9 -tetrahydrocannabinol (THC) on working memory performance but not on the occurrence of psychotic experiences

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Abstract

Cannabis use can induce cognitive impairments and psychotic experiences. A functional polymorphism in the catechol-O-methyltransferase (COMT) gene (Val¹⁵⁸Met) appears to influence the immediate cognitive and psychotic effects of cannabis, or Δ^9 -tetrahydrocannabinol (THC), its primary psychoactive ingredient. This study investigated the moderation of the impact of experimentally administered THC by COMT. Cognitive performance and psychotic experiences were studied in participants without a psychiatric diagnosis, using a between-subjects design (THC vs. placebo). The effect of COMT Val¹⁵⁸Met genotype on the cognitive and psychotic effects of THC, administered intravenously in a double-blind, placebo-controlled manner to 78 participants who were vulnerable to paranoia, was examined. The results showed interactive effects of genotype and drug group (THC or placebo) on working memory, assayed using the Digit Span Backwards task. Specifically, THC impaired performance in COMT Val/Val, but not Met, carriers. In contrast, the effect of THC on psychotic experiences, measured using the Community Assessment of Psychic Experiences (CAPE) positive dimension, was unaffected by COMT genotype. This study is the largest to date examining the impact of COMT genotype on response to experimentally administered THC, and the first using a purely non-clinical cohort. The data suggest that COMT genotype moderates the cognitive, but not the psychotic, effects of acutely administered THC.

Keywords

Cannabis, dopamine, psychosis

Introduction

Cannabis is the most widely used illicit drug, with approximately 180 million users worldwide (UNODC, 2013). Although it is generally considered a safe drug, cannabis intoxication is associated with a number of specific deleterious effects. Specifically, administration of cannabis (or Δ^9 -tetrahydrocannabinol (THC), its primary psychoactive compound) to non-clinical volunteers induces transient psychotic symptoms and cognitive impairments (Kaufmann et al., 2010; Morrison et al., 2009; Ranganathan and D'Souza, 2006).

Independently of its acute effects, numerous longitudinal studies have suggested that cannabis use is also a risk factor for the development of psychosis, with early use of cannabis, and use of high-potency cannabis, associated with greater risk (Arseneault et al., 2004; Di Forti et al., 2009; Moore et al., 2007). Nevertheless, despite the robust link between cannabis use and psychosis, the majority of cannabis users do not suffer any long-term adverse effects, leading to the suggestion that

genetic factors may influence vulnerability (Casadio et al., 2011; Henquet et al., 2005). A well-studied candidate gene in this regard is catechol-O-methyltransferase (COMT).

Rodent studies demonstrate that the COMT enzyme is important for regulating levels of cortical dopamine and influences cognitive function: frontal cortical dopamine is increased, and

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cognitive function is improved, in animals with pharmacologically or genetically reduced COMT activity (Papaleo et al., 2008; Tunbridge et al., 2004; Yavich et al., 2007). COMT has been extremely widely-investigated in neuroscience (Tunbridge et al., 2006), in part because the human COMT gene contains a functional polymorphism in its sequence (Val¹⁵⁸Met) that directly influences enzyme activity: Met¹⁵⁸ homozygote COMT activity is approximately 40% lower than that of Val¹⁵⁸ homozygotes (Chen et al., 2004). COMT Val¹⁵⁸Met is robustly associated with human prefrontal cortex activation (as measured with the fMRI BOLD response) during working memory (Mier et al., 2010), and the low-activity Met¹⁵⁸ allele has also been linked with better cognitive function, compared with Val¹⁵⁸, in a number of studies (Barnett et al., 2007; Egan et al., 2001; Farrell et al., 2012). However, links between COMT¹⁵⁸Met and cognition are less consistent with rodent studies of COMT's function (Barnett et al., 2008), likely in part due to the presence of other genetic variants within COMT that moderate the functional effects of Val¹⁵⁸Met (Gothelf et al., 2014).

Several studies have suggested that the COMT Met allele may act as a protective factor against the negative impact of cannabis/THC. The first demonstration came from a longitudinal study that demonstrated that adolescent cannabis use increased the risk of later development of a psychotic illness, but only in those with the COMT Val/Val (odds ratio (OR) = 10.9), and to a lesser extent Val/Met (OR=2.5), genotype. Met/Met homozygotes did not show an increased risk (OR = 1.1) (Caspi et al., 2005). Several subsequent studies failed to replicate this initial finding (van Winkel, 2011; Zammit et al., 2011), whilst others support a more complex relationship that is dependent on another environmental factor, namely exposure to abuse in childhood (Alemany et al., 2014; Vinkers et al., 2013). The initial findings are convergent with studies investigating the acute effect of cannabis on psychotic experiences. These studies suggest that the Val allele is associated with greater psychotic effects of both cannabis, used recreationally (Henquet et al., 2009), and THC (Henquet et al., 2006), administered experimentally in a within-subjects design, compared with the Met allele. Notably, both of these studies were conducted in a mixed group of participants, including patients with a psychotic disorder ($n=31$ (Henquet et al., 2009) or 30 (Henquet et al., 2006)) as well as non-clinical volunteers ($n=25$ (Henquet et al., 2009) or 32 (Henquet et al., 2006)). In both studies, the genotype difference was limited to those with prior evidence of psychometric psychosis liability (for both, 'high' or 'low' liability was encoded as a binary variable determined using a trait version of the Community Assessment of Psychic Experiences (CAPE) dichotomized at either the 50th (Henquet et al., 2006) or the 75th (Henquet et al., 2009) percentile). Thus, whilst not explicitly detailed, it seems likely that the 'high' prior psychosis liability groups disproportionately contained participants with a psychotic disorder.

Studies investigating the impact of COMT Val¹⁵⁸Met genotype on the cognitive effects of cannabis/THC are few in number, but are consistent. Thus, the single prior study of the impact of COMT genotype on the response to experimentally administered THC (detailed above) showed impaired verbal memory and attention in Val/Val homozygotes, but not Met carriers (Henquet et al., 2006). However, in contrast to the genotype effects observed by the authors on acutely administered THC-induced psychotic experiences, the impact of Val¹⁵⁸Met on cognitive measures was not contingent on prior psychosis liability. A

second study, conducted in recreational cannabis users, indicates that COMT genotype-dependent effects may persist beyond the period of acute intoxication: compared with non-users, Val/Val, but not Met carrier, cannabis users showed poorer attentional performance under conditions of abstinence (Verdejo-Garcia et al., 2013). Similar effects were also seen for executive function (Verdejo-Garcia et al., 2013).

Given these findings, we aimed to investigate whether the COMT Val¹⁵⁸Met polymorphism was associated with differences in the psychotic and cognitive effects of experimentally administered THC, in order to clarify whether genotype effects are seen in a non-clinical cohort. To do this, we conducted a secondary analysis of a previously published (Freeman et al., 2015) randomised, placebo-controlled study of the effects of intravenously administered THC on paranoid experiences, specifically examining the impact of COMT Val¹⁵⁸Met genotype on psychotic experiences and working memory. We predicted that carriers of the COMT Met allele would be relatively protected from the negative impact of THC on working memory performance and, perhaps, psychotic experiences, consistently with the literature outlined above.

Materials and methods

The study was approved by a NHS Research Ethics Committee and all participants gave written, informed consent. The results presented here are a secondary analysis of the double-blind arms of a larger study, which aimed to investigate the mechanisms by which cannabis causes paranoia. Participants in a third group (the 'Cognitive Awareness' condition in Freeman et al. (2015); $n=39$) were excluded from the current study, since both they, and the study researcher, were aware that they would receive THC. The full study is described in detail elsewhere (Freeman et al., 2015), so only a brief overview is given here.

Procedure

Participants, who had used cannabis at least once in their lifetime, and who reported at least one paranoid thought in the last month (as assessed by the Paranoid Thoughts Scale Part B (Green et al., 2008)), were recruited by advertisement (since the primary aim of the study was to investigate how cannabis causes paranoia (Freeman et al., 2015)). Exclusion criteria included a self-reported history of major mental illness or substance dependence, or major mental illness in a first-degree relative (see earlier study (Freeman et al., 2015) for full details of inclusion/exclusion criteria). Following completion of baseline cognitive measures, they were randomized to receive either placebo or THC ($n=41$ per group) administered in a double-blind manner. Randomization was carried out by a researcher independently of recruitment and testing, using randomized permuted blocks of varying size with a plan created from www.randomization.com. Genomic DNA was extracted from buccal swabs and participants were genotyped for the COMT Val¹⁵⁸Met polymorphism (rs4680) using the appropriate Taqman SNP Genotyping Assay (Applied Biosystems, Life Technologies Ltd., Paisley, UK) in duplicate. Polymerase chain reaction (PCR) amplification failed for four of the participants ($n=2$ from each drug group), giving final group sizes of $n=39$ for both placebo and THC. The Val¹⁵⁸Met polymorphism was the only genetic variant assessed.

Table 1. Demographic details of the sample.

	Placebo		THC	
	Val/Val	Met carrier	Val/Val	Met carrier
Gender (M/F)	6/1	23/9	7/5	18/9
Age (SEM)	33.4 (4.4)	29.3 (1.5)	36.8 (2.5)	28.6 (1.4)
Number of times used cannabis over lifetime (SEM)	271.4 (146.6)	576.8 (217.7)	746.3 (599.2)	587.7 (191.9)
Number of times used cannabis in last month (SEM)	0.57 (0.4)	2.7 (1.1)	2.4 (2.3)	5.4 (2.8)
WASI 2 subscale IQ	120 (0.9)	116.8 (2.0)	110.7 (3.9)	115.2 (2.5)

Drug administration

Indistinguishable vials containing either 1.5mg THC (Dronabinol, THC Pharm GmbH, Frankfurt am Main, Germany) or placebo (10 mL saline), which were identical in appearance, were prepared by Bichsel Laboratories (Interlaken, Switzerland) as described previously (Freeman et al., 2015; Morrison et al., 2009; Naef et al., 2004). Participants received either THC or placebo, administered by a trained psychiatrist, via an indwelling forearm cannula in 1mL pulses every minute for 10 min.

Assessments

Testing began 10 min after drug or placebo administration and was completed by an average of 83 min (SD=18) post-drug administration. The full study included a detailed neuropsychological assessment (including the Wechsler Abbreviated Scale of Intelligence, and several indices of paranoia, the study's focus (Freeman et al., 2015)). However, with regards to COMT genotype, we have analysed only two measures in order to avoid problems of multiple comparisons: the CAPE (administered after THC administration) positive dimension, an index of psychotic experiences that has previously shown sensitivity to COMT*THC interactive effects (Henquet et al., 2006), and the Digit Span Backwards (the number of correctly recalled strings of numbers in reverse order of presentation, a component of the Wechsler Abbreviated Scale of Intelligence), a test of working memory, since this is the cognitive domain for which COMT has been best studied (Mier et al., 2010). The CAPE was administered as a state assessment once (post-drug administration), whilst the Digit Span Backwards was administered both pre- and post-drug. The CAPE was administered as a state measure ('since having the drip, have you...'), as previously (Henquet et al., 2006), except that one item ('Have you felt as if things in magazines or on TV were written especially for you?') was omitted, as participants were not exposed to magazines or the television during this period. In the current study, all participants completed the CAPE in full. However, CAPE positive dimension scores were expressed as a proportion of the total number of positive dimension items completed (i.e. all were divided by 19), to permit direct comparison with previous results (Henquet et al., 2006).

Data analysis

Data were analysed using SPSS Statistics v.20 (IBM UK Ltd, Portsmouth, UK). Since previous studies had found that differential effects of COMT Val¹⁵⁸Met genotype on the response to THC were driven by differences between Val/Val homozygotes and

other COMT genotype groups (Caspi et al., 2005; Henquet et al., 2006; Verdejo-Garcia et al., 2013), Val/Met and Met/Met individuals were pooled into a single 'Met carrier' group for analysis purposes. Data were analysed using analysis of variance (ANOVA) with genotype (Val/Val vs. Met carrier) and drug (THC vs. placebo) as between-subjects factors, and age as a covariate (although essentially the same results were obtained with or without age, IQ and lifetime cannabis use as covariates, and none of the covariates interacted with drug, genotype or their interaction). Bootstrapping (1000 samples) was performed as CAPE and Digits Backwards scores were non-normally distributed (Efron and Tibshirani, 1993). Bootstrapped results (B coefficient \pm SEM; 95% confidence intervals (CI) and *p* values) are presented throughout.

Results

COMT Val¹⁵⁸Met genotypes were in Hardy-Weinberg equilibrium (19 Val/Val; 43 Val/Met; 16 Met/Met; $\chi^2=0.8$; *p*=0.36). Demographic information for the four genotype/drug groups is shown in Table 1.

COMT Val¹⁵⁸Met moderates the impact of THC on cognitive function

As anticipated, participants given THC were impaired on the Digit Span Backwards task compared with those given placebo ($B = -3.55 \pm 0.94$; 95% CI: -5.37 to -1.59 ; *p*=0.001). Consistently with previous studies, whilst there was no main effect of COMT genotype ($B = -1.18 \pm 0.80$; 95% CI: -2.68 to 0.50 ; *p*=0.13), there was a drug*genotype interaction ($B = 2.58 \pm 1.08$; 95% CI: 0.22 to 4.63 ; *p*=0.018; Figure 1) for performance. Post-hoc analysis demonstrated that this interaction was due to an effect of drug in the Val/Val group ($B = -3.55 \pm 0.94$; 95% CI: -5.37 to -1.59 ; *p*=0.001) that was absent in the Met carriers ($B = -0.97 \pm 0.62$; 95% CI: -2.26 to 0.12 ; *p*=0.126). In contrast, there were no main effects of genotype ($B = -1.20 \pm 1.07$; 95% CI: -3.52 to 0.78 ; *p*=0.24) or drug ($B = -1.67 \pm 1.31$; 95% CI: -4.06 to 1.12 ; *p*=0.18), and no drug*genotype interaction ($B = 1.73 \pm 1.41$; 95% CI: -1.16 to 4.31 ; *p*=0.20; Figure 1) on Digit Span Backwards performance assessed prior to drug administration. There was an effect of IQ on Digit Span Backwards score both prior to ($B = 0.075 \pm 0.02$; 95% CI: 0.37 to 0.12 ; *p*=0.002) and after ($B = 0.067 \pm 0.024$; 95% CI: -0.019 to 0.114 ; *p*=0.008) drug administration. However, neither age (*p*>0.36), nor lifetime cannabis use (*p*>0.07) affected Digit Span Backwards performance, either prior to or after drug administration.

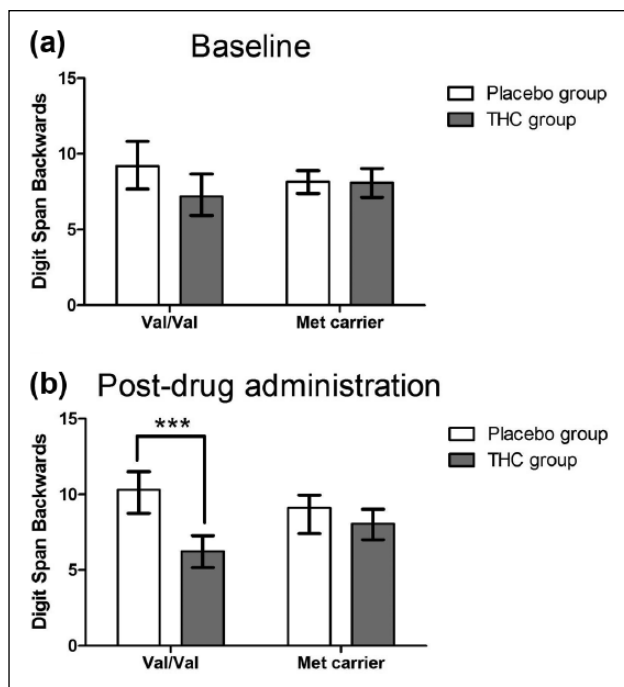


Figure 1. COMT Val¹⁵⁸Met genotype alters the cognitive effects of THC. (a) There were no group differences in working memory performance prior to drug administration. (b) Following drug administration, working memory performance, assessed using the Digit Span Backwards measure, was poorer in Val/Val volunteers given THC (closed bars) compared with placebo (open bars). This drug group difference was not significant in Met carriers. Error bars show bootstrapped 95% confidence intervals. *** $p=0.001$.

COMT Val¹⁵⁸Met does not moderate the effect of THC on psychotic experiences

In contrast to Digit Span Backwards performance, whilst the CAPE positive dimension score was greater in participants administered THC than those given placebo ($B = 0.094 \pm 0.042$; 95% CI: 0.024 to 0.186; $p=0.031$), this was not altered by COMT genotype (Figure 2). Thus, there was no drug*genotype interaction ($B = -0.038 \pm 0.048$; 95% CI: -0.137 to 0.053 ; $p=0.521$). There was no robust main effect of COMT genotype (after bootstrapping: $B = 0.042 \pm 0.015$; 95% CI: 0.010 to 0.072; $p=0.013$; but this was not seen prior to bootstrapping, or with or without bootstrapping for pairwise comparisons), nor was there an effect of age, IQ or lifetime cannabis use on CAPE positive dimension score ($p>0.25$).

Discussion

Here, we demonstrate that working memory impairments, but not psychotic experiences, induced by THC administration are dependent on COMT genotype, in non-clinical volunteers prone to paranoia. Our data provide further evidence for interactive effects of COMT Val¹⁵⁸Met and experimentally administered cannabis/THC. Consistently with earlier findings (Henquet *et al.*, 2006), they suggest that COMT genotype effects are more prominent for THC-induced cognitive impairments than psychotic

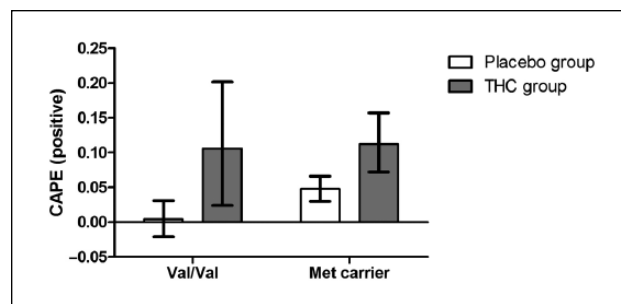


Figure 2. COMT genotype did not alter the impact of THC on psychotic experiences. Psychotic experiences were greater in those given THC (closed bars) compared with those given placebo (open bars). However, this difference was unaltered by COMT genotype. Error bars show bootstrapped 95% confidence intervals.

experiences, at least in non-clinical individuals. This suggestion of possibly divergent effects of COMT on working memory, compared with psychotic experiences, is notable given our earlier report that showed that THC-induced working memory changes do not lead to paranoia (Freeman *et al.*, 2015).

Our data demonstrate that COMT Val homozygosity is associated with greater cognitive impairment in response to THC, compared with the Met allele. In our participants, the administration of THC had little effect in Met carriers, impairing performance by ~12% compared with those given placebo (a difference that did not reach statistical significance). In contrast, Val/Val carriers given THC were dramatically impaired (~40%) compared with those given placebo. These findings are consistent with the single previous laboratory-based study of COMT and THC, which showed that THC-induced impairments in verbal memory and sustained attention were limited to the Val/Val genotype group (Henquet *et al.*, 2006). The consistency between our findings is striking given the differences between the methodological approaches: our study was a between-subjects design, in which THC was administered to non-clinical participants via the intravenous route; in contrast, the previous study used a within-subjects design in a mixed group of patients with psychosis, unaffected relatives and healthy controls, with THC administered via inhalation (Henquet *et al.*, 2006). Taken together, these data suggest a robust effect of COMT genotype on THC-induced cognitive impairments that cuts across several cognitive domains and is present in both patients with psychosis and healthy controls. It will be of interest to investigate the mechanisms underlying this interactive effect: we have already demonstrated interactive effects of COMT and THC on dopamine levels in a rodent model (Stumpfenhorst *et al.*, 2012), providing a potential mechanism, given dopamine's key role in multiple aspects of cognitive function (Goldman-Rakic *et al.*, 2000).

In contrast to the interactive effects of COMT and THC on cognitive function, we did not find evidence for an effect of COMT on the psychotogenic effects of THC. Thus, whilst THC led to increases in psychotic experiences (as measured using the CAPE positive dimension score), this increase occurred irrespective of COMT genotype. At first glance, these findings contrast with previous studies, which demonstrated that the Val allele was linked with a poorer response in terms of psychosis symptoms to acute administration of cannabis or THC, compared with the

Table 2. Digits Backwards and CAPE positive scores in the four groups, presented as mean (bootstrapped 95% confidence intervals).

	Placebo		THC	
	Val/Val	Met carrier	Val/Val	Met carrier
Digits Backwards (pre-drug)	9.13 (7.67 to 10.83)	8.18 (7.45 to 8.97)	7.09 (5.75 to 8.33)	8.11 (7.22 to 9.00)
Digits Backwards (post-drug)	10.32 (8.75 to 11.499)	9.11 (8.28 to 9.96)	6.24 (5.17 to 7.29)	8.05 (7.00 to 9.02)
CAPE positive dimension (post-drug)*	0.004 (-0.021 to 0.023)	0.048 (0.030 to 0.066)	0.106 (0.024 to 0.202)	0.112 (0.072 to 0.157)

*Expressed per item, as detailed in methods.

Met allele (Henquet et al., 2006; Henquet et al., 2009). However, both of the earlier studies found COMT genotype-dependent effects of THC only in those with high psychosis liability in mixed cohorts including both non-clinical participants and those with psychotic disorder. COMT genotype did not alter the psychotic response to THC in those with low psychosis liability (for both, 'high' or 'low' liability was encoded as a binary variable determined using a trait version of CAPE dichotomized at either the 50th (Henquet et al., 2006) or the 75th (Henquet et al., 2009) percentile). Although the participants in our sample were recruited on the basis of having experienced at least one paranoid thought in the last month, none had a history of clinical psychosis. Thus, our data provide evidence that COMT does not affect the psychotic response to THC in non-clinical individuals. However, it remains possible that it may be relevant in those with a psychotic disorder (or in groups with a particularly high psychosis liability).

Our study is the largest to date to examine the impact of COMT genotype on the response to experimentally administered THC. Nevertheless, studies of this type require detailed phenotyping and so are necessarily relatively small in scale; therefore, we focused our attention on a single genetic polymorphism and the outcome of two specific measures based on clear hypotheses arising from the existing literature (namely, the Digits Span Backwards and the CAPE positive dimension) to avoid problems of multiple comparisons. A limitation of our study is that the groups were not well matched for age, most notably, but also for IQ and lifetime cannabis use; however, none of the measures that we studied were significantly affected by these factors, nor were our findings altered by their exclusion or inclusion as covariates in the analyses. Thus, we consider it unlikely that our results are driven by between-group differences in these variables. Similarly, although there were numerical differences in pre-drug Digit Span Backwards performance between Val/Val individuals randomized to placebo vs. those randomized to THC, the Val/Val-THC group was the only one to show a notable drop in performance from the pre- to post-drug period (Table 2; note that the Val/Val-placebo group showed an improvement in performance from the pre- to post-drug period). Therefore, we do not believe that the (non-significant) group difference explains our findings. Since this study was a secondary analysis of a study designed to examine the effects of THC in participants with paranoid thoughts, our population should not be considered to be healthy controls, although none had a psychiatric diagnosis. Therefore, further studies in fully screened, healthy volunteers are warranted. Finally, our study, for ethical reasons, was restricted to volunteers who had had prior exposure to cannabis. It will be of interest to investigate the impact of COMT on the first exposure to THC in animal models, to see whether COMT impacts on the response to THC in the drug-naïve state.

In conclusion, our data provide further evidence that COMT genotype alters the cognitive, but not the psychotic, effects of acutely administered THC in healthy volunteers. These findings are consistent with the sparse existing literature suggesting that carriers of the Val/Val genotype might be particularly sensitive to the cognitive impairments induced by THC, but also add weight to the better-studied field of psychotic experiences, in which it has been demonstrated that COMT has little impact on THC's effects, at least in non-clinical volunteers. Further studies are needed to define the neurobiological mechanisms underlying this interactive effect; our studies suggest that alterations in dopamine transmission may contribute (Stumpfenhorst et al., 2012). Finally, our data provide an example of how hypothesis-driven experimental medicine studies can have utility in clarifying the mechanisms underlying individual differences in drug responses.

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