

Effects of Cigarette Smoking on Spatial Working Memory and Attentional Deficits in Schizophrenia

Involvement of Nicotinic Receptor Mechanisms

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Background: Cigarette smoking rates in schizophrenia are higher than in the general population.

Objectives: To determine whether cigarette smoking modifies cognitive deficits in schizophrenia and to establish the role of nicotinic acetylcholine receptors (nAChRs) in mediating cigarette smoking-related cognitive enhancement.

Design: Neuropsychological assessments were performed at smoking baseline, after overnight abstinence, and after smoking reinstatement across 3 separate test weeks during which subjects were pretreated in a counterbalanced manner with the nonselective nAChR antagonist mecamylamine hydrochloride (0, 5, or 10 mg/d).

Participants: Twenty-five smokers with schizophrenia and 25 control smokers.

Setting: Outpatient mental health center.

Main Outcome Measures: Visuospatial working

memory (VSWM) and Continuous Performance Test (CPT) scores.

Results: In smokers with schizophrenia and control smokers, overnight abstinence led to undetectable plasma nicotine levels and an increase in tobacco craving. While abstinence reduced CPT hit rate in both groups, VSWM was only impaired in smokers with schizophrenia. Smoking reinstatement reversed abstinence-induced cognitive impairment. Enhancement of VSWM and CPT performance by smoking reinstatement in smokers with schizophrenia, but not the subjective effects of smoking, was blocked by mecamylamine treatment.

Conclusions: Cigarette smoking may selectively enhance VSWM and attentional deficits in smokers with schizophrenia, which may depend on nAChR stimulation. These findings may have implications for understanding the high rates of smoking in schizophrenia and for developing pharmacotherapies for cognitive deficits and nicotine dependence in schizophrenia.

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SCHIZOPHRENIA IS ASSOCIATED with wide-ranging deficits in neurocognitive function, including attention, verbal learning and memory, executive function, and spatial working memory.^{1,2} Many of these deficits are associated with dysfunction of the prefrontal cortex, are evident during periods of symptom remission, and significantly affect quality of life even in optimally treated patients.³ Furthermore, antipsychotic drugs, especially neuroleptics, may contribute to neurocognitive deficits in schizophrenia.⁴

In animal studies, spatial working memory and executive cognitive task performance have been shown to be dependent in part on prefrontal cortical dopamine function.^{5,6} Dopamine release in cortical regions is enhanced by nicotine administration,⁷⁻¹⁰ and conversely, nicotine

withdrawal has been associated with reductions in dopamine function.^{8,11,12} Correspondingly, there is evidence to suggest that nicotine administration can improve attentional and working memory deficits in schizophrenia,¹³⁻¹⁵ while abstinence may worsen spatial working memory deficits.¹⁶ Therefore, individuals with schizophrenia may be vulnerable to cigarette smoking as a means of self-administering nicotine to remediate cognitive deficits,^{15,16} which may partly explain why smoking rates are higher in schizophrenia (58%-88%) compared with the general population (approximately 23%).¹⁷⁻²¹

Furthermore, nicotine and smoking have been shown to remediate deficits in attention such as P50 auditory evoked potential gating deficits.^{22,23} Moreover, there is genetic evidence to suggest that the $\alpha 7$ subunit of the nicotinic acetylcholine re-

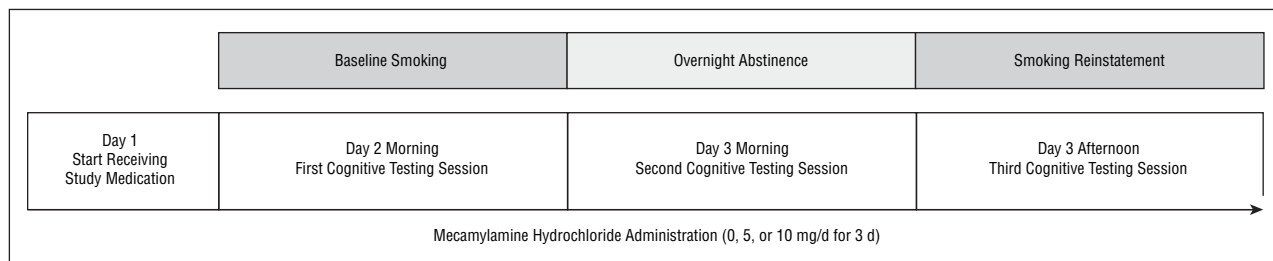


Figure 1. Single subject study timeline for smokers with schizophrenia and control smokers.

ceptor (nAChR) is associated with P50 gating deficits in this disorder²⁴ and that polymorphisms in the $\alpha 7$ nAChR subunit promoter region are linked to severity of P50 gating deficits in individuals with schizophrenia and their first-degree relatives. In addition, postmortem studies have demonstrated that tritiated nicotine binding is reduced in schizophrenic compared with healthy control brain regions, including the striatum, thalamus, hippocampus, and prefrontal cortex.²⁵

More direct evidence linking particular cognitive deficits with particular neuroreceptors can be gathered by in vivo manipulation of receptors with appropriate agonists and antagonists. While there are few pharmacological agents available for use besides nicotine to study nAChR function in human subjects, mecamylamine hydrochloride (MEC) is a ganglionic blocker approved for the treatment of mild to moderate hypertension and a non-selective nAChR antagonist.²⁶ In vitro studies have suggested that MEC is a noncompetitive antagonist (at the ion channel site) of several nAChR subtypes in the low-micromolar (0.5-5.0) range, including $\alpha 4\beta 2$, $\alpha 3\beta 4$, $\alpha 3\beta 2$, and $\alpha 7$.²⁷ In addition, MEC may block effects of nicotine by reducing its transport into the brain.²⁸ Mecamylamine does not disrupt the rodent analogue of P50 responses (N40 responses), and studies in humans have shown that it does not alter P50 deficits,²⁹ suggesting that MEC does not antagonize $\alpha 7$ nAChRs.³⁰ The role of nAChRs in mediating the effects of nicotine^{14,15} and smoking-related¹⁶ cognitive enhancement in patients with schizophrenia and in cigarette smokers without psychiatric disorders, however, has not been convincingly established. Evidence to solidly implicate nAChR involvement in mediating such cognitive enhancement would provide justification for the development of nAChR agents in the treatment of neurocognitive deficits associated with schizophrenia.

Accordingly, the purpose of this study was to: (1) establish the effects of short-term cigarette smoking and abstinence on neuropsychological function in subjects with schizophrenia and nonpsychiatric control subjects, and (2) to determine the involvement of central nAChRs in mediating the effects of cigarette smoking on these cognitive tasks by pretreating subjects with MEC.

METHODS

SUBJECTS

Seventy-five smokers with schizophrenia and 80 control smokers were screened for study participation. After baseline evalu-

ations, 32 smokers with schizophrenia and 28 control smokers were enrolled in this study. Twenty-five smokers with schizophrenia and 25 control smokers who completed the entire study were judged to be free of protocol violations. Seven smokers with schizophrenia and 3 controls were excluded because of an inability to abstain from smoking overnight for a single test session, leading to withdrawal of informed consent (3 smokers with schizophrenia); housing problems (1 smoker with schizophrenia); a positive urine toxicology screen for drugs of abuse (1 smoker with schizophrenia, 2 controls); positive alcohol breathalyzer results (1 control); and unwillingness to complete study procedures (2 smokers with schizophrenia). Patients were recruited from the Connecticut Mental Health Center in New Haven, while controls were recruited from the community using newspaper advertisements and flyers. Written informed consent was obtained from all participants and the protocol was approved by the Yale Medical School Human Investigation Committee.

Subjects were screened using the Structured Clinical Interview for DSM-IV Axis I Disorders.³¹ Subjects meeting criteria for schizophrenia or schizoaffective disorder were included in the schizophrenia group. Subjects with schizophrenia were outpatients who were judged to be psychiatrically stable by the study psychiatrist (T.P.G.) and another trained professional (J.C.V. or K.A.S.) and were prescribed a stable dose of antipsychotic medication (typical or atypical) for at least 3 months prior to study assessments. Controls demonstrated no current Axis I disorder on the Structured Clinical Interview for DSM-IV Axis I Disorders; those with a history of major depression or drug and alcohol abuse in remission for at least 1 year were included if they satisfied other study criteria. Intellectual ability was assessed using the Shipley Institute of Living Scale³² from which an estimated Full Scale Wechsler Adult Intelligence Scale-Revised IQ score was derived³³; subjects were required to have an estimated IQ of greater than 80 to be eligible for study participation.

All subjects were cigarette smokers meeting criteria that included smoking more than 15 cigarettes per day, which was assessed using a self-reported, 7-day timeline follow-back measuring number of cigarettes smoked per day,³⁴ expired breath carbon monoxide levels of more than 10 ppm, and plasma cotinine levels of more than 150 ng/mL. Subjects were classified as nicotine dependent using DSM-IV criteria³⁵ and as defined by a score of more than 5 on the Fagerstrom Test for Nicotine Dependence.³⁶

PROCEDURES

Weekly test sessions spanned 3 consecutive days per week during 3 separate test weeks and included 4 laboratory sessions (day 1, day 2, day 3 morning, day 3 afternoon) (**Figure 1**). Subjects (>90%) completed the 3 weekly test sessions over the course of 3 consecutive weeks, or at a maximum during a 2-month period, with no more than 3 intervening weeks between experimental testing weeks. Day 1 consisted of the administration of study medication along with psychiatric rating scales (psychi-

atric group) and nicotine dependence and withdrawal measures. On the first day of testing (day 2 morning), subjects underwent the neurocognitive test battery while being permitted to smoke during hourly smoke breaks. Subjects remained abstinent on the evening of day 2 after 8 PM in order to undergo the neurocognitive battery during short-term abstinence on the following morning (day 3). Once smoking abstinence was verified on the morning of day 3 (approximately 9 AM, using the criterion of expired breath carbon monoxide levels <10 ppm), they were eligible to proceed with day 3 testing. Following completion of the day 3 morning session, smokers recommenced smoking as needed for satiety and were instructed to "smoke until you are satisfied." The final neurocognitive battery was administered during the afternoon session (day 3). Subjects were paid \$25 for completing each day 2 morning session and \$100 if they successfully remained abstinent from smoking overnight and successfully completed the day 3 morning and afternoon sessions. If they were not successful in quitting overnight, subjects were paid \$5 and given 1 additional opportunity the following week. This 20:1 ratio of contingent reinforcement for achieving overnight abstinence was effective in more than 90% of schizophrenic and control test sessions, consistent with previous reports on the use of contingent reinforcement in persons with schizophrenia.^{37,38} All subjects were administered MEC study medication (0, 5, and 10 mg/d) counterbalanced across 3 separate test weeks (Figure 1). For subjects with schizophrenia, psychotropic medications were held during testing sessions.

Tobacco craving was measured using the Tiffany Questionnaire for Smoking Urges.³⁹ Changes in mood were assessed using the Beck Depression Inventory.⁴⁰ Psychotic symptoms were rated at each session in the patient group using the Positive and Negative Syndrome Scale.⁴¹ Study medication-related adverse events were assessed using the Adverse Events Checklist.⁴²

NEUROPSYCHOLOGICAL TEST BATTERY

Before administration of the test sessions, all subjects were given a training session conducted by the study neuropsychologist (K.A.S.) to ensure understanding of each task. Administration of the visuospatial working memory (VSWM) task, Stroop Color-Word Test (SCWT), and Word Serial Position Test (WSPT) was done using PsyScope 1.1.⁴³ (Carnegie Mellon University, Pittsburgh, Pa) on a Macintosh G4 computer (Apple, Cupertino, Calif), while the Continuous Performance Test (CPT) and the Wisconsin Card Sorting Test (WCST) were administered on a Pentium III personal computer (Dell Computer, Round Rock, Tex).

Visuospatial Working Memory Task

The VSWM task¹⁶ is a delayed-response spatial working memory task that assesses working memory for nonverbal (object) visuospatial stimuli. It presents the subject with an object at a particular location on the computer screen (screen 1), then presents a "distractor task" screen, which entails a sham performance task ("tic-tac-toe"; screen 2), appearing for variable fixed intervals (eg, delay 30 or 60 seconds), followed by a final screen that prompts the subject to identify where the original object had been located (screen 3). Performance is reported as the averaged "distance from target" in centimeters for 16 trials at each delay condition, with higher scores indicating more impaired VSWM performance.¹

Continuous Performance Test

The Connors' CPT-X⁴⁴ (MS-DOS version; Multi-Health Systems Inc, North Tonawanda, NY) is designed to measure sustained attention, concentration, response inhibition, and impulsivity. Sub-

jects 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.

Word Serial Position Test

The WSPT is a verbal memory test known to be deficient in schizophrenia and related to frontal cortical activation during functional magnetic resonance imaging.⁴⁵ Each of 36 trials begins with 4 nouns spoken with 1 second between words. One word is then repeated after a delay of 1, 5, or 9 seconds. Subjects are instructed to remember the 4 words in the order presented and indicate the serial position of the repeated word by pushing the appropriate number on the keyboard.

Stroop Color-Word Test

The SCWT measures subjects' 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.⁴⁶ Participants report the color ink in which the names of colors are printed. The difference in response time (in milliseconds) when the ink is a different color than the color name compared with a response time when the ink is the color name is "Stroop interference." Performance of the SCWT activates the anterior cingulate cortex.⁴⁷ Stroop interference is impaired in many neuropsychiatric disorders including schizophrenia.⁴⁸

Wisconsin Card Sorting Test

The WCST⁴⁹ assesses executive functions, including cognitive flexibility in response to feedback, and performance on this task is known to be impaired in schizophrenia and thought to relate to dorsolateral prefrontal cortex function.⁵⁰ 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 outcomes are categories completed, percentage of total errors, percentage of perseverative errors, and percentage of nonperseverative errors.

STUDY MEDICATION PROCEDURES AND PLASMA NICOTINE DETERMINATION

Mecamylamine hydrochloride as 2.5-mg tablets and matching placebo were obtained from Layton BioSciences, Inc (Sunnyvale, Calif) under an investigational new drug protocol (58 680) for use in neuropsychiatric disorders. Medication was administered as 2 tablets twice daily under double-blind conditions. Subjects were administered the first, third, fifth, and sixth doses in the outpatient laboratory by a trained research assistant, and the second and fourth doses of the study medication were given to subjects as take-home doses after the day 1 and 2 procedures were completed.

Venous plasma, to measure levels of nicotine and its metabolite cotinine, was obtained on day 2 (9 AM) and repeated on day 3 (9 AM and 1 PM, 1 hour after cigarette smoking reinstatement). Nicotine and cotinine concentrations (in nanograms per milliliter) were determined by reverse-phase high-pressure liquid chromatography. The procedure, adapted from Hariharan and VanNoord,⁵¹ was modified to enable an aqueous micro back-extraction clean-up step in place of solvent

Table 1. Demographic and Clinical Characteristics of 25 Smokers With Schizophrenia and 25 Control Smokers*

Variable	Smokers With Schizophrenia (n = 25)	Control Smokers (n = 25)	P Value
Age, y	42.5 ± 9.4	41.9 ± 10.9	.84
Sex†			.57
Male	13	11	
Female	12	14	
Race†			.31
White	12	17	
African American	11	6	
Other	2	2	
Education, y	12.3 ± 2.5	14.6 ± 2.7	.005‡
Shipley IQ	84.4 ± 14.1	102.2 ± 12.0	<.001‡
CPD	22.2 ± 11.9	21.2 ± 5.8	.73
Baseline CO level	21.9 ± 9.0	20.3 ± 10.1	.57
FTND score ³⁶	6.6 ± 1.5	6.6 ± 1.5	.97
Baseline plasma cotinine level, ng/mL	435 ± 208	292 ± 181	.02‡
Baseline plasma nicotine level, ng/mL	32.4 ± 16.3	22.2 ± 11.6	.02‡
Plasma cotinine level–CPD ratio	26.8 ± 20.8	15.3 ± 8.4	.02‡
BDI score ⁴⁰	10.6 ± 8.8	4.0 ± 3.2	<.001‡
PANSS score ⁴¹			
Positive	13.8 ± 2.5	NA	...
Negative	12.7 ± 3.2	NA	...
General	27.5 ± 4.1	NA	...
Total	54.0 ± 8.1	NA	...
Psychotic diagnosis†		NA	...
Schizophrenia	18		
Schizoaffective disorder	7		
Antipsychotic class†		NA	...
Atypical antipsychotic drug	18		
Typical antipsychotic drug	7		
Antimuscarinic treatment†			
Yes	14		
No	11		
CPZ equivalents, mg/d	720 ± 531	NA	...

Abbreviations: BDI, Beck Depression Inventory; CO, carbon monoxide; CPD, cigarettes per day; CPZ, chlorpromazine; FTND, Fagerstrom Test for Nicotine Dependence; NA, not applicable; PANSS, Positive and Negative Syndrome Scale; Shipley, Shipley Institute of Living Scale IQ Score from the Wechsler Adult Intelligence Scale–Revised.

*Values are expressed as mean ± SD unless otherwise indicated.

†Values are expressed as number of subjects.

‡Significant at $P < .05$.

evaporation. Briefly, following addition of an internal standard, 2-phenylimidazole, nicotine and cotinine were extracted from alkalized serum with a 40:60 mixture of dichloromethane hexane. Between-day precision coefficients of variation, at concentrations of 200 ng/mL (cotinine) and 20 ng/mL (nicotine), were 6.6% and 6.3%, respectively.

STATISTICAL METHODS

Demographic and clinical variables were compared between groups with independent samples t test or χ^2 analyses. Baseline differences in cognitive performance between groups were evaluated with independent t tests. There were 3 primary experimental questions: (1) Do smoking abstinence and reinstatement have different effects on cognition in patients and controls? This was evaluated for each neuropsychological test during the placebo test week with a 2-way (diagnosis \times session) analysis of variance (ANOVA). (2) Does MEC pretreatment alter the effects of reinstatement? Percentage enhancement produced by smoking reinstatement (calculated as day 3 afternoon session–day 3 morning session/day 3 morning session $\times 100\%$) was calculated in the schizophrenic and control group sessions for each drug dose condition and compared using 2-way (diagnosis \times dose) ANOVA. For pairwise post

hoc comparisons within sessions (day 2 morning, day 3 morning, day 3 afternoon) using a 1-way ANOVA model, a Bonferroni-corrected $\alpha = .05/3 = 0.0167$ was used to define statistical significance. (3) Does MEC itself alter cognitive performance at baseline in smokers with schizophrenia and control smokers? One-way ANOVAs in both schizophrenic and control smoker groups were performed to determine MEC dose effects in the baseline session (day 2), with Bonferroni-corrected post hoc analyses. All statistical analyses were performed using SPSS software version 12.0 for Windows (SPSS Inc, Chicago, Ill), and statistical significance in the ANOVA models was defined with $P < .05$.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF SAMPLE

Demographic and clinical variables are presented in **Table 1**. There were no differences between groups in age, sex, race, or cigarette smoking. Patients had significantly higher cotinine levels and plasma cotinine level–

Table 2. Baseline Comparisons of Smokers With Schizophrenia and Control Smokers on Various Neuropsychological Tasks*

Variable	Smokers With Schizophrenia (n = 25)	Control Smokers (n = 25)	P Value
CPT ⁴⁴			
Hit rate, %	97.8 ± 2.7	99.2 ± 0.5	.01†
Commission rate	36.2 ± 22.1	24.9 ± 19.4	.06
Hit rate reaction time, ms	395 ± 69	356 ± 67	.051
Hit rate variability index	14.6 ± 11.6	7.3 ± 4.7	.005†
Attentional index	2.6 ± 1.0	3.4 ± 1.1	.01†
VSWM, cm ¹⁶			
30-s delay	1.5 ± 0.8	1.2 ± 0.7	.09
60-s delay	1.9 ± 1.2	1.1 ± 0.5	.003†
WCST ⁴⁹			
Categories completed	4.6 ± 2.2	5.5 ± 1.3	.08
Perseverative errors, %	14.2 ± 12.4	8.6 ± 4.8	.045†
Total errors, %	24.1 ± 16.6	16.3 ± 10.6	.052
Perseverative responses, %	16.6 ± 16.3	9.0 ± 5.2	.03†
Nonperseverative responses, %	9.8 ± 7.0	7.5 ± 6.3	.23
WSPT ⁴⁵ correct responses,	71.4 ± 23.9	88.2 ± 15.4	.006†
SCWT, ⁴⁶ ms			
Incongruent	1203 ± 470	1061 ± 444	.28
Congruent	926 ± 271	792 ± 196	.053
Neutral	926 ± 203	780 ± 177	.01†
Interference	292 ± 383	259 ± 307	.74

Abbreviations: CPT, Continuous Performance Test; SCWT, Stroop Color-Word Test; VSWM, visuospatial working memory task; WCST, Wisconsin Card Sorting Test; WSPT, Word Serial Position Test.

*Data are derived from assessment of neuropsychological performance after completion of the baseline cognitive training session. Values are expressed as mean ± SD.

†Significant at $P < .05$.

cigarettes per day ratio at baseline than the control group. Subjects with schizophrenia also demonstrated significantly lower Shipley IQ scores ($P < .001$), less education ($P = .005$), and higher depression scores on the Beck Depression Inventory ($P < .001$).

BASILINE NEUROPSYCHOLOGICAL PERFORMANCE

After completion of the training session, smokers with schizophrenia exhibited significant ($P < .05$) deficits compared with control smokers on the CPT (hit rate percentage, reaction time, variability index, attentional index), VSWM task (60-second delay condition), WCST (percentage of total errors, percentage of perseverative errors, percentage of perseverative responses), the WSPT (percentage of correct responses), and the SCWT (neutral and congruent conditions) (**Table 2**). There were trends toward group differences on CPT commission rate ($P = .06$), VSWM 30-second delay ($P = .09$), and WCST categories completed ($P = .08$). These baseline neuropsychological data, compared with data from the study testing sessions, suggest that smokers with schizophrenia and controls had achieved asymptotic performance on the VSWM task and CPT prior to beginning testing sessions.

EFFECTS OF SMOKING ABSTINENCE AND REINSTATEMENT ON PLASMA NICOTINE LEVELS AND TOBACCO CRAVING

Plasma nicotine levels were higher in smokers with schizophrenia vs control smokers at baseline (day 2

morning session) in the placebo condition (mean ± SD, smokers with schizophrenia, 32.4 ± 16.3 ng/mL vs controls, 22.2 ± 11.6 ng/mL; $t_{47} = 2.56$; $P < .05$) (**Figure 2**), decreased to undetectable levels with abstinence in both groups ($P < .01$), and returned to levels comparable with baseline (day 2 morning session) with reinstatement of smoking in both groups (day 3 afternoon session) (Figure 2). There was no significant effect of MEC administration on plasma nicotine levels (Figure 2) at either baseline (day 2 morning session) or after smoking reinstatement (day 3 afternoon session). In the placebo condition, there was a significant increase in tobacco craving on the Tiffany Questionnaire of Smoking Urges during short-term abstinence in the day 3 afternoon session and reversal of abstinence-induced increases in craving with smoking reinstatement during the day 3 afternoon session in both smokers with schizophrenia and control smokers (data not shown). These effects on the Tiffany Questionnaire of Smoking Urges were not modified by MEC administration (data not shown).

VISUOSPATIAL WORKING MEMORY TASK

Effect of Smoking Abstinence and Reinstatement in the Placebo Condition

There was a significant diagnosis × session interaction in the placebo condition ($F_{2,144} = 4.53$; $P < .01$). In smokers with schizophrenia ($n = 25$), we observed a main effect of session on VSWM 30-second delay performance in the

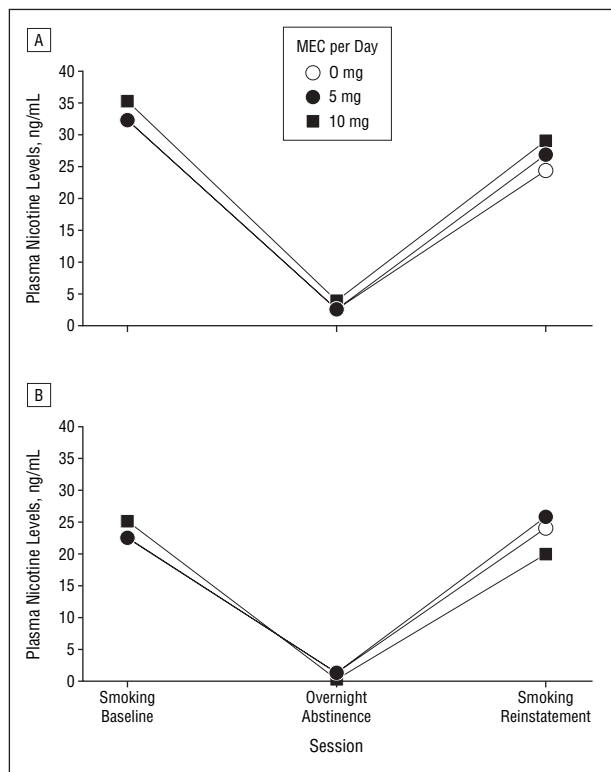


Figure 2. Effects of smoking abstinence, reinstatement, and mecamylamine hydrochloride (MEC) dose (in milligrams per day) on plasma nicotine levels in smokers with schizophrenia (n=25) (A) and control smokers (n=25) (B).

placebo (0 mg/d) condition (1-way ANOVA, $F_{2,72}=7.21$; $P<.01$). Post hoc analysis indicated that the schizophrenic group demonstrated significant impairment in VSWM 30-second delay performance after short-term (overnight) smoking abstinence during the day 3 morning session and significant reversal of abstinence-induced VSWM impairment with smoking reinstatement during the day 3 afternoon session ($P<.01$) (**Figure 3A**). In the control group (n=25), no main effect of session on VSWM 30-second delay performance was observed in the placebo condition (1-way ANOVA, $F_{2,72}=0.27$; $P=.76$) (Figure 3B).

Effects of MEC Pretreatment on Smoking-Induced Changes in VSWM 30-Second Delay Performance

The diagnosis \times dose interaction for VSWM percentage enhancement during smoking reinstatement was significant ($F_{2,143}=7.85$; $P<.01$) (**Figure 4A**). In smokers with schizophrenia, there was a mean \pm SD $31.4\% \pm 21.8\%$ enhancement of VSWM performance in the day 3 afternoon session compared with the day 3 morning session in the placebo condition, which was robustly reduced by MEC pretreatment at 5 (mean \pm SD, $-8.9\% \pm 49.9\%$; $P<.01$) and 10 mg/d (mean \pm SD, $-14.5\% \pm 53.8\%$; $P<.01$) (1-way ANOVA for MEC dose, $F_{2,71}=8.02$; $P<.01$) (Figure 4A). In controls, smoking reinstatement produced an impairment (mean \pm SD, $-16.9\% \pm 58.1\%$) of VSWM performance in the day 3 afternoon session compared with the day 3 morning session, which was not sig-

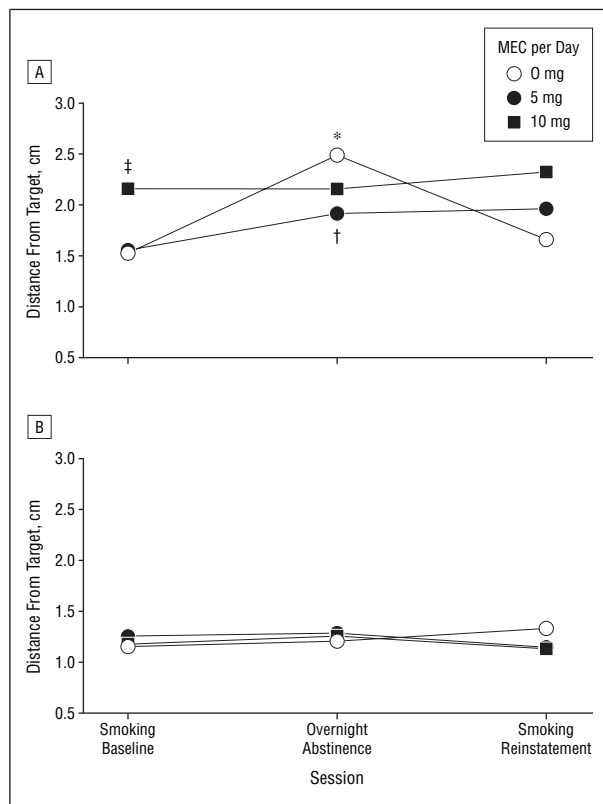


Figure 3. Effects of mecamylamine hydrochloride (MEC) administration (in milligrams per day) and manipulation of smoking status on visuospatial working memory 30-second delay performance in smokers with schizophrenia (n=25) (A) and control smokers (n=25) (B). * indicates $P<.01$ vs day 2 morning session and $P<.01$ vs day 3 afternoon session; †, $P=.10$ vs 0 mg of MEC per day (day 3 afternoon session); ‡, $P<.05$ vs 0 mg of MEC per day.

nificantly altered by MEC pretreatment at 5 (mean \pm SD, $2.1\% \pm 51.3\%$) and 10 mg/d (mean \pm SD, $5.4\% \pm 35.5\%$) (1-way ANOVA for MEC dose, $F_{2,72}=1.50$; $P=.23$) (Figure 4A).

Effect of MEC Pretreatment on Baseline VSWM 30-Second Delay Performance

Pretreatment with MEC at 5 mg/d did not alter baseline (day 2 morning session) VSWM performance compared with the placebo condition ($P=.91$) in smokers with schizophrenia but led to a nonsignificant reduction of abstinence-induced impairment (day 3 morning session) compared with the placebo condition ($P=.10$) (Figure 3A). However, pretreatment with MEC at 10 mg/d impaired baseline performance compared with the 0 mg/d condition ($P<.05$) (Figure 3A), an effect that persisted with smoking abstinence and reinstatement. There were no effects of MEC pretreatment on baseline performance in the control group (Figure 3B). The order of MEC dose in the counterbalanced sequence (eg, 0, 5, or 10 mg/d in the first test week) did not significantly influence the pattern of results with VSWM in either smokers with schizophrenia or controls (data not shown), suggesting no significant carryover effects between test weeks.

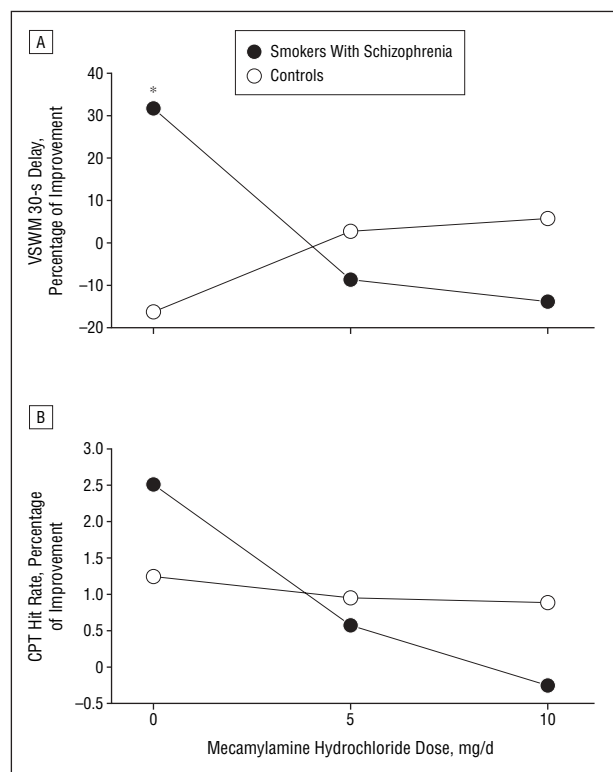


Figure 4. Effects of mecamylamine hydrochloride dose on percentage enhancement of visuospatial working memory (VSWM) 30-second delay performance (A) and Continuous Performance Test (CPT) hit rate (B) in smokers with schizophrenia and control smokers. Percentage enhancement for VSWM 30-second delay performance was calculated as [(day 3 morning session)–day 3 afternoon session/day 3 morning session] \times 100%, while that for CPT hit rate was calculated as [(day 3 afternoon session)–day 3 morning session/day 3 afternoon session] \times 100%. Asterisk indicates $P < .01$ vs 5 mg of mecamylamine hydrochloride per day and $P < .01$ vs 10 mg mecamylamine hydrochloride per day in the schizophrenia group and $P < .01$ vs control group.

Effects of Smoking Abstinence, Reinstatement, and MEC Pretreatment on VSWM 60-Second Delay Performance

There were no significant changes in the 60-second delay condition of the VSWM task with short-term smoking abstinence and reinstatement and no effects of MEC dose (data not shown).

CONTINUOUS PERFORMANCE TEST

Effect of Smoking Abstinence and Reinstatement in the Placebo Condition

The diagnosis \times session interaction in the placebo condition was not significant for CPT hit rate ($F_{2,144}=0.44$; $P=.64$). However, in smokers with schizophrenia ($n=25$), there was a trend toward a main effect of session in the placebo condition (0 mg/d) (1-way ANOVA, $F_{2,72}=4.91$; $P=.09$). Post hoc testing revealed that within the 3 test sessions in the placebo condition in smokers with schizophrenia, overnight smoking abstinence (day 3 morning session) produced a nonsignificant decline in performance ($P=.13$) compared with baseline (day 2 morning session) (**Figure 5A**), while smoking reinstatement (day 3 afternoon session) reversed abstinence-induced perfor-

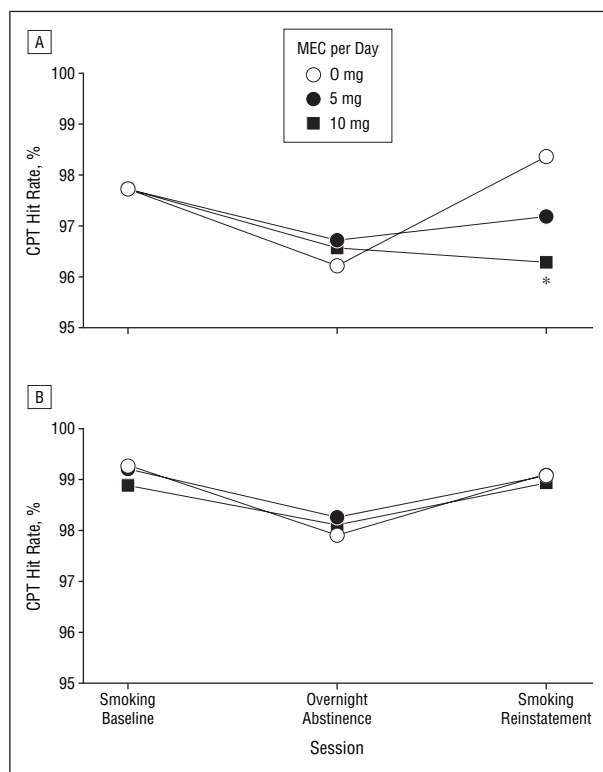


Figure 5. Effects of mecamylamine hydrochloride (MEC) administration and manipulation of smoking status on Continuous Performance Test (CPT) hit rate percentage in smokers with schizophrenia ($n=25$) (A) and control smokers ($n=25$) (B). Asterisk indicates $P < .05$ vs 0 mg of MEC per day (day 3 afternoon session).

mance deficits (day 3 morning session) ($P=.03$). In the control group, there was a significant effect of session ($F_{2,72}=3.28$; $P < .05$) following a pattern similar to that in the patients with schizophrenia. Post hoc analyses demonstrated impairment in CPT hit rate after overnight abstinence ($P < .05$) and reversal of this abstinence-induced deficit with smoking reinstatement ($P < .05$) (Figure 5B).

Effects of MEC Pretreatment on Smoking-Induced Changes in CPT Hit Rate

The diagnosis \times dose interaction for CPT hit rate was non-significant ($F_{2,138}=1.51$; $P=.22$). In the placebo condition, smokers with schizophrenia demonstrated a mean \pm SD $2.5\% \pm 5.0\%$ enhancement of CPT hit rate, which was dose-dependently (Figure 4B) reduced by pretreatment with MEC at 5 (mean \pm SD, $0.6\% \pm 2.9\%$; $P=.28$) and 10 mg/d (mean \pm SD, $-0.3\% \pm 3.3\%$; $P=.05$) (1-way ANOVA for dose, $F_{2,66}=3.19$; $P < .05$). Controls demonstrated a mean \pm SD $1.2\% \pm 3.2\%$ enhancement of CPT hit rate, which, in contrast to the schizophrenia group, did not differ significantly with MEC pretreatment at 5 (mean \pm SD, $0.9\% \pm 2.9\%$) or 10 mg/d (mean \pm SD, $0.9\% \pm 3.1\%$) (1-way ANOVA for dose, $F_{2,72}=0.11$; $P=.90$) (Figure 4B).

Effect of MEC Pretreatment on Baseline CPT Hit Rate Performance

In both the schizophrenia and control groups, pretreatment with MEC at the 5 and 10 mg/d doses did not alter

baseline (day 2 morning session) CPT hit rate performance compared with the placebo (0 mg/d) condition (Figure 5A and B). Similar to VSWM, the order of MEC dose in the counterbalanced sequence did not significantly influence the pattern of results of the CPT hit rate in either group (data not shown).

Other CPT Outcome Measures

There were no significant effects of smoking abstinence, reinstatement, or MEC dose on other measures of the CPT-X, including commission errors, reaction time variability index, and attentional index (d') (data not shown).

EFFECTS OF ATYPICAL ANTIPSYCHOTIC DRUGS AND ANTIMUSCARINIC DRUGS ON NEUROPSYCHOLOGICAL OUTCOMES

In subgroup analyses of smokers with schizophrenia ($n=25$), we found no significant differences in either atypical ($n=18$) vs typical ($n=7$) antipsychotic agents or antimuscarinic ($n=14$) vs nonantimuscarinic ($n=11$) drugs on either (1) baseline VSWM 30-second delay or CPT hit rate performance or (2) the effects of smoking abstinence, reinstatement, or MEC dose on these outcome measures (data not shown).

SCWT, WSPT, AND WCST

There were no significant changes in Stroop interference, the WSPT percentage of correct responses, or WCST categories completed or percentage of perseverative errors with short-term smoking abstinence and reinstatement and no effects of MEC dose (data not shown).

POSITIVE AND NEGATIVE SYNDROME SCALE

There were no significant changes in positive or negative symptoms with short-term smoking abstinence and reinstatement and no effects of MEC dose (data not shown).

ADVERSE EVENTS RELATED TO STUDY MEDICATION

Adverse effects reported by smokers with schizophrenia and control smokers (respectively) taking study medications included: headache (20.3% vs 25.6%), constipation (18.9% vs 18.6%), sedation (28.4% vs 34.9%), dry mouth (14.9% vs 32.6%), difficulty concentrating (35.1% vs 16.3%), and orthostatic hypotension (18.9% vs 17.4%). With the exception of dry mouth and difficulty concentrating ($P<.01$ for both), differences between diagnostic groups were not significant.

COMMENT

Our results suggest that cigarette smoking has selective effects on VSWM 30-second delay performance and sustained attention performance on the CPT in schizophrenia. Calculated effect sizes (Cohen d^{52}) for overnight

smoking abstinence effects ranged from $d=0.40$ for CPT hit rate to $d=1.01$ for VSWM 30-second delay, suggesting that there are clinically significant effects³ of smoking abstinence on neuropsychological performance. Similarly, smoking reinstatement produced effect sizes for cognitive enhancement of $d=0.58$ for CPT hit rate and $d=0.90$ for VSWM 30-second delay. Neither antipsychotic drug class (eg, atypical vs typical agents) nor exposure to antimuscarinic agents modified these neuropsychological outcomes. Interestingly, the longer spatial working memory delay (VSWM 60-second delay) was unaffected by smoking and MEC administration, and this may relate to the observation that longer delay durations are not specific to prefrontal cortex mechanisms and recruit hippocampal mechanisms.⁵³ Accordingly, differences in the neuroanatomical substrates of long vs short delay in our VSWM task may explain differences we observed with smoking and MEC administration. Our results suggest that cigarette smoking may be an attempt to remediate neurocognitive deficits associated with schizophrenia, as previously proposed for psychophysiological,^{22,54-56} working memory,^{14-16,57} and attentional^{13,14} deficits in schizophrenia. These observations suggest that neurocognitive deficits in schizophrenia may constitute a vulnerability factor for the initiation and maintenance of cigarette smoking.^{16,18,58,59} An important caveat is that the present study is a model of abstinence-induced cognitive deficits in schizophrenia, and further studies are needed to determine the direct effects of nicotine on endogenous neurocognitive deficits without confounding effects of tobacco withdrawal. Nonetheless, since the majority of patients with schizophrenia are daily smokers, we believe that our findings have substantial clinical relevance.

In the present study, reversal of abstinence-related deficits in VSWM and sustained attention in subjects with schizophrenia by smoking reinstatement was blocked by pretreatment with MEC. This is the first evidence that the effects of smoking on cognitive function in patients with schizophrenia are mediated by stimulation of central nAChRs.

Baseline impairment of VSWM 30-second delay performance was observed in patients receiving the highest MEC dose (10 mg/d). Several other studies have reported dose-dependent impairment of cognitive performance in healthy and elderly subjects receiving MEC.^{60,61} In contrast, we did not observe that MEC administration impaired VSWM 30-second delay in control smokers. This suggests that smokers with schizophrenia are more sensitive to MEC at higher doses of the drug, and this could relate to reduced tritiated nicotine binding to high-affinity nAChRs in the schizophrenic brain.²⁵ Interestingly, smoking abstinence did not appear to alter VSWM 30-second delay performance in control smokers matched for nicotine dependence level with the schizophrenic sample (Figure 3B). This suggests a differential response to smoking in the control as compared with the schizophrenic group.¹⁶ The disparate effects of acute smoking on VSWM 30-second delay in subjects with schizophrenia compared with controls may relate to impairments in the functional upregulation of high-affinity nAChRs,²⁵ such that the presence of exogenous

nicotine derived from cigarette smoking is required to sustained performance in subjects with schizophrenia.⁶² Since subjects with schizophrenia were prescribed antipsychotic agents and control subjects were not, it is possible that antipsychotic agents could interact with nAChR systems either directly by binding to nAChRs⁶³⁻⁶⁵ or indirectly by increasing prefrontal cortex and hippocampal acetylcholine levels⁶⁶ to alter nAChR-mediated neurotransmission, leading to diagnosis-based performance differences in VSWM. Future studies in medication-naïve and nonsmoking patients with schizophrenia, as well as other mentally ill populations (eg, bipolar disorder), are needed to test the specificity of these findings to schizophrenia.

Continuous Performance Test hit rate was impaired in both subjects with schizophrenia and controls with overnight smoking abstinence and reversed by smoking reinstatement. No consistent effects of smoking or MEC administration were found on other CPT measures, suggesting that the positive effects of smoking in these patients were confined sustained attention and not impulsivity or risk taking. Sustained attention is considered the most basic of attentional processes on which other derivative attentional and neuropsychological (eg, working memory, learning, executive functioning) measures are based.⁶⁷ Selective effects of a nicotine patch on CPT hit rate were also found in subjects with schizophrenia by Depatie et al.¹³

The effects of smoking reinstatement on reversal of CPT hit rate decrements were dose-dependently blocked by MEC administration in smokers with schizophrenia but not control smokers, suggesting involvement of nAChR stimulation in the attention-enhancing effects of smoking in those with schizophrenia and dysregulation of nAChR systems in this disorder.²⁵ Accordingly, blockade of smoking-related CPT hit rate enhancement by MEC pretreatment in subjects with schizophrenia suggests that attentional function in schizophrenia is selectively modulated by cigarette smoking secondary to dysregulation of (high-affinity) nAChRs. The CPT hit rate performance levels in both smokers with schizophrenia and control smokers were prone to "ceiling effects" (Figure 5), but this would not explain the differential effects of MEC administration during smoking reinstatement. This observation will require further study, including the use of nicotine or nAChR agonists, in nonsmoking subjects with schizophrenia as compared with control subjects, to rule out the confounding effects of nicotine withdrawal on cognitive function. Interestingly, the effects of smoking on attentional outcomes on this version of the CPT (CPT-X) in these studies is also consistent with rodent studies of the effects of nicotine on attention using the CPT analogue, the 5-choice serial reaction time test.⁶⁸

Both smokers with schizophrenia and control smokers completed a training session prior to beginning study procedures to familiarize them with the various neuropsychological tests. Our findings (Table 2) (Figure 4 and Figure 5) suggest that for VSWM 30-second delay and CPT hit rate percentage, both patients and controls achieved asymptotic performance on these tasks, further strengthening our conclusions that the effects on VSWM 30-second delay and CPT performance we ob-

served were directly related to smoking status changes and MEC administration rather than learning effects with repeated test performance. Furthermore, we have shown that after similar training in nonsmoking subjects with schizophrenia and controls (where there are no confounding effects of smoking on test performance), there is little evidence of learning effects on VSWM 30-second delay and CPT performance with repeated task administration (K.A.S. and T.P.G., unpublished data, June 2004), consistent with these subjects having attained asymptotic task performance.

We observed that subjects with schizophrenia had significantly higher plasma nicotine and cotinine levels compared with controls and a significantly higher ratio of plasma cotinine to cigarettes smoked per day, an index of nicotine extracted per cigarette smoked,⁶⁹ consistent with findings of Olincy et al.⁷⁰ Interestingly, the lack of effect of MEC administration on plasma nicotine concentration, tobacco craving, and smoking consumption in both smokers with schizophrenia and control smokers is consistent with the notion that subjective effects of cigarette smoking are not mediated by nAChR stimulation but by non-nicotine components of cigarette smoke such as tar.⁷¹⁻⁷³ Non-nicotine contributions to smoking-related cognitive enhancement in subjects with schizophrenia have been suggested in a study using nicotine-free cigarettes.¹⁵ Further studies in our smoking abstinence and reinstatement model of the relative contributions of nicotinic vs non-nicotinic contributions to cognition are warranted.

Taken together, our findings suggest a critical role for central nAChRs in mediating smoking-related enhancement of VSWM and sustained attention in schizophrenia. Furthermore, these findings may have implications for understanding factors that may predispose to the initiation and maintenance of nicotine and tobacco use in schizophrenia, where high rates of comorbid smoking have been shown in both clinical^{19,58,74} and epidemiological^{75,76} samples and patients are predisposed to smoking cessation treatment failure.^{21,42,76-80} The implication of nAChR systems in cigarette smoking-related cognitive enhancement suggests that nicotine, or nAChR agonists devoid of the harmful effects of tobacco and smoking,⁸¹ may be beneficial for pharmacological treatment of cognitive dysfunction associated with schizophrenia.

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