

Sexually dimorphic effects of acute nicotine administration on arousal and visual-spatial ability in non-smoking human volunteers

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Abstract

The effect of an acute administration of nicotine on arousal and visual-spatial ability in healthy non-smoking participants was investigated. Healthy adult volunteers with a mean age of 19.98 years received a transdermal nicotine or placebo patch prior to completing a water-level task and two mental rotation tasks while concurrent psychophysiological recordings were taken. Nicotine administration showed a sexually dimorphic effect on arousal (skin conductance level and heart rate). Evidence of superior performance in males compared to females was found in reaction time and accuracy measures for the visual-spatial tasks. However, performance reflected the interaction between sex and nicotine. Nicotine slowed reaction times in the mental rotation tasks more extensively in females than males. Nicotine also reduced confidence in performance during the water-level task in males, but not in females. The effects of nicotine on visual-spatial ability may reflect the interactive effects of sex and changes in arousal levels induced by nicotine administration.

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1. Introduction

Nicotine is the major pharmacological agent in cigarettes and its addictive properties are a major factor implicated in cigarette smoking. Research also indicates that nicotine can have cognitive effects (Levin et al., 2006; Pogun, 2001) that can be traced to specific brain areas (Kumari et al., 2003). Nicotine administration facilitates orienting and alerting aspects of attention (Levin et al., 1998; Witte et al., 1997). Nicotine administration may also facilitate memory function (e.g., Perkins et al., 1994), although there are also reports that it may have no effect or even impair memory (e.g., Kleykamp et al., 2005). Inconsistent results such as these suggest that a variety of variables can modulate the cognitive effects of

nicotine. The role of individual difference variables has been considered mainly in the comparison of smokers and non-smokers. The biological variable of sex has received less attention (but see, Acheson et al., 2006; Algan et al., 1997; Furedy et al., 1999; Perkins et al., 2002; Trimmel and Wittberger, 2004). Sex may be important when examining the question of whether nicotine influences visual-spatial ability. Independent research has shown that visual-spatial ability (Halpern, 2000) and brain metabolic responses to nicotine (Fallon et al., 2005) show sex differences.

Research conducted on rats (Kanit et al., 1998, 2005) and humans (Algan et al., 1997) has provided direct experimental evidence of sexually dimorphic effects of nicotine on visual-spatial ability. Kanit et al. (1998) examined water maze escape performance and found that chronic injections of nicotine shifted the cognitive style of female rats to a conceptual navigational style normally adopted by male rats. The result was that during a novel test trial in which a perceptual cognitive style would have produced the best performance, as found in female rats given saline, female rats given nicotine and male rats

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given nicotine or saline showed significantly poorer escape latencies. [Algan et al. \(1997\)](#) examined visual-spatial ability using a task that required participants to determine if geometric images matched or mismatched. Smoking and non-smoking participants completed the matching task, and after a 15 min break in which the smokers smoked a cigarette (1.12 mg nicotine) and non-smokers rested, repeated the task again. An interaction between sex and smoking status was found for accuracy and these two factors also interacted with the acute smoking manipulation for reaction time. Male non-smokers showed a deterioration in performance, as reflected in longer reaction times, between the first and second sessions, which was not present in male smokers. There was no difference between female smokers and non-smokers. Increased confidence, as reflected in a lower rate of non-responding, was also present in female smokers relative to all males and female non-smokers.

The results reported by [Algan et al. \(1997\)](#) complement the animal research by [Kanit et al. \(1998\)](#) by suggesting that nicotine administration can have sexually dimorphic effects on visual-spatial task performance in humans. However, two aspects of their results warrant further investigation. The first is that they compared smokers who smoked a cigarette with non-smokers who rested. This procedure does not separate the effects of acute nicotine administration from chronic smoking status. The use of non-smokers who are administered nicotine may help to isolate these factors. [Trimmel and Wittberger \(2004\)](#) provide an excellent example in which transdermal nicotine or placebo was administered to a sample of smokers and non-smokers to result in several sexually dimorphic effects in tasks assessing attention. The second point is that visual-spatial ability was examined with only one type of task (a matching task). Meta-analyses have suggested that visual-spatial ability involves distinct categories, including spatial perception and mental rotation ([Linn and Peterson, 1985](#)). For instance, the water-level task, which requires individuals to draw the water level in a tilted cup, is an example of a spatial perception task. The use of one or more tasks that are representative of these components would seem appropriate in further research.

The present experiment tested for the presence of sexually dimorphic effects of nicotine administration during tasks that assessed spatial perception and mental rotation. Male and female non-smokers were administered a transdermal nicotine patch or a placebo patch and were asked to complete a water-level task and a 2-dimensional and 3-dimensional version of a mental rotation task. In addition to behavioral measures of performance, psychophysiological measures of general arousal (skin conductance level) and cardiovascular arousal (heart rate) were also taken. Participants also provided subjective ratings to indicate their confidence during the water-level task in order to examine the effects of nicotine on this measure ([Algan et al., 1997](#)). It was expected that males would perform better than females, consistent with prior research indicating superior visual-spatial ability in males ([Halpern, 2000](#); [Voyer et al., 1995](#)). However, if nicotine produces a sexually dimorphic effect, this would be reflected in the administration of nicotine affecting performance differently in males and females.

2. Method

2.1. Participants

Thirty-nine male and 32 female Griffith University first year psychology students aged between 17 to 42 years ($M=19.98$, $SD=4.39$ years) participated in exchange for course credit. Prior to arrival at the laboratory, participants were requested to abstain from consuming caffeine containing drinks for 10 h. All participants were screened to ensure that they did not use any tobacco product in the past 12 months and prior to that had no more than one cigarette per week on average. All participants reported that they did not have current or history of hypertension, cardiac disease, cerebrovascular disease, impaired renal function, pregnancy, seizure, abuse or dependence on alcohol or other drugs, skin disease, sensitivity to medical dressing or tapes, skin allergies, psychiatric illness, and current use of any medications. Furthermore, the blood pressure and heart rate of the participants were measured with an Omron T9P Intelli-sense blood pressure meter. Six male participants were subsequently excluded due to high blood pressure ($>140/90$). Although no measurements of the severity of possible side effects resulting from the administration of nicotine were taken (cf. [Foulds et al., 1997](#)), the participants were monitored by the experimenter for adverse effects. One male participant withdrew from the experiment due to experiencing nausea and vomiting following nicotine administration. The final sample consisted of 64 participants (32 male, 32 female) in which half of each sex were randomly allocated to receive nicotine via a transdermal skin patch and the remaining received a placebo skin patch. The nicotine administration was further split into two dosage conditions either receiving a 5 mg (8 males, 8 females) or a 10 mg (8 males, 8 females) skin patch as we also wanted to test whether the effects of nicotine on visual-spatial ability varied as a function of the dosage of the transdermal patch. All groups were similar in age and prior years of education in addition to heart rate, diastolic blood pressure, and systolic blood pressure assessed during screening (all $p>.05$). Prior to participation, all participants provided informed consent in a protocol approved by the Griffith University Human Research Ethics Committee.

2.2. Apparatus

2.2.1. Nicotine administration

Nicotine was administered via a Nicorette™ 5 mg or 10 mg 16 h transdermal patch applied to a hairless site on the upper arm. Following [Trimmel and Wittberger \(2004\)](#), we chose the Nicorette patch because it provides a rapid onset of nicotine delivery ([Benowitz, 1988](#)). Patches were applied 90 min before participants began the experimental tasks and remained on the participant throughout the entire experiment (approximately 3 h in total). The patches administer 5 mg or 10 mg of nicotine over a 16 h period. As reviewed by [Gore and Chien \(1998\)](#), the pharmacokinetic C_{max} ($\pm SD$) values for the 5 mg and 10 mg patches are 3.5 ng/mL (.7) and 6.9 ng/mL (2.0) respectively, and the T_{max} ($\pm SD$) value for both patches is 9 h (4). The dosage and

absorption periods were chosen to minimize the possible side effects of the nicotine in the non-smoking participants. The same patches were also used in the placebo condition, but the adhesive protector was not taken off prior to application. All patches were covered with surgical tape.

2.2.2. Psychophysiological response measurement

Recordings of skin conductance level and heart rate were obtained via a PowerLab Model 4/20 data acquisition system (ADInstruments, Sydney). Skin conductance level was measured with an ADInstruments Model ML116 GSR amp and MLT116F electrodes attached to the distal phalanges of the first and second fingers of the non-preferred hand. Heart rate was measured by an ADInstruments Model MLT1010 Piezo Electric Pulse transducer attached to the distal phalange of the third finger of the non-preferred hand. Physiological responses were sampled at 1000 Hz and stored off-line for later quantification. Sampling started with task onset and terminated with task offset and did not include any practice trials for any tasks. The recordings were screened to exclude movement artefacts and the final values were taken as the mean across the entire duration of each task.

2.2.3. Visual-spatial tasks

All tasks were presented on Dell Optiplex Models GX240 and GX1 computers. The paper-and-pencil version of the water-level task (Robert and Morin, 1993) was adapted for administration on a computer. Participants were first shown a schematic picture of a cup (approximately $4.6^\circ \times 3.8^\circ$ visual angle) placed above a level table. The cup was tilted to the right at one of five different angles of orientation (20° , 30° , 40° , 50° , or 60°) from horizontal. A red indicator was placed at one of three locations along the right side of the cup (20%, 50%, or 80% of the cup length) to indicate the amount of water in the cup. Participants were able to draw a line, indicating the orientation of the water level, using the computer mouse. After participants completed each trial the program asked the participants to rate how confident they were in their answers on a scale ranging from 0 (not very confident) to 7 (very confident). The angle of error from horizontal and the confidence rating were recorded for each trial.

Two versions of the mental rotation task were used: a 2-dimensional and a 3-dimensional version. The tasks differed in the nature of the stimuli that were used. The 2-dimensional stimuli used images of a four bar histogram (Prinzel and Freeman, 1995). Six different histograms ($6.9^\circ \times 7.4^\circ$ visual angle) were developed by varying the relative length of the bars. Each of these six histograms was rotated clockwise at angles of 0° , 90° , 180° , and 270° . Furthermore, mirror images of the resulting histograms were developed to serve as the mismatch stimuli. The complete stimulus set thus contained 48 images composed of the standard and mirror images of the six histograms that had been rotated about four different angles of rotation. The stimuli for the 3-dimensional mental rotation task were developed along similar lines. The stimuli were based on Vandenberg and Kuse's (1978) version of the mental rotation task. Ten cubes were stacked upon each other in different configurations to produce 3-dimensional block arrangements

(the final arrangements varied from $5.7^\circ \times 10.3^\circ$ to $10.3^\circ \times 10.3^\circ$ visual angle) each rotated about a central axis at 0° , 90° , 180° , and 270° . The stimuli for the mental rotation tasks were presented in pairs on the computer monitor. One image was presented on the left and the image on the right was rotated 0° , 90° , 180° , or 270° relative to the image on the left, but regardless of rotation was either the same (match) or the mirror image (mismatch).

2.3. Procedure

Upon arrival at the laboratory, participants completed the screening procedure and were randomly assigned to receive a placebo patch or a nicotine patch. Following patch administration, participants sat quietly and watched an animated DVD film or television show during the absorption period. Participants were next directed to the testing room for psychophysiological response measurement and to complete the experimental tasks. The order of the tasks was counterbalanced, such that half of the participants in each group received the mental rotation tasks first and the remaining half received the water-level task first. The 2-dimensional mental rotation task always preceded the 3-dimensional mental rotation task. The three tasks took approximately 30 min to complete, during which time the nicotine or placebo patch remained on the participant. For the water-level task, participants completed 15 trials of the task, in which one trial consisted of a unique combination of the five angles of tilt (0° , 30° , 40° , 50° , and 60°) crossed with the three levels of water (20%, 50%, and 80%). Trial order was randomized for each participant.

In the mental rotation tasks, participants were instructed to respond with a match response if the two images matched each other regardless of whether one of the images was rotated relative to the other. Responses were made by pressing the letters B or N (counterbalanced) on the keyboard with the first and second fingers of the preferred hand. Each trial in the task consisted of a central fixation cross presented for 1500 ms and followed by a pair of images. The images remained on the screen until the participant made a response or until 7000 ms had elapsed. After the participant made a response, the feedback "Correct" or "Wrong button press" was displayed for 525 ms. Prior to the main trials, participants completed 16 practice trials, which consisted of two presentations each of one of the images presented at the four different angles of rotation (0° , 90° , 180° , 270°) for both match and mismatch trials. The participants next completed the main experimental trials consisting of the five remaining images at the four angles of rotation for match and mismatch trials presented twice each (80 trials total). Following the 2-dimensional mental rotation task, participants completed the 3-dimensional mental rotation task in a similar fashion. Following administration of all tasks, the patches were removed and the participants were debriefed.

3. Results

To take into account the differences between males and females in body size, ANCOVA analyses were used by entering in

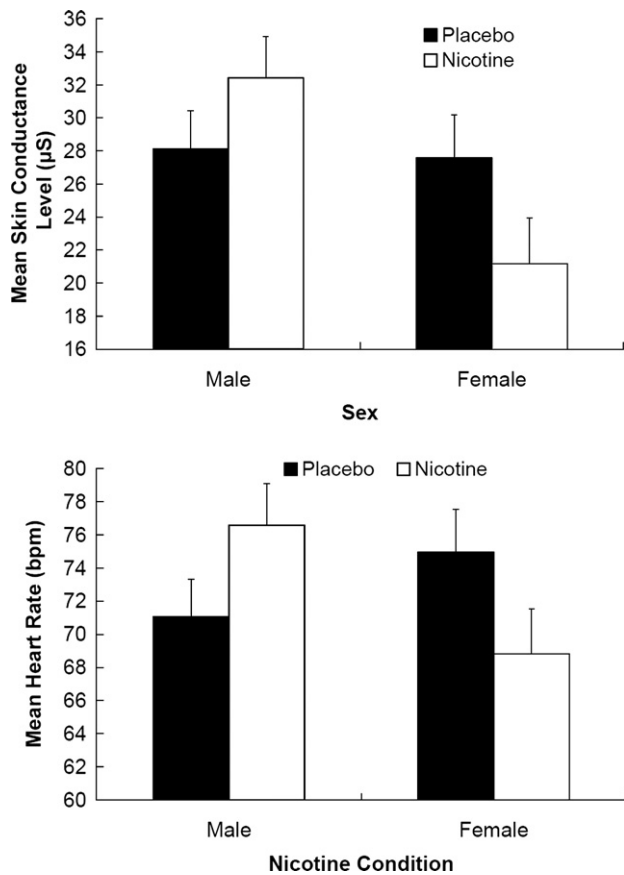


Fig. 1. Mean skin conductance level (top panel) and heart rate (bottom panel) as a function of nicotine condition and sex averaged across all visual-spatial tasks. Error bars depict the standard error of the mean.

body weight as the covariate. Greenhouse Geisser adjusted degrees of freedom were employed for all within subject factors with more than two levels. The unadjusted degrees of freedom and the epsilon used in the correction are reported. Post hoc pairwise comparisons employed an adjusted α -value based on Šidák's multiplicative inequality (Games, 1977) to correct the accumulation of Type I error arising from multiple comparisons. The data from one male administered the placebo was missing for the 3-dimensional mental rotation task due to equipment error.

3.1. Psychophysiological responses

Preliminary analyses indicated that there were no differences between the two nicotine dosages and the data for this and all subsequent analyses were subsequently collapsed across the dosage groups prior to analysis. The mean skin conductance level and heart rate recorded during the three visual-spatial tasks were analysed with separate $2 \times 2 \times 3$ (Sex \times Nicotine \times Task) ANCOVAs. As shown in Fig. 1 (top panel), mean skin conductance level was affected by nicotine administration differently in males and females. The analyses showed a significant main effect for Sex, $F(1,59)=7.55$, $p=.008$, and a significant Sex \times Nicotine interaction, $F(1,59)=6.61$, $p=.013$. Post hoc comparisons showed that nicotine administration was associated with lower skin conductance level in females,

$t=2.52$, $p<.025$, although the increase in males did not reach the required level of statistical significance, $t=1.31$, $p>.05$. The mean skin conductance level did not differ between the three tasks, all $F_s < 1.91$, $p > .05$.

As with the skin conductance level results, the effect of nicotine administration on tonic heart rate differed between the sexes, Sex \times Nicotine interaction, $F(1,59)=5.28$, $p=.025$. As shown in Fig. 1 (bottom panel) nicotine administration was associated with a small increase in heart rate in males, whereas the opposite effect occurred for females. However, pairwise comparisons showed that the increase in males, $t=1.61$, $p=.12$, and the decrease in females, $t=1.66$, $p=.11$, were not statistically significant if the comparisons were adjusted for the accumulation of Type I error ($\alpha_{adj}=.0253$). Similar to skin conductance level, heart rate did not differ between the tasks, all $F_s < 1.35$, $p > .05$.

3.2. Task performance

3.2.1. Water-level task

The mean degree of error of the participants answer was analysed with a $2 \times 2 \times 5 \times 3$ (Sex \times Nicotine \times Angle \times Volume) ANCOVA. A significant sex difference in performance was shown by a smaller error in males ($M=7.01^\circ$, $SD=12.11$) than in females ($M=14.68^\circ$, $SD=13.19$), main effect for Sex, $F(1,59)=4.07$, $p=.048$. However, nicotine administration had no significant effect on accuracy, all $F_s < 2.09$, $p > .05$. The mean confidence ratings during the water-level task were analysed with a $2 \times 2 \times 5 \times 3$ (Sex \times Nicotine \times Angle \times Volume) ANCOVA. Males were more confident in their responses than females, main effect for Sex, $F(1,59)=19.20$, $p<.0005$. Moreover, the difference between sexes was influenced by nicotine, as reflected in a significant Sex \times Nicotine interaction, $F(1,59)=4.72$, $p=.03$. As shown in Fig. 2, the two-way interaction reflected that confidence in males given nicotine administration was lower than in males given placebo, $t=2.28$, $p=.025$, whereas there was no significant difference between the nicotine and placebo conditions for females, $t=1.01$, $p>.05$. No other main effects or interactions were significant, all $F_s < 3.04$, $p > .05$.

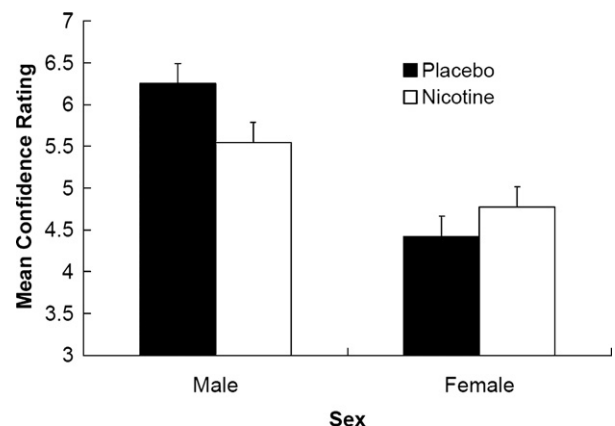


Fig. 2. Mean confidence ratings during the water-level task as a function of nicotine condition and sex. Error bars depict the standard error of the mean.

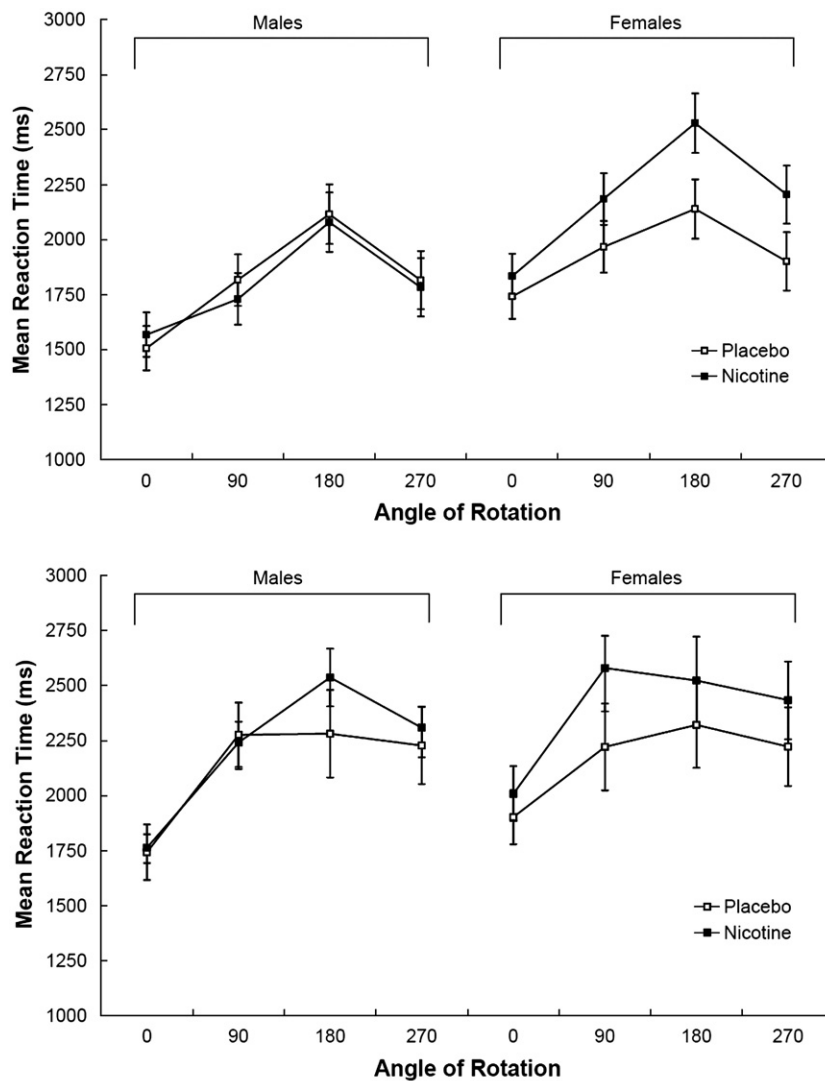


Fig. 3. Mean reaction time during the 2-dimensional (top panel) and 3-dimensional (bottom panel) mental rotation task as a function of nicotine condition and sex. Error bars depict the standard error of the mean.

3.2.2. 2-Dimensional mental rotation task

The mean proportion of errors and mean reaction time on correct trials during the 2-dimensional mental rotation task were analysed with separate $2 \times 2 \times 2 \times 4$ (Sex \times Nicotine \times Match \times Angle) ANCOVAs. As shown in Fig. 3 (top panel), males showed a faster reaction time than females, but nicotine affected RTs differently in each sex. There was minor support for a faster reaction time in males than in females, main effect for Sex, $F(1,59)=3.12$, $p=.08$. The effect of nicotine was reflected in a significant Sex \times Nicotine \times Angle interaction, $F(3,177)=3.44$, $\epsilon=.86$, $p=.02$. The three-way interaction reflected that for females, reaction time was slower in those administered nicotine than in those administered the placebo at the 90°, 180°, and 270° angles of rotation, all $t_s > 3.39$, $p < .006$, but not at the 0° angle of rotation, $t=1.44$, $p > .05$. In contrast, there were no differences between the nicotine and placebo conditions for males, all $t_s < 1.34$, $p > .05$. For the proportion of errors, the Sex \times Nicotine interaction approached significance, $F(1,59)=3.00$, $p=.088$, and all other $F_s < 2.62$, $p > .05$.

3.2.3. 3-Dimensional mental rotation task

Separate $2 \times 2 \times 2 \times 4$ (Sex \times Nicotine \times Match \times Angle) ANCOVAs were conducted on the mean proportion and mean reaction time on correct trials. As with the 2-dimensional mental rotation task, there was evidence of a three-way interaction between Sex, Nicotine, and Angle, $F(3,180)=2.43$, $\epsilon=.83$, $p=.078$. Fig. 3 (bottom panel) shows that the interaction reflected that the administration of nicotine affected reaction time differently in males and females. Post hoc comparisons ($\alpha_{adj}=.006$) showed that in females, reaction time was slower in those given nicotine than in those given placebo, with the difference reaching significance at the 90° angle of rotation, $t=4.27$, $p < .006$, approaching significance in the 180° and 270° angles of rotation, both $t_s > 2.40$, $p < .011$, but not significantly different at the 0° angle of rotation, $t=1.25$, $p > .05$. In males, reaction time was significantly slower in those given nicotine than in those given placebo at the 180° angle of rotation, $t=3.04$, $p < .006$, but not at the other angles of rotation, all $t_s < .95$, $p > .05$. The analyses also yielded a significant

Match \times Angle interaction, $F(3,177)=3.13$, $\epsilon=.99$, $p=.027$. No other significant main effects and interactions were found, all $F_s < 1.79$, $p > .05$. The proportion of errors in males ($M=.18$, $SD=.11$) tended to be lower than in females ($M=.25$, $SD=.14$), main effect for Sex, $F(1,59)=3.27$, $p=.07$. There was also modest evidence for a Sex \times Nicotine \times Angle interaction, $F(1,174)=2.29$, $p=.08$, and a Sex \times Nicotine interaction, $F(1,58)=3.58$, $p=.06$, for the proportion of errors, all other $F_s < 2.29$, $p > .05$.

4. Discussion

The present experiment showed that nicotine administration had no overall effect (i.e., main effect) on arousal and performance during tasks that assessed visual-spatial ability in non-smokers. If the data were examined without considering the potential influence of the differential variable of sex, it might be concluded that nicotine does not influence visual-spatial ability. However, the statistical analyses indicated that the effect of nicotine was moderated by sex in some rather unique ways. Moreover, these effects were found even when physical differences (body weight) were partially out through covariate analyses. Nicotine was associated with a lower skin conductance level in females. While nicotine administration did not affect accuracy on the water-level task, it significantly reduced confidence in task performance for males only. Nicotine administration also tended to slow reaction time in females much more extensively than in males during the 2-dimensional and 3-dimensional mental rotation tasks. The results support the notion that the effects of smoking or nicotine on cognitive functions or mood can be moderated by sex (Acheson et al., 2006; Algan et al., 1997; Perkins et al., 2002; Trimmel and Wittberger, 2004).

The psychophysiological measures showed that the administration of a transdermal nicotine patch was associated with lower skin conductance level in females. The observation that nicotine administration can influence arousal in smokers and non-smokers is well known (e.g., Perkins et al., 1994), although the fact that the physiological effect was moderated by sex is noteworthy. Skin conductance level is influenced only by activation of sympathetic postganglionic cholinergic fibres. This measure has been noted to provide a physiological measure of psychological functions that may specifically index an individual's general level of arousal during task performance (Furedy et al., 1999). The pattern observed with this objective, psychophysiological index was consistent with that found with subjective self-reports of smoking in females who report that they smoke for stress reduction (e.g., Ikard and Tomkins, 1973; Spielberger, 1986). It is also consistent with a recent study conducted on light smokers (1 to 10 cigarettes per day) showing that females gave lower subjective ratings on a composite scale of the Profile of Mood States (cf. Boyle, 1987; McNair et al., 1971) of "Arousal" than males following the administration of a 14 mg nicotine patch (Acheson et al., 2006).

The administration of nicotine produced sexually dimorphic effects on performance during the visual-spatial tasks. Nicotine administration was associated with lower confidence ratings in males, but had no effect in females, during the water-level task.

It is noteworthy that the lower confidence ratings for males given nicotine occurred in the absence of any performance decrements. Thus, nicotine administration had the effect of reducing confidence in a group of male participants that were performing a task at a relatively high level, whereas it had no impact in female participants who were performing the task less accurately (double the angle of error). The dissociation between performance and confidence ratings suggests that the effect of nicotine in males was to primarily alter the mood of the males. Although sex differences in the effects of nicotine on mood are not always examined (but see Perkins et al., 1994 for an example) the results are generally consistent with the observation that nicotine can have primarily adverse effects on mood when administered to "never smokers" or "former smokers" (see Kalman, 2002, for a review). In particular, nicotine administration has resulted in an increase in subjective ratings of confusion in never smokers (Grobe et al., 1998; Perkins et al., 1994), which is a psychological state that would likely impact upon confidence.

As with the effects of nicotine administration on confidence ratings, the effect of nicotine on reaction time during mental rotation tasks was an adverse one. The finding that nicotine administration can be associated with a slowing of response speed has also been observed in other cognitive domains (e.g., attention), although it may depend on the task used (Trimmel and Wittberger, 2004). In the present experiment, the extent of the impairment differed between males and females. The effect of nicotine administration on performance was clearest in the 2-dimensional version of the task in which nicotine administration slowed reaction times in females. Moreover, the slowing was observed only when the image was rotated relative to the other. The nicotine effects were thus present when the task involved a conceptual cognitive process (i.e., mental rotation was required), rather than a perceptual cognitive process (i.e., no mental rotation was required). Males may be more immune to the effects of nicotine than females due to their general superior ability in performing mental rotation and are thus able to more readily absorb the detrimental effects of nicotine.

Research that has shown that nicotine enhances psychological functions has been typically conducted with smokers or clinical populations, whereas studies that have shown that nicotine impairs psychological functions have used healthy non-smoking individuals (Newhouse et al., 2004). The sample of non-smoking university students used in the present experiment, may differ from other populations in that they could perform the visual-spatial tasks at an optimal level independent of any nicotine administration. Such optimal performance was likely to be reinforced by the use of pre-training (practice trials) and the generally high motivation of the participants. As described by Newhouse et al. (2004), the level of cognitive performance might be related to nicotine administration in an inverted U curvilinear function according to the Yerkes and Dodson (1908) principle. An individual who is performing at a high level of functioning might be expected to be near the peak of the inverted U function. The effect of nicotine administration might be to produce either stimulation or depressant effects depending on the interaction between

pharmacological variables (e.g., dose) and individual difference variables (e.g., sex). This has the consequence of shifting performance to the left or right along the inverted U to result in an impairment of performance. The reduction in arousal in females administered nicotine may have had the effect of slowing reaction time during mental rotation tasks. No effect on task performance was observed during the water-level task for females administered nicotine because this task did not require speeded responses, but emphasized accuracy. In contrast, the heightened arousal in males administered nicotine might have influenced subjective feelings of confidence based on research showing that arousal is negatively correlated with confidence (Yancey et al., 1992) and that participants who attribute increases in arousal as related to the competence in a task show reduced confidence (Savitsky et al., 1998).

Some aspects of the present study place limitations on the conclusions that can be drawn. A relatively low dosage patch and short absorption period was used in order to minimize the potentially negative side effects following nicotine administration in our sample of non-smokers. It is also possible that the absorption period was too short to allow for a plateauing of blood nicotine levels, thus suggesting that the pharmacological manipulation we used was relatively weak. Nevertheless, the present experiment shows that even when a relatively weak pharmacological manipulation is used, it is important to consider the differential variable of sex as it may moderate the effects of nicotine. Future research could use a longer absorption period, high dosage patch, or alternative nicotine administration method to increase the size of the pharmacological manipulation. A second aspect of the study is that there may have been individual variation in the final blood nicotine or cotinine levels across participants. For instance, the lower physiological arousal and slower reaction times in females given nicotine may reflect that these participants as a group had higher cotinine levels than the group of males given nicotine. Although this is a possibility, it does not appear to be consistent with the finding that nicotine administration in males was associated with lower confidence in the water-level task, whereas nicotine administration did not affect confidence in females. We also used body weight as a covariate in the statistical analyses in order to account for the difference in body size between the sexes. Nevertheless, future research would benefit from the direct measurement of blood nicotine and cotinine levels and using it as a covariate. In this way, a more sensitive test of the interactive effects of sex and nicotine on arousal and performance may result.

Fallon et al. (2005) reported that females administered placebo showed higher brain metabolism than in males in the prefrontal, temporal, and inferior parietal lobe systems, including those areas involved in executive function, choice, and attention. This difference was reversed or eliminated by nicotine administration. The results reported by Fallon et al. (2005) highlight the importance of considering sex in the investigation of brain metabolic effects of nicotine. The present study supports this conclusion and extends it to the consideration of behavioral and physiological effects during tasks that reliably yielded sex differences in performance. While sex is a

biological variable that is relevant to take into account in a biobehavioral investigation of psychological functions (Furedy and Pogun, 2001) it is becoming clear that it deserves attention in studies that investigate the effects of smoking or nicotine. Nicotine may have complex effects according to the interaction between the pharmacological effects of nicotine, individual difference variables, and the specific cognitive ability that is tested. Such complexity needs to be disentangled in order to provide definitive conclusions about the role of nicotine in the maintenance of cigarette smoking or its potential therapeutic application in the amelioration of cognitive decline associated with ageing or neurological disorders.

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