Reduced Cortical Thickness as an Outcome of Differential Sensitivity to Environmental Risks in Schizophrenia

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Background: The etiology of schizophrenia is thought to involve differential—likely genetically mediated—sensitivity to environmental exposures. However, examination of differential sensitivity in models of psychopathologic constructs is subject to bias because psychopathology itself may distort exposure assessment. The use of neuroimaging phenotypes, conversely, may provide unbiased evidence for differential sensitivity to environmental exposures. This study examined the impact of two environmental exposures associated with both schizophrenia and magnetic resonance imaging (MRI) cerebral alterations in models of cerebral cortical thickness.

Methods: T1-weighted MRI scans were acquired from 88 patients with schizophrenia, 98 healthy siblings at higher than average genetic risk for schizophrenia, and 87 control subjects. Freesurfer software was used to measure cortical thickness for 68 brain regions. Associations between 1) cortical thickness and 2) cannabis use and developmental trauma were examined.

Results: A significant group × developmental trauma interaction ($\chi^2 = 9.65$, $p = .01$), as well as a significant group × cannabis interaction ($\chi^2 = 6.04$, $p = .05$) was apparent, indicating differential sensitivity of the patient group, which displayed stronger reductions of cortical thickness for both exposures. A similar pattern was found in the sibling–control comparison for cannabis. For developmental trauma, siblings did not differ from control subjects, displaying an increase in cortical thickness with higher levels of trauma.

Conclusions: The findings suggest that schizophrenia and its genetic liability are associated with differential cerebral cortical sensitivity to developmental environmental exposures such as cannabis. Gene–environment interactions may underlie some of the brain alterations observed in patients with schizophrenia and their relatives.

Key Words: Cannabis, cerebral cortex, child abuse, diagnosis, genetic predisposition to disease, genetics, magnetic resonance imaging, pathology, schizophrenia

It is thought that most of the differences in liability to schizophrenia can be explained by genetic variation (1–3) occasioning differential sensitivity to environmental risk factors impacting during critical phases of development (4–7), a phenomenon known as gene–environment interaction (G×E) (8–10). Examining G×E is difficult because, for ethical reasons, people cannot be assigned randomly to, for example, heavy cannabis use or childhood trauma. The problems related to G×E research can be circumvented to a degree by 1) replacing the dependent variable in G×E analyses with an objective biological measure that is only weakly associated with (risk for) schizophrenia and 2) including siblings of patients as a group at high genetic risk but without the illness phenotype (Figure 1). This method was pioneered by Cannon and colleagues (11), who showed that obstetric complications (an environmental risk factor for schizophrenia) (12) was related to gray matter reductions and increased cerebrospinal fluid in patients and siblings. Thus, patients may overreport childhood trauma and start using cannabis because of their illness (reverse causality). However, such overreporting cannot readily explain, for example, why a difference in cortical gray volume matter between exposed and unexposed patients and particularly siblings is greater than between exposed and nonexposed control subjects. Thus, although only random assignment can overcome reporting bias and reverse causality, several alternatives exist in observational research that, in combination, have complementary value in the interpretation of G×E.

Because schizophrenia is associated with cortical gray matter alterations that, to a lesser degree, are also observed in healthy siblings (13,14), and two environmental exposures associated with schizophrenia, cannabis use (15–18) and developmental trauma (19–21), are also associated with cerebral alterations (22–30), the environmentally sensitive (31) measure of cortical thickness (CT) was used in the analyses. The analyses focused on differential sensitivity to two environmental risk factors as a function of risk for schizophrenia, comparing patients (high genetic risk), their siblings (intermediate genetic risk), and control subjects (low genetic risk) and using measures of CT as the outcome. The hypothesis was that higher genetic risk would be associated with greater impact of environmental exposures on the cortical phenotype.

Methods and Materials

Subjects

Data pertain to baseline measures of an ongoing longitudinal magnetic resonance imaging (MRI) study in Maastricht, the Netherlands. In selected representative geographic areas in the Netherlands and Belgium, patients were identified through representative clinicians whose caseload was screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services either as outpatients or inpatients were recruited for the study. First-degree relatives were sampled through participating patients. Control subjects were recruited from the same population as the cases using random mailings in nearby municipalities and through advertisement in newspapers. All interviews were con-

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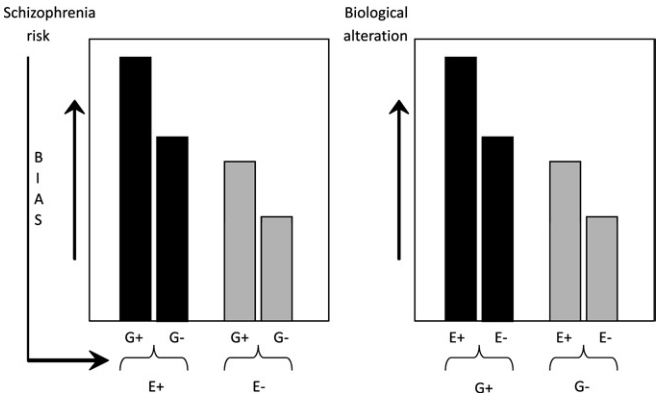

Figure 1. Environment to genotype design using biological alterations. G+, high genetic risk; G–, low genetic risk; E+, exposed to environmental risk; E–, nonexposed to environmental risk. A common problem in gene–environment interaction (G×E) studies is that the illness phenotype under investigation, and the dependent variable in the statistical model, influences assessment of the environmental exposure, giving rise to risk of bias (left-side figure of case–control study of G×E). Although only experimental designs can overcome this issue, an alternative that reduces the risk of bias is to replace the outcome under investigation by a biological phenotype that is weakly associated with (risk of) the disease and examine differential impact of the environmental exposure in groups at high and low genetic risk with and without the illness phenotype (right-side figure). This study used a family-based design in which cases and siblings represent high genetic risk groups (with and without the illness phenotype respectively) and control subjects the low genetic risk group.

ducted by trained psychology graduates. The sample consisted of 88 schizophrenia patients, 98 siblings of schizophrenia patients, and 87 control subjects. The sample included 62 families, of which 39 families contributed one patient and one discordant sibling, three families contributed one patient and two discordant siblings, and one family contributed one patient and three discordant siblings. Two families contributed two patients, seven families contributed two discordant siblings, and one family contributed three discordant siblings. In the control group, nine families contributed two siblings. In addition, 41 independent patients, 33 independent siblings, and 69 independent control subjects were included. Inclusion criteria were 1) age 16 to 50 years, 2) diagnosis of nonaffective psychotic disorder, and 3) good command of the Dutch language. In a few instances, the patient refused but the sibling wished to participate, in which case the sibling was included; the majority represented sib-pairs with at least one ill relative. Siblings had to be free of any lifetime nonaffective psychotic disorder. For the control subjects, the occurrence of any psychotic disorder in either the subject or any first-degree family member, assessed using the Family Interview for Genetic Studies (32), constituted an exclusion criterion.

Diagnosis was based on DSM-IV criteria (33), assessed with the Comprehensive Assessment of Symptoms and History (CASH) interview (34). Patients were diagnosed with schizophrenia ($n = 62$), schizoaffective disorder ($n = 9$), schizophreniform disorder ($n = 4$), brief psychotic disorder ($n = 2$), and psychotic disorder not otherwise specified ($n = 11$). The CASH was also used to confirm the absence of a diagnosis of nonaffective psychosis in the siblings and absence of a lifetime diagnosis of any psychotic disorder or any current affective disorder in the healthy control subjects. Twenty-one siblings and 14 control subjects had a history of major depressive disorder, but none presented in a current depressive episode.

Before MRI acquisition, participants were screened for the following exclusion criteria: 1) brain injury with unconsciousness of greater than 1 hour, 2) meningitis or other neurological diseases that might have affected brain structure or function, 3) cardiac arrhythmia requiring medical treatment, and 4) severe claustrophobia. In addition, subjects with metal corpora aliena were excluded from the study, as were women with intrauterine device status and (suspected) pregnancy.

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

Measures

The Positive and Negative Syndrome Scale (PANSS) (35) was used to measure psychotic symptoms over the previous 2 weeks. Educational level was defined as highest accomplished level of education. Antipsychotic medication (AP) use was determined using the reports of the participant's psychiatrist. Best estimate lifetime (cumulative) AP use was determined by multiplying the number of days of AP use with the corresponding haloperidol equivalents and summing these scores for all periods of AP use (36).

Substance Use

Substance use was assessed using the Composite International Diagnostic Interview (CIDI) Sections B, J, and L (37).

Cannabis use was assessed as the reported lifetime number of instances of cannabis use, ranging from 1 to 5, 6 to 9, 10 to 19, 20 to 39, 40 to 59, 60 to 79, 80 to 99, or 100 times or more. In the analyses, three groups were created, allowing for the assessment of dose–response: 1) subjects who had never used cannabis, 2) subjects who used cannabis between 1 and 39 times, and 3) subjects who used cannabis at least 40 times in their life, because previous research in the Dutch and German general populations has shown that severity of exposure, defined in terms of frequency of use, represents an excellent trade-off between sensitivity and specificity with regard to clinical and subclinical psychosis outcomes (16,38). CIDI cannabis lifetime frequency data were available for 235 subjects (14% missing data).

Hard drug use, such as stimulants, sedatives, opiates, cocaine, PCP, psychedelics, inhalants, or other (e.g., ecstasy, poppers) was assessed as reported frequency of use 1) during the previous 12 months and 2) lifetime.

Alcohol use was defined as the reported number of weekly consumptions during the previous 12 months.

Developmental Trauma

Developmental trauma was assessed with the Dutch version of the Childhood Trauma Questionnaire Short Form (CTQ). The short CTQ consists of 25 items rated on a 5-point Likert scale (1 = never true to 5 = very often true) inquiring about traumatic experiences in childhood. Five types of childhood maltreatment were assessed: emotional, physical and sexual abuse, and emotional and physical neglect, with five questions covering each type of trauma (39). A general measure of developmental trauma was created by calculating the mean of the 25 items. The CTQ data were missing for one person.

MRI Acquisition and Processing

The MRI scans were acquired using a 3T Siemens scanner (Erlangen, Germany) and the following acquisition parameters: Modified Driven Equilibrium Fourier Transform (MDEFT) sequence = 176 slices, 1 mm, echo time 2.4 msec, repetition time 7.92 msec, inversion time 910 msec, flip angle 15°, total acquisition time 12 min 51 sec; Magnetization Prepared Rapid Acquisition Gradient-Echo (MPRAGE; Alzheimer's Disease Neuroimaging Initiative) se-

quence = 192 slices, 1 mm, echo time 2.6 msec, repetition time 2250 msec, inversion time 900 msec, flip angle 9°, total acquisition time 7 min 23 sec. The matrix size and field of view was 256 × 256. The number of excitations was one. Two sequences were used because of a scanner update during data collection. The MPRAGE and MDEFT are similar, but to prevent any systematic bias, the total proportion of MPRAGE scans (approximately one third) was balanced between the groups.

MRI Preprocessing. Scans were processed and analyzed using Freesurfer stable release version 4.5.0. Technical details of these procedures are described in prior publications (40–46). Data were automatically transformed into Talairach standard space.

Cortical Thickness Measurement. Before CT measurement, the cerebral cortex was parcelled into units based on gyral and sulcal structure (47,48). A variety of surface-based data were also created, including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three-dimensional magnetic resonance volume in segmentation and deformation procedures to produce representations of CT, calculated as the closest distance from the gray–white boundary to the gray–cerebrospinal fluid boundary at each vertex on the tessellated surface (41). The maps are created using spatial intensity gradients across tissue classes and are not restricted to the voxel resolution of the original data, thus they can detect submillimeter differences between groups. The CT measurement procedures have been validated against histological analysis (49) and manual measurements (50,51).

Statistical Analyses

The CT surface map was loaded, for each individual and for each hemisphere, in a group file, where individual CT values for each predefined region of interest (hereafter region; adapted from the Desikan atlas, 34 regions per hemisphere) (47) were calculated and exported to Stata version 11 (52). The data set was transformed from a wide format to a long format, resulting in a hierarchically structured data set, with 68 regional CT measures (Level 1) nested in subjects (Level 2) who were part of the same families (Level 3). Because of the three-level grouping structure of the data, compromising statistical independence of the observations, multilevel random regression models were fitted (53) using the XTMIXED command in Stata with CT measures as the dependent variable and subject number and family number modeled as random effects. Mixed models contain both fixed and random effects, the fixed effects being analogous to standard regression coefficients (β).

To test the hypothesis that groups differed in their sensitivity to developmental trauma, analyses were conducted with trauma and group (patients, siblings, and control subjects) as well as their interaction term as independent variables and CT as the dependent variable [$CT = \beta_0 + \beta_1(\text{trauma}) + \beta_2(\text{group}) + \beta_3 (\text{trauma} \times \text{group})$]. The trauma × group interaction was fitted with the control group as the reference category. The trauma exposure was entered both as a linear variable and as dummy variables representing the distribution of the trauma score divided by its quartiles, allowing visualization of dose–response (0 = no trauma, 1 = low trauma, 2 = medium trauma, 3 = high trauma).

Interaction terms were evaluated by Wald test (54). Stratified effect sizes for all trauma levels were assessed by calculating the appropriate linear combinations from the model containing the interaction, using the LINCOM procedure in Stata. Analyses were adjusted for the a priori hypothesized confounders age, sex, and level of education.

Similar multilevel random regression analyses were conducted with the cannabis exposure as independent variable [$CT = \beta_0 + \beta_1(\text{cannabis use}) + \beta_2 (\text{group}) + \beta_3 (\text{cannabis use} \times \text{group})$]; cannabis exposure entered both as a linear variable and as dummy variables (0 = no cannabis use, 1 = moderate cannabis use, 2 = heavy cannabis use).

Power Analysis

The power of the two-way and three-way interaction analyses was calculated by empiric statistical simulation in Stata (http://www.stata.com/support/faqs/stat/power.html), as described previously (55). Effect sizes used were based on published work in this area. These power simulations showed that the two-way interactions in the study had a power of 75% to find a significant effect at an alpha of .05.

The study was not powered to examine whether the differential impact of trauma and cannabis varied not only with group status but also with brain region. Thus, the three-way interaction (trauma/cannabis × group × region) modeling these effects had only 10% power. Therefore, results of these three-way interactions will only be described exploratively to generate hypotheses for future research.

Results

Descriptive Analyses

Patients had lower educational level than control subjects and siblings (Table 1). There were more men than women in the patient group, whereas the opposite held for the control group. Siblings used more alcohol than control subjects and patients. Patients reported more cannabis use than siblings and control subjects and more lifetime and present (previous 12 months) hard drug use than siblings and control subjects, with no large or significant differences between the latter two groups. For all groups, the age of first cannabis use was in adolescence, with a mean age of 16.9 years in patients, 16.8 years in siblings, and 16.5 years in control subjects [*df* (2,106), $F = .10$, $p = .90$]. Patients reported more developmental trauma than siblings and control subjects, the latter groups having similar levels of reported trauma.

Seventy-three patients were receiving AP (second generation: $n = 70$; first generation: $n = 3$). Furthermore, 17 patients used antidepressants, 6 used benzodiazepines, 5 used antiepileptic drugs, and 2 used lithium. Three siblings and three control subjects used antidepressants, and one control subject used benzodiazepines. Lifetime AP use was associated with neither CT ($\beta = .00$, $p = .39$) nor cannabis use ($\beta = .00$, $p = .50$; Table 1).

Main and Interaction Effects

Main Effects of Environmental Exposure and Group on Cortical Thickness. In the model without interaction terms, there was no significant association between developmental trauma and CT in the total group of patients, siblings, and control subjects ($\beta = -.001$, $p = .78$). Heavy cannabis use was significantly associated with CT ($\beta = -.05$, $p = .00$), indicating that heavy cannabis users had lower CT values. There was no significant association between group and CT (Table 2).

Interaction Between Group Status and Developmental Trauma. There was a significant group × trauma (linear variable) interaction ($\chi^2 = 9.65$, $p = .01$), indicating that the effect of trauma on CT differed between groups. Stratified analyses revealed that patients had significantly lower CT values when exposed to higher levels of developmental trauma ($\beta = -.02$, $p = .03$), which was not found in control subjects ($\beta = .003$, $p = .72$). The opposite pattern was found in siblings ($\beta = .02$, $p = .05$), indicating higher CT values when exposed to higher levels of developmental trauma. Visualizing the effect over the four quartile groups of trauma exposure

Table 1. Subject Demographics

	Patients ($n = 88$)	Siblings ($n = 98$)	Control Subjects ($n = 87$)	F/χ^2	p
Age at Scan	28.2 ± 6.9	29.5 ± 8.7	30.7 ± 10.8	1.8	.17
Level of Education	4.3 ± 2.0[a,b]	5.1 ± 2.1	5.4 ± 1.8	7.8	.00
Sex *n* (%), Male	59 (67%)	50 (51%)	33 (38%)	14.9	.00
Cannabis Use *n* (%)					
None	28 (35%)	53 (62%)	48 (70%)		
Moderate	14 (17.5%)	15 (17%)	11 (16%)		
Heavy	38 (47.5%)	18 (21%)	10 (14%)	26.1	.00
Mean Number of Times Hard Drug Use Previous Year	10.9 ± 30.4[a,b]	.90 ± 8.3	1.2 ± 7.8	8.6	.00
Mean Number of Times Hard Drug Use Lifetime	54.2 ± 99.9[a,b]	12.8 ± 42.8	3.3 ± 14.1	13.9	.00
Alcohol Use	4.8 ± 9.0[b]	9.5 ± 16.9[a]	4.6 ± 6.9	4.5	.01
PANSS Positive	12.3 ± 6.1[a,b]	7.6 ± 1.2	7.4 ± 1.4	45.4	.00
PANSS Negative	12.1 ± 5.8[a,b]	8.4 ± 2.1	8.2 ± 1.0	29.2	.00
PANSS Disorganization	13.3 ± 4.5[a,b]	10.3 ± .7	10.3 ± 1.2	31.7	.00
PANSS Excitement	10.3 ± 2.8[a,b]	8.6 ± 1.4	8.3 ± 1.1	25.9	.00
PANSS Emotional Distress	13.9 ± 5.4[a,b]	10.1 ± 2.7	9.4 ± 2.3	33.7	.00
Emotional Abuse	1.9 ± .9[a,b]	1.4 ± .6	1.5 ± .7	11.3	.00
Physical Abuse	1.3 ± .7[a]	1.1 ± .4	1.1 ± .3	3.9	.02
Sexual Abuse	1.3 ± .7[a,b]	1.1 ± .2	1.1 ± .3	9.6	.00
Emotional Neglect	2.3 ± .9[a]	2.0 ± .8	1.9 ± .8	5.5	.00
Physical Neglect	1.5 ± .6[a,b]	1.2 ± .3	1.2 ± .4	12.2	.00
CTQ Total	7.2 ± 2.9[a,b]	5.9 ± 1.6	5.7 ± 1.8	12.3	.00
Age of Onset	22.7 ± 6.4				
Illness Duration	5.5 ± 3.7				
Lifetime Exposure to AP	2743.4 ± 4,625.7				

Means ± SD*s* are reported. F/χ^2 and p values refer to between-group differences.
AP, antipsychotics; CTQ, Childhood Trauma Questionnaire; PANSS, Positive and Negative Syndrome Scale.
[a]Significantly different from control subjects.
[b]Significantly different from siblings.

revealed progressively lower values of CT with progressively higher levels of trauma in exposed patients and exposed control subjects, whereas an opposite trend was apparent in the sibling group (Figure 2A, Table 3).

Interaction Between Group Status and Cannabis. There was a significant group × cannabis interaction (linear variable; $\chi^2 = 6.04$, $p = .05$), indicating that the effect of using cannabis on CT varied as a function of group. Stratified analyses showed that patients with heavy cannabis use had significantly lower CT values compared with patients with no cannabis use ($\beta = -.07$, $p = .002$), and a similar pattern of results was found for siblings ($\beta = -.06$, $p = .01$), but not for control subjects ($\beta = .01$, $p = .65$; Figure 2B, Table 3). The p values were only marginally affected after adjustment for hard drug use in patients ($\beta = -.06$, $p = .01$) and siblings ($\beta = -.06$, $p = .01$). Patients with moderate cannabis exposure had CT values that were intermediate to those with no or heavy use, whereas for siblings, the effect on CT was confined mainly to the group of heavy use (Figure 2B, Table 3).

Explorative Group × Exposure × Region Interactions. Explorative analyses of three-way interactions examining regional

Table 2. Comparisons of Cortical Thickness by Group and Environmental Exposure

	No. of Observations[a]	Cortical Thickness Mean ± SD	β[b]	p
Control Subjects[c]	5916 (87)	2.59 ± .37		
Siblings	6664 (98)	2.58 ± .37	.00	.94
Patients	5984 (88)	2.57 ± .37	−.02	.17
No Cannabis Users[c]	8772 (129)	2.59 ± .37		
Moderate Cannabis Users	2720 (40)	2.59 ± .37	−.01	.36
Heavy Cannabis Users	4488 (66)	2.56 ± .36	−.05	.00
No Childhood Trauma[c]	4624 (68)	2.57 ± .37		
Low Childhood Trauma	4760 (70)	2.59 ± .36	.02	.29
Medium Childhood Trauma	4692 (69)	2.59 ± .37	.02	.29
High Childhood Trauma	4420 (65)	2.57 ± .37	−.01	.71

[a]No. of observations = number of subjects × number of regions (68); numbers in parentheses indicate number of subjects.
[b]βs represent the regression coefficients from multilevel linear regression analyses, adjusted for age, sex, and level of education.
[c]Reference level.

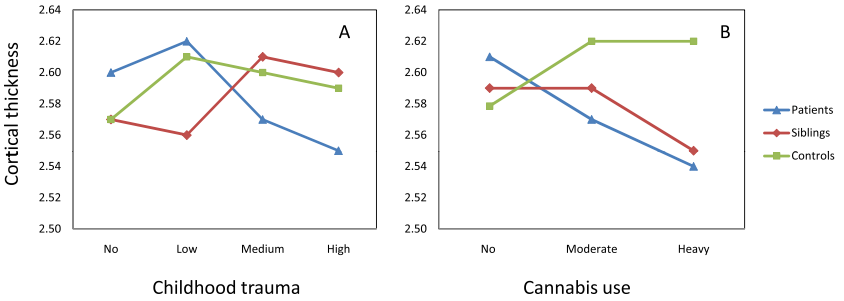

Figure 2. Interaction between environmental risk factors and group on cortical thickness. **(A)** Interaction between childhood trauma and group (linear trauma × group interaction, $p = .01$). **(B)** Interaction between cannabis use and group (cannabis x group interaction, $p = .05$).

variation of differential sensitivity revealed no significant interactions for trauma. There was some suggestion for regional group interactions with cannabis in that in patients (compared with control subjects), cortical thinning in relation to heavy cannabis use, compared with nonusers, was apparent in the left frontal pole ($\chi^2 = 3.75$, $p = .05$) and left ($\chi^2 = 4.65$, $p = .03$) and right ($\chi^2 = 9.67$, $p = .00$) parahippocampal gyrus. In siblings, findings were partly similar in that cortical thinning for heavy cannabis users compared with nonusers was apparent in the left frontal pole ($\chi^2 = 5.32$, $p = .02$), right entorhinal cortex ($\chi^2 = 3.72$, $p = .05$), and the right parahippocampal gyrus ($\chi^2 = 3.70$, $p = .05$).

Discussion

Our results showed that exposure to cannabis, as well as exposure to trauma in childhood, was associated with cerebral cortical thinning in individuals at high genetic risk for schizophrenia (patients), whereas this was not the case in those at low genetic risk (control subjects). For the cannabis exposure, the pattern of results in individuals with intermediate genetic risk (siblings) was similar to that of the patient group. Furthermore, there was a suggestion of a similar pattern of regional thinning in patient and sibling cannabis users in frontal and parahippocampal regions. For the developmental trauma exposure, siblings revealed CT increases with higher trauma levels, although this pattern was not significantly different from control subjects.

Differential Impact of Environmental Exposures on the Brain

No previous studies on the relationship between trauma and brain alterations in schizophrenia are available. However, childhood trauma has been associated with structural brain changes, such as volume loss in the hippocampus, corpus callosum, and prefrontal cortex (22,24,29,30,56,57).

The finding that cannabis use had a differential impact on CT in not only patients but also siblings extends earlier findings indicating that G×E interactions may underlie the association between cannabis and psychosis (5,58–60). Furthermore, the findings are suggestive of a dose–response relationship (higher cannabis exposure associated with more severe CT alteration) in the group most at risk (patients). Studies investigating the effect of cannabis on the brain in healthy subjects have reported only minimal evidence for cannabis-induced brain alterations (23,25,26,61). In schizophrenia, studies are scarce and have produced inconsistent findings ranging from no effect of cannabis on brain morphology (62) to decreased gray matter volume (27). The fact that similar findings were apparent in the sibling–control comparison for the cannabis exposure is in line with the initial hypothesis: siblings, at higher than average genetic risk, also displayed differential sensitivity.

For the trauma exposure, there was evidence for an opposite effect in patients and siblings, whereas the pattern of results in siblings did not significantly differ from the pattern in control subjects. The directionally opposite finding in the siblings may represent chance or noise. Alternatively, siblings and control subjects may differ from patients in that the effect of exposure to traumatic experiences may be neutral (control subjects) or even trophic (siblings). To the degree that the effects of trauma on the brain are mediated by long-term psychological adaptation, resilience, and coping may moderate the outcome of traumatic experiences over time, possibly mitigating the risk for later psychotic outcomes. In other words, not only sensitivity may be an important moderator determining the psychiatric outcome but also individuals' resilience and coping. An individual's resilience is thought to be mediated by adaptive functioning of distinct molecular machineries and brain circuits that allow the individual to experience positive emotions rather than negative and search positive ways to reframe stressful events (63). Given the fact that siblings only share some of their genes and environments with patients, the opposite effect in patients and siblings observed for childhood trauma may be explained by 1) genetic variants not shared between the sibs, 2) nonshared environmental exposures, and 3) illness effects. In addition, evidence has emerged that this type of contrast in the findings may indicate genetic plasticity (64): the same gene may confer positive sensitivity to an exposure in some environments, but negative sensitivity in others. To the degree that differential negative sensitivity to childhood trauma may be contingent on illness expression, underlying illness-related brain changes or treatment factors such as antipsychotic medication may play a role. For the cannabis exposure, however, genes contributing to differential sensitivity to the environment may be shared between patients and their siblings and not be illness-dependent.

Final Common Pathway

The effects of cannabis or traumatic stress may have an impact along a final common pathway. Prefrontal cortical alterations could have an impact on the stress-buffering system, resulting in mesolimbic hyperdopaminergia. Repeated exposure to stress or cannabis may lead to prolonged changes in dopaminergic signaling and eventually to dopamine sensitization (65–68). There was some evidence that cannabis-related regional thinning in patients and siblings was anatomically congruent with the hypothesis of impact on dopamine projections because there was a suggestion of differential impact of cannabis on the frontal pole, the entorhinal cortex, and the parahippocampal gyrus.

Possible Underlying Mechanisms

During childhood, the brain is still in full development and thus vulnerable to environmental exposures. Studies suggest that developmental trauma alters hypothalamic-pituitary-adrenal (HPA) axis functioning (69). These neurobiological abnormalities (70) could, in concert with an existing genetic liability, contribute to an increased risk for schizophrenia. The changes in the HPA axis could be the result of a hypersensitive glucocorticoid release or abnormalities in glucocorticoid receptors consequently on (chronic)

Table 3. Cortical Thickness as a Function of Group Status and Environmental Exposure

	Patients				Siblings				Control Subjects						
Environmental Exposure	No. Obs (*n*)[a]	CT[b]	β	*p*	No. Obs (*n*)[a]	CT[b]	β	*p*	No. Obs (*n*)[a]	CT[b]	β	*p*		Wald test	χ^2	*p*
													Low Childhood Trauma	P vs. C	.22	.64
No Childhood Trauma[c]	816 (12)	2.60 ± .37			1564 (23)	2.57 ± .37			2244 (33)	2.57 ± .36				S vs. C	.56	.45
Low Childhood Trauma	1156 (17)	2.62 ± .37	.02	.65	2244 (33)	2.56 ± .36	.01	.69	1360 (20)	2.61 ± .35	.03	.17	Medium Childhood Trauma	P vs. C	.32	.57
Medium Childhood Trauma	1768 (26)	2.57 ± .37	−.01	.81	1632 (24)	2.61 ± .37	.04	.13	1292 (19)	2.60 ± .38	.02	.55		S vs. C	.39	.53
High Childhood Trauma	2244 (33)	2.55 ± .37	−.05	.12	1224 (18)	2.60 ± .36	.05	.09	952 (14)	2.59 ± .38	.01	.84	High Childhood Trauma	P vs. C	1.55	.21
β Linear Trend[d]			−.02	.03			.02	.05			.00	.72		S vs. C	1.07	.30
No Cannabis Use[c]	1904 (28)	2.61 ± .38			3604 (53)	2.59 ± .37			3264 (48)	2.58 ± .37			Moderate Cannabis Use	P vs. C	1.48	.22
Moderate Cannabis Use	952 (14)	2.57 ± .38	−.04	.18	1020 (15)	2.59 ± .36	−.02	.52	748 (11)	2.62 ± .36	.01	.69		S vs. C	.54	.46
Heavy Cannabis Use	2584 (38)	2.54 ± .36	−.07	.00	1224 (18)	2.55 ± .34	−.06	.01	680 (10)	2.62 ± .36	.01	.65	Heavy Cannabis Use	P vs. C	4.85	.03
β Linear Trend[d]			−.03	.00			−.03	.01			.01	.59		S vs. C	4.28	.04

CT, cortical thickness; Obs, observations; P, patients; S, siblings; C, controls.

The χ^2 and *p* values represent the results of the Wald test, testing the significance of stratified effects calculated from the model with the group × environment interaction term; β represents the effect sizes of level of environmental exposure compared with the reference level.

[a]No. of Obs = number of subjects × number of regions (68); (*n*) = number of subjects.

[b]Mean ± SD.

[c]Reference level.

[d]Summary change in cortical thickness with one unit change in exposure level.

stress exposure (71). Because of synergism between the activity of the HPA axis and the dopaminergic circuits, glucocorticoid secretion may increase dopamine activity in the mesolimbic system (71). Some brain regions, such as the hippocampus or the prefrontal lobe, may be particularly sensitive to stressors (57,72).

Delta-9-tetrahydrocannabinol (δ-9-THC), the active psychotropic ingredient of cannabis, activates the cannabinoid-1 (CB1) receptor, the primary binding site of endogenous cannabinoids. THC may influence dopamine firing in the ventral tegmental area, resulting in increased striatal DA levels; in addition, THC is also believed to affect synaptic plasticity, which is thought to be impaired in schizophrenia (73). Furthermore, THC-related glutamatergic effects may affect gray matter volume, and possibly CT, through a mechanism of neurotoxicity (74,75). However, the exact influence of THC on endocannabinoid, dopamine, gamma-aminobutyric acid, and glutamate signaling remains to be elucidated, as is the relationship with neuronal network alterations and psychosis.

Limitations

Gene–environment interaction studies assume that the interacting variables are independent. In some instances, this assumption did not hold because patients reported more cannabis use and trauma than both control subjects and siblings. The consequence of this is that the interpretation of interaction cannot distinguish between moderation (genetic risk influences sensitivity to the environment) and mediation (genetic risk influences exposure to the environment). The fact that the violation of independence for the cannabis exposure does not apply to the siblings suggests that moderation rather than mediation is the underlying mechanism because siblings displayed similar differences from the control subjects as did patients. Although for trauma exposure we cannot exclude mediation in the case–control comparison, it is unlikely that mediation is the only underlying mechanism because for most exposures in psychiatry, both moderation and mediation usually apply (76).

Assessments of childhood trauma in patients with psychotic disorder may be biased. However, recent work suggests that patient reports of environmental exposures such as childhood trauma have good reliability and validity and are not subject to reverse causality (77).

Although our design including a biological measure as dependent variable reduces the risk of reporting bias and thus represents an alternative to previous studies using this paradigm, it cannot be ruled out that brain alterations that are weakly associated with the illness still have a minor impact on the reporting of childhood trauma or cannabis use. This, of course, applies to all neuroimaging studies that are observational in nature and cannot experimentally assign individuals to cannabis use or childhood trauma.

Although the effect of heavy cannabis use on mean CT was larger in patients (standardized effect size: –.18) relative to control subjects (standardized effect size .03), giving rise to the reported significant two-way interaction, absolute effect sizes were small and difficult to interpret in terms of biological and clinical relevance. Effects were analyzed across 68 CT measures, hierarchically clustered within persons, so that larger effect sizes (as, e.g., hypothesized in frontal areas and temporal areas) were averaged with smaller effect sizes. Future studies with larger sample sizes may provide more precise estimates of regional CT effect sizes associated with cannabis use.

Patients used cannabis more often than control subjects, which may distort interaction analysis given more precise estimates of cannabis effects on gray matter in the patients; however, siblings

and control subjects did not differ in cannabis exposure, and a similar interaction was apparent in these groups.

Freesurfer CT measurements appear to be relatively robust to differences in MRI protocols and scanners (41). Thus, in our data, no large or significant interaction was found between scan type and group on CT ($\chi^2 = .99$ $p = .61$). Similarly, adjusting for scanning sequence did not affect direction or significance of the results (results available upon request).

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