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ORIGINAL PAPER

Cognitive performance and smoking in first-episode psychosis: the self-medication hypothesis

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Abstract The self-medication hypothesis attempts to explain the extraordinary high levels of cigarette smoking in schizophrenia; patients may smoke in an attempt to reduce their cognitive deficits, symptoms, or the side effects of antipsychotics. In a previous report, we detected beneficial performance in attention and working memory in patients with first-episode psychosis who smoked compared to non-smoking patients soon after stabilization. In the present study, we examine differences in the course of those deficits 12 months after the initiation of antipsychotic treatment. We also explore the association between smoking and symptoms and side effects of medication. Neuropsychological assessments were performed at baseline, month 6 and month 12 using a computerized battery that included measures of sustained attention (Continuous Performance Test CPT-O), selective attention (Stroop interference task) and working memory (CPT-XO). Patients met the criterion of fitting in the same smoking category throughout the study: non-smoker ($n = 15$; 0 cigarettes/day) and smoker ($n = 26$; >15 cigarettes/day). The non-smoking patients showed significant cognitive improvements, whereas smoking patients lost their superior baseline performance, which was probably obtained through nicotinic stimulation, at the 6- and 12-month assessments due to a static course of deficits. Smokers did not obtain any cognitive benefit after instauration of treatment and worsen their symptoms over the first year. These results suggest that smoking may constitute a marker of a more severe illness. Smoking was not associated with fewer extrapyramidal side effects. Smoking might improve attention and working memory to a similarly modest extent as atypical antipsychotics and could reflect an effort to ameliorate these cognitive dysfunctions previous to treatment instauration.

Keywords First-episode psychosis · Cognitive deficits · Cigarette smoking · Nicotine · Self-medication

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Introduction

Patients with psychosis (particularly schizophrenia) present a higher prevalence of cigarette smoking (60–90%) than the general population (25–30%) [16]. This elevated prevalence has been observed in different countries and cultures, leading to the suggestion that a hypothetical

biological factor could make these patients more prone to smoking [12]. The self-medication hypothesis [13, 28 for a review] is a multidimensional attempt to clarify this possible mediating factor. For example, it supports the idea that patients smoke in an attempt to reduce the side effects of antipsychotic medication. Accordingly, smoking patients present lower prevalence and severity of extrapyramidal symptoms with higher doses of antipsychotics than non-smoking patients [13], probably as a result of the increased metabolism of antipsychotic drugs induced by smoking [10, 15]. However, controversy has grown, since negative results for this effect have been obtained for risperidone, quetiapine, ziprasidone and aripiprazole [13]. Treatment itself may not exclusively explain the high prevalence of smoking, which is similar among patients with first-episode psychosis (FEP) and chronic patients [44]. Additionally, 86–90% of smokers initiate the habit before the diagnosis of their illness [8, 27 respectively], and people who are going to develop schizophrenia may present risk factors that make them more vulnerable to start smoking [45]. Therefore, the primary factor mediating the association between smoking and psychosis might be an inherent characteristic of the illness that may be expressed as a premorbid symptom. This may be the case of cognitive deficits, which have been characterized as a core feature of the illness that probably predates its overt manifestation [9].

The cognitive approach to the self-medication hypothesis maintains that patients smoke in an attempt to improve their cognitive deficits. This approach is based on the stimulating effects of nicotine on neural nicotinic acetylcholine receptors (nAChR), whose expression is altered in schizophrenia [33], and their important role for cognitive processes has been underlined [34]. The results of double-blind cross-over placebo-controlled studies in which acute doses of nicotine were administered to non-smoking patients [6, 7, 21, 40] and/or to smoking patients after abstinence [1, 5, 6, 14, 21, 24, 30, 39, 40, 42, 43] show that administration of nicotine transiently reverses neurophysiological alterations related to genetic liability to schizophrenia, such as eye-tracking abnormalities [3, 6, 14, 22, 37, 40] and auditory sensory gating (P50) deficit, both in patients and in their relatives [1, 2, 19, 29]. Nicotine also improves deficits in attention and working memory [7, 14, 21, 24, 30], and reverses abstinence-related impairments in these cognitive domains in smoking patients [5, 20, 42, 43]. Moreover, the ameliorating effect of nicotine on working memory deficits is susceptible to be blocked by the administration of mecamylamine hydrochloride, a nAChR antagonist [39]. However, negative results for the beneficial effects of nicotine on attention and working memory are also found in the literature [21, 36]. Positive effects of nicotine on delayed memory deficits in schizophrenia have also been reported [36, 42], although not without controversy [21, 30, 39, 43], while no positive effects have yet been described for language, constructional abilities [21] or executive function [39].

Another approach to the self-medication hypothesis suggests that schizophrenic patients smoke in an attempt to ameliorate their positive or negative symptoms. However, there is little support for this view, as clinical studies are lacking and the results of available studies are not conclusive [13, 28]. Smoking has also been related to poorer prognosis and outcome, and it has been associated with a more severe form of the illness [4, 28].

Based on these findings, we conducted an observational study to determine the extent of the cognitive benefit, if any, achieved via smoking by comparing the cognitive performance of smoking and non-smoking FEP patients. To our knowledge, no previous studies have assessed this issue. In our baseline report, we found that smoking FEP patients performed better in tasks measuring attention and working memory than non-smoking patients after stabilization [46]. In the present longitudinal report, we followed these patients up in order to determine possible differences in attention and working memory between smoking and non-smoking patients 1 year after the initiation of antipsychotic treatment, by considering that smoking may offer a cognitive benefit in these areas, and that second-generation antipsychotics (SGA) at this early stage [26] may also provide a positive cognitive effect. Our secondary objective was to explore the relationship between smoking and the symptoms and side effects of antipsychotics.

Methods

This article analyses the longitudinal neuropsychological results of our previous baseline sample based on smoking data [46].

Participants

The study population comprised both inpatients and outpatients aged 15–65 years with FEP, which was defined as the presence of at least one of the following symptoms: delusions, hallucinations, formal thought disorder and catatonic symptoms (score greater than or equal to 4 for items 1, 2 or 3 of the Positive and Negative Syndrome Scale [PANSS]). The exclusion criteria included previous hospitalizations or outpatient psychiatric treatment for psychotic symptoms, significant medical or neurological illness, history of head trauma with loss of consciousness, mental retardation, current diagnosis of substance dependence (except tobacco), and participation in a clinical trial.

The institutional review boards of the two participating hospitals approved the study. All patients provided written informed consent. A total of 89 patients were enrolled. Seven patients with FEP were not enrolled due to substance dependence (alcohol, $n = 4$; cannabis, $n = 3$).

Classification of smoking status

Smoking was self-reported in a personal interview. Patients were grouped according to previous classifications [39] as non-smokers (0 cigarettes/day; $n = 35$) or smokers ($\geq$15 cigarettes/day; $n = 43$). Mild or occasional smokers (1–14 cigarettes/day; $n = 11$) were not included due to their low frequency and the large dispersion of the number of cigarettes smoked. Five non-smokers and 6 smokers did not collaborate with the baseline neuropsychological assessment. At 12-months of follow-up, 5 patients were lost and 10 were smoking (6 heavy and 4 mild smokers) in the non-smoking group. In the smoking group, 9 patients were lost, 1 reduced to mild consumption and 1 quitted. If we consider only patients who remained in the same smoking category throughout the study, longitudinal data were available for 26 smoking and 15 non-smoking FEP patients.

Psychiatric assessment

The SCID I [18] was used for diagnostic purposes. FEP was defined as the first time a patient displayed positive psychotic symptoms. Duration of untreated psychosis was calculated as the number of weeks between the first psychotic symptom, and the date antipsychotic treatment was started.

At 12-months of follow-up, the diagnostic distribution for non-smoking patients was as follows: schizophrenia 33% ($n = 5$), schizophreniform disorder 27% ($n = 4$), delusional disorder 13% ($n = 2$), brief psychotic disorder 13% ($n = 2$), atypical psychosis 7% ($n = 1$), and bipolar disorder 7% ($n = 1$) For smoking patients, the distribution was as follows: schizophrenia 31% ($n = 8$), schizophreniform disorder 19% ($n = 5$), delusional disorder 4% ($n = 1$), brief psychotic disorder 11% ($n = 3$), schizoaffective disorder 8% ($n = 2$), atypical psychosis 8% ($n = 2$), bipolar disorder 15% ($n = 4$), and depression with psychotic features 4% ($n = 1$).

The clinical instruments completed were the PANSS [38] and the Montgomery Asberg Depression Rating Scale (MADRS) [35]. The side effects of antipsychotic treatment were assessed using the UKU Side Effect Rating Scale [32] and the Simpson–Angus Neurological Rating Scale [41]. The clinical presentation data correspond to the discharge examination at baseline and assessments at 6 and 12 months of follow-up.

Neuropsychological assessment

Cognitive function was assessed at baseline, 6, and 12 months using a computerized neuropsychological test battery that included measurements of sustained attention (Continuous Performance Test-O/CPT-O), selective attention (Stroop Color-Word Test Interference score/Stroop-I) and working memory (Continuous Performance Test-XO/CPT-XO). The CPT-O and CPT-XO scores analysed were mean reaction time (RT) for hits and percentage of omission errors. For Stroop-I, the mean RT of response and the percentage of errors were analysed.

An experienced clinical neuropsychologist who was blind to the smoking status of the patient administered the tests. At baseline, cognitive evaluations were performed when symptoms remitted, during or immediately after discharge, and approximately 2 months after enrolment in the study. Before the assessment, patients smoked as desired.

Statistical analysis

Because of the small sample sizes, data analysis was performed using non-parametric tests. Descriptive data are tabulated as frequencies or means and standard deviations. Differences in demographic, clinical characteristics and cognitive performance between groups (smokers and non-smokers) were assessed using the Kruskal–Wallis test for continuous data and Fisher's exact test for nominal data. The Wilcoxon test for paired samples was performed to assess within-group differences in cognitive performance and clinical ratings between baseline and the 12-month assessment. Spearman's correlations were performed in order to assess possible associations between cognitive changes and course of symptoms. Both for cognition (all variables) and symptoms (PANSS Negative and PANSS Total), changes in scores were summarized into two variables: mean difference from month 6 to baseline scores and mean difference from month 12 to baseline scores. The Bonferroni correction method was used to address the problem of multiple comparisons. All statistical tests were 2-tailed and analyses were performed using STATA, version 10.1.

Results

Socio-demographic and clinical characteristics

There were no significant differences in socio-demographic or baseline clinical variables between those who completed the 12-month follow-up ($n = 41$) and those who were lost at this assessment point ($n = 14$): age $\chi^2(1) = 1.516$,

$P = 0.218$; gender $P = 0.554$; years of education $\chi^2(4) = 1.933$, $P = 0.748$; working status $P = 0.609$; DUP $\chi^2(1) = 0.617$, $P = 0.432$; PANSS total $\chi^2(1) = 2.876$, $P = 0.090$; MADRS $\chi^2(1) = 1.614$, $P = 0.204$.

Socio-demographic data at baseline and clinical scores at the different assessment points are presented in Table 1 for the 41 patients who completed the study, according to their smoking status. No significant differences were detected between smoking and non-smoking patients in socio-demographic characteristics, severity of symptoms, antipsychotic treatment or side effects at any assessment point. There were no significant differences in the distribution of diagnoses between the groups (Fisher's exact test, $P = 0.914$).

Cognitive performance

The performance profile for attention and working memory in smoking and non-smoking FEP patients is shown in Fig. 1.

Between-group comparisons

Mean cognitive scores for smoking and non-smoking FEP patients at the 3 assessment points are summarized in Table 2. At baseline, smokers showed significantly faster RTs with a lower percentage of errors than non-smokers in the Stroop-I task. They also showed a significantly lower percentage of omission errors in the CPT-XO task. At the 6-month assessment, smokers only maintained faster RTs in the Stroop-I task than non-smokers, while at 12 months, no cognitive differences were detected between the groups.

Within-group comparisons

Mean differences in cognitive scores from baseline to 12 months and intra-group analyses are presented in Table 2. For the smoking group, no significant differences were detected in any cognitive variable between baseline and the 12 months. At 12 months, the non-smoking group showed the following significant improvements: faster mean RT and lower percentage of omission errors in the CPT-O task, lower percentage of errors in the Stroop-I task, and lower percentage of omission errors in the CPT-XO task.

Course of symptoms

Although no overall differences between the two groups across time points in PANSS total score or MADRS score were detected, intra-group analysis revealed that smokers significantly increased their total PANSS score at 12 months of follow-up (mean difference -10.44 ± 21.65; $Z = -2.005$, $P = 0.045$), while no differences were detected for non-smokers (mean difference -0.86 ± 21.60; $Z = -0.503$, $P = 0.615$). Scores for individual symptom dimensions in smokers only reached significance in the negative subscale (mean difference -3.52 ± 7.38; $Z = -2.020$, $P = 0.043$), with no significant differences for the positive or general subscales (mean difference -2.96 ± 7.57; $Z = -1.593$, $P = 0.111$; mean difference -3.96 ± 10.83; $Z = -1.455$, $P = 0.146$, respectively). No significant intra-group differences were detected for MADRS in any group (smokers [mean difference 0.77 ± 9.74; $Z = 0.661$, $P = 0.509$]; non-smokers [mean difference 2.07 ± 6.27; $Z = 1.568$, $P = 0.117$]).

Associations between cognitive performance and course of symptoms

Considering the differential course of symptoms over time in the two groups for PANSS total and PANSS negative subscales, we performed further analysis in order to consider possible associations between course of symptoms and cognitive performance. No significant correlations were detected for changes from month 6 to baseline or from month 12 to baseline between clinical (PANSS total and negative subscales) and cognitive scores.

Discussion

Our results suggest that patients with FEP had a differential pattern of change in cognitive performance according to their smoking status during the first year of antipsychotic treatment. While smokers obtained higher scores in attention and working memory tasks after the first stabilization that remained static, non-smokers demonstrated significant gains during the same period. After 1 year of treatment, performance in attention and working memory was equivalent between the groups.

Superior performance in attention and working memory tasks is observed for smokers soon after the first stabilization

According to our previous baseline analysis of the sample [46], cognitive performance was better in patients with FEP who smoked than in non-smoking patients in selective attention and working memory after the first stabilization. To our knowledge, no previous studies have assessed possible differences between smokers and non-smokers in cognitive performance at this early stage of illness. However, this result is consistent with the overall suggestion that the main effect of stimulation of the nAChR system in schizophrenic

Table 1 Socio-demographic and clinical information of non-smoking and smoking first-episode psychosis patients

	Non-smokers ($n = 15$)	Smokers ($n = 26$)	Statistical analysis
Age (range)	32.53 ± 13.11 (17–60)	25.08 ± 6.22 (18–39)	$\chi^2(1) = 3.024$, $P = 0.082$
Gender			
Male	9 (60%)	19 (73%)	$P = 0.492$
Female	6 (40%)	7 (27%)	
Education (years)			
≤5	3 (20%)	5 (19%)	$P = 0.222$
6–8	5 (33%)	13 (50%)	
9–11	5 (33%)	8 (31%)	
>11	2 (14%)	0	
Work status			
Active	4 (27%)	11 (42%)	$P = 0.502$
Non-active	11 (73%)	15 (58%)	
DUP (weeks) (range)	75.22 ± 94.68 (0.14–332.57)	106.47 ± 156.43 (0.71–536.29)	$\chi^2(1) = 0.103$, $P = 0.748$
PANSS total			
Baseline	54.53 ± 20.63	54.40 ± 13.54	$\chi^2(1) = 0.200$, $P = 0.655$
6 months	57.50 ± 21.72	61.50 ± 21.66	$\chi^2(1) = 0.443$, $P = 0.506$
12 months	55.50 ± 23.75	66.12 ± 21.61	$\chi^2(1) = 1.421$, $P = 0.233$
MADRS			
Baseline	7.53 ± 5.72	8.65 ± 5.65	$\chi^2(1) = 0.342$, $P = 0.559$
6 months	9.71 ± 7.94	8.64 ± 7.99	$\chi^2(1) = 0.327$, $P = 0.567$
12 Months	5.47 ± 6.79	8.58 ± 7.82	$\chi^2(1) = 1.871$, $P = 0.171$
Simpson–Angus			
Baseline	1.40 ± 2.56	1.08 ± 2.45	$P = 0.860$
6 months	2.14 ± 3.13	1.83 ± 3.43	$P = 0.227$
12 months	2.20 ± 3.32	2.12 ± 3.47	$P = 0.129$
UKU			
Baseline	0.67 ± 0.82	0.62 ± 1.02	$P = 0.228$
6 months	0.71 ± 0.91	0.61 ± 0.99	$P = 0.730$
12 months	0.80 ± 1.08	1.23 ± 2.47	$P = 0.882$
Antipsychotic treatment			
Baseline			
Olanzapine	7 (47%)	11 (42.5%)	$P = 0.834$
Risperidone	5 (33%)	11 (42.5%)	
Others	3 (20%)	4 (15%)	
6 months			
Olanzapine	8 (53%)	8 (31%)	$P = 0.536$
Risperidone	3 (20%)	10 (38%)	
Others	1 (7%)	3 (12%)	
Free	3 (20%)	5 (19%)	
12 months			
Olanzapine	8 (53%)	9 (35%)	$P = 0.611$
Risperidone	3 (20%)	10 (38%)	
Others	2 (13.5%)	3 (12%)	
Free	2 (13.5%)	4 (15%)	

Data reported as means ± standard deviations or frequencies

DUP duration of untreated psychosis, *PANSS* Positive and Negative Syndrome Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *Simpson–Angus* the Simpson-Angus Neurological Rating Scale, *UKU* the UKU Side Effect Rating Scale

patients is an improvement in impulsivity and inhibitory dysfunction [7, 14, 21, 39, 43]. Consequently, the superior performance we observed in working memory processes among smokers could be associated with an improvement in the selectivity of perceptual processing, a process on which selective attention is based [24].

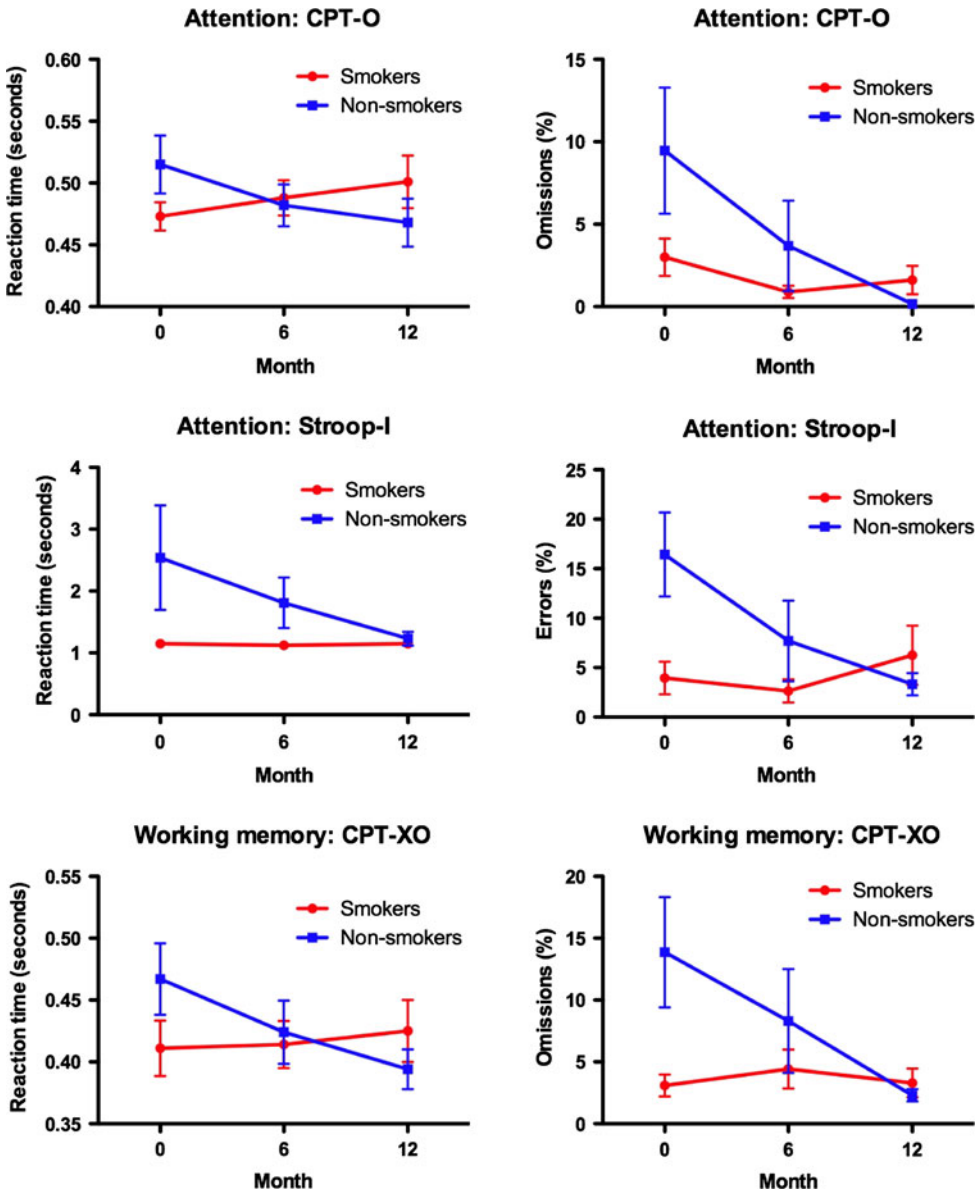

Fig. 1 Course of cognitive performance for non-smoking and smoking first-episode psychosis patients. *Bars* indicate mean and standard deviation. Same sizes for each group at the different assessment points as reported in Table 2

The beneficial cognitive performance for smokers is no longer observed at 6 and 12 months

After 6 months initiation of antipsychotic treatment, baseline differences in selective attention and working memory parameters were no longer significant between smokers and non-smokers, with the exception of Stroop-I mean RT. After 1 year, performance was similar between the groups. One possible explanation for this finding would be that non-smokers obtain more benefit from practice effects, since they start with a more disadvantageous performance than smokers. Recent clinical trials have pointed out that lower (worse) baseline composite scores predict greater cognitive improvement [11, 25]. Improvements in non-smokers might be also explained by the therapeutic effects of SGA on cognition, which have been reported to occur in patients with FEP. Olanzapine and risperidone (primary treatments prescribed to our patients) have been reported to provide a modest cognitive improvement during the early phase [26]. This may have led non-smokers to achieve the superior baseline cognitive performance of smokers, which was probably obtained through nicotinic stimulation. Therefore, it could be interpreted in support to the self-medication hypothesis that nicotine use leads to a cognitive benefit also achievable from antipsychotic medication during the early course of the illness (6–12 months). The loss of differences between groups from baseline to the 12-month assessment stresses the relevance of timing when comparing cognitive performance between smoking and non-smoking patients [20].

Table 2 Cognitive performance for non-smoking and smoking first-episode psychosis patients: between-group comparisons for each assessment point and intra-groups differences over a 1-year follow-up

Cognitive tests	Non-smokers Mean ± SD (*n*)	Smokers Mean ± SD (*n*)	Between groups Kruskal–Wallis	Intra-group Non-smokers Mean difference ± SD Wilcoxon	Intra-group Smokers Mean difference ± SD Wilcoxon
CPT-O—Reaction time (s)					
Baseline	0.515 ± 0.091 (15)	0.473 ± 0.056 (24)	$\chi^2(1) = 0.805$, $P = 0.369$	0.032 ± 0.067	−0.033 ± 0.113
6 months	0.468 ± 0.067 (12)	0.501 ± 0.097 (21)	$\chi^2(1) = 0.009$, $P = 0.926$	$Z = 2.200$, $P = 0.028$	$Z = -0.131$, $P = 0.896$
12 months	0.482 ± 0.061 (13)	0.488 ± 0.064 (20)	$\chi^2(1) = 0.990$, $P = 0.320$		
CPT-O—Omissions (%)					
Baseline	9.47 ± 14.82 (15)	3 ± 5.56 (24)	$\chi^2(1) = 0.973$, $P = 0.324$	5.5 ± 10.31	0.8 ± 6.3
6 months	0.17 ± 0.58 (12)	1.62 ± 3.93 (21)	$\chi^2(1) = 0.101$, $P = 0.751$	$Z = 2.412$, $P = 0.016$	$Z = 0.885$, $P = 0.376$
12 months	3.69 ± 9.89 (13)	0.9 ± 1.65 (20)	$\chi^2(1) = 3.424$, $P = 0.064$		
Stroop-I—Reaction time (s)					
Baseline	2.54 ± 3.16 (14)	1.15 ± 0.25 (19)	$\chi^2(1) = 4.708$, $P = 0.030$	0.35 ± 0.78	−0.03 ± 0.39
6 months	1.23 ± 0.39 (12)	1.15 ± 0.26 (20)	$\chi^2(1) = 4.116$, $P = 0.043$	$Z = 1.160$, $P = 0.246$	$Z = -0.158$, $P = 0.874$
12 months	1.81 ± 1.47 (13)	1.12 ± 0.25 (19)	$\chi^2(1) = 0.173$, $P = 0.678$		
Stroop-I—Errors (%)					
Baseline	16.43 ± 15.86 (14)	3.95 ± 7.18 (19)	$\chi^2(1) = 7.370$, $P = 0.007$	10.45 ± 14.22	−3.21 ± 14.62
6 months	3.33 ± 3.89 (12)	6.25 ± 13.36 (20)	$\chi^2(1) = 2.798$, $P = 0.094$	$Z = 2.196$, $P = 0.028$	$Z = -0.915$, $P = 0.360$
12 months	7.69 ± 14.67 (13)	2.63 ± 5.10 (19)	$\chi^2(1) = 0.121$, $P = 0.728$		
CPT-XO—Reaction time (s)					
Baseline	0.467 ± 0.112 (15)	0.411 ± 0.105 (22)	$\chi^2(1) = 2.401$, $P = 0.121$	0.053 ± 0.086	−0.028 ± 0.100
6 months	0.394 ± 0.056 (12)	0.425 ± 0.112 (20)	$\chi^2(1) = 0.030$, $P = 0.863$	$Z = 1.766$, $P = 0.077$	$Z = 0.538$, $P = 0.538$
12 months	0.423 ± 0.092 (13)	0.414 ± 0.083 (19)	$\chi^2(1) = 0.003$, $P = 0.953$		
CPT-XO—Omissions (%)					
Baseline	13.87 ± 17.25 (15)	3.09 ± 4.13 (22)	$\chi^2(1) = 5.868$, $P = 0.015$	9.67 ± 16.10	0.59 ± 6.25
6 months	2.33 ± 1.72 (12)	3.3 ± 5.15 (20)	$\chi^2(1) = 0.131$, $P = 0.717$	$Z = 2.484$, $P = 0.013$	$Z = -0.072$, $P = 0.943$
12 months	8.31 ± 15.15 (13)	4.42 ± 6.85 (19)	$\chi^2(1) = 0.197$, $P = 0.657$		

Smoking as a marker of more severe illness

Smokers did not show any cognitive response to SGA, with no synergic effects observed for nicotine and antipsychotics. Although the pharmacodynamics of nicotine and antipsychotics are not the same, SGA have been reported to modulate cholinergic neurotransmission [23]. One possible explanation for the lack of an additional cognitive benefit in smokers is a possible ceiling effect of the agonist activity that may be obtained through smoking and/or SGA. We might also consider the possibility of an aetiologically differentiated system with more marked alterations among smokers, which might prevent smokers from benefitting from practice effects. Some authors have suggested that smoking may be a marker of more severe illness and/or of its neurodevelopmental phenotype [4, 28]. Although our results indicate that the initial clinical presentation is the same between groups, our finding that negative symptoms worsen significantly in smokers supports the notion of a more severe illness. The clinical data obtained are also consistent with the hypothesis that smoking, considered as a self-medication behaviour, is not necessarily associated with fewer symptoms [13].

Smoking, antipsychotic medication, and side effects

Our results do not support that patients with FEP smoke in an attempt to reduce the side effects of antipsychotic drugs; smokers did not show fewer extrapyramidal side effects than non-smokers. In fact, the relationship between medication and smoking appears to be specific for the antipsychotic drug prescribed; whereas smoking increases cytochrome P450 1A2 activity and diminishes plasma olanzapine concentrations [10], this effect has not been described for risperidone [13]. Consequently, we cannot rule out possible differential interactions between smoking and antipsychotic treatment. We conducted exploratory comparisons between smokers on olanzapine ($n = 9$) and risperidone ($n = 10$) for possible differences in clinical characteristics and extrapyramidal side effects at 12 months.

There were no significant differences according to PANSS Total ($\chi^2(1) = 0.276$, $P = 0.5990$), MADRS ($\chi^2(1) = 1.128$, $P = 0.2882$), Simpson–Angus (Fisher's exact $P = 0.474$) or UKU (Fisher's exact $P = 0.628$).

Limitations of the study

The principal limitation of this study is that the sample size is too small to apply a parametric test to establish a possible interaction between smoking and cognitive change over time. We were also unable to normalize some outcome variables and to obtain balanced treatment groups. Therefore, the results presented should be considered as preliminary data. Due to a reduction in the sample size in relation to our previous report, resulting from the double requirement of having to complete 12 months of follow-up and remain in the same smoking category, we were not able to replicate significant baseline differences in the mean RT for the sustained attention and working memory tasks between groups [46]. The small sample size also limits the power to analyse possible differences between smokers on different SGA. Although exploratory analyses revealed similarities in clinical variables and extrapyramidal side effects between smokers on olanzapine and risperidone, and similarities in the course of cognitive performance between these two groups of smokers (data not shown), the reliability of these comparisons is limited.

The study is also limited by the lack of data on mean duration of antipsychotic treatment at the baseline neuropsychological assessment. Nevertheless, the protocol stipulates that evaluations are to be performed 2 months after enrolment and prescription of treatment, and the cognitive effects of antipsychotics have been described 12 weeks after initiation [26]. If medication affects our baseline results, it would be in the direction of masking more marked differences between groups, as non-smokers would be benefiting from the modest cognitive effects of antipsychotics, even at the first assessment. Also it should be considered that nicotine administration has been associated with considerable inter-individual response variability [17]. However, this is a naturalistic study where measurement of this complex factor is beyond its scope. Finally, the absence of a healthy control group limits the possibility of monitoring the results for practice effects. Although our results support the cognitive approach to the self-medication hypothesis, this is specific for attention and working memory processes. As no other cognitive domains have been assessed in this study, we cannot generalize about the positive effects of nicotine consumption on cognition.

Summary

The possible positive cognitive effects on attention and working memory processes that are probably derived from smoking in FEP seem to be similar to the modest therapeutic cognitive effects of SGA early in the course of this illness. This result offers new support to the cognitive approach to the self-medication hypothesis, and new evidence that may help explain the high prevalence of smoking in individuals even before they develop psychosis. For them, smoking may reflect self-medication behaviour during the premorbid stage, which might be providing a similar effect to that observed in non-smoking patients after initiation of treatment with SGA.

Greater understanding of the role of smoking in psychosis will contribute to the development of new approaches to treatment for cognitive deficits in these patients based on nicotinic receptor mechanisms. These mechanisms have been identified as a therapeutic target by MATRICS, and although different trials are being performed, the results are not yet conclusive [31].

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Conflict of interest None.

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