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# **Exploring the relationships between tobacco smoking and schizophrenia in first-degree relatives**

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## **Abstract**

Up to 90% of individuals with schizophrenia suffer from nicotine dependence. Both schizophrenia and nicotine consumption have strong genetic components, which may overlap. The relationship between schizophrenia and nicotine dependence remains unclear, due in part to confounding factors. Studies of the relationship between nicotine consumption and milder schizophrenia-related phenotypes, such as schizotypy, in first-degree relatives of individuals with schizophrenia could help to better understand the relationship between smoking and schizophrenia while avoiding such confounders. We assessed the proportion of smokers, their level of nicotine dependence and their level of schizotypy in a sample of 98 first-degree relatives of schizophrenic subjects and 110 healthy controls. Partial correlation analysis was used to assess the relationship between schizotypal dimensions and smoking dependence. The prevalence of smoking and nicotine dependence levels were higher in the relatives than in the healthy control group. We found no relationship between nicotine dependence and the magnitude of schizotypal features in either group. Our results support the hypothesis that the relationship between schizophrenia and smoking is largely mediated by common familial factors, which may be genetic.

**Keywords:** nicotine; smoking; schizotypy; schizophrenia; genetic; relatives.

## 1. Introduction

Individuals with schizophrenia tend to be heavy smokers. Despite the smoking cessation programs and anti-smoking campaigns implemented in many countries, up to 90% of schizophrenic subjects smoke cigarettes and are nicotine dependent (De Leon and Diaz, 2005). One of the hypotheses most frequently put forward to explain the relationship between smoking and schizophrenia is that patients may use smoking as a form of self-medication to decrease the symptoms of schizophrenia or the side effects of treatment.

Convincing data have been obtained indicating that nicotine may improve sensory gating abnormalities (Adler *et al.*, 1993), smooth pursuit eye movements (Olinicy *et al.*, 2003) and cognitive deficits in schizophrenic subjects (Ochoa and Lasalde-Dominicci, 2007). Tobacco smoking has also been shown to reduce the side-effects of antipsychotic medication by improving dopamine release in the nigrostriatum or inducing metabolic enzymes that decrease the levels of antipsychotic drugs in the blood (Aguilar *et al.*, 2005). Several studies have shown that the level of nicotine dependence is correlated with either positive (Ziedonis *et al.*, 1994; De Leon *et al.*, 2006) or negative (Patkar *et al.*, 2002) symptoms. These findings led to the suggestion that schizophrenic subjects self-medicate with nicotine, mostly to alleviate positive and negative symptoms (Lavin *et al.*, 1996), but also to relieve symptoms of depression and anxiety (Glynn and Sussman, 1990, Taiminen *et al.*, 1998, Herran *et al.*, 2000). However, studies systematically examining the relationship between tobacco use and particular symptom dimensions or antipsychotic side-effects in schizophrenia patients have yielded inconsistent findings, despite these promising neurobiological rationales. Some studies have higher levels of positive and/or negative symptoms in schizophrenic patients that smoke than in those that do not (Ziedonis *et al.*, 1994; Fukui *et al.*, 1995; Beratis *et al.*, 2001; Patkar *et al.*, 2002), whereas others have found no relationship between smoking and schizophrenia symptoms (Dalack *et al.*, 1999; Addington *et al.*, 1998; Herran *et al.*, 2000;

Aguilar *et al.*, 2005; Fatemi *et al.*, 2005), and still others (Arias *et al.*, 1997; Beratis *et al.*, 2001) have reported negative symptoms to be inversely correlated with nicotine dependence.

There may be many reasons for these discrepancies, including the heterogeneity of the populations studied (i.e., severe vs. less severe forms of schizophrenia, acute vs. chronic forms, or inpatients vs. outpatients), the lack of continuous scale for the measurement of dependence (subjects are often classified as heavy, mild or non-smokers), the use of inadequate measurements of nicotine dependence for schizophrenic patients (Steinberg *et al.*, 2005), and the influence of pharmacological treatment (McEvoy *et al.*, 1995).

However, these conflicting results also suggest that self-medication is not the only explanatory hypothesis and that schizophrenic patients smoke due to a combination of factors including self-medication and genetic susceptibility. It has been suggested that some susceptibility genes for schizophrenia and nicotine dependence are common to these two conditions (Dalack *et al.*, 1998), and there is genetic evidence to support this hypothesis. Strong genetic components have been found for both predisposition to tobacco use (Saccone *et al.*, 2007) and susceptibility to schizophrenia (Owen *et al.*, 2004; Harrison and Weinberger, 2005). Several nicotinic receptor gene variants have recently been reported to be associated with an increase in the risk of nicotine dependence (Saccone *et al.*, 2007). Faraone *et al.* (2004) also found evidence for linkage between smoking in schizophrenia and the nicotinic receptor  $\alpha 2$  (8p21),  $\beta 2$  (1q21), and  $\alpha 7$  (15q14) subunit genes. The locus of the  $\alpha 7$  subunit gene has also been linked to the P50 deficit in schizophrenia, with a LOD score of 5.3 (Freedman *et al.*, 1997). Linkage between this locus and schizophrenia has also been demonstrated in a number of other studies (Freedman *et al.*, 2001a, 2001b; Tsuang *et al.*, 2001; Liu *et al.*, 2001).

By studying nicotine consumption in individuals with a high genetic risk of developing schizophrenia, it may be possible to avoid some of the methodological problems of previous

studies and to improve our understanding of the relationship between smoking and schizophrenia. Studies of relatives of schizophrenic subjects are free from several problems that can potentially confound studies in schizophrenic patients, including the effects of long-term and (usually) ongoing medication, multiple hospital admissions or institutionalization, prolonged functional impairment due to chronic disease and a deterioration of social skills. Only a few studies have investigated nicotine consumption in the first-degree relatives of schizophrenic subjects. This group has been reported to contain a higher proportion of smokers than control groups (Lyons *et al.*, 2002; Smith *et al.*, 2008). Studies of the relationship between nicotine consumption and schizotypy in the relatives of schizophrenic patients could thus provide indirect information about the relationship between smoking and schizophrenic symptoms. Indeed, genetic and developmental links have already been found between schizotypy and schizophrenia (Kendler *et al.*, 1995), and these two conditions are composed of the same symptomatic dimensions (Vollema and van den Bosch, 1995). Furthermore, the symptoms in schizophrenic probands are predictive of similar schizotypal traits in relatives (Mata *et al.*, 2000; Fanous *et al.*, 2001).

To our knowledge, only one study has investigated the relationship between nicotine dependence and schizotypy in a sample of 42 first-degree relatives of schizophrenic probands, most of whom were African-American. The authors found a positive relationship between smoking status and the level of schizotypy in relatives (Esterberg *et al.*, 2007).

We aimed to replicate the results of Esterberg *et al.* (2007) in a large Caucasian sample. We therefore investigated the relationship between specific dimensions of schizotypy and tobacco smoking in unaffected first-degree relatives of schizophrenic subjects and in healthy controls. We assessed the proportion of smokers and the severity of nicotine dependence in our two samples, and then investigated the association between schizotypal traits (positive, negative and disorganized) and the severity of nicotine dependence.

## **2. Method**

### **2.1. Subjects**

We recruited Caucasian probands meeting the DSM-IV-TR (APA, 2000) criteria for schizophrenia, consecutively admitted to a university hospital (Psychiatry Department, Paris-Est University). For confirmation of the diagnosis, patients were interviewed directly by an experienced psychiatrist using the French version of the Diagnostic Interview for Genetic Studies (DIGS), which has a high inter-rater and test-retest reliability (Nurnberger *et al.*, 1994; Preisig *et al.*, 1999).

Unaffected first-degree relatives of the probands were contacted and asked to participate in the study. We recruited healthy Caucasian controls from blood donors. Relatives and controls were also interviewed with the French version of the DIGS to confirm the absence of schizophrenia. Controls were interviewed with the FIGS (Family Interview for Genetic Studies) (Maxwell, 1992) to confirm the absence of psychiatric disorders in their family history.

None of the subjects had a history of neurological disease, or was currently dependent on any substance other than nicotine, as evaluated with the DIGS, which has a detailed section for assessing current and past episodes of substance abuse or dependence (alcohol, cocaine, cannabis, hallucinogens, opiates, sedatives, inhalants, etc.). Written informed consent was obtained from each subject.

### **2.2. Measurements**

Information about age, sex, level of education and other demographic characteristics was collected from the DIGS for each subject.

We used the validated French translation of the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991; Dumas *et al.*, 1999, 2000) to assess schizotypal dimensions (positive, negative and disorganized dimensions). Subjects also completed the French translation of the Fagerström Test for Nicotine Dependence (FTND) (Heatherton *et al.*, 1991; Etter *et al.*, 1999). This six-item instrument assesses nicotine dependence: it is widely used in the general population and has been shown to be highly reliable and valid (Heatherton *et al.*, 1991). Former smokers were included in the non-smoker group for two main reasons: 1) former smokers were considered to be non-smokers in previous studies; and 2) smoking dependence was evaluated with the Fagerström test, which investigates current dependence.

For inclusion in the study, relatives and controls had to be euthymic as evaluated with the MADRS (Montgomery and Asberg, 1979) and the Bech-Rafaelson (Beck *et al.*, 1978) mania rating scale (MAS).

### ***2.3. Statistical analysis***

Differences between groups (controls and relatives) were assessed with the Mann-Whitney test for continuous variables and with chi-squared or Fischer's exact tests for discrete variables. Partial correlation analysis (Spearman's rank correlation coefficient) was carried out to investigate the relationships between schizotypal dimensions and smoking dependence, making it possible to control for the potentially confounding influences of sex, age and level of education.

## **3. Results**

The final samples consisted of 98 first-degree relatives of schizophrenic subjects and 110 healthy controls. Most of the relatives were the parents of patients (70.4%). All subjects were euthymic at the time of the study, with MADRS and MAS scores  $< 5$ . The demographic and clinical characteristics of these subjects are displayed in Table 1. The relatives were older than the controls ( $51.7 \pm 14.7$  vs.  $41.9 \pm 11.7$ ;  $p < 0.0001$ ). Sex ratios were similar for relatives and controls (48.9% and 55.4% men, respectively). The highest completed school grade (level of education) was recorded, according to the usual conventions (Pichot *et al.*, 1993) as a trichotomous variable (1 = elementary school; 3 = completion of high school or above; 2 = intermediate between 1 and 3). However, we finally decided to merge levels 1 and 2 because level 1 was infrequent in both groups. Level of education did not differ significantly between the two samples ( $p = 0.33$ ).

The proportion of smokers were more higher among the relatives than among the controls (44.9% vs. 23.6%;  $p = 0.001$ ) and nicotine dependence was greater among the relatives than among the controls that smoked, as shown by FTND scores ( $2.66 \pm 2$  vs.  $1.65 \pm 1.99$ ;  $p = 0.04$ ) (Table 1).

Schizotypy levels were low, with similar values obtained for the two groups ( $11.36 \pm 10.9$  for controls and  $10.58 \pm 7.98$  for relatives) (Table 1).

#### *INSERT TABLE 1*

Mean schizotypal (SPQ) scores did not differ between smokers and non-smokers in either group ( $9.84 \pm 9.1$  vs.  $12.59 \pm 12.2$  in relatives;  $10.7 \pm 8.6$  vs.  $10.74 \pm 7.8$  in controls) (Table 2).

#### *INSERT TABLE 2*

We found no correlation between nicotine dependence and SPQ score (full score, or scores for the positive, negative and disorganized dimensions) in either relatives or healthy controls (Table 3).

*INSERT TABLE 3*

#### **4. Discussion**

The goal of our study was to examine the relationship between nicotine dependence and schizotypy in a sample of healthy first-degree relatives of schizophrenic patients and healthy controls without a family history of schizophrenia. The only previous study of this relationship, to our knowledge, is that of Esterberg *et al.* (2007), which dealt with a smaller sample.

One of the most striking findings of this study was the differences in the proportion of smokers and the level of nicotine dependence between the two groups. The proportion of smokers was higher and the level of nicotine dependence was greater in first-degree relatives than in controls. The proportion of smokers in our control group is similar to that reported for the general population (20-30%) (Lyons *et al.*, 2002). The proportion of smokers in the group of relatives was intermediate between that in samples of schizophrenic patients (70% or greater) and that in the general population. Our results are consistent with those of previous studies (Lyons *et al.*, 2002; Smith *et al.*, 2008). However, Esterberg *et al.* (2007) reported a higher proportion of smokers in their control group, with similar levels of nicotine dependence in the two groups. The prevalence of smoking among healthy controls (66%) in the study by Esterberg *et al.* was much higher than the prevalence of smoking in the general

population (20-30%), suggesting a possible recruitment biases. Furthermore, 90.2% of the subjects included in their sample were African-American, whereas our sample was entirely Caucasian. These two ethnic groups metabolize nicotine differently and have different specific smoking habits, with African-American reported to have higher levels of nicotine dependence and lower smoking cessation rates despite smoking fewer cigarettes per day (Benowitz, 2008; Gandhi *et al.*, 2009). The level of nicotine dependence in study by Esterberg *et al.* may therefore have been underestimated. Our results suggest that familial – possibly genetic – factors may make a major contribution to the relationship between schizophrenia and smoking. This hypothesis is clearly supported by several lines of genetic, biological and clinical evidence. The heritability of smoking behavior (Spitz *et al.*, 1998; Shields *et al.*, 1998; Kendler *et al.*, 1999) and the linkage demonstrated between schizophrenia and specific nicotinic receptor genes or nicotine-metabolizing enzyme genes confirm this genetic susceptibility (Freedman *et al.*, 1997, 2001b; Leonard *et al.*, 2002; Yoshimasu and Kiyohara, 2003; Leonard *et al.*, 2007). Furthermore, genetic linkage studies of smoking in schizophrenia have shown that these linkage sites coincide with replicated sites of linkage in schizophrenia (Faraone *et al.*, 2004). However, environmental factors common to schizophrenic patients and their relatives may contribute to the higher prevalence of smoking in these two groups. The hypothesis that relatives are mimicking the behaviour of schizophrenic subjects by smoking is unlikely, as most of the relatives in our sample were parents, who presumably started smoking before the probands.

We found no correlation between either smoking status or nicotine dependence and the level of schizotypy in either group of subjects. Several studies have reported a positive correlation between schizotypy and smoking status in the general population (Williams *et al.*, 1996; Larrison *et al.*, 1999; Joseph *et al.*, 2003). Interestingly, Esterberg *et al.* (2007) found a positive relationship between smoking status and the level of schizotypy in their sample of

first-degree relatives of schizophrenic subjects, but not in the control group. Our findings, conducted in a larger sample, do not support the hypothesis that relatives use nicotine as a form of “self-medication” to improve schizotypal traits. Unaffected first-degree relatives probably carry schizophrenia susceptibility genes, but, typically, do not suffer from the confounding effects of chronic illness and ongoing treatment. They are therefore, ideal subjects for studies of the possible trait-related markers of susceptibility to schizophrenia. Our results argue against the self-medication theory of smoking in schizophrenia, consistent with previous findings, including the observation that 90% of schizophrenic subjects begin smoking before they become ill, even before the prodromal phase (De Leon *et al.*, 2002; Gurpegui *et al.*, 2005). The convincing evidence that smoking does not greatly alleviate schizophrenic symptoms is probably the absence of major changes to schizophrenic symptom scores in most trials in which schizophrenic subjects either stopped smoking or smoked less (Dalack *et al.*, 1999; Evins *et al.*, 2001, 2005; Smith *et al.*, 2002; Fatemi *et al.*, 2005).

Our study has several limitations. Firstly, the relatives had SPQ scores that were similar to those of the controls and therefore, lower than expected. There are several possible reasons for this. The relatives of schizophrenic patients may be more defensive in their responses to schizotypy questionnaires (Calkins *et al.*, 2004) and there may be a selection effect, with only relatives with fewer schizotypal traits agreeing to participate in research studies. Secondly, although all relatives were euthymic at the time of assessment, we cannot not rule out the hypothesis that they smoke to improve their mood (Berlin *et al.*, 1995; Lerman *et al.*, 1998), as being the parent of a schizophrenic patient may lead to depressive states. Similarly, we could not exclude the possibility of relatives smoking to improve cognitive deficits or due to a low socio-economic status, as shown for schizophrenic subjects. Thirdly, we did not take into account the fact that the relatives were older than the controls, and have therefore probably been exposed to more antismoking campaigns.

Our results provide support for the hypothesis that familial factors increase the prevalence of smoking in first-degree relatives of schizophrenic subjects, who have a “high genetic risk” of schizophrenia. If it can be confirmed that genetic factors make people at risk of schizophrenia more likely to smoke, this would have major implications for our understanding of the aetiology of schizophrenia.

The relatives of schizophrenic patients are at greater risk of becoming cigarette smokers. They therefore also have a greater risk of developing chronic health problems. Efforts should therefore be made to prevent nicotine dependence in these relatives and, if necessary, to help them quit smoking if they have already started.

Moreover, as some studies have suggested that nicotine may play a role in conversion to psychosis (Kristensen and Cadenhead, 2007) and that heavier smoking is associated with a greater risk of schizophrenia (Weiser *et al.*, 2004), special psychiatric monitoring could be proposed for young heavy smokers related to schizophrenic subjects, who are at greater risk of developing schizophrenia.

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