Effects of nicotine administration via a sublingual tablet on arousal and verbal ability in non-smokers

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The effects of nicotine administration via a sublingual tablet on arousal and verbal ability in non-smokers
Abstract

Tobacco smoking or nicotine administration on its own can influence cognitive task performance. This study examined the effects of acute nicotine administration on verbal task performance and a physiological index of arousal. Healthy non-smoking participants received either a 2 mg sublingual nicotine tablet or placebo. Participants next completed various verbal tasks while heart rate recordings were taken concurrently. Nicotine increased heart rate relative to a pre-administration baseline period to indicate that the new method of nicotine administration increased cardiovascular arousal. Nicotine was associated with reduced accuracy in a verbal matching task and reduced accuracy and increased reaction time in an anagram task, but had no effect on performance during an analogy or verbal fluency task. The data suggest that nicotine naïve individuals are unlikely to gain any benefit to their verbal ability from the single acute intake of nicotine, such as that obtained from cigarette smoking or by using nicotine replacement therapy products.
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Introduction

Nicotine activates nicotinic acetylcholine receptors that are located in many brain areas important for cognitive function (Levin, McClernon, & Rezvani, 2006). This may provide the psychopharmacological basis for why many smokers report that smoking improves functions such as attention and memory (Piper et al., 2004). However, somewhat surprisingly based on these reports, Newhouse, Potter, and Singh (2004) concluded in a review that there were an almost equal number of studies that showed improvements in cognition as there were studies that showed impairments (see also Heishman, Taylor, & Henningfield, 1994; Levin et al., 2006; Pogun 2001). For example, there are reports that nicotine enhances selective attention (e.g., Trimmel & Wittberger, 2004), sustained attention (Foulds et al., 1996; Levin et al., 1998), updating of working memory as reflected in P300 latency (Edwards, Wesnes, Warburton, & Gale, 1985; Houlihan, Pritchard, & Robinson, 1996), retrieval from working memory (Kerr, Sherwood, & Hindmarch, 1991), and recognition memory (Perkins et al., 1994). In contrast, there are reports that nicotine has no effect or impairs selective attention (Foulds et al., 1996; Heishman, Snyder, & Henningfield, 1993; Perkins et al., 1994), sustained attention (Wesnes, Warburton, & Matz, 1983), P300 latency (Ilan & Polich, 2001; Lindgren, Stenberg, & Rosen, 1998), retrieval from working memory (Foulds et al., 1996), and spatial working memory (Park, Knopick, McGurk, & Meltzer, 2000). These contradictory findings make it difficult to draw conclusions about the effects of nicotine on selective cognitive functions.

The inconsistent findings may reflect any one of several factors. It has been argued that nicotine has a beneficial effect in smokers and individuals with neurological disorders and a detrimental effect in non-smokers (Newhouse et al., 2004). However, this is not always the case because there are reports in which nicotine impaired performance in smokers (e.g., Park et al., 1994) and improved performance in non-smokers (e.g., Trimmel & Wittberger, 2004). A more consistent finding is that the administration of nicotine reverses the negative impact of nicotine deprivation in smokers (Heishman et al., 1994), but from this it cannot be concluded that
nicotine has a cognitive enhancing effect *per se*. To make this conclusion requires that studies utilise non-smokers who are free from the chronic effects of nicotine use. A potential difficulty in the use of non-smokers is that nicotine may have negative effects on mood and arousal (Kalman, 2002; Newhouse et al., 2004). Heishman and Henningfield (2000) provided a test of such claims when they administered nicotine to non-smokers across eight days. In spite of the participants developing tolerance to the negative subjective effects of nicotine, no performance improvements on a range of cognitive tasks were found.

Research areas that contain contradictory findings will benefit from the accumulation of evidence from studies that employ a range of methods. The aggregated evidence will permit identification of patterns in the findings and the weight of evidence supporting a particular conclusion will become more apparent. The present study aimed to contribute to this gathering of knowledge by examining the effects of nicotine on tasks that have a verbal component.

Nicotine administered to smokers has improved performance on a word recognition test (Foulds et al., 1996), a word matching task (Algan, Furedy, Demirgoren, Vincent, & Pogun, 1997), recall of words after a semantic processing task (Warburton, Skinner, & Martin, 2001), and recall of semantically related words (Rusted, Graupner, Tennant, & Warburton, 1998). The recall of words after five trials of learning a list of words (Min, Moon, Wo Ko, & Sang Shin, 2001) and the retrieval of words in a verbal fluency task (Howe & Price, 2001) is also enhanced by nicotine administration in elderly non-smokers at risk for dementia. However, no effect of nicotine was found with healthy non-smokers on a task that required the order of two pairs of letters to be determined (Ernst, Heishman, Spurgeon, & London, 2001), an anagram task (Marchant, Trawley, & Rusted, 2008; Rusted & Alvares, 2008), and an ongoing lexical decision task (Marchant et al., 2008). Also in non-smokers, nicotine has improved the retrieval-induced forgetting observed in episodic list learning (Rusted & Alvares, 2008) and performance in a lexical-semantic processing task (Holmes, Chenery, & Copland, 2008).
In contrast to past research, the present experiment used a range of verbal tasks within one experiment. The tasks were selected to represent the components of verbal ability as defined by Campito (1994) as being composed of two broad facets: the amount and structure of verbal knowledge and the ability to reason with verbal information. A verbal fluency task (Halpern & Wright, 1996), anagram task (Walker, Liston, Hobson, & Stickgold, 2002), word matching task (Algan et al., 1997), and an analogy task (Gitomer, Glaser, Curtis, & Lensky, 1982) were used. The first three tasks are most closely linked to verbal knowledge and the last task is related to the ability to reason with verbal information. While these tasks will involve other aspects of cognitive function, such as attention and memory, they are ecologically valid with respect to these verbal components. This is particularly relevant given that smoking often occurs in situations involving interpersonal communication (e.g., social gatherings and work breaks) and many work tasks use printed and spoken words.

The present experiment also tested a new method of nicotine administration. The typical use of transdermal nicotine skin patches (e.g., Howe & Price 2001; Min et al., 2001) requires a long absorption period of two hours or more to reach peak levels of nicotine. Absorption of nicotine through the oral mucosa is faster than absorption through the external skin (Molander & Lunell 2001). The present experiment thus employed a sublingual tablet that contained 2 mg of nicotine bound to β-cyclodextrin. Peak levels of nicotine are reached at 1 hour and do not substantially decline until after 2 hours following administration (Molander & Lunell, 2001). A measure of cardiovascular arousal (heart rate; HR) was taken independent from and during the verbal tasks to document the physiological effect of the nicotine tablet. Furthermore, non-smoking participants were tested to avoid the potentially confounding effects of chronic nicotine use in smoking participants.

Method

Participants

Thirty-nine female and 43 male first year psychology students aged between 18 and 29
years ($M = 19.0, SD = 2.00$) participated in exchange for course credit. All except one participant reported to have never smoked. The remaining participant had quit smoking five years previously. Inclusion or exclusion of this participant did not affect the outcome of the statistical analyses and the participant was retained. No participants reported use of any nicotine replacement therapy product. All participants were required to have English as their primary language and reported that they did not have a history of hypertension, cardiac disease, cerebrovascular disease, impaired renal function, pregnancy, seizure, abuse or dependence on alcohol or other drugs, psychiatric illness, and current use of any medications. Blood pressure and HR was also measured. Seven males and one female were excluded due to high blood pressure (>140/90) and two females were excluded due to a non-English speaking background. The final sample consisted of 72 participants (36 male, 36 female) wherein half of each sex were randomly allocated to receive nicotine or placebo. The demographic characteristics of each group are shown in Table 1. All groups were similar in age, weight, prior years of education, heart rate, as well as diastolic and systolic blood pressure assessed during screening, all $t < 0.85$, $p > .05$. All participants provided informed consent to a protocol approved by the Griffith University Human Research Ethics Committee.

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Insert Table 1 about here
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*Apparatus*

*Nicotine administration.* Participants were given either a sublingual Nicorette® Microtab containing 2 mg of nicotine or a placebo that was matched as closely as possible to the nicotine tablet in size, color, and taste. To negate the sensory properties of the tablets (e.g., size, taste), they were placed under each participant’s tongue to dissolve using a blind protocol. Pilot research indicated that participants are unaware of the nature of the tablet using this administration method. Participants were instructed not to chew, not to move the tablet around,
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and not to swallow more than once per minute (a timer was used to assist this requirement). The participants watched the same video program for 45 min and were subsequently escorted to a testing room for set up of the HR recordings and instructions for the experimental tasks. Testing began 1 hour after administration. Prior research has indicated that nicotine plasma concentrations reach a peak mean level of $3.8 \pm \text{ng/ml (SD = 1.0)}$ at 1 hour following administration of a single 2 mg microtab (Molander & Lunell, 2001). The presence of adverse reactions to the nicotine tablet and placebo was monitored through observation and questioning by an experimenter. The most common side effects reported by participants were a dry mouth and an increase in coughing. One participant that was administered nicotine reported feelings of dizziness. This participant (female), however, was not sufficiently unwell to discontinue the experiment; she completed the entire experimental protocol. An examination of her data indicated that she was not deviant from the other females in her group, exclusion of her data did not change the pattern of results, and her data was thus retained in the analyses.

Physiological response measurement. Recordings were obtained via a PowerLab Model 4/20 data acquisition system (ADInstruments, Sydney). 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. Responses were sampled at 1000 Hz starting with the onset of the task or baseline period and terminated at the end of the task or the baseline period.

Verbal tasks. Three of the verbal tasks (word matching, analogy, and anagram) were presented on Dell Optiplex Model GX240 and GX1 computers. The word matching task (Algan et al., 1997) consisted of 16 practice trials and 112 test trials. On each trial, participants were presented with a fixation cross for 1000 ms, followed by a visual display for 600 ms. The display consisted of two letter pairs above and to the left and right of the fixation cross and one letter pair below and to either the left or right of the fixation cross. A match occurred when one of the letter pairs above the fixation cross (e.g., BA) formed an English word when combined
with the letter pair below (e.g., NK). A mismatch occurred when a word could not be formed. An equal number of trials were match and mismatch trials. To manipulate difficulty, 192 high frequency four letter words ($M = 1117.29$ times per million) and 192 low frequency four letter words ($M = 9.45$ times per million) were selected (see Leech, Rayson, & Wilson, 2001). Participants were asked to answer as quickly and accurately as possible by pressing either the letter “B” or “N” (counterbalanced) for a match or mismatch response on the keyboard. The dependent measures were correct RT and proportion of correct responses.

The analogy task used six practice trials and 32 test trials. In each trial, participants were presented with an analogy stem (e.g., car : road :: train : _) for 5 s, followed by four possible answers (e.g., (a) wheel (b) vehicle (c) fast (d) track ) for a maximum of 15 s. Participants were required to infer a relationship between the first two words in the analogy stem, and transfer that relationship to the third word and one of the answers. Participants indicated their answer on the keyboard and were asked to answer as accurately as possible. Difficulty was varied by categorizing the word answer for half as a high frequency ($M = 74.12$ per million) and half as low frequency ($M = 5.43$ per million) (Leech et al., 2001). The dependent measures were the proportion of correct answers and RT to enter the answer.

The anagram task used six practice trials and 32 test trials (Rajaram & Roediger, 1993). Participants were presented with a scrambled word for a maximum of 20 s and were to unscramble the letters to form a concrete word (e.g., ETNPAU = PEANUT). Participants were required to answer as quickly and accurately as possible by typing their answer on the keyboard. To manipulate difficulty, half of the words comprised five to six letters (short words) and the remaining comprised seven to eight letters (long words). The dependent variables were the proportion of correct responses and the RT to enter the first letter of the answer.

In the verbal fluency task participants were presented with four letters (F, A, S and N), each separately on paper. Starting with the letter F, participants were asked to generate as many words as possible that begin with the letter for 60 s. The procedure continued for the remaining
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letters of A, S, and N. Participants were required to write the words down, rather than say them out aloud (cf. Halpern & Wright, 1996), because another participant in the experiment may have been completing the tablet administration in an adjacent room. Participants could not derive words from those they had already written (e.g., play, to form plays, played and playing). The total number of unique English words produced was counted.

Procedure

After consent and screening, participants rinsed their mouth with water and were directed to the testing room for attachment of the electrodes for HR recordings. Participants sat quietly for 3 min during which time pre-administration recordings for HR were taken. The nicotine or matched placebo tablet was next administered. After the absorption period, the tasks were administered. The experimenter gave the instructions for the word matching task and participants completed the practice trials. After any questions were answered, the participant completed the main experimental trials, while HR was recorded continuously. A similar procedure followed for the analogy task, anagram task, and verbal fluency task. At the end of the verbal fluency task, participants sat for another 3 min while no task post-administration recordings were taken. Participants were debriefed at the end of the experiment.

Data reduction

Heart rate was taken as the mean value across the entire duration of each verbal task and the no task baseline periods. The mean proportion correct for the word matching task, analogy task, and anagram task were calculated across all trials. Non-responses were counted as incorrect. The RTs for these three tasks were also calculated using only correct responses. Preliminary analyses indicated that the within-subjects manipulations of task difficulty did not interact with either nicotine or sex. For this reason, the performance data were collapsed across all trials and statistical analyses employed a 2 x 2 (Nicotine x Sex) factorial design and assessed against a two-tailed $\alpha = .05$. Effect sizes are reported as Cohen’s $d$.

Results
Heart rate measures

To take into account individual differences in baseline levels, HR obtained during the pre-administration baseline period was subtracted from that obtained during the verbal tasks and the no-task baseline period following administration. A positive change indicates that HR was higher following the administration of nicotine or placebo than during the pre-administration period. As shown in Figure 1, HR tended to be higher in participants given nicotine than in participants given placebo. A series of 2 x 2 (Nicotine x Sex) ANOVAs confirmed that the difference was significant during the no-task baseline period, $F(1, 67) = 9.37$, $d = .74$, $p < .05$, and during all verbal tasks, all $F$s > 5.53, $d > .56$, $p < .05$. No other main effects or interactions were found, all $F$s < 1.64, $p > .05$.

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Insert Figure 1 about here

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Performance measures

Performance on each verbal task was examined with separate 2 x 2 (Nicotine x Sex) ANOVAs. Table 2 shows the mean values for each performance measure in each task. In no cases was there a significant Nicotine x Sex interaction, all $F$s < 3.94, $p > .05$. However, as can be seen, the nicotine and placebo groups did differ in performance for some tasks, but not others. Participants administered nicotine showed significantly lower accuracy in the word matching task, $F(1, 68) = 4.10$, $d = .56$, $p < .05$, significantly lower accuracy in the anagram task, $F(1, 68) = 5.08$, $d = .54$, $p < .05$, and significantly longer RT in the anagram task, $F(1, 68) = 8.64$, $d = .70$, $p < .05$, than participants administered placebo. Performance did not differ significantly between the nicotine and placebo administration conditions for the analogy task or the verbal fluency task, all $F$s < 3.21, $d < .42$, $p > .05$.

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Insert Table 2 about here
A number of sex differences also emerged with the tasks. Females ($M = 983$ ms, $SD = 333$) had a shorter RT than males ($M = 1226$ ms, $SD = 427$) for the word matching task, $F(1, 68) = 7.18$, $d = .63$, $p < .05$. Accuracy on the word matching task was higher in males ($M = 0.72$, $SD = 0.10$) than in females ($M = 0.65$, $SD = 0.07$), $F(1, 68) = 9.35$, $d = .81$, $p < .05$. Finally, the expected sex difference in the analogy task of higher accuracy for males ($M = 0.55$, $SD = 0.11$) than females ($M = 0.50$, $SD = 0.11$) was present, $F(1, 68) = 4.63$, $d = .64$, $p < .05$. The differences between males and females for the anagram task or the verbal fluency task were not significant, all $F$s $< 2.88$, $p > .05$.

**Discussion**

The administration method that was used, the application of a sublingual tablet containing 2 mg of nicotine, increased HR during the verbal tasks and during a no task baseline period. The observation that nicotine increases HR is consistent with prior reports (e.g., Foulds et al., 1997; Furedy, Algan, Vincent, Demirgoren, & Pogun, 1999). The mean size of the HR increase across all measurement periods was 3.12 bpm ($SD = 1.59$). Foulds et al. reported an increase of 2.8 bpm following a 0.3 mg injection of nicotine in non-smokers. One study that administered a 7 mg transdermal nicotine patch to smokers and non-smokers showed a transient increase in HR of 3.14 bpm between 180 and 240 minutes following administration (Poltavski & Petros, 2005). It may be concluded that the effect of the 2 mg sublingual tablet on increasing cardiovascular arousal is comparable to that obtained in some other studies that administer nicotine via other means and supports the utility of sublingual tablets as a nicotine administration method. The use of nicotine tablets affords one advantage in that it provides a non-invasive means to deliver a dose of nicotine within a convenient timeframe for testing. It also avoids variation across participants caused by differences in the speed and intensity of chewing movements when nicotine gum is used to administer nicotine orally.
Nicotine administration influenced verbal task performance for some tasks, but not others, and it was not influenced by sex or task difficulty. The null effects of nicotine in solving verbal analogy problems replicated the findings reported by Marchant et al. (2008) and Rusted and Alvares (2008). Nicotine did have an effect on performance in the word matching and anagram task. In both cases, nicotine was associated with poorer performance on these tasks.

The tasks seem to depend on verbal knowledge (Campito, 1994), specifically lexical knowledge for the word matching task (Brand, Bekhum, Stumpel, & Kroeze, 1983) and lexical knowledge in addition to verbal flexibility for the anagram task (Walker et al., 2002). The tasks also depend on non-verbal cognitive functions such as sustained attention and memory retrieval and these factors may also be implicated in the impairments found. The impairments in performance for the word matching and anagram tasks contribute to the accumulating evidence that nicotine can have no effect or impair performance on tasks that have a verbal component (Ernst et al., 2001; Marchant et al., 2008; Rusted & Alvares, 2008) or on tasks that assess other cognitive functions (e.g., Foulds et al., 1996; Heishman et al., 1993; Ilan & Polich, 2001; Lindgren et al., 1998; Park et al., 2000; Perkins et al., 1994).

Performance on cognitive tasks may also be mediated by nicotine-induced changes in other states. For instance, changes in mood (see review by Kalman, 2002; Kalman & Smith, 2005) or physical state induced by nicotine may have been an important factor. The low dosage (2 mg) nicotine tablet was selected in order to reduce the potential for adverse reactions from the participants. Moreover, participants were carefully monitored and questioned by the experimenter and only one participant reported significant side effects (dizziness). No participant withdrew from the study from adverse reactions. This suggests that the effects of nicotine on changing mood or producing side-effects in the present study were, if present, minor. The study by Heishman and Henningfield (2000) also suggested that negative subjective effects may not always explain a lack of performance improvement following nicotine administration. In addition, nicotine did not impair performance on all of the tasks used. The
selective effect of nicotine on specific tasks suggests that global mood or physical states may not have caused the performance decrement. However, this argument is tentative because inspection of the mean values for the analogy and verbal fluency tasks indicated that the differences between groups, though nonsignificant, were in a direction consistent with poorer performance following nicotine administration. The argument would be stronger if the differences between groups were reversed in these tasks or if there was an interaction in which the anagram and word matching tasks showed significantly larger impairments by nicotine than the analogy and verbal fluency tasks. Further research should aim to provide measures of mood and side-effect states (e.g., Foulds et al., 1997). Appropriate statistical analyses could thus determine if any mood changes that are found mediate the effects of nicotine on verbal ability or merely represent an independent effect of nicotine administration.

Males and females have been shown to differ in performance during some tasks that assess verbal ability. Prior research has shown better performance in females than in males on the verbal fluency, anagram, and word matching tasks, whereas the opposite results are seen with the analogy task (Algan et al., 1997; Halpern, 2000; Hyde & Linn, 1988). In the present study, females performed better than males (shorter RT) in the word matching task, whereas males performed better (higher accuracy) in the word matching task. The sex differences observed for the word matching task thus appear to reflect a speed-accuracy tradeoff in that females, relative to males, responded faster at a cost of reduced accuracy. The expected sex difference of higher accuracy in males than females in the analogy task was also found. However, the effects of nicotine did not interact with sex for any tasks to suggest that the effects of nicotine were independent of any sex differences in task performance.

In conclusion, the present results indicate that acute nicotine administration impairs performance on verbal tasks linked to verbal flexibility and lexical knowledge. While the use of non-smoking participants in the present study may limit generalizations that can be made to a smoking population, this methodology allowed the effects of nicotine administration to be
examined independent of chronic smoking status and withdrawal effects present in smokers. Additional research is required that uses the present tasks, which are more ecologically valid than many verbal tasks used in previous research, to determine the performance effects in smokers. Nevertheless, nicotine naïve individuals would appear unlikely to gain any benefits in verbal performance from the single acute intake of nicotine, such as that obtained after smoking a cigarette or the use of nicotine replacement therapy products. Such outcomes should act as a deterrent to individuals who are contemplating the use of tobacco or nicotine products because of any putative enhancement of verbal function.
Acknowledgements

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Table 1

Mean values for the demographic characteristics for the participants administered nicotine (n = 36) and placebo (n = 36) (standard deviations are in parentheses).

<table>
<thead>
<tr>
<th>Measure</th>
<th>Administration condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nicotine</td>
</tr>
<tr>
<td>Male:Female ratio</td>
<td>18:18</td>
</tr>
<tr>
<td>Age (years)</td>
<td>19.17 (2.04)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.14 (10.37)</td>
</tr>
<tr>
<td>Years of education</td>
<td>12.78 (1.25)</td>
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<tr>
<td>Pre-administration heart rate</td>
<td>71.97 (12.31)</td>
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<tr>
<td>(bpm)</td>
<td></td>
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<tr>
<td>Pre-administration systolic</td>
<td>125.86 (9.35)</td>
</tr>
<tr>
<td>blood pressure</td>
<td></td>
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<tr>
<td>Pre-administration diastolic</td>
<td>74.78 (8.62)</td>
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<tr>
<td>blood pressure</td>
<td></td>
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</tbody>
</table>
Table 2.

*Mean values for the performance measures in participants administered nicotine (n = 36) and placebo (n = 36) for the word matching, analogy, anagram, and verbal fluency task (standard deviations are in parentheses).*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Administration Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nicotine</td>
</tr>
<tr>
<td>Word matching</td>
<td></td>
</tr>
<tr>
<td>Reaction time (ms)</td>
<td>1063 (373)</td>
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<tr>
<td>Proportion correct</td>
<td>0.66 (0.09)</td>
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<tr>
<td>Analogy</td>
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<td>Reaction time (ms)</td>
<td>4486 (926)</td>
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<tr>
<td>Proportion correct</td>
<td>0.51 (0.12)</td>
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<tr>
<td>Anagram</td>
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<tr>
<td>Reaction time (ms)</td>
<td>10562 (2231)</td>
</tr>
<tr>
<td>Proportion correct</td>
<td>0.33 (0.12)</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td></td>
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<tr>
<td>Number of words</td>
<td>43.47 (8.67)</td>
</tr>
</tbody>
</table>
Figures

Figure 1. Mean change in heart rate from the pre-administration period as a function of administration condition during the verbal tasks and post-administration period for the Nicotine and Placebo groups. Error bars depict the standard error of the mean.
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![Graph showing mean change in heart rate (bpm) for different task types: Word matching, Analogy, Anagram, Verbal fluency, No task. The graph compares Nicotine and Placebo conditions.](image-url)