

Reactions to Reduced Nicotine Content Cigarettes in a Sample of Young Adult, Low Frequency Smokers

Psychopharmacology

Maggie M. Sweitzer, Ph.D.¹, Lauren R. Pacek, Ph.D.¹, Rachel V. Kozink, M.S.¹, Erin Locey, B.S.¹, Scott H. Kollins, Ph.D.¹, Eric C. Donny, Ph.D.², & F. Joseph McClernon, Ph.D.¹

¹Department of Psychiatry & Behavioral Sciences, Duke University Medical Center

²Department of Physiology & Pharmacology, Wake Forest School of Medicine

Supplementary Information

Research Cigarettes

The study utilized SPECTRUM research cigarettes made available through the NIDA drug supply. Three different cigarettes with the following characteristics were used (yield and nicotine content approximate and as characterized by both NIDA and CDC:

Normal nicotine content (NNC) cigarettes. Cigarettes in the NNC condition had 0.8 nicotine yield with 15.8 mg/g nicotine content and 10.5 mg tar yield (non-menthol: SPECTRUM NRC 600, menthol: SPECTRUM NRC 601). The nicotine and tar yields of the NNCs are comparable to those of commercially available cigarettes in the U.S.

Intermediate nicotine content (INC) cigarettes. Cigarettes in the INC condition had 0.12 nicotine yield with 2.4 mg/g nicotine content and 9.0 mg tar yield (non-menthol: SPECTRUM NRC 300, menthol: SPECTRUM NRC 301).

Very low nicotine content (VLNC) cigarettes. Cigarettes in the VLNC condition had 0.03 nicotine yield with 0.4 mg/g nicotine content and 9.0 mg tar yield (non-menthol: SPECTRUM NRC 102, menthol: SPECTRUM NRC 103).

Participant Characteristics: Other Tobacco Product Use

Participants were asked to indicate the number of days out of the past 30 in which a variety of different tobacco products were used. Participants endorsing multiple product use (including combustible cigarettes) were asked to indicate whether these products were used on the same or different days.

The mean number of days of other tobacco product use for the overall sample was 3.2 (SD=3.6); mode = 0; median = 2. When restricted to those endorsing any use ($n=62$), the mean was 4.5 (SD=3.5); mode = 2; median = 4. Products used, in order of popularity, were e-cigarettes (45% of days on which any non-cigarette tobacco products were used), blunts (33%), hookah (11%), cigarillos (4%), cigars (2%), and chewing tobacco (2%); little cigars, pipes, snus, and snuff each comprised less than 1% of product use.

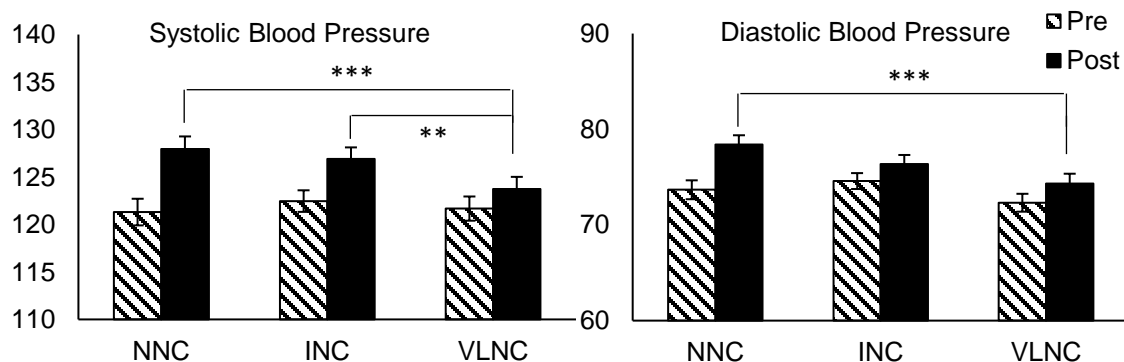
A total of 6 participants reported using other tobacco products on more days than cigarettes in the past month, while still not exceeding 15 total days of tobacco product use per month. Of these, 4 reported use of e-cigarettes on 12 to 15 days, while using cigarettes on 6 to 8 days. One participant reported smoking blunts on 8 days compared with 5 days of cigarettes; the remaining participant used e-cigarettes on 6 days and cigarettes on 4 days. All primary results were unchanged when these 6 individuals were excluded from analyses.

Fixed Dose Sessions Systolic and Diastolic Blood Pressure

Heart rate and blood pressure were assessed using a Criticare eQuality 506DN Vital Signs Monitor (<https://www.criticare.com/products/vital-sign-devices/equality-506dn>), with measurement cycle < 40 seconds.

During fixed dose sessions, both systolic, $F(1,85)=49.2$, $p<.001$, $\eta_p^2 = .37$, and diastolic, $F(1,85)=25.5$, $p<.001$, $\eta_p^2 = .23$, blood pressure increased from pre to post cigarette (see eFigure 1). Significant effects of Dose were observed for both measures: $F(2,170)=4.8$, $p<.01$, $\eta_p^2 = .05$, for systolic, and $F(2,170)=6.3$, $p<.01$, $\eta_p^2 = .07$, for diastolic. The Time x Dose interaction was also significant for both systolic, $F(2,170)=4.3$, $p<.05$, $\eta_p^2 = .05$, and diastolic, $F(2,170)=3.3$, $p<.05$, $\eta_p^2 = .04$, blood pressure. Dose effects were driven by significant differences during post-exposure measures. Specifically, both systolic and diastolic blood pressure were lower following exposure to VLNCs compared with NNCs, $t(86)=3.5$, $p<.001$, Hedge's $g_{av} = .36$, and $t(86)=4.0$, $p<.001$, Hedge's $g_{av} = .43$, for systolic and diastolic, respectively. Post-cigarette blood pressure measures in the INC condition were intermediate to the VLNC and NNC conditions, but direct comparisons did not survive Bonferroni correction, with the exception that systolic blood pressure was higher following INC exposure compared with VLNC, $t(86)=3.1$, $p<.005$, Hedge's $g_{av} = .27$. There were no pre-exposure differences between conditions.

eFigure 1. Systolic and diastolic blood pressure during fixed-dose sessions



eFigure 1. Systolic and diastolic blood pressure, mm Hg, taken before (striped bars) and after (solid bars) administration of cigarettes with normal nicotine content (NNC), intermediate nicotine content (INC), and very low nicotine content (VLNC) during fixed dose sessions. Error bars represent standard error of the mean. **Indicates statistical significance of $p < 0.01$; ***indicates $p < 0.001$.

eTable 1. Effect sizes* for pairwise comparisons between cigarette conditions for positive, negative, and dizzy subjective reactions.

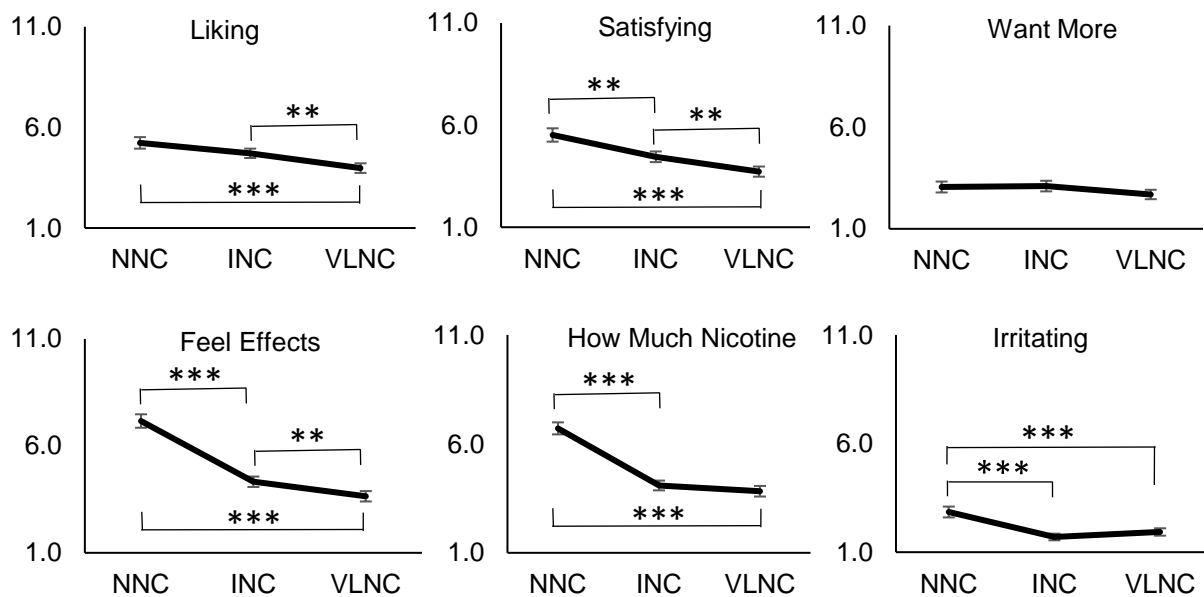
	NNC	INC
<i>Positive Reactions</i>		
VLNC	.80	.36
INC	.50	---
<i>Negative Reactions</i>		
VLNC	.54	<i>ns</i>
INC	.52	---
<i>Dizziness</i>		
VLNC	.86	<i>ns</i>
INC	.72	---

*Effect size is reported as Hedge's g_{av} . Effect size is shown only for comparisons reaching Bonferroni corrected statistical significance of $p < .017$, following significant omnibus F test.

Fixed Dose Sessions Subjective Reactions

Results of subjective ratings for additional items followed a similar pattern to that observed for composite scales of Positive and Negative reactions. Specifically, effects of Dose were observed for ratings of Liking, $F(2,172)=8.6$, $p<.001$, $\eta_p^2 = .09$; Satisfying, $F(2,172)=14.5$, $p<.001$, $\eta_p^2 = .14$; Feel the Effects, $F(2,172)=67.0$, $p<.001$, $\eta_p^2 = .44$; How Much Nicotine, $F(2,172)=51.9$, $p<.001$, $\eta_p^2 = .38$; and Irritation, $F(2,172)=12.6$, $p<.001$, $\eta_p^2 = .13$ (see eFigure 2). Ratings for all of these items were significantly higher in the NNC condition than both the INC and VLNC conditions (all p 's $<.01$), with the exception of Liking, which did not differ between NNC and INC, $t(86)=1.6$, ns. (See eTable 2 for effects sizes for post-hoc pairwise comparisons.) Interestingly, and consistent with composite scale ratings, ratings that reflected positive reactions, including Liking and Satisfying, were both significantly higher in the INC condition compared with VLNC, $t(86)=3.0$, $p<.005$, whereas ratings of How Much Nicotine and Irritation did not differ. Ratings of Feel the Effects were also significantly higher following INC compared with VLNC, $t(86)=3.0$, $p<.01$, although the effect was much smaller relative to comparisons with NNC (eTable 2). No effect of Dose was observed for ratings of Want More.

eFigure 2. Subjective reactions to individual items during fixed-dose sessions



eFigure 2. Subjective reactions following fixed dose administration of cigarettes with normal nicotine content (NNC), intermediate nicotine content (INC), and very low nicotine content (VLNC) during fixed dose sessions. Error bars represent standard error of the mean. **Indicates statistical significance of $p < 0.01$; ***indicates $p < .001$.

eTable 2. Effect sizes* for pairwise comparisons between cigarette conditions for subjective reactions on additional items.

	NNC	INC
<i>Liking</i>		
VLNC	.51	.33
INC	<i>ns</i>	---
<i>Satisfying</i>		
VLNC	.66	.33
INC	.37	---
<i>Feel the Effects</i>		
VLNC	1.35	.30
INC	1.10	---
<i>How Much Nicotine</i>		
VLNC	1.19	<i>ns</i>
INC	1.12	---
<i>Irritating</i>		
VLNC	.46	<i>ns</i>
INC	.59	---

*Effect size is reported as Hedge's g_{av} . Effect size is shown only for comparisons reaching Bonferroni corrected statistical significance of $p < .017$, following significant omnibus F test.

Associations between Demographic and Smoking Characteristics and Cigarette Choice

For continuous variables (e.g., age), univariate ANOVA with polynomial contrasts was used to examine group differences in demographic or smoking characteristics as a function of cigarette choice during the choice session. For categorical variables (e.g., sex), group differences were examined using Pearson Chi-Square tests. As shown in eTable 3, there were no significant differences between groups for any demographic or smoking history variable.

eTable 3. Demographic and baseline smoking characteristics as a function of cigarette choice during the choice session.

Variable	Cigarette Choice			P Value
	NNC (n= 37)	INC (n=22)	VLNC (n=28)	
Age, mean (SD)	21.2 (1.4)	21.1 (1.7)	21.0 (1.8)	.605
Sex, no. (%) Female	19 (51%)	11 (50%)	13 (46%)	.924
Cigs per month, mean (SD)	15.5 (15.7)	16.6 (9.8)	13.5 (6.6)	.507
Years smoking, mean (SD)	1.9 (2.2)	2.3 (2.0)	2.5 (1.6)	.202
Ever daily smoking, no. (%)	7 (19%)	5 (23%)	7 (25%)	.836
TU days per month, mean (SD)	9.3 (3.3)	9.6 (4.5)	10.7 (3.5)	.127
Menthol, no. (%)	14 (38%)	7 (32%)	9 (32%)	.852
HONC, mean (SD)	1.5 (1.5)	1.8 (1.6)	1.4 (1.9)	.822

TU: Tobacco use; HONC: Hooked on Nicotine Checklist; P Value reflects ANOVA linear contrast (for continuous variables) or Chi-Square (for categorical variables).