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Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers

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Abstract In a double-blind placebo-controlled cross-over study the effects of two doses of subcutaneous nicotine and saline were compared on a range of performance measures in 18 abstaining smokers and 18 never-smokers. Each subject received two injections (40 min apart) of saline, 0.3 mg nicotine, or 0.6 mg nicotine in a balanced order over three sessions. Performance was assessed before and after the injections on nine tests [news recall, Sternberg memory task, finger tapping, logical reasoning, rapid visual information processing (RVIP), long-term word recognition, digit recall, Stroop test, and critical flicker fusion threshold]. In the abstinent smokers, nicotine produced significantly faster correct responses on the logical reasoning test, more target hits, faster reaction times and improved sensitivity on the RVIP task, and more correct responses on word recognition. In never-smokers, nicotine produced faster reaction times on the RVIP and digit-recall tasks, although in the latter case this was at the expense of fewer correct responses. There were no significant differences between the two groups' responses to nicotine but smokers performed worse than never-smokers prior to injections, even controlling for background characteristics. These results are consistent with other recent research suggesting a primary effect of nicotine in enhancing cognitive performance.

Key words Nicotine · Subcutaneous · Smoker · Nonsmoker · Cognitive performance

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Introduction

The issue of whether nicotine enhances human cognitive performance continues to be controversial. Some researchers have suggested that nicotine enhances performance and that smokers recognise and use this quality as a resource for managing their lives (e.g. Mangan and Golding 1978; Warburton 1992). However, it has been pointed out that most of the research on this issue has involved giving nicotine to abstinent smokers, and hence cannot establish whether any resulting enhancement is a primary effect of nicotine, or simply a reversal of a withdrawal-induced deficit (Hughes 1991).

In a review of over 100 experiments, Heishman, Taylor and Henningfield (1994) found that most published studies failed to find an enhancing effect of nicotine on cognition, and the majority of those which did were based on tobacco-deprived smokers and hence could not distinguish direct enhancement from withdrawal-relief. This review also highlighted a number of frequent methodological shortcomings in studies on this topic, and recommended improvements for future studies. Among these recommendations were: the administration of nicotine and placebo under double blind conditions, the use of a nicotine delivery system which provides a measured dose in a standardised manner, testing the effects of nicotine in non-smokers, and the use of a variety of tests which span the range of human abilities.

These recommendations have been implemented in the present study by administering subcutaneous nicotine to abstinent smokers and never-smokers in a placebo-controlled, double-blind study. Subcutaneous nicotine administration has been found to be suitable for acute dose-response studies (e.g. Russell et al. 1990; Jones et al. 1992; Le Houezec et al. 1993). A pilot study identified a dosing schedule which produced significant increases in heart rate and dominant EEG alpha frequency and was tolerated by non-smokers (Foulds et al. 1994). The present study used two doses of

nicotine in a within-subject design with pre- and post-injection measures to minimize the influence of both subject and day-to-day variation in performance. A variety of cognitive tests were selected which have been shown to be sensitive to pharmacological manipulations, and most of which have been found to be affected by nicotine or smoking in previous studies.

The key focus of the present study was the effect of nicotine on cognitive performance in never-smokers. Any enhancing effect in this group must be interpreted as a primary nicotine effect, rather than withdrawal relief. A group of abstinent smokers was also included in the study, (a) to replicate previous findings with this subject group, (b) to verify the sensitivity of the measures and (c) to compare the magnitude of effect against that in never-smokers. Provided the doses of nicotine were well tolerated, a lack of performance enhancement in never-smokers and an improvement in performance in smokers would be consistent with the view that this improvement was entirely due to withdrawal relief.

Materials and methods

Subjects

Thirty-six subjects (18 smokers and 18 never-smokers), recruited by advertisements in a local newspaper, completed the study. Smokers were required to have smoked at least 15 cigarettes per day for 2 years, while never-smokers were those with a life-time consumption of less than 20 cigarettes (or other tobacco equivalent), and no tobacco in the previous year. All subjects were paid £80 for completing the study, plus a bonus of £20 contingent on their performance on the tests (all subjects were given the maximum bonus). The study was approved by the Institute of Psychiatry Ethical Committee and all subjects provided written informed consent. The characteristics of the two subject groups are shown in Table 1. The negligible saliva cotinine concentrations in the never-smokers validate their claim to be non-smokers.

Design and drug administration

This was a double-blind, placebo-controlled cross-over study with the three conditions (saline, 2 × 0.3 mg nicotine base and 2 × 0.6 mg nicotine base) tested at weekly intervals after an initial practice session. Order of conditions was counterbalanced and randomized, such that three smokers and three never-smokers were allocated to each of the six treatment orders. The doses were given in the form of two injections in order to minimize any unpleasant symptoms and also to maintain moderate nicotine levels for a sufficient time period. They were given subcutaneously, 40 min apart, into the left arm using a fine needle (gauge 25). The average dose per injection was 4.4 μg/kg (0.3 mg dose) and 8.8 μg/kg (0.6 mg dose). A pilot study indicated that the 0.6 mg dose produced plasma nicotine concentrations within the range 3–11 ng/ml during the 40 min after the second injection (mean C_{max} = 8.5 ng/ml, mean t_{max} = 10 min after the second injection), with the 0.3 mg dose producing about half these concentrations (Foulds et al. 1994).

Table 1 Main baseline characteristics of the two subject groups. Unless otherwise stated the values are mean (SD)

	Smokers	Never-smokers
Number (no. female)	18 (9)	18 (9)
Age in years	30.9 (5.2)	25.4 (5.4)
Years of education	14.0 (2.2)	16.1 (2.5)
Hight (cm)	173 (9.3)	169 (9.2)
Weight (kg)	69.0 (10.5)	66.8 (11.2)
Years of smoking	16.4 (7.8)	0
Current cigarettes/day	20.9 (7.7)	0
Saliva cotinine (ng/ml)	315 (130)	0.8 (0.6)

Procedure

Subjects attended a practice visit to familiarise themselves with the procedures and to check that the never-smokers were not unusually sensitive to nicotine by twice administering the 0.3 mg dose, single blind. Smokers smoked as usual prior to this visit but were required to abstain from all tobacco use for 24 hours prior to visits 2–4, validated by expired breath carbon-monoxide <10 ppm. All subjects were required to abstain from alcohol (24 h) and caffeine (2 h) prior to each visit. Visits began at the same time and on the same day of the week for each subject.

On arrival subjects rated how they had been feeling over the previous 24 h on a tobacco withdrawal symptom questionnaire. This included an item on "difficulty concentrating", rated, 0 = "not at all", 1 = "a little", 2 = "somewhat", 3 = "very much" and 4 = "extremely". They then completed the tests of cognitive performance (pre-injection measure). Various subjective and physiological measures were recorded before and after the first injection, the details of which will be described in a subsequent report. Forty minutes after the first injection, subjects received another (same dose) injection. Immediately after this second injection they completed the cognitive test battery again (post-injection measure).

Cognitive tests

The cognitive test battery was administered in the order described below, taking about 35 min to complete. All the tests (other than news recall and critical flicker fusion threshold) were administered by computer with response time and accuracy being recorded automatically. The tests were as follows:

News recall – immediate and delayed (3 min)

Subjects were presented with a short "news story" containing 22 "idea" units and 54 words using a tape-recorder. Subjects had to write down the story as fully and accurately as possible (1) immediately after hearing it and (2) at the end of the other computerised tests. Scoring was 2 points for each idea unit recalled perfectly or for an exact synonym, and 1 point for partial recall. This test has not been previously used to evaluate nicotine effects but has been shown to be sensitive to the effects of other psychotropic drugs (Curran et al. 1988).

Sternberg Memory Search Task (9 min)

A short list of digits (the positive set) was presented for 3 s, followed by a series of "probe digits". The subject's task was to indicate (by pressing the appropriate key on the keyboard) whether or not each probe digit was or was not a member of the positive set. Subjects were instructed to respond as quickly as possible with as few errors as possible. The task involved one practice trial with positive set size 2 and one with positive set size 5. Each trial consisted

of 16 probe digits, eight of which were randomly chosen from the positive set. After the practice trials the subjects had four trials with positive set size 2 interspersed with four trials with positive set size 5. The subjects' mean response times for correct responses were calculated separately for set sizes 2 and 5, and the memory search time was indexed by the difference between the two. This task was virtually identical to that used by West and Hack (1991), who found that a nicotine cigarette produced a faster memory search rate than a non-nicotine cigarette in both regular and occasional smokers, regardless of the abstinence conditions.

Finger tapping(1 min)

Subjects were required to tap the space bar on the computer with the first finger of their dominant hand for 200 taps as quickly as possible (after completing a 30-tap practice trial). West and Jarvis (1986) found that nicotine increased finger-tapping speed in non-smokers but Perkins et al. (1990) failed to find a significant enhancement in non-smokers. This task is a measure of motor speed which requires minimal cognitive processing.

Logical reasoning (3 min)

Each problem involved presentation of the letter pair A and B, one above the other, along with a statement which either correctly or incorrectly described the position of the letters (e.g. "B is above A" or "A is not below B"). The subject had to decide whether the statement was true or false and press the appropriate response button as soon as they knew the answer. Each test involved 32 trials and both the number of correct responses and the reaction time of correct responses were analyzed. This was a slightly modified version of the reasoning test used by Snyder and Henningfield (1989). They found that correct response time was slowed significantly after 12 h of smoking deprivation and that this decrement was reversed by nicotine gum. This task was included as a measure of complex processing of verbal information.

Rapid Visual Information Processing(RVIP) (11 min)

A series of single digits were presented on the computer screen at a rate of 100 digits per minute for 10 min. Targets were defined as three consecutive odd digits or three consecutive even digits. There were eight targets per minute with 5–30 digits between each target (i.e. a total of 80 targets in 10 min). Subjects were instructed to press the space bar as soon as they noticed a target, with a response window of 1500 ms. Both the number of hits and reaction time were analyzed, as well as a commonly used index of sensitivity (A') (Sahgal 1987; Jones et al 1992) which takes account of the number of false alarms (f). A' was computed as:

$$A' = (0.5 + [(h\text{-}f) + (h\text{-}f)^2]/[4 \times h(1\text{-}f)]) \times 1000 \qquad \text{(where h=hits).}$$

This measure of sustained attention has been frequently used in assessing the effects of nicotine since the early work of Wesnes and Warburton (1984a, b) suggested that target detection and reaction-time to targets were improved by smoking and that nicotine tablets prevented a slowing of responses over time in non-smokers.

Long term word recognition (2 min)

Immediately after completing the immediate recall of the news story, subjects were presented (on the computer) with a series of 16 words (2 s each) of similar length and frequency of occurrence. Twenty-four minutes later (immediately after the RVIP task) subjects were presented with a series of 32 words, of which 16 were in the original series. Subjects had to respond by pressing the appropriate button to indicate whether each word was in the original list or not. The number of correct responses and sensitivity were analyzed. This relatively short recognition task involved virtually no opportunity for rehearsal and so provides a measure of efficiency of storage of verbal material which is relatively uninfluenced by other non-specific factors such as sustained attention which are inevitably involved when long word lists are used and subjects are allowed to rehearse the material. Perkins et al. (1994) used a similar recognition memory test and found that nicotine improved performance over placebo in both smokers and non-smokers (although only at low doses in the non-smokers).

Digit recall (2 min)

Each trial consisted of nine random digits displayed in a row across the centre of the screen for 1 s. After a 3-s blank retention interval eight of the original nine digits were displayed in a different random order, and the subject was required to enter the missing digit. The number of correct responses and the correct reaction time were analyzed. Previous studies have found response time increased and accuracy decreased when smokers abstained and that these effects are reversed by nicotine gum (Snyder and Henningfield 1989; Snyder et al. 1989). This task was included as a measure of short-term memory capacity and attention, and consisted of ten trials.

Stroop (2 min)

Subjects were presented with a series of words written in different colours (red, green and blue) and were required to press one of three response buttons according to the colour in which the word was written. Within the series of words, the words red, green and blue were themselves presented. Sometimes they were presented in the colour of the ink they represent (congruent) and sometimes in another colour (incongruent). The difference in response time between the congruent and incongruent trials (subjects tend to respond more slowly to incongruent trials: the "stroop effect") was used as an index of response-selection interference (Provost and Woodward 1991).

Wesnes and Warburton (1983) have reported that nicotine reduces the size of the stroop effect in both smokers and non-smokers and suggested that nicotine aids selective attention and reduces distractibility. More recently, it has been found that this effect was only apparent at the end of a long series of trials and it was suggested that rather than having a direct effect on selective attention, nicotine speeds up the rate at which the task becomes "automatic" and can therefore be performed without complex processing (Provost and Woodward 1991). A short version (20 colour words including ten congruent and ten incongruent) was included at the end of the test battery to try to clarify this issue. If nicotine was found to reduce the size of the stroop effect in the present study, this could not be attributed to automaticity as the task was too short for this to develop.

Critical Flicker Fusion Threshold (CFFT)(3 min).

An additional task, thought to measure central nervous system (CNS) arousal rather than cognitive performance, was the CFFT (Clark et al. 1963). Subjects were presented with four lights at a distance of 1 m. One of the lights flashed and the subject had to guess which one it was. The flicker frequency was adjusted in half Hertz increments (both ascending and descending) until the highest frequency at which the subject could identify the flickering light on four out of four trials (the CFFT). A number of studies (generally involving tobacco-deprived subjects) have found that nicotine increases CFFT (e.g. Waller and Levander 1980), whereas others have not found any effect (e.g. Kerr et al. 1991).

Statistical analysis

The response to each condition was measured by pre- first injection to post- second injection changes in performance. As no a-priori assumptions could be made about the form of response across saline, 0.3 mg and 0.6 mg nicotine (particularly for never-smokers), the effect of each nicotine dose was assessed separately by comparison with placebo. Smokers and never-smokers were analyzed separately prior to a comparison between them. No attempt was made to adjust for drug-sequence effects given the adequacy of the wash-out period and the inadequacy of adjustment procedures (Freeman 1989; Senn 1992). Nicotine versus saline comparisons were made by *t*-test, based on within-subject variance, adjusting for time-period effects. Analysis of covariance was used to compare the nicotine effect between smokers and never-smokers with nicotine minus saline scores as the dependent variable and background characteristics as covariates. No assessment was made of the overall probability of one or more type II errors among the many tests conducted and some caution is required when interpreting results which do not follow a general pattern.

After the study was completed it was discovered that the computer programme running the RVIP task had failed to record responses during the 150 ms prior to each digit presentation. In order to provide results comparable to other studies using this task, the number of missing responses on each occasion was imputed as the total number of known responses in the 75-ms period either side of the missing period. The actual response times of these hits were imputed according to random sampling from a linear distribution over the missing period. Two analyses were then conducted for the measures affected by missing data: (1) using only responses recorded in the first 450 ms after target presentation, i.e. before the computer error occurred, and (2) using the partially imputed data.

Results

Smokers

The mean pre-post injection change on each performance variable in smokers is shown in Table 2. There was no evidence of an effect of nicotine on recall of news stories, either immediately after presentation of the story, or after performing the rest of the performance battery. There was also no nicotine effect on the Sternberg task. As expected, subjects made few errors on this task (averaging about 95% correct) and reaction time was faster when two as opposed to five digits were presented (mean difference = 132 ms). Unlike some previous studies there was only weak evidence for an effect on the finger tapping task with the 0.3 mg injections producing an estimated change of 15 taps per minute more than placebo. There were few errors on the logical reasoning task, with an overall average of around 90% correct responses and there was evidence that both nicotine doses produced an improvement in correct reaction times of 7% and 9% for 0.3 mg and 0.6 mg, respectively. In the case of the 0.3 mg doses there was some evidence that this was accompanied by a reduction in accuracy.

Subjects made few false alarms (mean = 4.6 per 10-min test session) on the RVIP task and their frequency was unaffected by nicotine. There was good evidence that nicotine improved all RVIP response measures using the partially imputed data (Table 2). The 0.6 mg doses produced a 20% increase in the number of correct responses and a 10% improvement in reaction time. The effect was more pronounced in the analysis of "fast hits" (target hits with a reaction time less than 450 ms), which was unaffected by the computer error. The mean improvements in number of fast hits were +5.3 ($t = 2.4$, $P = 0.027$) and +9.3 ($t = 3.8$, $P < 0.01$) for 0.3 and 0.6 mg nicotine, respectively. There was evidence of a nicotine effect on both correct responses (+16%) and sensitivity (+18%) on the word recognition task, but only at the higher dose. There was no effect at either

Table 2 Abstinent smokers: pre-post injection changes on the main measures of cognitive performance

Measure	Saline mean (SD)	0.3 mg nicotine mean (SD)	0.6 mg nicotine mean (SD)	0.3 mg-saline difference mean (95% CI)	0.6 mg-saline difference mean (95% CI)
News recall (immediate)	+1.5 (9.2)	−0.33 (7.4)	+0.06 (5.3)	−1.8 (−7.9, +4.2)	−1.4 (−5.0, +2.2)
News recall (delayed)	+0.67 (8.2)	−1.5 (9.2)	+0.28 (6.5)	−2.2 (−8.4, +4.1)	−0.39 (−4.4, +3.6)
Sternberg memory search time (RT on set-five minus set-size two)	−15 (74)	−3.2 (55)	−20 (99)	+12 (−34, +57)	−4.7 (−50, +40)
Finger tapping (taps per min)	−2.3 (29)	+13 (27)	+4.4 (33)	+15 (−2.6, +33)#	+6.7 (−9.7, +23)
Logical reasoning (no. correct)	+1.1 (2.4)	−0.22 (3.4)	+1.1 (1.8)	−1.3 (−2.9, +0.24)#	−0.06 (−1.4, +1.3)
Logical reasoning (correct RT[a])	−57 (328)	−223 (255)	−274 (351)	−166 (−297, −34)*	−217 (−329, −106)**
RVIP (no. of hits)	+1.5 (9.6)	+3.1 (11)	+10.4 (12)	+1.5 (−4.5, +7.7)	+8.9 (+0.90, +17)*
RVIP (sensitivity)	+4.5 (32)	+10 (34)	+33 (38)	+5.9 (−14, +26)	+29 (+0.71, +57)*
RVIP (RT on target hits)	+0.31 (45)	−42 (37)	−46 (55)	−42 (−72, −12)*	−46 (−80, −13)*
Word recognition (no. correct)	−2.1 (5.5)	+0.55 (5.4)	+1.4 (3.9)	+2.6 (−0.73, +6.0)	+3.5 (+0.03, +7.0)*
Word recognition (sensitivity)	−81 (196)	+19 (214)	+55 (171)	+100 (−43, +242)	+135 (+2.8, +268)*
Digit recall (no. correct)	+0.29 (1.9)	−0.35 (1.9)	+0.41 (2.1)	−0.62 (−1.9, +0.65)	+0.13 (−1.1, +1.3)
Digit recall (correct RT in s)	−0.48 (1.6)	+0.43 (0.96)	−0.39 (1.4)	+0.91 (−2.1, +0.31)	+0.10 (−1.3, +1.5)
Stroop effect (incongruent-congruent RT)	+12 (119)	−35 (163)	+26 (165)	−47 (−163, +69)	+15 (−64, +93)

[a] *RT* reaction time in ms unless otherwise stated

Nicotine-saline difference: #$P < 0.1$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

dose on the digit recall, stroop or critical flicker fusion tasks.

Never-smokers

There was no evidence of effects on news recall, Sternberg, finger tapping, stroop, word recognition or critical flicker fusion in never-smokers (Table 3). There was, however, evidence of effects on RVIP and digit recall. Using the partially imputed data, RVIP correct reaction time showed a 12% improvement on the 0.6 mg dose. Similarly there was an improvement in the number of fast hits (<450 ms) on both 0.3 mg (mean = +6.0, $t = 2.8$, $P = 0.013$) and 0.6 mg (mean = +6.8, $t = 2.4$, $P = 0.027$). Unlike in smokers, there was a clear improvement in Digit Recall correct reaction times (18% and 21% for 0.3 mg and 0.6 mg, respectively), but this appeared to be at the expense of fewer correct responses (−28% and −32%).

Comparison between smokers and never-smokers

The size of the nicotine effect (i.e. difference between nicotine and placebo responses) in smokers and never-smokers was compared. Although the observed effect was generally larger in smokers than never-smokers across the range of tasks and doses, there was only modest evidence ($P < 0.1$) against this having occurred by chance. Figures 1–3 show the responses for the two groups on the logical reasoning and RVIP tasks. The apparent difference between smokers and never-smokers on RVIP reaction time at the 0.3 mg dose (Fig. 3) has only modest statistical support ($P = 0.08$).

Baseline differences between smokers and never-smokers

The first visit, when smokers were not abstinent, was designed as a practice and familiarization session and consequently the performance data were not regarded as reliable enough to be used with the data from subsequent visits in an analysis of the effect of tobacco abstinence on performance. Smokers' pre-injection performance was generally worse than never-smokers' (see Figs. 1, 2 and 3 for an indication of the size of pre-injection group differences on the logical reasoning and RVIP tasks). The size of these pre-injection group

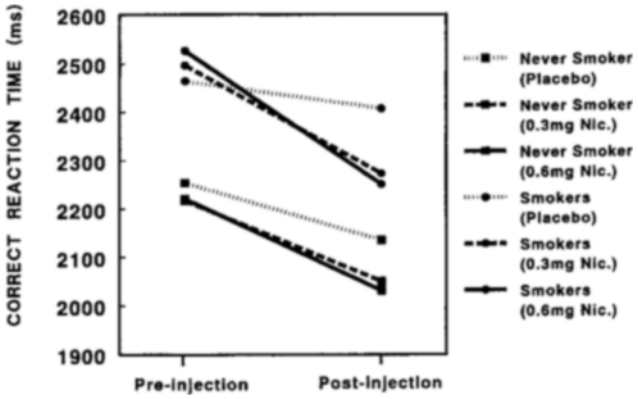

Fig 1 Mean reaction time on correct responses in the logical reasoning task

Table 3 Never-smokers: pre-post injection changes on the main measures of cognitive performance

Measure	Saline mean (SD)	0.3 mg nicotine mean (SD)	0.6 mg nicotine mean (SD)	0.3 mg-saline difference mean (95% CI)	0.6 mg-saline difference mean (95% CI)
News recall (immediate)	+3.1 (7.4)	+2.8 (5.6)	+1.1 (6.3)	−0.24 (−5.1, +4.7)	−2.0 (−6.5, +2.5)
News recall (delay)	+2.9 (6.9)	+2.8 (5.8)	+0.71 (5.6)	−0.18 (−5.5, +5.2)	−2.2 (−6.0, +1.5)
Sternberg memory search time (RT on set-five minus set-size two)	+5.7 (45)	−2.3 (62)	+3.9 (54)	−8.0 (−47, +31)	−1.8 (−38, +34)
Finger tapping (taps per min)	−24 (24)	−19 (33)	−28 (26)	4.9 (−7.4, +17)	−4.7 (−18, +8.3)
Logical reasoning (no. correct)	+0.22 (2.6)	+0.61 (3.1)	−0.89 (1.8)	+0.39 (−1.8, +2.5)	−1.1 (−2.5, +0.23)#
Logical reasoning (correct RT[a])	−119 (267)	−166 (240)	−190 (409)	−47 (−179, +85)	−71 (−317, +176)
RVIP (no. of hits)	+0.53 (12)	+7.1 (8.7)	+3.3 (9.6)	+6.5 (−0.94, +14)#	+2.8 (−5.9, +11.4)
RVIP (sensitivity)	+1.7 (37)	+26 (34)	+13 (30)	+24 (−2.7, +51)#	+11 (−16, +38)
RVIP (RT on target hits)	+7.1 (28)	−2.3 (51)	−48 (42)	−9.4 (−34, +15)	−55 (−84, −25)**
Word recognition (no. correct)	−0.83 (2.1)	−0.33 (4.0)	+0.28 (2.9)	+0.50 (−1.8, +2.8)	+1.1 (−0.57, +2.8)
Word recognition (sensitivity)	−16 (54)	−4.1 (94)	−3.5 (83)	+12 (−46, +70)	+12 (−29, +54)
Digit recall (no. correct)	+1.4 (2.3)	−0.19 (2.0)	−0.38 (2.4)	−1.6 (−3.2, −0.10)*	−1.8 (−3.7, +0.08)#
Digit recall (correct RT in s)	+0.49 (0.82)	−0.13 (0.94)	−0.34 (0.96)	−0.63 (−1.2, +0.11)*	−0.77 (−1.5, −0.08)*
Stroop effect (incongruent-congruent RT)	+57 (169)	+3.9 (151)	−10 (175)	−53 (−187, +80)	−67(−185, +51)

[a] *RT* reaction time in MS unless otherwise stated
Nicotine saline difference: #$P < 0.1$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

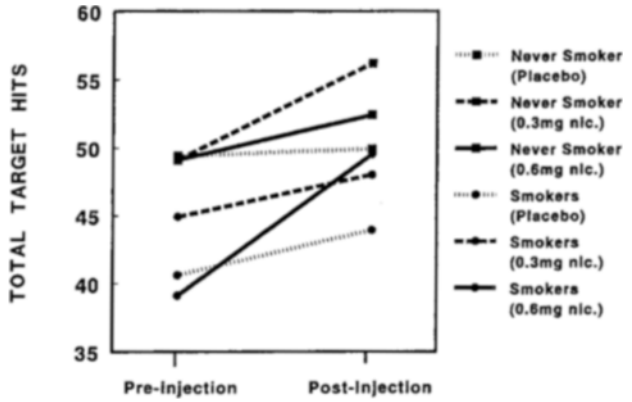

Fig. 2 Mean number of target hits in the rapid visual information processing task

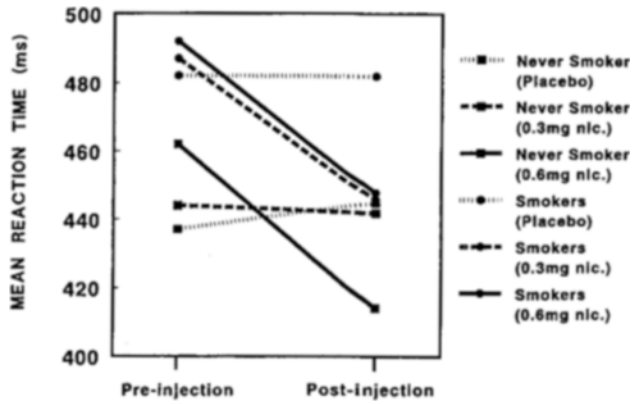

Fig. 3 Mean reaction time on target hits in the rapid visual information processing task

differences was generally attenuated but still significant when background variables were controlled for. For example, in the word recognition task the never-smokers' mean pre-injection recognition sensitivity was 897, compared with 790 in the smokers (i.e. smokers worse by 107). When demographic variables (age, sex, years of education, height, weight and time of day) were controlled for this difference was reduced to 79 ($P = 0.013$), group being the only significant predictor of pre-injection performance. The pattern of ratings of "difficulty concentrating" on the 24 h withdrawal questionnaire were also examined. There was a significant group × visit interaction [F (1, 34) = 8.0, $P = 0.008$] in the analysis comparing the visit 1 rating (when the smokers were not abstinent) with the other 3 weeks. The mean ratings of "difficulty concentrating" over the previous 24 h are shown in Fig. 4.

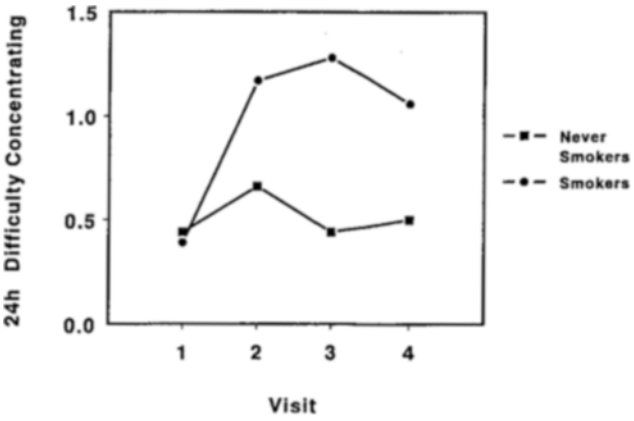

Fig. 4 Mean ratings of "difficulty concentrating" during the previous 24 h at each visit. The smokers abstained for 24 h prior to visits 2, 3 and 4

Drop-outs

All 18 never-smokers who started the study completed all visits, but seven smokers who started the study dropped out within the first two visits and had to be replaced. One was advised to discontinue after complaining of a stomach upset (not thought to be due to experimental procedures) and the others provided various reasons (e.g. "I'm too busy at work" or "You don't pay enough money"). It is likely that this differential dropout rate was partly due to the smokers finding it difficult to abstain for 24 h on three separate occasions. The smokers who dropped out were not markedly heavier smokers than those who completed the study.

Unblinding

At the end of the study subjects were reminded of the three doses they had received during the last three visits and were asked to nominate which dose they thought they had received at each visit. Never-smokers were able to guess the dose received with considerable accuracy: 13 (72%), 13 (72%) and 17 (94%) correctly identified the visit on which they received the placebo, 0.3 mg and 0.6 mg injections, respectively. They never confused the placebo with 0.6 mg. Smokers were not able to discriminate the doses, with only eight (44%), six (33%) and seven (39%) correctly naming the visit on which they received placebo, 0.3 mg and 0.6 mg injections.

Discussion

Perhaps the most interesting result from this study is the evidence that nicotine can improve performance on the RVIP task in never-smokers (in addition to the expected effects in abstinent smokers). Confidence that the effect in never-smokers is not a chance finding is strengthened by other evidence. Firstly, this was the task which was most sensitive to nicotine effects in smokers. Secondly, previous studies by another group have found similar results (e.g. Wesnes and Warburton

1984b). Finally, preliminary results from a similar study in ex-smokers in our laboratory also suggest that nicotine improves performance on the RVIP task. The finding that nicotine increases the number of fast target hits (reaction time less than 450 ms) on this task is very similar to that of Le Houezec et al. (1994) using a choice reaction time task. They found that a single 0.8 mg subcutaneous nicotine injection increased the number of responses at the fast end of the reaction time distribution in non-smokers. Our results in never-smokers, taken together with recent studies finding smoking-induced enhancements in smokers who have not been deprived of nicotine for a lengthy period (Pritchard et al. 1992; Warburton and Arnall 1994), suggest that nicotine can have beneficial effects on performance which are not attributable to a reversal of a deficit induced by withdrawal.

In abstaining smokers in this study there was clear evidence that nicotine improved performance on three cognitive tasks (RVIP, logical reasoning, word recognition). Estimates of the magnitude of improvement attributable to nicotine varied between 5% and 20%. The lack of an effect on several of the measures suggests that nicotine may not have a widespread effect on all aspects of cognitive performance. Unlike some previous studies, we did not find effects of nicotine in abstinent smokers on certain tasks (e.g. finger tapping and Sternberg memory search). Indeed, the results of the present study mirror the history of research on cognitive effects of nicotine in humans, which has been characterised by individual positive findings followed by failures to replicate. This pattern of inconsistent results requires an explanation.

One clue has been provided by a recent study (Perkins et al. 1994) which found that the effect of nicotine on performance exhibits an inverted-U shaped relationship with plasma nicotine concentration in both smokers and non-smokers (with the smokers' curve shifted to the right). The second factor which may contribute to inconsistent results is the large inter-individual variation in blood nicotine concentration achieved by a given dose of nicotine (Sutherland et al. 1992; Foulds et al. 1994). One consequence of these two factors is that any given dosing procedure may potentially produce such a range of blood nicotine concentrations that some subjects will experience little effect, some will experience an "optimal" nicotine concentration and a beneficial effect, while others may obtain excessively high nicotine concentrations, having a negative effect on performance. Such factors may make it difficult to obtain consistent results both within and between samples.

We did not measure nicotine concentrations in the present study as it was felt that repeated blood sampling could affect both subject recruitment and some of the measures being used. We were therefore unable to assess the relationship between performance and actual plasma nicotine levels. However, the 0.3 mg dose was sufficient to produce improvement in smokers' logical reasoning and the 0.6 mg dose was not too large to prevent improvement on the RVIP task in never-smokers, suggesting that the doses given were within the appropriate range to detect, if not maximize, enhanced performance. It is interesting that like the present study, other investigators (e.g. Le Houezec et al. 1994; Perkins et al. 1994) found performance enhancements at relatively low nicotine concentrations (<10 ng/ml) and using methods of nicotine administration which do not deliver the high concentration nicotine boli (e.g. 100 ng/ml) to the brain which follow smoke inhalation (Henningfield et al. 1993).

It is tempting to conclude that the RVIP task requires cognitive functions which are particularly affected by nicotine (e.g. sustained attention to rapidly changing stimuli). However, it could be that this task was consistently affected by nicotine in this study because of its position in the test battery (possibly occurring just after peak nicotine concentrations were obtained), or simply because, being the longest task in the test battery, it enabled a more reliable measure of performance. Nonetheless, the lack of effects on measures which are largely measuring motor speed (e.g. finger tapping), together with evident effects on measures such as logical reasoning and word recognition (in smokers), suggest that nicotine is acting directly on cognitive functions (e.g. memory, information processing speed) rather than simply speeding up motor responses.

Having found evidence of a primary cognition enhancing effect of nicotine in this study, the issue of to what extent the performance enhancement in smokers is attributable to a primary or withdrawal-reversal effect remains a complex one. A comparison of performance in smokers and never-smokers in this study may provide some clues but cannot give clear answers. The demonstration of a primary effect in never-smokers on the RVIP task implies that at least part of the effect on this task in smokers could be a primary one. The pattern of responses on the self-reported measure of concentration difficulty indicated that while smoking, the smokers' perceived ability to concentrate was generally similar to that of never-smokers but was reduced by tobacco abstinence. This would suggest a major role for nicotine-withdrawal reversal, above any primary effect. The pre-injection performance of the smokers' was also consistently below that in the never-smokers (even after adjustment for background characteristics). Assuming that this reflects their state of tobacco withdrawal (as suggested by their ratings of difficulty concentrating) rather than inherent differences between the groups, this would suggest a major role for withdrawal reversal, above a primary effect, in the performance-enhancing effect of nicotine in smokers. On the other hand, the similar magnitude of nicotine effects in the two groups would seem to imply that withdrawal-relief was not a major part of the effect in smokers. It might be expected that if all or the larger part of the enhancement was due to a reversal of a withdrawal-induced performance

deficit, then the enhancement in smokers would be greater than in never-smokers. However, only modest statistical support for this could be provided. The lower statistical power of the between group comparisons may have hampered clear conclusions, especially on measures where there was no evidence of a positive effect in never-smokers e.g. word recognition sensitivity (+18% for smokers, +2% for never-smokers, $P = 0.071$ at 0.6 mg dose), but cannot be implicated on the single measure where there was a clear effect in both groups (RVIP) in which the levels of enhancement were very similar (about 10%). These results also imply that smokers do not develop chronic tolerance to nicotine's effects on cognitive performance.

In conclusion, the present study has added to recent evidence suggesting that nicotine can produce modest enhancements in certain aspects of cognitive performance in never-smokers as well as in smokers (Le Houezec et al. 1994; Perkins et al. 1994). Given the severe health consequences of tobacco smoking, smokers who claim to smoke (or relapse) in order to help their mental abilities should be informed that they could probably obtain similar effects at much less risk to their health by using a nicotine replacement product rather than tobacco or drinking a caffeinated beverage (Jarvis 1993; Cohen et al. 1994).

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