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Effects of transdermally administered nicotine on aspects of attention, task load, and mood in women and men

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Abstract

This double-blind placebo-controlled study was conducted to determine nicotine effects on diverse types of attentional performance, task load, and mood considering sex effects as suggested by animal studies. Twelve smokers, 12 deprived smokers and 12 nonsmokers (6 females, 6 males in each group) were investigated. Participants were treated either by 5 mg/16 h nicotine patches (Nicorette) or placebo. Effects of treatment were examined by a computerized attention-test battery; mood was assessed by the Berliner-Alltagssprachliches-Stimmungs-Inventar and task load by the NASA Task Load Index (NASA-TLX). Results showed that nicotine significantly increased the number of hits and decreased reaction time (RT) in the vigilance task. In the selective attention task combined with irrelevant speech as background noise, nicotine enhanced rate of hits. Although it was indicated that nicotine leads to a generally higher accuracy in attention tasks, response time of visual search was prolonged, contradicting a universal facilitation by nicotine. Participants experienced mental demand and temporal demand lower and rated alertness higher when in the nicotine condition. These effects were independent of smoking status, indicating "true" nicotine effects. Females took significant advantage of nicotine in the vigilance task, reaching the performance level of males, accompanied by a higher rated alertness. Results indicate task- and sex-dependent nicotine effects.

Keywords: Nicotine; Attention; Selective attention; Vigilance; Mood; Sex differences

1. Introduction

Nicotine can improve performance on a range of cognitive tasks, most notably those tasks requiring attention (Baldinger et al., 1995; Ernst et al., 2001; Lawrence et al., 2002). In particular, specific aspects of attention—like focussed attention (Heishman et al., 1994; Sherwood, 1993) and sustained focussed attention (vigilance)—were rather consistently reported to be enhanced by nicotine in humans and animals (Evenden et al., 1993; Lindgren et al., 1998; Mancuso et al., 1999; Mirza and Stolerman, 1998). For example, the detection rate in both modalities of a visual and auditory divided attention task improved significantly after smoking a cigarette. Nicotine also prevented an increase in reaction time (RT), which occurred in the nonsmoking condition (Warburton and Walters, 1988). On other attention-related cognitive functions, like sensory abilities, visual search, learning, or problem solving, "true" effects of nicotine are less well studied (Heishman et al., 1994; Heishman, 1998). Psychological theories imply several distinctive functional aspects of attention, such as selective attention, divided attention, pattern recognition, visual search, vigilance, and others (McLeod and Driver, 1993; McLeod et al., 1991; Parasuraman, 1998; Parasuraman and Davies, 1984; Trimmel, 2003a,b). Using a within-participant design to investigate the effects of nicotine on these diverse aspects of attention-related performance would be appropriate.

Cheeta et al. (2001), File et al. (2000, 2001a,b, 2002), Genn et al. (2003), and Tucci et al. (2003) investigated the impact of smoking/nicotine on mood, in particular anxiety. They concluded that effects of nicotine are unusual in that it can have both anxiolytic and anxiogenic effects, depending on regimen of administration, route of administration, time interval, and behavioral state of the experimental participant (Tucci et al., 2003). Moreover, it was demonstrated that

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nicotine effects on mood are mediated by gender. While nicotine has calming effects on stress-induced mood changes in females, it enhances aggressive mood in males (File et al., 2001b). Sex differences concerning the effects of tobacco smoking were also reported for verbal information processing, where female smokers showed an increased rate of responding (confidence) in comparison to female nonsmokers (Algan et al., 1997). In animal experiments, female rats were found to be more sensitive to the anxiolytic effect of nicotine than male rats, suggesting important sex differences of nicotine effects (Cheeta et al., 2001). Furthermore, female rats were found to be chemically and behaviorally more sensitive to nicotine than male rats (Battig, 1981; Rosecrans, 1972) and an interaction with gonadal hormones was suggested (Booze et al., 1999) as a potential responsible underlying mechanism.

The interpretation of nicotine effects can be confounded by a participant's nicotine deprivation or nondeprivation, smoking history, and smoking status (Ernst et al., 2001; File et al., 2002; Heishman, 1998). It is well known that nicotine can reverse deprivation-induced negative effects on attention, whereas a "true" enhancement of performance can more clearly be demonstrated on nonsmokers or nondeprived smokers (Heishman, 1998). Thus, the present study included nonsmokers, and deprived and nondeprived current smokers. All participants completed tasks testing their attention-related cognitive performance, and rated their subjective task load and mood. Participants in the experimental group were subjected to transdermally administered nicotine, and it was assumed that participants' sex would modulate nicotine effects as it was found in animal studies (Battig, 1981; Rosecrans, 1972).

2. Materials and methods

2.1. Participants

Twenty-four smokers and 12 nonsmokers participated in the study. Nonsmokers (mean age 22.75 years, S.D. = 2.49) were defined by a lifetime consumption of less than 100 cigarettes. Smokers smoked on average 16.25 cigarettes per day and had a mean Fagerström score of $M = 2.96$ (S.D. = 1.08) for nicotine dependence (Heatherton et al., 1991). Smokers were randomly assigned either to the group of smokers ($n = 12$, mean age 23.03 years, S.D. = 3.17) or deprived smokers ($n = 12$, mean age 23.50 years, S.D. = 3.68). Each of the three groups consisted of six women and six men. It has been suggested that testing a smoker 30 min postsmoking qualifies as "nondeprived" (Pritchard and Robinson, 1998). Therefore, smokers had a cigarette within the last 30 min before being investigated to avoid potential withdrawal effects. Participants assigned to the deprived-smokers group were not allowed to smoke about 12 h prior to the beginning of the experimental tests; however, researchers did not biochemically or behaviorally verify this condition, but ratings of mood in the placebo condition support participants' abstinence.

All participants confirmed that they had abstained from the consumption of alcohol on the day of the experiment. Some participants took the contraceptive pill on the same day (smokers $n = 3$, abstaining smokers $n = 4$, and nonsmokers $n = 3$). To avoid an interaction of nicotine effects with baseline mood (Shytle et al., 2002a), no participants with diagnosed affective disorders were included in the study. All participants reported to have had enough sleep and to have eaten adequately according to the time of the day. All participants, in order not to bias the performance on the computer tasks, were sufficiently familiar with the operation of a computer.

The study was approved by the Institutional Ethic Commission for the use of Human or Animal Subjects and all participants agreed to their inclusion without compensation. Each person gave written informed consent and received a booklet informing about the administration of a low-dose nicotine skin patch or a placebo patch and which stated that participants were to complete cognitive tasks on the computer. The participants were not informed about the expected outcomes of the study.

2.2. Nicotine treatment

In the experimental condition, participants received a 5 mg/16 h nicotine patch (Nicorette), which is the lowest dose of Nicorette available. This was chosen to minimize potential side effects (Shytle et al., 2002b) like nausea and dizziness on nonsmokers. The Nicorette patch was selected for this study because it provides a rapid onset of nicotine delivery after initial administration (Benowitz, 1988). In the placebo condition, an identical appearing patch was applied. Treatment was given in a double-blind and balanced order. After the final task, the patch was removed.

2.3. Procedure

Each participant underwent the testing procedures on the morning of two fixed dates with an interval of 1–4 days between testings. After patch administration on the shoulder, participants completed a self-administered questionnaire for 15–20 min, thereafter mood was assessed. About 30 min after patch application, participants completed the computerized attention tasks (described below), followed by the NASA Task Load Index (NASA-TLX). The sequence of the nicotine or placebo treatment was balanced in each group (i.e., six participants received nicotine patch first followed by placebo second with the remaining six participants getting the reverse assignment to conditions). By the reason not to be visible to the participant, all patches were applied on the shoulder. A single testing session lasted approximately 1.5 h.

2.3.1. Computerized attention tasks

The attention tasks were presented, recorded, and analysed on a notebook-based test battery (McLeod et al., 1991; McLeod and Driver, 1993; Parasuraman, 1998; Parasuraman and Davies, 1984; Trimmel, 2003a,b; Weidlich and Trimmel, 2001). Participants received written instructions on the respective task and completed a trial run on each task, to familiarise them with characteristics and timing of the tasks, form of presentation, and operation of response keys. All stimuli were presented for a certain amount of time, no matter how (right or false response) or whether the participant reacted to the item or not.

2.3.1.1. Task 1: Visual anticipation. Two arrows, which moved towards each other horizontally or vertically, were presented. Participants were instructed to press the key at the very moment the arrows stood exactly opposite to each other. The numbers of prematured/delayed reactions as well as the average RT were recorded in 12 trials.

2.3.1.2. Task 2: Selective attention I. This choice reaction task required participants to react to 120 presented stimuli (presented for 2 s; 60 target stimuli, 60 distractors) in 4 min by pressing different keys. The letters "p" and "d" were used as stimuli. Above or below these letters, up to four vertical lines appeared. All "p"s with two lines were target stimuli whereas the remaining 10 stimuli served as distractors (Brickenkamp, 1962).

2.3.1.3. Task 3: Selective attention II. Subtest 3 was similar to task 2, but the letters "p" and "d" were replaced by the symbols "^" and "o." The "circle with two lines" was the target stimulus whereas the other stimuli served as distractors.

2.3.1.4. Task 4: Divided attention. In Subtest 4, subjects were presented 120 visual stimuli similar to Task 3, but intermixed with acoustic stimuli. Participants were required to react to the visual and 26 acoustical stimuli of high (2000 Hz) and low (1000 Hz) tones of 100-ms duration on four different response keys.

2.3.1.5. Task 5: Selective attention and acoustic distractor. Subtest 5 consisted of Task 3, but participants were exposed to "irrelevant speech" (a tape with German language comedy played backwards) with a moderate intensity while completing the task.

2.3.1.6. Task 6: Attention in reference to objects. This choice reaction task referred to the visual perception of objects. Forty objects of four categories, (1) "real objects" like everyday things, such as shoes, chair, etc.; (2) "abstract objects" (symbols); (3) "social pictures" (faces); and (4) "meaningful words" with two letters (e.g. "in" or "at"), were presented for a short period of time (500 ms). The same picture was displayed on the left and the right side of a fixation point in the center of the screen. However, only one of the two pictures displayed simultaneously could be seen clearly while the other one was blurred. The participants had to decide whether the picture on the left or the one on the right was more clearly recognisable.

2.3.1.7. Task 7: Visual search I—filtering form and color. For this visual search task, 12 red circles and 12 blue "x" were displayed for 2 s on the screen 10 times. The target stimulus was a red "x", which appeared instead of a blue "x" in half of the trials. Participants had to react when the target stimulus, i.e., the red "x", was present.

2.3.1.8. Task 8: Visual search II—filtering form and movement. Twelve white circles and 12 white "x" were displayed for 2 s on the screen 10 times. While all circles moved simultaneously vertically upwards, the "x" remained stationary. The target stimulus was a moving (1.66 cm/s) "x", which appeared instead of a stationary "x" in half of the trials. Participants had to decide whether the target stimulus was present or not.

2.3.1.9. Task 9: Visual search III—filtering color, form, and movement. Subtest 9 was a combination of Tasks 7 and 8. Twelve stationary blue "x" and 12 vertically upwards-moving red circles were displayed for 2 s on the screen 10 times. The target stimulus is a moving (1.66 cm/s) red "x", which appeared in half of the trials. Again, participants had to decide whether the target stimulus was present or not.

2.3.1.10. Task 10: Vigilance. Participants had to watch a white dot moving in continuous steps (every second) along an invisible circular track. Every once in a while, the dot took a double step. Participants had to respond immediately to a double step (Mackworth, 1950). Altogether, 15 double steps appeared in this 15-min-lasting test within a total of 900 stimuli.

2.3.2. Mood

Mood was assessed by the Berliner-Alltagssprachliches-Stimmungs-Inventar (Schimmack, 1997), an instrument which assesses three bipolar global dimensions of mood: pleasant vs. unpleasant (pleasure), excited vs. calm (excitedness), and alert vs. tired (alertness). It consisted of 26 mood-related items which had to be rated in their intensity on a seven-point Likert scale ranging from no to very weak, weak, middle, strong, very strong, and extremely strong.

2.3.3. Task load

Experienced task load was assessed by the NASA-TLX of the *Human Performance Research Group* of the *NASA Ames Research Centers* (CA). Participants had to rate their *mental demand* (thinking, deciding, calculating, remembering, looking, searching, etc.), *physical demand* (pushing, pulling, turning, controlling, activating, etc.), *temporal* *demand*, *performance* (How successful do you think you were in accomplishing the goals of the task?), and *effort* (How hard did you have to work—mentally and physically—to accomplish your level of performance?) by the tasks performed on a 20-unit scale.

2.4. Statistics

Data were analysed by four-way analyses of variance (ANOVAs) with smoking status (nonsmoker, deprived smoker, and smoker), sex, treatment (nicotine patch or placebo), and task (Subtests 1–10) as independent variables. Treatment and task were treated as repeated factors, where appropriate degrees of freedom were epsilon corrected according to Greenhouse–Geißer (GG). Probability levels are cited for results close to or reaching significance (P=.05), while nonsignificant results are indicated by ns. Subsequently, effects of treatment and/or sex on single subscales were assessed by university tests for repeated measures; however, only for the case that a significant main effect of treatment, smoking status, or sex occurred, or a significant interaction of treatment/smoking status/sex with task occurred.

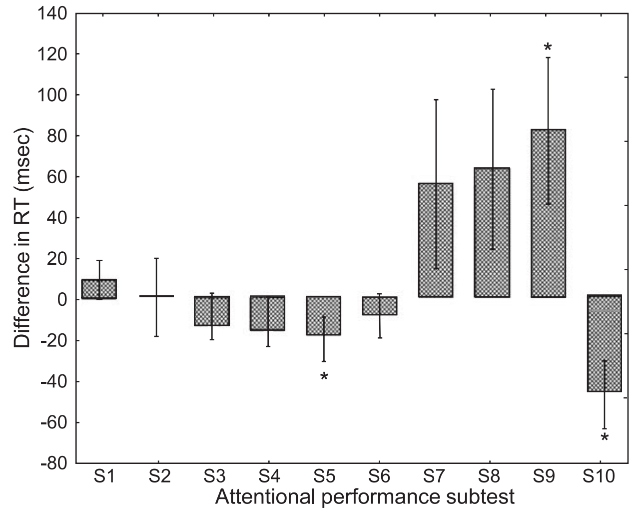

Fig. 1. Mean ± S.E.M. of the differences in RT for participants in the nicotine condition minus the placebo condition for the 10 subtests of the attention task (S1 visual anticipation; S2 selective attention I; S3 selective attention II; S4 divided attention; S5 selective attention and acoustic distractor; S6 attention in reference to objects; S7 visual search I—form and color; S8 visual search II—form and movement; S9 visual search III—color, form, and movement; and S10 vigilance). Significant ($P<.05$) differences to the placebo condition are marked by an asterisk.

3. Results

3.1. Attentional performance

3.1.1. Reaction time

Analysis of RT (mean values of the difference in RT for participants in the nicotine condition minus the placebo condition are given in Fig. 1) indicated a significant interaction of Treatment × Task [$F(9,270)=3.66$, $P_{GG}<.009$] beside an obvious main effect for task [$F(9,270)=520.63$, $P_{GG}<.001$]. Subsequent univariate tests revealed a tendency [$F(1,30)=2.95$, P=.096] to shorter RTs for participants in the nicotine condition in Subtest 5 (selective attention and acoustic distractor), shorter RTs [F(1,30 = 9.18, $P<.01$] for the nicotine condition in Subtest 10 (vigilance), and longer RTs [$F(1,30)=5.05$, $P<.05$] for the nicotine condition in Subtest 9 (visual search III). No other main effect or interaction appeared, indicating that the reported effects were independent of sex as well as of smoking status.

3.1.2. Number of hits

Percentage of hits (see Fig. 2 for difference scores of hits from the participants in the nicotine condition minus the placebo condition) was obviously different comparing tasks [$F(9,270)=29.40$, $P_{GG}<.001$] and was higher for participants in the nicotine condition vs. the placebo condition [$F(1,270)=5.28$, $P<.029$]. However, significant interactions of Treatment × Task [$F(9,270)=4.09$, $P_{GG}<.007$] and of Treatment × Task × Sex [$F(9,270)=2.76$, $P_{GG}<.040$] indicate additional subtest-specific effects depending on treatment and sex. Subsequent univariate tests indicate that in Subtest 5 [selective attention with an acoustic distractor, $F(1,30)=4.84$, P=.036] and Subtest 10 [vigilance condition, $F(1,30)=12.30$, P=.0014], participants in the nicotine condition achieved more hits compared to participants in the placebo condition. Sex differences were found in Subtest 7 (filtering form and movement) where nicotine enhanced the number of hits for women but reduced it for men [$F(1,30)=6.67$, P=.014] and in Subtest 10 (vigilance) where women had a much higher benefit from nicotine than men [$F(1,30)=P<.032$] as well.

3.2. Mood

Analysis of mood (see Fig. 3 for mean values) indicated a highly significant main effect for treatment [$F(1,60)=51.03$, $P<.001$] with higher scores for the nicotine condition. A statistical trend in the interaction of Treatment × Smoking status [$F(2,60)=2.91$, P=.068] revealed that this difference was only significant in smokers and in deprived smokers. The interaction of Subscale × - Treatment [$F(2,60)=23.19$, $P_{GG}<.001$] and subsequent univariate tests indicate that treatment was highly significant [$F(1,30)=10.57$, P=.003] for Subscale 2 (excitedness) and for alertness (Subscale 3), both with higher scores for participants in the nicotine condition [$F(1,30)=48.37$, $P<.001$] but not significant for pleasure [$F(1,30)=2.53$, ns]. The interaction of Subscale × Smoking status [$F(4,60)=3.83$, P_{GG}=.011] indicates that deprived smokers had lower pleasure scores than the two other groups [$F(1,30)=4.06$, $P<.006$]. The impact of sex appeared as

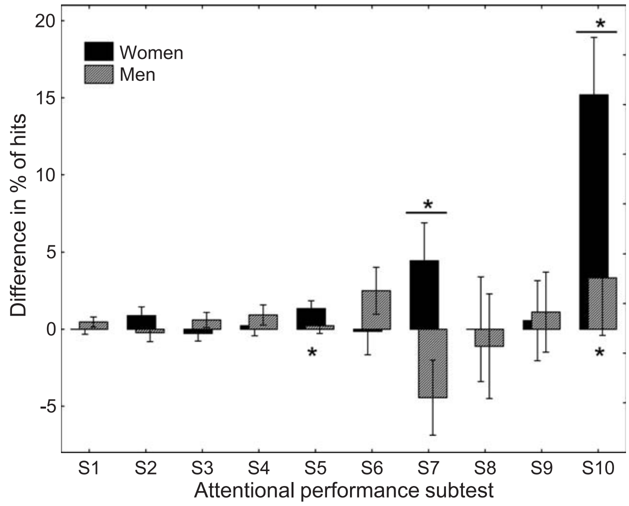

Fig. 2. Mean ± S.E.M. of the differences of percentage of hits for participants in the nicotine condition minus the placebo condition for the 10 subtests of the attention task (S1 visual anticipation; S2 selective attention I; S3 selective attention II; S4 divided attention; S5 selective attention and acoustic distractor; S6 attention in reference to objects; S7 visual search I—form and color; S8 visual search II—form and movement; S9 visual search III—color, form, and movement; and S10 vigilance) in women and men. A significant ($P<.05$) main effect of treatment appeared, indicating a higher percentage of hits in the nicotine condition. Significant differences in subtests are marked by an asterisk below the bars and significant sex effects are marked by an asterisk above the crossbar.

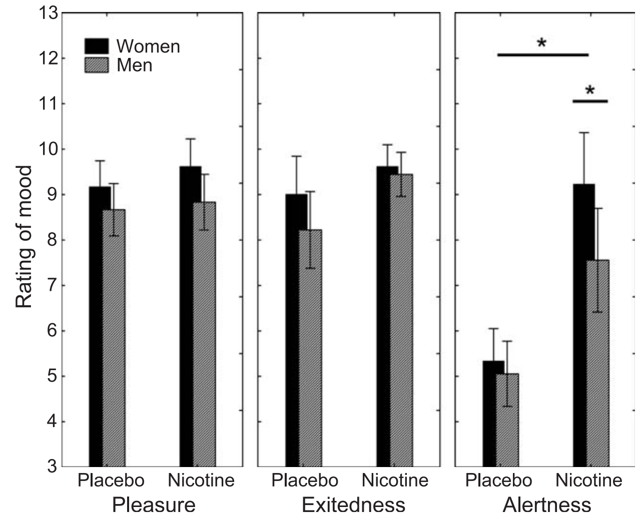

Fig. 4. Mean ± 95% CI of rated moods (pleasure, excitedness, and alertness) in female and male participants in the nicotine and the placebo condition. For each emotion, significant treatment effects and sex effects are indicated (* $P<.05$).

a statistical trend in the three-way interaction of Treatment × Subscale × Sex [$F(2,60)=2.51$, P_{GG}=.097] and subsequent univariate tests revealed that women scored higher alertness in the nicotine condition than men [$F(1,30)=4.45$, P=.043, see Fig. 4 for mean values].

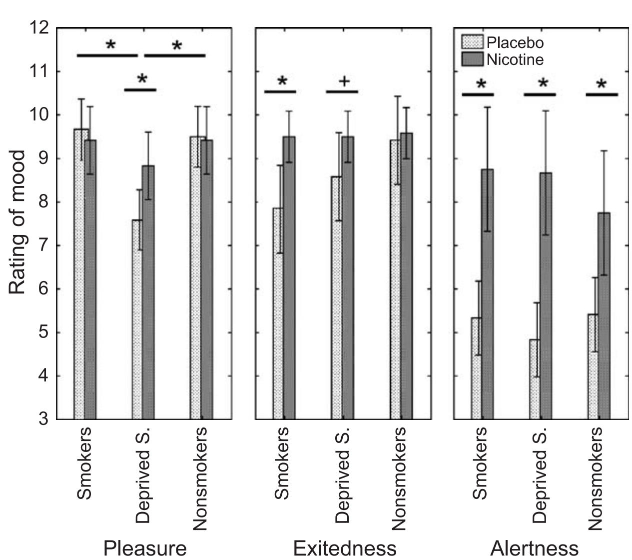

Fig. 3. Mean ± 95% CI of rated moods (pleasure, excitedness, and alertness) in the three groups of smoking status (smokers, deprived smokers, and nonsmokers) in participants in the nicotine and the placebo condition. For each emotion, treatment effects and group effects are indicated (* $P<.05$ and $^{+}P<.10$).

3.3. Task load

Task load was generally experienced lower by participants in the nicotine condition [$F(1,120)=8.11$, P_{GG}=.008], but the interaction of Treatment × Scale [$F(4,120)=2.52$, P_{GG}=.038] and subsequent univariate tests revealed that mental demand [$F(1,30)=5.83$, P=.022] and experienced time pressure [$F(1,30)=6.87$, P=.013] showed significant treatment effects with lower scores for nicotine vs. placebo (mental demand: $M=4.75 \pm 2.13$ vs. $M=5.46 \pm 1.94$; time pressure $M=5.58 \pm 1.71$ vs. $M=6.15 \pm 1.76$). No other main effect or interaction appeared statistically significant.

4. Discussion

Relative to the placebo control condition, participants within the nicotine condition performed better in nearly all tasks in the present experimental study. This finding was statically significant for the vigilance task and the selective attention task with an acoustical distractor. Nicotine enhanced accuracy and reduced RT (selective attention with distractor by 20 ms; vigilance by 50 ms), indicating a real benefit by nicotine treatment. Positive effects of nicotine on visual vigilance (sustained attention) are well known and have already been reported for humans and animals (Evenden et al., 1993; Koelega, 1983; Mancuso et al., 1999; Mangan, 1982; Mirza and Stolerman, 1998; Waller and Levander, 1980; Wesnes et al., 1983). In detecting the effects of stimulants, vigilance has been described as the most sensitive performance test as no other task showed a consistency like this (Koelega, 1983). This conclusion is fully supported by the present study.

No sex effects appeared in RTs, but for accuracy, women showed a much greater benefit from nicotine than men by reaching the same level of performance like men in the nicotine condition (women 88% hits, men 88% hits). Women in the placebo condition displayed a strong disadvantage compared to men (women 73% hits, men 84% hits). This sex-related increase in performance in vigilance tasks has not been reported yet and points to the question of underlying responsible mechanisms. Enhanced performance in vigilance has been attributed to enhanced activation (Evenden et al., 1993; Parasuraman and Davies, 1984; Wesnes et al., 1983) and was indicated, e.g., by the critical flicker fusion (Waller and Levander, 1980) and the EEG (Lindgren et al., 1998). This viewpoint is supported by the mood ratings within the present sample. Women in the nicotine condition rated their alertness remarkably higher compared to men—independent of smoking status (Fig. 3). Thus, in consideration of sex, the pattern of subjectively rated alertness corresponds to the objective performance in the vigilance task. Interaction with gonadal hormones (Booze et al., 1999) and sex differences in response to 5-HT_{1A} receptor agonists (Blanchard et al., 1992), which mediate anxiogenic effects of nicotine (Cheeta et al., 2000), have been discussed as possible underlying mechanisms for sex differences when reacting to nicotine.

The faster and more accurate performance of participants in the nicotine condition in the selective attention task combined with irrelevant speech as background noise was also found to be independent of smoking status. This specific task is characterised by additional workload caused by (environmental) stress, for which a compensatory effect of nicotine has already been reported (Perkins et al., 1992). The hypothesis that nicotine can reduce stress is also supported by participants' ratings of task load, with a generally lower score given by participants in the nicotine condition. Participants in the nicotine condition also rated mental demand and time pressure (two factors usually associated with stress) significantly lower compared to participants in the placebo control group. Moreover, this result supports the common notion of many smokers that smoking can improve their capacity to concentrate (File et al., 2001b) and also the attempt to improve attention in participants with attention deficit hyperactivity disorder (ADHD) by transdermally applying nicotine patches (Shytle et al., 2002b). Again, our findings were independent of sex and smoking status, indicating a general and "true" effect of nicotine (Heishman, 1998).

The only performance-reducing effect of nicotine was observed for response time in the visual search tasks, which was found to be significant in the task investigating form, color, and movement (visual search III), contradicting the general facilitation hypothesis of nicotine (Pritchard and Robinson, 1998). As there have not been reported any comparable findings previously, one can only make speculations about the reasons for this result. Given the higher alertness stated by participants in the nicotine condition, one can speculate that mental processes, which may normally be carried out unconsciously, could be prolonged by higher awareness caused by higher alertness. This speculative mechanism may also be responsible for the sex effect of visual search I (investigating color and form filter), where women showed a benefit and men a disadvantage, in terms of the analysis of color vs. form being biased by sex if a higher awareness/alertness appears. However, further research on individual differences/sex effects within the visual search task in interaction with nicotine is necessary to increase our understanding of this finding.

An association between participants' smoking status and participants' mood was observed within the present study. Not surprisingly, deprived smokers displayed less pleasure, which was most pronounced in participants in the placebo condition. Most likely, this finding reflects the withdrawal effect of not having smoked for the last 12 h. Smokers, and to some extent also deprived smokers, rated excitedness significantly lower if in the placebo condition, whereas nonsmokers gave no difference in pleasure or excitedness between the treatment conditions. Moreover, smokers and deprived smokers reached the level of nonsmokers when rating their excitedness only in the nicotine condition. All participants in the nicotine condition rated their alertness higher compared to participants in the placebo control condition; however, the effect of nicotine was more pronounced in the smoking groups. When in the nicotine condition, men rated their alertness lower compared to women, independent of smoking status.

Our study findings suggest that nicotine may have a more pronounced effect on alertness in women than men, supporting earlier suggestions (Cheeta et al., 2001; File et al., 2002; Pomerleau et al., 1991). Furthermore, only some aspects of attentional performance were found to be sensitive to nicotine and/or sex effects, whereas others were not. Thus, further investigations should be undertaken while accessorily considering time-related aspects of cognitive processes, as can be achieved by EEG recordings and analysing event-related potentials or brain DC potentials (Trimmel, 1990).

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