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# Neuropsychological deficits are associated with smoking cessation treatment failure in patients with schizophrenia

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## Abstract

Schizophrenics have deficits in neuropsychological performance, some of which are modified by cigarette smoking. These patients also have high rates of smoking and resistance to smoking cessation interventions. We examined whether the presence of neuropsychological deficits prior to smoking cessation treatment was associated with smoking cessation treatment failure in schizophrenic as compared to non-psychiatric control smokers. Neuropsychological assessments were performed prior to treatment with pharmacological agents during the course of placebo-controlled trials in schizophrenic and non-psychiatric control smokers, and included the Wisconsin Card Sorting Test (WCST), a Visuospatial Working Memory (VSWM) task, the Stroop Color Word Test (SCWT) and the Continuous Performance Test (CPT). In schizophrenics ( $n=32$ ), subjects who had greater deficits in VSWM and WCST performance were significantly less likely to quit smoking, but this association was not observed in controls ( $n=40$ ). Differences between quitters and non-quitters were not likely related to atypical antipsychotic treatment or differences in depressive symptoms. No associations between baseline performance on CPT or SCWT and quit status were found in either group. These preliminary data suggest that in schizophrenics, neuropsychological deficits are associated with smoking cessation treatment failure.

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## 1. Introduction

Schizophrenia is associated with a variety of neuro-cognitive deficits, including those mediated by the prefrontal cortex (PFC) such as executive function

(Goldberg and Weinberger, 1988; Green, 1996; Morice and Delahunty, 1996) and spatial working memory (e.g., Park and Holzman, 1992; Keefe et al., 1995). Such PFC-related cognitive deficits may be related to cortical dopamine (DA) hypofunction, which has been proposed to be associated with schizophrenia (Knable and Weinberger, 1997) and may underlie the negative symptoms (e.g., anhedonia, affective blunting, poor social relationships) of schizophrenia. Furthermore, structural imaging studies have shown decreased gray

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matter volumes in regions of the PFC of schizophrenics as compared to controls (Schlaepfer et al., 1994; Sullivan et al., 1998; Gur et al., 2000), suggesting that there are prefrontal cortical structural as well as neurochemical abnormalities associated with this illness.

There is some evidence that nicotine administration through cigarette smoking can alleviate clinical and neurocognitive deficits associated with schizophrenia. Laboratory studies of neurocognitive function have shown that nicotine and cigarette smoking can reduce or even normalize attentional (Adler et al., 1993, 1998; Freedman et al., 1997; Smith et al., 2002) and haloperidol-induced working memory (Levin et al., 1996) deficits. More recently, smoking abstinence has been found to worsen Visuospatial Working Memory (VSWM) deficits in schizophrenic, but not control, smokers (George et al., 2002c). Since VSWM has been shown to be mediated in part by DA function in the PFC, which is known to be dysregulated in schizophrenia, these patients may smoke to remediate DA hypofunction in the PFC and associated cognitive deficits, which may be one factor leading to smoking persistence in these patients. Consistent with this possibility, persons with serious mental illness, especially schizophrenia, smoke at much higher rates (45–88%) than persons without mental illness (22.9%; Lasser et al., 2000; CDC, 2002; George et al., 2002a). In addition, schizophrenics have lower trial endpoint abstinence rates in smoking cessation trials with both nicotine replacement patch (36–42%; Addington et al., 1998; George et al., 2000b) and bupropion (11–50%; Evins et al., 2001; Weiner et al., 2001; George et al., 2002a) than non-psychiatric smokers (50–75%; Hughes et al., 1999).

Given the elevated rates of smoking in this population, and the difficulties that these patients have with smoking cessation which renders them at high risk for the development of smoking-related medical morbidity and mortality, it is important to develop improved methods for smoking cessation in this population. Accordingly, an examination of the relationship between neurocognitive function and smoking in schizophrenics may suggest novel approaches for treating nicotine addiction in schizophrenia. To date, however, few studies have examined the relationship between neurocognitive function and smoking cessation. Using a prospective design, Postma et al. (2001) examined

the relationship between smoking cessation and acoustic startle reflex in non-psychiatric smokers attempting smoking cessation. They measured acoustic startle response at baseline, after 24 h of smoking abstinence, and after 1 month of abstinence. Two variables predicted smoking cessation success at 1 month: (1) high baseline (while still smoking) startle responses; and (2) a significant decrease in startle amplitude after 24 h of smoking abstinence. Thus, this approach may prove fruitful for trying to understand how differences in neurocognitive function may predict success in smoking cessation for patients with schizophrenia.

The present study explores the relationship between a variety of measures of baseline neurocognitive function and smoking cessation treatment outcome in schizophrenic and control smokers participating in controlled smoking cessation trials. We hypothesized that PFC-related neuropsychological function, assessed prior to participation in a combined pharmacological/behavioral smoking cessation treatment, would be associated with treatment outcomes in schizophrenic, but not in control smokers, as schizophrenics have deficits in PFC-mediated cognitive functions as compared to non-psychiatric controls. Specifically, we hypothesized that in schizophrenics, poorer performance on tests of PFC-dependent executive function (WCST) and spatial working memory (VSWM), would be associated with smoking cessation treatment failure; in control smokers, our prediction was that there would be no such relationship between neuropsychological test performance and smoking cessation treatment outcome.

## 2. Methods

### 2.1. Participants

Non-psychiatric control smokers were recruited through advertisements in local newspapers in the Greater New Haven, CT area, while schizophrenic smokers were recruited through advertisements, and referrals by the clinicians at the Connecticut Mental Health Center in New Haven, CT. All research protocols were approved by the Human Investigation Committee at the Yale University School of Medi-

cine. Subjects provided written informed consent, and after they were screened for inclusion/exclusion criteria, completed intake psychiatric and smoking assessments.

A total of 72 (32 schizophrenic and 40 non-psychiatric control) nicotine-dependent smokers were studied. Participants came from two separate randomized, controlled, double-blind studies of the use of pharmacotherapies for smoking cessation. Selegiline hydrochloride (Eldepryl<sup>®</sup>), a monoamine oxidase B inhibitor, was used in healthy control smokers (George et al., 2003), and sustained-release bupropion (Zyban<sup>®</sup>), a DA and norepinephrine reuptake inhibitor, was used in schizophrenic smokers (George et al., 2002b).

All psychiatric diagnoses were established using the SCID-I for DSM-IV, administered by two trained research staff (J.C.V. and A.T.). Participants were included in the studies if they had a primary diagnosis of schizophrenia or schizoaffective disorder and were clinically stable on psychotic and affective symptomatology at the time of study entry (patients) or no current Axis I diagnosis or past psychotic disorder (controls); all subjects required an Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) score of  $\geq 5$ , self-reported smoking of  $\geq 20$  cigarettes per day in the week prior to assessment, an expired carbon monoxide (CO) level  $\geq 10$  ppm, and plasma cotinine level  $\geq 150$  ng/ml at baseline for study inclusion. Participants were excluded if they met criteria for any substance use disorder (except nicotine and caffeine) in the previous 6 months or reported any contraindications to the study medications (i.e., seizure history for bupropion and treatment with antidepressant medication for selegiline, (George et al., 2002b, 2003).

## 2.2. Schizophrenic smokers

Thirty-two subjects were randomized to either bupropion, 300 mg/day or placebo groups in a 10-week trial; all patients received weekly smoking cessation counseling groups [described in (George et al., 2000b)]. Ten of 32 subjects (31.3%) achieved smoking cessation at the end of the 10-week trial, including 8/16 subjects randomized to active bupropion, and 2/16 subjects randomized to placebo (George et al., 2000b).

## 2.3. Control smokers

Forty subjects were randomized to receive selegiline hydrochloride, 10 mg/day or placebo in an 8-week trial; all subjects received weekly individual smoking cessation therapy. Twelve of 40 subjects (30%) achieved smoking cessation at the end of the 8-week trial, including 9/20 subjects randomized to active selegiline and 3/20 subjects randomized to placebo (George et al., 2003).

## 2.4. Determination of smoking abstinence

Smoking abstinence (7-day point prevalence) was defined by an absence of self-reported cigarette use in the 7 days prior to, and including the day of assessment; this was biologically verified each week by CO  $< 10$  ppm (George et al., 2002b, 2003). In some cases, smoking abstinence was additionally verified by a plasma cotinine level of  $< 15$  ng/ml. Participants who dropped out of their respective studies prior to trial completion were classified as non-quitters.

## 2.5. Neuropsychological assessment procedures

The computerized neuropsychological tasks were administered at the baseline assessment. Specifically, all subjects were tested during the first week of the smoking cessation trial, prior to initiation of study medication. Neuropsychological tests administered included the Continuous Performance Test (CPT), a test of Visuospatial Working Memory (VSWM), Stroop Color Word Test (SCWT), and Wisconsin Card Sorting Test (WCST). Not all subjects participated in all tasks, and numbers tested on each task are given in the Results section. All participants smoked ad lib during the neuropsychological testing session (e.g., they were allowed cigarette breaks whenever they requested), and CO levels were assessed prior to each neuropsychological testing session to verify current smoking status. The procedures for the computerized VSWM and SCWT were adapted from previously published “pen-and-paper” versions of these tests (Keefe et al., 1995; Hepp et al., 1996), using PsyScope version 1.1 on a Macintosh computer. CPT and WCST were administered on a PC, using commercially available software (from Multi-Heath Systems, Toronto, Canada and Psycho-

logical Assessment Resources, Lutz, FL, respectively). For all neuropsychological tests, subjects sat in front of the computer with a viewing distance of 60 cm, and a visual field of  $\sim 50^\circ$ .

#### 2.5.1. Visuospatial Working Memory (VSWM)

In this task (described in detail in George et al., 2002c), the subject first views a dot presented at one of 16 possible locations on the computer screen (Screen 1), then performs a tic-tac-toe task (Screen 2) for 30 s (not an outcome measure, but used as a distractor to increase task difficulty), and then is required to indicate on a blank screen exactly where the dot had been located on screen 1 (Screen 3). The computer measures the distance (in cm) between the location the subject places the dot on Screen 3 in comparison to the actual location of the dot in Screen 1. Sixteen trials were done and VSWM performance results are reported as the averaged “distance from target” in cm (Keefe et al., 1995). Larger “distance from target” scores indicate poorer VSWM performance.

#### 2.5.2. Wisconsin Card Sorting Test (WCST)

The WCST (Heaton et al., 1993) is a task designed to assess executive functions, including planning and set-shifting. Outcome measures include number of categories completed, percent total errors, percent perseverative errors, percent non-perseverative errors, and number of trials to complete first category. Performance on this task has been linked with activation of the dorsolateral prefrontal cortex (Egan et al., 2001).

#### 2.5.3. Continuous Performance Task (CPT)

The CPT-X (Connors, 1995), the classic, non-degraded version of the task, is a test designed to measure sustained attention, concentration and impulsivity. With this task, participants are required to monitor a continuous presentation of stimuli for a specific target in a string of letters presented in a visual modality, and they are required to hit the space bar for every letter presented except for “X”. Percentage of hits, or correct selections of the target, percentage of omission errors, percentage of commission errors, reaction time (in ms) for hits, the attentiveness index ( $d'$ ), and the variability of hit rate reaction time standard errors were the dependent measures (Connors, 1995).

#### 2.5.4. The Stroop Color Word Test (SCWT)

The SCWT (Hepp et al., 1996) is a measure of selective attention that assesses a participant’s ability to shift their perceptual set to conform to changing conditions. It also assesses executive functions including mental control, response flexibility, the occurrence of perceptual interference, and response inhibition. In one condition, subjects are asked to identify the color in which a word is presented when the word itself is the name of that color (congruent condition). In the other condition, the word itself is the name of a color other than the color of the print (incongruent condition). Level of interference (in ms), the outcome measure, is the reaction time for incongruent condition minus the reaction time for the congruent condition (George et al., 2002c). SCWT performance has been found to be linked to activation of the anterior cingulate cortex (Carter et al., 1998).

#### 2.5.5. Statistical analyses

All 32 schizophrenic (SCZ) and 38 out of 40 control (CON) subjects randomized into the respective clinical trials participated in the baseline neuropsychological testing. Of these groups, subsets completed each of the tests and provided useable data (VSWM: 27 SCZ, 38 CON; WCST: 18 SCZ, 26 CON; SCWT: 22 SCZ, 31 CON; CPT: 16 SCZ, 24 CON). Independent samples *t*-tests were performed on neuropsychological test performance outcomes, comparing SCZ or CON subjects who quit smoking at trial endpoint (quitters) to those who did not quit (non-quitters) in diagnostic group. Chi square was used to compare SCZ and CON subjects performance as a function of the median split of VSWM scores and as a function of quit status (quit or not quit) at trial endpoint. Differences were considered significant when  $p < 0.05$ . Two-way ANOVA analyses were used to determine interactions of Diagnosis and Quit Status on neuropsychological measures across the four groups (SCZ vs. CON, quitters vs. non-quitters).

ANCOVA analyses were used to determine whether the effects of neuropsychological function on smoking cessation treatment outcome were mediated by demographic variables that were significantly different between quitters and non-quitters (i.e., Beck Depression Inventory scores) in the schizophrenia sample.

Finally, to analyze the specificity of the neuropsychological deficits in schizophrenics, convergent

and discriminant Pearson correlations were performed for neuropsychological tests administered to this group.

### 3. Results

#### 3.1. Demographic and clinical characteristics of schizophrenic and control groups

Subjects were compared as a function of quitting on a variety of clinical and demographic variables. In the schizophrenic sample (Table 1), 5 males and 5 females were smoking abstinent at trial endpoint, and 13 males and 9 females were still smoking.

The patients were moderately nicotine dependent and smoking  $\geq 1$  pack of cigarettes per day. Ages of

Table 1  
Demographic and clinical characteristics of schizophrenic smokers

	Quit ( $n=10$ )	Not quit ( $n=22$ )	$p$ -value
Age (years)	39.5 $\pm$ 11.3	44.8 $\pm$ 10.4	0.20
Gender	5 M/5 F	13 M/9 F	0.63
Race	4 W/5 B/1 O	16 W/6 B	0.10
Education (years)	12.2 $\pm$ 1.5	11.3 $\pm$ 1.9	0.15
CPD	23.0 $\pm$ 14.0	24.6 $\pm$ 8.7	0.69
FTND	6.6 $\pm$ 1.4	7.4 $\pm$ 1.1	0.07
Baseline urine cotinine (ng/ml)	1741 $\pm$ 752	1819 $\pm$ 1317	0.87
Number of previous quit attempts	3.5 $\pm$ 3.5	3.6 $\pm$ 4.6	0.94
BDI	7.0 $\pm$ 3.9	14.1 $\pm$ 10.5	<0.05
Antipsychotic medication type	0Typ/10 Atyp	10 Typ/12 Atyp	<0.05
CPZ equivalents (mg/day)	645 $\pm$ 509	808 $\pm$ 546	0.43
Pos PANSS	11.5 $\pm$ 3.5	13.6 $\pm$ 4.1	0.17
Neg PANSS	10.0 $\pm$ 2.4	12.7 $\pm$ 4.1	0.07
Gen PANSS	23.8 $\pm$ 3.7	25.8 $\pm$ 5.2	0.29
Total PANSS	45.3 $\pm$ 7.2	52.0 $\pm$ 10.0	0.07

M= male, F= female; W= White, B= Black, O= Other race; CPD= Number of cigarettes smoked per day; FTND= Fagerstrom test for nicotine dependence; BDI= Beck depression inventory; Typ= Typical, Atyp= Atypical; CPZ= Chlorpromazine; Pos PANSS= Positive symptoms subscale of the Positive and Negative Syndrome Scale; Neg PANSS= Negative symptom subscale of the Positive and Negative Syndrome Scale; Gen PANSS= General psychopathology subscale of the Positive and Negative Syndrome Scale; Total PANSS= Sum of scores on all items of the Positive and Negative Syndrome Scale.

Table 2  
Demographic and clinical characteristics of control smokers

	Quit ( $n=12$ )	Not quit ( $n=28$ )	$p$ -value
Age (years)	50.8 $\pm$ 7.2	48.2 $\pm$ 9.3	0.38
Gender	4 M/8 F	11 M/17 F	0.72
Race	9 W/3 B	21 W/5 B/2 O	0.59
Education (years)	14.5 $\pm$ 1.6	13.7 $\pm$ 2.8	0.35
CPD	20.6 $\pm$ 7.7	23.61 $\pm$ 9.5	0.34
FTND	6.0 $\pm$ 1.3	6.9 $\pm$ 1.6	0.12
Baseline urine cotinine (ng/ml)	2032 $\pm$ 1050	1537 $\pm$ 551	0.16
Number of previous quit attempts	4.6 $\pm$ 2.6	8.1 $\pm$ 18.4	0.52
BDI	6.9 $\pm$ 6.2	8.3 $\pm$ 6.7	0.55

M= male, F= female; W= White, B= Black, O= Other race; CPD= Number of cigarettes smoked per day; FTND= Fagerstrom test for nicotine dependence; BDI= Beck depression inventory.

quitters and non-quitters were comparable. These patients had PANSS scores that indicated a moderate level of psychotic symptoms, and these scores were similar between the quitters and non-quitters. Only BDI scores were significantly different between quitters and non-quitters. An analysis of the potentially confounding effects of BDI scores is presented below (Results section #4).

There were no significant differences in any demographic variables between control quitters and non-quitters (Table 2).

Control subjects were also moderately nicotine dependent, and they smoked  $\geq 1$  pack of cigarettes per day. There was no statistically significant difference in BDI scores between quitters and non-quitters amongst the control smokers.

#### 3.2. Effects of baseline neuropsychological test performance on quit status at trial endpoint in schizophrenic and control smokers

We conducted two-factor ANOVA analyses comparing neuropsychological test performance across psychiatric diagnosis (SCZ vs. CON) and quit status at trial endpoint (quit vs. not quit), which revealed non-significant (though in some cases trends towards) Diagnosis  $\times$  Quit Status interactions for VSWM ( $F=2.31$ ,  $df=1,61$ ,  $p=0.13$ ), and all measures of the WCST (% Total Errors:  $F=3.54$ ,  $df=1,39$ ,  $p=0.07$ ; % Perseverative Errors:  $F=3.47$ ,  $df=1,39$ ,

$p=0.07$ ; % Non-Perseverative Errors:  $F=1.80$ ,  $df=1,39$ ,  $p=0.19$ ; Number of Trials to Complete First Category:  $F=1.64$ ,  $df=1,39$ ,  $p=0.21$ ; and Number of Categories Completed:  $F=2.38$ ,  $df=1,39$ ,  $p=0.13$ ). There were no significant Diagnosis  $\times$  Quit Status interactions for all CPT and SCWT outcome measures (all  $p$ 's $>0.27$ ). Given that we were underpowered to detect significant Diagnosis  $\times$  Quit Status interactions on promising VSWM and WCST outcome measures, independent samples  $t$ -tests were conducted to explore differences between quitters and non-quitters in both the SCZ and CON groups. In the SCZ group, when grouped by trial endpoint smoking abstinence outcomes, independent samples  $t$ -tests revealed a nearly significant difference in VSWM performance between schizophrenic quitters and non-quitters ( $p=0.052$ ; Fig. 1A), but no difference was found between quitters and non-quitters in the control group ( $p=0.39$ ; Fig. 1B). Alternatively, when VSWM data was analyzed by using the median split of VSWM scores in both schizophrenic (VSWM=4.70 cm) and control (VSWM=2.89 cm), it was observed that VSWM scores above the median split in schizophrenic smokers was associated with a significantly lower proportion of subjects quitting smoking at trial endpoint [ $\chi^2=4.75$ ,  $df=1$ ,  $p<0.05$ ], but that a similar relationship was not present in control smokers [ $\chi^2=0.49$ ,  $df=1$ ,  $p=0.49$ ] (Fig. 2).

Similarly, several significant differences on outcome measures of the WCST (Table 3) test were found between quitters and non-quitters in the schizophrenics, but not in the controls (Table 3). In schizophrenics, quitters took fewer trials to complete the first category ( $p<0.02$ ), completed more categories ( $p=0.05$ ) and made fewer errors ( $p<0.04$  for both % Total Errors and % Non-perseverative Errors) on the WCST as compared to quitters (Table 3). There was a similar strong trend for improved performance by quitters on WCST % Perseverative Errors ( $p=0.07$ ).

In schizophrenic patients, performance on the SCWT Interference score ( $p=0.64$ ) and various dependent measures of the CPT (all  $p>0.15$ ; Table 4) did not differ between quitters and non-quitters. Table 4 also shows that control smokers did not exhibit significant differences in baseline neuropsychological performance as a function of quit status on SCWT Interference ( $p=0.71$ ), CPT% Hits ( $p=0.30$ ), CPT% Omissions ( $p=0.30$ ), CPT% Commissions

( $p=0.48$ ), CPT Hit Reaction Time ( $p=0.80$ ), CPT Attentiveness Index ( $d'$ ) ( $p=0.08$ ), or CPT Variability ( $p=0.95$ ).

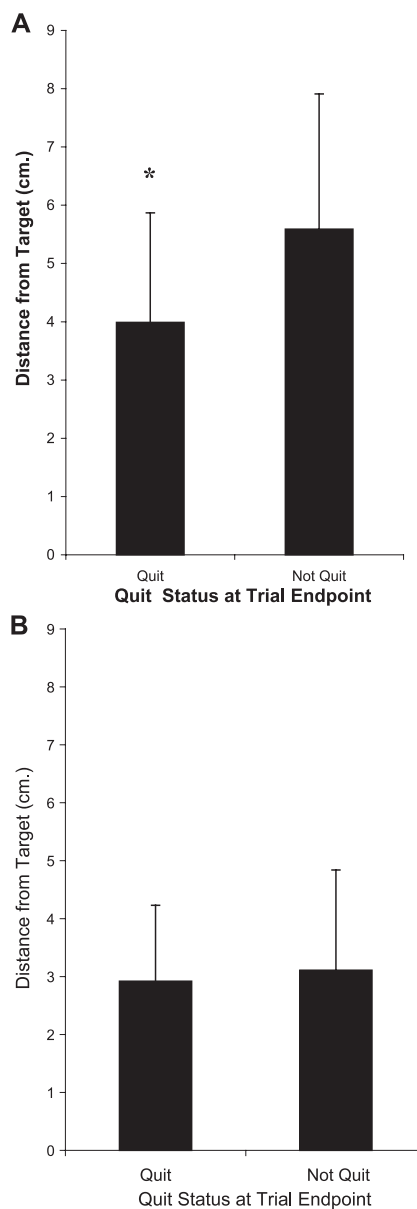


Fig. 1. Comparison of VSWM performance in schizophrenics (A) and controls (B) as a function of quit status at trial endpoint. Results given as mean  $\pm$  standard deviation. For schizophrenics, sample sizes were  $n=9$  for quitters and  $n=18$  for non-quitters. For controls, sample sizes were  $n=12$  for quitters and  $n=26$  for non-quitters. \* $p=0.052$  versus schizophrenic non-quitters.

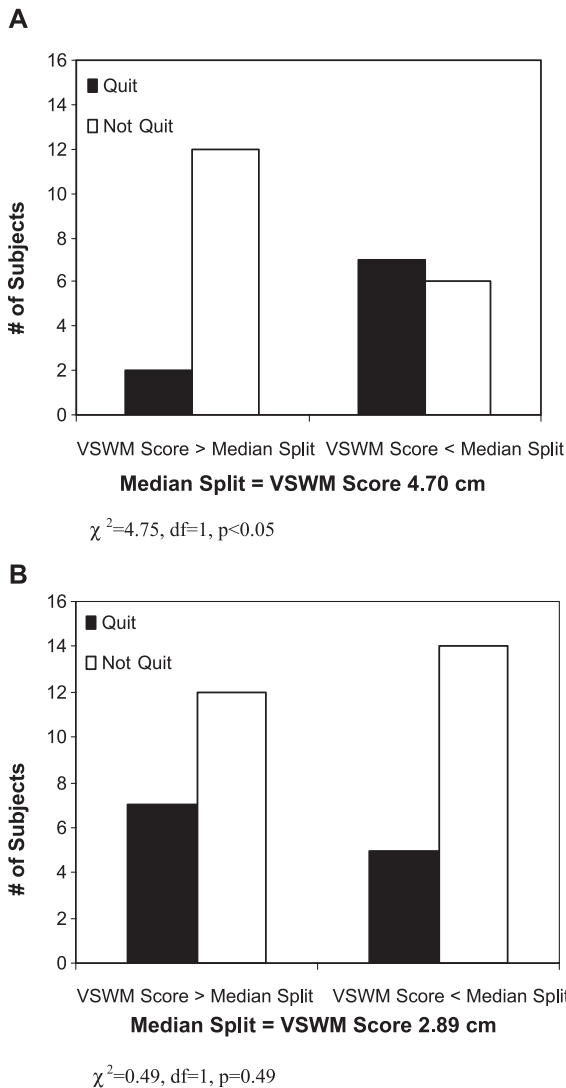


Fig. 2. Comparison of smoking cessation treatment outcomes in schizophrenics (A) and controls (B) as a function of a median split of baseline VSWM score in cm in each group. Results given as the number of quitters or non-quitters for VSWM performance below and above the median split for VSWM scores in each experimental group. For schizophrenics, sample sizes were  $n=9$  for quitters and  $n=18$  for non-quitters. For controls, sample sizes were  $n=12$  for quitters and  $n=26$  for non-quitters.

### 3.3. Effects of atypical antipsychotic treatment status on baseline neuropsychological performance

There is some evidence that atypical antipsychotic drug treatment may improve neurocognitive deficits

associated with schizophrenia (Lee et al., 1994; Meltzer et al., 1999), and that such treatment may be associated with improved smoking cessation outcomes in schizophrenic smokers as compared to those treated with classical neuroleptic agents (George et al., 2000b, 2002b). To examine the possible influence of antipsychotic drug class on smoking cessation treatment outcome in schizophrenic smokers, we performed independent samples *t*-tests on VSWM and WCST performance in schizophrenic non-quitters treated with typical vs. atypical antipsychotics. There were no significant differences in performance on these tasks between non-quitting schizophrenic subjects taking typical vs. atypical antipsychotic medication [VSWM distance from target scores (in cm): Typical ( $n=9$ ),  $4.79 \pm 2.70$  cm vs. Atypical ( $n=7$ ),  $5.90 \pm 2.07$  cm,  $t=0.90$ ,  $p=0.39$ ; WCST % Total Errors: Typical ( $n=8$ )  $40.37 \pm 12.02$  vs. Atypical ( $n=5$ )  $39.40 \pm 19.26$ ,  $t=0.11$ ,  $p=0.91$ ; % Perseverative Errors:  $22.63 \pm 8.24$  vs.  $22.20 \pm 12.52$ ,  $t=0.07$ ,  $p=0.94$ ; % Non-perseverative Errors:  $18.00 \pm 9.18$  vs.  $17.20 \pm 8.95$ ,  $t=0.15$ ,  $p=0.88$ ; Number of Categories Completed:  $3.00 \pm 1.19$  vs.  $3.4 \pm 2.6$ ,  $t=0.32$ ,  $p=0.76$ ; Number of Trials to Complete First Category:  $41.63 \pm 32.06$  vs.  $50.60 \pm 49.48$ ,  $t=0.04$ ,  $p=0.69$ ]. These results suggest that differential effects of typical versus atypical antipsychotic medication treatment was an unlikely explanation for our findings of improved performance on WCST and VSWM in schizophrenic quitters compared to non-quitters. Furthermore, there were no significant differences on SCWT or CPT performance in schizophrenic non-quitters treated with either typical or atypical antipsychotic drugs (data not shown).

### 3.4. Effects of depressive symptoms on baseline neuropsychological performance

Covariation of Beck Depression Inventory (BDI) scores between quitters and non-quitters using ANCOVA reduced the magnitude of the observed differences between baseline neuropsychological performance and quit status at trial endpoint in schizophrenics (VSWM,  $p=0.052$  to  $p=0.15$ ; WCST % Total Errors,  $p=0.04$  to  $p=0.08$ ; WCST % Perseverative Errors,  $p=0.07$  to  $p=0.14$ ; WCST % Non-perseverative Errors,  $p=0.04$  to  $p=0.08$ ; WCST Categories Completed,  $p=0.05$  to  $p=0.11$ ; and

Table 3  
Baseline Performance on Wisconsin Card Sorting Test (WCST) in schizophrenic and control smokers as a function of quit status

	Schizophrenics			Controls		
	Quit ( $n=5$ )	Not quit ( $n=13$ )	$p$ -value	Quit ( $n=7$ )	Not quit ( $n=19$ )	$p$ -value
% Total errors	23.0 ± 14.1	40.0 ± 14.4	0.04	19.0 ± 12.1	23.0 ± 14.6	0.52
% Perseverative errors	13.0 ± 7.8	22.5 ± 9.6	0.07	12.0 ± 8.0	12.6 ± 9.1	0.88
% Non-perseverative errors	7.5 ± 2.6	17.7 ± 8.7	0.04	7.7 ± 5.0	10.8 ± 7.4	0.31
No. of categories completed	5.0 ± 1.4	3.2 ± 1.8	0.05	5.7 ± 0.8	5.2 ± 1.8	0.43
No. of trials to complete first category	15.0 ± 4.1	45.1 ± 37.9	0.02	14.4 ± 5.1	18.6 ± 26.9	0.69

WCST Number of Trials to Complete First Category,  $p=0.02$  to  $p=0.10$ ). However, similar co-variation of BDI scores did not alter neuropsychological test performance in schizophrenic quitters and non-quitters for SCWT or CPT which remained non-significant (data not shown). Correlations between neuropsychological test performance and BDI scores in schizophrenics showed no consistent patterns since the majority of correlations examined between neuropsychological test performance and BDI scores were non-significant ( $p>0.05$ ), with the following exceptions: VSWM  $r=0.45$ ,  $p<0.04$ , WCST % Total Errors  $r=0.48$ ,  $p<0.05$ , WCST % Perseverative Errors  $r=0.52$ ,  $p<0.03$ , and CPT % Omissions  $r=0.60$ ,  $p<0.02$ . Collectively, our data suggests that these minimally elevated baseline BDI scores had modest and inconsistent effects on neuropsychological performance in this schizophrenic sample, and are unlikely to be a clinically significant mediator of

the observed relationship between baseline neuropsychological test performance and quit status.

### 3.5. Relationship amongst the various neuropsychological tests in schizophrenics

We found significant correlations between test performance in the schizophrenics on VSWM and the following WCST measures: % Total Errors ( $r=0.88$ ,  $p<0.01$ ), % Perseverative Errors ( $r=0.70$ ,  $p<0.03$ ), % Non-perseverative Errors ( $r=0.76$ ,  $p<0.02$ ), and Number of Categories Completed ( $r=-0.73$ ,  $p<0.02$ ), with a trend for significance between VSWM performance and WCST Number of Trials to Complete First Category ( $r=0.52$ ,  $p=0.12$ ). There were no significant correlations between these tests and CPT or SCWT (all  $p$ 's $>0.25$ , data not shown) or between CPT and SCWT (all  $p$ 's $>0.30$ , data not shown).

Table 4  
Baseline performance on Stroop Color Word Test (SCWT) and Continuous Performance Test (CPT) in schizophrenic and control smokers as a function of quit status

	Schizophrenia			Control		
	Quit	Not quit	$p$ -value	Quit	Not quit	$p$ -value
SCWT	$n=8$	$n=14$		$n=10$	$n=21$	
Congruent	1083.5 ± 372.8	1251.8 ± 590.3	0.48	952.2 ± 200.1	979.0 ± 231.1	0.76
Incongruent	1705.2 ± 857.1	1750.3 ± 884.2	0.91	1297.6 ± 405.8	1360.8 ± 454.4	0.71
Interference	621.8 ± 690.8	498.4 ± 506.8	0.64	345.4 ± 230.1	381.8 ± 261.7	0.71
CPT	$n=3$	$n=13$		$n=7$	$n=17$	
% Hits	98.2 ± 0.8	96.0 ± 3.2	0.25	98.9 ± 0.5	98.5 ± 1.0	0.30
% Omissions	1.8 ± 0.8	4.0 ± 3.2	0.25	1.1 ± 0.5	1.5 ± 1.0	0.30
% Commissions	29.6 ± 5.8	41.2 ± 26.6	0.17	26.2 ± 16.6	31.1 ± 17.5	0.48
Hit reaction time (ms)	431.4 ± 84.7	408.8 ± 96.0	0.71	360.9 ± 41.5	367.5 ± 62.7	0.80
Variability	11.4 ± 1.4	20.2 ± 14.1	0.31	9.5 ± 9.7	9.7 ± 4.8	0.95
Attentional index ( $d'$ )	2.7 ± 0.3	2.1 ± 0.8	0.30	3.4 ± 0.9	2.7 ± 0.6	0.08

## 4. Discussion

### 4.1. Specific neuropsychological deficits are associated with smoking cessation treatment failure in schizophrenics

We found that schizophrenic smokers who exhibited poorer performance on tests of PFC-related executive function (WCST) and spatial working memory (VSWM) prior to implementation of a smoking cessation intervention were less able to quit smoking. No such relationships existed in control smokers. The effect sizes for the differences between schizophrenic quitters and non-quitters on VSWM and WCST performance outcome measures (Cohen's  $d=0.7-1.4$ ; Cohen, 1988) were in the moderate to large effect size range that is considered clinically significant (Green, 1996), suggesting that this association could be clinically meaningful and requires further study. Furthermore, there were no associations between baseline performance on sustained and selective attention tasks (CPT and SCWT, respectively) and smoking cessation treatment outcome in either schizophrenics or controls. This finding, coupled with the significant correlations we found between VSWM and WCST measures, suggests that there could be some specificity for the association of PFC-related neuropsychological deficits with smoking cessation treatment failure in schizophrenics, though the small sample sizes in the present study limit firm conclusions insofar as task specificity. Further, another significant factor associated with smoking cessation treatment outcomes in schizophrenics, treatment with atypical antipsychotic medication, did not appear to mediate this difference in neuropsychological test performance. Previous work has shown that treatment with atypical antipsychotic medication can reduce smoking behaviors in schizophrenics (McEvoy et al., 1995, 1999; George et al., 2000b, 2002b; Procyshyn et al., 2001, 2002), but in the present study, although all schizophrenic quitters were prescribed atypical antipsychotics, treatment with atypical vs. typical antipsychotics did not significantly alter baseline neuropsychological test performance in schizophrenic non-quitters. Therefore, the relationship between impaired baseline neuropsychological test performance and smoking cessation outcome was not likely related to improvements produced by atypical antipsychotic treatment.

### 4.2. Depressive symptoms as a mediator between neuropsychological test performance and smoking cessation treatment outcome

We did find an effect of baseline depressive symptomatology on the relationship between poor neuropsychological performance on VSWM and WCST and smoking cessation failure. We examined the relationship between depressive symptoms and neuropsychological test scores at baseline because depressive symptoms are related to both poor smoking cessation treatment outcomes (Glassman et al., 1993, 2001; Burgess et al., 2002; George et al., 2003), and poor baseline neuropsychological test performance (Lezak, 1995; Mialet et al., 1996), suggesting that level of depressive symptoms may possibly mediate the relationship between neuropsychological function and smoking cessation outcomes. Results suggested that depressive symptoms may partially mediate the relationship between neuropsychological deficits and negative smoking cessation treatment outcome in schizophrenics. However, since BDI scores in quitters and non-quitters were in the normal to minimal depressed symptom score range (mean of 7.0 and 14.1, respectively; Table 1), and depressive symptom effects on performance were inconsistent across the various neuropsychological tests, we doubt that this mild degree of depressive symptomatology had a clinically significant effect on neuropsychological performance in schizophrenics. As such, we believe that the results of the current study suggest that pre-treatment test performance on neuropsychological tasks may be associated with, independent of antipsychotic class treatment or baseline level of depression, successful smoking cessation in schizophrenics.

### 4.3. Significance of these findings

This preliminary finding may have clinical relevance since the literature clearly demonstrates that patients with severe mental illness both have higher rates of smoking (George and Vessicchio, 2002) and find it more difficult to quit smoking (Addington et al., 1998; George et al., 2000b) than non-psychiatric controls. Further, it is thought that nicotine and cigarette smoking may alleviate attentional (Postma et al., 2001) and other neuropsychological performance-related deficits (Levin et al., 1996; Smith et

al., 2002; George et al., 2002c), lending support to a self-medication hypothesis. There is preliminary evidence that cigarette smoking improves deficits in spatial working memory function in schizophrenics (Termine et al., 2002; George et al., 2002c). Spatial working memory function is presumed to be mediated by PFC cortical DA levels (Goldman-Rakic, 1999; George et al., 2000a, 2002c), so VSWM performance may be an indirect indicator of PFC cortical DA function in schizophrenic smokers. Our data suggest that because schizophrenics with deficits in VSWM and WCST performance fail to achieve smoking abstinence following a smoking cessation trial, they may continue to smoke because of the neuropsychological benefits they receive from cigarette smoking. Our findings with respect to neuropsychological deficits and smoking cessation treatment failure are consistent with studies in alcohol-dependent individuals showing that neuropsychological impairments are associated with poorer alcoholism treatment outcomes (O'Leary et al., 1979; Abbott and Gregaon, 1981). To our knowledge, this is the first demonstration that smoking cessation treatment outcomes are related to deficits in neuropsychological test performance, and in particular to known endophenotypic and putative pathophysiological aspects of a major psychiatric disorder.

#### 4.4. Implications for treatment

Interventions aimed at remediating PFC-related neuropsychological deficits may assist these patients in efforts to quit smoking, especially for those patients with more severe deficits. There is a growing literature examining both pharmacological and behavioral interventions aimed at remediating cognitive deficits in schizophrenia. A number of studies have examined the effects of various antipsychotics on cognitive function, and the results have been mixed: some studies have found an improvement in PFC-related functions with atypical antipsychotics (Lee et al., 1994; McGurk et al., 1996; Nagamoto et al., 1996; Meltzer et al., 1999; Light et al., 2000; for reviews, see Davidson and Keefe, 1995; Friedman et al., 1999; Harvey and Keefe, 2001), but other studies have found little evidence for improvement in PFC-related cognitive function with administration of atypical

antipsychotics (Green et al., 2002). Specifically, risperidone has been found to improve spatial working memory deficits, clozapine has been shown to improve psychomotor speed, attention, and verbal fluency (Lee et al., 1999), as well as WCST performance (Meltzer and McGurk, 1999) and olanzapine may also have positive effects on WCST performance (Meltzer and McGurk, 1999).

Behavioral interventions for cognitive deficits in schizophrenia have also shown some efficacy. Neurocognitive Enhancement Therapy (Bell et al., 2001) and Cognitive Remediation Therapy (Wykes et al., 2002) involve intensive practice of skills found to be deficient in schizophrenia. For example, abilities like verbal working memory (Wexler et al., 2000), WCST performance (Kern et al., 1996), memory, perceptual and motor tasks (Wexler et al., 1997), if practiced extensively, can improve over a period of weeks to months. Further, similar behavioral interventions for neuropsychological deficits (e.g., neuropsychological rehabilitation focusing in particular on visuospatial processing) have been found to be effective in alcoholics (Goldman and Goldman, 1988), suggesting similar treatment strategies are effective for other patient groups with neuropsychological deficits. Taken together, it is possible that a combined pharmacological/behavioral treatment for remediation of cognitive deficits may increase the effectiveness of smoking cessation interventions in schizophrenics.

#### 4.5. Limitations of the present study

The following limitations of the present study must be acknowledged. First, because of the small sample size, our findings must be considered preliminary, as power to detect differences in performance on these tasks was limited, and most of the observed differences were at a borderline level of statistical significance. For example, because our analyses with respect to CPT performance may be underpowered due to the very small numbers of schizophrenic quitters ( $n=3$ ) tested, the inclusion of more subjects may have increased our ability to detect differences in CPT performance outcomes between schizophrenic quitters and non-quitters. Second, this was an analysis of data from two separate clinical trials with different pharmacological smoking cessation interventions (bupropion in schizophrenics and selegiline in controls), and

longitudinal evaluation of the relationship between baseline neuropsychological deficits and smoking cessation treatment outcomes in schizophrenic and control smokers requires further study using standardized interventions. Third, multiple statistical comparisons for various neuropsychological outcome measures increases the likelihood of Type II errors (false positives) in this study. Fourth, we did not have pre-trial measures of intelligence quotient (IQ) in schizophrenic quitters and non-quitters, which might have contributed to differences in neuropsychological performance between these subgroups. Fifth, we were not able to carefully control smoking availability during the testing session, and smoking deprivation therefore may have influenced these results, as we have found to be the case in controlled laboratory studies of smoking in schizophrenia (Sacco et al., 2003). However, the fact that we found differences in baseline neuropsychological function between quitters and non-quitters in a small sample is noteworthy and suggests that this is a promising area for future studies.

#### 4.6. Summary

The results of this study suggest that schizophrenic, but not control, smokers with more severe baseline deficits in PFC-related neuropsychological test performance may have greater difficulty in quitting smoking. These patients may continue to smoke cigarettes because of specific neuropsychological benefits they may receive from smoking and nicotine administration, and thus interventions aimed at remediating PFC-related neuropsychological deficits may lead to improved smoking cessation outcomes in schizophrenic patients. Thus, this preliminary study may have clinical importance given the high burden of nicotine dependence in schizophrenia, and the attendant vulnerability to smoking-related medical illness.

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