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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 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.

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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 <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 (3–9 mg/day); risperidone (2–6 mg/day) or olanzapine (5–20 mg/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 three 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 2 h 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 (≤2 h) 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.

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