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Nicotine consumption and schizotypy in first-degree relatives of individuals with schizophrenia and non-psychiatric controls

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Abstract

Individuals with schizophrenia have very high rates of cigarette smoking, and much has been discovered about the influence of nicotine on brain functioning in schizophrenia. However, less is understood about the relationship between nicotine consumption and milder phenotypes related to schizophrenia, specifically schizotypy. This study examined the relationship between nicotine consumption and schizotypy in two unmedicated samples that included first-degree relatives and non-psychiatric controls.

Forty-two first-degree relatives and 50 control participants were administered a self-report questionnaire on schizotypal features as well as a self-report questionnaire on smoking behavior. A positive relationship was found between smoking status and level of schizotypy, and higher levels of schizotypy significantly predicted the odds of being a smoker after controlling for gender and group status. Interestingly, group status was a significant moderator in the relationship between level of schizotypy and smoking status, such that the relationship between these two variables was only significant in the first-degree relatives.

This is the first study to investigate the relationship between these variables in a sample of first-degree relatives of individuals with schizophrenia. Those individuals with more schizotypal features are presumably at greater risk for schizophrenia-spectrum disorders and thus may be more likely to smoke cigarettes given the known biochemical effects of nicotine on overt positive and negative symptoms of schizophrenia. Although relatives did not differ from controls in their level of self-reported schizotypy, the significant relationship between smoking status and schizotypy in the former group is likely explained by their genetic vulnerability to schizophrenia-spectrum disorders.

Keywords

Schizotypy; Nicotine; Schizophrenia; Family members

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Role of contributors

Michelle L. Esterberg: wrote first draft of manuscript; conducted data analyses; assisted in data collection.

Erin M. Jones: co-wrote manuscript; assisted in data analyses.

Michael T. Compton: designed the study from which these data were obtained; co-wrote manuscript.

Elaine F. Walker: co-wrote manuscript.

Conflict of interest

All authors declare that they have no conflicts of interest.

1. Introduction

Cigarette smoking accounts for one out of every five deaths in the United States (U.S.), and remains the leading preventable cause of death (CDC, 2002, 2005). In 2004, approximately 20.9% of adults in the U.S. smoked cigarettes; however, between 45% and 90% of people with psychiatric disorders are cigarette smokers (Lasser et al., 2000; Lohr and Flynn, 1992; Ziedonis and George, 1997). Individuals with schizophrenia appear to have the highest rates of smoking, with up to 90% being identified as cigarette smokers (Dalack et al., 1998; de Leon and Diaz, 2005; de Leon et al., 1995; George et al., 2002; Strassnig et al., 2006).

Schizophrenia is a complex psychiatric disorder that is often chronic, severe, and disabling, and is characterized by a myriad of debilitating symptoms. The influence of nicotine on these symptoms has been greatly researched. Nicotine actively influences the increase in transmission of particular neurotransmitters in the brain (Avila et al., 2003; Gray et al., 1994; Jacobsen et al., 2004; Kumari and Postma, 2005; Lambe et al., 2003; Larrison-Faucher et al., 2004; Myers et al., 2004; Sacco et al., 2004; Sherr et al., 2002) and the reinforcing effects of nicotine are believed to result from its interaction with the mesocorticolimbic system. Others have suggested that nicotine enhances performance on cognitive tasks through an increase of the synaptic transmission of glutamate (Gray et al., 1996). These effects may be of particular importance in the context of schizophrenia, given that the dopaminergic and glutamatergic systems have been implicated in positive and negative symptoms (Dalack et al., 1998; Forchuk et al., 2002; Kumari and Postma, 2005).

Researchers have become increasingly interested in how nicotine potentially affects these symptoms. Studies have shown increased positive and negative symptoms among smokers with schizophrenia (Arias et al., 1997; Beratis et al., 2001; Goff et al., 1992; Hall et al., 1995), and positive associations between the level of nicotine dependence and positive symptoms (de Leon et al., 2006; Zeidonis et al., 1994) and negative symptoms (Fukui et al., 1995; Patkar et al., 2002). One study reported negative correlations between the level of nicotine dependence and negative symptoms (Arias et al., 1997). Finally, other studies have found no significant relationships between smoking and symptoms in schizophrenia (Aguilar et al., 2005; Herrán et al., 2000). Due to these conflicting findings, the relationship between symptoms of schizophrenia and nicotine dependence remains unclear, and more research is necessary. An area of further investigation relates to possible associations between nicotine dependence and subclinical manifestations of positive and negative symptomatology, *schizotypy*.

Schizotypy has both developmental and genetic links to schizophrenia in that elevated rates of schizotypal traits are present in both the early development of schizophrenia as well as in relatives of individuals with schizophrenia (Fanous et al., 2001; Mata et al., 2000; Schultz and Andreasen, 1999). A potential key to further understanding the relationship between schizophrenia and nicotine dependence is to investigate nicotine consumption and dependence in a milder phenotype that is genetically linked to schizophrenia. Studying the association between nicotine dependence and schizotypal traits avoids confounds introduced by illness chronicity and associated psychosocial decline, as well as medication effects.

There has been relatively little research conducted on the relationship between schizotypy and smoking. One study examined the relationships between smoking, schizotypy, and latent inhibition in a sample of healthy adults (Allan et al., 1995), and found a positive correlation between schizotypy and the number of cigarettes smoked per day. Another study found significantly higher scores on measures of schizotypy for smoking, healthy adults compared to non-smoking, healthy adults (Williams et al., 1996). Other studies have yielded similar results (Joseph et al., 2003; Larrison et al., 1999). The most recent study in this area found that

smokers in the general population of Great Britain had a 70% greater risk of experiencing incident psychotic symptoms when compared to nonsmokers (Wiles et al., 2006).

These previous studies have provided important information about the potential relationship between schizotypal symptoms and nicotine use. Despite these findings, a serious gap in the current literature concerns the lack of information regarding smoking and nicotine consumption in relatives of individuals with schizophrenia, who are at increased genetic risk. Furthermore, psychotropic medication would be expected to alter the neurochemical effects of smoking and its impact on behavioral correlates such as schizotypy. Thus, studying the relationship in unmedicated relatives of individuals with schizophrenia can provide information about the true symptom correlates of nicotine consumption.

The purpose of the current study was to examine the relationship between nicotine use and schizotypy in healthy first-degree relatives of individuals with schizophrenia and in healthy non-psychiatric controls without a family history of schizophrenia. This study had three main objectives: (1) to investigate differences in levels of schizotypy and proportion of smokers between relatives and controls; (2) to examine potential predictors of smoking status in the entire sample of participants; and (3) to examine and compare the relationship between level of schizotypy and smoking status in relatives and controls.

2. Method

2.1. Participants

The study took place at a university-affiliated, public-sector health system in the southeastern U.S. Patients with schizophrenia were recruited for this study, and were invited to ask one first-degree, biological relative to participate in the study ($n = 42$). Controls were recruited from an adult internal medicine clinic waiting room ($n = 20$) and from a local indoor market frequented by the general population served by the health system ($n = 30$; total control $n = 50$).

Exclusion criteria for all participants included: (1) inability to speak English fluently; (2) substance dependence (other than nicotine dependence) defined as an active substance dependence diagnosis; (3) history of mental retardation, neurological disease, or significant head injury. Exclusion criteria for first-degree relatives also included a personal history of psychotic or mood disorders. Controls were excluded if they endorsed any personal or family history of psychotic or mood disorders.

2.2. Measures

Information about age, gender, race, marital status, and education was collected for each participant. Participants were also administered the psychotic disorders, mood disorders, and substance use disorders modules from the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) (First et al., 2002). The test-retest reliability of the SCID-I for DSM-III-R Axis I diagnoses has been determined in a variety of populations, and the overall weighted kappa has been reported to be 0.61 in patient samples (APA, 2000).

The full version of the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) was administered to assess schizotypy. The SPQ is a 74-item self-report questionnaire designed to assess schizotypy in normal or pathological populations. Each question elicits a 'yes' or 'no' response, resulting in a total score range of 0 to 74. The SPQ has been shown to have good reliability and validity (Raine, 1991), and results from this sample show adequate internal consistency of the SPQ subscales.

All participants were given the Fagerström Test for Nicotine Dependence (FTND; Heatherton et al., 1991). The FTND is a 6-item researcher-administered test that measures nicotine

dependence, and scores range from 0 to 10. Good reliability and validity have been demonstrated for the FTND (Heatherton et al., 1991).

2.3. Procedure

The assessment required approximately one hour to complete. The university's institutional review board and the health system's research oversight committee approved the research protocol. All study subjects provided written informed consent before participation. To avoid any potential bias, two separate raters assessed smoking behavior/nicotine dependence and schizotypy.

2.4. Data Analysis

Distributional properties of the data were assessed. Basic descriptive statistics were examined for all variables, and bivariate analyses were conducted using chi-square tests, Student's *t*-tests, and correlation analyses. A Fisher's *r*-to-*z* transformation was performed to test for potential differences between correlations, and logistic regression analyses were conducted to examine potential predictors of smoking status. All statistics were conducted using *SPSS 14.0*.

3. Results

Demographic characteristics and information about level of schizotypy and nicotine dependence are displayed in Table 1. Relatives had a mean age of 42.9 ± 15.8 years and controls had a mean age of 44.4 ± 10.4 years. The two groups differed significantly with respect to gender and race, as shown in Table 1, but did not differ in terms of marital status or educational attainment.

Due to substantial positive skew in the level of schizotypy, a square root transformation was performed to approximate a normal distribution. For comparative purposes, the original SPQ scores are reported; however, the transformed variable was used in all statistical analyses. Relatives did not differ from control participants with respect to level of schizotypy. The control group had significantly more participants who smoked when compared to the relative group ($\chi^2 = 4.9$, $df = 1$, $p < 0.05$), though among those who smoked, the groups did not differ on level of nicotine dependence.

The results from point-biserial correlation analyses between smoking status and schizotypy are displayed in Table 2, with zero representing nonsmokers and one representing smokers. In the entire sample, smoking status was significantly associated with SPQ total score, as well as all three SPQ subscales.

To examine potential differences in the relationship between schizotypy and smoking status across the two groups, the entire sample was divided into relatives and controls and point-biserial correlations for the two groups were performed (Table 2). In the group of relatives, smoking status correlated significantly with SPQ total score, as well as all three subscales of the SPQ. However, in the group of control participants, smoking status was not significantly associated with schizotypy scores. Schizotypy was not significantly correlated with level of nicotine dependence in either sample.

Results from Student's *t*-tests that compared mean SPQ total scores between relative smokers and nonsmokers and control smokers and nonsmokers revealed similar findings. Using the transformed level of schizotypy, relative smokers had a mean total SPQ score of 26.0 ± 17.8 (transformed mean = 4.9 ± 1.8), compared to a mean total SPQ score of 11.1 ± 7.2 (transformed mean = 3.4 ± 1.1) in relative non-smokers ($t = 3.1$, $df = 25.3$, $p < 0.01$). However, control smokers (mean score of 18.5 ± 12.9 ; transformed mean = 4.1 ± 1.4) did not differ from control

nonsmokers (mean score of 16.1 ± 16.1 ; transformed mean = 3.6 ± 2.0) on mean total SPQ score ($t = 1.1$, $df = 48$, $p = 0.27$).

To test for potential differences between the correlations in the relatives and controls (Table 2), the correlations were transformed into z -scores using Fisher's r -to- z transformation, resulting in z -scores of 0.51 and 0.16 for the relatives and controls, respectively. A z -score based on the difference between these two values and the variance of the difference between the two scores was obtained. Using a one-tailed test of significance, the correlation between level of schizotypy and smoking status was found to be significantly higher in relatives than in controls ($z = 1.67$, $p < 0.05$).

Finally, a logistic regression was conducted to determine potential predictors of smoking status (Table 3). Given the differences in smoking status between relatives and controls and between males and females ($\chi^2 = 7.1$, $df = 1$, $p < 0.01$), group and gender were tested as covariates. Total SPQ score was tested as the main predictor in the logistic regression model. Additionally, given the differences in the relationship between level of schizotypy and smoking status in the relatives when compared to controls, group was tested as a potential moderator in the relationship.

Instead of employing logistic R^2 to report the goodness-of-fit of the model, the G index was used as an analog to the overall F test in ordinary least squares (OLS) regression to test for the significance of the overall model fit. Results of the likelihood ratio test showed that the model containing the four independent predictors was significantly different from the null model containing only the constant ($\chi^2 = 19.9$, $df = 4$, $p < 0.01$). Next, the goodness-of-fit of the model was tested using the Hosmer and Lemeshow goodness-of-fit test, and results indicated that the model's estimates fit the data at an acceptable level ($\chi^2 = 6.9$, $df = 8$, $p = 0.54$). Furthermore, the model classified 71.7% of the cases correctly.

For the second step of the regression analyses, individual predictors of smoking status were examined using a stepped procedure and entering each individual predictor into its own block. To test for the fit of each model, the G index was used. Results of the likelihood ratio test revealed that controlling for gender and group, level of schizotypy ($\chi^2 = 6.9$, $df = 1$, $p < 0.01$) independently predicted the probability of a participant being a smoker. Furthermore, group was a significant moderator in the relationship between schizotypy and smoking status ($\chi^2 = 3.6$, $df = 1$, $p < 0.05$).

4. Discussion

This study assessed smoking behavior and level of schizotypy among a sample of healthy first-degree relatives of patients with schizophrenia and healthy non-psychiatric controls without a family history of schizophrenia. To our knowledge, this is the first study to investigate this relationship among relatives of patients with schizophrenia and compare them to a sample of controls without a family history of schizophrenia.

The first aim of this study was to investigate differences in levels of schizotypy and smoking status between relatives and control participants. Interestingly, the two groups did not differ on level of schizotypy. This is in contrast to both our prediction and prior research that has found a higher level of schizotypy in relatives of individuals with schizophrenia (Asarnow et al., 2001; Kendler et al., 1993; Maggini and Raballo, 2003).

However, the sample consisted entirely of healthy individuals, and the levels of schizotypy overall were modest. Interestingly, SPQ scores of relatives in this sample were similar to or lower than relatives' SPQ scores reported in several other studies (Vollema et al., 2002; Yarlalian et al., 2000). Relatives involved in the study were willing to participate and were

involved in patient caregiving, and the inclusion of these individuals may have resulted in a biased group of relatives that had fewer schizotypal traits. Alternatively, some researchers explain the lack of difference between these groups as resulting from defensive reporting in schizophrenia patients' relatives (Calkins et al., 2004; Chang and Lenzenweger, 2005). It may be that relatives have a heightened awareness of schizophrenia symptoms, and as a result present themselves as psychologically healthy.

Another interesting finding was the difference in the proportion of smokers across the two groups. Contrary to our prediction and past research, our study showed a greater proportion of smokers in the control group. Past research has suggested that a genetic predisposition to schizophrenia may be linked with a vulnerability to smoking cigarettes (de Leon, 1996). Furthermore, one previous study found that relatives had higher rates of daily smoking than controls (Lyons et al., 2002), suggesting that nicotine consumption may be associated with a familial vulnerability to schizophrenia, raising the possibility that family members are at greater risk of smoking due to their genetic predisposition to schizophrenia.

The next aim of this study was to examine the relationship between level of schizotypy and smoking status, as well as determine potential predictors of smoking status. Interestingly, there was a relationship between smoking status and level of schizotypy in the entire sample. Participants who smoked had significantly higher levels of schizotypy when compared to participants who did not smoke. Furthermore, it was determined using logistic regression that level of schizotypy independently predicted whether a participant was a smoker, and that group moderated the relationship between schizotypy and smoking.

These results support past research on the relationship between schizotypy and nicotine. In a study examining the relationship between smoking, schizotypy, and latent inhibition, a significant positive correlation was found between schizotypy and number of cigarettes smoked per day (Allan et al., 1995). Another study found significantly higher scores on measures of schizotypy for smoking, healthy adults compared to non-smoking, healthy adults (Williams et al., 1996). Other studies have yielded similar results (Joseph et al., 2003; Larrison et al., 1999). Nicotine may have an effect on the biological substrates involved in the subclinical or personality-related symptoms of a schizophrenia-spectrum disorder, and individuals possessing more of these symptoms may be more likely to smoke cigarettes, given the known biochemical effects of nicotine on overt positive and negative symptoms of schizophrenia.

The final aim was to investigate potential differences in the relationship between smoking and schizotypy in relatives and controls. Both correlations and *t*-tests revealed a relationship between level of schizotypy and smoking status in first-degree relatives, but not in control participants. When relatives were removed from the analyses, the relationship between level of schizotypy and smoking status disappeared, and when the two correlations were compared statistically, it was determined that the relatives displayed a significantly stronger relationship when compared to the control participants. Furthermore, logistic regression analyses revealed that group was a significant moderator in the relationship between schizotypy and smoking, such that this relationship changed significantly as a result of being a relative versus a control participant.

These results are interesting in that although the relatives and controls do not differ on self-reported schizotypy, the relative group does differ from the control group in that some of them may possess a genetic vulnerability to schizophrenia, given their first-degree relation to an individual with schizophrenia. Although these relatives could not be differentiated from the controls based on self-reported schizotypy, their underlying predisposition to schizophrenia may provide some insight behind the significant relationship between schizotypy and smoking status.

Having a vulnerability to schizophrenia may place an individual at risk for smoking cigarettes, especially if there is a shared genetic vulnerability to both schizophrenia and nicotine dependence. A review of the literature on the genetics underlying nicotine dependence reported that candidate genes likely responsible for nicotine metabolism may also be related to schizophrenia (Yoshimasu and Kiyohara, 2003). This underlying vulnerability could explain the association between schizotypy and smoking status among first-degree relatives.

Overall, these findings support past research that has demonstrated a link between higher levels of schizotypy and being a cigarette smoker. However, to the authors' knowledge, this is the first study to date to demonstrate a stronger relationship between schizotypy and smoking status in relatives when compared to control participants. Although relatives did not display a greater amount of schizotypal traits or a greater likelihood of being cigarette smokers, the interaction between reported schizotypy and being a first-degree relative of an individual with schizophrenia may put them at increased risk of being a cigarette smoker.

There are many implications of these findings. Although this study did not find a higher level of schizotypy in these first-degree relatives, it has been shown that schizotypal features typically occur more frequently in relatives of individuals with schizophrenia. Furthermore, given this current result of a relationship between schizotypy and cigarette smoking in individuals with a genetic vulnerability to schizophrenia, it could be assumed that relatives are at greater risk of becoming cigarette smokers. Engaging in cigarette smoking puts these relatives at risk for the increased morbidity and mortality that results from smoking cigarettes. Not only do these findings present important conclusions about nicotine use and schizotypy in relatives of individuals with schizophrenia, they also present potential targets for future public health and psychiatric research.

Several methodological limitations should be considered when interpreting these results. First, this sample of urban, predominantly African American participants may not be representative of broader populations. Second, as suggested previously, the sample of relatives may have been composed of a particularly healthy group of individuals in terms of the level of schizotypy, due to the study's exclusionary criteria and the fact that meaningful levels of schizotypy (e.g., prominent suspiciousness, social withdrawal) may deter participation in research. Future studies may consider selecting a larger and more heterogeneous group of relatives.

Despite these limitations, this is the first study to date to demonstrate a relationship between schizotypy and smoking status in a sample of participants that included first-degree relatives of individuals with schizophrenia. Future directions in this area include comparing more heterogeneous groups of relative and control participants on these important measures and finding more support for this relationship.

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Table 1

Demographic characteristics of relative and control participants

	Relative Participants (<i>n</i> = 42)	Control Participants (<i>n</i> = 50)
Age	42.9 ± 15.8 (range = 20–73)	44.4 ± 10.4 (range = 23–66)
Gender (<i>Female</i>) **	34 (81.0%)	24 (48.0%)
Race **		
<i>African American</i>	34 (81.0%)	49 (98.0%)
<i>White</i>	8 (19.0%)	1 (2.0%)
Marital Status		
<i>Single, never married</i>	17 (40.5%)	28 (56.0%)
<i>Married, or living as married</i>	12 (28.6%)	10 (20.0%)
<i>Separated, divorced, or widowed</i>	13 (31.0%)	12 (24.5%)
Years of Education	13.1 ± 2.7 (range = 6–19)	12.4 ± 2.2 (range = 7–19)
Level of Schizotypy	17.7 ± 14.6 (range = 0–54)	17.7 ± 13.9 (range = 0–54)
Level of Schizotypy (Transformed)	4.0 ± 1.6 (range = 1–7.4)	3.9 ± 1.7 (range = 1–7.4)
Smoking Status (<i>Smoker</i>) *	18 (42.9%)	33 (66.0%)
Level of Nicotine Dependence Among Those Who Smoked	3.3 ± 1.9 (range = 1–7)	3.2 ± 1.9 (range 0–8)

* Represents a significant difference between the two groups at $p < 0.05$.

** Represents a significant difference between the two groups at $p < 0.01$.

Table 2

Point-biserial correlations between smoking status and level of schizotypy

	Entire Sample (<i>n</i> = 92)	Relative Participants (<i>n</i> = 42)	Control Participants (<i>n</i> = 50)
SPQ Total Score	0.29 **	0.47 **	0.16
Cognitive-Perceptual Subscale	0.26 *	0.44 **	0.09
Interpersonal Subscale	0.28 **	0.43 **	0.16
Disorganized Subscale	0.22 *	0.35 *	0.13

* Significant at $p < 0.05$.** Significant at $p < 0.01$.

Table 3

Logistic regression analysis: Factors associated with smoking status

Independent Predictor	B	SE	Wald	p-value	Odds ratio	95% Confidence Interval
Gender	0.99	0.53	3.57	.06	2.72	0.96–7.66
Group	–3.16	1.40	5.07	.02	0.04	0.01–0.66
Level of Schizotypy	0.74	0.27	7.23	.01	1.54	1.11–2.14
Schizotypy × Group Interaction	0.61	0.34	3.26	.03	1.84	1.77–7.12