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Smoking History and Nicotine Effects on Cognitive Performance

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This study examined the effects of abstinence from smoking, of smoking history, and of nicotine administration on visual attention (2-Letter Search Task), verbal information processing (Logical Reasoning Task), and working memory (N-Back Tasks). Fourteen smokers, 15 ex-smokers, and 9 never-smokers took part. All subjects participated in a training session (when smokers had been smoking ad libitum) and in two subsequent test sessions after administration of 4 mg nicotine gum or placebo, respectively. Smokers were 12-h abstinent when they received gum. An effect of acute nicotine administration (independent of smoking history) was seen only with respect to reaction time on the 2-Letter Search Task. Working memory performance was related to smoking history (smokers performed most poorly and never-smokers best). The Logical Reasoning Task showed no effects of either acute or chronic nicotine exposure. The findings indicate that nicotine may influence focusing of attention in smokers as well as nonsmokers, and that trait-like differences in some cognitive domains, such as working memory, may be either long-term effects or etiological factors related to smoking.
[Neuropsychopharmacology 25:313–319, 2001]

KEY WORDS: *Attention; Working memory; Nicotine withdrawal; Abstinence; Nicotine gum*

Tobacco and nicotine have complex effects on human performance, determined, in part, by whether a research subject is in a state of tobacco deprivation (i.e., nicotine withdrawal) (Heishman et al. 1994). In nicotine-dependent individuals, tobacco deprivation can impair attentional and cognitive abilities within 12 h of smoking cessation (Bell et al. 1999; Gross et al. 1993; Lyvers et al. 1994), and nicotine administration or cigarette smoking can reverse such deficits to predeprivation performance levels (Bell et al. 1999; Parrott and Roberts 1991). Whether improved performance associated with relief from withdrawal should be considered cognitive enhancement has been questioned (Heishman et al. 1994; Hughes 1991). True enhancement may be most clearly demonstrated when nicotine or smoking facilitates performance in nonsmokers or in nonabstinent smokers (Heishman 1998; Heishman et al. 1994).

Relatively few placebo-controlled studies have examined the acute effects of smoking or nicotine (Heishman 1998; Heishman et al. 1994; Sherwood 1993). The results have been discrepant, including improved performance in motor responses, sustained attention, and recognition memory, but no effect or impairment in selective attention, conditioned learning, and recall mem-

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Received February 8, 2000; revised March 14, 2001; accepted 22 March 2001.

Online publication: 3/23/01 at www.acnp.org/citations/Npp03230194.

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/01/$–see front matter
PII S0893-133X(01)00257-3

ory. Similarly, few studies have examined the cognitive effects of a history of smoking; and again, the results have been inconsistent (Perkins et al. 1990; Perkins et al. 1994; Foulds et al. 1996).

The purpose of this study was to examine the influence of past smoking history and acute nicotine administration on cognitive performance. We compared the effects of nicotine in 12-h abstinent smokers, ex-smokers, and never-smokers. The hypotheses were that cognitive performance would vary as a function of smoking history and that nicotine administration would have the strongest effects in smokers, possibly attributable to relief for nicotine withdrawal.

METHODS

Sample

Forty-one adults, 14 smokers, 15 ex-smokers, and 12 never-smokers completed the study. Data from only 38 participants were analyzed, because three never-smokers experienced severe nausea after receiving nicotine. All participants gave written informed consent after the study and its procedures were explained. Inclusion criteria were age between 21 and 45 years, IQ $>$ 85 (Shipley Institute of Living Scale; Zachary et al. 1985) and right-handedness (Physical and Neurological Examination for Soft Signs [PANESS] Scale; Werry and Aman 1976). Smokers reported a smoking history of at least 2 years, currently smoked more than 20 cigarettes/day, and had a score $>$ 5 on the Fagerström Test for Nicotine Dependence (range 0–10) (Heatherton et al. 1991). Ex-smokers reported a history of past exposure to nicotine ($\geq$ 5 cigarettes in lifetime), but no current smoking (nicotine abstinence for at least 2 weeks and no evidence of nicotine dependence for at least 3 years before the study). Never-smokers smoked fewer than five cigarettes in their lifetimes. Exclusion criteria were current psychopathology assessed by the SCL-90 (Derogatis et al. 1976) (global score $\geq$ 64), current history of DSM-IV axis I psychiatric disorders (Diagnostic Interview Schedule [DIS]; Robins 1981), including substance abuse disorders other than nicotine dependence and evidence of current acute or chronic medical problems (assessed by medical history, physical examination, and routine blood screen).

Study Design

Participants performed four computerized cognitive tasks (see below) in three sessions at 1-week intervals. During the initial session, they were trained to achieve a stable level of performance (mean correct responses of three consecutive trials within 10%), minimizing the effect of learning across sessions. In the two testing sessions, tasks were performed after the double-blind administration of polacrilex gum containing either nicotine (4 mg) or placebo, and smokers had to refrain from smoking for the previous 12 h. Testing always began at about 8:00 A.M. Treatment order (placebo, nicotine) was randomized across participants to avoid order effects.

Expired air CO levels were recorded on arrival at the research facility. A level above 10 parts per million (ppm), reflecting recent smoking, disqualified a participant from the study. Recordings of vital signs (blood pressure and pulse), nicotine withdrawal (Minnesota Nicotine Withdrawal Scale [MNWS]; Hughes and Hatsukami 1998) and side effects (Subjective Treatment Emergent Symptom Scale [STESS]; Guy 1976), were completed 5 min before and about 5 min after gum administration. Of the 32 items of the STESS, we selected four symptoms (difficulty paying attention, stomach-aches, dizziness, shakiness) on the basis of previous reports of side effects related to nicotine gum (West et al. 1984). A measure of state anxiety (State Trait Anxiety Index [STAI]; Spielberger et al. 1970) was obtained before gum administration.

Nicotine Administration Protocol

Participants received two pieces of nicotine polacrilex gum (Nicorette®) to chew for 15 min at a frequency of one chew every 3 s. Each piece of gum contained either nicotine (2 mg) or taste-matched placebo. Previous studies have shown that peak venous plasma levels of nicotine achieved using this procedure match those resulting from smoking a typical commercial American cigarette (Benowitz et al. 1988).

Cognitive Tasks

The computerized cognitive tasks included the Two-Letter Search, Logical Reasoning, Two-Back, and Three-Back Tasks. Testing began 10 min after the end of gum chewing and lasted about 25 min. The order of tasks was either: (1) Two-Back–Two-Letter Search–Logical Reasoning–Three-Back–Two-Letter Search–Logical Reasoning; or (2) Three-Back–Two-Letter Search–Logical Reasoning–Two-Back–Two-Letter Search–Logical Reasoning. The order of these two series was counterbalanced across participants, but kept constant for each participant.

Two of these tasks, the Two-Letter Search Task and the Logical Reasoning Task, were selected because of their reported sensitivity to nicotine withdrawal and subsequent acute nicotine administration (Snyder et al. 1989; Snyder and Henningfield 1989). The two others, the Two-Back and Three-Back Tasks, were included, because they test working memory, which is reportedly influenced by acute exposure to nicotine in animals and humans (Heishman et al. 1994; Levin et al. 1997; Levin 1992; Decker et al. 1995).

The Two-Letter Search Task assesses visual scanning and recognition abilities and consists of 20 trials. Each trial requires determination of whether two target letters appear in a series of 20 letters presented below the target letters. The 20-letter series could contain neither, one, or both of the target letters. This task is about 2-min long and measures focused attention.

The Logical Reasoning Task, adapted from Baddeley (1968), is a 3-min exercise in transformational grammar and measures verbal information processing. It comprises 32 trials, each of which presents the letter pair "AB" or "BA" and below it, a statement (e.g., B is not preceded by A) that correctly or incorrectly describes the order of the letters. The participant is instructed to determine whether the statement is true or false. The Two-Letter Search Task and Logical Reasoning Task were each administered twice (see order above). The averages of performance on the tasks were used for analysis.

The N-Back Task is a 5.5-min working memory task that requires participants to keep in memory a series of letters that are constantly being updated. The letters appear in the middle of the computer screen, one at a time, for 500 ms, with an interstimulus interval of 1,000 ms. The participants are instructed to press a "target" button (Psyscope Button Box, Research Methods, Pittsburgh, PA) whenever a letter is repeated with exactly one intervening letter in the Two-Back version and two intervening letters in the Three-Back version. When any other letter appears, the instruction is to press a "nontarget" button. We used the same task at two different levels of difficulty to assess whether the effect of nicotine might differ with task demands.

Analysis of the Results

Demographic data were compared between groups using one-way analysis of variance (ANOVA). Physiological and subjective characteristics were analyzed using three-way ANOVAs to evaluate the interactions and main effects of Group (smokers, ex-smokers, and never-smokers), Session (placebo, nicotine), and Order (pregum and postgum). Cognitive performance was analyzed using two-way ANOVAs to evaluate the interactions and main effects of Group (smokers, ex-smokers, and never-smokers) and Session (placebo and nicotine). The criterion for statistical significance was $p < .05$. Post-hoc simple comparison tests (ANOVA or Student's *t*-tests) were conducted for significant effects or interactions.

RESULTS

Demographics (see Table 1)

The three groups did not significantly differ with respect to age, gender, socioeconomic status, IQ level, and severity of psychopathology (all Fs < 2.7 and *p*s $> .1$; Table 1). Smokers consumed 25.4 ± 7.6 cigarettes/day. Both smokers and ex-smokers started smoking at about 15.5 years of age, and the average duration was 14.6 years in smokers and 6.5 years in ex-smokers. Mean abstinence length in ex-smokers was 7.3 ± 7.2 years (range 3 months –23 years). Given the wide variation in previous cigarette consumption by the ex-smokers, we re-analyzed all of the data presented below after removing the two subjects who had smoked more than 20 cigarettes/day and the two who had the lightest past smoking history (between 10 and 20 cigarettes in their lifetimes). The results were similar to those obtained with the full sample and are not presented herein (available on request).

Cardiovascular Measures (see Table 2)

Analysis of systolic blood pressure showed no significant interactions, but a significant main effect of Session [$F(1,35) = 6.74$, $p = .014$], which reflected higher levels

Table 1. Mean ± SD Subject Characteristics and Smoking History

	Smokers ($n = 14$)	Ex-Smokers ($n = 15$)	Never-Smokers ($n = 9$)
Gender (female/male)	8/6	5/10	6/3
Socioeconomic status[a]	66.2 ± 30.1	60.4 ± 26.8	59.9 ± 20.1
Estimated IQ[b]	107.6 ± 11.9	102.5 ± 10.3	105.9 ± 11.0
SCL-90[c]	43.6 ± 9.9	43.8 ± 12.6	41.0 ± 9.6
Age first smoked	15.7 ± 2.7	15.6 ± 3.3	NA[d]
Peak # cigarettes/day	27.4 ± 9.4	6.6 ± 13.3	NA
Current # cigarettes/day	25.4 ± 7.6	0	NA
Years smoking	14.6 ± 7.6	6.5 ± 9.6	NA
Years abstinent	0	7.3 ± 7.2	NA
Fagerström score[e]	6.8 ± 1.3	0	NA

[a]Hollingshead Rating Scale.
[b]Shipley Institute of Living Scale.
[c]Symptom Checklist-90.
[d]Not applicable.
[e]Fagerström Test for Nicotine Dependence.

Table 2. Mean ± SD of Physiological and Self-Report Measures

		Placebo			Nicotine		
Group/measure		**Pregum**	**Postgum**	**Difference[e]**	**Pregum**	**Postgum**	**Difference**
Smokers (n = 14)							
	Systolic BP	113.3 ± 14.4	114.3 ± 15.1	1.0 ± 6.8	117.0 ± 12.5	116.8 ± 11.9	−0.1 ± 6.8
	Diastolic BP	63.7 ± 9.7	65.1 ± 11.3	1.4 ± 7.5	65.5 ± 7.8	70.8 ± 9.1	5.2 ± 5.9*
	Pulse	71.4 ± 11.1	66.4 ± 10.0	−5.0 ± 4.5 *	72.0 ± 12.0	74.5 ± 9.6	2.5 ± 6.0
	Anxiety[a]	32.7 ± 11.2	—[b]		36.0 ± 11.6	—[b]	
	Side effects[c]	0.2 ± 0.3	0.2 ± 0.2	0.0 ± 0.2	0.3 ± 0.2	0.3 ± 0.3	0.1 ± 0.1
	Withdrawal[d]	22.2 ± 14.7	17.6 ± 8.3	−4.6 ± 9.7	26.9 ± 9.8	17.0 ± 11.6	−9.9 ± 7.3*
Ex-smokers (n = 15)							
	Systolic BP	113.8 ± 13.7	112.5 ± 13.7	−1.3 ± 6.8	113.2 ± 14.2	117.2 ± 13.5	4.0 ± 7.6
	Diastolic BP	70.1 ± 9.8	68.5 ± 12.1	−1.5 ± 5.1	67.5 ± 10.0	71.4 ± 9.4	3.9 ± 7.9
	Pulse	71.1 ± 11.3	69.4 ± 11.4	−1.7 ± 4.6	70.9 ± 12.6	74.1 ± 10.6	3.2 ± 6.1
	Anxiety[a]	24.1 ± 8.6	—[b]		24.1 ± 8.3	—[b]	
	Side effects[c]	0.1 ± 0.1	0.1 ± 0.1	0.0 ± 0.1	0.1 ± 0.1	0.5 ± 0.6	0.4 ± 0.5*
	Withdrawal[d]	3.7 ± 7.0	3.3 ± 6.3	−0.3 ± 2.1	3.5 ± 7.6	8.7 ± 12.8	5.3 ± 8.0*
Never-smokers (n = 9)							
	Systolic BP	118.4 ± 9.1	117.2 ± 7.6	−1.2 ± 5.0	120.6 ± 12.9	123.7 ± 16.7	3.2 ± 8.3
	Diastolic BP	68.6 ± 6.9	68.3 ± 3.6	−0.2 ± 5.8	69.4 ± 7.2	75.2 ± 12.4	5.8 ± 8.3
	Pulse	77.3 ± 14.8	71.3 ± 12.9	−6.0 ± 4.9	74.7 ± 15.9	77.3 ± 13.7	2.6 ± 7.8*
	Anxiety[a]	23.8 ± 3.1	—[b]		23.4 ± 4.0	—[b]	
	Side effects[c]	0.1 ± 0.2	0.1 ± 0.2	0.0 ± 0.1	0.0 ± 0.1	0.4 ± 0.4	0.4 ± 0.4*
	Withdrawal[d]	2.3 ± 5.6	2.7 ± 5.2	0.3 ± 1.6	0.7 ± 1.0	6.2 ± 4.9	5.6 ± 4.5*

[a]State Trait Anxiety Index.
[b]Not measured.
[c]Subjective Treatment Emergent Symptom Scale.
[d]Minnesota Nicotine Withdrawal Scale.
[e]Difference of post-gum minus pre-gum measures.
*Paired t-tests $p < .05$.

during the nicotine session than during the placebo session. There were no other significant main effects (Group, Order) on systolic blood pressure. In contrast, a significant Order × Session interaction was found on both diastolic blood pressure [$F(1,35) = 14.0$, $p < .001$] and pulse [$F(1,35) = 36.1$, $p < .001$]. Diastolic blood pressure increased more robustly and systematically after administration of the gum across groups in the nicotine condition than in the placebo condition, and pulse increased after nicotine gum and decreased after placebo. No other interactions were significant for diastolic blood pressure and pulse, and there was no significant main effect of Group.

Subjective Measures (see Table 2)

The factors analyzed for these measures were Group (smokers, ex-smokers, never-smokers), Session (nicotine, placebo), and Order (pregum, postgum), except for anxiety scores where only pregum measures were collected. Analysis of anxiety scores (STAI) showed no significant interaction (Session × Group), but a significant main effect of Group [$F(2,35) = 6.48$, $p = .004$], reflecting higher anxiety level in smokers than in the two other groups. The higher anxiety scores in smokers mainly reflected nicotine withdrawal. Indeed, the analysis of subjective measures of withdrawal (MNWS) showed a significant Session × Order × Group interaction [$F(2,35) = 7.68$, $p = .002$], where smokers displayed higher MNWS scores than the two other groups across sessions and periods [Group, $F(2,35) = 24.54$, $p < .001$], and showed a reduction of the scores in postgum period as compared to pregum period [smokers only, Order, $F(1,13) = 15.1$, $p = .002$], with a trend for higher reductions in the nicotine session as compared to the placebo session [smokers only, Order times; Session, $F(1,13) = 3.89$, $p = .07$]. The analysis of side effects (STESS) showed a significant Session × Order interaction [$F(1,35) = 16.4$, $p < .001$], where side effects increased in the postgum period of the nicotine session but not in the post-gum period of the placebo session. No other interactions were significant, and there was no main effect of Group.

Cognitive Tasks (see Table 3)

Reaction time is the critical variable assessed in this study. The literature indicates that nicotine tends to influence reaction time, but not accuracy (Heishman et al. 1994). Smoking history or acute nicotine had no effects on accuracy scores in any of the tasks. The factors analyzed for these analyses were Group (smokers, ex-smokers, never-smokers) and Session (nicotine, placebo).

Table 3. Mean and Standard Deviation (SD) of Reaction Time (ms) and Accuracy on the Four Performance Tests

	Smokers (n = 14)		Ex-smokers (n = 15)		Never-smokers (n = 9)	
	Placebo	Nicotine	Placebo	Nicotine	Placebo	Nicotine
Two-letter search						
Reaction time	5055.1	4668.2	4942.6	4659.2	5172	4836.7
SD	1889.1	1443.2	1534.9	1530.4	1936.4	1809.2
Logical reasoning						
Reaction time	4358	4619.5	4619.7	4484.7	4612.2	4554.3
SD	1523.6	1397.7	1605.6	1469.3	1335.5	1402
Two-Back						
Reaction time	559.4	570.1	508.1	499.3	454	440.9
SD	103.8	108.5	115.7	118.8	83.7	73.3
Three-Back						
Reaction time	603.9	590.4	515.6	523.6	492.9	471.8
SD	111.7	120	153.2	155	108.4	52.6

Two-Letter Search Task

Analysis of the mean reaction time showed no significant Group × Session interaction but a significant main effect for Session [$F(1,35) = 8.6$, $p = .006$], reflecting shorter reaction time in the nicotine session (mean ± SD: 470.5 ± 152.7 ms) than in the placebo session (mean ± SD: 503.8 ± 172.2 ms). Main effect of Group was not significant.

Logical Reasoning Task

Analysis of reaction time showed no significant interactions or main effects.

N-Back Tasks

In both Two-Back and Three-Back tasks, the Session × Group interaction and main effect of Session were not significant. However, the main effect of Group was significant for the Two-Back Task [$F(2,35) = 3.7$, $p = .036$] and at a trend level for the Three-Back Task [$F(2,35) = 3.20$, $p = .06$]. In both tasks, reaction time was longest in smokers (mean ± SD: Two-Back 564.8 ± 102.4 ms; Three-Back 597.2 ± 100.3 ms), shorter in ex-smokers (mean ± SD: Two-Back 503.7 ± 115.6 ms; Three-Back 519.6 ± 145.6 ms), and shortest in never-smokers (mean ± SD: Two-Back 447.5 ± 76.5 ms; Three-Back 482.3 ± 77.0 ms).

DISCUSSSION

Nicotine polacrilex (4 mg) produced physiological effects in smokers, ex-smokers, and never-smokers and reduced withdrawal symptoms in smokers. The nicotine-induced increase in diastolic blood pressure and heart rate in all three groups is consistent with previous observations that the first cigarette of the day increased blood pressure and heart rate in smokers (Ragueneau et al. 1999) as did intravenous nicotine in smokers and nonsmokers (Soria et al. 1996). Nicotine also increased side effects (i.e., difficulty paying attention, stomachaches, dizziness, and shakiness) in ex-smokers and never-smokers, but not in smokers. As mentioned earlier, never-smokers who experienced notable side effects to nicotine were excluded from the protocol, limiting the extent to which we can generalize the findings to individuals who do experience serious adverse reactions to nicotine. Although plasma nicotine concentration was not measured in the present study, previous data from our laboratory indicated that changes of nicotine levels from prenicotine gum to 30-min postnicotine gum administration (4 mg gum) did not differ between smokers and nonsmokers (Ernst et al. 2001). In addition, nicotine gum administration produces nicotine plasma levels that plateau for at least 1 h postgum (Russell 1988), suggesting the absence of differences in nicotine blood concentration between groups and across tasks (over 30 min).

Performance on one of the tasks (N-Back Task) varied with smoking history, independent of the acute administration of nicotine. Reaction time was fastest in never-smokers and slowest in smokers. One interpretation of this result is that chronic exposure to nicotine has a deleterious effect on working memory. The intermediate performance level of ex-smokers may reflect a dose effect; that is, less exposure to nicotine in ex-smokers than in smokers leading to less memory impairment or to a partial remission of memory deficits after long-term abstinence in ex-smokers. Nevertheless, the present study cannot distinguish deficits in working memory that preceded nicotine dependence from those that may be attributable to chronic nicotine exposure. Impaired memory performance, as seen here, is surprising in view of the reported improvement in memory performance in animals chronically exposed to nicotine (Attaway et al. 1999; Levin et al. 1997) and in humans (Perkins et al. 1994; Pineda et al. 1998). However, this finding is consistent with reports of impaired performance on complex information-processing tasks in

chronic smokers, independent of nicotine withdrawal or smoking abstinence (Spilich et al. 1992).

With respect to our objective to assess the cognitive effects of acute nicotine administration, performance only on the Two-Letter Search Task was sensitive to nicotine challenge. In all three groups, reaction time was shorter after nicotine gum than after placebo. The similarity of the decrease in reaction time attributable to nicotine administration by all three groups suggests that the effects of nicotine did not simply reflect a reversal of nicotine withdrawal. It also indicates that this effect did not manifest tolerance, which would predict a smaller effect in smokers than in nonsmokers (Perkins et al. 1994). The effects of acute nicotine administration were task specific, occurring only with the Two-Letter Search Task and not with the Logical Reasoning Task, the Two-Back, or Three-Back Task. The absence of effects of nicotine challenge on working memory performance is consistent with some reports (Parrott and Winder 1989; Ernst et al. 2001) but not with others (Heishman et al. 1994; Sherwood 1993).

The insensitivity of the Logical Reasoning Task to smoking history and acute challenge to nicotine conflicts with previous reports of abstinence-induced performance decrements and subsequent improvement after nicotine gum (Snyder and Henningfield 1989), or smoking (Bell et al. 1999). In the latter study, although performance did not differ between a nonabstinent state and 18-h abstinence, the smoking of two cigarettes after abstinence reduced reaction time. The absence of a double-blind placebo condition, the use of cigarettes instead of nicotine gum, and the history of illicit drug use may have contributed to this positive finding. The study by Snyder and Henningfield (1989) showed impaired performance on the Logical Reasoning Task in 12-h abstinent smokers ($n = 6$) during the placebo as compared to the nicotine condition. Possibly, the small sample size of that study ($n = 6$) may have produced an artifact responsible for the discrepancy between its findings and ours. Nevertheless, there is, overall, no consensus regarding the effects of nicotine on tasks that require manipulation of information (Sherwood 1993).

In conclusion, the results of this study are consistent with previous findings regarding nicotine-related improvements in reaction time rather than accuracy of task performance (Heishman et al. 1994). This effect is task specific, seen only in a test of focused attention in the present study. Smoking history is related to memory function, with smokers showing deficits in working memory, as tested in controlled laboratory conditions. Group differences in working memory may reflect detrimental effects of smoking or impairments that preceded the onset of smoking, possibly representing a factor that predisposes to nicotine dependence.

The present work indicates that future studies of cognitive function as related to acute nicotine exposure and smoking history are warranted. These studies would benefit from inclusion of smokers with a wide range of smoking frequency to permit a parametric approach to assessing cognitive correlates of chronic exposure. Similarly, the use of several doses of nicotine would permit dose-response analysis, particularly useful in characterizing tolerance (typified by a rightward shift in the dose-response curve). The additional data would also help interpret findings that may reflect complex (e.g., U-shaped or inverted U-shaped) dose-response curves. In addition, higher doses might also be needed to detect cognitive changes and produce substantial reversal of nicotine withdrawal.

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