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Influence of nicotine on simulator flight performance in non-smokers

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Abstract In a placebo-controlled study, we investigated the influence of nicotine on late-day aviation performance in 15 non-smoking subjects. In a within-subjects design, subjects were tested on 2 days, each lasting 8 h and consisting of three 75-min simulator flights (late-afternoon practice, evening test, night test). Prior to each test, subjects received either nicotine polacrilex 2 mg or placebo gum. As expected, overall performance was significantly better after nicotine, compared to placebo ($P < 0.01$). Post-hoc analysis of individual flight tasks showed that nicotine improved scores on approach to landing, a task which appears to require sustained attention. We conclude that nicotine may improve late-day flight performance in non-smoking aviators.

Key words Nicotine · Cognition · Psychomotor performance · Task performance and analysis · Aerospace medicine · Attention · Workload · Chewing gum · Non-smoker

Introduction

Acetylcholine systems have long been recognized to be important for cognitive functioning (Levin 1992). Nicotine, an acetylcholine receptor agonist, has been found to improve performance in smokers on tasks assessing attention, learning, reaction time and memory (Snyder et al. 1989; Sherwood et al. 1992; Warburton et al. 1992; Rusted et al. 1995; Pickworth et al. 1996). The interpretation of performance enhancements in studies conducted with nicotine-deprived smokers, however, is problematic because nicotine withdrawal leads to impaired performance, particularly on tasks requiring vigilance (Snyder et al. 1989; American Psychiatric Association 1994; Shiffman et al. 1995). Thus it can be argued that when smokers are tested following overnight smoking deprivation or shorter periods of abstinence, pre- to post-smoking improvements in performance are a result of relieving withdrawal-induced performance deficits, and therefore are not a result of nicotine per se. Indeed, nicotine withdrawal is the most consistent condition under which nicotine ingestion enhances performance. An effective way to avoid possible withdrawal deficits completely is to administer nicotine to non-smokers.

For those studies addressing the effect of nicotine on cognition in non-smokers, results have been mixed. Five studies reported significant effects of nicotine on performance (West and Jarvis 1986; Sherwood et al. 1990; Kerr et al. 1991; Le Houezec et al. 1994; Foulds et al. 1996). Four studies did not detect significant effects of nicotine in non-smokers (Wesnes and Revell 1984; Heishman et al. 1990, 1993; Hindmarch et al. 1990), including Heishman's studies which employed the same measures previously demonstrated to be sensitive to nicotine withdrawal-induced deficits, as well as their reversal by nicotine gum and patch administration in smokers (Snyder and Henningfield 1989; Snyder et al. 1989; Pickworth et al. 1996).

Two effects of nicotine that have often been found, enhanced information processing and improved sensorimotor performance (Sherwood et al. 1992), are relevant to driving a car or flying an airplane. Piloting an aircraft in particular demands a high level of psychomotor coordination, three-dimensional thinking, and alertness, and thus, is a complex information processing task comprised of many subtasks that compete for limited processing capacity. Since sophisticated measures of aviators' abilities have already been developed in our laboratory, these methods provide an

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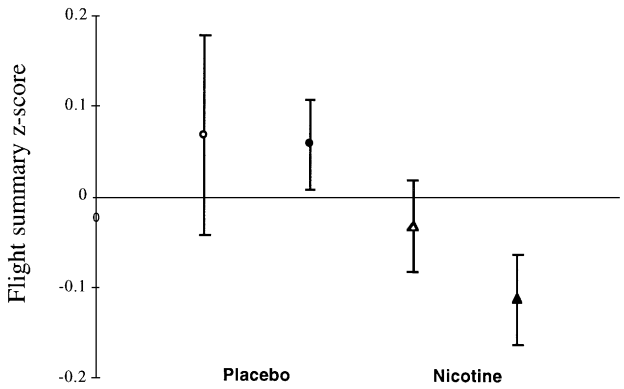

Fig. 1 Mean (± SEM) flight summary *z*-scores of evening and night flight on placebo and nicotine days (dose: nicotine polacrilex 2 mg prior to each evening and night flight). Lower scores mean better performance. Scores are standardized with respect to the mean and SD of the pretreatment scores. Mean practice flight performance = 0. Nicotine improved overall performance significantly, $P < 0.01$, $n = 16$. ○ Placebo evening, ● placebo night, △ nicotine evening, ▲ nicotine night

opportunity to investigate nicotine effects on complex performance. The present study examined the influence of nicotine in non-smokers, so that withdrawal relief could be ruled out as an explanation for possible post-nicotine improvements in performance. Most of the previous studies of non-smokers typically presented subjects with only one cognitive task at a time, such as finger tapping, choice reaction time, visual search, or digit recall. To our knowledge, this is the first published study that provides data about the effects of nicotine on flight simulator performance.

Materials and methods

Subjects

Subjects were seven female (mean age = 34.8, SD = 4.1) and nine male (mean age = 30.3, SD = 2.5) licensed aircraft pilots who had participated in a prior research study in our laboratory. They had an average flight experience of 1045 hours (SD = 752). All subjects were non-smokers with no history of regular smoking, and were in possession of at least a Class III Federal Aviation Administration (FAA) Medical Certificate. They were screened for health problems, consumption of nicotine and other psychoactive drugs, based on written questionnaires. Subjects were excluded if they were taking psychotropic medications or medications with arousal or sedative effects at any time during the study period. All subjects had at least 12 h of experience in the flight simulator model Frasca 141 from participation in a prior study. The protocol was approved by the Human Subject Committee of Stanford University and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects gave written informed consent to participate and could withdraw at any time.

Drug conditions

All subjects received nicotine in the form of polacrilex gum, 2 mg (SmithKline Beecham Consumer Health Care, Pittsburgh, Pa., USA) or placebo gum (confectionery gum of the same size), in a within-subjects design. The gum was administered blind and to disguise the presence of nicotine, one drop of hot chili (Tabasco) sauce was added to all pieces of gum. Subjects were told they would receive either nicotine or placebo and were instructed to chew the gum slowly and steadily for 20 min.

Equipment

The equipment consisted of a Frasca 141 flight simulator (Urbana, Ill., USA) linked to a UNIX-based IRIS 3115 computer (Silicon Graphics, Mountain View, Calif., USA) that generated sophisticated "through-the-window" graphics of the environment in which the pilots flew, and collected data concerning the aircraft's flight conditions. The instrumentation, control devices (e.g., yoke, rudder pedals, throttle), and flight characteristics simulated a small, fixed landing gear, fixed propellor, single engine aircraft. The simulator used is popular as an FAA-approved pilot training device and provides realistic aircraft performance. A speaker system was installed in the cockpit and connected to a tape recorder, through which the pilot received Air Traffic Control (ATC) messages in accordance with FAA standards (FAA Order 7110.650). Each ATC script contained a take-off clearance, 16 critical enroute messages and instructions for approach and landing.

Procedures

To minimize practice effects and insure stable, relatively reliable performance, each subject participated in four training sessions prior to the first test day. In these sessions aviators performed the same tasks to be performed on the test days. On two of the four training sessions, each subject received the medication prior to the practice flight, to familiarize them with the drug. On the remaining two training sessions, no drug was administered. Pilots were tested twice a day on each of 2 test days: placebo day and nicotine day. Thus, each subject served as his or her own control. Each test day lasted a total of 8 h, starting with a pre-treatment "warm-up" practice flight at 1600 hours. After the practice flight, 30 min before starting each subsequent testing (the first test flight started at 1930 hours, the second at 2200 hours) the subjects received a single dose of either nicotine polacrilex 2 mg or placebo gum. Because of potential practice effects, the order of testing of the nicotine or placebo treatment was counterbalanced. Between the "warm-up" and the test sessions, subjects had a 1-h dinner break (1800–1900 hours).

Scenario and tasks

Each flight lasted 75 min and consisted of a standard scenario with 19 flight segments (legs) around the airport, including leg 1: take-off, leg 2–17: enroute flying, leg 18: approach, leg 19: landing. After receiving take-off clearance, pilots were given a new ATC command every 3 min with new course (heading), altitude, radio frequency, and 50% of the legs, new transponder (identification) code. In order to increase the pilots' workload, we confronted them with three different emergency situations. Carburetor icing, or drop of engine oil pressure, or suddenly approaching air traffic occurred randomly and forced the pilots to react appropriately.

Flight scoring

The scoring system of the flight simulator-computer unit produced 23 flight-performance variables. These variables were scores derived from errors or deviations from ideal or assigned positions or

values (e.g., altitude in feet, heading in degrees, airspeed in knots, reaction time in seconds). Because these individual variables had different units of measurement, it was necessary to standardize each variable to a common scale such as *z*-scores. We used the sample mean and SD for each individual variable at the 1600 hours pre-treatment "warm-up" flight, as the basis for the *z*-scores. The 23 standardized variables were aggregated into eight flight scores: take-off, communication, traffic avoidance, cockpit monitoring (consisting of oil pressure and manifold pressure scanning), approach corrections, approach course deviation, runway alignment, flare (vertical speed at touch-down). Finally, a summary score was computed, which was the mean of the flight scores of the individual variables. Summary scores may be more sensitive to drug effects because of better test-retest reliability. Prior research in our laboratory (Taylor et al. 1994, 1996) has shown high variability and little drug effect on take-off and landing scores and we have not included these two scores in the summary score. More detailed descriptions of the flight scenario and scoring are provided in Taylor et al. (1994, 1996).

Data analysis

The primary dependent measure was the flight summary score, which was computed for each treatment condition (nicotine and placebo). Secondary dependent measures were the eight individual flight scores. The summary score and the individual flight task scores were analyzed by $2 \times 2 \times 2$ mixed-model ANOVAs with Treatment (nicotine versus placebo) and Time (evening versus night) as within-subjects factors, and Order (nicotine first versus placebo first) as a between-subjects factor. All effects, main and interaction, were tested. Of primary interest, however, was the drug effect and its interaction with time. Each effect and interaction was tested as $F(1,15)$, equivalent to a two-tailed *t*-test with 15 degrees of freedom. Significance levels were $P < 0.05$.

Results

For the flight summary score, there was a significant main effect of Drug, [$F(1,15) = 10.7$, $P < 0.01$], with pilots performing better after administration of nicotine gum (mean = -0.07; SD = 0.40) than in the placebo condition (mean = 0.06; SD = 0.40). No significant interaction was found of Drug × Time ($F < 1$), but the means were in the direction of larger nicotine influence during the night flight. These results are illustrated in Fig. 1. No statistically significant effect was found for Time ($F < 1$), or Order ($F = 1.34$, $P > 0.2$), or any interaction (Ps > 0.2).

The individual flight task showing the largest difference between placebo and nicotine treatment was the approach to landing. In order to stay on course, pilots executed significantly more and larger corrections on the yoke during the approach [$F(1,15) = 4.9$, $P < 0.05$] in the placebo condition (mean = -0.03; SD = 0.81) compared to the flights under nicotine (mean = -0.31; SD = 0.70). A similar, but not significant drug difference was observed in approach course deviation [$F(1,15) = 3.3$, $P < 0.1$], with the trend of pilots flying the ideal approach course more accurately under the influence of nicotine. The remaining six flight tasks (take-off, communication, traffic avoidance, cockpit monitoring, runway alignment, and flare) showed no significant drug effects, or interactions (Ps > 0.05).

Discussion

In this study, nicotine polacrilex 2 mg gum given to non-smoking aviators improved overall post-treatment flight performance significantly, compared to placebo. The fact that post-nicotine improvements could be shown in non-smokers rules out withdrawal relief as an explanation in this study. It remains to be determined how much withdrawal relief contributes to the performance enhancement observed in some studies of smokers. Our investigation adds to the literature by testing the effects of nicotine on highly skilled subjects on multiple tasks of high workload and complexity set over a longer period of time, as opposed to single short-term tasks utilized in prior studies. Testing the influence of nicotine on such overall performance scores might more adequately describe the drug's impact on "real world" tasks such as flying an airplane, or operating other complex machines. However, the gained data are more difficult to compare with those from prior studies which focused on more specific, and brief tasks. The results of the present study are consistent with the findings of Le Houezec et al. (1994), who showed that subcutaneous injection of low nicotine doses in non-smokers speeded information processing on a sophisticated choice reaction time task without increasing the number of errors. The authors suggested that a positive influence of nicotine on attention may account for their findings. Our results support this account since post-hoc analyses of individual flight scores found that nicotine particularly improved performance on tasks requiring sustained attention such as the approach to landing. Generally, our study seems to confirm prior findings (Koelega 1993; Heishman et al. 1994) that vigilance tasks, requiring subjects to sustain attention, appear to be sensitive to the effects of stimulant drugs.

There may be several reasons why some studies reported statistically nonsignificant nicotine effects on cognitive performance in non-smokers following orally administered nicotine (Wesnes and Revell 1984; Heishman et al. 1990,1993; Hindmarch et al. 1990). First, these studies used tests focusing on only one cognitive task at a time, while the flight simulator test presents multiple tasks simultaneously. Nicotine-induced performance enhancement in non-smokers might not be measurable until performance tasks are complex enough to reach the limit of the subject's workload capacity. Second, only 5–12 subjects were studied in three of the four negative studies, limiting statistical power (Wesnes and Revell 1984; Heishman et al. 1990; Hindmarch et al. 1990). Third, unlike the study of Heishman et al. (1993) and most other studies, we exposed all subjects to nicotine gum repeatedly prior

to the test sessions to attenuate side-effects such as nausea, and to enhance compliance with chewing instructions, thereby increasing the possibility of detecting positive effects of nicotine on performance.

We have assessed only a single dose of nicotine, and the absence of any dose-effect data makes it more difficult to determine which effects on performance were due to nicotine itself. Future studies should address this issue. In conclusion, we found nicotine-induced aviation performance enhancement in non-smoking subjects, ruling out withdrawal-relief as an explanation for the positive effect of nicotine observed in this study. Our findings clearly show that nicotine administration not only reverses nicotine withdrawal-induced performance decrements, but also appears to improve performance on certain types of attentional tasks, confirming the same conclusions drawn in two recent reviews (Koelega 1993; Heishman et al. 1994).

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References

American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Washington, D.C.

Foulds J, Stapleton J, Swettenham J, Bell N, McSorley K, Russell MA (1996) Cognitive performance effects of subcutaneous nicotine in smokers and never-smokers. Psychopharmacology 127: 31–38

Heishman SJ, Snyder FR, Henningfield JE (1990) Effect of repeated nicotine administration in nonsmokers. NIDA Res Monogr 105:314–315

Heishman SJ, Snyder FR, Henningfield JE (1993) Performance, subjective, and physiological effects of nicotine in non-smokers. Drug Alcohol Depend 34:11–18

Heishman SJ, Taylor RC, Henningfield JE (1994) Nicotine and smoking: a review of effects on human performance. Exp Clin Psychopharmacol 2:345–395

Hindmarch I, Kerr JS, Sherwood N (1990) Effects of nicotine gum on psychomotor performance in smokers and non-smokers. Psychopharmacology 100:535–541

Kerr JS, Sherwood N, Hindmarch I (1991) Separate and combined effects of the social drugs on psychomotor performance. Psychopharmacology 104:113–119

Koelega HS (1993) Stimulant drugs and vigilance performance: a review. Psychopharmacology 111:1–16

Le Houezec J, Halliday R, Benowitz NL, Callaway E, Naylor H, Herzig K (1994) A low dose of subcutaneous nicotine improves information processing in non-smokers. Psychopharmacology 114:628–634

Levin ED (1992) Nicotinic systems and cognitive function. Psychopharmacology 108:417–431

Pickworth WB, Fant RV, Butschky MF, Henningfield JE (1996) Effects of transdermal nicotine delivery on measures of acute nicotine withdrawal. J Pharmacol Exp Ther 279:450–456

Rusted J, Graupner L, Warburton D (1995) Effects of post-trial administration of nicotine on human memory: evaluating the conditions for improving memory. Psychopharmacology 119: 405–413

Sherwood N, Kerr JS, Hindmarch I (1990) No differences in the psychomotor response of heavy, light and non-smokers to the acute administration of nicotine. Med Sci Res 18:839–840

Sherwood N, Kerr JS, Hindmarch I (1992) Psychomotor performance in smokers following single and repeated doses of nicotine gum. Psychopharmacology 108:432–436

Shiffman S, Paty JA, Gnys M, Kassel JD, Elash C (1995) Nicotine withdrawal in chippers and regular smokers: subjective and cognitive effects. Health Psychol 14:301–309

Snyder FR, Henningfield JE (1989) Effects of nicotine administration following 12 h of tobacco deprivation: assessment on computerized performance tasks. Psychopharmacology 97:17–22

Snyder FR, Davis FC, Henningfield JE (1989) The tobacco withdrawal syndrome: performance decrements assessed on a computerized test battery. Drug Alcohol Depend 23:259–266

Taylor JL, Dolhert N, Morrow D, Friedman L, Yesavage JA (1994) Acute and 8-hour effects of alcohol (0.08% BAC) on younger and older pilots' simulator performance. Aviat Space Environ Med 65:718–725

Taylor JL, Dolhert N, Friedman L, Mumenthaler M, Yesavage JA (1996) Alcohol elimination and simulator performance of male and female aviators: a preliminary report. Aviat Space Environ Med 67:407–413

Warburton DM, Rusted JM, Fowler J (1992) A comparison of the attentional and consolidation hypotheses for the facilitation of memory by nicotine. Psychopharmacology 108:443–447

Wesnes K, Revell A (1984) The separate and combined effects of scopolamine and nicotine on human information processing. Psychopharmacology 84:5–11

West RJ, Jarvis MJ (1986) Effects of nicotine on finger tapping rate in non-smokers. Pharmacol Biochem Behav 25:727–731