Tobacco smoking and its association with cognition in First Episode Psychosis patients.

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Abstract

Available evidence suggests that nicotine may enhance cognitive functioning. Moreover, it has been suggested that the high prevalence of smoking in people with schizophrenia is in part due to self-medication behaviour to alleviate cognitive deficits. We assessed the association between tobacco smoking and cognitive functioning in a large population of first episode psychosis (FEP) patients (n = 304) and healthy controls (n = 156). Smokers were not tobacco deprived, or were minimally deprived (≤2 h). Verbal memory, visual memory, working memory, processing speed, executive function, motor dexterity and attention were assessed. The smoking prevalence among the FEP group was 57% (n = 174). The age at which patients began smoking cigarettes regularly was 16.2 years (SD = 3.1), an average of 12 years before experiencing the first frank symptoms of psychosis (age of onset = 28.8; SD= 9.3). The number of cigarettes smoked per day was 19.6 (SD = 9.4), significantly more than healthy controls [11.0 (SD=7.6); p<0.001]. ANCOVA analysis did not show any significant difference between smokers and non-smokers in the performance of any of the cognitive tasks in the FEP group or in the healthy control group, independent of gender, age, education or premorbid IQ. This suggests chronic exposure to nicotine through cigarette smoking is not associated with cognitive functioning in first-episode psychosis. These findings do not support the nicotine self-medication hypothesis as a contributor to the high prevalence of smoking among individuals suffering from serious mental illness.
1. INTRODUCTION

The prevalence of smoking in people with schizophrenia is two to three times higher than individuals without a psychiatric disorder (de Leon and Diaz, 2005). While the smoking rates have fallen dramatically in the general population, people with serious mental illness have not experienced the same rates of decline (Dickerson et al., 2013). In addition, serious mental illness has been associated with higher levels of nicotine dependence (de Leon and Diaz, 2005; Gurpegui et al., 2005). It has been suggested that one of the reasons why so many individuals diagnosed with psychosis smoke, is to improve cognitive deficits caused by their illness (Kumari and Postma, 2005; Mackowick et al., 2014). Several studies involving patients diagnosed with schizophrenia, and smoking ≥10-20 cigarettes per day, have shown an association between chronic smoking and improvements in cognition, especially in attention and working memory (Morisano et al., 2013; Sacco et al., 2005; Wing et al., 2011; Zabala et al., 2009). In addition, Hahn et al. (2013) found that participants administered nicotine performed significantly better on attention tasks compared to placebo, but nicotine demonstrated a u-shaped dose response pattern, suggesting nicotine dose has a variable effect on cognition. Wing et al. (2011) also found an association between smoking and improvements in sustained attention and processing speed in patients diagnosed with schizophrenia. But not all studies have found an improvement in cognition with nicotine use - Depp et al. (2015) saw cognitive deficits in smokers compared to non-smokers in a serious mental illness population. These inconsistencies may be explained by differences in study design and phase of illness, such as the use of chronic illness or those diagnosed with affective psychosis.

The ability of nicotine to enhance cognition has been well documented (Heishman et al., 2010; Poorthuis et al., 2009). Previous studies in healthy adult smokers have suggested that nicotine may have cognition-enhancing properties (Heishman et al., 2010). Studies have also found that nicotine administration may reduce cognitive impairments in some neurodegenerative diseases such as Alzheimer’s and Parkinson’s (Newhouse et al., 1996; White and Levin, 1999). Additional evidence from animal models have shown that acute administration of nicotine to rodents improved working memory performance when tested on a 16-arm radial maze (Levin et al., 1997). Nicotine has been involved in the neurological mechanisms underlying the symptomatic relief. Nicotine stimulates nicotinic acetylcholine receptors (nAChRs), causing a release of neurotransmitters, including dopamine, into the frontal cortex and mesolimbic areas (Benowitz, 2009; Poorthuis et al., 2009). It is hypothesised that nicotine would compensate the hypodopaminergic state in prefrontal areas which is thought to be responsible for the negative symptoms and cognitive deficits in patients suffering from schizophrenia (Howes and Kapur, 2009).

A clinical trial conducted by Lieberman et al. (2013) tested the effect of an α7 nicotinic receptor partial agonist (TC-5619) on cognition in patients diagnosed with schizophrenia. Administration of TC-5619 was found to improve executive functioning, especially in tobacco users and the authors suggested that nicotinic agonists improve cognition in both smokers and non-smokers diagnosed with schizophrenia. On the other hand, Smith et al. (2016) found that administration of Varenicline - a nicotinic receptor partial agonist- to patients diagnosed with schizophrenia did not improve cognitive function when compared to placebo.

There is not enough evidence to date as to the effects of nicotine or nicotine-related products on cognitive functioning. The main objective of this observational, cross-sectional study was to examine
the relationship between chronic exposure to nicotine through tobacco smoking on cognitive performance in a large population of first episode patients and healthy volunteers. Specifically, we assessed the relationship between smoking and cognition on seven cognitive domains in first-episode psychosis patients and healthy volunteers. Our hypothesis was that the smokers will obtain better scores than non-smokers in both groups.

2. METHOD

2.1. Design

The subjects included in this study were part of a cohort of first episode non-affective psychosis patients included in the first episode psychosis programme of Cantabria, Northern Spain (Pelayo-Terán et al., 2008). Patients referred to the program were selected if they met the following criteria: 1) age 15–60 years, 2) living in the catchment area, 3) experiencing their first episode of psychosis, 4) no prior treatment with antipsychotic medication or, if previously treated, a total lifetime exposure less than 6 weeks, and 5) meeting DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. Patients were excluded for any of the following reasons: 1) meeting DSM-IV criteria for drug dependence, except nicotine 2) meeting DSM-IV criteria for mental retardation, or 3) having a history of neurological disease or head injury. Diagnosis per DSM-IV criteria was confirmed by an experienced psychiatrist 6 months after the initial contact. After the patients provided written informed consent, they were randomly assigned to receive one of the following antipsychotic treatments: haloperidol (3–9mg/day); risperidone (2–6mg/day) or olanzapine (5-20mg/day) from February 2002 to February 2005; or aripiprazole (10–30 mg/day), quetiapine (200–600 mg/day), or ziprasidone (40–160 mg/day) from February 2005 to February 2011.

All the patients included in the first-episode psychosis (FEP) were invited to undergo a comprehensive cognitive assessment. To avoid the effects of acute symptoms of psychosis on cognitive performance, the tasks were administered by experienced psychologists after patients have achieved clinical stability, around 3 months of treatment with antipsychotic medication. The protocol was approved by the Marques de Valdecilla University Hospital Ethics Committee and was performed in accordance with international ethical standards. Written informed consent was obtained from all participants.

2.2. Cognitive battery

A detailed description has been reported elsewhere (González-Blanch et al., 2007). A subset of measures was selected from the cognitive battery to assess seven major cognitive areas, as well as an estimation of premorbid IQ:

1) Verbal memory was assessed with the Rey Auditory Verbal Learning Test (RAVLT), delayed recall (Rey, 1964).
2) Visual memory was assessed with the Rey Complex Figure (RCF) delayed reproduction (Osterrieth, 1944).

3) Executive functioning was assessed with the Trail Making Test (TMT), time to complete TMT-B minus TMT-A (Reitan and Wolfson, 1985).

4) Working memory was assessed with the WAIS-III Backward Digits scale, total sub-score (Wechsler, 1997).

5) Processing speed was measured with the WAIS-III Digit Symbol subtest (standard total score) (Wechsler, 1997).

6) Motor dexterity was assessed with the Grooved Pegboard Handedness (GP), time to complete with dominant hand (Lezak, 1994).

7) Attention was assessed with the Continuous Performance Test (CPT), total number of correct responses (Cegalis and Bowlin, 1991).

8) Estimation of IQ: WAISIII vocabulary (subtest standard total score) was used as measure of premorbid IQ (Wechsler, 1997). Vocabulary, as a measure of crystallized intelligence, has been extensively used to generate an estimate the intelligence quotient (IQ) (Ringe et al., 2002).

The battery took approximately two hours to administer, and smokers were permitted to take smoking breaks during testing if requested. The attention, motor dexterity, executive functioning, working/verbal memory and processing speed tests have been used in previous studies of the effect of nicotine on cognition (Depp et al., 2015; Heishman et al., 2010; Morisano et al., 2013; Sacco et al., 2005; Wing et al., 2011).

2.3. Healthy controls

Healthy comparison subjects (N=156) were recruited from the community through advertisements. They had no past or present psychiatric, neurological, or general medical illness as determined by using an abbreviated version of the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992). Healthy subjects were matched to the patients by age, sex and years of education, and the inclusion of a healthy control group allows us to determine whether chronic tobacco exposure is associated with cognitive functioning independently of psychotic illness. All participants provided informed consent after the study procedures were fully explained to them.

2.4. Tobacco smoking

Tobacco cigarette use per day and the age at which the patient initiated smoking regularly (daily) was obtained retrospectively based on patient’s self-report. Non-daily tobacco smokers (N=11; 2.4%) were classified as “smokers”, and former smokers were classified as “non-smokers”. Smokers were minimally deprived (≤2h) or non-deprived of nicotine when tested, as assessed by self-report.
2.5. Statistical Analyses:

Pearson’s chi-square for categorical data and Student’s t tests for continuous variables were used to compare demographic and clinical variables between smokers and non-smokers.

Each cognitive score was standardized to a z score (with a mean of 0 and a SD of 1) using the values of the healthy comparison group as reference. One-way ANCOVAs were used to compare the performance of smokers and non-smokers in 7 cognitive domains. Age, gender, level of education and premorbid IQ were used as covariates. Significance level was set a priori at p<0.05 and all hypotheses were 2-tailed. Data was analysed using SPSS 22 (IBM Corp., Armonk, NY).

3. RESULTS

Of the 397 FEP patients who were approached, 304 (77%) agreed to take part in the neurocognitive assessment (figure 1). Their mean age was 29.9 years (SD = 9.7); 58% (n = 173) were male and the majority of the participants had a diagnosis of schizophrenia (56.6%) or schizophreniform disorder (26%). There were no significant differences between those who consented to neurocognitive testing and those who refused in age, age of onset of psychosis, SAPS and SANS score at intake, cannabis use or sex (all p’s ≥0.05).

Figure 1. Participant flow chart.

Sociodemographic characteristics of FEP patients can be seen in figure 2. In the FEP group, the smoking prevalence was 57% (n = 174). The average age at which smokers began smoking cigarettes regularly was 16.2 years (SD = 3.1), an average of 12 years before experiencing the first frank symptoms of psychosis (age of onset = 28.8; SD= 9.3). Therefore the smokers had been smoking for an average of 13.9 years (SD=8.7) and the average number of cigarettes smoked per day was 19.6 (SD = 9.4), significantly more than the healthy controls [11.0 (SD=7.6); p<0.001].

When the FEP group was stratified by smoking status, significant differences emerged in age (smokers = 28.1±9.0 versus non-smokers = 32.3± 10.1; p < 0.01), years of education (smokers = 9.9±3.1 versus non-smokers = 11.3±3.5; p < 0.01) and gender (65% of males were smokers versus 47% of females; p< 0.01).

Figure 2. Demographics of FEP patients

A total of 156 healthy controls were recruited. They matched the FEP group by age (FEP = 29.9±9.0 versus controls = 29.0±7.8; p = 0.290), sex (57% of FEP and 61% in the control group were males; p = 0.340) and years of education (FEP =10.5±3.4 versus controls = 10.7±2.8; p = 0.414).
3.1. Cognitive performance

The ANCOVA analysis did not show any significant differences between FEP smokers and non-smokers in: verbal memory \((F(1,285)=0.676, p=0.412, \eta^2_p=0.002)\), visual memory \((F(1,283)=1.486, p=0.224, \eta^2_p=0.005)\), executive functioning \((F(1,280)=1.672, p=0.197, \eta^2_p=0.006)\), working memory \((F(1,285)=0.080, p=0.777, \eta^2_p<0.001)\), processing speed \((F(1,284)=2.943, p=0.087, \eta^2_p=0.010)\), motor dexterity \((F(1,276)=0.912, p=0.340, \eta^2_p=0.003)\) or attention \((F(1,262)=0.153, p=0.696, \eta^2_p=0.001)\) (figure 3). The lack of effect was observed to be independent of gender, age, education or premorbid IQ.

Similarly, there were no significant differences in the mean cognitive scores between smokers and non-smokers in the group of healthy volunteers after adjusting for covariates (figure 3). The group of smokers scored significantly lower than the non-smokers group \((p = 0.03)\) on the RCF test but this difference was no longer significant when Bonferroni correction for multiple testing was applied.

Figure 3. Z-scores of FEP patients and healthy controls, smokers and non-smokers groups.

4. DISCUSSION

A complete neurocognitive assessment was conducted in smokers and non-smokers who had recently been diagnosed with a FEP. As no significant difference in cognitive ability was found between smokers and non-smokers, our study suggests that chronic exposure to tobacco is not associated with cognitive performance in FEP patients or matched controls.

Our findings do not support the hypothesis that the use of nicotine via tobacco smoking enhances cognition in individuals diagnosed with a non-affective psychotic disorder. These results are inconsistent with some previous studies (Harris et al., 2004; Lieberman et al., 2013; Morisano et al., 2013; Sacco et al., 2005; Wing et al., 2011; Zabala et al., 2009), but concur with those of one of the few observational studies that have examined the relationship between smoking and cognition among FEP patients (Zhang et al., 2013).

One likely explanation for this disagreement is that nicotine may only enhance cognition in deprived smokers, with improvement in cognition as a benefit of withdrawal relief (Snyder et al., 1989). Sacco et al. studied 25 smokers diagnosed with schizophrenia and 25 control smokers, smoking 15 or more cigarettes a day (Sacco et al., 2005). Tobacco abstinence was associated with significantly reduced hit rates on the CPT (Cegalis and Bowlin, 1991) in both patients and controls, which reversed upon smoking reinstatement (Sacco et al., 2005). In addition, visuospatial working memory was only impaired among smokers (Sacco et al., 2005).

Zabala et al. (2009) found that smoker FEP patients outperformed their non-smoking counterparts in sustained/selective attention and working memory tests, but not in executive cognition. Segarra et al. (2011) assessed the same sample after 12-months and found that the superior cognitive performance associated with tobacco smoking was not maintained. The authors suggest that nicotine use results in cognitive benefits that are also attainable with antipsychotic medications, which both groups received.
In a recent epidemiological study of individuals diagnosed with serious mental illness, smokers experienced worse cognitive functioning compared to non-smokers (Depp et al., 2015). The authors suggest that smokers may be less susceptible to societal influences reducing the smoking rate, maybe as a result of cognitive impairment (Depp et al., 2015).

Our results support the findings of previous studies of nicotine effects on cognition in the general population (Ernst et al., 2001; S.J. Heishman et al., 2010). Heishman et al. (2010) did not find an association with smoking in all of the tested cognitive domains. Furthermore, an alternative study found no effect of nicotine on reasoning and working memory tasks (Ernst et al., 2001).

Our study employed a large population, which can be viewed as one of the main strengths. Furthermore, a thorough cognitive assessment was undertaken, using standardised tests. However, tobacco usage was self-reported, thus this variable may have been inaccurately reported. In addition, numerous confounding environmental variables are problematic in interpreting the results. Namely, the impact of withdrawal time and quantity of tobacco during smoking breaks on cognitive scores. The studies that exist on the subject are in most cases compromised by a lack of documentation of the amount and timing of nicotine exposure during cognitive testing. Therefore, biomarkers such as carboxyhaemoglobin, expired carbon monoxide and cotinine exposure should be measured in future studies to increase validity. A further limitation of this study is the lack of a measure of nicotine dependence, and it is unknown as to whether smokers may have changed their smoking behaviours over the years they have been smoking. In conclusion, the current results suggest there is no significant association between smoking and cognition in people diagnosed with first-episode psychosis or healthy controls after controlling for confounding factors.
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**Figure 1.** Participant flow chart

Source Population
(Cantabria region = 588,656 total population)

- FIRST EPISODE PSYCHOSIS
  - 522 REFERRED (from 2001 to 2011)
  - 428 ELIGIBLE
  - 397 ENROLLED
  - 304 COMPLETED COGNITIVE ASSESSMENT
    - 130 NON-SMOKERS
    - 174 SMOKERS

- MATCHED CONTROLS
  - 168 SCREENED
  - 156 COMPLETED COGNITIVE ASSESSMENT
    - 80 NON-SMOKERS
    - 76 SMOKERS

12 refused to take part
19 were excluded when diagnosis was confirmed

**Figure 2.** Demographics of FEP patients

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<th>FEP (smoker)</th>
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<th>p</th>
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<td>28.1</td>
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<td>Years smoking</td>
<td>-</td>
<td>14.1</td>
<td>-</td>
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<td>Cigs/day</td>
<td>-</td>
<td>19.6</td>
<td>-</td>
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<td>6.9</td>
<td>7.4</td>
<td>0.610</td>
<td>0.436</td>
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<tr>
<td>SAPS at intake</td>
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<td>13.6</td>
<td>0.574</td>
<td>0.449</td>
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<tr>
<td>Years of education</td>
<td>11.3</td>
<td>9.9</td>
<td>13.165</td>
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<td>Age of psychosis onset</td>
<td>31.0</td>
<td>27.2</td>
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<th>%</th>
<th>N</th>
<th>%</th>
<th>χ²</th>
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<td>Sex (male)</td>
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<td>113</td>
<td>64.9</td>
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<td>Schizophrenia</td>
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<td>26</td>
<td>10.5</td>
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Cigs/day= tobacco cigarettes per day
Figure 3. Z-scores of FEP patients and healthy controls, smokers and non-smokers groups.