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Effects of Smoking Abstinence on Visuospatial Working Memory Function in Schizophrenia

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Schizophrenic patients have impairments in cognitive function, including deficits in visuospatial working memory (VSWM). VSWM is mediated, in part, by prefrontal cortical dopamine (DA) function, and dysregulation of prefrontal cortical DA systems may contribute to the pathophysiology of schizophrenia. Nicotine has complex effects on spatial working memory (SWM) in animal studies, with most studies demonstrating enhancement of SWM. Cigarette smoking is highly prevalent in schizophrenia, and these patients may smoke cigarettes to remediate cognitive deficits. The present study examined the effects of acute (<1 week) and prolonged (8–10 weeks) smoking abstinence on VSWM in schizophrenic (n = 23) and control (n = 29) nicotine-dependent cigarette smokers during placebo-controlled smoking cessation trials. Schizophrenic and control smoking patients had significant impairments in VSWM compared to non-smoking controls, after adjusting for differences in age, education and depressive symptoms. Schizophrenic smokers who quit smoking had further impairments in VSWM, and control quitters had improvements in VSWM. Abstinence-induced changes in VSWM varied as a function of gender in controls, but not in schizophrenics. These changes in VSWM appeared to be independent of study medications, and smoking abstinence did not significantly alter performance on the Stroop Color Word Test in either group. These results suggest that smoking abstinence differentially alters VSWM in schizophrenic vs. control smokers, and that cigarette smoking has beneficial effects on VSWM in schizophrenic, but not control, smokers.

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KEY WORDS: *Schizophrenia; Nicotine; Cigarette smoking; Smoking abstinence; Prefrontal cortex; Visuospatial working memory; Stroop color word test*

Schizophrenic patients have high rates of cigarette smoking (58–88%) vs. 25% in the general population (Hughes et al. 1986; Ziedonis and George 1997; Dalack et al. 1998; NIDA/CPDD 1999). Numerous reasons for the high rates of cigarette smoking in these patients have been proposed including self-medication of psychopathology, shared genetic factors that confer susceptibility to both schizophrenia and nicotine dependence and environmental factors such as stress and peer modeling (Leonard et al. 1996; Dalack et al. 1998; George et al. 2000b). With respect to the self-medication hypothesis for smoking in schizophrenia, one specific reason for these high rates of cigarette smoking in these patients may be alleviation of cognitive dysfunction and the presumed hypofunctionality of cortical dopamine (DA) systems, which may be present in this illness (Knable and Weinberger 1997; Dalack et al. 1998; George et al. 1998; George et al. 2000a; George et al. 2000b).

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Deficits in spatial working memory (SWM) are one of the cognitive impairments that have been consistently demonstrated in schizophrenics compared to healthy individuals (Park and Holzman 1992; Keefe et al. 1995). Recent functional neuroimaging studies have confirmed deficits in prefrontal cortical activation during performance of SWM tasks in schizophrenic vs. control subjects (Callicott et al. 1998; Manoach et al. 2000). SWM is known to be dependent in part on prefrontal cortical DA systems, and the presumed cortical DA hypofunction in schizophrenia may explain deficits in SWM in this disorder (Williams and Goldman-Rakic 1995; Zahrt et al. 1997; Castner et al. 2000). Interestingly, deficits in SWM have also been shown in patients with Parkinson's disease, which is characterized neurochemically by nigrostriatal DA depletion (Owen et al. 1993; Postle et al. 1997) suggesting that alterations in other DA pathways influence SWM function. Nicotine administration has also been shown to improve spatial working memory function in rodents (Kim and Levin 1996; Levin et al. 1999) and reverse haloperidol-induced attentional deficits in schizophrenic subjects (Levin et al. 1996). A recent study of acute cigarette smoking on SWM found that SWM was impaired by smoking in healthy control smokers (Park et al. 2000), and this paradoxical effect of cigarette smoking in control smokers may relate to the phenomenon of "proactive interference" which has been described in animals, whereby pre-exposure to nicotine results in impaired working memory task performance after subsequent nicotine exposure (Dunnett and Martel 1990). However, the effects of cigarette smoking and smoking abstinence on spatial working memory in schizophrenic patients have not been reported.

There have been several studies of the effects of nicotine administration on DA systems in rats that suggest that nicotine stimulates central DA release and metabolism (Vezina et al. 1992; Nisell et al. 1996; George et al. 1998; George et al. 2000a; George et al. 2000c), in both subcortical and cortical DA terminal fields. The few studies of nicotine withdrawal in both animals (Ward et al. 1991; Fung et al. 1996; George et al. 1998) and humans (West et al. 1984; Ward et al. 1991) have suggested that nicotine withdrawal leads to decreases in central DA (and catecholamine) function. Since SWM is dependent on central DA function, smoking abstinence may lead to alterations in SWM function in both schizophrenic and control smokers.

In the present study, we sought to compare the effects of cigarette smoking, and smoking abstinence, on visuospatial working memory (VSWM) function in patients with schizophrenia and healthy control subjects. Specific goals were: 1) to compare VSWM function in schizophrenic and control smokers, and to non-smoking schizophrenic patients and controls; and, 2) to determine the effects of acute and prolonged smoking abstinence on VSWM in schizophrenic and control smokers during the course of placebo-controlled pharmacotherapy trials.

METHODS

Subjects

Twenty-three schizophrenic and 29 healthy control smokers, and 8 schizophrenic and 16 control non-smokers, were recruited into this study. Psychiatric diagnoses were established using the Structured Clinical Interview for DSM-IV (First 1994). Schizophrenic smokers were recruited from advertisements at The Connecticut Mental Health Center for a study comparing bupropion hydrochloride vs. placebo for smoking cessation in schizophrenia. Healthy control smokers were recruited through advertisements in local newspapers for a study comparing selegiline hydrochloride vs. placebo for smoking cessation. Schizophrenic and control non-smokers were recruited by local advertisements and word of mouth. The protocols were approved by the Human Investigation Committee of Yale University School of Medicine, and informed consent for study participation was obtained for all schizophrenic and control subjects.

Procedures

The computerized neuropsychological tasks were administered at study baseline (Week 1; prior to when subjects began study medication), during Week 4 of the trial (within one week of smoking quit date) and at trial endpoint (Week 8 in controls, Week 10 in schizophrenic subjects). The procedures for the computerized visuospatial working memory (VSWM) and Stroop Color Word Test (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. For both the VSWM and SCWT, subjects sat in front of the Macintosh computer with a viewing distance of 60 cm, and a visual field of $\sim$50 degrees. All subjects completed the VSWM task (the task of primary interest), while approximately 80% (60/76) of subjects completed the SCWT (See Figure 1).

For the VSWM task, each trial involved the presentation of three sequential screens. In Screen 1, subjects visualized a dot (1 cm in diameter) at one of 16 pre-set locations on the computer screen for a duration of three seconds. Screen 2 involved presentation of a "distractor task" screen with a sham performance task ("tic-tack-toe") which appeared for a fixed time delay (30 seconds); subjects were instructed to indicate with the keyboard whether the game was "won" or a "draw", and sequential "tic-tack-toe" screens appeared (with a default of five seconds if no response was received from the subject) until the 30 second delay period had

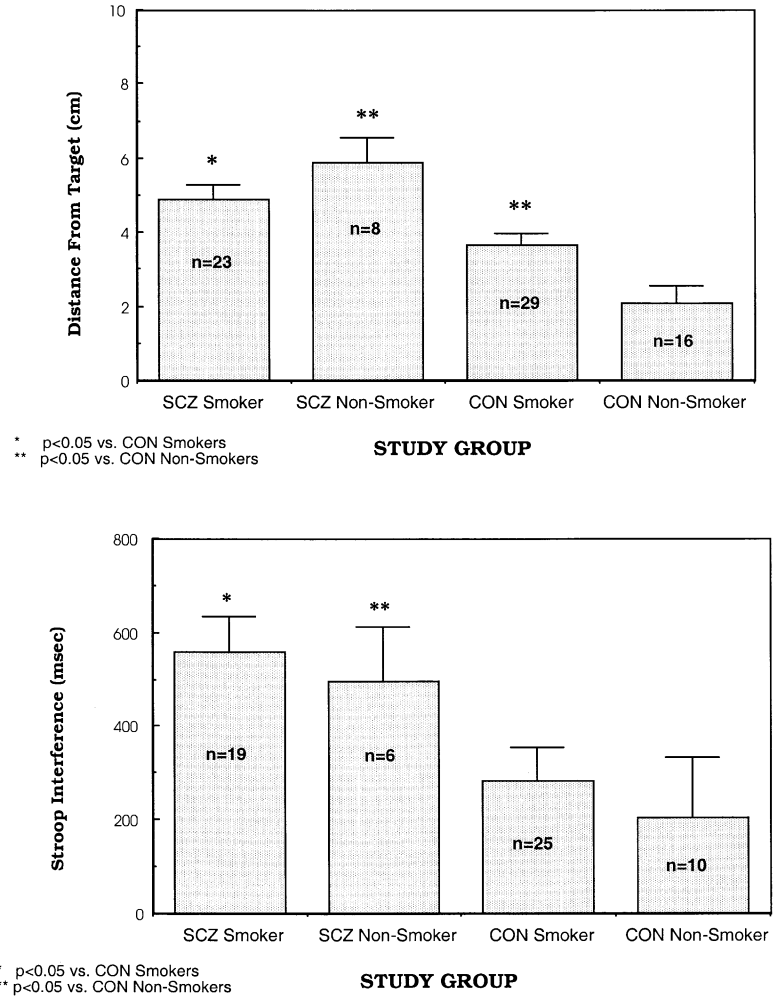


Figure 1. Baseline visuospatial working memory (VSWM, Top Panel) and Stroop Interference (SI, Bottom Panel) in schizophrenic vs. control smokers and non-smoking controls. SCZ = Schizophrenic; CON = Control. Bars indicate Mean ± Standard Error.

elapsed. The final screen (Screen 3) involved the subjects being prompted by a question mark to identify the exact location where the object in Screen 1 appeared on the screen (default length of 5 seconds), by moving the cursor to the screen location where the subject recalled the dot was located in Screen 1. A blank screen appeared for a total of two seconds between trials. A total of 16 trials were completed, and VSWM performance results are reported as the averaged "distance from target" in cm for the 16 trials. This computerized version of the VSWM task took approximately 15 minutes to complete.

The SCWT measures participants' ability to shift their perceptual set to conform to changing conditions, and also assesses executive functions such as mental control, response flexibility, and the occurrence of perceptual interference. Participants were required to report the color in which each word is printed, and used numbered keys on the computer keyboard (e.g. "1" for green, "2" for red, "3" for blue) to indicate color choice. Color words appeared for 500 msec. The difference in time (msec) to respond to the asynchronous color name (i.e. the word BLUE, presented in red letters) compared to the neutral condition (e.g. a series of Xs presented in red letters) is known as the Stroop Interference (SI). A total of 32 color-word pairs were presented. This computerized version of the SCWT takes approximately 15 minutes to complete.

Verification of Smoking Abstinence

At baseline, all subjects had assessment of Fagerstrom Test for Nicotine Dependence (FTND) scores (Heatherton et al. 1991), average weekly cigarettes/day smoked, expired breath carbon monoxide (CO) determination (Vitalograph CO Breathalyzer, Lenexa, KS) and plasma and urine cotinine levels (Foundation for Blood Research, Scarborough, ME). At baseline, all schizophrenic and control smokers had an FTND score >5, expired breath CO >10 ppm, self-reported smoking of at least 20 cigarettes/day in the week prior to assessment and plasma and urine cotinine levels >150 ng/ml and >600 ng/ml respectively. The smoking quit date was set at the beginning of Week 3 of each study for schizophrenic and control smokers, and all subjects whose neuropsychological data was analyzed attempted smoking abstinence at this time. Subjects were

classified as abstinent from smoking if at trial endpoint (Week 10 in schizophrenics, Week 8 in controls) if: 1) they endorsed smoking abstinence, and; 2) they had an expired breath CO level <10 ppm; in some cases, smoking abstinence was confirmed with a plasma cotinine level <50 ng/ml. The Tiffany Questionnaire for Smoking Urges (QSU) (Tiffany and Drobes 1991) was used to monitor nicotine craving and withdrawal symptoms during the trials. CO levels were obtained at the time of each neuropsychological testing session.

Statistical Analysis

Analysis of covariance (ANCOVA) was used to compare baseline VSWM ("distance from target" in cm) and Stroop Interference (SI, msec) measurements among the four groups, adjusting for differences in age, education and depressive symptoms between study groups. Two- and 3-factor repeated measures analysis of variance (ANOVA) (using diagnosis, smoking status and medication assignment as between-subject factors, and time as a within-subjects factor) was used to examine differences on VSWM and SI between quitters and non-quitters in both schizophrenic and control smoker groups during the course of the smoking cessation trials. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) v10.0 software.

RESULTS

Demographic and Clinical Characteristics of Study Subjects

The demographic and clinical characteristics of schizophrenic (SCZ) and control (CON) smokers and non-smokers are given in Table 1. SCZ and CON non-smokers significantly differed on age and years of education ($p < .05$). SCZ non-smokers had higher PANSS negative and total symptom scores, and lower Beck Depression Inventory (BDI) scores than SCZ smokers at baseline ($p < .05$). Control smokers were significantly older and less educated than CON non-smokers, and had significantly higher BDI scores than CON non-smokers ($p < .05$). There were no significant differences between SCZ smokers and non-smokers on medication side effect ratings. Of the SCZ non-smokers, 3/8 were nicotine-naïve,

Table 1. Baseline Demographic and Clinical Characteristics of Schizophrenic and Control Smokers and Non-Smokers

Variable	Schizophrenic Smokers (n = 23)	Schizophrenic Non-Smokers (n = 8)	Control Smokers (n = 29)	Control Non-Smokers (n = 16)
Age (years)	43.9 ± 12.1	41.5 ± 7.6	49.9 ± 8.1[a]	33.1 ± 12.5[b,c]
Race	14w/8b/1o	6w/2b	20w/7b/2o	14w/2o
Sex	12m/11f	6m/2f	8m/21f	6m/10f
Education (years)	11.5 ± 1.9	13.0 ± 2.2	14.1 ± 2.6[a]	17.7 ± 3.4[b,c]
Cigarettes Per Day	24.0 ± 11.3	n/a	21.6 ± 7.2	n/a
Baseline CO (ppm)	18.3 ± 9.7	n/a	21.8 ± 8.9	n/a
FTND	7.1 ± 1.3	n/a	6.6 ± 1.6	n/a
Plasma Cotinine (ng/ml)	306 ± 119	n/a	264 ± 99	n/a
Urine Cotinine (ng/ml)	1859 ± 1171	n/a	1904 ± 829	n/a
Diagnosis	15scz/8sca	4scz/4sca	n/a	n/a
PANSS Positive	11.8 ± 3.3	13.3 ± 2.1	n/a	n/a
PANSS Negative	11.4 ± 4.1	19.3 ± 3.5[a]	n/a	n/a
PANSS General	24.0 ± 4.3	21.8 ± 3.1	n/a	n/a
PANSS Total	47.3 ± 8.0	54.3 ± 3.7[a]	n/a	n/a
BDI	10.2 ± 7.2	4.0 ± 3.1[a]	8.3 ± 7.0	2.7 ± 2.7[b]
WEPS	2.0 ± 2.4	0.6 ± 1.2	n/a	n/a
AIMS	1.4 ± 2.1	0.4 ± 0.7	n/a	n/a
Antipsychotic Class	15 ATP/8 TYP	6 ATP/2 TYP	n/a	n/a

[a] $p < 0.05$ vs. SCZ smokers
[b] $p < 0.05$ vs. CON smokers
[c] $p < 0.05$ vs. SCZ non-smokers
W = white; B = black; O = other race; M = male; F = female; SCZ = schizophrenic; SCA = schizoaffective disorder; PANSS = Positive and Negative Symptom Scale for Schizophrenia; FTND = Fagerstrom Test for Nicotine Dependence; CO = Carbon Monoxide; WEPS = Webster Extrapyramidal Scale; AIMS = Abnormal Involuntary Movements Scale; BDI = Beck Depressive Inventory; ATP = Atypical Antipsychotic Drug; TYP = Typical Antipsychotic Drug; N/A = Not Assessed

and 5/8 had been smoking abstinent for at least one year prior to assessments.

Demographic and clinical characteristics of SCZ and CON smokers, as a function of smoking status at trial endpoint, are given in Tables 2 and 3 respectively. There were no baseline differences between SCZ patients who achieved smoking abstinence for up to 10 weeks after the quit date (Week 3) and non-abstainers, with the exception that quitters had significantly lower baseline BDI scores ($p < .05$) than non-quitters, and that all schizophrenic quitters were prescribed atypical antipsychotic agents ($p < .05$) (Table 2). There were no baseline differences between control quitters and non-quitters (Table 3). Similarly, there were no baseline differences between SCZ and CON smokers prescribed active vs. placebo study medication (data not shown).

Table 3. Baseline Demographic and Clinical Characteristics of Control Smokers

Variable	Quitters (n = 11)	Non-Quitters (n = 18)	*p*-value
Age (years)	49.6 ± 7.7	50.1 ± 8.4	$p = .89$
Race	7w/3b/1o	13w/4b/1o	$p = .08$
Sex	4m/7f	4m/14f	$p = .28$
Education (years)	15.2 ± 2.8	13.5 ± 2.3	$p = .10$
Cigarettes/Day	21.3 ± 8.5	21.7 ± 6.7	$p = .87$
Baseline CO (ppm)	24.6 ± 13.0	20.3 ± 5.8	$p = .23$
FTND	6.1 ± 1.2	6.8 ± 1.8	$p = .25$
Plasma Cotinine (ng/ml)	227 ± 108	294 ± 90	$p = .29$
Urine Cotinine (ng/ml)	1815 ± 671	1951 ± 915	$p = .68$
BDI	5.7 ± 4.7	9.7 ± 7.7	$p = .15$

CO = Carbon Monoxide
FTND = Fagerstrom Nicotine Dependence Test
BDI = Beck Depression Inventory

VSWM and SI in Schizophrenic vs. Control Smokers and Non-smokers

Differences in VSWM and SI as a function of psychiatric diagnosis and smoking status are shown in Figure 1. For VSWM (Top Panel), there was a significant main effect of Diagnosis ($F = 26.6$, 1,71, $p < .01$) but not Smoking Status ($F = 0.31$, df = 1,71, $p = .58$), and a significant Diagnosis X Smoking Status interaction ($F = 6.85$, df = 1,71, $p < .05$). VSWM function was significantly impaired in schizophrenic compared to control smokers ($p < .05$). Furthermore, schizophrenic smokers appeared to have improved VSWM function compared to non-smoking schizophrenics, but this difference was not significant ($p = .20$). Interestingly, healthy smokers had impairments in VSWM compared to non-smoking controls ($p < .05$). There were differences between groups insofar as age, education and depressive symptoms between subjects in the four groups (see Table 1), but a one-way ANCOVA adjusting for these covariates confirmed the Diagnosis X Smoking Status interaction on VSWM ($F = 5.08$, df = 3,69, $p < .01$).

Table 2. Baseline Demographic and Clinical Characteristics of Schizophrenic Smokers

Variable	Quitters (n = 8)	Non-Quitters (n = 15)	*p*-value
Age (years)	38.9 ± 12.3	46.6 ± 11.6	$p = .15$
Race	4w/3b/1o	10w/5b	$p = .34$
Sex	4m/4f	8m/7f	$p = .88$
Diagnosis	3scz/5sca	12scz/3sca	$p = .11$
Education (years)	12.3 ± 1.7	11.1 ± 1.9	$p = .18$
Cigarettes Per Day	25.3 ± 14.9	23.3 ± 9.4	$p = .70$
Baseline CO (ppm)	13.4 ± 4.7	20.9 ± 10.7	$p = .08$
FTND	6.9 ± 1.2	7.2 ± 1.3	$p = .58$
Plasma Cotinine (ng/ml)	250 ± 105	325 ± 126	$p = .48$
Urine Cotinine (ng/ml)	2197 ± 1333	1677 ± 1079	$p = .32$
PANSS Positive	10.6 ± 3.6	12.5 ± 3.0	$p = .21$
PANSS Negative	10.0 ± 2.2	12.2 ± 4.7	$p = .23$
PANSS General	22.9 ± 4.3	24.6 ± 4.4	$p = .38$
PANSS Total	43.5 ± 7.2	49.3 ± 7.8	$p = .10$
AIMS	1.4 ± 2.1	1.4 ± 2.2	$p = .98$
WEPS	2.1 ± 2.4	1.9 ± 2.4	$p = .81$
Antipsychotic Class	8 ATP	7 ATP/8 TYP	$p < .05$
BDI	6.1 ± 3.9	12.4 ± 7.8	$p < .05$

SCZ = Schizophrenia; SCA = Schizoaffective; PANSS = Positive and Negative Symptoms Scale for Schizophrenia; AIMS = Abnormal Involuntary Movements Scale; WEPS = Webster Extrapyramidal Scale; ATP = Atypical Antipsychotic Drug; TYP = Typical Antipsychotic Drug; BDI = Beck Depressive Inventory

For the SCWT (Bottom Panel), there was a main effect of Diagnosis ($F = 9.74$, df = 1,42, $p < .01$) on Stroop Interference (SI), with schizophrenic patients (irrespective of smoking status) having higher SI than controls ($p < .05$), but no main effects of Smoking Status ($F = 2.24$, df = 1,42, $p = .14$), and no Diagnosis X Smoking Status interaction ($F = 0.29$, df = 1,42, $p = .60$).

Smoking Abstinence in Schizophrenic and Control Subjects at Trial Endpoint

A total of 8/23 (34.8%) schizophrenic subjects and 11/29 (37.9%) control subjects met criteria for smoking abstinence at trial endpoint. Trial endpoint smoking abstinence rates by medication status were: Bupropion 6/12 (50.0%) vs. Placebo 2/11 (18.2%; chi-square = 2.56, df = 1, $p = .11$); Selegiline 8/14 (57.1%) vs. Placebo 3/15 (20.0%; chi-square = 2.89, df = 1, $p = .09$). Five of eight schizophrenic and 6/11 control quitters achieved continuous smoking abstinence from the quit date (Week 3) until trial endpoint. However, the directional changes in VSWM function in schizophrenic and control subjects were similar between continuous and non-continuous abstainers (see next section).

Effects of Smoking Abstinence on VSWM and SCWT Performance in Schizophrenics vs. Controls

VSWM. Smoking abstinence-related changes in VSWM in schizophrenic and control subjects are shown in Figures 2 and 3 respectively. Smoking abstinence leads to: 1) further impairment of baseline deficits in VSWM in schizophrenic smokers as evidenced by a significant Smoking Status X Time interaction ($F = 6.11$, $df = 2,22$, $p < .01$) (Figure 2), and; 2) improvement in VSWM in control smokers ($F = 3.16$, $df = 2,40$, $p < .05$) (Figure 3), confirming Diagnosis X Smoking Status interactions suggested by our between-groups data (see Figure 1). Furthermore, a repeated measures ANOVA procedure demonstrated a significant Diagnosis X Smoking Status X Time interaction for the combined VSWM data in schizophrenic and control smokers ($F = 3.70$, $df = 2,62$, $p < .05$). When effects of smoking abstinence on VSWM were assessed as a function of gender, we observed that there were no differences in abstinence-induced impairments in VSWM in male vs. female schizophrenic smokers, but that improvements in VSWM induced by smoking abstinence in controls were confined to female subjects. A 2-factor repeated measures ANOVA found a nearly significant Smoking Status X Gender X Time interaction ($F = 3.53$, $df = 1,21$, $p = .07$), and a significant *post-hoc* difference ($p < .05$) in VSWM between female and male control quitters at Week 8 (data not shown).

A comparison of VSWM at baseline (Week 1) compared to Week 4 and Week 10 in schizophrenic smokers treated with bupropion or placebo who did not achieve smoking abstinence suggested that there were no significant effects of bupropion on VSWM function in schizophrenic smokers (Bupropion Non-Quitter Group (n = 6), Week 1: 4.73 ± 1.02; Week 4: 5.44 ± 1.77; Week 10; 5.69 ± 2.14 cm; Placebo Non-Quitter Group (n = 9), Week 1: 6.20 ± 3.06; Week 4: 6.15 ± 2.08; Week 10: 5.76 ± 2.81; Medication X Time, $F = 2.34$. $df = 2,24$, $p = .12$), suggesting that the changes in VSWM with bupropion were most likely due to the effects of smoking abstinence in these patients, and were independent of study medications. In fact, the two schizophrenic subjects who achieved smoking abstinence in the placebo group had further impairments in VSWM during the trial (data not shown), and, in the total schizophrenic smoker sample, there were no significant Medication effects ($F = 0.48$, $df = 3,13$, $p = .70$) or Medication X Time interactions ($F = 0.34$, $df = 2,26$, $p = .71$) on VSWM in schizophrenic subjects. Similarly, improvements in VSWM in control smokers during smoking abstinence were likely due to the effects of smoking abstinence, and not due to the effects of the study medication (Selegiline Non-Quitter Group (n = 6), Week 1: 4.45 ± 2.46; Week 4: 5.76 ± 2.94; Week 8: 5.77 ± 2.49 cm; Placebo Non-Quitter Group (n = 12), Week 1: 3.61 ± 1.59; Week 4: 3.00 ± 2.29; Week 8: 3.43 ± 1.44; Medication X Time, $F = 1.65$, $df = 2,32$, $p = .21$). Three control subjects on placebo who quit smoking had the expected improvements in VSWM (data not shown), and there were no significant Medication effects ($F = 1.84$, $df = 3,20$, $p = .17$) or Medication X Time interactions ($F = 2.27$, $df = 2,40$, $p = .12$) in the total sample of control smokers. We also examined Medication X Smoking Status X Time effects on VSWM. In both schizophrenic ($F = 0.41$, $df = 2,26$, $p = .66$) and control ($F = 0.37$, $df = 2,40$, $p = .65$) groups, these interactions were not significant, but given the small group sizes for placebo quitters (n = 2 for schizophrenics, n = 3 for controls), our analysis had limited statistical power. Furthermore, sustained changes in VSWM at trial end-

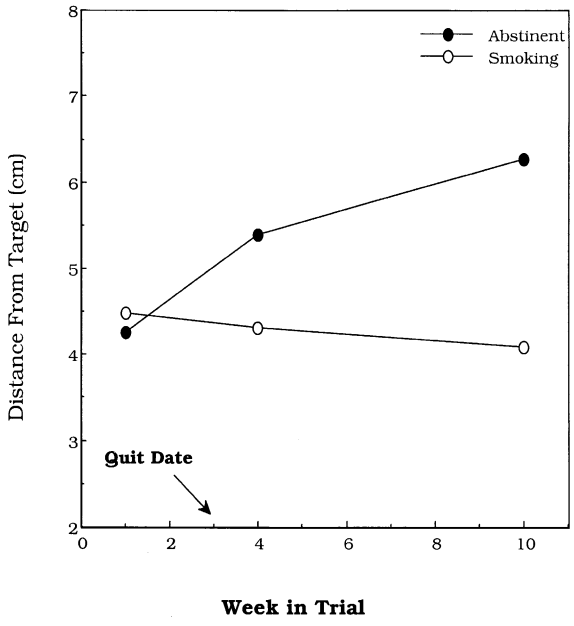


Figure 2. Effects of smoking abstinence on visuospatial working memory (VSWM) function in schizophrenic smokers.

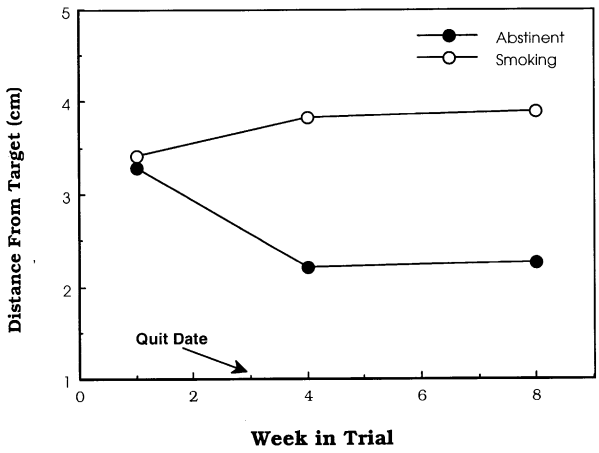
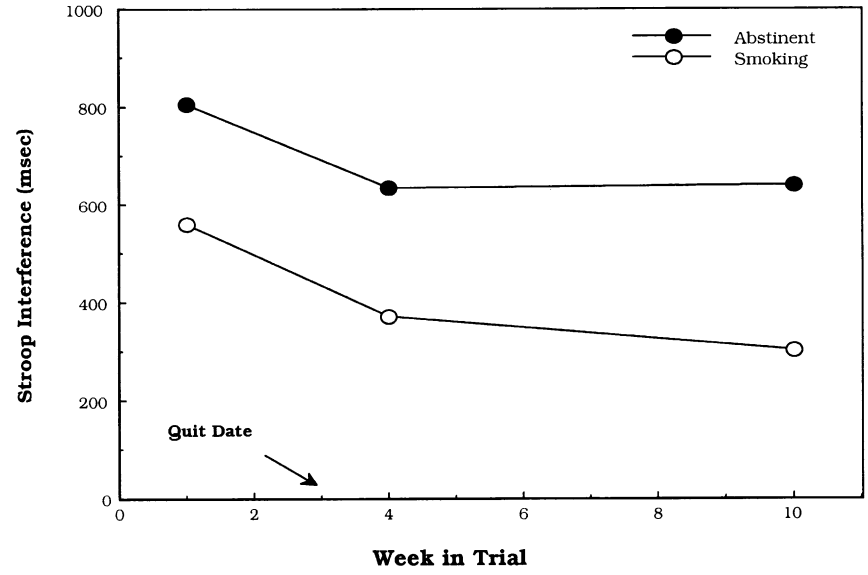


Figure 3. Effects of smoking abstinence on visuospatial working memory (VSWM) function in control smokers.

point in both schizophrenic and control quitters were not due to elevated nicotine craving and withdrawal symptom ratings, since there were reductions in nicotine craving and withdrawal scores on the Tiffany QSU at trial endpoint compared to baseline (Week 1) and one-week post quit date (Week 4) ratings (data not shown).

SCWT. The effects of smoking abstinence on SCWT performance in schizophrenic and control smokers are presented in Figure 4. Schizophrenic smokers exhibited significant increases in baseline SI reaction times (Figure 4, Top Panel) compared to control (Figure 4, Bottom Panel) smokers, but there were no significant Smoking Status X Time interactions in either schizophrenic ($F = 0.31$, $df = 2,22$, $p = .67$) or control ($F = 0.23$, $df = 2,34$, $p = .77$) smokers, suggesting that smoking abstinence did not significantly alter SI. An examination of Figure 4 suggested that smoking abstinence increased SI in schizophrenic smokers, and while non-significant, this difference appeared to be due to an increase in the incongruent reaction time (data not shown). There were practice effects (decreases in SI) with repeated SCWT administration in schizophrenic vs. control patients (Figure 4). Furthermore, there were no significant ef-



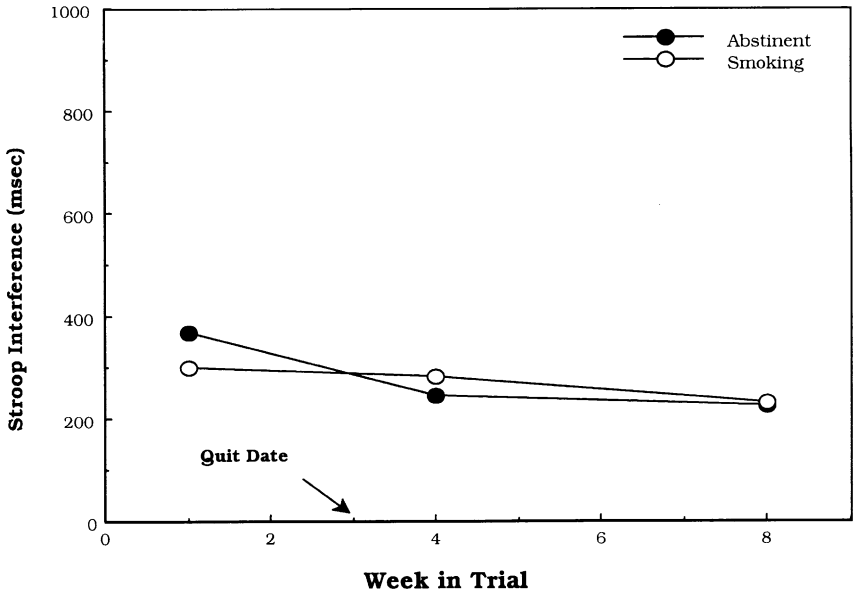


Figure 4. Effects of smoking abstinence vs. continued smoking on Stroop Interference in schizophrenic (Top Panel) vs. healthy control (Bottom Panel) smokers.

fects of Medication (Schizophrenic: F = 1.22, df = 3,11, p = .35, Control: F = 1.34, df = 3,17, p = .29), Medication X Time interactions (Schizophrenic: F = 0.81, df = 2,22, p = .46, Control: F = 0.11, df = 2,34, p = .90) or Medication X Smoking Status X Time interactions (Schizophrenic: F = 0.01, df = 2,22, p = .97, Control: F = 0.34, df = 2,34, p = .69) on SI in either schizophrenic or control smokers.

DISCUSSION

Our preliminary data suggests that smoking abstinence leads to further impairment in VSWM function in schizophrenic patients, but, in contrast, produces improvements in VSWM in control smokers. The effects of smoking abstinence on VSWM appear to be independent of the study medications (e.g. bupropion and selegiline) used for smoking cessation, and nicotine craving and withdrawal symptoms. This apparent lack of effect of bupropion on VSWM in our study is of particular interest since it has been shown that this agent is: 1) a catecholamine reuptake inhibitor (Ascher et al. 1995), and; 2) a non-competitive antagonist of nicotinic acetylcholine receptor sites (Slemmer et al. 2000). One potential explanation for our findings with respect to prolonged smoking abstinence and changes in VSWM is that smoking abstinence led to increases in plasma antipsychotic levels, since cigarette smoking is known to increase the hepatic clearance of certain antipsychotic agents (Perry et al. 1993; Ziedonis and George 1997). This possibility appears unlikely since changes in VSWM in response to smoking abstinence occurred within 1 week of abstinence, and the time course for the increase in antipsychotic plasma levels after smoking cessation is in the range of 2–4 weeks (Perry et al. 1993; Ziedonis and George 1997). Furthermore, it should be noted that neither the antipsychotic medication or dose was changed during the smoking cessation trial in schizophrenic smokers, so changes in VSWM observed in schizophrenic subjects during smoking abstinence were not likely due to antipsychotic medication effects, and were probably related to the effects of smoking abstinence. We also observed that all schizophrenic quitters (n = 8) were prescribed atypical antipsychotic agents (see Table 2), suggesting that atypical antipsychotic agents may enhance smoking cessation responses to bupropion (Head et al. 2001).

The effects of atypical antipsychotic drugs on spatial working memory deficits in schizophrenic patients have not been well-characterized (Meltzer et al. 1999; Meltzer and McGurk 1999). Clozapine is known to reverse drug-induced spatial working memory deficits in non-human primates (Jentsch et al. 1997; Murphy et al. 1997), and risperidone may modestly improve SWM deficits in schizophrenic patients (McGurk et al. 1996). While differences in the rates of prescription of atypical vs. typical antipsychotic drugs between the schizophrenic smoker and schizophrenic non-smoker groups could account for some of the differences (albeit non-significant) in VSWM between these groups (Figure 1), and in comparison to the control groups, they would not account for the differences in VSWM in schizophrenic smokers who achieved smoking abstinence vs. those who did not quit smoking (e.g. within-subjects comparison; Figure 2) since antipsychotic medications were not changed during the smoking cessation intervention.

Interestingly, Park et al. (2000) recently showed that acute cigarette smoking impairs spatial working memory function (but improves spatial selective attention) in healthy smokers. Thus, it appears that smoking may have differential effects in schizophrenic and healthy control smokers, and our results may support a "self-medication hypothesis" for cigarette smoking and cognitive dysfunction in schizophrenia. VSWM is dependent, in part, on cortical dopamine (DA) function that is presumed to be reduced in schizophrenia (Williams and Goldman-Rakic 1995). Furthermore, Parkinson's disease, which is characterized by nigrostriatal DA depletion, is also associated with impairments in SWM (Owen et al. 1993; Postle et al. 1997). Thus, our data is consistent with the notion that cigarette smoking may increase cortical DA hypofunction towards "normal" levels, thereby improving VSWM in schizophrenia. In contrast, cigarette smoking may augment normal cortical DA in control smokers to excessive levels, thus impairing VSWM. This is consistent with animal data that suggests an "inverted-U" shaped response between cortical DA function and SWM (Zahrt et al. 1997; George et al. 1998; George et al. 2000b; George et al. 2000c). Furthermore, our findings in schizophrenic smokers are consistent with the results of Kirrane et al. (2000) who observed that administration of the psychostimulant D-amphetamine improves deficits in VSWM function in schizophrenic spectrum personality disorders subjects, who may have cortical DA deficits that resemble those in schizophrenic patients.

We also observed that abstinence-induced changes in VSWM varied as a function of gender in controls (e.g., the improvements in VSWM in control quitters appeared to be confined to females). However, no gender differences in VSWM in response to smoking abstinence were observed in schizophrenic smokers, consistent with the lack of gender effects on cognitive dysfunction in schizophrenic patients (Goldberg et al. 1995). Our data in control smokers suggests that there may be gender-related differences in the effects of cigarette smoking on this aspect of cognitive function. This observation could relate to estrogen's potentiation of central DA function (Castner et al. 1993; Markowska 1999).

Differences in VSWM among the four groups (SCZ and CON smokers and respective non-smoking controls) are consistent with the smoking abstinence data from the within-subjects assessments, but are complicated by differences between the smoking and non-smoking groups, including age, educational attainment and depressive symptom ratings. The significantly higher negative symptom scores, and lower depression rating scores in schizophrenic non-smokers are consistent with greater chronicity of schizophrenic illness in this group (Kirkpatrick et al. 1995). It is unclear if non-smoking schizophrenics have some trait difference compared to schizophrenic smokers, or are incomplete responders to antipsychotic drug therapy. Further controlled evaluations of clinical and cognitive measures in schizophrenic smokers and non-smokers after careful matching on baseline measures is warranted, and should clarify these issues.

Our data with administration of the SCWT suggests that schizophrenic smokers have deficits in baseline SI compared to control smokers, consistent with previous studies (Hepp et al. 1996). In the present study, smoking abstinence does not appear to significantly alter Stroop Interference in schizophrenic or control smokers, though our sample size was smaller than with the VSWM task, and thus our ability to detect significant differences between abstinent and smoking SCZ and CON groups may have been limited. Previous studies of smoking abstinence effects on SCWT have shown increases in congruent and incongruent color naming reaction times but no significant changes in SI, consistent with our study results (Provost and Woodward 1991), while administration of nicotine gum has been shown to decrease SI in nicotine-naïve, non-smoking subjects (Provost and Woodward 1991).

Limitations of this study include: 1) the confounding influence of the two study medications and the small sample of subjects in the placebo groups who quit smoking ($n = 2$ in schizophrenic, and $n = 3$ in control smoking groups), limiting our ability to analyze Medication X Smoking Status X Time interactions (though our analysis suggests that both bupropion and selegiline did not significantly alter VSWM performance in both schizophrenic and control non-quitters); 2) failure of all subjects to attain continuous smoking abstinence (as documented by CO levels) from the quit date through trial endpoint in both schizophrenic and control subjects which may have influenced the VSWM data towards a reduced difference between abstinent vs. non-abstinent SCZ and CON smoking groups; 3) demographic and clinical differences between the study groups (e.g. age, education and depressive symptoms) which could account for some of the observed baseline differences in VSWM, and; 4) no assessment of acute smoking abstinence (<24 hours) effects on VSWM function in schizophrenic vs. control groups which could more clearly indicate the onset of abstinence-related changes in VSWM function in schizophrenic vs. control smokers.

Taken together, the present results have implications for understanding the effects of cigarette smoking and nicotine on VSWM, and suggest that cigarette smoking may have beneficial effects on VSWM function in schizophrenic, but not control, smoking subjects. Our results may have implications for the development of novel treatment approaches based on nicotinic receptor mechanisms for neuropsychiatric disorders characterized by neurocognitive dysfunction, including schizophrenia and other nicotine-responsive neuropsychiatric disorders (e.g., Parkinson's Disease, Tourette's Syndrome) (Piasecki and Newhouse 2000).

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