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Effects of transdermal nicotine and concurrent smoking on cognitive performance in tobacco-abstinent smokers

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Abstract

Smokers experience cognitive decrements during tobacco abstinence and boosts in performance upon resumption of smoking. Few studies have examined whether smoking cessation treatments such as transdermal nicotine ameliorate these decrements and/or attenuate the cognitive effects of smoking. Identifying the effects of nicotine on these tobacco-related changes in performance could guide the development of more efficacious treatments. The purpose of this double-blind, randomized, laboratory study was to use process-specific cognitive tasks to examine the effects of transdermal nicotine (TN) and tobacco smoking on attention and working memory in overnight-abstinent smokers (N=124; 54 women). Each participant completed four, 6.5-hour sessions corresponding to 0, 7, 14, or 21 mg TN doses, and smoked a single cigarette four hours after TN administration. Outcome measures were administered before and after smoking, and included tasks measuring attention (alerting, orienting, and executive function), working memory (verbal and spatial), and psychomotor function. Analysis of variance ($p < .05$) revealed that TN improved verbal and spatial working memory performance, as well as psychomotor function. Smoking, independent of TN dose, improved alerting, verbal working memory, and psychomotor function. Lastly, TN partially attenuated the effects of smoking on some working memory outcomes. These findings lend evidence to the idea that TN ameliorates some abstinence-related cognitive decrements and suggest that TN does not completely attenuate the cognitive effects of a concurrently smoked cigarette. Consequently, TN's efficacy as a smoking cessation treatment might be improved should these limitations be better addressed by either modifying or supplementing existing treatments.

Introduction

Smoking tobacco is a negative health behavior with life-threatening consequences and approximately 70% of the 46 million smokers in the United States report wanting to stop smoking (CDC, 2002; 2009). One of the most widely used treatments for smoking cessation is nicotine replacement therapy (NRT; Burton, Gitchell, & Shiffman, 2000; Shiffman, Fant, Buchhalter, Gitchell, & Henningfield, 2005). Despite evidence that NRT is an efficacious

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smoking cessation treatment there is room for improvement as indicated by the 83 to 93% of patients who return to smoking one or more years after stopping smoking (Daughton et al., 1999; Richmond & Kehoe, 2007; Richmond, Kehoe, & de Almeida Neto, 1997; Tonnesen et al., 1991).

One approach for improving the efficacy of NRT is to understand better its effects across a variety of outcome measures. Traditionally studies examining NRT have focused on physiological, subjective, and behavioral outcomes (e.g., heart rate, subjective ratings, smoking topography; Benowitz et al., 1998; Evans et al., 2006; Hughes et al., 1984; Nemeth-Coslett et al., 1987; Pickworth et al., 1996). Fewer studies have included cognitive performance outcomes, despite the fact that tobacco abstinence impairs and smoking improves cognitive performance (e.g., divided attention, working memory, attentional orienting; Bell, Taylor, Singleton, Henningfield, & Heishman, 1999; Heishman, Taylor, & Henningfield, 1994; Parrott & Roberts, 1991; Snyder, Davis, & Henningfield, 1989). Determining the extent to which NRT attenuates the cognitive effects of abstinence and smoking lapses is important because these cognitive changes have the potential to interfere with an individual's work and everyday functioning. Indeed, some cases of smoking relapse could be explained by a smoker's desire to maintain a level of cognitive functioning that is otherwise disrupted by tobacco abstinence (Ferguson et al., 2006; Patterson et al., 2010; Rukstalis et al., 2005).

Controlled laboratory studies that have explored the effects of tobacco abstinence and NRT on cognitive performance have included measures of attention and working memory (Heishman et al., 1994; Mancuso, Warburton, Melen, Sherwood, & Tirelli, 1999b; Myers, Taylor, Mulchan, & Heishman, 2008; Wesnes, Warburton, & Matz, 1983; Sherwood, 1993; see also Cook et al., 2003). Attention, a system that modulates the selection of stimuli from the surrounding environment can be divided into subsystems: alerting, orienting, and executive function (Fan, McCandliss, Sommer, Raz, & Posner, 2002; Posner & Peterson, 1990). Alerting is related to vigilance and sustained attention, orienting is concerned with the directing of attention, and executive function is associated with response inhibition and filtering out unnecessary information. Similarly, working memory, a system that assists in the temporary holding and manipulation of information, can be divided into subsystems: the central executive, the verbal loop, and the visual sketchpad (Baddeley, 1999). The latter "slave systems" maintain information to aid the central executive. Specifically, the verbal loop is responsible for maintaining verbal stimuli and the visual sketchpad deals with the maintenance of visual stimuli.

Overall, studies of attention and working memory suggest that several subsystems may be influenced by NRT. For example, there is some evidence that alerting is improved in abstinent smokers after NRT administration (e.g., Atzori, Lemmonds, Kotler, Durcan, & Boyle, 2008; Parrott & Craig, 1992; Mancuso, Andres, Ansseau, & Tirelli, 1999a; Wesnes et al., 1983). One task that has been used in the nicotine literature to measure alerting is the Rapid Visual Information Processing task (RVIP; e.g., Mancuso et al., 1999a; Parrott & Craig, 1992), which has shown RVIP target detection is improved after NRT relative to placebo. However, other studies using different tasks to measure alerting report no effects of NRT (AhnAllen et al., 2008; Cook et al., 2003; Snyder & Henningfield, 1989). The existing research on executive function is similarly inconsistent with some studies showing NRT-related enhancement of performance on tasks such as the Stroop task (Atzori et al., 2008; Hasenfratz & Battig, 1992), while other studies utilizing the Stroop task or related measures have shown no influence of NRT (e.g., AhnAllen et al., 2008; Cook et al., 2003; Foulds et al., 1996; Mancuso et al., 1999b; Parrott & Craig, 1992). In contrast, fewer studies have examined orienting in abstinent smokers exposed to NRT and null effects have been

observed in studies that have measured this cognitive process (e.g., AhnAllen et al., 2008; Knott et al., 1999).

The effects of NRT exposure are also inconsistent for verbal working memory. Null effects of NRT have been observed in studies using different measures of verbal working memory (Cook et al., 2003; Ernst et al., 2001; Foulds et al., 1996; Sherwood, Kerr, & Hindmarch, 1992; Snyder & Henningfield, 1989). However, in other studies nicotine improved working memory performance in smokers (Atzori et al., 2008; Grobe et al., 1998). In contrast to the multiple studies that have examined the effects of NRT on verbal working memory, we are aware of only one study to date that has examined visual working memory in abstaining smokers (Warburton & Mancuso, 1998). In this study no effect of TN was observed relative to placebo across three separate measures suggesting nicotine does not improve performance on this outcome in abstaining smokers. However, additional research is needed to confirm these isolated findings.

In summary, no effects of NRT have been reported for orienting or visual working memory performance, whereas the effects of NRT on other cognitive subsystems have been variable. There are several potential explanations for this variability. First, the cognitive tasks utilized are sometimes not designed to measure a specific subsystem and require more than one subsystem for proper completion. For example, neuro imaging research suggests that the RVIP task, described above as a measure of alerting, might also involve verbal working memory (Coull, Frith, Frackowiak, & Grasby, 1996). Second, the studies reviewed above most often include small sample sizes (most $N \leq 20$) and may not be powered to detect a true effect of NRT. Third, aspects of the study methodology often differ between studies (e.g., route of nicotine administration and nature of cognitive task).

A complete understanding of NRT's effects on cognition is also challenged because no study to date has explored systematically the effects that gender and a lapse cigarette (e.g., concurrent smoking while using NRT) have on performance outcomes. Gender differences in response to the acute effects of NRT might exist because cessation rates are sometimes higher for men using NRT relative to women (Bjornson et al., 1995; Cepeda-Benito, Reynoso, & Erath, 2004; Perkins & Scott, 2008; Swan et al., 1997). Results from the few studies that have examined gender and cognitive performance in response to nicotine suggest that differences may exist (Myers et al., 2008; Trimmel & Wittberger, 2004). However, additional research is needed to elucidate fully the nature of gender differences, if any, in response to nicotine's effects on cognition. The absence of research examining the cognitive effects of smoking a lapse cigarette during NRT use also is surprising given that NRT is thought to facilitate cessation in part by attenuating or blunting the effects of a concurrently smoked cigarette (Fant, Owen & Henningfield, 1999). If NRT does reduce the magnitude of the cognitive boost associated with smoking, then there is the potential for this effect to decrease the likelihood of a complete relapse to smoking after a lapse cigarette.

This study was designed to address the above questions in the following ways. First, to clarify what aspects of performance are altered by nicotine we incorporated established measures of specific attention [Attention Network Task (i.e., ANT; Fan et al., 2002)] and working memory subsystems [verbal and spatial N-back tasks]. In addition, we included the Digit Symbol Substitution Task (DSST; McLeod, Griffiths, Bigelow, & Yingling, 1982), a gold-standard performance outcome in the field of psychopharmacology with demonstrated sensitivity to nicotine's effects (e.g., Pickworth et al., 1996). To our knowledge the ANT and visual N-back tasks have never been used in a placebo-controlled study examining the effects of NRT and/or smoking in abstinent smokers, though they have been utilized to examine the effect of nicotine in non/never smokers (e.g., Blank, Kleykamp, Jennings, & Eissenberg, 2007; Kleykamp, Jennings, Blank, & Eissenberg, 2005). The present study also

has the potential to address concerns related to statistical power as we recruited a large sample of abstinent smokers (N = 124; 70 men) that was balanced for gender to address potential gender differences. Lastly, we selected transdermal nicotine in an effort to reduce within study variability of nicotine dosing as this mode of NRT requires no manipulation on part of the participants (for plasma levels see Kleykamp, Jennings, Sams, Weaver, & Eissenberg, 2008).

In summary, this study examined the effects of TN and concurrent smoking on specific cognitive processes. The study was part of a previously published experiment that examined the effects of TN on physiological, subjective, and smoking topography outcomes (Kleykamp et al., 2008). We predicted that TN would attenuate the cognitive effects of abstinence and concurrent smoking, and that these effects would differ as a function of gender.

Method

Recruitment and Inclusion/Exclusion Criteria

Participants were included for participation in this IRB-approved study if they: a) were 18 – 50 years of age, b) smoked 15 cigarettes/day for at least 2 years, c) provided an afternoon breath carbon monoxide (CO) level of 15 ppm (BreathCO; Vitalograph, Lenexa, KS), d) had a high school degree (or General Equivalency Diploma), and e) were healthy according to medical history and physical examination. Individuals were excluded if they a) reported a history of chronic health problems or psychiatric conditions, b) scored 17 or greater on the Beck Depression Inventory (Beck, Steer, & Brown, 1996), c) were pregnant or breastfeeding, d) were actively trying to quit or reduce their cigarette use, or e) had a previous head injury that required hospital care. Lastly, women were scheduled during the follicular to early luteal phase of their cycle (days 2 – 16, as indicated by self-report) to reduce menstrual cycle influence on study outcomes.

Demographic Summary

Fifty-four women and 70 men completed the study. Overall, mean screening expired CO levels were 23.5 (SD = 8.4) and participants were moderately tobacco dependent, as indicated by a mean score of 5.5 (SD = 1.9) on the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). There were no significant gender differences on the demographic characteristics most likely to influence cognitive performance: age (women = 31.1 years; SD = 9.5; men = 31.5 years, SD = 10.4), education level (women = 13.4 years, SD = 1.8; men = 13.7, SD = 1.7), and Beck Depression Inventory score (women = 4.2, SD = 4.0; men = 4.2, SD = 3.8). A complete description of the demographic characteristics can be found elsewhere (Kleykamp et al., 2008).

Procedure

After informed consent and eligibility for the study was established, participants completed four, randomly-ordered, 6.5-hour sessions corresponding to TN dose (0, 7, 14, or 21 mg). Conditions were double-blind, separated by at least 48 hours, and began at approximately 8AM. Tobacco abstinence (expired air CO levels 10 ppm) and negative urine pregnancy samples were confirmed prior to the start of each session. Approximately 3.5-hours after TN administration participants completed a computerized battery of cognitive tasks and 4-hours after TN administration the participants smoked an own-brand cigarette *ad libitum* (aside from the requirement of taking at least one puff). After completion of smoking, the cognitive tasks were re-administered. Participants were paid \$100 for each session and an additional \$100 after the final session.

In addition to the cognitive outcomes, physiological, subjective, and smoking behavior measures were administered and plasma nicotine samples were collected through an indwelling catheter throughout testing sessions. Outcomes associated with these measures are discussed in detail elsewhere (Kleykamp et al., 2008).

Study Medication and Placebo

The TN formulation was NicoDerm® CQ® (GlaxoSmithKline Consumer Healthcare, L.P., Pittsburgh, PA), TN dose was controlled by patch size, and all patches were administered on the participant's upper back, covered with taped gauze, and removed by staff with minimal participant contact (see Kleykamp et al., 2008).

Cognitive Tasks

Attention network task—The Attention Network Task (ANT) is designed to measure the alerting, orienting, and executive function aspects of attention (Fan et al., 2002). For each of 192 randomly generated trials, the participant was asked to indicate whether a target arrow presented in the center of the computer screen, above or below a fixation cross, pointed to the left or to the right. The target arrows were either flanked by distracting arrows pointing in the same direction, distracting arrows pointing in the opposite direction, or non-distracting dashes. In addition, there were four possible cueing conditions that indicated when and/or where the next trial would take place or provided no anticipatory information. The three components of the ANT, alerting, orienting, and executive function were calculated by carrying out subtractions among response times across the various flanker and cue conditions; other task details are described elsewhere (Kleykamp et al., 2005).

N-Back task—Separate N-back tasks were used to assess verbal (letters) and visuo-spatial (location) working memory. Participants determined whether or not each stimulus presented on a computer screen matched the stimulus that appeared “N” items back in the sequence. Two versions of each task were used, the 2-back and the 3-back. For each of the N-back task versions, accuracy was calculated as the proportion of hits (a participant responding “yes” when they should respond “yes”) minus the proportion of false positives (responding “yes” when they should say “no”). Response times to correct “yes” responses were also examined. Additional task details are described elsewhere (Kleykamp et al., 2005).

Digit symbol substitution task—The computerized version of the Digit Symbol Substitution Task (DSST; McLeod et al., 1982) consisted of randomly selected digits appearing at the center of the computer screen. The task consisted of a template presented on the top of a computer screen that included a series of digits (1–9) each shown above a corresponding, unique geometric pattern. During task completion, digits were randomly presented in the middle of the computer screen and participants were instructed to use a numeric keypad to indicate the geometric pattern associated with each digit during the 90 sec task. Scores on the DSST were composed of the number of correct responses minus the number of incorrect responses.

Missing Data and Data Analysis

Computer malfunction and human error led to some missing data points, which were excluded from the statistical analysis for a given task. Consequently, the final sample sizes for each task were: $n = 121$ (52 women) for the ANT, $n = 117$ (51 women) for the 2-back verbal task, $n = 118$ (53 women) for the 3-back verbal and visual tasks, $n = 116$ (52 women) for the 2-back visual task, and $n = 123$ (54 women) for the DSST.

Data analysis consisted of two steps. First, data collected immediately prior to smoking were entered into a mixed analyses of variance (ANOVA) with gender as a between-subject factor

and dose (four levels: 0, 7, 14, and 21 mg) as the within-subject factor. Then, all data collected before and after the cigarette smoking opportunity were entered into a separate mixed analyses of variance (ANOVA) in which gender was a between subject factor, and dose (four levels) and time (two levels: pre and post smoking) were within-subject factors. For all analyses, Huynh-Feldt corrections adjusted for violations of the sphericity assumption (Huynh & Feldt, 1976). After any significant F -value ($p < .05$), Tukey's HSD was used to explore possible differences among the means (e.g., Hurlburt, 1998).

Results

The dose effects of TN on cognitive performance after a period of tobacco abstinence (pre-smoking data) and any associated gender differences will be presented first. Then, the cognitive effects of smoking a cigarette (pre- and post-smoking data) and TN's influence on the effects of smoking will be reported, followed by any associated gender differences. An alpha level of .05 was used for all tests.

TN and the Effects of Tobacco/Nicotine Abstinence

TN-related suppression of abstinence-related cognitive decrements should be reflected by improvements in performance in active TN conditions relative to placebo (i.e., main effect of dose) prior to smoking. Statistical outcomes and descriptive statistics for these pre-smoking data can be found in Tables 1 and 2, respectively.

Attention network task—The only significant dose effect for the ANT occurred for executive function ($p < .05$; Table 1). As shown in Table 2, pre-smoking mean difference-score values for executive function were generally lower in the 7 mg condition relative to all other conditions suggesting improved performance (lower mean values for executive function indicate that distracting flankers were less detrimental to performance); however, only mean values in the 7 mg and 14 mg conditions were significantly different from one another. Significant effects of gender were not observed for any of the ANT outcomes (Table 1).

N-back tasks—Significant dose effects were observed on the 2-back verbal task (Table 1) such that participants were significantly faster to respond in the 14 and 21 mg conditions than in the placebo condition and more accurate in the 21 mg condition relative to placebo (see pre-smoking means, Table 2). In contrast, on the more challenging 3-back verbal task a significant main effect of dose was not observed ($p < .15$; Table 1), though the pattern of response time means suggests faster responding in active TN conditions relative to placebo (Table 2). Significantly faster responding as a function of TN dose was also observed for the 2-back visual task (Table 1); post hoc analysis revealed that participants were faster to respond in the 14 and 21 mg conditions relative to placebo on this task (Table 2). Although no significant effects of dose were observed for 2-back visual accuracy, there was a marginally significant trend ($p < .10$; Table 1) with the pattern of means suggesting improved accuracy in active TN conditions relative to placebo (Table 2). Similarly, though a dose effect for 3-back visual response time was only marginally significant ($p < .10$; Table 1), the direction of the means suggests faster responding in the active TN conditions relative to placebo (Figure 2). Further, a significant effect of dose was observed for 3-back visual accuracy (Table 1) such that performance was significantly better in all active TN conditions relative to placebo (see Table 2). Lastly, as also observed for the ANT, no significant effects of gender were observed for any of the above N-back tasks (Table 1).

DSST—As shown in Table 1, a significant effect of dose ($p < .01$) was observed for the DSST, such that the difference between correct and incorrect responses tended to be larger

in the active conditions relative to placebo indicating improved performance. However, the post hoc analyses revealed that the differences among the means were only significant for the 7 and 21 mg conditions relative to placebo (Table 2). No significant gender effects were observed (Table 1).

TN and Concurrent Smoking

Smoking-related boosts in cognitive performance should be reflected by improved performance post-smoking relative to pre-smoking (i.e., main effect of smoking). Further, TN-related blunting of the cognitive effects of smoking should be reflected by a smaller boost in performance from pre- to post-smoking in active TN conditions relative to placebo (i.e., interaction of smoking with TN dose). Main effects of dose will not be discussed because they are not representative of TN's effects alone given that they are collapsed across a smoking bout. Statistical outcomes and descriptive statistics for the pre vs. post smoking data can be found in Tables 2 and 3.

Attention network task—A significant main effect of smoking for alerting revealed that smoking improved performance ($p < .001$; Table 3): the post-smoking level (mean = 33.5 ms, SE = 1.8) of alerting regardless of TN dose was significantly higher than the pre-smoking level (mean = 25.9 ms, SE = 1.6), and this effect was not blunted by concurrent exposure to TN (i.e., a nonsignificant smoking by dose interaction; Table 3). Orienting and executive function were not significantly altered by smoking, nor was there a significant interaction of smoking by dose for these outcomes (Table 3). The only gender-related effect among the ANT measures was a main effect of gender for executive function ($F(1, 119) = 4.4, p < .05$). Overall, independent of smoking and TN, women's executive function mean difference scores were higher (mean = 84.7 ms, SE = 5.0) compared to men's (mean = 70.8 ms, SE = 4.4).

N-back tasks—Smoking significantly improved performance on both verbal tasks as reflected by faster responding and increased accuracy post-smoking relative to pre-smoking (i.e., significant main effects of smoking; Table 3). Both the 2-back and 3-back verbal response time effects were qualified by a smoking by dose interaction (Table 3) such that smoking-related reductions in response time were smaller in the TN conditions relative to placebo (see Table 2). More specifically, difference score calculations between pre- and post-smoking values for the 2-back task were as follows: placebo = 150.91 ms, 7 mg = 98.97 ms, 14 mg = 86.96 ms, and 21 mg = 84.21 ms. The incremental reductions in the size of the difference score values suggest that TN dose-dependently blunted the cognitive effects of smoking. However, post-hoc analyses revealed that responding was significantly faster post-smoking relative to pre-smoking in all TN conditions, suggesting that the effects of smoking were not completely attenuated by TN (Table 2). Similar to the 2-back task, smoking-related reductions in response time (faster responding) on the 3-back verbal task were largest in the placebo condition. Post-hoc analyses revealed a significant reduction from pre- to post-smoking only in the 0 and 7mg conditions suggesting the higher doses of TN effectively attenuated reductions in response time. A near significant smoking by dose interaction was also observed for accuracy in the 3-back verbal task ($p = .05$, Table 3) with the direction of the means suggesting larger improvements in performance in the placebo condition following smoking relative to the active TN conditions with the exception of the 14 mg dose. A similar pattern of results was observed for the 2-back verbal task although the smoking by dose interaction was not significant.

The 2-back visual task included faster response times post-smoking relative to pre-smoking (see Table 3) with faster responding due to smoking most pronounced in the placebo condition, again suggesting TN-related blunting of smoking's effects (i.e., significant

interaction of smoking and dose; Tables 2 and 3). However, as with other outcomes post-hoc analyses revealed significant differences from pre- to post-smoking in the 0, 7, and 21 mg conditions suggesting incomplete attenuation of smoking's effects. Similarly, 3-back visual response time was faster after smoking (significant main effect of smoking; Tables 2 and 3) and this reduction did not differ as a function of TN dose as reflected by a non-significant smoking by dose interaction (Table 3). In contrast, no significant main effects of smoking, or smoking by dose interactions, were observed for accuracy on either the 2-back or 3-back visual tasks.

Overall there was only one effect of gender for all N-back outcomes: a significant main effect of gender was observed for response time on the 3-back visual task ($F(1, 116) = 4.8$, $p < .05$). Collapsed across TN dose and time, women were faster to respond (mean = 768.0 ms, SE = 23.0) compared to men (mean = 836.3 ms, SE = 20.8).

DSST—There was a main effect of smoking for the DSST (see Table 3) such that the difference between correct and incorrect responses was smaller pre-smoking (mean = 31.1, SE = 1.0) relative to post-smoking (mean = 34.0, SE = 0.9) indicating a smoking-related boost in performance (Table 2); these effects were independent of TN (non-significant interaction). There were also no significant effects of gender for this measure.

Discussion

One reason smokers continue to smoke despite the negative consequences is to prevent abstinence-related cognitive decrements (Patterson et al., 2010; Rukstalis et al., 2005). In addition, a large body of pre-clinical research demonstrates that nicotine improves a variety of cognitive outcomes providing evidence that smokers experience cognitive changes when smoking (e.g., Eddins et al., 2009; Levin, McClernon, & Rezvani, 2006; Poorthuis et al., 2009). Therefore, it is reasonable to assume that the efficacy of smoking cessation treatments such as nicotine replacement therapy might depend, at least in part, on the extent to which such treatments attenuate the abstinence-related cognitive impairments and/or smoking-related boosts in performance. The present large sample, placebo-controlled, laboratory-based study is the first to examine the effects of TN on the cognitive consequences of abstinence and concurrent smoking simultaneously. Findings from the study support the idea that TN boosts performance after a period of tobacco abstinence and attenuates some effects of concurrent smoking; effects that were not influenced by gender.

More specifically, TN administration, independent of gender and prior to smoking, significantly improved working memory (verbal and visual) and psychomotor (DSST) performance. These effects appeared to be dose-dependent as they were most often observed in the 21 mg TN condition relative to placebo. For the working memory outcomes, TN-related performance improvements were most robust for the 2-back verbal task. The pattern of means for other working memory outcomes also suggested TN-related performance improvements, though significant main effects of TN dose were not observed (e.g., 3-back verbal response time, 2-back visual accuracy; reasons for this are addressed below). Although the finding that NRT facilitated psychomotor/motor function confirms previous research (Heishman et al., 1994; Pickworth et al., 1996; but see also Evans et al., 2006), the working memory results are in contrast to existing studies that have found an absence of TN-related improvement in working memory (e.g., Ernst et al., 2001, Foulds et al., 1996; Sherwood et al., 1992, Warburton & Mancuso, 1998). One reason for the disparate findings could be that earlier work included small sample sizes (i.e., $N_s < 20$) and might have been underpowered to detect nicotine's effects on cognition. Importantly, our findings correspond to those of a recent report indicating that 2-back verbal response time in abstaining smokers

predicts relapse to smoking (Patterson et al., 2010). Thus, ameliorating such impairments with treatments such as TN may have the potential to increase cessation rates.

In contrast to working memory, TN had no reliable effects on the alerting, orienting, or executive function aspects of attention. Although a main effect of TN was observed for executive function, follow up post hoc analyses revealed no significant differences between placebo and active TN conditions (see Table 2) suggesting the effect was not reliable, a result that is in keeping with previous work (Cook et al., 2003; Foulds et al., 1996; Mancuso et al., 1999b). Similarly, the absence of effects on alerting and orienting outcomes match null results reported in other studies (AhnAllen et al., 2008; Cook et al., 2003; Knott et al., 1999; Snyder & Henningfield, 1989; see also, Atzori et al., 2008; Parrott & Craig, 1992, Mancuso et al., 1999a, Wesnes et al., 1983).

A novel aspect of the present study was the examination of smoking alone and in combination with TN on cognitive performance outcomes. Consistent with our expectations, smoking, independent of TN condition, improved performance across most cognitive measures (i.e., alerting, response time and accuracy on both verbal working memory tasks, response times for the 2- and 3-back measures of visual working memory, and psychomotor function). TN attenuated the effects of smoking for some outcomes, including both versions of the verbal task and the 2-back visual task. For these tasks, smoking-related reductions in response time were smaller as TN dose increased suggesting some attenuation of the cognitive effects of smoking; however, attenuation was not complete as smoking-related reductions in reaction time, even at the highest dose of TN, were still observed (see Table 2). Furthermore, TN had no influence on smoking-related improvements for alerting attention and psychomotor function, as evidenced by a non-significant dose by time interaction. Therefore, smoking-related improvements in cognitive performance were observed across several outcomes and boosts in performance were only partially attenuated by TN. These findings are particularly important given the impact of TN on the cognitive effects of concurrent smoking has not been reported elsewhere.

In addition, our results yielded no evidence that the cognitive effects of TN or concurrent smoking differed as a function of gender (only main effects of gender were observed). The absence of gender differences is in contrast to previous reports (i.e., Myers et al., 2008 (N = 28); Trimmel & Wittberger, 2004 (N = 12)). Given the large sample size in the present study, we speculate that there are either no gender differences with regards to the outcomes in the present study, or if such differences do exist they are not large and likely not clinically relevant. However, it is possible that our sample population was inherently different from previous studies and that the particular variables, such as genetic polymorphisms, might account for gender differences in the cognitive effects of nicotine reported elsewhere.

When considering the aforementioned conclusions, three potential limitations of the present study should be taken into account: 1) statistical power, 2) practice effects, and 3) lack of baseline cognitive assessment. Although every effort was made to boost statistical power, including a large sample size and a within-subject design, the use of a conservative post hoc test such as Tukey's HSD limited statistical sensitivity. Such limitations on power were most evident when a significant F-value for a smoking by dose interaction was observed but no significant differences between pair wise comparisons of means were found upon application of the Tukey's. Despite such instances our use of Tukey's HSD maintained Type 1 error rate and thus limited the reporting of spurious findings.

In addition, practice effects associated with repeated task administrations might account for some variability in the effects of smoking or TN on the cognitive outcomes. The influence of smoking on performance was confounded by timing — task completion after smoking

always included pre-smoking experience with the task. Thus, smoking-related boosts in performance could be attributable to practice and analysis of the data as a function of session number indicated that performance on most measures improved as session number increased. However, these session-related effects were controlled by TN dose randomization across sessions.

One final concern is the lack of pre-deprivation baseline levels of cognitive functioning (e.g., performance prior to tobacco abstinence) in the present study. Such a condition is important for assessing the effects of tobacco withdrawal on performance (Heishman et al., 1994). Therefore, we cannot say with absolute certainty that TN-related performance increases were a result of ameliorating withdrawal and returning the smoker to a pre-deprivation baseline, or were instead due to absolute cognitive enhancement of performance. However, our results do speak to the effects of TN on “smoking-abstinence” as abstinence was biochemically verified (plasma nicotine and carbon monoxide levels) prior to beginning each study session and volunteers were monitored closely for 4 hours prior to cognitive testing while waiting for TN plasma nicotine levels to rise.

In sum, our study found that TN improves some aspects of performance after a period of tobacco abstinence and partially attenuates some of the cognitive boosts associated with smoking. Our observation that the highest dose of TN (21mg) was most reliable in influencing cognition is relevant for clinicians who might be contemplating the best dose to prescribe to smokers who are concerned with the cognitive consequences of a cessation attempt. Of equal note are the several cognitive outcomes in the present study that were either not altered by TN (attention performance prior to smoking; non-attenuation of alerting and psychomotor boosts from smoking), or were only partially affected (selective aspects of working memory performance related to smoking). Future research might aim to explore these shortcomings of TN in greater detail and investigate supplemental treatments that can address the full range of cognitive changes associated with a quit attempt. For example, it might be the case that non-nicotine factors associated with smoking (e.g., touch or taste of a cigarette) might affect cognition and pairing NRT with such stimuli (e.g., a denicotinized cigarette) might more adequately facilitate a cessation attempt (Kleykamp et al., 2007; Perkins, Sayette, Conklin, & Caggiula, 2003; Rose, 2006).

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Table 1

Results of statistical analyses for withdrawal suppression: cognitive outcomes.

Outcome Measures	Dose		Gender		Dose by Gender	
	F	p	F	p	F	p
Attention Network Task ^a						
Alerting	<1	n.s.	<1	n.s.	<1	n.s.
Orienting	2.1	n.s.	<1	n.s.	<1	n.s.
Executive function	4.6	<.01	2.8	n.s.	<1	n.s.
N-back tasks						
2-back phonological ^b						
Response time	3.5	<.05	1.8	n.s.	<1	n.s.
Accuracy	2.7	<.05	<1	n.s.	1.8	n.s.
3-back phonological ^c						
Response time	1.9	n.s.	3.3	n.s.	<1	n.s.
Accuracy	<1	n.s.	<1	n.s.	<1	n.s.
2-back visuospatial ^d						
Response time	5.7	<.01	1.1	n.s.	<1	n.s.
Accuracy	2.3	n.s.	1.4	n.s.	<1	n.s.
3-back visuospatial ^c						
Response time	2.2	n.s.	3.1	n.s.	<1	n.s.
Accuracy	3.8	<.05	2.9	n.s.	1.2	n.s.
Digit Symbol Substitution Task ^c						
correct-incorrect	4.8	<.01	<1	n.s.	<1	n.s.

Note.

^aN = 121: df dose, dose by gender (3, 357), df gender (1, 119)

^bN = 117: df dose, dose by gender (3, 345), df gender (1, 115)

^cN = 118: df dose, dose by gender (3, 348), df gender (1, 116)

^dN = 116: df dose, dose by gender (3, 342), df gender (1, 114)

^eN = 123; df dose, dose by gender (3, 363), df gender (1, 121)

Table 2

Mean results (SE) for cognitive measures by dose, pre- and post-smoking (collapsed across gender).

Outcome Measures		0 mg		7 mg		14 mg		21 mg	
		pre	post	pre	post	pre	post	pre	post
Attention Network Task									
	Alerting	25.8 (3.1)	35.9 (2.5)	26.1 (3.0)	29.8 (3.1)	23.3 (2.7)	33.7 (2.9)	28.4 (2.2)	34.6 (2.3)
	Orienting	39.1 (3.7)	42.9 (2.4)	46.5 (2.7)	43.3 (2.2)	38.7 (2.1)	39.2 (2.1)	40.3 (2.5)	37.1 (2.5)
	Executive Function	78.7 (4.7)	74.4 (3.7)	70.7 (3.5)	74.9 (2.9)	84.9 (5.0)	81.2 (4.4)	77.8 (4.0)	79.7 (3.9)
N-back tasks									
	2-back phonological								
	Response time (ms)	866.4 (23.5)	715.5 (19.0)	835.7 (18.6)	736.7 (19.8)	805.7 (21.6)	718.7 (19.9)	808.1 (20.5)	723.9 (17.8)
	Accuracy (%)	69.3 (2.0)	73.0 (2.0)	73.8 (1.9)	76.2 (2.0)	71.1 (2.1)	76.7 (1.9)	73.9 (1.8)	74.6 (1.9)
	3-back phonological								
	Response time (ms)	903.8 (20.3)	813.4 (19.7)	891.9 (20.5)	804.1 (17.9)	875.3 (21.5)	848.0 (20.2)	858.8 (17.6)	820.0 (20.6)
	Accuracy (%)	56.1 (2.2)	60.6 (2.2)	56.2 (2.2)	59.2 (2.1)	55.4 (2.1)	64.5 (0.2)	56.2 (2.2)	59.1 (2.2)
	2-back visuospatial								
	Response time (ms)	811.9 (19.6)	719.0 (19.0)	777.5 (21.8)	697.0 (18.4)	757.0 (21.0)	729.3 (18.8)	736.5 (20.4)	689.4 (18.7)
	Accuracy (%)	72.3 (2.1)	73.1 (2.3)	75.5 (2.2)	76.6 (2.0)	75.9 (2.0)	75.7 (2.1)	76.8 (1.9)	76.1 (2.1)
	3-back visuospatial								
	Response time (ms)	859.6 (22.8)	810.6 (19.1)	815.8 (20.5)	767.7 (17.8)	821.3 (21.0)	788.3 (21.9)	808.0 (21.6)	745.7 (18.8)
	Accuracy (%)	54.5 (2.5)	56.4 (2.6)	59.6 (2.5)	59.8 (2.6)	60.3 (2.3)	60.4 (2.4)	60.0 (2.5)	62.0 (2.5)
Digit symbol substitution task									
	correct-incorrect	28.8 (1.1)	32.7 (1.2)	31.9 (1.1)	34.9 (0.9)	31.2 (1.2)	34.6 (1.0)	32.4 (1.2)	34.0 (1.0)

Table 3

Results of statistical analyses for concurrent smoking: cognitive outcomes.

		Smoking		Smoking by Dose	
Outcome Measures		<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Attention Network Task ^a					
	Alerting	21.7	<.001	1.0	n.s.
	Orienting	<1	n.s.	<1	n.s.
	Executive function	<1	n.s.	1.9	n.s.
N-back tasks					
	2-back phonological ^b				
	Response time	146.1	<.001	3.5	<.05
	Accuracy	13.9	<.001	1.7	n.s.
	3-back phonological ^c				
	Response time	69.2	<.001	4.6	<.01
	Accuracy	24.9	<.001	2.7	=.05
	2-back visuospatial ^d				
	Response time	57.3	<.001	4.0	<.01
	Accuracy	<1	n.s.	<1	n.s.
	3-back visuospatial ^c				
	Response time	31.5	<.001	<1	n.s.
	Accuracy	1.0	n.s.	<1	n.s.
Digit Symbol Substitution Task ^e					
	correct-incorrect	73.4	<.001	1.8	n.s.

Note.

^aN = 121: df time (1, 119); df dose by time (3, 357)^bN = 117: df time (1, 115); df dose by time (3, 345)^cN = 118: df time (1, 116); df dose by time (3, 348)^dN = 116: df time (1, 114); df dose by time (3, 342)^eN = 123: df time (1, 121); df dose by time (3, 363)