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Cognitive Effects of Very Low Nicotine Content Cigarettes, with and without Nicotine
Replacement, in Smokers with Schizophrenia and Controls

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This work was conducted at the Center for Alcohol and Addiction Studies, Brown University,
Providence, RI, USA.

Abstract

Introduction: Beneficial effects of nicotine on cognitive functioning may contribute to the markedly high rates of smoking among people with schizophrenia. A reduction in the nicotine content of cigarettes to non-addictive levels is being considered as a regulatory strategy for reducing tobacco dependence in the United States. We examined whether switching to very low nicotine content (VLNC) cigarettes impairs cognitive functioning in smokers with and without schizophrenia, and whether nicotine replacement reverses these effects. **Methods:** Smokers with schizophrenia (SS, $n = 29$) and control smokers matched on smoking rate but without psychiatric illness (CS, $n = 28$) smoked usual-brand cigarettes, VLNC cigarettes while wearing 2 placebo patches (PLA), or VLNC cigarettes while wearing 2 nicotine patches totaling 42 mg (NIC) for 5 hours, and then completed computerized assessments of visual sustained attention, motor speed, visual working memory, processing speed, inhibitory control, and response variability. **Results:** Across conditions, SS were slower than CS in tasks of motor speed and visual working memory, and had poorer target detectability on a visual sustained attention task. Across groups, functioning in domains of visual sustained attention, inhibitory control, processing speed and response variability was impaired in the VLNC + PLA condition relative to the usual-brand and VLNC + NIC conditions. **Conclusions:** Dramatically reducing the nicotine content of cigarettes may impair cognitive functioning in heavy smokers with and without schizophrenia, but the use of nicotine replacement while smoking VLNC cigarettes may preserve cognitive functioning in these smokers.

Keywords: tobacco use disorder, comorbidity, denicotinized, nicotine replacement, attention

INTRODUCTION

Schizophrenia is associated with a 3-fold higher prevalence of cigarette smoking compared to the general population, and a 20% reduction in lifespan (Hennekens, Hennekens, Hollar, & Casey, 2005; McClave et al., 2010). One factor that may contribute to smoking persistence in this population is the disruptive effects of abstinence on neurocognitive functioning (Wing, Wass, Soh, & George, 2012). Cognitive deficits are considered a core feature of schizophrenia (Heinrichs & Zakzanis, 1998) and are associated with poor functional outcomes in these patients (Green, 1996). Consistent with this theory, experimental studies have found that smoking abstinence impairs attention and spatial working memory performance in smokers with schizophrenia (SS), and smoking reinstatement reverses these impairments (George et al., 2002; Sacco et al., 2005). Moreover, nicotine manipulations (as opposed to smoking manipulations) specifically affect performance on neurocognitive tasks tapping domains of attention, spatial organization, verbal memory and processing speed in SS (Weinberger, Creeden, Sacco, & George, 2007).

The US Food and Drug Administration (FDA) acquired regulatory authority over tobacco products in 2009, with the enactment of the Family Smoking Prevention and Tobacco Control Act (United States Congress. House Committee on Energy and Commerce, 2009). One of the top priorities of the FDA’s Center for Tobacco Products is to fund research studies that examine the effects of reducing the nicotine content of cigarettes (Ashely, Backinger, van Bommel, & Neveleff, 2014), which has been proposed as a means of reducing tobacco dependence in the US (Benowitz & Henningfield, 1994; Hatsukami, Benowitz, Donny, Henningfield, & Zeller, 2013). This regulatory strategy could be particularly beneficial to smokers, such as SS, who have difficulty accessing effective smoking cessation treatments. However, the effects of VLNC cigarette use in SS are largely unknown, and, given the effects of nicotine abstinence on

cognition in SS, it is possible that switching to VLNC cigarettes could negatively affect cognitive functioning.

To our knowledge, only one study has examined the effects of very low nicotine content (VLNC) cigarettes on cognitive functioning in SS (Smith, Singh, Infante, Khandat, & Kloos, 2002). That study found mixed support for the idea that switching to VLNC cigarettes may negatively affect cognitive performance. Therefore, more work is needed to examine the potential impact of VLNC cigarette use on cognitive performance in SS. Thus, the aim of the current study was to compare the effects of VLNC cigarette smoking, with and without 42 mg transdermal nicotine replacement, with usual-brand cigarette smoking on tasks assessing key domains of cognitive functioning in SS and control smokers without psychiatric illness (CS). We hypothesized that all participants would perform more poorly on these tasks after smoking VLNC cigarettes with placebo patches relative to usual-brand cigarettes, that these decrements would be greater in SS than CS, and that nicotine replacement would reverse these deficits in both groups.

METHOD

Participants

Participants were recruited from the local community for a study of the subjective and behavioral effects of VLNC cigarettes and nicotine replacement (Tidey, Rohsenow, Swift, Kaplan, & AhnAllen, 2013). Participants were 18+ years of age, had smoked 20-50 cigarettes per day for at least 1 year, and were highly nicotine-dependent (≥ 6 on the Fagerström Test for Nicotine Dependence, FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991). The Structured Clinical Interview for DSM-IV, Axis I (SCID-I; First, Spitzer, Gibbon, & Williams,

1994) was used to confirm diagnoses in SS and ruled out current Axis I psychiatric illness in CS. Exclusionary criteria included medical conditions that precluded transdermal nicotine use, positive pregnancy or drug toxicity tests at baseline, or positive breath alcohol level at any session. This study was approved by the Brown University Institutional Review Board.

Procedures

Participants underwent an initial session in which they provided a breath carbon monoxide (CO) sample and completed demographic and smoking history questionnaires. In SS, current psychiatric symptom levels were assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987).

In Session 2, participants completed a 5-hr assessment of smoking topography while smoking their usual-brand cigarettes using a Clinical Research Support System (CReSS; Borgwaldt KC, Richmond, VA) device. In the remaining sessions, participants underwent the following conditions during 5-hr periods, with order counterbalanced across participants: VLNC cigarettes + 42 mg transdermal nicotine replacement (NIC), VLNC cigarettes + placebo patches (PLA), no cigarettes + NIC, no cigarettes + PLA, usual brand cigarettes. After these 5-hr periods, participants completed measures of cigarette craving, nicotine withdrawal symptoms and cognitive performance, followed by an assessment of usual-brand smoking behavior. The current report focuses on comparing the effects of the usual-brand, VLNC + PLA and VLNC + NIC conditions on cognitive performance in SS and CS; effects of all conditions on craving, withdrawal symptoms and usual-brand smoking behavior have been reported (Tidey et al., 2013). The VLNC cigarettes in this study (Quest 3; Vector Tobacco, Timberlake, NC) contained less than 0.05 mg nicotine and 10 mg tar. To hold smoking behavior constant across sessions,

participants were cued to smoke the VLNC or usual-brand cigarettes according to the rate of their usual-brand smoking from Session 2. PLA and NIC patches (GlaxoSmithKline, Parsippany, NJ) were applied under double-blind conditions to participants' upper arms (one per arm), for a total of 0 or 42 mg NIC. A NIC dose of 42 mg was chosen given that 21 mg NIC had no effect on craving, withdrawal symptoms or usual-brand smoking in SS in a previous study (Tidey, Rohsenow, Kaplan, Swift, & Adolfo, 2008).

Cognitive Measures

Participants completed the Conners' Continuous Performance Test II (CPT II; Conners & MHS Staff, 2000), and the Motor Screening (MOT), Rapid Visual Information Processing (RVP), Delayed Matching to Sample (DMS; 12-sec delay condition) and Simple Reaction Time (SRT) tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Cambridge Cognition, Cambridge UK; Barnett et al., 2010). Cognitive domains of interest were assessed using the following variables from these tests: basic visual and motor functioning were assessed using the MOT mean latency variable, visual sustained attention was assessed using the percent omission errors variable from the CPT-II and the target detection (A') variable from the RVP, visual working memory was assessed using the accuracy (percent correct) and response latency variables from the DMS-12, inhibitory control was assessed using the percent commission errors variables from the CPT-II and SRT, processing speed was assessed using hit reaction time (RT) variables from the RVP and CPT-II, and response variability was assessed using the hit rate RT standard error variable from the CPT-II. The CPT-II, CANTAB, and other tasks assessing these domains have been found to be sensitive to smoking or nicotine manipulations in SS or CS in previous studies (Chamberlain et al., 2012; Dépatie et al., 2002; George et al., 2002; Hong et al.,

2011; Myers et al., 2004; Sacco et al., 2005; Smith et al., 2002; Smith et al., 2006). The CPT-II was administered on a Dell desktop computer and the CANTAB tests were administered on a Dell laptop computer with a 15” monitor and a touchscreen overlay (MagicTouch, Keytec, Inc.). Participants began with the MOT test, followed by the RVP, SRT, DMS and CPT-II tests; alternate test versions, when available, were used across sessions to reduce practice effects.

Data Analysis

Independent-samples *t*-tests and chi-square tests were performed to examine group differences on demographic and smoking history measures. Analysis of Variance (ANOVA) or Multivariate Analysis of Variance (MANOVA) tests were performed to examine the impact of Group (SS, CS) and Condition (VLNC + PLA, VLNC + NIC, usual-brand cigarettes) on variables within each domain; significant MANOVAs were followed by univariate ANOVAs and Bonferroni-corrected pairwise comparisons. Sphericity was evaluated using Mauchly’s *W* and, where violated, Greenhouse-Geisser corrections were implemented. Because the CANTAB battery was initiated after the CPT II, sample sizes are smaller for domains that include measures from CANTAB tasks; 29 SS and 28 CS completed the CPT II and 21 CS and 18 SS completed all cognitive tests. One outlier value (4 standard deviations about the mean) was removed from the data. Analyses were conducted with SPSS version 22 (IBM). Significance level was set at $p < 0.05$. Effect sizes (partial eta squared, η_p^2) are provided, with $\eta_p^2 \leq .05$ indicating small, $\eta_p^2 = .06 - .13$ indicating medium and $\eta_p^2 \geq .14$ indicating large effect sizes (Cohen, 1988). Note that speed of performance in the MOT, RVP and CPT-II tasks may be described as “latency” or “reaction time”, given that these terms are used distinctly according to each task.

RESULTS

Sample Characteristics

There were no significant differences between SS and CS on demographic or smoking variables including age, education, gender, race, ethnicity, CO level, cigarettes smoked per day, or FTND score (Table 1). SS had mild psychiatric symptom levels, similar to other studies of this type (e.g., George et al., 2002; Sacco et al., 2005).

Motor Speed

The mixed factorial ANOVA indicated a significant Group effect on mean latency in the MOT task ($F(1, 41) = 10.51, p < .01, \eta_p^2 = .20$). Across conditions, SS were slower to select a target than CS (Table 2). The Condition main effect and Group x Condition interaction on motor speed were not significant.

Visual Sustained Attention

MANOVA results indicated a significant Group effect on visual sustained attention measures (Pillai's Trace = .28, $F(2, 37) = 7.08, p < .01, \eta_p^2 = .28$). Follow-up univariate ANOVAs indicated that SS exhibited poorer RVP detectability (A') than CS ($F(1, 38) = 8.10, p < .01, \eta_p^2 = .18$). There was also a significant main effect of condition on this domain (Pillai's Trace = .27; $F(4, 35) = 3.26, p < .05, \eta_p^2 = .27$). Follow-up univariate ANOVAs indicated trend-level effects of condition, with medium effect sizes, on each measure (RVP A' : $F(1.5, 58.6) = 3.14, p = .06, \eta_p^2 = .08$; CPT omission errors: $F(1.7, 65.3) = 2.95, p = .07, \eta_p^2 = .07$). Across both groups, errors tended to be higher in the VLNC+PLA condition relative to the Usual Brand or VLNC+NIC conditions (Table 2). The Group x Condition interaction was not significant.

Visual Working Memory

MANOVA results indicated a significant Group effect on visual working memory measures (Pillai's Trace = .25, $F(2, 36) = 5.87, p < .01, \eta_p^2 = .25$). Follow-up univariate ANOVAs indicated that SS were slower to correctly identify DMS-12 targets than CS ($F(1, 37) = 8.66, p < .01, \eta_p^2 = .19$; Table 2). The Condition main effect and the Group x Condition interaction were not significant.

Inhibitory Control

MANOVA results indicated a significant Condition effect on measures of inhibitory control (Pillai's Trace = .46, $F(4, 36) = 7.58, p < .001, \eta_p^2 = .46$). Follow-up univariate ANOVAs indicated significant effects of Condition on each measure (CPT commission errors: $F(2, 78) = 5.23, p < .01, \eta_p^2 = .12$; SRT commission errors: $F(1.6, 62.7) = 14.11, p < .001, \eta_p^2 = .27$). Post-hoc comparisons indicated that participants made more CPT commission errors in the VLNC+PLA condition than in the Usual Brand condition, with errors in the VLNC+NIC condition intermediate between the other two conditions (Table 2). Similarly, participants made significantly more SRT commission errors in the VLNC+PLA condition than in the Usual Brand or VLNC+NIC conditions, which did not differ from each other. The Group main effect and the Group x Condition interaction were not significant.

Processing Speed

There was a significant Condition main effect on measures of processing speed (Wilk's $\lambda = .67, F(4, 35) = 4.32, p < .01, \eta_p^2 = .33$). Follow-up univariate ANOVAs indicated significant

effects of condition on each measure (RVP latency: $F(2, 76) = 5.68, p < .01, \eta_p^2 = .13$; CPT hit RT: $F(1.5, 56.4) = 6.12, p < .01, \eta_p^2 = .14$). Across both groups and in both tasks, processing speed was significantly longer in the VLNC+PLA condition than in the Usual Brand or VLNC+NIC conditions, which did not differ from each other (Table 2). The Group main effect and the Group x Condition interaction were not significant.

Response Variability

There was a significant main effect of Condition on CPT-II hit reaction time standard error ($F(2, 110) = 6.82, p < .01, \eta_p^2 = .11$). Simple effects tests indicated that error variability was significantly higher in the VLNC+PLA condition than in the Usual Brand or VLNC+NIC conditions, which did not differ from each other (Table 2). The Group main effect and the Group x Condition interaction were not significant.

DISCUSSION

The findings from this study indicate that acute use of VLNC cigarettes, compared to usual-brand cigarettes, negatively affected attention, inhibitory control, processing speed and response time variability in both SS and CS, and that 42 mg NIC reversed this impairment. These findings contrast with our previous report that smoking VLNC cigarettes without co-administration of nicotine was as effective as smoking usual-brand cigarettes at reducing cigarette craving, nicotine withdrawal symptoms and usual-brand smoking in SS and CS (Tidey et al., 2013). As impairments in these domains are thought to have direct implications for the functional outcomes of tobacco users, including smokers with schizophrenia (Mohamed et al., 2008), the current findings suggest the need to consider adjunctive nicotine and alternative

agents for preservation of cognition in all smokers, should cigarette nicotine content be reduced in the future by regulatory authorities.

The inclusion of non-psychiatric smokers matched on daily smoking rate is an important feature of this study. While some studies have found that SS are more sensitive than CS to the effects of nicotine or smoking manipulations on cognitive measures, these effects differ by task and study. For example, Dépatie et al. (2002) found that SS were more sensitive than CS to the effects of NIC on a measure of sustained attention (CPT hit rate), but not on measures of inhibitory control or processing speed (CPT commission errors and reaction time). Sacco et al. (2005) found that SS were more sensitive than CS to the effects of smoking abstinence on visuospatial working memory, but not on sustained attention (CPT II hit rate). Others, as in the present study, have not found that SS and CS differ in their responses to nicotine manipulations (Hahn et al., 2013, Hong et al., 2011). Some of this inconsistency may be due to different demands of the tasks involved; for example, the visual working memory task in the current study appears less demanding than that used by Sacco et al. (2005). Thus, more demanding tasks may reveal differential effects of nicotine manipulations on cognitive performance in SS vs. CS.

Given the FDA’s interest in a nicotine regulatory policy, it is notable that few studies have examined the acute or long-term effects of VLNC cigarette smoking in people with psychiatric illness, who smoke almost half of the cigarettes consumed in the US (Lasser et al., 2000). A nicotine regulatory strategy could be particularly effective for helping these smokers quit smoking, and additional research on the potential effects of nicotine regulation on health and psychiatric measures in these smokers is urgently needed to inform the empirical basis for this regulatory policy.

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DECLARATION OF INTERESTS

The authors have no conflicts of interest to report.

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Table 1:

Baseline Characteristics of Smokers with Schizophrenia (SS) and Control Smokers (CS)

	SS	CS	SS vs. CS	
	(<i>n</i> = 29)	(<i>n</i> = 28)	Statistic	<i>p</i>
Age [<i>M</i> (<i>SD</i>)]	46.4 (8.1)	45.1 (11.0)	$t_{55} = 0.50$	0.62
Male	62%	57%	$\chi^2(1) = 0.14$	0.71
Education (years)	12.0 (2.2)	12.4 (1.8)	$t_{55} = 0.68$	0.50
Race			$\chi^2(4) = 3.29$	0.51
White	76%	61%		
Black/African-American	14%	29%		
American Indian/Alaskan Native	7%	4%		
Asian-American	0%	4%		
Multiracial/Other	3%	4%		
Hispanic ethnicity	0%	4%	$\chi^2(1) = 1.05$	0.31
FTND score	6.9 (1.5)	6.9 (1.8)	$t_{55} = 0.01$	0.99
Cigarettes per day	25.8 (10.0)	24.3 (6.9)	$t_{55} = 0.64$	0.52
Baseline breath CO level (ppm)	33.1 (24.6)	27.6 (14.3)	$t_{55} = 1.03$	0.31
PANSS Total Score	52.6 (14.7)			
Antipsychotic Drug Class	69% atypical 17% typical 7% both			

Note: FTND, Fagerström Test for Nicotine Dependence; CO, Carbon monoxide; ppm, parts per million; PANSS, Positive and Negative Syndrome Scale.

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Table 2. Cognitive task performance (Mean [SD]) by group and experimental condition.

	Control Smokers			Smokers with Schizophrenia		
	Usual Brand	VLNC + PLA	VLNC + NIC	Usual Brand	VLNC + PLA	VLNC + NIC
<i>Motor Speed</i>						
MOT latency **	887 (271)	919 (240)	896 (264)	1162 (401)	1190 (394)	1096 (307)
<i>Visual Sustained Attention</i> ¹						
CPT-II Omissions (%)	1.40 (2.82)	3.00 (5.71)	1.19 (2.48)	2.83 (5.33)	3.89 (7.63)	1.94 (2.52)
RVP A' **	0.99 (0.02)	0.98 (0.03)	0.99 (0.02)	0.95 (0.06)	0.96 (0.04)	0.97 (0.03)
<i>Visual Working Memory</i>						
DMS 12s accuracy	81.0 (20.5)	82.9 (17.1)	84.8 (17.8)	82.2 (22.6)	71.1 (27.6)	75.6 (18.9)
DMS 12s latency **	3009 (635)	3144 (1153)	2969 (1030)	3917 (1406)	3972 (1293)	4130 (1863)
<i>Inhibitory Control</i>						
CPT-II Commissions (%) ++	32.6 (25.4) ^a	38.1 (28.1) ^b	37.8 (29.4) ^{ab}	32.1 (20.4) ^a	39.1 (22.1) ^b	38.4 (17.1) ^{ab}
SRT Commissions (%) +++	1.13 (1.32) ^a	2.00 (1.83) ^b	1.09 (1.65) ^a	0.67 (1.64) ^a	2.94 (3.06) ^b	1.22 (2.98) ^a
<i>Processing Speed</i>						
RVP latency ++	346 (72.8) ^a	367 (62.6) ^b	346 (71.0) ^a	407 (122) ^a	426 (112) ^b	382 (109) ^a
CPT-II Hit RT ++	377 (70.1) ^a	407 (94.3) ^b	382 (77.9) ^a	428 (79.9) ^a	442 (87.3) ^b	413 (78.9) ^a
<i>Response Variability</i>						
CPT-II Hit RT s.e. ++	6.9 (3.8) ^a	9.0 (6.2) ^b	7.4 (5.7) ^a	8.5 (7.1) ^a	11.4 (8.1) ^b	8.4 (5.3) ^a

Note. VLNC = Very low nicotine content cigarette; PLA = Placebo patch condition; NIC = 42 mg Nicotine patch condition; MOT = CANTAB Motor Screening Test; CPT-II = Continuous Performance Test II; DMS = CANTAB Delayed Matching to Sample test; RVP = CANTAB Rapid Visual Information Processing test; SRT = CANTAB Simple Reaction Time test; RT = reaction time; s.e. = standard error.

Asterisks indicate significant effects of Group (** p < .01).

Plus signs indicate significant effects of Condition (++ p < .01; +++ p < .001; conditions with different letters (a, b) are significantly different.

¹MANOVA results indicated a significant effect of Condition on this domain, but follow-up univariate ANOVAs examining effects on each task were not significant.