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Lower but not higher doses of transdermal nicotine facilitate cognitive performance in smokers on gender non-preferred tasks

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ABSTRACT

One of the most widely used treatments for smoking cessation is nicotine replacement therapy (NRT). There is some evidence that smokers experience abstinence-induced deficits in cognitive function, which are attenuated by NRTs. Additionally it's been suggested that the degree of reversal of cognitive deficits may depend on the NRT dose and the smoker's gender. In the present placebo-controlled study we investigated effects of three doses of transdermal nicotine (7 mg, 14 mg and 21 mg) on cognitive performance of 48 male and 48 female smokers after overnight abstinence and 6 h of patch application. Cognitive tasks used in the study included the Conners' CPT, emotional Stroop, mental arithmetic, and verbal recall of affective prose passages. The results showed greater probability of attentional problems in the male sample compared to females as identified by the Conners' CPT. Within gender women showed improved performance in the 7 mg and 14 mg conditions on several measures of the Conners' CPT, and faster hit reaction time on the emotional Stroop test compared to women in the placebo and 21 mg of nicotine groups. Conversely, males showed a moderate overall advantage on the mental arithmetic task and were differentially sensitive to nicotine treatment on the prose recall task, on which the greatest improvement in recall of affective material was observed for the 14 mg group compared to the 21 mg group. The results are explained on the basis of an inverted U-shaped relationship between nicotinic stimulation and cognitive performance as well as greater sensitivity to nicotine dose manipulation on gender non-preferred cognitive tasks.

1 . Introduction

One of the most widely used treatments for smoking cessation is nicotine replacement therapy (NRT; Burton et al., 2000). Despite the well-supported efficacy of NRTs, however, the best available quit rates do not exceed 25%, even when pharmacological treatments are complimented with behavioral counseling and follow-up support (Silagy et al., 2004). There is also some evidence indicating that different forms of NRT may differ in overall effectiveness with nicotine patch (the most popular form of NRT) being the least effective at 12 month follow-up (13.7% quit rate) compared to nicotine gum (17.4% quit rate), nicotine inhaler (17% quit rate) and intranasal spray (24% quit rate; see Silagy et al., 2004).

Some studies (e.g. Davis et al., 1994; Swan et al., 1997; Perkins, 1996; Gourlay et al., 1994; Wetter et al., 1999; West et al., 2001) have also showed a significantly lower success rate of NRTs in women than in men despite a generally lower self-reported nicotine dependence in women, fewer number of cigarettes smoked per day and lower nicotine exposure than in men.

One of the reasons for this difference could be a difference in cognitive performance between abstaining male and female smokers receiving NRT. There is sufficient evidence that smokers experience abstinence-induced deficits in cognitive function (Jacobsen et al., 2005; Mendrek et al., 2006; Myers et al., 2008). Research also suggests that some instances of relapse may be predicted by this disrupted cognitive functioning during tobacco abstinence (Ferguson et al., 2006; Patterson et al., 2010; Rukstalis et al., 2005), which may not be fully reversed by administration of NRTs (Kleykamp et al., 2011).

Furthermore NRTs may not be attenuating cognitive decrement in abstaining male and female smokers to the same extent. For example, women have been found to show greater sensitivity to smoking and stress-related cues than men (e.g. Perkins, 1996; 2001; Sayette and Hufford, 1995; Colamussi et al., 2007). Nevertheless, Kleykamp et al. (2011) did not find any gender differences in a large sample of abstaining smokers receiving transdermal nicotine treatment of varying doses (0, 7, 14, and 21 mg) on measures of attention, working memory or psychomotor function suggesting that these differences may not exist. While the measures used by Kleykamp et al. (2011) had previously shown sensitivity to nicotine, the authors did not specifically consider any measures that may also be sensitive to gender. At the same time nicotine administration has been demonstrated to produce sex-dependent differences on

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some vigilance (e.g. Trimmel and Wittberger, 2004; File et al., 2002), verbal and recognition tasks (e.g. Algan et al., 1997; File et al., 2002), and mental arithmetic (Myers et al., 2008).

Specifically, greater speed and accuracy on vigilance tasks (e.g. CPT, RVIP) have been observed in male smokers (e.g. Trimmel and Wittberger, 2004; File et al., 2002) compared to female smokers. Another cognitive task on which men typically perform better in European and American samples is mental arithmetic (Lynn and Irwing, 2008). In predominantly male samples of smokers having either a cigarette of the smoker's habitual yield (Sakurai and Kanazawa, 2002) or receiving smokeless tobacco treatment (2 g; Landers et al., 1992) significantly improved mental arithmetic performance compared to placebo.

Additionally, a male advantage has also been reported in the general population on measures of reaction time on the emotional Stroop task and similar choice reaction time tasks (Sass et al., 2010; Conroy and Polich, 2007). In smokers a modified version of the emotional Stroop task is often used on which affective words are related to smoking (e.g. tobacco, cigarette, smoke etc.; Waters et al., 2003). Considering that there is some evidence of greater sensitivity of female smokers to smoking cues (see Perkins, 2001), it would be of interest to examine gender differences on this task with several doses of NRT.

On the other hand, women typically do better than men on verbal and recognition tasks (Burton et al., 2004). In nicotine studies female smokers tend to outperform male smokers after smoking a cigarette of their usual yield (e.g. Algan et al., 1997; File et al., 2002).

Furthermore, in their review of cognitive effects of nicotine Newhouse et al. (2004) pointed out that the impact of nicotine tends to conform to the Yerkes–Dodson principle with intermediate levels of stimulation producing optimal performance and high levels of stimulation impairing performance. Indeed, some studies in humans (using male smokers as subjects) showed impairment in prose recall following administration of higher nicotine doses (e.g. 21 mg of nicotine patch: Poltavski and Petros, 2005). Trimmel and Wittberger (2004) also reported that nicotine treatment of abstaining smokers and non-smokers with a low-dose of nicotine (5 mg nicotine patch) normalized a gender difference of the Conners' CPT task only after only 30 min of patch application, bringing females to the level of performance of males irrespective of their smoking status.

Finally Myers et al. (2008) reported dose-dependent gender differences on a mental arithmetic test with male smokers showing improved accuracy and reaction time after intranasal nicotine treatment with 1 mg and 2 mg doses and women only improving after the 1 mg dose.

It is thus possible that on tasks favoring cognitive strategies of a particular gender less sensitivity to nicotine dose manipulation may be observed compared to tasks on which a given gender typically shows a cognitive disadvantage. On the latter tasks larger NRT doses may not be as beneficial to the reversal of cognitive deficits as has been suggested (e.g. Kleykamp et al., 2011).

In the present study we hypothesized that on tasks on which women generally do better than men (i.e., prose recall), small and intermediate doses of transdermal nicotine (7 mg and 14 mg, respectively) would improve male smokers' performance compared to placebo, while the highest nicotine dose (21 mg) would hinder it. In contrast, we did not expect female smokers' performance on this task to be affected by nicotine dose with an overall improvement observed across all transdermal nicotine doses compared to placebo. The above dose effect would be reversed on those tasks on which men generally do better than women (Conners' CPT, E-Stroop and mental arithmetic).

2 . Method

2.1. Participants

All recruitment procedures, consent documents, and the experimental protocol with associated instruments were approved by the University of North Dakota Institutional Review Board. Forty-eight male and 48 female smokers participated in the study. The age range for both male and female participants was between 18 and 45. General inclusion criteria required that a participant did not report any prior history of cardiovascular disease or hypertension, did not show elevated blood pressure during baseline measurement (systolic > 140 or diastolic greater > 90), did not report current use of psychiatric medication, had no previous diagnosis of psychiatric disorder or substance abuse (other than nicotine) or history of skin problems (e.g. dermatitis, eczema etc.) and was not markedly obese (BMI ≥ 30). Obese individuals have been reported to have an attenuated thermogenic response to nicotine treatment (Audrain et al., 1995) and to be at a higher risk for cardiovascular complications associated with nicotine administration (Botella-Carretero et al., 2004). Specific inclusion criteria were as follows:

2.1.1 . Smoking status

Eligible smoking status was based on self-reported daily cigarette smoking of at least 10 cigarettes per day for the previous one or more years.

2.1.2 . Non-OC-users

The female sample comprised smokers who did not report using oral contraceptives (OCs) or any other hormonal form of birth control for at least 3 months prior to their participation in the study, had regular menstrual cycles between 28 and 31 days, were not pregnant, and did not report severe dysmenorrheal or incapacitating menstrual symptoms during the three cycles prior to screening.

Participants were recruited from the area through advertisements placed in the local newspaper. Upon initial telephone contact an individual's potential eligibility was determined through a brief phone interview. If preliminary eligibility was established the individual was scheduled for a personal meeting with one of the investigators who measured his/her blood pressure and verified his/her smoking status using expired alveolar carbon monoxide measurements (CO > 8 ppm). If eligibility was confirmed male participants were scheduled for the experimental session and instructed to sleep normally the night before the experiment and abstain from alcohol use 24 h prior to the experimental session. They were additionally instructed to abstain from cigarette smoking for at least 12 h prior to their participation in the experiment.

Female participants were given Menstrual Cycle Diaries and were instructed to complete them until their scheduled experimental session that was projected to overlap with the follicular phase of their next menstrual cycle. Following the methodology of the study by Franklin et al. (2004) women were considered in the follicular phase during day 1 through day 13 of their menstrual cycle, which was verified through the records made in the Menstrual Cycle Diary. On average participants monitored their menstrual cycle for 2–3 weeks prior to their experimental session. All participants were paid $80.00 for their participation in the experiment. Female participants were also paid an additional $40.00 for monitoring their cycles.

2.2. Instruments

2.2.1 . Transdermal nicotine delivery system

A transdermal nicotine patch (NicoDerm CQ) with nicotine concentrations of 7 mg, 14 mg, and 21 mg with sustained nicotine release over 24 h was used in the study. As a form of nicotine replacement therapy the 21 mg dose is recommended for smokers who smoke 10 or more cigarettes per day while the two lower doses are recommended for those smoking fewer than 10 cigarettes a day. The bioavailability of nicotine in a transdermal patch has been determined to be around 82% (Benowitz et al., 1991). The patch is self-adhesive after a protective film is removed. Thus in the study all three nicotine doses were used with smokers whose daily nicotine intake was equivalent to or exceeded 10 cigarettes/day. A placebo patch was constructed

using a regular 7 mg NicoDerm CQ patch but without removing its protective film (non-activated). Its adhesion to the skin was ensured by using a surgical tape applied over the surface of the patch and extending ½ inch beyond its edges. A similar masking procedure was used for activated patches. This technique had been previously used by Poltavski and Petros (2005) and Poltavski and Petros (2006) with both smokers and non-smokers.

2.2.2 . Nicotine dependence

The Fagerstrom Test for Nicotine Dependence (FTND; Heatherton et al., 1991) was used in the present study to assess smokers' level of nicotine dependence. It is a 6-item questionnaire that primarily emphasizes physical nicotine tolerance and is widely used in combination with other measures of nicotine dependence (Shiffman et al., 2005).

2.2.3 . Cravings

The Tobacco Craving Questionnaire (TCQ) has been shown to be a reliable and valid tool in assessment of tobacco cravings (Heishman et al., 2003) and was used in the present study. The questionnaire comprises 17 items grouped around 4 separate factors that best describe tobacco cravings: (1) emotionality, or smoking in anticipation of relief from withdrawal symptoms or negative mood, (2) expectancy, or anticipation of positive outcomes from smoking, (3) compulsivity, or lack of control over tobacco use, and (4) purposefulness, or intention and planning to smoke for positive outcomes.

2.2.4 . Withdrawal

Nicotine withdrawal was assessed using the Minnesota Nicotine Withdrawal Scale (MNWS; Hughes and Hatsukami, 1986), which is an 8-item scale listing only one item for each of the following 8 withdrawal symptoms: *irritability/anger, anxiety/tension, difficulty concentrating, restlessness, increased appetite, depressed or sad mood, craving and impatience*. The scale ranges from 0 to 4 with 0 = 'not present' and 4 = 'severe'. The summary score of the eight items minus the craving item score has been recommended to measure the participants' overall withdrawal symptomatology (Hughes and Hatsukami, 1998).

2.2.5 . Verbal ability

To isolate nicotine effects and gender differences on the prose recall task (see below) from baseline differences in background knowledge and verbal ability, participants' verbal ability was assessed using the vocabulary subset of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981). The major function of the vocabulary subset is to measure vocabulary level by asking the individual to give definitions to a list of words of varying degree of difficulty. The scale has been previously used in nicotine studies employing verbal tasks (e.g. Krebs et al., 1994; Poltavski and Petros, 2005).

2.2.6 . Mental arithmetic

On this task participants were asked to count backward by a certain number for 5 min. The test consisted of 2 blocks, two and a half minutes each. In the first block participants counted backward by 7 starting at 2193. In the second block they were asked to count backward by 13 starting at 1022. All the calculations were performed mentally without the use of paper or a calculator. Participants were instructed to perform calculations as quickly and as accurately as possible and tell the researcher the answer immediately. Every time they made a mistake, they received error feedback and were given a chance to correct themselves until they arrived at the right answer. Number of errors and number of correct responses were used as dependent measures on this test.

2.2.7 . Conners' Continuous Performance Test

For the purposes of the present study the Conners' Continuous Performance Test (CPT; Conners, 1994) was used as a measure of sustained attention. The test takes 14 min to complete and requires participants to make a response as quickly as possible to any letter displayed on a computer screen except the letter "X" (probability of occurrence = 0.10). Each letter is displayed for 250 ms over 18 blocks of 20 trials. The signal in each block is presented at one of the three interval rates, i.e., 1, 2, or 4 s in a counterbalanced order. Dependent measures include hit reaction time, accuracy (errors of omission and commission), signal detection parameters of d′ (sensitivity) and Beta (response bias) as well as response variability between and within the blocks (the standard error estimate of hit reaction time).

2.2.8 . Emotional Stroop test

A modified Stroop test was included in the present study to explore nicotine dose by gender interactions in abstaining smokers. On this test participants are asked to ignore the meaning of the word presented on a computer screen and just respond to its color as quickly as possible by pressing a corresponding color-coded key on the computer keyboard. Each word was presented three times, once in blue, once in green, and once in red. The test incorporated smoking stimuli (words such as *tobacco, cigarette, smoke, ashtray, pack, puff, drag, inhalation, nicotine, craving, and urge*) and neutral stimuli (words such as *arrival, clock, fold, locker, metal, trophy, nettle, pause, glycerin, shiver, and tablespoon*) previously used by Waters et al. (2003) and Gross et al. (1993). In addition the test included non-smoking affective stimuli previously used by Strauss et al. (2005) with a non-clinical sample, which included general emotional words from 4 categories: anxiety, anger, happiness and sadness (e.g. happy, sad, anxious etc.). The standard emotional Stroop task using general emotional words from above categories has shown high test–retest reliability ($r > 0.84$; Strauss et al., 2005). The task took to approximately 10 min to complete and included 44 words (11 words per condition, repeated 3 times each). Prior to the presentation of the words participants completed 33 practice trials that comprised letter strings (e.g. HHH), which were randomly repeated 3 times. Participants had to achieve at least 80% accuracy on the practice trials to advance to the experimental session. Accuracy and reaction times were used as dependent measures on this test.

2.2.9 . Prose memory

In the present study we used 7 (6 + 1 practice) narrative stories with three themes: positive, neutral and negative. Each theme was represented by two passages of 200 words in length. All stories were at the reading level of 7th to 8th grade and had been previously rated for the type of content in our lab by an independent group of 141 male and female college students. Each story's target affective purport was endorsed by at least 90% of the raters. Additionally, each story had been divided by a different group of 40 college students into idea units of high, medium, and low importance. Stories were presented one idea unit at a time on a computer screen in a counterbalanced order. The rate of presentation was controlled by the participant by clicking on the 'next' button. After reading each story participants were asked to orally recall as much from the story's content as they could. Free recall was digitally recorded and subsequently transcribed for the number of propositions at each importance level.

2.3. Procedure

All experimental sessions began in the morning at either 8 am or 9 am. Two days prior to the scheduled appointment each participant was contacted by a research associate and reminded to abstain from alcohol use at least 24 h before the experimental session and from cigarette smoking at least 12 h prior to the scheduled appointment. Participants were also instructed to refrain from consuming caffeine-containing beverages on the day of the experiment. Upon each participant's arrival to the lab his/her smoking abstinence was confirmed

using expired alveolar carbon monoxide measurements (CO ≤ 8 ppm). Female participants were also asked to take a basic urine pregnancy test (Aim MidStream OTC hCG) to verify their non-pregnant status at the time of the experiment.

Baseline measures of blood pressure and heart rate were taken next using a Dinamap Pro 100 automated oscillometric device (GE Medical Systems Information Technologies, Inc., Milwaukee, Wisconsin) followed by administration of self-report measures that included the vocabulary subset of the Wechsler Adult Intelligence Scale Revised (WAIS-R), the Fagerstrom Test for Nicotine Dependence (FTND), the Tobacco Craving Questionnaire (TCQ) and the Minnesota Nicotine Withdrawal Scale (MNWS). Upon completion of the questionnaires a transdermal nicotine patch of the dose corresponding to the participants' random double-blind assignment was applied to his/her left shoulder. The patch was masked with an adhesive surgical tape applied over the surface of the patch and extending ½ an inch beyond it. Once the patch was applied participants entered a 6-hour absorption period. Stable isotope analysis of transdermal nicotine absorption revealed that the maximum rate of absorption occurs 6 to 12 h after the activation of the patch, and after about 6 h average levels of nicotine in the blood plateau and are similar to trough levels found in a smoker during a smoking day (i.e., about half of the peak levels achieved at the end of each cigarette (Benowitz et al., 1991). All participants were allowed to go for lunch approximately 3 h following patch application and were instructed not to consume any caffeine containing foods or beverages. Once back in the lab participants' smoking abstinence was again verified using the CO measure.

At the end of the 6-hour period the participants were asked to fill out the TCQ and the MNWS again. Next participants began cognitive testing which consisted of the mental arithmetic test, the emotional Stroop task, Conners' CPT and affective prose passages. All tasks were administered in a counterbalanced order with 5 minute intervals between the tasks. Immediately after the completion of the cognitive battery the participants again completed the TCQ and the MNWS. The testing period took approximately 1 h, after which the patch was removed, the participant received compensation and was dismissed. Each participant was followed up with a phone call later that day to ensure that he/she did not experience any adverse reactions to nicotine treatment.

2.3.1. Research design and data analysis

The study utilized a between-subject design with between-subject variables being nicotine dose (0 mg, 7 mg, 14 mg, 21 mg) and gender (male and female), Within-subject variables included time of assessment (0, 6, and 7 h) for MNWS and TCQ, word type for E-Stroop (positive, negative, neutral and smoking-related), story type (positive, negative, neutral) and importance level of idea units (high, medium, low) for prose recall. Statistical analyses included 4 (nicotine dose) × 2 (gender) analyses of variance (ANOVA). Whenever a within-subject variable was present, a mixed ANOVA was used. Significant main effects for variables with more than two levels were programmed in SPSS 19.0 for an automatic follow-up with the Bonferroni procedure (also known as Dunn–Bonferroni), while significant interactions were manually broken down using the Tukey's HSD test. The latter test controls the familywise error rate for the set of all possible comparisons. When the number of such comparisons exceeds 4 (which was the case with the significant interactions), the Tukey's HSD test becomes more powerful than the Bonferroni procedure as it yields narrower 95% confidence intervals (Myers and Well, 2003).

3 . Results

3.1. Demographic characteristics

A frequency analysis of demographic characteristics of the sample showed that 88.5% of the participants were at least high school graduates with 18.0% being college graduates. The majority of the participants had a relatively long smoking history with 83.6% reporting having smoked for at least 3 years and 67.2% indicating that they had smoked for over 5 years. Approximately 17% of the sample also reported concurrent use of other tobacco products mostly smokeless tobacco (80%). Furthermore, 64.4% of the participants also indicated having had alcohol in the 30 days preceding the survey. Seventy-five percent of them reported not having any drinks on a typical day, with the remainder of the participants ($n = 16$) not exceeding two drinks per day.

There were no significant main effects of nicotine for age, weight, verbal ability and nicotine dependence. No significant main effect of gender was observed for either age or nicotine dependence. A significant main effect of gender was found for weight, $F\ (1, 88) = 8.24$, $p < 0.01$. Men on average were significantly heavier than women ($M = 192.51$, $SE = 7.06$ vs. $M = 164.87$, $SE = 6.54$). A significant main effect of gender was also found for verbal ability (WAIS-R), $F\ (1, 88) = 12.06$, $p < 0.01$. Specifically, women showed significantly higher vocabulary scores ($M = 41.38$, $SE = 1.65$) than men ($M = 32.96$, $SE = 1.78$). There was no significant gender by nicotine dose interactions for any of the above dependent variables (see Table 1).

3.2 . Cigarette cravings and withdrawal

Significant main effects of gender, $F\ (1, 88) = 19.96$, $p < 0.01$, and nicotine, $F\ (3, 88) = 3.19$, $p = 0.03$ were found on the total score of the Tobacco Cravings Questionnaire. Specifically, significantly greater cravings were reported by female smokers ($M = 72.51$, $SE = 1.89$) compared to male smokers ($M = 59.61$, $SE = 2.19$). Cravings in the placebo condition were also significantly greater ($M = 72.24$, $SE = 3.15$) than reported cravings in the nicotine conditions ($M = 63.98$, $SE = 2.79$). The analysis also revealed a significant gender by nicotine interaction, $F\ (3, 88) = 4.74$, $p < 0.01$, and a significant 3-way interaction of time, nicotine dose and gender, $F\ (6, 176) = 2.62$, $p = 0.02$. The follow-up Tukey's HSD test showed that immediately after testing females in the 14 mg condition had significantly greater total cravings scores ($M = 83.58$, $SE = 4.36$) than males in the same nicotine group after testing ($M = 57.00$, $SE = 5.03$). These results are presented in Table 1.

A significant time by dose interaction, $F\ (6, 176) = 4.21$, $p < 0.01$, along with a 3-way interaction of time, nicotine dose, and gender were found on the expectancy subscale, $F\ (6, 176) = 2.17$, $p = 0.05$, of the TCQ. The Tukey procedure revealed that males in the 14 mg and 21 mg conditions had significantly lower expectancy scores at most time points than females treated with corresponding nicotine doses. There were no significant main effects or interactions for the scores on the remaining 3 subscales of the TCQ (emotionality, compulsivity, and purposefulness).

On the Minnesota Nicotine Withdrawal Scale a significant 3-way interaction, $F\ (6, 176) = 2.54$, $p = 0.02$, was found for the participants' total scores. A follow-up Tukey's HSD test showed that males in the 21 mg group had significantly greater post-test withdrawal scores ($M = 13.67$, $SE = 2.14$) than females in the 21 mg nicotine group immediately following cognitive testing ($M = 7.90$, $SE = 11.95$ see Table 2). There were no significant main effects of gender, dose or time, or any of the 2-way interactions.

3.3. Cognitive testing

3.3.1 . Mental arithmetic

The analyses showed a significant main effect of gender, $F\ (1, 88) = 5.55$, $p = 0.02$, for the number of correct responses on the mental arithmetic test. Specifically, men were significantly more accurate than women ($M = 35.5$, $SE = 3.40$ vs. $M = 24.68$, $SE = 3.08$). There was no significant main effect of nicotine or a significant gender by dose interaction. No significant main effects or interactions were noted for the number of errors.

Table 1
Means (standard deviations) for baseline characteristics of the sample and total scores on measures of tobacco craving and withdrawal.

Measure	Placebo		7 mg		14 mg		21 mg	
	Male	Female	Male	Female	Male	Female	Male	Female
Age	29.50	27.70	27.13	24.92	23.60	25.55	28.00	34.30
	(7.50)	(8.19)	(7.06)	(5.81)	(5.06)	(6.69)	(10.79)	(8.64)
Weight (lb)	208.44	188.37	183.22	157.25	179.10	154.36	199.29	159.50
	(13.80)	(14.65)	(13.80)	(11.96)	(13.10)	(12.49)	(15.66)	(13.10)
WAIS-R vocabulary	37.90	43.80	29.44	43.50	36.50	37.92	28.00	40.33
	(11.92)	(6.48)	(13.12)	(7.04)	(8.45)	(9.62)	(16.13)	(12.60)
FTND	4.25	4.70	5.56	4.58	4.30	5.33	5.33	5.80
	(2.25)	(2.3)	(1.88)	(2.02)	(1.95)	(3.00)	(2.56)	(1.81)
TCQ total score								
Baseline	66.17	76.20	64.12	56.60	52.56	81.83	50.67	79.90
	(14.32)	(17.75)	(7.02)	(13.05)	(6.02)	(13.09)	(18.54)	(13.59)
6 h	62.67	79.40	62.25	59.00	58.33	77.33	56.89	65.50
	(14.88)	(19.73)	(8.88)	(13.49)	(6.44)	(13.06)	(6.86)	(19.43)
Post testing	67.00	82.00	60.75	59.00	57.00_a	83.58_a	56.89	69.80
	(11.45)	(17.21)	(12.83)	(18.04)	(5.15)	(13.75)	(9.31)	(22.71)
MNWS total score								
Baseline	8.00	12.60	15.38	11.09	8.33	9.00	8.78	12.20
	(4.20)	(7.83)	(5.91)	(6.64)	(5.15)	(5.97)	(4.02)	(6.83)
6 h	9.00	11.60	10.63	9.00	8.11	9.08	10.33	8.30
	(4.52)	(7.79)	(7.31)	(5.59)	(6.21)	(5.81)	(5.36)	(6.58)
Post testing	11.00	12.80	10.63	10.45	9.56	10.83	13.67_b	7.90_b
	(3.95)	(7.89)	(6.39)	(6.24)	(6.43)	(4.89)	(7.33)	(6.81)

Note. Means in a row sharing subscripts are significantly different at alpha = 0.05.

3.3.2 . CPT

Dependent measures of the Conners' CPT included number of omissions, number of commissions, hit reaction time, hit reaction time standard error, variability, detectability (d′), response style (β), number of perseverations, hit reaction time block change, hit standard error block change, hit reaction time interstimulus change, and hit standard error interstimulus change (Table 2).

A significant main effect of gender was found for the probability of clinical classification on the Conners' CPT, $F(1, 88) = 15.59$, $p < 0.01$). This measure represents a discriminant function indicating what the chances are out of 100 that the overall results of testing match a clinical profile for ADHD. The pattern of male responses was significantly more likely to be associated with a clinical population than that of females ($M = 0.53$, $SE = 0.03$ vs. $M = 0.38$, $SE = 0.03$). The main effect of nicotine dose on this variable was not significant. There were no significant main effects of either nicotine dose or gender for other CPT variables. None of the interactions were statistically significant.

3.3.2.1 . Simple effect analyses. Planned simple effect analyses of nicotine dose conducted within each gender showed a significant main

Table 2
Means (standard deviations) for dependent measures on Conners' CPT as a function of gender and nicotine dose.

Variable	Placebo		7 mg		14 mg		21 mg	
	Male	Female	Male	Female	Male	Female	Male	Female
Clinical p	0.55	0.47	0.50	0.31	0.52	0.34	0.53	0.40
	(0.19)	(0.09)	(0.20)	(0.15)	(0.19)	(0.16)	(0.18)	(0.15)
Omissions	3.70	2.50	2.50	3.67	4.30	2.75	1.56	3.50
	(5.87)	(2.76)	(2.76)	(3.45)	(5.46)	(3.36)	(2.01)	(4.60)
Commissions	15.50	13.60	16.89	15.75	10.70	13.93	17.22	11.0
	(7.43)	(6.19)	(6.19)	(7.4)	(6.67)	(7.35)	(8.18)	(6.33)
Hit RT	373.88	392.87	365.97	352.38_a	379.88	369.80	350.11	405.98_a
	(76.55)	(49.17)	(59.43)	(39.16)	(60.75)	(49.08)	(67.85)	(46.83)
Hit RT SE	5.81	$7.78_{a,b}$	6.07	5.11_a	5.48	4.90_b	5.38	5.76
	(1.52)	(1.89)	(3.28)	(1.80)	(2.73)	(1.51)	(2.40)	(2.60)
Variability	7.61	15.02_a	10.08	8.71	7.60	6.82_a	8.46	8.45
	(2.97)	(8.00)	(10.50)	(5.94)	(6.33)	(2.30)	(7.30)	(9.57)
Detectability	0.62	0.72	0.54	0.64	0.88	0.64	0.56	0.88
	(0.30)	(0.20)	(0.37)	(0.34)	(0.43)	(0.30)	(0.29)	(0.49)
Response style	0.56	0.42	0.46	0.49	0.70	0.42	0.29	0.78
	(0.49)	(0.46)	(0.37)	(0.45)	(0.61)	(0.41)	(0.24)	(0.71)
Persevera-tions	2.90	0.90	0.67	0.42	0.70	0.17	1.00	0.20
	(6.47)	(1.60)	(2.00)	(0.90)	(1.64)	(0.40)	(1.94)	(0.42)
Hit RT block change	0.0	0.0	−0.01	0.0	0.00	0.0	0.01	0.01
	(0.02)	(0.03)	(0.04)	(0.02)	(0.02)	(0.02)	(0.03)	(0.02)
Hit SE block change	0.03	0.04	−0.04	0.01	0.02	−0.01	0.03	0.02
	(0.06)	(0.12)	(0.08)	(0.10)	(0.06)	(0.07)	(0.14)	(0.07)
Hit RT ISI change	0.07	0.08_a	0.06	0.05_a	0.05	0.05	0.07	0.05
	(0.03)	(0.02)	(0.06)	(0.03)	(0.04)	(0.03)	(0.05)	(0.03)
Hit SE ISI change	0.03	0.15_a	0.03	0.04	0.01	0.01_a	0.07	0.05
	(0.09)	(0.13)	(0.17)	(0.08)	(0.13)	(0.12)	(0.17)	(0.11)

Note. Means in a row sharing subscripts are significantly different at alpha = 0.05.

Table 3
Means (standard deviations) for the dependent measures on the emotional Stroop test as a function of gender and nicotine dose.

Measure	Placebo		7 mg		14 mg		21 mg	
	Male	Female	Male	Female	Male	Female	Male	Female
Proportion errors in negative condition	0.04	0.03	0.01	0.02	0.03	0.04	0.04	0.02
	(0.05)	(0.03)	(0.02)	(0.03)	(0.03)	(0.06)	(0.07)	(0.03)
Proportion of errors in the neutral condition	0.04	0.02	0.02	0.02	0.03	0.05	0.04	0.02
	(0.05)	(0.03)	(0.02)	(0.02)	(0.02)	(0.07)	(0.02)	(0.04)
Proportion of errors in positive condition	0.04	0.04	0.0	0.04	0.05	0.03	0.04	0.03
	(0.06)	(0.05)	(0.01)	(0.05)	(0.05)	(0.04)	(0.06)	(0.04)
Proportion of errors in the smoking condition	0.07	0.03	0.01	0.02	0.04	0.05	0.03	0.01
	(0.10)	(0.03)	(0.02)	(0.03)	(0.04)	(0.07)	(0.03)	(0.02)
RT in the negative condition	653.45	704.67	684.02	668.07	646.49	642.28	645.19_a	715.42_a
	(113.49)	(61.83)	(86.77)	(86.92)	(109.54)	(132.94)	(49.66)	(109.16)
RT in the smoking condition	642.76_a	736.41_a	685.20	670.72	643.60	648.16	673.89	695.66
	(100.22)	(52.95)	(83.32)	(109.35)	(102.85)	(119.78)	(72.53)	(101.16)
RT in the neutral condition	664.78	707.90	701.82	672.63	626.80	667.27	671.96	713.94
	(108.30)	(61.46)	(110.52)	(103.00)	(92.38)	(134.59)	(69.54)	(109.91)
RT in the positive condition	649.41	694.81	675.43	673.86	629.21	659.04	615.83_a	699.92_a
	(104.74)	(37.99)	(110.20)	(89.92)	(110.91)	(127.37)	(53.96)	(94.73)

Note. Means in a row sharing subscripts are significantly different at alpha = 0.05.

effect for nicotine dose in women on the measure of hit reaction time, $F(3, 44) = 2.94$, $p = 0.04$. Using pairwise comparisons with Bonferroni adjustment significant differences were found between the 7 mg and 21 mg nicotine conditions ($M = 352.38$, $SE = 13.30$ vs. $M = 405.98$, $SE = 14.57$, $p = 0.05$).

Additionally, a significant main effect of nicotine was found for women on the measure of hit reaction time standard error, $F(3, 44) = 4.73$, $p < 0.01$. Pairwise comparisons showed that women in the placebo group had the greatest mean hit reaction time standard error ($M = 7.78$, $SE = 0.62$) than either those in the 7 mg ($M = 5.11$, $SE = 0.57$, $p = 0.02$) or 14 mg ($M = 4.90$, $SE = 0.57$, $p < 0.01$) groups.

The main effect of nicotine was also significant for the hit reaction time interstimulus interval change. Women in the placebo group had significantly greater differences in hit reaction time among different interstimulus intervals ($M = 0.08$, $SE = 0.01$) than those in the 7 mg group ($M = 0.05$, $SE = 0.01$, $p = 0.03$). The standard error of the hit reaction time interstimulus interval change was significantly greater for the placebo group ($M = 0.15$, $SE = 0.04$) compared to the 14 mg group ($M = 0.01$, $SE = 0.03$, $p = 0.03$).

Finally, simple effect analyses on the measure of variability showed a significant main effect of nicotine for women, $F(3, 44) = 3.62$, $p = 0.02$. Pairwise comparisons revealed significantly greater variability in the placebo group ($M = 15.02$, $SE = 1.94$) compared to the 14 mg of nicotine group ($M = 6.83$, $SE = 1.77$, $p = 0.02$). Table 2 summarizes the above findings. No significant nicotine dose effects were found for men.

3.3.3 . E-Stroop

The analysis of reaction times on the emotional Stroop test showed a significant main effect of word type, $F(3, 264) = 4.02$, $p < 0.01$. Follow-up comparisons revealed that the mean reaction time in the positive word condition ($M = 662.19$ ms, $SE = 10.87$) was significantly faster than either in the smoking word condition ($M = 677.20$ ms, $SE = 10.85$) or in the neutral word condition ($M = 678.39$ ms, $SE = 11.53$).

The analysis also showed a 3-way interaction between word type, gender and nicotine dose. A follow-up Tukey's HSD test showed that females in the placebo condition displayed a significantly slower reaction time in response to smoking-related words ($M = 736.41$ ms, $SE = 30.63$) than males in the placebo group exposed to the same word type ($M = 642.76$ ms, $SE = 30.63$). Additionally, females in the 21 mg condition were significantly slower in their responses to negative ($M = 715.42$ ms, $SE = 31.42$) and positive ($M = 699.92$ ms, $SE = 30.70$) words than males in the 21 mg condition presented with negative ($M = 645.19$ ms, $SE = 35.13$) and positive words ($M = 615.83$ ms, $SE = 34.33$), respectively (see Fig. 1 and Table 3). A 2 (group) × 4 (dose) × 4 (word type) mixed analysis of variance (ANOVA) performed on the proportion of errors found no significant effects.

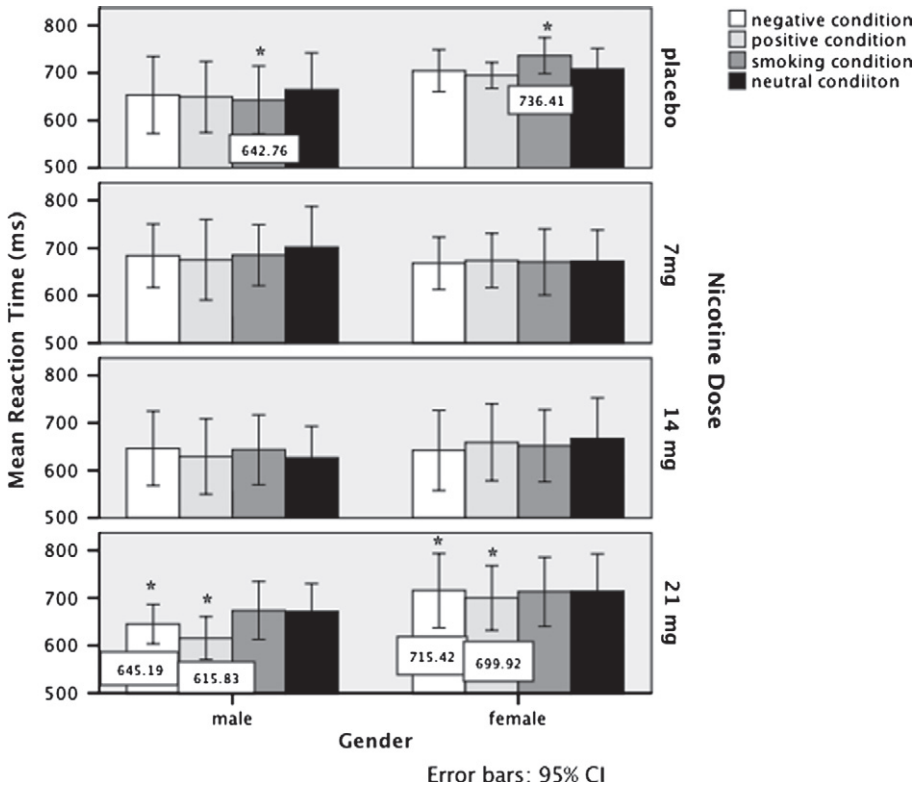
3.3.4 . Prose recall

All recall protocols were scored (blind) for the presence or absence of the gist of each idea unit. Recall of each passage was expressed as the proportion of the idea units remembered at each level of importance for each story type. The results showed a significant main effect of nicotine, $F(3, 88) = 2.75$, $p = 0.05$ for these recall sores. The Bonferroni follow-up comparisons revealed that the proportion of idea units recalled in the 14 mg condition was significantly greater ($M = 0.47$, $SE = 0.02$) than in the 21 mg condition ($M = 0.37$, $SE = 0.02$). Pairwise comparisons for the placebo ($M = 0.43$, $SE = 0.02$) and 7 mg groups ($M = 0.43$, $SE = 0.02$) were not significant.

Significant main effects were also found for story type, $F(2, 176) = 15.93$, $p < 0.01$) and importance level, $F(2, 176) = 3.93$, $p = 0.02$ along with a significant story type by importance level interaction, $F(4, 352) = 10.20$, $p < 0.01$. Bonferroni comparisons within story type showed that a significantly greater proportion of idea units were remembered from negative ($M = 0.46$, $SE = 0.01$) and positive ($M = 0.44$, $SE = 0.01$) stories than from neutral stories ($M = 0.39$, $SE = 0.01$). Pairwise comparisons within importance level revealed that propositions of high ($M = 0.44$, $SE = 0.02$) and low importance ($M = 0.44$, $SE = 0.02$) were recalled significantly better than propositions of medium importance ($M = 0.39$, $SE = 0.01$).

A post hoc Tukey's HSD test showed that the number of propositions recalled of medium importance in the neutral story condition was significantly lower ($M = 0.31$, $SE = 0.02$) than the number of propositions of medium importance in the negative story condition ($M = 0.45$, $SE = 0.01$) and the number of propositions of all importance levels in the positive story condition ($M = 0.47$, $SE = 0.03$; 0.42, $SE = 0.02$; 0.42, $SE = 0.02$ respectively). There was no significant main effect of gender or any significant interactions of either story type or importance level with the between-subject variables of dose and gender.

Nevertheless, in light of the significant main effects of nicotine, story type and importance level as well as a significant story type by importance-level interaction, it was of interest to examine which story types are more likely to be affected by nicotine treatment and whether these effects will differ as a function of importance level. For this reason separate 2 (gender) by 4 (dose) analyses of variance were also conducted for each condition of story type and importance level. These analyses showed a significant main effect of nicotine for the proportion of idea units of medium importance in the negative



Note. 21mg: M=715.42 > (M=645.19 and M=615.83) at alpha=0.05;
M=699.92 > M =615.83 at alpha =0.05

Fig. 1. Mean reaction times (ms) in the 4 word conditions of the emotional Stroop as a function of nicotine dose and gender. * — significant at alpha = 0.05. Note. 21 mg: M = 715.42 > (M = 645.19 and M = 615.83) at alpha = 0.05;. M = 699.92 > M = 615.83 at alpha = 0.05.

story condition, F (3, 88) = 2.96, p = 0.04. Using pairwise comparisons it was found that a significant mean difference existed between the 14 mg and 21 mg of nicotine conditions (M = 0.63 vs. M = 0.45, p = 0.04).

Table 4
Proportion of idea units of high, medium, and low importance recalled in the three story conditions as a function of gender and nicotine dose.

Story type	Placebo		7 mg		14 mg		21 mg	
	Male	Female	Male	Female	Male	Female	Male	Female
Negative story								
High	0.41	0.43	0.56	0.46	0.44	0.48	0.44	0.35
	(0.25)	(0.17)	(0.18)	(0.14)	(0.16)	(0.25)	(0.19)	(0.14)
Medium	0.51	0.47	0.42	0.45	0.59_a	0.43	0.40_a	0.38
	(0.11)	(0.16)	(0.13)	(0.12)	(0.19)	(0.11)	(0.15)	(0.12)
Low	0.39	0.53	0.46	0.44	0.59	0.45	0.41	0.38
	(0.18)	(0.21)	(0.20)	(0.18)	(0.19)	(0.14)	(0.19)	(0.15)
Neutral story								
High	0.45	0.46	0.39	0.43	0.47	0.39	0.38	0.34
	(0.21)	(0.15)	(0.13)	(0.14)	(0.19)	(0.16)	(0.13)	(0.14)
Medium	0.34	0.30	0.31	0.34	0.35	0.30	0.28	0.27
	(0.19)	(0.16)	(0.13)	(0.11)	(0.13)	(0.14)	(0.18)	(0.11)
Low	0.44	0.47	0.46	0.44	0.52	0.36	0.40	0.38
	(0.15)	(0.17)	(0.21)	(0.22)	(0.15)	(0.13)	(0.19)	(0.20)
Positive story								
High	0.43	0.46	0.47	0.47	0.59	0.50	0.42	0.39
	(0.27)	(0.21)	(0.17)	(0.17)	(0.18)	(0.18)	(0.22)	(0.22)
Medium	0.40	0.41	0.38	0.48	0.53_a	0.44	0.33_a	0.39
	(0.17)	(0.17)	(0.11)	(0.16)	(0.07)	(0.15)	(0.19)	(0.17)
Low	0.42	0.46	0.39	0.44	0.54	0.39	0.36	0.37
	(0.26)	(0.18)	(0.12)	(0.20)	(0.16)	(0.14)	(0.12)	(0.14)

Note. Means in a row sharing subscripts are significantly different at alpha = 0.05.

Additionally a significant main effect of nicotine was found for the proportion of idea units of low importance in the negative story condition, F (3, 88) = 2.59, p = 0.05. Pairwise comparisions again showed a significantly greater proportion of idea units recalled in the 14 mg of nicotine condition (M = 0.58, SE = 0.03, p = 0.05) than in the 21 mg condition (M = 0.39; SE = 0.03).

3.3.4.1 . Simple effect analyses. Planned simple effect analyses within gender further showed a significant main effect for nicotine dose in men on the measure of idea units of medium importance in the negative story condition, F (3, 44) = 3.18, p = 0.04. Using pairwise comparisons significant mean differences were found between the 14 mg and 21 mg nicotine conditions (M = 0.59, SE = 0.05 vs. M = 0.40, SE = 0.05, p = 0.05; see Fig. 2 and Table 4).

A significant main effect of nicotine was also found in men for idea units of medium importance in the positive story condition, F (3, 44) = 3.22, p = 0.03; see Fig. 3 and Table 4. Pairwise comparisons with Bonferroni adjustment showed that men in the 14 mg group again remembered a significantly greater proportion of propositions of medium importance (M = 0.53, SE = 0.05, p = 0.04) than those in the 21 mg group (M = 0.33, SE = 0.04). No significant main effect of nicotine was found for any of the story types and importance levels in women.

4 . Discussion

4.1. Cognitive effects

Overall the results of the study supported the hypothesis of dose-related differences in cognitive performance in smokers treated with transdermal nicotine that were also contingent on whether a particular gender typically performs better on a given cognitive task.

Specifically, in the present study women in the placebo condition displayed significantly slower reaction times to smoking words on the emotional Stroop test than male smokers in the same treatment group. Additionally, the highest nicotine dose (21 mg) significantly impaired reaction times of female smokers in both the negative and positive E-Stroop word conditions compared to males treated with the same nicotine dose. This finding supports the conclusion of Newhouse et al. (2004) that improvement in performance on cognitive tasks performed sub-optimally at baseline will be best observed with smaller and intermediate levels of nicotinic stimulation and impaired performance is more likely to be observed with higher nicotine doses. Since men have also been previously reported to show somewhat better performance on this task (Sass et al., 2010; Conroy and Polich, 2007), the lack of the 21 mg impairment in their group could be related to a more successful use of compensatory strategies.

Nicotine, however, did not have any effect on the measures of the mental arithmetic test. This is somewhat contrary to the previous research findings that showed facilitating effects of nicotine treatment in smokers on this test (Sakurai and Kanazawa, 2002; Myers et al., 2008). One of the reasons why similar benefits of nicotine administration were not observed in the present study may be related to the differences in nicotine delivery systems used in the previous studies and the current one. For example, Sakurai and Kanazawa, 2002 used cigarettes of the smoker's habitual yield, while Myers et al. (2008) employed intranasal nicotine spay. Both types of administration routes have been shown to produce significantly faster nicotine delivery (arterial "boli"; Schneider et al., 1996) and significantly greater subjective effects (Benowitz, 1996) than a transdermal nicotine patch.

At the same time the significant main effect of gender on the mental arithmetic test was in the predicted direction (favored male performance) and was of medium magnitude (Cohen's $d = 0.55$), which is consistent with previous results reported by Lynn and Irwing (2008) and Nyborg (2005).

Although males did not outperform females on the Conners' CPT, analyses within gender demonstrated that in agreement with the original hypothesis women were more sensitive to nicotine dose manipulations than men. Namely, as predicted smaller doses of transdermal nicotine (7 mg and 14 mg) were associated with significantly better performance of women on measures of hit reaction time, hit reaction time standard error, hit reaction time interstimulus change, and response variability compared to either placebo or 21 mg of nicotine (depending on the measure). No such differences among the nicotine doses were observed in men.

Furthermore, the highest dose of transdermal nicotine (21 mg) resulted in significantly slower hit reaction time in women than the 7 mg of nicotine treatment. Both 7 mg and 14 mg of nicotine were also effective in reducing women's variability in responses and reaction time compared to either placebo or 21 mg group. These indices of variability have been linked with inattention (Bekker et al., 2005; Kollins et al., 2009) and dysfunctional arousal systems (Fassbender et al., 2009). The Yerkes–Dodson principle seems to be the best descriptor of the above findings with intermediate doses of nicotine facilitating and highest and lowest doses (i.e., placebo) impairing cognitive performance in a smoker, whose gender is usually associated with suboptimal performance on this task.

Similarly, the results of the prose recall task suggest that facilitation of verbal memory in smokers was best in the intermediate nicotine dose condition (14 mg) compared to the highest dose (21 mg). In our previous study (Poltavski and Petros, 2005) we found that treatment of male smokers with a 21 mg of nicotine transdermal patch resulted in recall of a significantly lower number of idea units of medium importance compared to the placebo group. Non-smokers, however, used in that study showed improved recall of idea units of medium importance when receiving a 7 mg of nicotine patch. At the time we speculated that there may be a dose-related nicotine effect on verbal memory. Only one dose of nicotine was used with smokers (21 mg) and non-smokers (7 mg) in that study. The results of the present study seem to confirm this hypothesis.

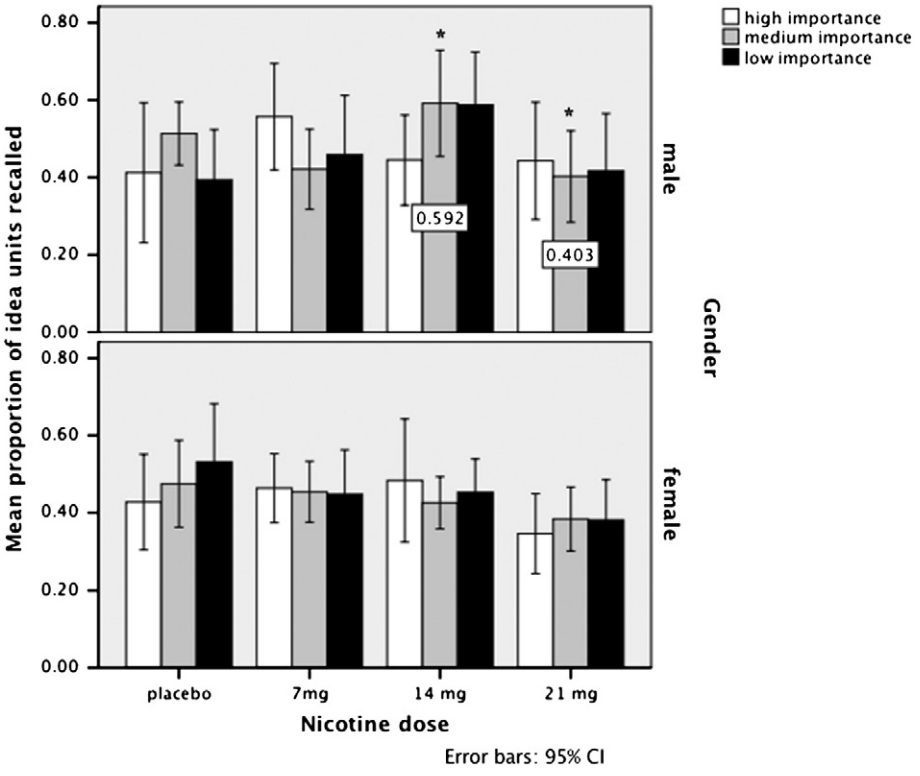


Fig. 2. Mean proportion of idea units of 3 importance levels recalled in the negative story condition as a function of nicotine dose and gender. * — significant at alpha = 0.05.

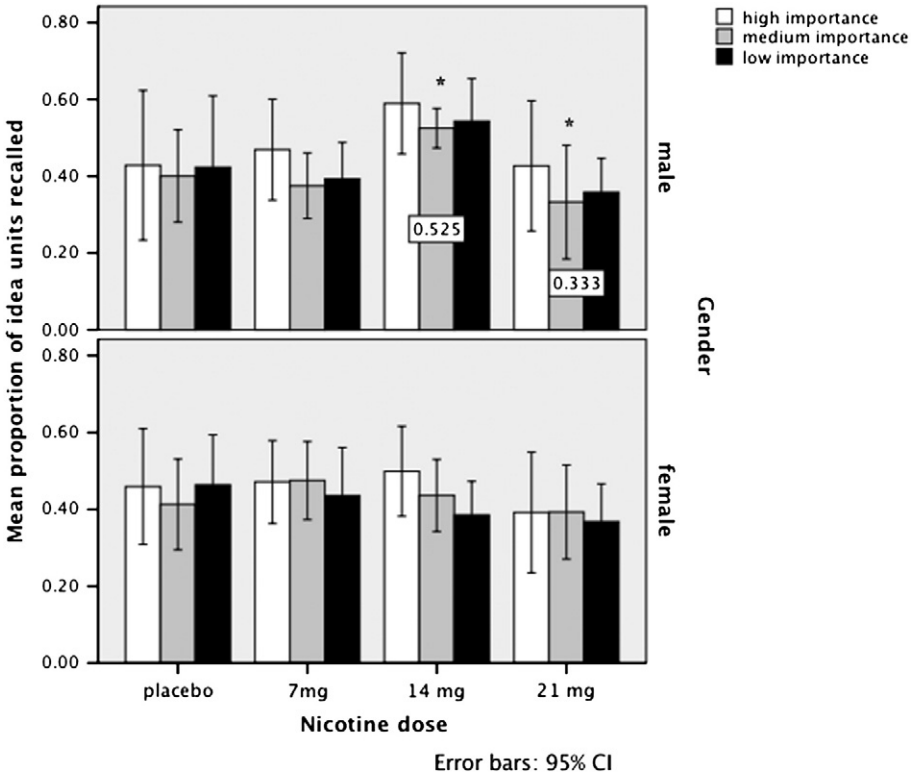


Fig. 3. Mean proportion of idea units of three importance levels recalled in the positive story condition as a function of nicotine dose and gender. * — significant at alpha = 0.05.

Moreover simple effect analyses within gender showed that the greatest facilitation of recall was observed for the idea units of medium importance in the affective prose material (negative and positive stories) in the group of male smokers treated with the intermediate NRT dose of 14 mg of nicotine. No such differences were found for women. Propositions of medium importance refer to more peripheral details of a story rather than its central features (propositions of high importance). Previously males had been reported to exhibit better recall of central features of a negatively valenced story while women had been found to show greater recall of peripheral details in such stories possibly due to differences in lateralized activation of emotion-processing areas in the brain (see Cahill, 2003). Coupled with the fact that baseline comparisons of verbal ability between men and women in the present study showed an initial female advantage (based on vocabulary scores on the WAIS-R), men were thus at a disadvantage on the verbal task especially for memory of non-central information. Moreover, the recall of idea units of medium importance in both types of affective prose passages was significantly lower for men treated with a 21 mg nicotine patch than for those receiving 14 mg.

In aggregate these findings support our original hypothesis of greater sensitivity to nicotine dose manipulations in the gender, whose cognitive strategies are not favored by the demands of a particular task (men). Both Algan et al., 1997 and File et al. (2002) found that female smokers outperformed male smokers on verbal tasks after smoking a cigarette of their usual yield (e.g. Algan et al., 1997; File et al., 2002). On these tasks men have also been found to show significantly greater recall of affective rather than neutral prose material while no such differences have been observed in women (Burton et al., 2004). These differences in men have been attributed to greater reactivity in their memory systems to emotional content while women may regard all verbal information as important (Burton et al., 2004).

4.2. Withdrawal and cravings

In the affective domain men in the 21 mg condition experienced significantly greater withdrawal immediately following the completion of the cognitive battery than women in the 21 mg condition. This finding is not unexpected as male smokers have been reported to be more dependent on physiological rather than sensory factors in maintenance of their smoking habits and more likely than female smokers to be sensitive to physiological effects of nicotine dose (Perkins, 1996; Perkins et al., 1999; Perkins et al., 2002). Thus a higher dose of nicotine may have counteracted potential withdrawal effects following completion of a stressful cognitive battery in women but may not have been large enough to do the same for men.

At the same time women in the 14 mg condition exhibited significantly greater cigarette cravings on the TCQ than men in the equivalent patch condition. These differences appear to be primarily related to the differences in the expectancy scores on the TCQ, which refers to the anticipation of positive outcomes from smoking. Expectations have been reported to play a major role in responses to drugs and drug stimuli (Heishman et al., 2003).

Perkins et al. (2006) further found that female smokers reported increased nicotine cigarette liking only if they anticipated smoking a nicotine-containing cigarette, whereas the reverse was true for men: smoking a nicotine-containing cigarette decreased subjective ratings of reward, if they expected to receive a nicotine-containing cigarette. Perkins (2001) also reported that blockade of both visual and olfactory cues while smoking a cigarette significantly reduced subjective liking of cigarettes in women but not in men. These findings suggest greater sensitivity of female smokers to smoking cues compared to men.

In the present study women were exposed to smoking cues (i.e., emotional Stroop containing smoking-related words) in close temporal proximity to the post-test assessment of their withdrawal and

cravings. They also anticipated an opportunity to smoke (they were told they would be dismissed immediately after the completion of the questionnaires). Thus our results of greater reward expectancy and thus overall cigarette cravings in women in the 14 mg condition seem to be consistent with the findings of Perkins (2001), Perkins et al. (2006).

4.3 . Study limitations

The findings of the present study do not purport to suggest that specific nicotine doses may facilitate performance in smokers as a function of gender. Our design that included a 12-hour smoking abstinence period did not allow us to test this assumption. Rather the intent of the study was to show that reversal of cognitive deficits in smokers following nicotine administration is both dose and gender-dependent, as male and female smokers may be differentially susceptible to nicotine based on the rigors of the task. By implication there may be gender differences among abstaining smokers in response to certain environments and social situations. These findings may, therefore, have relevance for smoking cessation trials and possibly account for some instances of gender differences in quit rates. For example, cognitive demands of a work environment that involves vigilance and sustained attention (e.g. air-traffic control) may be more challenging for an abstaining female smoker treated with a 21 mg nicotine patch, while the reverse may be true for an abstaining male smoker in a work/social environment emphasizing verbal memory (e.g. lecturer). In both instances higher NRT doses may not facilitate optimal performance on a gender non-preferred task despite effective attenuation of nicotine withdrawal and cigarette cravings.

The notion of gender advantage on specific cognitive tasks, however, is rather controversial with the best evidence probably available for verbal memory tasks (e.g., Berenbaum et al., 1997; Herlitz et al., 1997; Hultsch et al., 1991; Kramer et al., 1997). Nevertheless, in the present study sensitivity to nicotine dose manipulation was most strongly observed for the gender that was hypothesized not to be favored by the demands of the specific task. It seems that on gender-preferred tasks smokers have a greater range of tolerance to nicotinic stimulation before they start showing suboptimal performance on behavioral measures.

This relationship is certainly worth investigating further as in the present study despite a large overall sample of 96 smokers we only had 12 smokers per cell to test a sex by dose interaction. It is thus possible that we may not have had sufficient power to observe smaller effects of either gender, nicotine dose, or their interaction, which may partly explain the lack of significant findings on some other cognitive measures such as the Conners' CPT. It is less likely that the failure to observe significant nicotine group differences on this test was due to insufficient nicotine deprivation at baseline as the smokers' scores on the TCQ instrument exceeded the 50th percentile while their withdrawal scores were slightly above the 30th percentile thus indicating at least moderate deprivation. Nevertheless, we did not monitor blood plasma levels of nicotine. Consequently any inferences about nicotine dose effects are still somewhat speculative and are based on average absorption rates reported elsewhere (e.g. Benowitz et al., 1991).

Disclosures

The authors do not have any real or potential conflict(s) of interest, including financial, personal, or other relationships with other organizations or pharmaceutical/biomedical companies that may inappropriately impact or influence the research and interpretation of the findings.

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All authors have contributed in a significant way to the manuscript and have read and approved the final manuscript.

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