ORIGINAL ARTICLE

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Evidence That Familial Liability for Psychosis Is Expressed as Differential Sensitivity to Cannabis

An Analysis of Patient-Sibling and Sibling-Control Pairs

Genetic Risk and Outcome in Psychosis (GROUP) Investigators

Context: Individual differences in cannabis sensitivity may be associated with genetic risk for psychotic disorder.

Objectives: To demonstrate and replicate, using 2 conceptually different genetic epidemiological designs, that (familial) liability to psychosis is associated with sensitivity to cannabis.

Design, Setting, and Participants: Sibling-control and cross-sibling comparisons using samples of patients with a psychotic disorder (n=1120), their siblings (n=1057), and community controls (n=590) in the Netherlands and Flanders.

Main Outcome Measures: Positive and negative schizotypy using the Structured Interview for Schizotypy–Revised (for siblings and controls) and self-reported positive and negative psychotic experiences using the Community Assessment of Psychic Experiences (for siblings and patients). Cannabis use was assessed as current use (by urinalysis) and lifetime frequency of use (by Composite International Diagnostic Interview).

Results: In the sibling-control comparison, siblings displayed more than 15 times greater sensitivity to positive schizotypy associated with particularly current cannabis use by urinalysis (adjusted $B=0.197$, $P<.001$) than controls (adjusted $B=0.013$, $P=.86$) (P interaction=.04) and a similar difference in sensitivity to its effect on negative schizotypy (siblings: adjusted $B=0.120$, $P<.001$; controls: $B=-0.008$, $P=.87$; P interaction=.03). Similarly, siblings exposed to cannabis resembled their patient relative nearly 10 times more closely in the positive psychotic dimension of the Community Assessment of Psychic Experiences (adjusted $B=0.278$, $P<.001$) compared with nonexposed siblings (adjusted $B=0.025$, $P=.12$) (P interaction $<.001$). No significant effect was apparent for the Community Assessment of Psychic Experiences negative domain, although the association was directionally similar (2 times more resemblance; P interaction=.17). Cross-sibling, cross-trait analyses suggested that the mechanism underlying these findings was moderation (familial risk increasing sensitivity to cannabis) rather than mediation (familial risk increasing use of cannabis).

Conclusions: Genetic risk for psychotic disorder may be expressed in part as sensitivity to the psychotomimetic effect of cannabis. Cannabis use may synergistically combine with preexisting psychosis liability to cause positive and negative symptoms of psychosis.

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RANDOMIZED CONTROLLED experiments have shown that acute exposure to Δ9-tetrahydrocannabinol, the main psychotropic component of *Cannabis sativa*, induces psychotic symptoms in a substantial proportion of healthy controls.[1,2] Meta-analysis[3,4] of prospective epidemiological studies indicates that cannabis use not only predicts onset of psychotic disorder but also is associated with subthreshold expression of psychosis either in the form of schizotypy[5-7] or subclinical psychotic experiences.[8-10] Schizotypy and subclinical psychotic experiences represent related phenotypes; the positive and negative dimensions of the Structured Interview for Schizotypy–Revised (SIS-R) correlate strongly with the equivalent dimensions of self-reported psychotic experiences,[11] and both measures of schizotypy and measures of subclinical psychotic experiences display familial clustering with psychotic disorder.[12-18] The results therefore

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suggest that cannabis may provoke a psychotic response in individuals with higher-than-average vulnerability for psychotic disorder.

Follow-up experimental and observational work indeed has suggested that psychosis liability is associated with differential sensitivity to the psychotomimetic effects of Δ9-tetrahydrocannabinol.[2,5,8,10,19,20] Differential sensitivity to the psychotomimetic effects of Δ9-tetrahydrocannabinol has been linked to both familial/genetic factors[21-23] and environmental exposures including childhood trauma,[24,25] suggesting that complicated interactions between genetic and environmental factors over the life course may affect adult cannabis sensitivity. The findings to date suggest that genes may interact with early environmental exposures associated with psychotic disorder, creating a sensitized state[26] with regard to later exposure to cannabis and the onset of psychotic symptoms.[27]

Interacting causes are difficult to examine and require large samples and special designs.[28] The initial focus was therefore on indirect, nonmolecular measures of genetic risk that, although not precise with regard to molecular variation, represent the first stage of examination given the unique possibility to model net genetic contribution in low-power interaction paradigms.[29]

The indirect measure of genetic risk used in this study was sibling status given that the risk for schizophrenia in siblings of patients is increased 5- to 10-fold, and twin studies indicate that familial clustering is mainly due to genetic factors.[30] A sibling thus represents an individual who is genetically at higher-than-average risk for psychotic disorder, allowing for a sibling-control comparison of the hypothesis that genetic risk for psychotic disorder is expressed in part as sensitivity to the effect of cannabis using interview-based schizotypy as the outcome. The advantage of a sibling-based design to test for differential sensitivity to an environmental exposure is that it avoids the confounds and biases occasioned by the presence of illness and its treatment with antipsychotic medication. An added advantage is that a sibling-based design may aid in teasing apart moderation (genetic control of sensitivity to the psychotomimetic effects of cannabis) from mediation (genetic control of exposure to cannabis; more details follow later).[31] Finally, a design based on 2 siblings pertaining to the same family effectively controls for a range of unobserved and unmeasured confounding factors given that siblings share a range of socioeconomic and developmental circumstances.[32]

A combined unaffected sibling–control (sibling-control) and patient–unaffected sibling (cross-sibling) design was used to examine the hypothesis that familial liability to psychotic disorder is associated with differential sensitivity to the psychotomimetic effects of cannabis. The sibling-control design is based on the prediction that the psychotomimetic effect of cannabis in unaffected siblings at higher-than-average genetic risk for psychotic disorder is greater than the psychotomimetic effect of cannabis in healthy controls. The cross-sibling design is based on the prediction that in unaffected siblings who are not exposed to cannabis, vulnerability for psychosis will remain largely latent and is expressed at a low level of schizotypal symptoms. Thus, when the degree of sibling resemblance for psychosis is examined (by calculating the phenotypic correlation for expression of psychosis between the patient and the unaffected sibling), the correlation will be low. However, when the unaffected sibling is exposed to cannabis, latent psychosis vulnerability may become expressed to a greater degree, at the level of schizotypal symptoms. This would cause the phenotypic correlation between the patient and the unaffected sibling to become more visible, reflecting familial differences in the tendency to express psychotic symptoms.[33-35]

METHODS

SUBJECTS

Data pertain to baseline measures of an ongoing longitudinal study (Genetic Risk and Outcome in Psychosis [GROUP]) in Europe. In selected representative geographical areas in the Netherlands and Belgium, patients were identified through representative clinicians working in regional psychotic disorder services whose caseloads were screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services as either outpatients or inpatients were recruited for the study. Controls were selected through a system of random mailings to addresses in the catchment areas of the cases.

The full GROUP sample consisted of 1120 patients with nonaffective psychotic disorder, 1057 siblings of these 1120 patients, 919 parents of the patients and their siblings, and 590 unrelated controls. Inclusion criteria were the following: (1) age range of 16 to 50 years; (2) diagnosis of nonaffective psychotic disorder; and (3) good command of the Dutch language. Controls had no first-degree relative with a psychotic disorder as established by the Family Interview for Genetic Studies[36] with the control as informant. Diagnosis was based on the *DSM-IV-TR* criteria,[37] assessed with the Comprehensive Assessment of Symptoms and History interview[38] or Schedules for Clinical Assessment for Neuropsychiatry version 2.1.[39] The *DSM-IV-TR* diagnoses of the patients were as follows: schizophrenia and related disorders (*DSM-IV-TR* code 295.x; n=945 [84%]), other psychotic disorders (*DSM-IV-TR* code 297/298; n=149 [13%]), and psychotic illness in the context of substance abuse or somatic illness (n=9 [1%]). Six patients had a missing diagnosis but fulfilled inclusion criteria, and 11 patients had a final diagnosis of affective psychosis but fulfilled criteria of clinical diagnosis of nonaffective psychosis at study entry; these individuals were retained in the sample assuming subtle diagnostic changes between the time of identification for inclusion and actual assessment that could occur in any patient included in the cohort at any time and taking into account that for the focus of underlying genetic liability the diagnostic change would not be relevant.[40] In the sibling and control groups, there were 149 participants (14%) and 59 participants (10%), respectively, with a history of a common mental disorder, the great majority of whom had a mood disorder (*DSM-IV-TR* code 296.x).

The study was approved by the standing ethics committee, and all of the subjects gave written informed consent in accordance with the committee's guidelines.

SUBSTANCE USE

Substance use was assessed using the Composite International Diagnostic Interview (CIDI) sections B, J, and L[41] and through urinalysis. Two different definitions of cannabis exposure were used in the analyses: (1) CIDI cannabis pattern of use during the lifetime period of heaviest use (hereafter called *CIDI lifetime use*): none (scored as 0), less than weekly (scored as 1), weekly (scored

as 2), and daily (scored as 3); and (2) current cannabis use assessed by urinalysis (hereafter called *current use*): none (scored as 0) and present (scored as 1). Urinalysis was carried out as a screen for the presence of cannabis at the national Alcohol and Drug Use Jellinek Laboratory. The method used was immunoassays with a cutoff of 50 ng/mL. In addition, as an integrity parameter, the creatinine level of every sample was measured. Cannabis urine screening has a detection window of up to 30 days, but the detection time has been documented in literature to be even longer (up to 3 months) depending on the level of cannabis use.[42] Given the relatively high cutoff level of 50 ng/mL, a conservative detection window of 1 month can be inferred.

PSYCHOSIS MEASURES

For the sibling–healthy control comparison, an interview-based measure of schizotypy was used. For the patient–unaffected sibling cross-sibling design, a self-reported measure of psychotic symptoms was used given that interviews based on clinical instruments are not suitable for nonpatients (floor effects) and schizotypy interviews are not suitable for patients (ceiling effects).

Interview-Based Psychosis Measures

The SIS-R[43,44] was administered to controls and siblings. The SIS-R is a semistructured interview containing 20 schizotypal symptoms and 11 schizotypal signs rated on a 4-point scale. Symptoms are defined as verbal responses to standardized questions concerning, for example, magical ideation, illusions, and referential thinking. Signs refer to behaviors that are rated by the interviewer such as goal directedness of thinking and flatness of affect. Questions and rating procedures are standardized. Guided by previous research,[33] item scores were reduced a priori to 2 dimensional scores, representing the means of positive schizotypy items (referential thinking, psychotic phenomena, derealization, magical ideation, illusions, and suspiciousness; score range, 0-2.7) and negative-disorganized schizotypy items (social isolation, sensitivity, introversion, restricted affect, disturbances in associative and goal-directed thinking, poverty of speech, and eccentric behavior; score range, 0-1.8).

Self-report Psychosis Measures

The Community Assessment of Psychic Experiences (CAPE; http://cape42.homestead.com) was developed to rate self-reports of lifetime psychotic experiences and was completed by patients and their siblings. Items are modeled on patient experiences as contained in the Present State Examination, ninth edition[45] and the schedules assessing negative symptoms such as the Scale for the Assessment of Negative Symptoms[46] and the Subjective Experience of Negative Symptoms.[47] Items are scored on a 4-point scale. In the current analyses, CAPE dimensions of frequency of positive experiences (20 items) and negative experiences (14 items) were included, representing the person's perceived psychosis load over the lifetime. A total score representing the mean of all items was calculated for each dimension and weighted for partial nonresponse (CAPE positive: score range, 0-2.9; CAPE negative: score range, 0-2.8). Previous research with the CAPE has yielded the following: (1) a factor structure with separate positive and negative dimensions in a large and representative sample of young men[48] and in a large sample of undergraduate female students[9]; (2) discriminative validity across groups of individuals with schizophrenia, affective disorders, and anxiety disorders and individuals from the general population[49]; (3) family-specific variation for positive and negative subclinical psychosis dimensions[33]; and (4) stability over time and specific and independent associations with the corresponding dimensions based on interview.[11]

ANALYSIS

Approach 1: Sibling-Control Using SIS-R

The moderation model operates on the assumption that the relationship between cannabis use and psychotic symptoms changes as a result of the copresence of a family history of psychotic disorder, indexed by sibling illness status. Thus, in the sibling-control design, continuous SIS-R scores were regressed on cannabis use, sibling-control status, and their interaction. Given that some families contributed more than 1 sibling, hierarchical clustering of data at the level of family was modeled using the multilevel random regression XTREG routine in STATA version 11 statistical software (StataCorp LP, College Station, Texas). In the case of significant interaction, stratified effect sizes were calculated using the appropriate linear combinations from the interaction model with the STATA LINCOM routine.

Approach 2: Cross-Sibling Associations Using CAPE

In the case of genetic influence on differential sensitivity to the psychotomimetic effects of cannabis, one prediction is that the sibling correlation should be higher in exposed environments.[28] Therefore, in this study, correlations in the level of CAPE psychosis measures were calculated for patient–unaffected sibling pairs as a function of cannabis use in the unaffected sibling. To model these relationships in patient-sibling pairs, the continuous CAPE positive and negative dimensions in the unaffected sibling were regressed on cannabis use in the unaffected sibling, the corresponding CAPE dimension in the patient, and their interaction. In the case of families contributing more than 1 patient or more than 1 sibling, all possible patient–unaffected sibling pairs were included in the analyses. As some families thus contributed more than 1 sibling pair, the STATA multilevel random regression XTREG routine was used, followed by calculation of stratified effect sizes as explained earlier.

Adjustment for Other Drug Use

Analyses using the CIDI cannabis exposure were adjusted for CIDI variables indicating lifetime use of other psychotomimetic drugs, defined as stimulants, cocaine, 1-(1-phenylcyclohexyl) piperidine (PCP), psychedelics, and other drugs (3,4-methylenedioxymethamphetamine [MDMA], alkyl nitrites, designer drugs), scored as none (0) and present (1).

Analyses using the urinalysis cannabis exposure were adjusted for the use of other drugs assessed with urinalysis: presence of cocaine (benzoylecgonine) and amphetamines/MDMA. Cloned enzyme donor immunoassays were used with a cutoff of 300 ng/mL for cocaine and a cutoff of 1000 ng/mL for amphetamine/MDMA, with additional analyses added when the first screening result was positive.

As both CIDI lifetime cannabis use and current cannabis use by urinalysis were associated not only with case-sibling-control status but also with age (in years), sex (0=men, 1=women), ethnicity (0=white, 1=nonwhite), and educational level (for categories, see **Table 1**) and as various a priori conservative (in the direction of the null hypothesis of no association) and anticonservative (in the direction of rejection of the null hypothesis) confounding mechanisms may be plausibly hypothesized, adjusted estimates included correction for these variables.

Table 1. Exposure, Outcome, and Demographic Confounding Variables in Controls, Siblings, and Patients

Variable	Controls		Siblings		Patients		χ^2 (*df*) or *F* (*df*)[a]	*P* Value
	No. (%)	Total No.	No. (%)	Total No.	No. (%)	Total No.		
Age, mean (SD), y	30.4 (10.6)	590	27.8 (8.3)	1057	27.7 (8.1)	1120	22.0 (2,2764)	<.001
Male	270 (46)	590	482 (46)	1057	853 (76)	1120	254.6 (2)	<.001
Education		590		1057		1120	255.9 (12)	<.001
None/primary only	16 (3)		79 (8)		141 (13)			
Lower secondary	86 (15)		202 (19)		340 (30)			
Lower vocational	91 (15)		231 (22)		185 (17)			
Higher secondary	185 (31)		208 (20)		266 (24)			
Higher vocational	149 (25)		187 (18)		100 (9)			
University	58 (10)		122 (12)		44 (4)			
Unknown	5 (1)		28 (3)		43 (4)			
White	530 (90)	590	877 (83)	1057	857 (77)	1120	47.6 (2)	<.001
Living together	235 (41)	573	411 (40)	1019	96 (9)	1041	305.9 (2)	<.001
CIDI pattern of cannabis use		590		1057		1120	384.3 (6)	<.001
None	428 (75)		660 (62)		434 (39)			
Less than weekly	79 (13)		145 (14)		93 (8)			
Weekly	40 (7)		101 (10)		120 (11)			
Daily	43 (7)		151 (14)		473 (42)			
Positive for cannabis use by urinalysis	27 (5)	556	75 (8)	956	158 (16)	964	61.6 (2)	<.001
Positive drug use by CIDI								
Cocaine	27 (5)	590	86 (8)	1057	244 (22)	1120	136.4 (2)	<.001
Stimulants	23 (4)	590	69 (7)	1057	239 (21)	1120	159.6 (2)	<.001
PCP	1 (0.2)	590	1 (0.1)	1057	7 (1)	1120	5.3 (2)	.07
Psychedelics	21 (4)	590	60 (6)	1057	210 (19)	1120	137.3 (2)	<.001
Other	33 (6)	590	119 (11)	1057	292 (26)	1120	149.4 (2)	<.001
Positive drug use by urinalysis								
Cocaine	1 (0.2)	555	10 (1)	956	13 (1)	965	5.1 (2)	.08
Amphetamines/MDMA	1 (0.2)	547	5 (1)	931	8 (1)	945	2.7 (2)	.26
SIS-R score, mean (SD)								
Positive	0.32 (0.35)	580	0.38 (0.42)	1038	...	...	10.2 (1,1616)	.001
Negative	0.24 (0.23)	579	0.27 (0.26)	1038	...	...	7.1 (1,1615)	.008
CAPE score, mean (SD)								
Positive	...	...	0.21 (0.20)	916	0.67 (0.49)	869	535.1 (2,2344)	<.001
Negative	...	...	0.55 (0.38)	916	1.02 (0.54)	869	360.9 (2,2344)	<.001
PANSS score, mean (SD)								
Positive	...	...	...	...	13.9 (6.6)	1023	...	...
Negative	...	...	...	...	15.0 (6.7)	1013	...	...

Abbreviations: CAPE, Community Assessment of Psychic Experiences; CIDI, Composite International Diagnostic Interview; MDMA, 3,4-methylenedioxymethamphetamine; PANSS, Positive and Negative Syndrome Scale; PCP, 1-(1-phenylcyclohexyl)piperidine; SIS-R, Structured Interview for Schizotypy–Revised; ellipses, not applicable.

[a] For *F* scores, the *df* between and within groups are given.

In the cross-sibling analyses, estimates were adjusted for values of confounders (demographic characteristics, drug use) of both siblings.

Mediation vs Moderation

In the sibling-control comparison, moderation (genetic control of sensitivity to the psychotomimetic effects of cannabis) cannot be distinguished directly from mediation (genetic control of exposure to cannabis). In other words, it is important to distinguish whether findings are due to familial risk for psychotic disorder making a person more sensitive to cannabis (moderation) or to familial risk for psychotic disorder making a person more likely to start using cannabis (mediation). Mediation may be relevant because patients more often used cannabis than siblings, and siblings in turn more often used cannabis than controls (Table 1). To examine the possibility of mediation, we examined the cross-sibling cross-trait association between cannabis (both current use as assessed by urinalysis and lifetime use as assessed with the CIDI and recoded dichotomously as 0 = no use vs 1 = any use) and psychosis by regressing, using multilevel logistic regression in STATA statistical software, (1) cannabis use

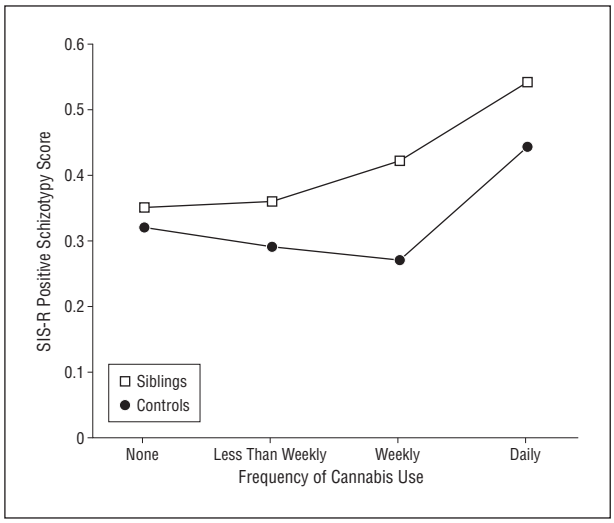

Figure 1. Structured Interview for Schizotypy–Revised (SIS-R) positive schizotypy score as a function of lifetime frequency of cannabis use in controls and siblings of patients with a psychotic disorder.

Table 2. Composite International Diagnostic Interview Lifetime Cannabis Use and Schizotypy in Controls and Siblings of Patients With Nonaffective Psychotic Disorder

CIDI Pattern of Lifetime Cannabis Use	Controls				Siblings					
	SIS-R Score, Mean (SD)	No.	Adjusted *B* (95% CI)[a]	*P* Value	SIS-R, Mean (SD)	No.	Adjusted *B* (95% CI)[a]	*P* Value	χ^2 Interaction[b]	*P* Value
Positive Schizotypy										
None	0.32 (0.35)	420	0[c]	...	0.35 (0.38)	644	0[c]	...	0[c]	...
Less than weekly	0.29 (0.37)	78	−0.002 (−0.093 to 0.089)	.97	0.36 (0.41)	145	0.009 (−0.058 to 0.076)	.79	0.03	.85
Weekly	0.27 (0.30)	39	−0.084 (−0.207 to 0.039)	.18	0.42 (0.48)	100	0.084 (0.005 to 0.163)	.04	5.20	.02
Daily	0.44 (0.38)	43	0.109 (−0.016 to 0.235)	.09	0.54 (0.50)	149	0.185 (0.109 to 0.261)	<.001	1.18	.28
Unadjusted *B* linear trend[d]	0.016 (−0.018 to 0.051)			.36	0.056 (0.035 to 0.076)			<.001	3.66	.06
Adjusted *B* linear trend[a,d]	0.012 (−0.024 to 0.047)			.53	0.055 (0.031 to 0.078)			<.001	4.51	.03
Negative Schizotypy										
None	0.25 (0.23)	420	0[c]	...	0.27 (0.26)	644	0[c]	...	0[c]	...
Less than weekly	0.20 (0.19)	77	−0.047 (−0.106 to 0.013)	.12	0.22 (0.18)	145	−0.055 (−0.099 to −0.012)	.01	0.05	.82
Weekly	0.18 (0.21)	39	−0.080 (−0.160 to 0.003)	.049	0.25 (0.22)	100	−0.014 (−0.065 to 0.038)	.61	1.92	.17
Daily	0.27 (0.22)	43	0.022 (−0.059 to 0.103)	.60	0.36 (0.33)	149	0.079 (0.029 to 0.129)	.002	1.61	.20
Unadjusted *B* linear trend[d]	−0.008 (−0.030 to 0.014)			.47	0.021 (0.007 to 0.034)			.003	4.69	.03
Adjusted *B* linear trend[a,d]	−0.012 (−0.035 to 0.012)			.33	0.015 (0.001 to 0.031)			.049	4.16	.04

Abbreviations: CI, confidence interval; CIDI, Composite International Diagnostic Interview; SIS-R, Structured Interview for Schizotypy–Revised; ellipses, not applicable.

[a] Adjusted for age, sex, ethnicity, educational level, and use of stimulants, cocaine, 1-(1-phenylcyclohexyl)piperidine (PCP), psychedelics, and other drugs (3,4-methylenedioxymethamphetamine [MDMA], alkyl nitrites, designer drugs).

[b] The interaction term compares the effect size of cannabis use (separate for each level and, in the last 2 rows, as linear trend) in the siblings with the effect size in controls.

[c] Reference category.

[d] The *B* linear trend is the summary change in schizotypy with 1 unit change in CIDI lifetime cannabis use.

in the sibling on CAPE positive psychotic experiences in the patient controlling for age, sex, ethnic group, and educational level of both the sibling and the patient and (2) cannabis use in the patient on CAPE positive psychotic experiences in the sibling similarly adjusted for age, sex, ethnicity, and educational level. A positive association would be suggestive of familial risk for psychotic disorder predisposing for both cannabis use and CAPE positive psychotic experiences. The mediation model thus operates under the assumption that the association between an environmental factor (cannabis) and a psychopathological outcome (CAPE psychotic symptoms) across related individuals at risk for psychotic disorder is dependent on the shared familial risk for schizophrenia.

RESULTS

SAMPLE

The sample consisted of 590 controls and 1066 families who contributed 1057 siblings and 1120 patients with nonaffective psychotic disorder. Families contributed a single patient (206 families, 206 subjects), a single sibling (6 families, 6 subjects), a patient and a sibling (634 families, 1268 subjects), 2 patients (25 families, 50 subjects), 1 patient and 2 siblings (130 families, 390 subjects), 2 patients and 1 sibling (15 families, 45 subjects), 3 patients (2 families, 6 subjects), 1 patient and 3 siblings (28 families, 112 subjects), 2 patients and 2 siblings (5 families, 20 subjects), 3 patients and 1 sibling (1 family, 4 subjects), 4 patients (1 family, 4 subjects), 1 patient and 4 siblings (8 families, 40 subjects), 2 patients and 3 siblings (2 families, 10 subjects), 3 patients and 2 siblings (2 families, 10 subjects), and 1 patient and 5 siblings (1 family, 6 subjects).

The median illness duration of patients was 3.3 years (interquartile range, 1.3-6.2 years), and the mean (SD) Global Assessment of Functioning scores were 56 (16) for Global Assessment of Functioning symptoms and 55 (16) for Global Assessment of Functioning disability.

Patients and their siblings more often used cannabis than controls and more often were male and nonwhite. Use of other drugs was also more common in siblings and patients (Table 1). The SIS-R positive and negative dimensions in controls and siblings were moderately correlated ($r=0.50$, $P<.001$), as were the CAPE positive and negative dimensions in patients and siblings ($r=0.62$, $P<.001$).

SIBLING-CONTROL STUDY USING SIS-R

The association between CIDI lifetime use and positive schizotypy assessed with the SIS-R was stronger in siblings than in controls (adjusted interaction $\chi^2=4.51$, $P=.03$) (**Figure 1** and **Table 2**), and a similar result was apparent for negative schizotypy (adjusted interaction $\chi^2=4.16$, $P=.04$) (**Figure 2** and Table 2). Similarly, the association between current cannabis use by urinalysis and schizoptypy was stronger in siblings compared with controls for both the positive (adjusted interaction $\chi^2=4.19$, $P=.04$) (**Figure 3** and **Table 3**) and negative (adjusted interaction $\chi^2=4.95$, $P=.03$) (Figure 3 and Table 3) dimensions.

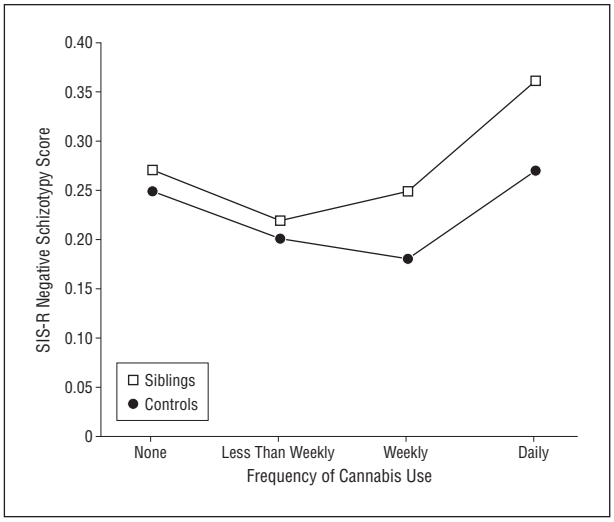

Figure 2. Structured Interview for Schizotypy–Revised (SIS-R) negative schizotypy score as a function of lifetime frequency of cannabis use in controls and siblings of patients with a psychotic disorder.

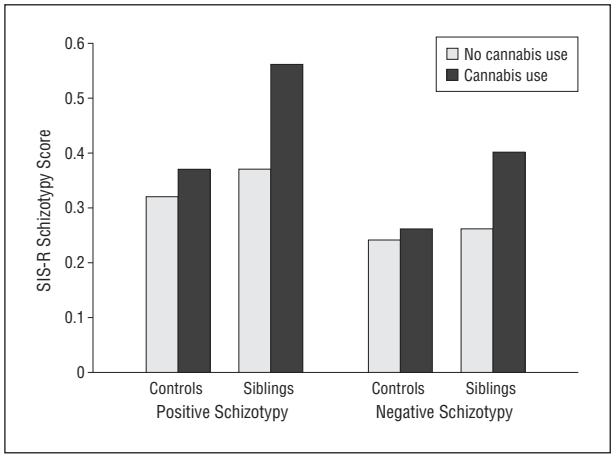

Figure 3. Positive and negative Structured Interview for Schizotypy–Revised (SIS-R) schizotypy scores in controls and healthy siblings of patients with psychotic disorder as a function of cannabis use assessed by urinalysis.

Table 3. Current Cannabis Use by Urinalysis and Schizotypy in Controls and Siblings of Patients With Nonaffective Psychotic Disorder

	Controls				Siblings					
Cannabis Use by Urinalysis	SIS-R Score, Mean (SD)	No.	Adjusted *B* (95% CI)[a]	*P* Value	SIS-R Score, Mean (SD)	No.	Adjusted *B* (95% CI)[a]	*P* Value	χ^2 Interaction[b]	*P* Value
Positive Schizotypy										
None	0.32 (0.35)	520	0[c]	...	0.37 (0.40)	871	0[c]	...	0[c]	...
Positive	0.37 (0.42)	27	0.013 (–0.135 to 0.161)	.86	0.56 (0.57)	73	0.197 (0.099 to 0.295)	<.001	4.19	.04
Negative Schizotypy										
None	0.24 (0.23)	519	0[c]	...	0.26 (0.25)	871	0[c]	...	0[c]	...
Positive	0.26 (0.22)	27	–0.008 (–0.102 to 0.086)	.87	0.40 (0.34)	73	0.120 (0.057 to 0.182)	<.001	4.95	.03

Abbreviations: CI, confidence interval; SIS-R, Structured Interview for Schizotypy–Revised; ellipses, not applicable.
[a] Adjusted for age, sex, ethnicity, educational level, and use of amphetamines/3,4-methylenedioxymethamphetamine (MDMA) and cocaine by urinalysis.
[b] The interaction term compares the effect size of cannabis use in siblings with the effect size of cannabis use in controls. The unadjusted interactions were as follows: positive schizotypy, χ^2=2.71, *P*=.10; negative schizotypy, χ^2=4.77, *P*=.03.
[c] Reference category.

CROSS-SIBLING ASSOCIATIONS USING CAPE

There were 826 families who contributed a total of 1092 possible patient–unaffected sibling pairs; 826 families contributed 1 sibling pair, 192 two pairs, 47 three pairs, 18 four pairs, 5 five pairs, and 4 six pairs. The cross-sibling association of lifetime severity of CAPE positive symptoms was greater if the unaffected sibling had indicated greater CIDI lifetime cannabis use (adjusted interaction χ^2=4.64, *P*=.03) (**Table 4**) and particularly if the unaffected sibling scored positive for current cannabis use by urinalysis (adjusted interaction χ^2=16.89, *P*<.001) (**Figure 4** and **Table 5**). No significant interactions were observed for the CAPE negative dimension, although findings were directionally similar for cannabis use by urinalysis (Figure 4 and Table 5).

MEDIATION VS MODERATION

Cross-sibling, cross-trait analyses of dichotomous lifetime cannabis use and psychosis were carried out in sibling pairs. This revealed that CAPE positive dimension scores in the patient did not predict cannabis use in the sibling controlling for age, sex, ethnic group, and educational level of patient and sibling (χ^2_1=1.27, *P*=.26), nor did CAPE positive dimension scores in the sibling predict cannabis use in the patient (χ^2_1=0.86, *P*=.35). Similar results were apparent for the CAPE negative dimension (χ^2_1=0.19, *P*=.67, and χ^2_1=0.92, *P*=.34, respectively). Analyses with cannabis assessed by urinalysis yielded similar inconclusive results (results not shown).

COMMENT

FINDINGS

Sensitivity to the psychotomimetic effects of cannabis was examined in a case-control comparison involving 1057 unaffected siblings of patients with psychotic disorder and 590 controls as well as a cross-sibling analysis of 1092 pairs of patients and their unaffected siblings. The results suggest that familial liability to psychosis is expressed in part as the tendency to develop psychotic ex-

Table 4. Cross-Sibling Associations in Lifetime Perceived Severity of Community Assessment of Psychic Experiences Symptoms as a Function of Composite International Diagnostic Interview Lifetime Cannabis Use in the Unaffected Sibling

CIDI Pattern of Lifetime Cannabis Use	Siblings		Patients		CAPE Cross-Sibling Association, Adjusted *B* (95% CI)[a]	*P* Value	χ^2 Interaction[b]	*P* Value
	CAPE Score, Mean (SD)	No.	CAPE Score, Mean (SD)	No.				
CAPE Positive Dimension								
None	0.20 (0.20)	598	0.68 (0.50)	574	0.010 (–0.023 to 0.045)	.55	0[c]	. . .
Less than weekly	0.18 (0.16)	131	0.69 (0.43)	122	0.035 (–0.046 to 0.115)	.40	0.31	.58
Weekly	0.22 (0.22)	89	0.68 (0.49)	85	0.007 (–0.080 to 0.094)	.88	0.01	.94
Daily	0.30 (0.25)	132	0.76 (0.52)	125	0.102 (0.035 to 0.169)	.003	5.91	.02
Unadjusted *B* interaction linear trend[d]					χ^2=4.26, *P*=.04			
Adjusted *B* interaction linear trend[a,d]					χ^2=4.64, *P*=.03			
CAPE Negative Dimension								
None	0.53 (0.38)	598	1.04 (0.56)	575	0.103 (0.045 to 0.162)	.001	0[c]	. . .
Less than weekly	0.51 (0.33)	131	1.02 (0.52)	122	0.037 (–0.096 to 0.169)	.59	0.84	.36
Weekly	0.59 (0.43)	89	1.09 (0.49)	85	0.238 (0.071 to 0.404)	.005	2.30	.13
Daily	0.73 (0.44)	132	1.09 (0.57)	125	0.064 (–0.055 to 0.182)	.29	0.35	.55
Unadjusted *B* interaction linear trend[d]					χ^2=0.00, *P*=.98			
Adjusted *B* interaction linear trend[a,d]					χ^2=0.00, *P*=.95			

Abbreviations: CAPE, Community Assessment of Psychic Experiences; CI, confidence interval; CIDI, Composite International Diagnostic Interview; ellipses, not applicable.

[a] Adjusted for age, sex, ethnicity, educational level, and use of stimulants, cocaine, 1-(1-phenylcyclohexyl)piperidine (PCP), psychedelics, and other drugs (3,4-methylenedioxymethamphetamine [MDMA], alkyl nitrites, designer drugs).

[b] The interaction tests whether the cross-sibling association at each level of cannabis use is increased compared with the reference category of no cannabis use.

[c] Reference category.

[d] The interaction linear trend tests whether the cross-sibling association increases significantly per unit increase in CIDI lifetime cannabis use.

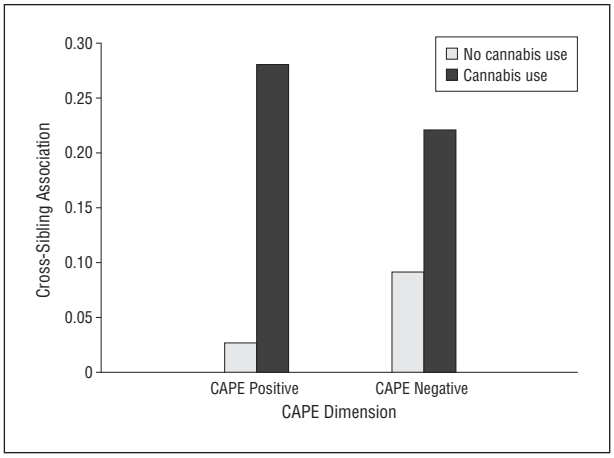

Figure 4. Patient–healthy sibling cross-sibling associations in Community Assessment of Psychic Experiences (CAPE) positive and CAPE negative symptoms as a function of cannabis use assessed by urinalysis in the healthy sibling.

periences in response to cannabis. This result was evident not only in the case-control comparison of individuals at higher-than-average genetic risk using subclinical expression of psychosis as the outcome but also in the cross-sibling comparison correlating levels of psychotic symptoms in patients and their unaffected siblings. Both patients and siblings displayed higher rates of cannabis use, suggesting that some of the apparent differential sensitivity to the psychotomimetic effects of cannabis may in fact represent a mechanism of psychotic disorder liability contributing not only to sensitivity for cannabis but also to the tendency to start using cannabis (gene-environment correlation).[50] However, the results of the cross-sibling, cross-trait analyses examining whether cannabis use and psychosis liability were associated with each other across siblings did not support a gene-environment correlation. This is in agreement with a previous study examining this issue[51] and with genetic epidemiology findings indicating that cannabis use in (early) adolescence—the relevant timing of exposure with regard to psychotic disorder[52]—is influenced by environmental rather than genetic factors.[53] Thus, it is likely that the findings reflect, at least in part, moderation of the psychotomimetic effects of cannabis by familial liability to psychotic disorder. The results in Table 3 indicate that current cannabis use, defined as dichotomous presence by urinalysis, was associated with an effect size of about 0.3 SD in the siblings, at least 15 times greater than the effect size observed in the control group for both positive and negative schizotypy. These differences suggest strong underlying interaction between cannabis use and preexisting psychosis liability. Similarly, cannabis use assessed by urinalysis increased the sibling correlation by an approximate factor of 10 for positive symptoms and a factor of 2 (not statistically significant) for negative symptoms (Table 5).

It has been suggested that the main psychotropic component of cannabis, Δ9-tetrahydrocannabinol, interacts with dopaminergic neurotransmission.[54] The net result of this may be increased mesolimbic dopamine signaling,[55,56] which in turn may be associated with psychotic symptoms.[57] This theory remains at the initial level of hypothesis testing[58]; the current findings suggest that inclusion of genetic moderation may be necessary to elucidate specific neurobiological mechanisms. An initial observational study[22] supported by experimental work[21] suggested an interaction between cannabis use and the *COMT* Val158Met polymorphism.

Table 5. Cross-Sibling Associations in Community Assessment of Psychic Experiences Dimensions as a Function of Current Cannabis Use by Urinalysis in Patients With Nonaffective Psychotic Disorder and Their Unaffected Siblings

Cannabis Use by Urinalysis	Siblings: CAPE Score, Mean (SD)	Siblings: No.	Patients: CAPE Score, Mean (SD)	Patients: No.	CAPE Cross-Sibling Association, Adjusted *B* (95% CI)[a]	*P* Value	χ^2 Interaction[b]	*P* Value
CAPE Positive Symptoms								
None	0.20 (0.19)	806	0.68 (0.49)	772	0.025 (–0.007 to 0.057)	.12	0[c]	. . .
Positive	0.32 (0.30)	65	0.83 (0.47)	57	0.278 (0.162 to 0.396)	<.001	16.89	<.001
CAPE Negative Symptoms								
None	0.55 (0.39)	806	1.05 (0.55)	773	0.103 (0.047 to 0.160)	<.001	0[c]	. . .
Positive	0.77 (0.44)	65	1.10 (0.54)	56	0.256 (0.042 to 0.470)	.02	1.87	.17

Abbreviations: CAPE, Community Assessment of Psychic Experiences; CI, confidence interval; ellipses, not applicable.
[a] Adjusted for age, sex, ethnicity, educational level, and use of amphetamines/3,4-methylenedioxymethamphetamine (MDMA) and cocaine by urinalysis.
[b] The interaction tests whether the cross-sibling association is significantly greater in the cannabis-positive group compared with the cannabis-negative group. The unadjusted interactions were as follows: positive schizotypy, χ^2=17.99, $P < .001$; negative schizotypy, χ^2=1.38, P=.24.
[c] Reference category.

Genetic Risk and Outcome in Psychosis (GROUP) Investigators

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A later study, however, could not replicate this finding.[59] Future work likely should focus on a more extended range of genetic variation acting on pathways associated with endocannabinoid-dopamine and other biologically plausible interactions.

An important issue revealed by this study is that while the relative effect sizes of differential sensitivity were high, absolute effect sizes, for example, of cannabis on schizotypy in unaffected siblings, were small. It therefore follows that any study examining differential sensitivity will require a very large sample to demonstrate differences in sensitivity for an environmental risk factor between groups.

The paradigm used in this study was based on the notion that psychotic symptoms can be expressed below the threshold of diagnosis and are meaningful in relation to the clinical phenotype. Meta-analytic work of subdiagnostic expression of psychotic experiences in the general population has shown etiological, psychopathological, and longitudinal continuity between the extended subclinical phenotype and clinical expression of psychotic disorder as well as a similar age-related developmental pattern of expression[60]; a recent landmark general population birth cohort study confirmed this pattern of findings.[14] The current findings also support this notion as expression of psychosis, measured by the CAPE, was correlated in patient-sibling pairs, although this was contingent on concurrent cannabis use (Table 5).

The results were more apparent and effect sizes were stronger with recent cannabis use as assessed by urinalysis. This suggests that differential sensitivity predominantly reflected response of schizotypal signs and symptoms to recent cannabis use in genetically vulnerable siblings rather than longer-term stable expression of schizotypy associated with developmental lifetime exposure to cannabis.

STRENGTHS AND LIMITATIONS

Strengths of the study include the within-study sibling-control and cross-sibling replication of differential sensitivity, the large sample, and the exposure assessment by urinalysis. In addition, the patient-sibling correlational analysis has the important advantage of automatic control for a range of confounders that may affect case-control comparisons in unrelated subjects given that siblings share a range of demographic factors and life circumstances that may affect mental health and substance use.

The results should be interpreted in light of the following limitations. As schizotypy is not a measure that can be assessed in patients with psychotic disorder (ceil-

ing effects) and, vice versa, an interview for clinical psychotic disorder is not applicable to healthy siblings (floor effects), the psychosis measure used in the cross-sibling analysis was self-reported psychotic experiences using the CAPE. It could be argued that the CAPE does not measure the same phenotype in patients and siblings. However, for the purpose of the cross-sibling association analyses, phenotypic similarity is not required; what is required is that the measure in both groups taps into the same underlying liability, at the level of behavioral expression of liability in the siblings and at the level of illness-related symptoms in the patients. As previous work has shown strong concurrent validity of the CAPE with schizotypy in healthy controls[11] and concurrent validity with positive psychotic symptoms in patients, regardless of level of insight,[61] the cross-sibling association can be interpreted as the sibling correlation in the level of psychosis liability.

The fact that our mediation analyses were inconclusive suggests that the difference in use between patients/siblings and controls is not due to shared liability for psychotic disorder (therefore not affecting the interpretation of the moderation analyses) but to another factor. One explanation is that patients and siblings as a population are more closely matched to each other than the controls so that sampling variation will affect both groups in the same direction compared with controls. Although efforts were made to ensure that controls were sampled from the same population as the cases/siblings, differences may always exist. As our study focused on differential sensitivity to cannabis and not on differences in the rate of cannabis use per se, this is not important for the results, at least to the degree that group differences in the rate of cannabis use are not the result of mediation. Previous work in epidemiological samples has reported no differences in the rate of cannabis use between controls and siblings of patients with psychotic disorder.[51]

In conclusion, differential sensitivity to cannabis was demonstrated in the form of greater response to recent cannabis use in individuals at higher-than-average risk for psychotic disorder and related disorders. These findings provide a rationale for a more detailed analysis of the molecular substrate underlying differential cannabis sensitivity.

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