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Neuropsychological performance in patients with schizophrenia and controls as a function of cigarette smoking status

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ABSTRACT

Schizophrenia is associated with many neurocognitive deficits, some of which are improved by nicotine and cigarette smoking. To better understand the relationship between smoking and cognitive function in schizophrenia, cross-sectional assessment of neuropsychological performance as a function of smoking status (smoker or non-smoker) and smoking history (current, former or never-smoker) in clinically stable outpatients with schizophrenia and controls was evaluated. Subjects ($n=140$) were divided into subgroups on the basis of self-report and biochemical verification of smoking history. Current smokers with schizophrenia ($n=38$), former smokers with schizophrenia ($n=17$), never-smokers with schizophrenia ($n=12$), control smokers ($n=31$), control former smokers ($n=16$), and control never-smokers ($n=26$) were administered a comprehensive neuropsychological battery. Smokers were studied under non-deprivation conditions. Comparison of neuropsychological performance in schizophrenia and control subjects revealed significant main effects of diagnosis. Analysis of the data as a function of smoking history demonstrated that never-smokers with schizophrenia performed the poorest on measures of sustained attention, processing speed and response inhibition, when compared to the other schizophrenia subgroups. Cigarette smoking did not alter neuropsychological performance in controls. Our findings suggest that smoking status and history differentially alters neuropsychological outcomes in schizophrenia compared to non-psychiatric controls, and that never-smokers may present with more severe neurocognitive impairments.

1. Introduction

It has been suggested that the higher rates of tobacco smoking in schizophrenia compared to the general population may relate, at least in part, to pro-cognitive effects of nicotine (Adler et al., 1993; Levin et al., 1996; Dalack et al., 1998; Depatie et al., 2002; George et al., 2002b; Smith et al., 2002; Sacco et al., 2005; Smith et al., 2006; Barr et al., 2008). In fact, patients with schizophrenia may selectively derive cognitive enhancement by cigarette smoking in the areas of attention, working memory and information processing (Adler et al., 1993; Sacco et al., 2005). Such putative amelioration of neurocognitive deficits associated with schizophrenia may also contribute to the reduced likelihood of smoking cessation in this population which has been observed both in epidemiological (Lasser et al., 2000; Etter et al., 2004) and clinical studies (Addington et al., 1998; George et al., 2000; Evins et al., 2001; George et al., 2002a; Dolan et al., 2004; Evins et al., 2005; Culhane et al., 2008; Moss et al., 2009). However, little is known about the effects of smoking status on neurocognitive deficits in schizophrenia, or of clinical characteristics that may differ between smokers and non-smokers with schizophrenia.

Neurocognitive deficits are a core feature of schizophrenia (Park and Holzman, 1992; Keefe et al., 1995) but since it is estimated from clinical samples that approximately 58–88% of patients with schizophrenia are smokers (Ziedonis and Williams, 2003; Kalman et al., 2005), the nature of the cognitive deficits which exist in non-smoking patients with this disorder is unclear. Preliminary data suggests that visuospatial working memory is worse in non-smokers with schizophrenia compared to smokers with schizophrenia but this effect did not reach statistical significance as the sample sizes were low ($n=8$ and $n=23$, respectively) (George et al., 2002b). In addition, the classification of a non-smoking sample into never- and former smokers, in comparison to current smokers, would facilitate the parsing of state- versus trait-dependent effects, which may be of particular relevance to the neurocognitive endophenotypes associated with schizophrenia, as well as their relationships to treatment outcomes.

Accordingly, baseline data from studies examining the effect of smoking on cognitive function in schizophrenia was used to compare the effects of smoking status on neuropsychological performance in schizophrenia in comparison to controls without a psychiatric illness.

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Current (non-deprived), former (quit for at least 6 months) and never- (less than 100 cigarettes in lifetime (Hughes et al., 2000)) smokers were studied using a comprehensive battery of neuropsychological tests.

2. Methods

2.1. Subjects

The majority of the data (~70% of sample) were derived from a study of the effects of cigarette smoking on cognitive function in schizophrenia, and the role of nicotinic acetylcholine receptors, conducted at Yale University (Sacco et al., 2005; Sacco et al., 2006); the remainder of the data (~30% of the sample) were derived from a cross-sectional study of cognitive function in smokers and non-smokers with schizophrenia at the Centre for Addiction and Mental Health (CAMH), Toronto. Patients with schizophrenia were recruited from clinician referrals and flyers; controls were recruited from the community using newspaper and internet advertisements. Written informed consent was obtained from all subjects seeking participation as approved by the Human Investigation Committee at Yale University and the CAMH Research Ethics Board. All subjects were screened by trained staff members using the Structured Clinical Interview for DSM-IV (SCID) for Axis I disorders (First, 1994). Subjects with schizophrenia or schizoaffective disorder were outpatients at the time of the interview, judged to be psychiatrically stable, scored <70 on the PANSS (Kay et al., 1987) and were on a stable dose of antipsychotic medication for at least three months prior to study enrollment. Control (CON) subjects did not meet criteria for any current Axis I disorder on the SCID. Participants who met SCID criteria for alcohol or substance abuse or dependence in the last 3 months, other than nicotine dependence for those assigned to the current smoker groups, were not enrolled. All enrolled subjects tested negative for illicit substances using urine toxicology (Medtox®; Wilmington, NC) and were not using nicotine replacement therapy.

Subjects ($n=140$) were divided into six groups: current smokers with schizophrenia ($n=38$), former smokers with schizophrenia ($n=17$), never-smokers with schizophrenia ($n=12$), control smokers ($n=31$), control former smokers ($n=16$) and control never-smokers ($n=26$). Smokers reported smoking ≥10 cigarettes per day, had expired breath carbon monoxide (CO) levels >10 ppm, and scored ≥5 on the Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton et al., 1991; Weinberger et al., 2007). Non-smoking participants were either never-smokers, reporting smoking fewer than 100 cigarettes in their lifetime (Hughes et al., 2000), or former smokers who had quit smoking at least 6 months prior to participation in this study. Non-smoking status was established by self-report, and biochemically verified by expired breath CO levels less than 10 ppm.

2.2. Study design

Data from participants were derived from a single baseline neuropsychological assessment. To minimize tobacco deprivation, all smoking subjects were given frequent smoke breaks, to ensure that deprivation from cigarette smoking did not exceed 30 min. Details of the neuropsychological test battery have been previously described (Sacco et al., 2005), but are given briefly in the sections below. The battery of neuropsychological tasks took approximately 2.5–3.0 h to complete.

2.3. Neuropsychological tests

2.3.1. Conners' Continuous Performance Test (CPT)

The Conners' CPT-X is designed to measure sustained attention, concentration, response inhibition and impulsivity (Connors, 1995). Subjects press the space bar as quickly as possible after each of a series of similar visual stimuli except when presented with the letter "X". Commonly reported outcome measures include: percentage of hits, percentage of commission errors, reaction time for hits (in milliseconds), a measure of overall attentiveness (d'), and hit rate reaction time standard error variability. Schizophrenia is associated with attention and response inhibition deficits when compared to non-psychiatric population (Cornblatt and Keilp, 1994; Enticott et al., 2008).

2.3.2. Stroop Color Word Test (SCWT)

The SCWT measures participants' ability to shift their perceptual set to conform to changing conditions requiring mental control, response inhibition, response flexibility and selective attention with the occurrence of perceptual interference (Stroop, 1935). Participants report the color of the ink in which the names of colors are printed. The difference in response time (milliseconds) when the ink is a different color than the color name compared to a response time when the ink is the color named, is called "Stroop Interference" (SI). Facilitation occurs when the word is the same as the print color. Other common outcome measurements are neutral, congruent, and incongruent reaction times. Performance of the SCWT is known to activate the anterior cingulate cortex (Peterson et al., 1999; Swick and Jovanovic, 2002). SI is impaired in many neuropsychiatric disorders including schizophrenia (Hepp et al., 1996; Henik and Salo, 2004).

2.3.3. Wisconsin Card Sorting Test (WCST)

Participants were administered the computerized WCST (Heaton et al., 1993). The WCST assesses executive functions including cognitive flexibility in response to feedback which is thought to relate to dorsolateral prefrontal cortex function (Goldberg and Weinberger, 1988). A total of 128 cards are presented and the test requires participants to sort the cards on the basis of the color, shape, or number of figures. The only feedback provided to the subject is whether responses are correct or incorrect. Common outcome measures are categories completed, % total errors, % perseverative errors and % non-perseverative errors. Performance on this task is known to be impaired in schizophrenia (Berman et al., 1986).

2.4. Statistical analysis

There were three primary experimental questions: 1) Are there baseline differences in demographic and clinical features between current, former and never-smokers in the schizophrenia or control groups? We used 2 (diagnosis) × 3 (smoking history i.e., current, former and never-smokers) ANOVAs and Chi square tests to analyze data across all study groups, and one-way ANOVA and Chi square within diagnostic groups. 2) Are there differences between smoking and non-smoking (combination of former and never-smokers) schizophrenia or control subjects on neuropsychological outcome measures? 2 (diagnosis) × 2 (smoking status i.e., smoker versus nonsmoker) were used to analyze data across these groups, and independent samples *t*-tests were used to look for effects of smoking status within each diagnostic group. 3) Are there differences amongst current, former and never-smokers in each diagnostic group on neuropsychological outcomes? 2 (diagnosis) × 3 (smoking history i.e., current, former and never-smokers) ANOVAs were performed to examine interactive effects of these two between-subject factors. One-way ANOVAs followed by Bonferroni post hoc tests corrected for multiple comparisons were conducted to identify differences between smoking histories within each diagnostic group. ANCOVAs were employed to control for differences in IQ across smoking subgroups. All statistical analyses were conducted using SPSS version 15.0 and statistical significance was set at $p<0.05$.

3. Results

3.1. Demographic and clinical characteristics

The clinical and demographic variables of the schizophrenia and control current, former and never-smoker subgroups are shown in Table 1. The six groups were similar in terms of sex but there were significant differences in race within the smoking history subgroups ($p=0.04$). There was a significant difference in age in the control, but not schizophrenia, subgroups ($p<0.01$); never-smokers were significantly younger than former and current smokers ($ps<0.05$). One-way ANOVAs found differences in IQ across smoking history subgroups in both the schizophrenia ($p=0.01$) and control ($p<0.01$) groups; IQ scores in the control current smoker control were significantly lower than the never-smoker control group and in the schizophrenia participants current smokers had a significantly lower IQ than the former smokers ($ps<0.01$). Years of education did not differ across the schizophrenia groups but did in the control group ($p<0.01$); control current smokers had significantly less years of education than control former smokers ($p<0.01$).

Smoking measures including cigarettes per day, expired breath CO and level of nicotine dependence measured by FTND scores did not significantly differ between schizophrenia and control smokers. Current, former and never-smokers in the schizophrenia group demonstrated similar levels of clinical symptoms as measured by the PANSS and among the subgroups there were no significant differences in the proportion of subjects with schizophrenia versus schizoaffective disorder.

3.2. Comparison of neuropsychological performance in schizophrenia and control groups as a function of current smoking status

We compared neuropsychological task performance in control smokers ($n=31$), control nonsmokers ($n=42$), smokers with schizophrenia ($n=38$) and nonsmokers with schizophrenia ($n=29$). The data were analyzed using a two-way ANOVA for diagnosis and current smoking status. There was a main effect of diagnosis on most neuropsychological measures with poorer performance in the schizophrenia group compared controls on CPT Hit Rate (%), Hit Rate Reaction

Table 1
Demographic and clinical data of current, former, and never-smokers as a function of psychiatric diagnosis.

	SZ current smokers ($n=38$)	SZ former smokers ($n=17$)	SZ never-smokers ($n=12$)	Smoking history effect[a]		CON current smokers ($n=31$)	CON former smokers ($n=16$)	CON never-smokers ($n=26$)	Smoking history effect[a]		Diagnosis effect[a]		Smoking history effect[a]		Diagnosis × smoking interaction[a]	
				F or χ^2 (d.f.)	p				F or χ^2 (d.f.)	p	F, χ^2 or t (d.f.)	p	F or χ^2 (d.f.)	p	F (d.f.)	p
Age	41.9 ± 9.4	42.6 ± 10.2	42.5 ± 9.1	0.03 (2,63)	0.97	42.2 ± 9.8	45.7 ± 12.9	34.0 ± 12.7[c,d]	5.8 (2,67)	<0.01	0.7 (1,130)	0.40	2.6 (2,130)	0.08	2.7 (2,130)	0.07
Sex																
Male	24	9	8	0.7 (2)	0.70	14	7	15	1.1 (2)	0.56	2.0 (1)	0.16	1.0 (2)	0.60	-	-
Female	14	8	4			17	9	11								
Race																
Caucasian	19	14	6	6.8 (6)	0.34	21	14	14	8.7 (6)	0.19	8.0 (3)	0.11	13.2 (6)	0.04	-	-
African-American	14	3	5			7	1	4								
Hispanic	2	0	0			1	0	2								
Other	3	0	1			2	1	6								
Education (years)	12.2 ± 2.6	13.6 ± 4.3	12.8 ± 1.9	1.1 (2,63)	0.33	14.0 ± 0.5[d]	16.4 ± 0.6	15.7 ± 0.5	5.2 (2,69)	<0.01	23.1 (1,132)	<0.01	5.2 (2,132)	0.01	0.6 (2,132)	0.56
Estimated IQ	85.4 ± 12.12[b]	99.8 ± 13.4	91.0 ± 12.2	7.6 (2,61)	<0.01	99.6 ± 13.0[e]	105.7 ± 13.7	111.7 ± 6.8	7.6 (2,65)	<0.01	37.3 (1,126)	<0.01	10.3 (2,126)	0.01	3.1 (2,136)	0.05
Cigarettes per day	20.7 ± 10.5	–	–	–	–	17.7 ± 7.6	–	–	–	–	1.3 (62)	0.20	–	–	–	–
Expired CO (ppm)	25.5 ± 12.6	1.6 ± 1.6	1.2 ± 0.8	–	–	20.2 ± 7.8	0.9 ± 1.0	0.8 ± 0.8	–	–	2.0 (67)	0.05	–	–	–	–
FTND	6.8 ± 1.4	–	–	–	–	7.1 ± 2.0	–	–	–	–	0.5 (27)	0.61	–	–	–	
PANSS positive	13.4 ± 2.7	13.6 ± 3.1	13.9 ± 2.4	0.3 (2,64)	0.74	–	–	–	–	–		–	–	–	–	–
PANSS negative	14.0 ± 3.1	14.2 ± 2.9	13.9 ± 2.2	.05 (2,64)	0.95	–	–	–	–	–		–	–	–	–	–
PANSS general	26.7 ± 5.4	29.8 ± 4.7	27.7 ± 2.1	2.7 (2,64)	0.07	–	–	–	–	–		–	–	–	–	–
PANSS Total	54.1 ± 9.1	57.6 ± 9.4	55.2 ± 3.7	1.2 (2,64)	0.30	–	–	–	–	–		–	–	–	–	–
Diagnosis																
Schizophrenia	26	8	5	3.2 (2)	0.20	–	–	–	–	–		–	–	–	–	–
Schizoaffective	12	9	6													

Abbreviations: CO, carbon monoxide; FTND, Fagerstrom Test of Nicotine Dependence; PANSS, Positive and Negative Syndrome Scale; SZ, schizophrenia; CON, control.
Significant differences in performance compared to other subgroups (Bonferroni post hoc tests corrected for multiple comparisons, $p<0.05$) are represented by: [b] compared to the SZ former smokers; [c] compared to the CON current smokers; [d] compared to CON former smokers; [e] compared to CON never-smokers.
[a] Analysis of variance, independent t-tests and Chi-square tests were used for continuous and categorical data respectively.

Time and Variability Index; SCWT reactions times in the incongruent, congruent and neutral conditions; and errors, perseverative errors, nonperseverative responses and categories completed on the WCST ($ps \leq 0.03$). Smoking main effects and the diagnosis × smoking status interactions were non-significant.

t-Tests were conducted to compare smokers and non-smokers within the psychiatric groups. Within the patients with schizophrenia, non-smokers had significantly slower SCWT reaction times in the Congruent condition ($t(38) = 2.24$, $p = 0.03$). No significant differences were found between control smokers and non-smokers.

3.3. Comparison of neuropsychological performance in schizophrenia and control groups as a function of smoking history

We compared neuropsychological task performance in control current smokers ($n = 31$), control former smokers ($n = 16$), control never-smokers ($n = 26$), smokers with schizophrenia ($n = 38$), former smokers with schizophrenia ($n = 27$) and never-smokers with schizophrenia ($n = 12$) (Table 2). The data were analyzed using a two-way ANOVA for diagnosis and smoking history. Performance was significantly impaired in the schizophrenia participants on the majority of measures compared to controls: CPT Hit Rate ($F(1,134) = 12.0$, $p = 0.001$), Commission Rate ($F(1,134) = 4.94$, $p = 0.028$), Hit Rate Reaction Time ($F(1,134) = 8.35$, $p = 0.005$) and Variability Index ($F(1,134) = 17.8$, $p < 0.001$); SCWT reaction times in the incongruent ($F(1,80) = 5.39$, $p = 0.023$), congruent ($F(1,80) = 14.8$, $p < 0.001$), and neutral conditions ($F(2,80) = 9.16$, $p = 0.003$); WCST errors ($F(1,129) = 6.13$, $p = 0.015$), perseverative errors ($F(1,129) = 4.20$, $p = 0.042$), nonperseverative responses ($F(1,129) = 5.43$, $p = 0.021$) and categories completed ($F(1,129) = 6.44$, $p = 0.012$). A significant effect of smoking history was observed on SCWT reaction times in the Incongruent ($F(2,80) = 3.27$, $p = 0.043$), Congruent ($F(2,80) = 5.44$, $p = 0.006$) and Neutral ($F(2,80) = 5.14$, $p = 0.008$) conditions. A significant interaction between smoking history and diagnosis was found on CPT Hit Rate ($F(2,134) = 6.30$, $p = 0.002$), Commission Rate ($F(2,134) = 3.42$, $p = 0.036$), Variability Index ($F(2,134) = 3.71$, $p = 0.045$) and Attentional Index ($F(2,134) = 4.95$, $p = 0.008$); and SCWT reaction times in the Incongruent ($F(2,80) = 3.51$, $p = 0.035$) and Congruent ($F(2,80) = 6.52$, $p = 0.002$) conditions.

Inspection of Table 2 suggests that in general task performance in patients with schizophrenia was the most impaired in the never-smoker group compared to former and current smokers. However, one-way ANOVAs for the effect of smoking history on performance in the schizophrenia participants, only identified significant effects on measures of sustained attention (CPT Hit Rate: $F(2,66) = 3.76$, $p = 0.03$), processing speed (SCWT Congruent: $F(2,39) = 9.04$, $p = 0.001$; SCWT Neutral: $F(2,39) = 8.92$, $p = 0.001$) and response inhibition (SCWT Incongruent condition: $F(2,39) = 4.69$, $p = 0.02$). Bonferroni post hoc comparisons (with $\alpha = 0.0167$ to correct for multiple comparisons) revealed that never-smokers had poorer performance than both current and former smokers on SCWT reaction times in the Neutral ($ps < 0.01$), Congruent ($ps < 0.01$) and Incongruent ($p = 0.02$ and $p = 0.04$ respectively) conditions, lower CPT Hit Rates than former smokers ($p = 0.02$). Because of observed differences in IQ scores across these three schizophrenia subgroups, ANCOVAs of neuropsychological performance on these tasks were performed in order to co-vary for IQ level; all significant effects persisted after this adjustment.

Analysis of neuropsychological performance across the three smoking history subgroups in controls identified no differences in performance on neuropsychological tests employed.

4. Discussion

There has been considerable study of neuropsychological deficits in patients with schizophrenia, but given the high prevalence of cigarette smoking in schizophrenia (Hughes et al., 1986; Kalman et al., 2005) there has been surprisingly little investigation of cross-sectional differences in neurocognitive function in smoking versus non-smoking patients with schizophrenia. We recently demonstrated that smoking status modifies pre-pulse inhibition (PPI) deficits, a neurophysiological measure of information processing, in schizophrenia; PPI deficits were present in nonsmokers with schizophrenia but in smokers with schizophrenia, studied under satiated conditions, PPI levels were elevated to that of non-psychiatric control smokers (Woznica et al., 2009). To our knowledge, the present study is the first study to report on cross-sectional differences in neuropsychological performance in schizophrenia as a function of smoking status or smoking history. Taken together, our results suggest smoking status (i.e., smoker versus non-smoker) only has a significant effect on neuropsychological deficits in patients with schizophrenia in the area of processing speed (SCWT Congruent and Neutral reaction times). However, when non-smokers were subdivided into former and never-smokers, a deficit in task performance in never-smokers with schizophrenia was identified across a range of measures. Selected neuropsychological measures such as sustained attention (CPT Hit Rate), processing speed (SCWT Congruent and Neutral reaction times) and response inhibition (SCWT Incongruent reaction times) were significantly impaired in never-smokers compared to current and former smokers, even after adjusting for IQ differences across schizophrenia subgroups. Such differences in neuropsychological performance as a function of smoking status and smoking history were not observed in the non-psychiatric controls.

Our results may suggest that never-smokers with schizophrenia have the most severe deficits in neuropsychological performance, and that some of these impairments, are likely to be independent of smoking exposure given our historical and biochemical verifications of non-smoking status. Therefore, we suggest that patients with schizophrenia who do not initiate (and maintain) smoking behavior may constitute a subgroup of patients with more severe impairment of neuropsychological task performance. Accordingly, this group of never-smoking patients with schizophrenia may thus represent a specific subtype of the illness with more severe neuropsychological impairment. This has implications for our understanding of cigarette smoking effects on endophenotypes associated with this disorder, and suggest that the presence or absence of cigarette smoking may have prognostic implications for the severity of neuropsychological deficits, and possibly treatment and rehabilitative outcomes in patients with schizophrenia. Whether these subjects would obtain cognitive enhancement from nicotine or nicotine-like pharmacotherapies is an open question. Studies in non-smokers with schizophrenia (including former and never-smokers) have reported that the cognitive deficits in these patients are insensitive to treatment with the nicotinic acetylcholine receptor (nAChR) antagonist mecamylamine (Sacco et al., 2006) but that nicotine replacement therapy can improve some aspects of cognitive performance (CPT, SCWT and episodic memory) (Barr et al., 2008; Jubelt et al., 2008). The cholinesterase inhibitor galantamine (Dyer et al., 2008; Sacco et al., 2008) and DMXB-A, a partial α7-nAChR agonist, had limited pro-cognitive effects in non-smokers with schizophrenia (Olincy et al., 2006; Freedman et al., 2008).

As is commonly observed, IQ and years of education were lower in the schizophrenia group compared to controls (Kondel et al., 2003). Within the control group, current smokers had both the lowest level of education and the lowest IQ, consistent with previous reports in the literature on the interaction between cigarette smoking, IQ and education (Hemmingsson et al., 2008; Weiser et al., 2010). It is noteworthy that the IQ of the control smokers (ca. 100) falls directly within expectation of a naturally occurring control group, and that all control groups fall within one standard deviation of the average. Lower IQ scores were also observed in current smokers with schizophrenia as compared to the former smokers with schizophrenia. This observation

Table 2
Neuropsychological performance of current, former and never-smokers as a function of psychiatric diagnosis.

Neuropsychological outcome measure	SZ current smokers ($n=38$)	SZ former smokers ($n=17$)	SZ never-smokers ($n=12$)	Smoking history effect (one-way ANOVA)		CON current smokers ($n=31$)	CON former smokers ($n=16$)	CON never-smokers ($n=26$)	Smoking history effect (one-way ANOVA)		Diagnosis effect (two-way ANOVA)		Smoking history effect (two-way ANOVA)		Diagnosis × smoking history interaction	
				F (d.f.)	*p*				*F* (d.f.)	*p*	*F* (d.f.)	*p*	*F* (d.f.)	*p*	*F* (d.f.)	*p*
CPT Hit Rate (%)	98.0 ± 2.6	[a] 99.0 ± 1.0	96.1 ± 4.6	3.8 (2,64)	0.03	99.1 ± 1.0	98.6 ± 2.1	99.4 ± 0.8	2.1 (2,70)	0.13	12.0 (1,134)	.001	2.2 (2,134)	0.12	6.3 (2,134)	<0.01
CPT Commission Rate (%)	28.6 ± 14.6	25.8 ± 18.1	39.1 ± 27.2	2.0 (2,64)	0.14	26.2 ± 18.7	26.4 ± 15.7	19.8 ± 13.1	1.3 (2,70)	0.27	4.9 (1,132)	0.03	0.3 (2,132)	0.73	3.4 (2,132)	0.04
CPT Hit Rate reaction time (ms)	422.4 ± 92.3	441.8 ± 90.2	441.8 ± 74.2	0.4 (2,64)	0.68	373.2 ± 82.5	424.7 ± 84.8	371.4 ± 84.4	2.5(2,70)	0.09	8.4 (1,134)	<0.01	1.9 (2,134)	0.15	0.8 (2,134)	0.45
CPT Variability Index	13.7 ± 10.6	10.6 ± 5.2	19.2 ± 17.6	2.1 (2,64)	0.13	8.3 ± 5.9	8.5 ± 4.6	6.6 ± 5.7	0.8 (2,70)	0.45	17.8 (1,134)	<0.01	1.3 (2,134)	0.29	3.2 (2,134)	0.05
CPT Attentional Index	2.1 ± 1.1	2.8 ± 1.1	1.9 ± 1.5	2.4 (2,64)	0.10	3.0 ± 1.3	1.9 ± 1.6	2.6 ± 1.4	2.8 (2,70)	0.07	1.1 (1,134)	0.29	0.6 (2,134)	0.57	4.9 (2,134)	<0.01
SCWT Incongruent (ms)	[a]1179 ± 468	[a]1040 ± 106	1855 ± 1050	4.7 (2,37)	0.02	1054 ± 450	1006 ± 300	1027 ± 603	0.02 (2,43)	0.97	5.4 (1,80)	0.02	3.3 (2,80)	0.04	5.4 (2,80)	0.04
SCWT Congruent (ms)	[a] 894 ± 249	[a] 859 ± 78	1392 ± 512	9.0 (2,37)	<0.01	780 ± 203	739 ± 155	750 ± 396	0.09 (2,43)	0.92	14.8 (1,80)	<0.01	5.4 (2,80)	<0.01	6.5 (2,80)	<0.01
SCWT Neutral (ms)	[a] 914 ± 190	[a] 865 ± 133	1314 ± 422	8.9 (2,36)	<0.01	744 ± 234	765 ± 147	843 ± 530	0.3 (2,44)	0.68	9.2 (1,80)	<0.01	5.1 (2,80)	0.01	2.0 (2,80)	0.14
SCWT Interference (ms)	286 ± 374	130 ± 114	448 ± 869	0.8 (2,37)	0.46	306 ± 347	162 ± 128	236 ± 423	0.4 (2,41)	0.75	0.2 (1,80)	0.64	0.8 (2,80)	0.46	0.6 (2,80)	0.57
SCWT facilitation	7.6 ± 185	6.6 ± 124	22.0 ± 294	0.01(2,36)	0.98	39.6 ± 249	128 ± 222	55.6 ± 207	0.02 (2,41)	0.69	1.1 (1,80)	0.29	0.2 (2,80)	0.83	0.2 (2,80)	0.82
WCST errors (%)	24.9 ± 15.5	30.2 ± 17.5	30.3 ± 18.2	0.8 (2,60)	0.46	20.5 ± 17.1	25.0 ± 20.7	17.3 ± 10.0	1.1 (2,69)	0.33	6.1 (1,129)	0.02	0.9 (2,129)	0.40	0.8 (2,129)	0.45
WCST perseverative errors (%)	14.4 ± 11.2	16.1 ± 10.1	18.8 ± 17.3	0.6 (2,60)	0.55	11.4 ± 11.0	15.2 ± 16.0	9.2 ± 5.4	1.6 (2,69)	0.24	4.2 (1,129)	0.04	0.6 (2,129)	0.57	0.3 (2,129)	0.28
WCST perseverative responses	13.9 ± 9.9	18.1 ± 12.3	22.6 ± 23.6	1.8 (2,60)	0.17	12.3 ± 14.5	17.6 ± 20.3	9.5 ± 5.9	1.5 (2,67)	0.21	3.6 (1,125)	0.06	1.3 (2,125)	0.28	2.1 (2,125)	0.12
WCST nonperseverative responses (%)	10.5 ± 6.7	14.3 ± 8.8	11.3 ± 5.7	1.4 (2,60)	0.25	9.0 ± 8.2	9.9 ± 6.5	8.0 ± 5.5	0.4 (2,69)	0.69	5.4 (1,129)	0.02	1.3 (2,129)	0.27	0.5 (1,129)	0.63
WCST categories completed	4.7 ± 2.2	4.0 ± 2.7	4.3 ± 2.2	0.5 (2,60)	0.60	5.2 ± 1.7	4.9 ± 2.1	5.8 ± 1.0	1.9 (2,69)	0.16	6.4 (1,129)	0.01	0.9 (2,129)	0.40	0.8 (2,129)	0.47

Abbreviations: CPT, Continuous Performance Test; SCWT, Stroop Color Word Test; WCST, Wisconsin Card Sorting Task; SZ, Schizophrenia; CON, Control.
[a] Represents a significant difference in performance compared to the SZ never-smoker subgroup (Bonferroni post hoc tests corrected for multiple comparisons, $p \leq 0.04$).

argues against there being a contribution of IQ to the observed group differences in task performance as never-smokers, not current smokers, generally had the greatest deficiencies in task performance of the three schizophrenia subgroups. Furthermore, ANCOVAs controlling for group differences in IQ across these schizophrenia subgroups ruled out a contribution of IQ disparities between subgroups to the observed differences in neuropsychological performance. Interestingly, we and other laboratories have observed that patients who quit smoking have better prefrontal cortical neuropsychological performance (assessed by the CPT, visuospatial working memory task, WCST, and Trail Making Test B) than those who did not quit smoking (Dolan et al., 2004; Culhane et al., 2008; Moss et al., 2009). While our moderately small sample size in the schizophrenia former groups ($n=17$) may not have allowed for detection of significant differences versus the current smokers, task performance on several CPT and SCWT measures tended to be better in former smoker groups than in the other two groups.

In summary, we compared patients with schizophrenia and controls as a function of smoking status (smokers and non-smokers) and smoking history (current, former and never-smokers) on a broad array of neuropsychological outcome measures. While there were clear deficits in all subgroups of patients with schizophrenia compared to controls, the deficits in performance, predominantly in the areas of sustained attention, processing speed and response inhibition, were the most pronounced in non-smokers with schizophrenia and in particular in the never-smoking subgroup. Our findings may suggest that never-smoking patients with schizophrenia may constitute a subtype of schizophrenia associated with more severe neurocognitive dysfunction. Since treatment and rehabilitative outcomes in schizophrenia have been associated with severity of baseline neurocognitive impairment (Green, 1996), smoking status should be considered as a potential predictor of treatment outcome in future studies in schizophrenia. However, given our small subgroup sample sizes and that the data are derived from a secondary analysis of baseline data from larger prospective laboratory studies of the effects of smoking and cognition in schizophrenia (Sacco et al., 2005, 2006) our findings should be considered preliminary and in need of replication using larger samples.

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Declarations:

Drs. Wing, Bacher and Sacco have no conflicts to report. Dr. George reports that he has received grant support from Pfizer, Inc., and has received consulting fees from Pfizer, Evotec, Eli Lilly, Janssen-Ortho and Astra-Zeneca in the past two years.

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