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Elevated rates of substance use disorders in non-psychotic siblings of individuals with schizophrenia

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ABSTRACT

Background: Individuals with schizophrenia use psychoactive substances more frequently than the general population. The genetic vulnerability to develop schizophrenia may also increase risk for the development of substance use disorders. We examine this hypothesis by assessing the rates of substance use disorders and nicotine use in non-psychotic siblings of individuals with schizophrenia.
Methods: Participants included 59 individuals with DSM-IV schizophrenia, 53 of their siblings, 80 community controls, and 75 of their siblings. Statistical regression was used to assess the rates of substance use disorders and nicotine use in study participants while controlling for age, gender, lifetime diagnosis of a mood or anxiety disorder, and a family history of substance use disorder.
Results: Individuals with schizophrenia and their non-psychotic siblings reported higher rates of alcohol and cannabis use disorders and nicotine use when compared to siblings of comparison subjects.
Conclusions: The vulnerability to develop schizophrenia may also extend to substance use disorders. Future research is needed to investigate the neurobiological basis of increased substance use in non-psychotic siblings and the psychosocial mechanisms that may contribute to increased substance use in non-psychotic siblings.

1. Introduction

Substance use disorders for alcohol, cannabis, cocaine, as well as nicotine use, occur with a higher prevalence in patients with schizophrenia than in the general population (Roick et al., 2007; de Leon et al., 2002; Buckley, 1998; Dixon et al., 1991; Mueser et al., 1990). Some experts have suggested that schizophrenia patients develop these co-morbidities as the unintended consequence of their attempts to use substances to alleviate aversive symptoms (Mueser et al., 1990). In support of this hypothesis, nicotine has been reported to improve cognition, negative symptoms, and physiological abnormalities in schizophrenia patients (Smith et al., 2002; Beratis et al., 2001; Clementz and Sweeney, 1990). Alpha 7 nicotinic receptor agonists may also have similar beneficial effects (Martin and Freedman, 2007). While it is plausible that schizophrenia patients also seek to alleviate symptoms through the euphoric effects of alcohol, cannabis, and cocaine (Hall and Solowij, 1998; Lysaker et al., 1994; Brown et al., 1980), the salutary effects of these substances on their symptoms is much less easy to appreciate. Alternately, it has been suggested that the neurobiological factors that predispose individuals to develop schizophrenia – perhaps including genetic influences – may also predispose them to develop substance use disorders (Chambers et al., 2001). For

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example, abnormal development of the hippocampus has been implicated in the pathogenesis of both schizophrenia and addictive behavior (Chambers et al., 2001).

First-degree relatives of individuals with schizophrenia have an increased vulnerability to develop schizophrenia (Gottesman and Gould, 2003). Thus, if there is shared genetic vulnerability between schizophrenia and substance use disorders, one should find a higher prevalence of substance use disorders in first-degree relatives than in the general population. However, studies examining substance use among non-psychotic siblings or other first-degree relatives of individuals with schizophrenia have had mixed results. A study of nicotine and schizophrenia liability in co-twins reported that the unaffected co-twins had higher rates of smoking behaviors than the siblings of healthy controls (Lyons et al., 2002), while another study found a higher morbidity for cannabis use disorders in non-psychotic siblings (Varma and Sharma, 1993). The latter study also reported similar rates of alcoholism between siblings and controls (Varma and Sharma, 1993). In contrast, Gershon et al. (1988) found a similar morbidity for both alcoholism and drug abuse between first-degree relatives of individuals with schizophrenia and controls. The prevalence of cocaine use in first-degree relatives has not been explicitly studied.

In the current study, we tested the hypothesis that the non-psychotic siblings of individuals with schizophrenia have higher rates of substance use disorders and nicotine use than the siblings of community controls. Also, we examined the effect of having a family history of specific substance use disorders as an alternative explanation for the transmission of substance use liability.

2. Methods

2.1. Participants

Participants included 59 individuals with DSM-IV schizophrenia (SCZ), 53 non-psychotic siblings of individuals with schizophrenia (SCZ-SIB), 80 healthy controls (CON), and 75 siblings of controls (CON-SIB). All participants (aged 14 to 30) gave written informed consent for participation, and the protocol was approved by the institutional review board at Washington University School of Medicine. SCZ were recruited after release from local inpatient and at local outpatient treatment centers to participate in a study focused on the clinical and neurobiological features of schizophrenia. With the consent of the SCZ (or guardian if the participant was a minor), SCZ-SIB were then asked to participate in the study. CON and CON-SIB were recruited through local advertising. In the main study, CON were excluded for a lifetime history of an Axis I psychotic, mood, or anxiety disorder, or a first-degree relative with a psychotic disorder in order to compare the neuromorphology of schizophrenia to an unaffected control group. SCZ-SIB and CON-SIB were excluded for a lifetime history of an Axis I psychotic disorder (including bipolar disorder), but neither were excluded for a lifetime history of a mood or anxiety disorder. The history of non-psychotic Axis I disorders in CON-SIB gives them greater representation to the general population than CON, thus they were selected as a comparison group for SCZ and SCZ-SIB in this analysis of substance use disorders. Data on CON is presented, but was only used to estimate the family history of substance use disorders for CON-SIB.

All participants were excluded if [1] they met DSM-IV criteria for substance dependence or moderate/severe substance abuse within the last 3 months (not including nicotine; current substance abuse/dependence was excluded as it may impact the neuromorphology examined in the main study), [2] had a severe medical disorder, [3] had a head injury with documented neurological sequelae, or [4] met DSM-IV criteria for mental retardation. These inclusion and exclusion criteria were selected because the main goal of the study was to examine brain structure and function in individuals with and without schizophrenia. Notably, we did not differentially select against a lifetime history (not current) of substance abuse or dependence in the controls.

Table 1 presents the demographic characteristics of the study sample. SCZ and SCZ-SIB were older than CON-SIB. There were more males among SCZ when compared to the other groups. The frequency of lifetime diagnoses of mood or anxiety disorders was not statistically different between SCZ-SIB and CON-SIB. Due to the high co-morbidity of substance use disorders among individuals diagnosed with a mood or anxiety disorder (Compton et al., 2007; Kessler et al., 1997), we examined the lifetime diagnosis of these disorders as a covariate in our analyses. We also examined age and gender as covariates due to between-group differences and evidence that males may be more likely than females to have a substance use disorder (Compton et al., 2007).

2.2. Measures

Participants were assessed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID) (First et al., 2002). The SCID identified whether participants had a lifetime diagnosis of a mood or anxiety disorder (present: yes=1, no=0), or lifetime diagnosis of a substance use disorder for alcohol, cannabis, and cocaine. Substance use disorders were defined as meeting DSM-IV-TR criteria for abuse or dependence (present: yes=1, no=0).

Nicotine use was estimated with a semi-structured interview adapted from Sullivan et al. (2000), and the Lifetime Alcohol Consumption Assessment Procedure (Skinner, 1982). Clinicians assessed whether the participant smoked regularly

Table 1
Background characteristics

Variable	SCZ (n=59)	SCZ-SIB (n=53)	CON-SIB (n=75)	CON (n=80)
Mean age (SD) [a]	23.5 (3.2)	23.1 (3.8)	21.3 (3.5)	21.2 (3.5)
Sex (% male) [b]	83.1	50.9	26.7	52.5
Race (% Caucasian)	55.9	60.4	74.7	72.5
Mean years of education (SD) [c]	11.6 (1.9)	13.2 (2.7)	12.9 (2.5)	13.2 (2.5)
Lifetime DSM-IV Axis I anxiety or mood disorder (% present) [d]	49.2	41.5	30.7	.0

[a] F=7.8, df=3,267, p<.001.
[b] χ^2=42.1, df=3, p<.001.
[c] F=5.8, df=3,267, p<.001, SCZ<SCZ-SIB, CON-SIB, CON (p<.01).
[d] CON were excluded for a lifetime diagnosis of a mood or anxiety disorder, χ^2 analysis on this variable was compared between SCZ-SIB and CON-SIB.

Table 2
Frequency of substance use disorders across study groups

Disorder	SCZ (n=59)	SCZ-SIB (n=53)	CON-SIB (n=75)	CON (n=80)
Alcohol	49.2%	43.4%	10.7%	11.3%
Cannabis	62.7%	39.6%	13.3%	6.3%
Cocaine	8.5%	7.5%	2.7%	.0%
Cigarette smoker	66.1%	50.9%	18.7%	23.8%
Mean cigarettes/year (SD)	3540.1 (4625.7)	1651.3 (2520.9)	266.4 (886.5)	352.1 (1077.9)

over the past 2 years (at least 1 cigarette/month). The total quantity of cigarettes smoked over the previous 2 years (and annually) was then calculated. Based on criteria from epidemiological research (U.S. Department of Health and Human Services, 2005), participants were coded "1" (smoker) if they smoked >100 cigarettes over the previous 2 years and "0" (non-smoker) if they smoked <100 cigarettes.

Variables for a family history of alcohol, cannabis, or cocaine use disorders or being a smoker were created as described above to determine the presence or absence of a history of substance use disorders in SCZ and CON. SCZ-SIB and CON-SIB were coded "1" if their paired sibling (SCZ or CON) was assessed as having a substance use disorder or was a smoker, and coded "0" if not. Separate variables were created for each substance and used as a covariate for those specific substances only.

2.3. Data analysis

We used logistic regression to model the effect of sibling group status on the rates of substance use disorders and being a smoker. We used a linear regression to model the effect of sibling group status on the number of cigarettes smoked over the past year. Age, gender, a lifetime diagnosis of a mood or anxiety disorder, and a family history of the dependent variable were added to the regression models as covariates.

3. Results

3.1. Bivariate analyses

SCZ and SCZ-SIB had higher rates than CON-SIB for alcohol (49.2% and 43.4% vs. 10.7%), cannabis (62.7% and 39.6% vs. 13.3%), and cocaine use disorders (8.5% and 7.5% vs. 2.7%). SCZ and SCZ-SIB also had higher rates of being a smoker (66.1% and 50.9% vs. 18.7%) and smoked more cigarettes over the last year than CON-SIB (3540.1 and 1651.3 vs. 266.4) (Table 2).

3.2. Multivariate analyses

After controlling for group differences in age and gender, the effects of a lifetime diagnosis of a mood or anxiety disorder and a family history of alcohol use disorder or smoking, SCZ-SIB had a significantly greater risk than CON-SIB for developing an alcohol (OR=4.0, p=.009) or cannabis use disorder (OR=2.8, p=.033) (Table 3). Also, we found that SCZ-SIB were more likely to be a "smoker" than CON-SIB (OR=2.8, p=.021). Among the covariates, we found that being male was related to a greater risk for developing an alcohol (OR=4.3, p=.005) or cannabis (OR=6.3, p<.001) use disorder, while an older age was related to higher risk for an alcohol use disorder (OR=1.2, p=.013). A family history of smoking was also a significant risk factor for being a smoker (OR=2.6, p=.027), while a family history of alcohol use disorder was not a significant risk factor for an alcohol use disorder in the non-psychotic siblings. We also found that being male was a significant risk factor for smoking at the trend level (OR=2.4, p=.064). In the linear regression, SCZ-SIB smoked significantly more cigarettes in the past year than CON-SIB (B=1052.7, p=.003), while there was a trend that having a family history of smoking was related to smoking more cigarettes over the past year (B=651.1, p=.062) (Table 3). There were no significant risk factors related to having a cocaine use disorder.

In regards to cannabis use disorder, we found that the family history of cannabis use disorder and sibling status were highly correlated (r=.60, p<.001). For this reason, we did not examine family history of cannabis use disorder as a covariate (i.e., to avoid multi-collinearity).

Table 3
Odds ratios (95% CI) and unstandardized regression coefficient (Standard Error) for risk of substance use disorders and smoking behaviors in SCZ-SIB [a]

	OR or B (95% CI or SE)	Significant covariates
Alcohol use disorder	4.0** (1.4,11.4)	Age 1.2 (1.0,1.4)* gender 4.3 (1.5,11.8)** Gender 4.3 (1.5,11.8)**
Cannabis use disorder [b]	2.8* (1.1,7.4)	Gender 6.3 (2.3,17.1)***
Cocaine use disorder	2.0 (.3,14.1)	None
Nicotine use (smoker)	2.8* (1.2,6.6)	Gender 2.3 (1.0,5.8)+ family history of smoker 2.6 (1.1,6.3)* Family history of smoker 2.6 (1.1,6.3)*
Cigarettes/year	1052.7 (347.3)**	Family history of smoker 651.1 (345.9)+

***p<.001, **p<.01, *p<.05, +p<.07.

[a] Logistic regression used to analyze alcohol, cannabis, cocaine and nicotine use linear regression used to analyze cigarettes over the past year.

[b] Family history of cannabis use disorder was excluded as covariate to avoid multi-collinearity with sibling status.

4. Discussion

In this study, we found that the non-psychotic siblings of individuals with schizophrenia have increased rates of alcohol and cannabis use disorders, as well as nicotine use, when compared to the siblings of community controls. These findings support prior research indicating that non-psychotic siblings had higher rates of smoking and cannabis use disorders than controls (Lyons et al., 2002; Varma and Sharma, 1993). However, our results are contrary to findings suggesting similar rates of alcoholism and drug abuse between first-degree relatives of individuals with schizophrenia and controls (Gershon et al., 1988). There were several methodological differences that may account for the variability between these studies. The present study examined non-psychotic siblings only, while first-degree relatives

in the latter study may have included parents and offspring. Also, the present study examined substance use disorders (abuse or dependence), while the latter study examined drug abuse only (all drugs collapsed into a single variable) and alcoholism. Collapsing across drug types may have masked the potentially higher rates of cannabis abuse in first-degree relatives.

We also found the expected differences between the frequencies of these disorders in individuals with schizophrenia and the siblings of controls. The differences in the rates of substance use disorders between non-psychotic siblings and siblings of controls are not likely to be secondary to non-specific influences associated with substance use, since non-psychotic siblings still had higher rates of alcohol and cannabis use disorders and smoking than siblings of controls after controlling for age, gender, the lifetime prevalence of a mood or anxiety disorder, as well as a family history of that specific substance use disorder (family history was not included when modeling cannabis use disorder).

The rate of an alcohol use disorder found in the non-psychotic siblings was high compared to the results of an epidemiological study on similarly-aged peers from the general population (43.4% vs. 11.9%, respectively) (Harford et al., 2005). Our findings are also consistent with prior reports of high rates of alcohol abuse or dependence among schizophrenia patients (Buckley, 1998; Dixon et al., 1991; Mueser et al., 1990). Moreover, the rate of alcohol use disorders found in the siblings of controls (10.7%) in the present study is similar to the rate found in controls by Harford et al. (2005). These findings suggest that individuals with schizophrenia and their siblings may have a higher likelihood of facing the physical health risks associated with alcohol use, including neurological problems, cardiovascular problems, and liver disease (Corrao et al., 2004; Rehm et al., 2003; Sanap and Chapman, 2003).

The non-psychotic siblings were also more likely to smoke than the siblings of community controls. Comparing the rates of smoking in our sample groups to adults aged 18–24 who participated in the National Health Interview Survey (U.S. Department of Health and Human Services, 2006), we found that non-psychotic siblings smoked at a much higher rate (50.9% vs. 25%), while the siblings of community controls (18.7%) smoked at rates similar to subjects from the population sample (U.S. Department of Health and Human Services, 2006). Our findings also support previous research indicating a high prevalence of tobacco use in individuals with schizophrenia when compared to controls (66.1% vs. 46–70%) (Roick et al., 2007; de Leon et al., 2002).

The non-psychotic siblings smoked an estimated 1052.74 more cigarettes/year than the siblings of controls. These findings suggest that non-psychotic siblings, like individuals with schizophrenia, are at increased risk for the chronic health conditions that have been related to smoking. The 2004 Surgeon General's Report on the health consequences of smoking found that smoking is causally related to several types of cancer, respiratory diseases, and reproductive deficits (U.S. Department of Health and Human Services, 2004).

Finally, the non-psychotic siblings were more likely to develop a cannabis use disorder than the siblings of controls. Additionally, the rate of a cannabis use disorder found in the non-psychotic siblings was high compared to a survey of the general population of adults aged 18–24 (39.6% vs. 8.5%) (Compton et al., 2007). We also found that the individuals with schizophrenia had high rates of a cannabis use disorder (62.7%) which is consistent with prior research (Buckley, 1998; Dixon et al., 1991; Mueser et al., 1990). However, the rate of a cannabis use disorder in the siblings of controls was similar to the rates of adults aged 18–24 (13.3% vs. 8.5%) (Compton et al., 2007). Thus, non-psychotic siblings are also at greater risk for the adverse outcomes associated with cannabis abuse and dependence, including proneness to accidents while under the influence, greater risk of psychosis, chronic bronchitis, and chronic memory and attention impairments (van Os et al., 2002; Hall and Solowij, 1998).

The role of a family history for the particular substance use disorder being studied was examined in each model except for cannabis use disorder, because in that case, it was highly correlated with sibling status. We found that a family history of smoking was a significant risk factor for being a smoker in this sample; however, accounting for this risk factor did not negate the additional increase in risk associated with having a brother or sister with schizophrenia. Perhaps surprisingly, family history was not found to be a significant risk factor for alcohol or cocaine use disorders.

Nicotine, alcohol, and cannabis are consumed at much higher levels by individuals with schizophrenia when compared to the general population (de Leon et al., 2002; McCreadie, 2002), and the results of the present study support the hypothesis that there is a shared genetic vulnerability between schizophrenia and these specific substance use disorders, which is expressed in attenuated form in non-psychotic siblings. Future research needs to examine genetic association between the vulnerability for schizophrenia and substance use disorders. Also, substance use can become a coping mechanism in the absence of alternative strategies for dealing with stress (Revell et al., 1985; Marlatt et al., 1975). Avoidant strategies for coping with stress were predictive of alcohol use in individuals who believed in the positive effects of coping via alcohol (Cooper et al., 1988), and the reliance on alcohol as a coping mechanism is predictive of alcohol abuse (Mulford, 1983). Future research needs to examine the types of coping strategies used by non-psychotic siblings to determine whether such strategies can influence the risk of developing these disorders.

A limitation to this study was that participants were not ascertained using epidemiological methods. Rather, this was a study designed to examine the neurobiology of individuals with schizophrenia and their non-psychotic siblings in which we had the opportunity to examine rates of substance use disorders. The siblings of controls were included as an additional comparison group because they were ascertained with less stringency related to non-specific forms of psychopathology, including psychopathology that may be associated with substance use. Thus, they may have been more representative of the general population and a better comparison group for the siblings of the individuals with schizophrenia than controls.

Furthermore, given that the sample of individuals with schizophrenia was a clinical one, our findings may have greater generalization to siblings of individuals with schizophrenia who have been identified as needing treatment (though this may be the majority of individuals with schizophrenia). Such individuals with schizophrenia may be

more likely to have co-morbid substance abuse. Although we included gender as a covariate, the majority of control siblings were females. Hence, future research will be strengthened by recruiting sibling samples better matched on gender. Also, a large majority of the individuals with schizophrenia were male. Thus, the results of this study may not fully generalize to rates of substance use disorders and nicotine use in siblings of females with schizophrenia.

The non-random selection of cases could contribute to spurious findings in this study; however, there is no evidence that the bias should be differential across the study groups. Thus, future research will be strengthened by obtaining a randomly selected sample. Given that this analysis is secondary to the investigation of neurobiology in schizophrenia, future research will also be strengthened by designing a study to specifically examine substance use among the non-psychotic siblings of individuals with schizophrenia. The data for this study was collected via self-report which might be biased towards under-reporting of cannabis use by siblings of controls who are concerned about reporting the use of illegal substances and over-reporting by non-psychotic siblings eager to help with research. However, it is difficult to obtain substance use data with non-self-report methods. Lastly, sibling status and a family history of cannabis use disorder were highly correlated. Thus, we could not control for family history when examining the relationship between sibling status and cannabis use disorder. In future studies, it may be helpful to examine the history of substance use disorders in parents as well as siblings.

In conclusion, our findings suggest that the non-psychotic siblings of individuals with schizophrenia are at increased risk for developing substance use disorders related to alcohol, cannabis and nicotine than similarly-aged peers. These findings need to be replicated with a larger randomly selected sample and with a greater frequency of siblings of females with schizophrenia. However, because siblings of individuals with schizophrenia can have a limited understanding of the risks of developing mental illness (Smith and Greenberg, 2008), it may be prudent to offer them information about the risks of developing substance use disorders as well as schizophrenia. Future research is needed to investigate the neurobiological basis of increased substance use in non-psychotic siblings and the psychosocial mechanisms that may contribute to increased substance use.

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Contributors

All authors have made significant scientific contributions to this manuscript. Matthew J. Dr. Smith contributed to the conceptualization of the study, conducted the statistical analyses, and wrote the first draft of the manuscript. Dr. Barch contributed to the conceptualization and implementation of the study, secured funding and contributed to the editing of the manuscript. Dr. Wolf contributed to the conceptualization of the study and assisted with editing the manuscript. Dr. Mamah contributed to the conceptualization of the study and assisted with editing the manuscript. Dr. Csernansky contributed to the conceptualization and implementation of the study, secured funding, and contributed to the editing of the manuscript. All authors approved the final manuscript.

Conflict of interest

The authors report no competing interests. Dr. Csernansky has received research grants from the NIMH and NIA, royalties from Medtronic for a patent held jointly with Washington University School of Medicine, has been a paid consultant for Eli Lilly and Sanofi-Aventis, and has received speaker's honoraria from Janssen Pharmaceutica, Eli Lilly and Bristol-Myers Squibb.

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