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ORIGINAL PAPER

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Cognitive performance and cigarette smoking in first-episode psychosis

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Abstract The purpose of this study is to describe possible differences in cognitive functioning between smoking and non-smoking patients with first-episode psychosis and to determine whether there is a better cognitive profile associated with smoking. We assessed 61 first-episode psychosis patients with a neuropsychological battery that included computerized measurements of attention, working memory, and executive functioning. Patients were grouped into two categories: non-smokers (0 cigarettes/day; $n = 30$) and smokers (≥20 cigarettes/day; $n = 31$). No significant differences were detected in sociodemographic and clinical data between the two groups. For attention tasks, smokers exhibited shorter reaction times in the sustained attention test than non-smokers ($P = 0.039$) and needed less time to complete the Stroop interference test ($P = 0.013$). In the working memory task, smokers exhibited shorter reaction times ($P = 0.029$) and presented a significantly lower percentage of omission ($P = 0.002$) and commission errors ($P = 0.020$) than non-smokers. For executive functioning, no differences were detected between groups in performance on the Wisconsin Card Sorting Test. Results indicate that first-episode psychosis patients who are nicotine users have better cognitive functioning in the areas of attention and working memory than patients who are not nicotine users. This study supports the cognitive approach to the self-medication hypothesis, to explain the high rates of cigarette smoking among psychosis patients. These results may be relevant for developing new strategies involving nicotinic receptors for cognitive enhancement in psychosis.

Key words cognition · nicotine · smoking · first episode · psychosis

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Introduction

It is well recognized that cigarette smoking is more prevalent among patients with psychosis, especially in schizophrenia, with rates of 70–80% versus 25–30% in the general population [13, 14, 21, 22]. The evidence for a relationship between cigarette smoking and schizophrenia is undeniable; however, the mechanisms underlying this relationship remain unclear.

The remarkably high prevalence of smoking in schizophrenia patients has prompted speculation that smoking is an attempt at self-medication. One of the most popular approaches to the self-medication hypothesis is that smoking reverses the side effects of antipsychotic medication [15]. It has been reported that nicotine increases the metabolism of antipsychotics and decreases their therapeutic effects [9, 35], leading smoking patients to display fewer antipsychotic induced side effects, e.g., extrapyramidal symptoms [15, 20, 32]. However, controversy has arisen, as the metabolism of some atypical antipsychotics (e.g., risperidone, quetiapine, ziprasidone, and aripiprazole) has proven to be not sensitive to the effects of smoking [12]. Other contradictory evidence derives from the fact that 90% of patients who smoke start smoking before the onset of the illness and, therefore, before antipsychotic medications are prescribed [30]. Consequently, antipsychotic treatment alone may not explain the high rates of cigarette smoking among schizophrenia patients.

Another explanatory approach to the self-medication hypothesis is that smoking partly counteracts some of the cognitive deficits involved in the physiopathology of schizophrenia itself [38, 43, 46]. Cognitive deficits have been extensively studied in psychosis and have been characterized as an inherent feature of the illness [23]. Neuropsychological studies have consistently described deficits affecting attention, working memory, executive functioning, learning and memory [27]. These impairments have been described in first-episode patients, seem to be stable over time [1], are not exclusively explained by clinical symptomatology, and are present in individuals even before they develop psychotic symptoms [11].

There is increasing evidence that the altered expression of central nicotinic cholinergic receptors in schizophrenia may be related to the cognitive deficits associated with the illness [33, 42]. The hypothesis that smoking in psychosis may be a self-medication behavior to directly reverse cognitive deficits has been supported by evidence showing that cigarette smoking and other forms of nicotine administration (nasal spray, gum, or patch) produce positive effects on some of the psychophysiological abnormalities and neuropsychological impairments related to the illness. The literature has reported that nicotine administration transiently reverses eye-tracking abnormalities [3, 5, 39] and normalizes the auditory sensory gating (P50) deficit, both in patients and their relatives [2]. Studies also suggest that nicotine administration can improve attention and working memory deficits [6, 16, 28, 32, 44] and may reverse abstinence-related impairments in these cognitive domains in smoking patients [19, 45]. Additionally, nicotine has been shown to have positive effects on verbal memory deficits [37, 44], although not without controversy [32, 45], while no positive effects have yet been described on executive functioning deficits [42].

The main objectives of this study were to describe possible differences in cognitive functioning between smoking and non-smoking patients with first-episode psychosis (FEP) and to determine whether there is a better cognitive profile associated with smoking. We hypothesized that smoking patients would perform better on attention, working memory, and executive functioning tests than non-smoking patients. To our knowledge, no previous studies have evaluated this issue in FEP. Research on this population affords an opportunity to study the early phases of this disease and avoids dealing with certain confounding variables such as chronicity or long-term antipsychotic treatment that could interfere with the results.

Materials and methods

This article reports the baseline neuropsychological results based on smoking data from a prospective longitudinal study of FEP.

Subjects

Patients were recruited from inpatient and outpatient facilities in Vizcaya (a region in the North of Spain) that covered a catchment area of approximately 500,000 inhabitants. All patients consecutively seen in these facilities between March 2003 and November 2005 who fulfilled the inclusion criteria described below were invited to participate in the study. Visits were performed at two general hospitals in the geographical region.

Inclusion criteria for participation in the study were: (1) age between 15 and 65 years, (2) presence of FEP defined as the existence of at least one of the following symptoms: delusions, hallucinations, formal thought disorder, and catatonic symptoms, and symptoms were determined to be present when the Positive and Negative Syndrome Scale (PANSS) score for item 1, 2, or 3 was greater than or equal to 4, and (3) presence of a first degree relative to act as an informant, when necessary. Exclusion criteria were: (1) previous hospitalizations or outpatient psychiatric treatment for psychotic symptoms, (2) significant medical or neurological illness, (3) history of head injury with loss of consciousness, (4) mental retardation, (5) current diagnosis of substance dependence (except tobacco), and (6) participation in a clinical trial. A total of 89 patients with FEP were enrolled in a general FEP research project. Nicotine consumption was assessed by self-report in a personal interview and patients were classified into smoking categories according to previous literature [17, 19, 48]. Considering the specific aims of the present study, patients were selected from the general sample if they were non-smokers (0 cigarettes/day; $n = 35$) or if they were smokers and clearly habitual nicotine users (≥20 cigarettes/day; $n = 36$). Five patients in the group of non-smokers and five in the group of smokers did not cooperate with the neuropsychological evaluation, leaving a final sample of 61 patients divided into two groups as follows: (a) non-smoking FEP patients, $n = 30$; and (b) smoking FEP patients, $n = 31$. Mild smokers (1–19 cigarettes/day; $n = 18$) were not included in the analyses, as significant intra-subject variations in daily consumption were detected in this group, also reflecting a large dispersion of frequencies.

The institutional review boards of the participating hospitals approved the study. After receiving a comprehensive explanation of the study procedures, all patients provided written informed consent.

Psychiatric assessment

The Structured Clinical Interview for DSM-IV Axis I disorders [18] was used for diagnostic purposes. FEP was defined as the first time

a patient displayed positive psychotic symptoms. All subjects satisfied the DSM-IV [4] criteria for a schizophreniform disorder, schizoaffective disorder, schizotypal disorder, delusional disorder, brief psychotic disorder, bipolar I/II disorder, substance-induced psychosis, or atypical psychosis. For diagnostic distribution, see Table 2. The presence and severity of psychotic symptoms at baseline were evaluated using the Spanish version of the Positive and Negative Syndrome Scale (PANSS) [41]. Other scales used for the clinical baseline assessment were: the Montgomery-Asberg Depression Rating Scale (MADRS) [36], the Young Mania Rating Scale (YMRS) [47], and the Clinical Global Impression (CGI) Scale [25]. The clinical presentation data (Table 2) correspond to discharge examinations at baseline. At the time of the neuropsychological assessment, all patients were on antipsychotic treatment (92% with an atypical antipsychotic).

Neuropsychological assessment

The cognitive functioning of patients was assessed with a neuropsychological test battery that included computerized measurements of sustained and selective attention, working memory, and executive functioning. In the sustained attention task, the subject was instructed to press the button as quickly as possible when the letter O appeared on the screen. In the working memory task the subject was instructed to respond only when the letter O was preceded by the letter X. For both tasks, the following results were analyzed: mean reaction time for hits, percentage of commissions, and percentage of omissions. Selective attention was evaluated with the Stroop Color-Word Test-Interference (Stroop-I), in which the subject is asked to report when the color of the ink in which the color name is printed do not match each other, causing perceptual interference. The mean time to complete this task and the percentage of errors were recorded. Executive functioning was assessed using the Wisconsin Card Sorting Test (WCST). In this task, 128 cards are presented to the subject, who is asked to sort the cards on the basis of three different categories (color, shape, number) that the subject has to identify, maintain, and change throughout the test. The only feedback provided in this task is whether responses are correct or not. The WCST variables analyzed were number of categories completed (with a maximum of 6) and percentage of perseverative errors.

The tests were always administered by the same experienced clinical psychologist, trained in neuropsychological assessment, who was blind to the smoking status of the patient. Cognitive evaluations were performed during or immediately after discharge, when symptomatology was properly remitted.

Data analysis

Distributions of variables were examined and log-transformations were done in order to correct for skewness, where appropriate. Descriptive data are tabulate as means and standard deviations (SD) or medians and inter-quartile ranges (IQR). Differences in the demographic and clinical characteristics between groups were assessed using Student's *t* tests for the continuous data and chi-square analyses for the nominal data. Differences in cognitive performance between patient groups were analyzed with a full factorial multivariate analysis of covariance (MANCOVA) model, using group (smoker, non-smoker) as fixed factor, neuropsychological test performance scores as dependent variables, diagnosis as the covariate and Bonferroni correction for multiple comparisons. All statistical tests were two-tailed and analyses were performed using SPSS for Windows software, version 11.5.1.

Results

No significant differences were detected between smoking and non-smoking FEP patients with respect to sociodemographic data (Table 1) or clinical features (Table 2). There were no significant differences in distribution of antipsychotic treatment among the groups, $\chi^2(2) = 0.238$, $P = 0.888$. Forty-three percent ($n = 13$) of the non-smoking patients were on olanzapine, 40% ($n = 12$) on risperidone, and 17%

Table 1 Sociodemographic information on non-smoking and smoking first-episode psychosis patients

	Non-smokers ($n = 30$)	Smokers ($n = 31$)	Statistical analysis
Age (range)	27.20 ± 10.89 (17–60)	26.65 ± 9.93 (18–60)	t (59) = 0.208, $P = 0.836$
	n (%)	n (%)	
Gender			
Male	20 (67)	23 (74)	$X^2(1) = 0.415$, $P = 0.519$
Female	10 (33)	8 (26)	
Education (years)			
≤ 5	7 (23)	8 (26)	$\chi^2(3) = 2.464$, $P = 0.482$
6–8	11 (37)	14 (45)	
9–11	10 (33)	9 (29)	
>11	2 (7)	0	
Marital status			
Single	24 (80)	26 (84)	$X^2(2) = 1.064$, $P = 0.587$
Married	5 (17)	5 (16)	
Divorced/separated	1 (3)	0	
Residence			
Alone	1 (3)	4 (13)	$X^2(3) = 2.982$, $P = 0.394$
Couple	4 (14)	5 (16)	
Parents	24 (80)	22 (71)	
Children	1 (3)	0	
Work Status			
Active	9 (30)	14 (45)	$\chi^2(1) = 1.492$, $P = 0.222$
Non-active	21 (70)	17 (55)	

Values for age are mean ± SD

Table 2 Clinical information on non-smoking and smoking first-episode psychosis patients

	Non-smokers*N* (%)	Smokers*N* (%)	Statistical analysis
Diagnoses			$\chi^2(7) = 13.131$, $P = 0.069$
Schizophreniform disorder	13 (43%)	16 (52%)	
Schizoaffective disorder	0	1 (3%)	
Schizotypal disorder	1 (3%)	0	
Delusional disorder	4 (14%)	0	
Brief psychotic disorder	7 (23%)	5 (16%)	
Bipolar disorder	2 (7%)	2 (6.5%)	
Substance induced psychosis	2 (7%)	0	
Atypical psychosis	1 (3%)	7 (22.5%)	
	Median (IQR)	Median (IQR)	
PANSS positive scale	24.5 (19–31)	24 (21–28)	$t(57) = -0.140$, $P = 0.889$
PANSS negative scale	17.5 (11–26)	18 (10–27)	$t(57) = 0.263$, $P = 0.793$
PANSS general scale	45 (37–54)	42 (36–54)	$t(51.28) = -0.723$, $P = 0.473$
MADRS	12.50 (7–25)	13 (9–20)	$t(58) = -0.757$, $P = 0.452$
YMRS	16 (10.5–20)	18 (12–24)	$t(41) = 0.357$, $P = 0.723$
CGI	6 (5–6)	5 (5–6)	$t(56) = -0.734$, $P = 0.466$

IQR Inter-quartile range; *PANSS* Positive and Negative Syndrome Scale; *MADRS* Montgomery-Asberg Depression Rating Scale; *YMRS* Young Mania Rating Scale; *CGI* Clinical Global Impression Scale

($n = 5$) on other antipsychotic treatments. Similarly, 48% ($n = 15$) of the smoking patients were on olanzapine, 39% ($n = 12$) on risperidone, and 13% ($n = 4$) on other antipsychotic treatments.

Neuropsychological data are summarized in Table 3. Smoking patients exhibited shorter reaction times than non-smokers in the sustained attention task, with no differences in the percentage of omission or commission errors. Compared to non-smokers, smokers needed significantly less time to complete the Stroop-I task with no significant differences in the percentage of correct responses. For the working memory task, smokers exhibited shorter reaction times than non-smokers and presented a significantly lower percentage of omission errors, with no differences in the percentage of commission errors. No differences were detected between groups in the number of categories completed or in the percentage of perseverative errors on the WCST.

Discussion

The primary result of this study is the detection of a different cognitive profile for smoking and non-smoking patients with FEP. Those patients who were classified as smokers showed better neuropsychological performance on attention and verbal working memory tasks than non-smoking patients. However, the potential benefits of nicotine on cognition in our sample of smoking patients did not extend to all areas, since no differences in executive functioning were detected between groups. This outcome is in accordance with previous reports in which it has been concluded that nicotine improves performance on specific domains of cognition in schizophrenia patients, with attention and working memory being the most replicated areas [26, 42, 45].

Table 3 Cognitive performance of non-smoking and smoking first-episode psychosis patients

	Non-smokers ($n = 30$)Median (IQR)	Smokers ($n = 31$)Median (IQR)	Statistical analysis
Sustained attention			
Reaction time (s)	0.49 (0.44–0.55)	0.47 (0.43–0.50)	$F(1, 40) = 4.079$, $P = 0.050$
Omissions (%)	2.00 (0.00–7.50)	2.00 (0.00–4.00)	$F(1, 40) = 2.353$, $P = 0.133$
Commissions (%)	0.00 (0.00–1.00)	0.00 (0.00–0.00)	$F(1, 40) = 2.128$, $P = 0.152$
Selective attention			
Stroop-I			
Total time (s)	31.00 (24.00–41.00)	27.00 (22.50–30.00)	$F(1, 40) = 5.196$, $P = 0.028$
Errors (%)	10.00 (0.00–25.00)	10.00 (0.00–20.00)	$F(1, 40) = 0.065$, $P = 0.800$
Working memory			
Reaction time (s)	0.44 (0.37–0.53)	0.37 (0.33–0.45)	$F(1, 40) = 4.167$, $P = 0.048$
Omissions (%)	9.50 (2.00–17.00)	2.00 (0.00–6.00)	$F(1, 40) = 4.476$, $P = 0.041$
Commissions (%)	1.00 (0.00–2.25)	0.00 (0.00–0.67)	$F(1, 40) = 3.369$, $P = 0.074$
Executive functioning			
WCST			
Categories	5.00 (2.00–6.00)	5.00 (3.25–6.00)	$F(1, 40) = 3.452$, $P = 0.071$
% Perseverative errors	16.00 (10.50–26.50)	13.00 (9.75–20.25)	$F(1, 40) = 0.746$, $P = 0.393$

IQR inter-quartile range

The group of smoking patients showed significantly overall lower reaction times on attention and verbal working memory tasks than non-smokers. Results also indicate that the accuracy in the response was not negatively affected by a faster response in the attention tasks, but even accuracy was increased in the verbal working memory test. This pattern indicating beneficial scores with faster perceptual processing speed for those patients who are cigarette smokers in the areas of attention and working memory is supported by recent studies that have described how nicotine withdrawal in smoking schizophrenia patients led to a worsen performance in sustained attention and spatial working memory tasks and how reinstatement reversed abstinence-related impairments in these cognitive domains [42, 45]. Similarly, other studies assessing the cognitive effects of smoking and nicotine administration in schizophrenia patients have reported a nicotine mediated benefit on sustained attention and spatial working memory measures in smoking schizophrenia patients [16, 31, 42]. However, it should be noted that the potential benefits of nicotine on selective attention in psychosis has not been as consistently reported. During short-term/overnight abstinence, no significant changes in Stroop-I performance have been detected [42] and conversely to our results, a previous study comparing smoking ($n = 23$) versus non-smoking ($n = 8$) patients did not find differences in response time in Stroop-I baseline performance between groups [19]. However, this same study supports the idea of this positive influence of nicotine on selective attention, as those patients who quit smoking ($n = 8$) showed an increase in reaction times on the Stroop-I task compared with patients who continued smoking ($n = 15$) in a 3-week follow-up assessment. The fact that nicotine may have a beneficial effect not only on sustained attention but also on selective attention has been described in a healthy non-smoking population and in non-smoking schizophrenia patients after transdermal nicotine administration, with the improvement in scores being greater in the latter group [6].

We did not detect significant differences in performance on the WCST between our smoking and non-smoking FEP patients. In keeping with this result, no previous studies have reported potential nicotine-related benefits to executive functioning in patients with psychosis [42].

The specific differences in the cognitive pattern described between our smoking and non-smoking patients support a possible nicotine mediated enhancement that may affect selectively concrete areas of cognition such as attention and working memory. Additionally, our results offer new evidence that in this last domain, the positive effects of nicotine described in schizophrenia may be not exclusive to visuospatial information processing but also apply to its verbal modality. To our knowledge no previous studies have compared performance on a verbal working memory task between smoking and non-smoking patients. Enhancement of performance on a verbal task similar to the one used in this study has been reported in a healthy non-smoking population and in non-smoking schizophrenia patients after transdermal nicotine administration [6].

Overall, our results support the cognitive approach to the self-medication hypothesis, to explain the high rates of smoking in psychosis patients [48]. Based on the assumption that nicotine administration enhances specific cognitive deficits and on the reported reduction in central nicotinic cholinergic receptors in schizophrenia and its relationship to the cognitive impairment associated with the illness, new pharmacological strategies are being developed for cognitive augmentation. For example, alpha-7 nicotinic acetylcholine receptor agonists appear to be viable candidates for the treatment of cognitive deficits in schizophrenia [33, 42], whereas negative results have been recently reported for the cholinesterase inhibitor donepezil [29].

One limitation of the present study is that it was not designed with an experimental methodology and, therefore, it is not clear if the differences detected are due to nicotine, other components of cigarettes, or the fact of smoking. A second limitation is that, although non-significant differences were detected in the distribution of the type of antipsychotic treatment between groups, we did not control our results for the potential effects of medication and its relationship to the smoking status of the patient. One of the most popular explanations for the high rates of cigarette smoking in schizophrenia has been that patients smoke primarily to reverse the side-effects of the antipsychotic drugs. However, this hypothesis may be controversial considering the following facts: (a) the metabolism of some atypical antipsychotics is not sensitive to the effects of smoking [30], (b) rates of noncompliance with antipsychotic medication have been estimated around 43–78% in chronic patients [40] and up to 59% in first-episode patients after a one-year follow-up [8], (c) first-episode patients present the same prevalence of smoking as chronic patients, [34] and (d) 90% of smoking patients with schizophrenia start smoking before the onset of the illness [30]. On the contrary, there is evidence to support direct beneficial effects of cigarette smoking on cognition in psychosis, independent of its interactions with antipsychotics, as these beneficial effects have been described not only in patients, but also in their first-degree relatives [24]. Deficits in attention and working memory processes have been described in a population at high risk for development of psychosis and are considered to be present in the premorbid phases [7, 10]. Some authors have asserted that neurocognitive deficits may constitute a vulnerability factor for the initiation and maintenance of cigarette smoking in schizophrenia [42], supporting the direct therapeutic effects of nicotine on cognition.

These findings may indicate that it is the illness and not its treatment with antipsychotic drugs that determines the high prevalence of cigarette smoking in psychosis [34].

Conclusion

First-episode psychosis patients who are nicotine users present better cognitive functioning in the areas of attention and working memory than first-episode patients who are not nicotine users. Smoking may constitute a self-medication behavior to enhance neuropsychological dysfunction. This may be relevant to developing new pharmacotherapies for cognitive deficits in psychosis and establishing strategies to reduce cigarette-smoking rates in this population.

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