Moderation of the Effect of Adolescent-Onset Cannabis Use on Adult Psychosis by a Functional Polymorphism in the Catechol-O-Methyltransferase Gene: Longitudinal Evidence of a Gene X Environment Interaction

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Background: *Recent evidence documents that cannabis use by young people is a modest statistical risk factor for psychotic symptoms in adulthood, such as hallucinations and delusions, as well as clinically significant schizophrenia. The vast majority of cannabis users do not develop psychosis, however, prompting us to hypothesize that some people are genetically vulnerable to the deleterious effects of cannabis.*

Methods: *In a longitudinal study of a representative birth cohort followed to adulthood, we tested why cannabis use is associated with the emergence of psychosis in a minority of users, but not in others.*

Results: *A functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis. Carriers of the COMT valine^{158} allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder if they used cannabis. Cannabis use had no such adverse influence on individuals with two copies of the methionine allele.*

Conclusions: *These findings provide evidence of a gene × environment interaction and suggest that a role of some susceptibility genes is to influence vulnerability to environmental pathogens.*

Key Words: Cannabis, catechol-O-methyltransferase, gene–environment interaction, psychosis

Cannabis is the most widely used illicit drug in the world, but it is not wholly free from potentially harmful side effects (Ashton 2002; Iversen 2003). Worldwide evidence documents that cannabis use is a modest statistical risk factor for the emergence of psychosis, ranging from psychotic symptoms such as hallucinations and delusions to clinically significant disorders such as schizophrenia. Prospective studies estimate that cannabis use is associated with a twofold increase in later schizophrenia outcomes, and early, adolescent-onset cannabis use is associated with a higher risk (Arseneault et al 2004), possibly because individuals who begin to use cannabis when the brain is still developing are most vulnerable to its deleterious effects (Ehrenreich et al 1999; Pistis et al 2004; Pope et al 2003; Schneider and Koch 2003). Nonetheless, the vast majority of young people who use cannabis do not develop psychosis, suggesting the hypothesis that, if cannabis is indeed causal, some individuals may be genetically vulnerable to its effects. The presence of such a gene by environment (G × E) interaction is indicated by the finding that the association between cannabis and psychosis outcomes is most marked in subjects with an established vulnerability to psychosis (Henquet et al 2004; van Os et al 2002; Verdoux et al 2003). In this study, we tested whether a functional polymorphism of the catechol-O-methyltransferase (COMT) gene moderates the association between cannabis use and the risk of developing psychosis.

COMT was a logical candidate gene for this study for three reasons. First, the COMT gene is located on chromosome 22q11, a region implicated in genome scans of schizophrenia (Lewis et al 2003). Second, a microdeletion of 22q11 is associated with velo-cardio-facial syndrome, which has a high rate of psychosis (Murphy et al 1999). Third, the COMT gene product, catechol-O-methyltransferase, is involved in the metabolism of dopamine released into synapses, and disturbances in dopaminergic function are implicated in the pathogenesis of schizophrenia (Kapur 2003; Moore et al 1999). Of particular interest is a G to A missense mutation that generates a valine (Val) to methionine (Met) substitution at codon 158 (Val^{158}Met), producing less enzymatic activity and slower break down of dopamine (Lachman et al 1996; Lotta et al 1995). Individuals carrying the Met/Met genotype have the lowest COMT activity, whereas those with Val/Val have the highest; heterozygotes are considered to be of intermediate activity because the two alleles are codominant (Männisto et al 1999). Family-based studies have found evidence for differential transmission of the high-activity COMT Val allele in individuals with schizophrenia, but this effect is not consistently observed in case–control studies (Glatt et al 2003) and remains inconclusive (Owen et al 2004). It has been suggested, however, that the COMT Val^{158}Met polymorphism may operate as a risk factor for psychosis in the context of exposure to environmental pathogens (Bilder et al 2004).

Although the individual contributions to psychosis outcomes of cannabis and the COMT genotype are small, we reasoned that

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their joint effect could be larger because both appear to influence cognitive and physiologic processes that are implicated in schizophrenia. First, chronic cannabis use (Block et al 2002; Lundqvist et al 2001; Solowij et al 2002) and the COMT Val allele (Egan et al 2001) have been independently associated with deficits in prefrontal cortex functions, such as impaired memory and attention, which are characteristic of schizophrenia (Bunney and Bunney 2000; Weinberger et al 2001) and represent an endophenotype for the disorder (Gottesman and Gould 2003). These effects are probably mediated through diminished dopamine transmission in the prefrontal cortex (Egan et al 2001; Verrico et al 2003). Second, cannabis use (Tanda et al 1997; Voruganti et al 2001) and, indirectly, the Val allele (Akil et al 2003) are associated with increased mesolimbic dopamine transmission, a mechanism implicated in hallucinations and delusions (the "positive" symptoms of schizophrenia; Moore et al 1999). We thus hypothesized that carriers of the Val allele would be at greatest risk for the potential long-term psychotogenic effects of cannabis. We tested this G × E hypothesis using data from an epidemiologic birth cohort followed longitudinally across the first three decades of life.

Methods and Materials

Participants

Participants were members of the Dunedin Multidisciplinary Health and Development Study. The birth cohort of 1,037 children (52% male children) was established at age 3 when the investigators enrolled 91% of consecutive births between April 1972 and March 1973 in Dunedin, New Zealand. Cohort families represent the full range of socioeconomic status in the general population of New Zealand's South Island. Follow-ups have been carried out at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and most recently age 26, when we assessed 96% of the living cohort members. At each assessment, study members are invited to the research unit for a full day of data collection. The study members have a long history of reporting sensitive information to us, with no violation of their confidentiality. The analyses presented here are based on 803 individuals. Individuals not studied were deceased (2%), lacked prospective data on cannabis use (7%), lacked assessment of psychosis outcomes (4%), did not give DNA (3%), or were not genotyped (7% non-Caucasians). Written informed consent was obtained from all participants after a detailed description of the study, which was approved by the institutional review boards of the three participating universities (Otago Ethics Committee; Institute of Psychiatry/South London and Maudsley National Health Service Trust Ethical Committee, Research; University of Wisconsin—Madison Social and Behavioral Science Internal Review Board).

Measurement

DNA Extraction and Genotyping. At age 26, DNA was obtained from 953 study members (97% of those assessed; 51% male); 93% of DNA samples were obtained via blood and 7% via buccal swabs for those not wishing to undergo phlebotomy. The COMT functional SNP ($Val^{158}Met$) was assayed using the SNiPTag technique, an adaptation of competitive allele-specific polymerase chain reaction (PCR; McClay et al 2002). In this reaction, two fluorescently labeled allele-specific (AS) primers are employed in conjunction with a third, common primer and the products assayed using automated sequencing machinery. The AS primers were as follows (AS nucleotide in bold): COMT-4bC (GCA CAC CTT GTC CTT CA**C**) labeled with the FAM fluorophore and COMT-4bT (GCA CAC CTT GTC CTT CA**T**) labeled with the NED fluorophore. The common primer was COMT-4a (ACT GTG GCT ACT CAG CTG TG), which was unlabeled. Reactions were carried out using an optimized version of the protocol described by McClay et al (2002). Per reaction: 1X PCR buffer IV (ABgene, Epsom, United Kingdom), 1.5 mmol/mL magnesium chloride, .2 mmol/mL dNTPs (Amersham, Little Chalfont, United Kingdom), 4 pmol COMT-4a, 2 pmol each of COMT-4bC and COMT-4bT, .5 U Native *Taq,* 25 ng genomic DNA template, deionized and microfiltered water to final reaction volume of 10 μL. Polymerase chain reaction was carried out on a PTC-225 DNA engine (MJ Research, Hercules, California), using the following cycling conditions: initial 2-min denaturing step at 95°C, followed by 35 cycles of 94°C for 1 min, 65.0°C for 1 min, 72°C for 1 min, and a final extension phase of 72°C for 1 min. The PCR products were assayed on an Applied Biosystems 3100 automated sequencer, set up in genotyping mode, under Applied Biosystems Filter Set D. Results were analyzed using GeneScan v3.5.1 and Genotyper v3.7 analysis software (Applied Biosystems, Foster City, California). Genotyping was performed blind to study members' cannabis exposure and psychosis outcome status.

Cohort members reporting Maori ethnicity (7%) were not included in analyses. Allele frequencies among Caucasians included in our study were consistent with previously reported allele frequencies in Caucasian populations: 50% for the low activity (Met) allele and 50% for the high activity (Val) allele (Palmatier et al 1999). The sample was split into three groups on the basis of genotype: individuals homozygous for the low-COMT-activity allele (Met/Met; 25% of sample, 52% male); individuals homozygous for the high-COMT-activity allele (Val/Val; 25% of sample, 49% male), and heterozygotes (Val/Met; 50% of sample, 52% male). The three groups were in Hardy–Weinberg equilibrium ($\chi^2(2) = .02$, $p = .99$); there was no significant difference in genotype frequencies between genders ($\chi^2(2) = .56$, $p = .75$).

Psychosis outcomes were assessed at age 26 using a standardized psychiatric interview, the Diagnostic Interview Schedule (Robins et al 1995), administered by health professionals (medicine, clinical psychology, public health). Interviewers had no knowledge of study members' history of cannabis use or genotype. We examined three types of outcome measures.

First, we established whether study members met diagnostic criteria for schizophreniform disorder during the year before the age-26 assessment according to criteria from the *DSM-IV* (American Psychiatric Association 1994). Symptoms of this disorder include hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behavior, and negative symptoms such as avolition, flat affect, or alogia (*DSM-IV* Criterion A group), plus evidence of social, occupational, or self-care dysfunction (*DSM-IV* Criterion B group). Symptoms must have lasted at least 1 month. To enhance validity of the research diagnosis, we required hallucinations (not related to drug or alcohol use) plus at least two other Criterion A symptoms. We further required objective evidence of Criterion B impairment from informants and our staff clinicians to supplement study members' self-reports. Following this protocol, 1% of the cohort met criteria for schizophrenia at age 26 years (symptom duration > 6 months), and a further 2.6% met criteria for schizophreniform disorder (i.e., symptom duration from 1–6 months). We combined the two, hereafter referred to as schizophreniform disorder; 3.6% were so classified. Of these individuals, 70% had received mental health treatment as adults. There was no gender difference in the

prevalence of schizophreniform-spectrum disorder ($\chi^2(1) = .81$, $p = .37$). Further details about schizophreniform cases in this cohort are provided elsewhere (Cannon et al 2002; Poulton et al 2000).

Second, we computed a continuous scale of psychotic symptoms by summing study members' reports about hallucinations and delusions from the psychiatric interview (Table 1; 24 questions: M = 1.58, SD = 4.23, Cronbach's alpha = .95). Specifically, 13% of study members reported at least one hallucinatory experience symptom, and 21% reported at least one delusional belief symptom; these groupings were studied as categoric outcomes. These rates of psychotic symptoms are comparable to those observed in U.S. and European epidemiologic studies (Myin-Germeys et al 2003). Of those reporting at least one hallucinatory experience symptom, 58% reported at least one delusional belief symptom; of those reporting at least one delusional belief symptom, 38% also reported at least one hallucinatory experience symptom.

Third, we collected informant reports about symptoms related to psychosis, to document that findings from this study were not based solely on self-reports. A 60-item questionnaire was mailed to persons nominated by each study member at age 26 as "someone who knows you well" and responses were returned for 96% of the cohort. Informants were best friends, partners, or other family members. As part of the questionnaire, informants rated study members, using a 3-point rating scale (0 = no, doesn't apply; 1 = applies somewhat; 2 = certainly applies) on three symptoms related to psychosis: "hears things that aren't there," "suspicious of other people," "thinks others are out to get him/her." We summed these three symptom ratings (M = .47; SD = .78; Cronbach's alpha = .72).

Adolescent-onset cannabis users were study members who reported using cannabis in adolescence, as follows: at ages 13 and 15, study members had been asked whether they had used cannabis in the past year; by their 15th birthday, 15% of study members reported using cannabis. At age 18, study members were asked about the frequency with which they used cannabis in the past year; 17% of study members reported using cannabis at least once per month. Of the total sample, 26% of study members were classified as adolescent-onset cannabis users if they had used cannabis before age 15 or if they were at least monthly cannabis users by age 18. By age 18, these users had a median cannabis use of 25 days per year (range 12–365 days), and 25% met *DSM-IV* diagnostic criteria for cannabis dependence (compared with a prevalence rate of less than 1% among cohort members not classified as adolescent onset). There was no gender difference in adolescent-onset cannabis use, $\chi^2(1) = .14$, $p = .71$. Of study members with the Met/Met, Val/Met, and Val/Val genotype, 24%, 23%, and 27%, respectively, were adolescent-onset cannabis users, $\chi^2(2) = 1.19$, $p = .55$. Thus, the three COMT genotypes did not differ on exposure to cannabis in adolescence nor on cannabis dependence, $\chi^2(2) = 2.63$, p = .27.

Control Variables. Adult cannabis use was assessed at ages 21 and 26 years, when study members reported how often they used cannabis in the past year. Thirty-eight percent of the study members used cannabis on at least a monthly basis as adults. We identified a group (19% of the sample) of adult-onset cannabis users who used cannabis on at least a monthly basis at ages 21 years, 26 years, or both, but not before age 18. At age 26, these adult-onset cannabis users had a median cannabis use of 30 days per year (range 12–365 days), and 17% met *DSM-IV* diagnostic criteria for cannabis dependence.

Use of amphetamines or hallucinogens in the past year was

Table 1. Symptoms of Psychosis Covered in the Psychiatric Interview and Endorsement Frequencies Among Study Members ($N = 803$)

	% Endorsed
Hallucinatory Experiences (Not Drug or Alcohol Related)	
Hear things or voices that other people cannot hear	3.4
Hear voices commenting on what you were doing or thinking	1
Hear voices telling you what to do	.6
Hear two or more voices talking to each other that other people could not hear	.6
Carry on conversations with the voices that other people could not hear	1.1
Bothered by strange smells that no one else could smell	2.2
Had unusual feelings inside or on your body	5.5
Bothered by strange tastes that were not from anything you had eaten	2.5
Seen things or people that others could not see or had a vision when completely awake	4.6
Delusional Beliefs (not drug or alcohol related)	
Believed you were being secretly tested on	2.6
Believed someone was plotting against you or trying to hurt or poison you	2.2
Believed someone was spying on you	4.9
Believed that someone was following you	5.6
Thoughts that people you didn't know were talking about you or laughing at you	9.5
Believed that someone was reading your mind	3.1
Believed you could hear what another person was thinking even though they were not speaking	4.4
Believed others could hear your thoughts	3.1
Believed that a power could control your movements or thoughts against your will	1.9
Believed that someone could put thoughts into your mind that were not your own	3.6
Believed that someone took your thoughts out of your mind	1.5
Believed that someone you have not met was in love with you	1
Believed you were sent special messages through the media	1.5
Believed strange forces were working on you (e.g., hit by x-rays, having magic performed on you)	.6
Believed you've done something terrible for which you should be punished	5.1

Table 2. The Influence of Adolescent-Onset Cannabis Use on Adult Psychosis: Results of Final Regression Analyses Testing Gene by Environment Interaction Effects (see Statistical Analysis section for details)

	Predictor Variables															
		Covariate				COMT Genotype				Early-Onset Cannabis Use				COMT Genotype x Early-Onset Cannabis Use			
Psychosis outcomes at age 26	Intercept	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*
Diagnosis of Schizophreniform Disorder																	
A. Baseline model[a]	−3.19	—	—	—	—	−.56	.39	1.45	.15	−.19	.73	.26	.80	1.26	.57	2.24	.025
B. Controlling for adult cannabis use	−3.34	.50	.45	1.12	.26	−.62	.40	1.53	.13	−.33	.76	.44	.66	1.20	.58	2.06	.039
C. Controlling for adolescent use of drugs other than cannabis	−3.19	.01	.55	.02	.98	−.56	.39	1.45	.15	−.19	.76	.25	.80	1.26	.57	2.23	.025
D. Controlling for adult use of amphetamines and hallucinogens	−3.24	.29	.43	.67	.50	−.56	.39	1.45	.15	−.30	.75	.40	.69	1.27	.57	2.24	.025
E. Controlling for childhood psychotic symptoms	−3.64	1.42	.35	3.99	.01	−.68	.46	1.48	.14	−.25	.81	.30	.76	1.42	.66	2.14	.032
F. Controlling for childhood IQ	1.47	−.04	.01	3.00	.01	−.63	.40	1.57	.12	−.30	.74	.04	.69	1.36	.58	2.35	.019
G. Controlling for adolescent conduct disorder	−3.30	.76	.43	1.78	.07	−.59	.39	1.52	.13	−.50	.75	.67	.50	1.30	.56	2.31	.021
Self-Reports of Psychotic Symptoms																	
A. Baseline model	.97	—	—	—	—	.01	.22	.04	.97	1.04	.56	1.88	.06	.88	.45	1.97	.049
B. Controlling for adult cannabis use	.86	.58	.32	1.83	.07	−.03	.23	.13	.90	.67	.58	1.15	.23	.92	.45	2.04	.042
C. Controlling for adolescent use of drugs other than cannabis	.96	1.50	.52	2.87	.01	.005	.22	.02	.98	.45	.59	.77	.44	.88	.44	1.97	.049
D. Controlling for adult use of amphetamines and hallucinogens	.80	1.09	.34	3.22	.01	.004	.22	.02	.98	.65	.57	1.15	.25	.98	.44	2.02	.040
E. Controlling for childhood psychotic symptoms	.86	.67	.37	1.84	.07	−.04	.23	.15	.88	.52	.59	.88	.38	1.06	.47	2.23	.026
F. Controlling for childhood IQ	1.79	−.01	.01	.71	.48	.005	.23	.02	.98	1.08	.57	1.90	.06	.90	.45	1.99	.047
G. Controlling for adolescent conduct disorder	.81	1.69	.36	4.72	.01	−.04	.22	.19	.85	.39	.57	.69	.49	.98	.44	2.22	.027
Evidence of Hallucinatory Experiences																	
A. Baseline model[a]	−1.92	—	—	—	—	−.34	.20	1.70	.09	.21	.40	.54	.59	.73	.32	2.31	.021
B. Controlling for adult cannabis use	−1.95	.21	.25	.85	.39	−.40	.20	1.96	.05	.01	.42	.03	.97	.82	.33	2.51	.012
C. Controlling for adolescent use of drugs other than cannabis	−1.93	.35	.34	1.03	.30	−.34	.20	1.70	.09	.07	.43	.16	.87	.73	.32	2.31	.021
D. Controlling for adult use of amphetamines and hallucinogens	−1.99	.39	.25	1.59	.11	−.34	.21	1.71	.09	.07	.41	.17	.87	.74	.32	2.33	.020
E. Controlling for childhood psychotic symptoms	−1.91	.70	.25	2.77	.01	−.57	.23	2.50	.01	−.01	.45	.03	.98	.95	.37	2.58	.010
F. Controlling for childhood IQ	−.32	−.01	.01	1.78	.08	−.35	.20	1.74	.08	.18	.40	.45	.65	.75	.32	2.35	.019
G. Controlling for adolescent conduct disorder	−1.99	.60	.25	2.37	.02	−.36	.20	1.80	.07	−.03	.41	.07	.94	.77	.32	2.43	.015

Table 2. (continued)

	Predictor Variables															
		Covariate				COMT Genotype				Early-Onset Cannabis Use				COMT Genotype x Early-Onset Cannabis Use			
Psychosis outcomes at age 26	Intercept	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*
Evidence of Delusional Beliefs																	
A. Baseline model[a]	−1.72	—	—	—	—	.04	.16	.23	.82	.78	.34	2.32	.02	.19	.26	.70	.482
B. Controlling for adult cannabis use	−1.79	.44	.20	2.16	.03	.003	.16	.02	.99	.50	.35	1.42	.16	.23	.27	.84	.400
C. Controlling for adolescent use of drugs other than cannabis	−1.72	.04	.30	.15	.88	.04	.16	.23	.82	.76	.36	2.14	.03	.19	.26	.70	.483
D. Controlling for adult use of amphetamines and hallucinogens	−1.83	.61	.20	2.98	.01	.03	.16	.21	.83	.56	.35	1.61	.11	.20	.27	.75	.450
E. Controlling for childhood psychotic symptoms	−1.74	.36	.23	1.55	.12	−.07	.18	.37	.72	.71	.38	1.87	.06	.29	.30	.95	.342
F. Controlling for childhood IQ	−.85	−.008	.01	1.15	.25	.01	.16	.09	.93	.77	.34	2.27	.02	.21	.27	.79	.430
G. Controlling for adolescent conduct disorder	−1.83	.93	.21	4.42	.01	.001	.16	.01	.99	.40	.35	1.14	.26	.26	.27	.95	.342
Informant Reports of Psychotic Symptoms																	
A. Baseline model	.38	—	—	—	—	.004	.04	.10	.92	.12	.11	1.09	.28	.17	.09	1.92	.055
B. Controlling for adult cannabis use	.33	.16	.06	2.55	.01	.01	.04	.27	.79	.07	.11	.60	.55	.15	.09	1.72	.086
C. Controlling for adolescent use of drugs other than cannabis	.37	.21	.10	2.01	.05	.004	.04	.08	.93	.04	.12	.32	.75	.16	.09	1.91	.057
D. Controlling for adult use of amphetamines and hallucinogens	.35	.16	.07	2.35	.02	.004	.04	.09	.93	.07	.11	.60	.55	.17	.09	1.94	.053
E. Controlling for childhood psychotic symptoms	.34	.19	.07	2.72	.01	−.003	.04	.06	.95	.10	.11	.89	.37	.16	.09	1.79	.074
F. Controlling for childhood IQ	1.40	−.009	.002	4.66	.01	−.005	.04	.12	.91	.09	.11	.80	.43	.19	.09	2.21	.027
G. Controlling for adolescent conduct disorder	.35	.35	.07	4.98	.01	−.007	.04	.17	.87	−.02	.11	.15	.88	.18	.09	2.14	.033

Model A is the baseline model estimating the interaction of catechol-O-methyltransferase (COMT) and adolescent-onset cannabis use. Model B contains a covariate controlling for monthly, adult cannabis use; Model C contains a covariate for adolescent use of drugs other than cannabis; Model D contains a covariate controlling for adult use of amphetamines and hallucinogens; Model E contains a covariate controlling for childhood psychotic symptoms, before onset of cannabis use; Model F contains a covariate controlling for childhood IQ; Model G contains a covariate controlling for adolescent conduct disorder.

[a]The logistic regression models test for interaction on the multiplicative scale for the binary variables (in the three cases of predicting presence of schizophreniform disorder, evidence of hallucinatory experiences, and evidence of delusional beliefs). In addition to analyses presented in the table, we reestimated these three regression models testing for interactions on an additive scale, using a risk difference model (binomial regression with identity link; Hardin and Hilbe 2001). These analyses were performed using BINREG in Stata (StataCorp, 2003). The results for the interaction terms were robust to the type of model specification and were equivalent to the results presented in the table. There was a significant interaction on the additive scale between COMT and adolescent-onset cannabis predicting schizophreniform disorder ($\chi^2(1) = 4.5$, $p = .034$) and evidence of hallucinatory experiences ($\chi^2(1)$ 4.9, $p = .027$), but not for evidence of delusional beliefs ($\chi^2(1) = .73$, $p = .39$).

reported at ages 21, 26, or both by 25% of study members. At ages 15, 18, or both, use of these other drugs (as well as glue sniffing) was reported by 12% of study members.

Psychotic symptoms at age 11 years were assessed as part of the Diagnostic Interview Schedule for Children, administered by a child psychiatrist to 789 study members. (One quarter of the cohort was assessed at school and did not see the psychiatrist.) The interview included five questions regarding possible psychotic symptoms, which were rated by the psychiatrist as no (0); yes, likely (1); and yes, definitely (2). Most children (85%) obtained a score of 0; 13% obtained a score of 1 and were called the weak-symptom group; the remaining 2% obtained a score of 2 or higher and were called the strong-symptom group. Elsewhere we have reported that study members with schizophreniform disorder at age 26 years were likely at age 11 years to have been in the strong-symptom group (odds ratio [OR] = 16.4; 95% confidence interval [CI]: 3.9–67.8) or in the weak-symptom group (OR = 5.1; 95% CI: 1.7–18.3; Poulton et al 2000).

IQ was measured at ages 7, 9, 11, and 13 years with the Wechsler Intelligence Scale for Children—Revised (Wechsler 1974).

Conduct disorder was used as a covariate because it is a risk factor for both cannabis use (Moffitt et al 2001) and adult schizophreniform disorder (Kim-Cohen et al 2003). Twenty-two percent of the cohort had met *DSM-IV* criteria for conduct disorder when assessed at ages 11, 13, 15, or 18 (Moffitt et al 2001).

Statistical Analysis

We used a moderated regression framework (Cohen et al 2003) to estimate the influence of 1) adolescent cannabis use, 2) the COMT genotype, and 3) their interaction on adult psychosis outcomes. For continuous measures (self-reports and informant reports of psychotic symptoms), we used ordinary least squares (OLS) regression; for categoric measures (diagnosis of schizophreniform disorder; evidence of a hallucinatory experience symptom; evidence of a delusional belief symptom), we used logistic regression. The equation is as follows:

$$\text{Psychosis} = b0 + b1(\text{COMT}) + b2(\text{adolescent-onset cannabis use}) + b3(\text{COMT} \times \text{adolescent-onset cannabis use}),$$

where b0 is the intercept; b1 is the regression coefficient associated with the effect of variations in the COMT gene (which is here coded as 2 = val/val; 1 = val/met; 0 = met/met); b2 is the coefficient associated with the effect of adolescent-onset cannabis use (dummy-coded as 1 = adolescent-onset cannabis use; 0 = others); and b3 is the coefficient associated with the interaction effect, which is the multiplicative product of the two variables (COMT and adolescent-onset cannabis use).

In Results, we present the results from a hierarchical analysis, in which the main effects of COMT and cannabis use are entered on the first step of the regression model and the interaction effect of COMT × cannabis use is entered on the second step (after main effects are partialed). Table 2 provides the results of final models with main effects and interactions entered simultaneously. Table 4 provides the data for each of the six exposure cells in the analyses.

Results

Figure 1A shows the percentage of individuals meeting diagnostic criteria for schizophreniform disorder at age 26, as a function of COMT genotype and adolescent-onset cannabis use. In a hierarchical logistic regression model, the main effect of genotype was not significant, $b = .05$, SE = .27, $z = .17$, $p = .87$, the main effect of adolescent cannabis exposure was significant, $b = 1.13$, SE = .38, $z = 2.96$, $p = .003$, and the interaction between genotype and adolescent cannabis exposure was significant, $b = 1.26$, SE = .57, $z = 2.24$, $p = .025$. Adolescent cannabis use was associated with increased risk of schizophreniform disorder in adulthood among Val/Val individuals (OR = 10.9, 95% CI: 2.2–54.1) and, to a lesser extent, among Val/Met individuals (OR = 2.5, 95% CI: .78–8.2), but not among Met/Met individuals (OR = 1.1, 95% CI = .21–5.4).

Figure 1B shows the means (and standard errors) for age-26 self-reports of symptoms of psychosis (hallucinations and delusions). In a hierarchical (OLS) regression model, the main effect of genotype was not significant, $b = .23$, SE = .19, $t = 1.20$, $p = .23$, the main effect of adolescent cannabis exposure was significant, $b = 1.94$, SE = .32, $t = 6.04$, $p < .001$, and the interaction between genotype and adolescent cannabis exposure was significant, $b = .88$, SE = .45, $t = 1.97$, $p = .049$. Adolescent cannabis use was significantly and positively associated with self-reports of psychosis symptoms among Val/Val individuals ($b = 2.21$, SE = .72, $t = 3.08$, $p = .002$) and among Val/Met individuals ($b = 2.63$, SE = .48, $t = 5.50$, $p < .001$), but not among Met/Met individuals ($b = .37$, SE = .45, $t = .83$, $p = .41$).

Figure 1C shows the percentage of individuals reporting at least one hallucination experience at age 26. In a hierarchical logistic regression model, the main effect of genotype was not significant, $b = -.05$, SE = .15, $z = .31$, $p = .76$, the main effect of adolescent cannabis exposure was significant, $b = .96$, SE = .22, $z = 4.31$, $p < .001$, and the interaction between genotype and adolescent cannabis exposure was significant, $b = .73$, SE = .32, $z = 2.31$, $p = .02$. Adolescent cannabis use was associated with increased risk of hallucinatory experiences in adulthood among Val/Val individuals (OR = 5.3, 95% CI: 2.2-12.7) and, to a lesser extent, among Val/Met individuals (OR = 2.6, 95% CI: 1.4-4.9), but not among Met/Met individuals (OR = 1.2, 95% CI: .50-3.0).

Figure 1D shows the percentage of individuals reporting at least one delusional belief at age 26. The main effect of genotype was not significant, $b = .10$, SE = .13, $z = .82$, $p = .41$, and the main effect of adolescent cannabis exposure was significant, $b = .97$, SE = .19, $z = 5.15$, $p < .001$. The interaction between genotype and adolescent cannabis exposure was not statistically significant, $b = .19$, SE = .26, $z = .70$, $p = .48$, but the pattern of results was in the predicted direction: adolescent cannabis use statistically increased the risk of delusional beliefs in adulthood among Val/Val individuals (OR = 3.5, 95% CI: 1.7–7.0) and, to a lesser extent, among Val/Met (OR = 2.4, 95% CI: 1.4–4.1) and Met/Met individuals (OR = 2.4, 95% CI: 1.1–5.2).

Figure 1E shows the means (and standard errors) on age-26 informant reports of symptoms of psychosis. In a hierarchical (OLS) regression model, the main effect of genotype was not significant, $b = .05$, SE = .04, $t = 1.22$, $p = .22$, the main effect of adolescent cannabis exposure was significant, $b = .29$, SE = .06, $t = 4.57$, $p < .001$, and the interaction between genotype and adolescent cannabis exposure was marginally significant, $b = .17$, SE = .09, $t = 1.92$, $p = .055$. Adolescent cannabis use was significantly and positively associated with informant reports of psychosis symptoms among Val/Val individuals ($b = .40$, SE = .13, $t = 3.07$, $p = .002$) and among Val/Met individuals ($b = .32$, SE = .09, $t = 3.81$, $p < .001$), but not among Met/Met individuals ($b = .08$, SE = .13, $t = .60$, $p = .55$).

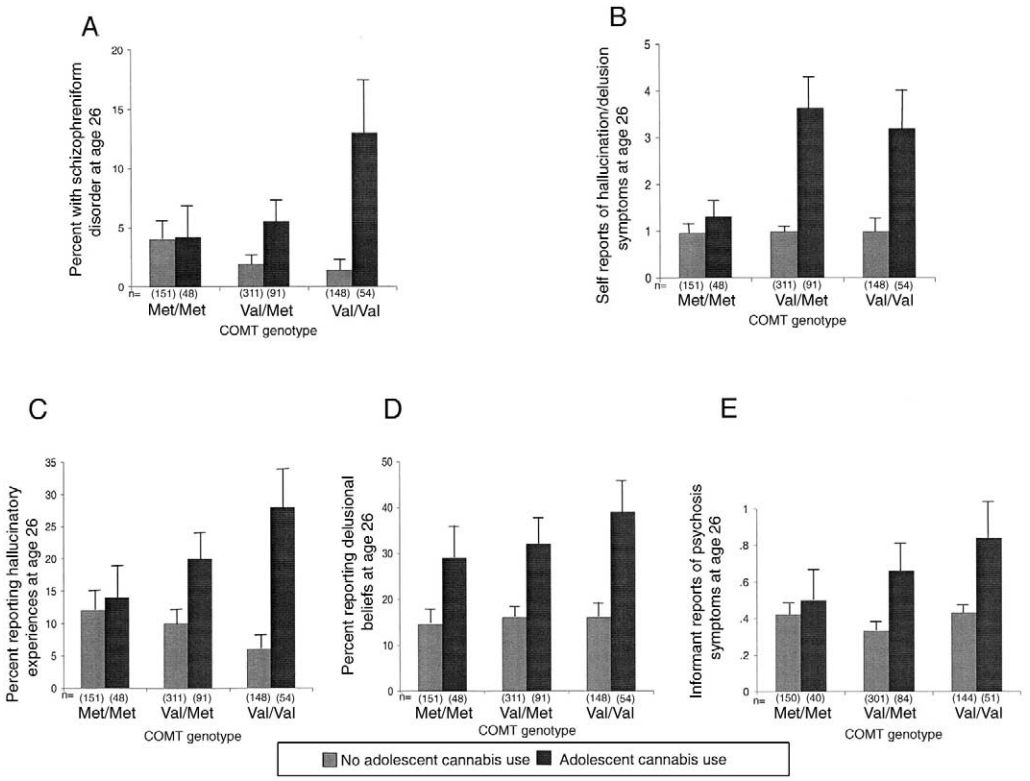

Figure 1. The influence of adolescent-onset cannabis use on adult psychosis is moderated by variations in the COMT gene. **(A)** The percentage of individuals meeting diagnostic criteria for schizophreniform disorder at age 26. **(B)** Means (and standard errors) on age-26 self-reports of symptoms of psychosis (hallucinations and delusions). **(C)** The percentage of individuals reporting at least one hallucination experience at age 26. (**D**) The percentage of individuals reporting at least one delusional belief at age 26. (**E**) Means (and standard errors) on age-26 informant reports of symptoms of psychosis.

In additional analyses, we tested whether the G × E interactions were moderated by gender. The three-way interactions were not significant; adolescent-onset cannabis use was associated with psychosis outcomes among both male and female Val carriers, but not among Met/Met homozygotes.

Testing Adolescent- Versus Adult-Onset Cannabis Exposure

Previous research suggests that adult-onset users might be less vulnerable than adolescents to the potential psychotogenic effect of cannabis (Arseneault et al 2004). Consistent with this hypothesis, we found that, unlike adolescent-onset cannabis users, adult-onset cannabis users were not at increased risk of psychosis, whether measured as schizophreniform disorder ($b = .004$, SE = .50, $z = .01$, $p = .99$), self-reports of psychotic symptoms ($b = -.36$, SE = .37, $t = .99$, $p = .32$), hallucinatory experiences ($b = .02$, SE = .28, $z = .09$, $p = .93$), delusional beliefs ($b = -.15$, SE = .24, $z = .62$, $p = .53$), or informant reports of psychotic symptoms ($b = .03$, SE = .07, $t = .45$, $p = .66$). Moreover, there were no significant interactions between adult-onset cannabis use and COMT in predicting psychosis outcomes (Table 3). In addition, the COMT × adolescent-onset cannabis use interactions remained significant when we controlled for cannabis use in adulthood (Table 2).

Testing Possible Alternative Explanations

We ruled out four alternative interpretations of the observed G × E interaction. The first alternative was that early cannabis use is a gateway to using amphetamines and hallucinogens (Lynskey et al 2003), which can induce psychosis, and that cannabis users with the Val allele could be most susceptible to these potent drugs. During adolescence, cannabis users also used other drugs (Table 4), but the G × E interactions remained significant when use of drugs other than cannabis was statistically controlled in regression analyses (Table 2). Adolescent cannabis users were also likely to use amphetamines and hallucinogens as adults (Table 4), but controlling for this drug use did not alter the results (Table 2). (Similar controls for adult tobacco and alcohol dependence also did not alter the G × E results.)

The second alternative was that individuals with the Val allele could have already been exhibiting psychotic symptoms before they began to use cannabis. To test this, we compared the 3 (genotype) × 2 (adolescent-onset cannabis use) groups on their self-reports of psychotic symptoms at age 11 years. The six groups did not differ from each other in the extent to which they experienced psychotic symptoms before they began to use cannabis (Table 4), and the G × E interactions remained significant after controlling for these prodromal childhood psychotic symptoms (Table 2).

The third alternative was that individuals with the Val allele could have had preexisting childhood cognitive deficits that put them at risk for both early cannabis use and later psychosis (Cannon et al 2002); however, the groups did not differ from each other in childhood IQ (Table 4), and controlling for IQ did not alter the results (Table 2).

A fourth alternative was that adolescent-onset cannabis use merely signals the presence of conduct problems, which increase

Table 3. Comparisons of the Three (Genotype) by Two (Adolescent-Onset Cannabis Use) Groups on Covariates and Outcomes

	Non-Cannabis-Using Adolescents			Early-Onset Adolescent Cannabis Users		
Covariates[a]	Met/Met ($n = 151$)	Val/Met ($n = 311$)	Val/Val ($n = 148$)	Met/Met ($n = 48$)	Val/Met ($n = 91$)	Val/Val ($n = 54$)
Adult cannabis use (%)[b]	21.8	25.2	25.7	70.2	69.6	71.7
Adolescent use of drugs other than cannabis (%)[c]	1.3	1.0	2.0	41.7	40.0	42.6
Adult use of amphetamines and hallucinogens (%)[d]	15.2	16.7	16.2	52.1	50.6	50.0
Childhood psychotic symptoms (%)[e]	15.4	10.0	13.6	21.6	18.3	14.3
Childhood IQ (M, SD)	110 (13)	107 (13)	108 (14)	107 (13)	107 (13)	107 (12)
Adolescent conduct disorder (%)[f]	10.5	11.5	16.9	52.1	42.4	46.3
Outcomes						
Diagnosis of schizophreniform disorder (%)	4.0	2.3	1.4	4.2	5.5	13.0
Self-reports of psychotic symptoms (M, SD)	.96 (2.8)	.99 (2.8)	.98 (3.1)	1.3 (2.4)	3.6 (6.7)	3.2 (7.1)
Evidence of hallucinatory experiences (%)	12.6	9.7	6.8	14.6	22.0	27.8
Evidence of delusional beliefs (%)	14.6	16.4	15.5	29.2	31.9	38.9
Informant reports of psychotic symptoms (M, SD)	.42 (.71)	.33 (.54)	.44 (.67)	.50 (.87)	.66 (1.1)	.84 (1.1)

[a]The covariates offer alternative explanations of the obtained G × E results. There was no significant association between genotype and any of the covariates (all p values exceed .35). There was a significant association between adolescent-onset cannabis use and adult cannabis use ($p < .001$), use of other drugs in adolescence ($p < .001$), use of amphetamines and hallucinogens in adulthood ($p < .001$), and adolescent conduct disorder ($p < .001$), but not between adolescent-onset cannabis use and childhood psychotic symptoms ($p = .06$) and childhood IQ ($p = .27$). Moreover, the observed G × E interaction could not be accounted for by the pattern of associations in the six exposure cells; that is, when stratified by adolescent-onset cannabis use, the three genotype groups did not differ from each other on any of the covariates.

[b]Percent study members reporting using cannabis, on average, on a monthly basis at age 21 years, 26 years, or both.

[c]Percent study members reporting trying other drugs at age 15 years, 18 years, or both.

[d]Percent study members reporting using amphetamines, hallucinogens, or both at age 21 years, 26 years, or both.

[e]Percent study members reporting "strong" or "weak" psychotic symptoms at age 11 years.

[f]Percent study members meeting diagnostic criteria for conduct disorder between ages 11 and 18 years.

the likelihood of cannabis use and which can be part of the adolescent prodromal phase of schizophrenia (Kim-Cohen et al 2003). Although study members who had conduct disorder were likely to be adolescent-onset cannabis users (Table 4), controlling for conduct disorder did not alter the results (Table 2).[1]

Discussion

This study provides evidence that a functional polymorphism in the COMT gene interacted with adolescent-onset cannabis use to predict the emergence of adult psychosis. An alternative causal hypothesis must be considered. It is possible that preexisting early behavior or cognitive problems lead psychosis-prone carriers of the Val allele to take up cannabis use as teenagers. There was no main-effect risk for developing psychosis among carriers of the Val allele, however, and Val allele carriers were not more likely to use cannabis. Moreover, analyses of prospective data established that the G × E antedated onset of psychosis and ruled out alternative accounts relating to preexisting childhood psychotic symptoms, preexisting cognitive deficits, use of other drugs, and prodromal conduct disorder.

The results provide evidence that adolescent cannabis use, but not adult-onset use, is associated with later psychosis outcomes and that the COMT Val[158]Met polymorphism moderated the link between psychosis and adolescent-onset cannabis use, but not adult-onset cannabis use. These results, together with studies finding cannabis effects on the brain limited to adolescence in both human research (Ehrenreich et al 1999; Pope et al 2003) and in experimental animal models (Pistis et al 2004; Schneider and Koch 2003), suggest the hypothesis that the observed G × E interaction may be limited to a sensitive period of brain development in adolescence. Alternatively, it could be that adult-onset users in our study had not used cannabis long enough for an association with psychotic symptomatology to be manifest.

There is also the question of whether cannabis use represents a true environmental risk factor or is merely a proxy for unmeasured genes. Drug initiation and use are influenced, in part, by genetic factors (Rhee et al 2003); however, the G × E reported in this study did not apply to initiation and use of drugs

[1]After ruling out alternative explanations for our finding, we proceeded to evaluate systematically whether the G × E interaction showed specificity to the hypothesized triad of gene, environmental risk factor, and psychiatric outcome (Licinio 2003) by replacing one element in the triad while holding the other two constant. We replaced the COMT genotype with candidate genes we have previously studied (MAOA and 5-HTTLPR; Caspi et al 2002, 2003), but these did not moderate the influence of early-cannabis use on psychosis outcomes. We replaced cannabis use with other environmental risks previously studied (maltreatment and stressful life events; Caspi et al 2002, 2003), but COMT did not moderate the influence of these risks on psychosis outcomes. Finally, we tested whether the COMT × early-cannabis use interaction was specific to psychosis outcomes or extended to other adult psychiatric disorders (including anxiety, major depression, alcohol dependence, and cannabis dependence); the observed G × E interaction extended only to depression ($p < .05$), suggesting the explanation behind this G × E may ultimately involve neurobiological processes shared by affective and psychotic disorders. Equally, this finding was not hypothesized in advance and may capitalize on chance.

Table 4. The Nil Influence of Adult-onset Cannabis Use on Adult Psychosis: Results of Final Regression Analyses Testing G×E Interaction Effects

	Predictor Variables											
		COMT Genotype				Adult-Onset Cannabis Use				COMT Genotype × Adult-Onset Cannabis Use			
Psychosis Outcomes at Age 26	Intercept	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*	*b*	*SE*	*t/z*	*p*
A. Diagnosis of Schizophreniform Disorder	−3.44	.11	.31	.35	.73	.59	.81	.73	.47	−.62	.74	.84	.40
B. Self-Reports of Psychotic Symptoms	1.16	.34	.22	1.53	.13	.15	.65	.22	.82	−.50	.53	.94	.35
C. Evidence of Hallucinatory Experiences	−2.04	.07	.17	.42	.67	.67	.45	1.49	.14	−.70	.41	1.69	.09
D. Evidence of Delusional Beliefs	−1.48	.11	.14	.81	.42	−.14	.44	.33	.74	−.004	.34	.01	.99
E. Informant Reports of Psychotic Symptoms	.38	.06	.04	1.33	.18	.05	.13	.38	.71	−.02	.10	.15	.88

other than cannabis or to onset of cannabis use in adulthood, and thus it appears that adolescent-onset cannabis use can be considered an environmental risk factor in this G × E, not simply a proxy for unmeasured genes increasing susceptibility to drug use.

Speculation about implications of this finding should be guarded until it is replicated, and several caveats should be noted. First, this study does not imply that cannabis poses a major risk to the public's mental health, because the majority (92%) of cannabis users in this, as in other studies (Arseneault et al 2004), did not develop psychosis. The interaction between adolescent cannabis use and genotype suggests, however, that adolescence could be a sensitive period of neurobiological vulnerability to cannabis for some young people (Chambers et al 2003) and, if so, policy should discourage adolescents' access to cannabis. Second, this study does not identify a major cause of schizophrenia. Val homozygotes who used cannabis characterized only one fifth of the schizophreniform cases in our cohort. This suggests that a historical rise in cannabis use would not necessarily produce an observable increase in the prevalence of psychosis, although it might be associated with earlier onset of psychotic disorders in recent cohorts (Di Maggio et al 2001; Veen et al 2004) or possibly with increases in subtle alterations in positive and negative psychotic experiences (Stefanis et al 2004). Moreover, psychotic disorders are a product of multiple heterogeneous disease processes (Kennedy et al 2003). We must allow for the possibility that this G × E results in a clinical presentation that meets research diagnostic criteria for schizophrenia but might be a phenocopy.

This study has several limitations. First, we focused on the broader phenotype of schizophrenia-spectrum psychosis rather than on clinic-registered schizophrenia cases; however, 70% of the cohort's cases exhibiting this broader phenotype had received treatment. Moreover, like other epidemiological research groups, we have found that psychotic-type syndromes (not all of which have come to clinical attention) are more common in the young-adult population than previously suspected (Johns and van Os 2001), and we have shown that the same developmental risk factors apply to this broader phenotype as to more narrowly defined schizophrenia (Cannon et al 2002). Dimensional models of psychosis are becoming established as conceptually and clinically useful (Myin-Germeys et al 2003). Second, the variable indexing adolescent cannabis use was not ideal. Study members were interviewed about cannabis use at ages 13, 15, and 18 years, but frequency data were collected only at age 18 years (using a 1-year reporting period), and we did not have exposure information about the period 15–17 years. Nonetheless, there was a significant main effect of adolescent cannabis use predicting psychosis outcomes 10 years later. Moreover, of study members who used cannabis by age 15, more than 90% continued to use cannabis at age 18. Omitting from analyses those few pre-age-15 cannabis users who did not report continued cannabis use at age 18 did not alter the findings substantively or in terms of significance levels. Third, although we endeavored to test and rule out several alternative, plausible explanations of the G × E, statistical controls with the available data are necessarily imperfect. For example, we were able to control for childhood IQ, but there is a further possibility that some aspect of prefrontal cortical function that does not affect IQ may have been a risk factor for cannabis use, psychosis, or both.

Our finding does add to the growing evidence implicating the COMT Val^{158}Met functional polymorphism in psychosis, but possibly only in the context of exposure to environmental pathogens (Bilder et al 2004). Further investigations need to identify the mechanisms underlying this G × E interaction. The joint effect of the Val allele and adolescent-onset cannabis use on psychosis risk likely reflects dopaminergic dysregulation. One view is that this dysregulation may include reduced prefrontal dopamine activity (Block et al 2002; Lundqvist et al 2001; Solowij et al 2002) coupled with increased mesolimbic dopamine transmission (Tanda et al 1997; Voruganti et al 2001). Other COMT polymorphisms associated with the Val^{158}Met polymorphism (Shifman et al 2002) are thought to increase subcortical dopamine levels (Bray et al 2003), and it is possible that these polymorphisms may also interact with cannabis use. Moreover, the interactive effects of COMT polymorphisms and cannabis use may increase psychosis risk via neurotransmitter aberrations beyond dopamine dysregulation (Carlsson et al 2001). Equally, the G × E could operate through a cascade of knock-on environmental experiences. Many chronic cannabis users, as frequent buyers (and sellers) of an illegal drug, become involved in drug-market cultures where they are exposed to threatening situations (Blumstein 1995). Adolescent carriers of the Val allele may be neurobiologically ill equipped for an illicit lifestyle, oversensitive to threat, or predisposed to exaggerate threat to psychotic proportions. Although we could not test these various mechanisms in our epidemiologic study, brain endophenotypes and sociological processes are not mutually exclusive and together may account for this G × E interaction.

Evidence linking the COMT Val allele to schizophrenia has

been inconsistent (Glatt et al 2003), and in this study we did not observe any direct association between the Val[158]Met functional polymorphism and psychosis outcomes. Instead, our G × E finding raises the possibility that research evidence is inconsistent because allelic variants of the COMT gene confer risk only to persons additionally exposed to psychotogenic environmental risks, including cannabis. This pattern of a significant G × E in the presence of an initial nil main effect of the measured gene has emerged in other studies of common complex diseases (e.g., Caspi et al 2002, 2003; Foley et al 2004; Kendler et al, in press; Ordovas et al 2002) and, if the pattern is widespread, it will have implications for gene hunters: if a gene-to-disorder connection is apparent only among individuals in a sample who have been exposed to specific environmental risks, the connection will be diluted across all individuals and may remain undetected. Most psychiatric genetics designs, including linkage pedigrees, candidate-gene association studies, and genomewide scans, aim to identify genes having direct connections to disorders (i.e., main-effect associations with phenotype irrespective of the environment). Common complex disorders are heritable, but they are also known to have nongenetic environmental causes. Our findings suggest that a role of some susceptibility genes may be to influence response to these pathogenic environments (Moffitt et al, in press). The standard direct-effect approach will not be efficient for detecting such genes, because their connection to a disorder is conditional on exposure to an environmental pathogen. Research aiming to uncover new genes for diseases might be made more powerful by recruiting samples on the basis of known exposure to an environmental pathogen and asking which genes discriminate between exposed individuals who did, versus did not, become ill.

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