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BRIEF COMMUNICATION

# Preliminary Validity of the Modified Cigarette Evaluation Questionnaire in Predicting the Reinforcing Effects of Cigarettes That Vary in Nicotine Content

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Validity studies evaluating self-report measures in relation to behavioral preference of cigarettes varying in nicotine content are needed. The current study examined the relationship between ratings on the modified Cigarette Evaluation Questionnaire (mCEQ) and the relative reinforcing effects of Spectrum research cigarettes (15.8, 5.2, 2.4, 0.4 mg per gram of tobacco). Data for this secondary analysis were obtained from a double-blind study (Higgins et al., 2017) evaluating the subjective and reinforcing effects of Spectrum cigarettes under acute smoking abstinence. Current smokers ($N$ = 26) were recruited from three vulnerable smoking populations (economically disadvantaged women of reproductive age, opioid-maintained individuals, individuals with affective disorders). In Phase 1 (five sessions), the mCEQ (Satisfaction, Psychological Reward, Enjoyment of Respiratory Tract Sensations, Craving Reduction, Aversion subscales) was administered following ad lib smoking of Spectrum cigarettes and subscale differences scores were calculated by subtracting ratings of the 15.8 mg/g cigarette from ratings of the reduced nicotine content cigarettes. In Phase 2 (six sessions), participants completed six 2-dose concurrent choice tests. The relationship between mCEQ subscale difference scores from Phase 1 and nicotine dose choice from Phase 2 was examined using mixed-model repeated-measures analyses of variance. Higher Satisfaction and lower Aversion subscale difference scores were associated with choosing the 15.8 mg/g cigarette more than the 5.2, 2.4, and 0.4 mg/g cigarettes. Scores on the other mCEQ subscales were not associated with nicotine choice. These results provide support for validity of the mCEQ Satisfaction and Aversion subscales predicting the relative reinforcing effects and abuse liability of varying nicotine content cigarettes.



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***Public Health Significance***

To our knowledge this is the first systematic investigation examining the validity of a smoking self-report measure for predicting behavioral preference for cigarettes that vary in nicotine content. Results indicate that the Satisfaction and Aversion subscales independently predicted the relative reinforcing effects between a normal nicotine content cigarette and reduced nicotine cigarettes, suggesting that these subscales are valid tools for examining the abuse potential of varying nicotine content cigarettes.

*Keywords:* abuse liability, acute exposure, reinforcing effects, subjective effects, very low nicotine content cigarettes



In 2009, the U.S. Food and Drug Administration acquired regulatory authority over tobacco products, including the authority to reduce, although not eliminate, the nicotine content of cigarettes (Family Smoking Prevention & Tobacco Control Act, 2009). Benowitz and Henningfield (1994, 2013) hypothesized that mandating a reduction in the nicotine content of cigarettes would reduce smoking-related morbidity and mortality. Assessing the influence of nicotine content on the reinforcing effects of cigarettes is critical to informing tobacco regulatory policy regarding potential abuse liability of modified risk tobacco products. Studies using single-dose operant self-administration procedures suggest that very low nicotine content (VLNC) and normal nicotine content (NNC) cigarettes each maintain responding and are self-administered at similar rates (Shahan, Bickel, Madden, & Badger, 1999; Shahan, Bickel, Badger, & Giordano, 2001). However, when both cigarette types are available in concurrent choice arrangements, NNC are strongly preferred over VLNC cigarettes (Perkins, Grobe, Weiss, Fonte, & Caggiula, 1996; Perkins, Jacobs, Sanders, & Caggiula, 2002; Perkins, Kunkle, Karelitz, Michael, & Donny, 2016). Although controlled laboratory choice procedures are ideal for assessing the relative abuse potential of modified risk tobacco products, they are often time- and labor-intensive.

Self-report measures have been widely used as a proxy measure of reinforcing effects and associated abuse liability of modified risk tobacco products. Subscales measuring cigarette liking, satisfaction, taste, and enjoyment have been shown to be sensitive to nicotine content. Studies evaluating cigarettes that vary across a range of doses suggest that pleasurable subjective effects typically increase as a function of dose (Benowitz, Jacob, & Herrera, 2006; Hatsukami et al., 2013a; Higgins et al., 2017). Subjective experiences of nicotine toxicity may also be dose-dependent, with higher nicotine content cigarettes producing greater aversive effects (Benowitz et al., 2006; Henningfield et al., 1986; Pickworth, Moolchan, Berlin, & Murty, 2002).

Conversely, dose effects appear to be less pronounced on scales assessing craving and withdrawal (Hatsukami et al., 2013a; Pickworth et al., 2002).

To our knowledge, no studies have directly examined the relationship between subjective and behavioral measures of cigarette reinforcement across a range of nicotine doses. In a related study with oral tobacco products, Hatsukami and colleagues (Hatsukami, Zhang, O'Connor, & Severson, 2013b) had smokers sample different brands of snus and dissolvables and report subjective effects. Participants then chose which product they preferred to use during a subsequent clinical trial. Chosen products were rated significantly higher in terms of satisfaction and relief of withdrawal and lower in terms of aversive effects compared to other products during the initial sampling period.

A recent paper reported acute subjective and reinforcing effects of varying nicotine content cigarettes (0.4, 2.4, 5.2, 15.8 mg per gram of tobacco) among three vulnerable smoking populations (Higgins et al., 2017). Satisfaction subscale scores on the modified Cigarette Evaluation Questionnaire (mCEQ) increased as a function of dose whereas scores on the other mCEQ subscales were not dose dependent. Relative reinforcing effects assessed within free-operant concurrent choice tests indicated greater preference for the 15.8 mg/g compared to the 0.4 and 2.4 mg/g cigarettes but not the 5.2 mg/g cigarette. The purpose of the present study was to conduct a secondary analysis using these data to evaluate whether subjective responses to varying nicotine content cigarettes are associated with the relative reinforcing effects of these products.

## Method

Twenty-six current smokers were recruited from three vulnerable populations, namely socioeconomically disadvantaged women ($n = 9$), opioid-maintained patients ($n = 11$), and individuals with affective disorders ($n = 6$). These subpopulations were evaluated as they are disproportionately overrepresented among current smokers and may be at greater risk for nicotine dependence (Higgins et al., 2016). A complete description of the study procedures of the parent study can be found in Higgins et al. (2017). Details pertinent to the current investigation are described below.

### Participants

Recruitment was conducted through media platforms at the University of Vermont, Brown University, and Johns Hopkins University School of Medicine. Participants had to be 18 years of age or older, smoke 5 or more cigarettes per day, and provide a breath carbon monoxide (CO) sample (CoVita, Haddonfield, NJ) that exceeded 8 ppm (Jarvis, Tunstall-Pedoe, Feyerabend, Vesey, & Saloojee, 1987). A negative urine toxicology screen for illicit drug use except for cannabis and a breath alcohol sample less than 0.01% were also required (Alco-Sensor IV, Intoximeter, Inc., St Louis, MO; Rapid CHECK 9 panel Multi-Drug Test Card, Craig Medical, Vista, CA). Participants were excluded if they planned to quit smoking or regularly used other nicotine products. The local institutional review board at each participating research site approved this study, and all participants provided written informed consent. Demographic and smoking characteristics are presented in Table 1.

Table 1
*Baseline Characteristics by Subpopulation and for the Total Sample*

| | Disadvantaged women ($n$ = 9) | Opioid-maintained individuals ($n$ = 11) | Individuals with affective disorders ($n$ = 6) | Total sample ($N$ = 26) |
|---|---|---|---|---|
| Demographic characteristics | | | | |
| Age | 30.33 ± 1.62 | 40.72 ± 2.04 | 38.83 ± 2.32 | 36.69 ± 2.12 |
| % Female | 100 | 63 | 66 | 76 |
| % Caucasian | 44 | 90 | 100 | 76 |
| % Educational attainment ≤12 years | 100 | 45 | 49 | 65 |
| % Never married | 88 | 36 | 83 | 65 |
| Smoking characteristics | | | | |
| Cigarettes per day | 12.55 ± 1.29 | 22.81 ± 2.30 | 15.16 ± 1.47 | 17.50 ± 1.98 |
| Age started smoking regularly | 15.11 ± .39 | 15.27 ± .44 | 15.50 ± .40 | 15.27 ± .40 |
| Fagerstrom Test for Nicotine Dependence | 4.33 ± .55 | 6.09 ± .46 | 4.66 ± .56 | 5.15 ± .51 |
| % Menthol | 66 | 27 | 33 | 42 |

*Note.* Values represent mean ± *SE* unless otherwise specified.



## Research Cigarettes

Spectrum menthol and nonmenthol research cigarettes were manufactured by 22nd Century (Clarence, NY) in conjunction with National Institute on Drug Abuse. Characteristics of Spectrum cigarettes have been described previously (Donny et al., 2015). The different cigarettes contained 15.8, 5.2, 2.4, and 0.4 mg of nicotine per gram of tobacco (mg/g). At study onset participants choose menthol or nonmenthol cigarettes to smoke for the duration of the study.

## Modified Cigarette Evaluation Questionnaire (mCEQ)

To our knowledge, the mCEQ is the only instrument psychometrically validated for examining subjective effects of smoking. The mCEQ contains 5 independent subscales: Satisfaction ("Was smoking satisfying?", "Did the cigarette taste good?", "Did you enjoy smoking?"), Psychological Reward ("Did smoking calm you down?", "Did smoking make you feel more awake?", "Did smoking make you feel less irritable?", "Did smoking help you concentrate?", "Did smoking reduce your hunger for food?"), Enjoyment of Respiratory Tract Sensations ("Did you enjoy the sensations in your throat and chest?") and Craving Reduction ("Did smoking immediately reduce your craving for a cigarette?"), Aversion ("Did smoking make you dizzy?", "Did smoking make you nauseous?"). Each item is rated on a 7-point Likert scale ranging from 1 (*not at all*) to 7 (*extremely*). Convergent validity and reliability for each of the 5 subscales has been established across three independent samples (total $N$ = 1,565). Confirmatory factor analysis indicated that goodness of fit was > .90 and root mean square error of approximation was <.10 in each of the samples. Test–retest reliability for each subscale was also supported (mean r's > .70; Cappelleri et al., 2007).

**Procedure.** Participants completed 11 experimental sessions in two phases. Sessions ranged between 2 and 4 hours (≥48 hours between sessions). In Phase 1 (Sessions 1–5), subjective effects were assessed after participants sampled their usual brand and each of the experimental cigarettes. In Phase 2 (Sessions 6–11), nicotine choice was examined within six concurrent choice tests. Physiological measures were collected at the beginning of each session and participants were required to provide a breath CO sample that was <50% of their baseline CO level to meet the overnight smoking abstinence criterion. Participants were then seated in a ventilated room and were instructed to smoke 2 puffs of their usual brand cigarette followed by a 30-min wait period to equate time since last cigarette across participants.

**Phase 1 (Sessions 1–5).** Participants smoked their usual brand cigarettes in Session 1 to become familiar with the CReSS (Clinical Research Support System) smoking topography device (Borgwaldt KC, Richmond, VA) used in Sessions 2–5. Neither staff nor participants were blind to usual brand cigarettes. In Sessions 2–5, participants sampled the different dose research cigarettes, one dose per session. Research cigarette packs were letter coded and labeled corresponding to the four different nicotine doses. Order of exposure to the varying nicotine content cigarettes was randomized across participants. Both staff and participants were blind to the nicotine content of the research cigarettes and participants were informed that the aim of the study was to examine the impact of different nicotine levels in cigarettes. During each session, participants smoked two research cigarettes of equivalent nicotine content using the CReSS device. Participants smoked the first cigarette ad libitum. Participants were then encouraged to make written notes about the experimental cigarette. Notes could be referenced in Phase 2 when participants could choose between the varying nicotine content cigarettes. Approximately two minutes after extinguishing the first cigarette, participants smoked the second cigarette to practice the standard controlled puffing procedures (see below) that were used in Phase 2.

Immediately after smoking the second cigarette, subjective effects were assessed on the mCEQ.

**Phase 2 (Sessions 6–11).** Nicotine dose choice was examined using two-dose concurrent choice tests to assess preference between all dose-pairs of the 4 research cigarettes. Six dose comparison sessions, lasting 3 hours each, were conducted on separate days with 2 doses compared per session (i.e., 15.8 mg/g vs. 0.4 mg/g, 15.8 mg/g vs. 2.4 mg/g, 15.8 mg/g vs. 5.2 mg/g, 5.2 mg/g vs. 0.4 mg/g, 5.2 mg/g vs. 2.4 mg/g, 2.4 mg/g vs. 0.4 mg/g). Dose comparisons were conducted in random order and under double-blind conditions. Participants were given any notes they made in Phase 1 and were informed that they could choose to smoke as many or as few of either of the two research cigarettes during each

session. Puffs were earned by making 10 mouse clicks on one of two letter coded buttons presented on a computer screen that corresponded with two labeled research cigarette packs. After meeting the response requirement, participants took two puffs of the selected cigarette using controlled puffing procedures. Participants followed instructions displayed on a computer monitor that prompted them to inhale until 60-mL volume had been reached, then hold inhalation for 5-s followed by exhalation and a 25-s interpuff interval. Response options on the computer screen remained inactive for 3 min following each choice selection after which a new choice could be made. A representative number of sessions were monitored by staff to ensure adherence to controlled puffing procedures during choice sessions.

## Statistical Analysis

The focus of the analysis was on the three dose comparisons examining differences between the 15.8 mg/g (NNC) and each of the reduced nicotine content cigarettes (i.e., 15.8 mg/g vs. 0.4 mg/g, 15.8 mg/g vs. 2.4 mg/g, 15.8 mg/g vs. 5.2 mg/g). To quantify subjective evaluations on each of the mCEQ subscales assessed in Phase 1, difference scores were calculated by subtracting ratings for each of the reduced nicotine content cigarettes from ratings of the 15.8 mg/g cigarette. Difference scores ranged from (−6) to (+6) with higher scores reflecting greater subjective effects of the 15.8 mg/g cigarettes. Choices between the varying nicotine content cigarettes assessed in Phase 2 were determined by calculating nicotine choice ratios for each of the 3 dose comparisons using the following formula:

$$\frac{\text{total puffs earned for 15 . 8 mg/g}}{(\text{total puffs earned for a reduced nicotine cigarette} + \text{total puffs earned for 15.8 mg/g})}$$

Ratios were multiplied by 100 to produce a percentage, with higher percentages indicating more choices for the 15.8 mg/g cigarette. Demographic and smoking characteristics as well as mCEQ subscale difference scores and relative reinforcing effects did not differ between subpopulations, therefore data were collapsed across subpopulations prior to statistical analysis. Statistical Analysis Software (SAS) version 9.4, PROC MIXED procedure, was used for all analyses. To determine whether mCEQ subscale difference scores predicted nicotine dose choice, mixed-effects repeated-measures analysis of variance was used, with the dose comparison as the repeated (fixed) effect, the mCEQ subscale difference scores and the dose comparison × mCEQ subscale difference score interaction as fixed effects and subject as a random effect. mCEQ subscales that significantly predicted nicotine dose choice were then modeled simultaneously to determine the independent contribution of each mCEQ subscale on nicotine dose choice as well as interactive effects of dose comparison and mCEQ subscale difference scores on nicotine dose choice. Total puffs earned for experimental cigarettes was entered as a covariate in each of the models to account for within subject differences in absolute number of puffs earned. Nonsignificant interactions were dropped from the models. Significance for all tests was set at $p < .05$.

## Results

mCEQ subscale difference score means, standard errors (*SE*), and range are presented for each dose comparison in Table 2. As reported in Higgins et al. (2017), 66%, 61%, and 49% of responses were allocated to the 15.8 mg/g cigarette when it was paired with the 0.4, 2.4, and 5.2 mg/g cigarettes, respectively.

There was a significant main effect for the Satisfaction and Aversion subscale difference scores predicting nicotine dose choice across the three dose comparisons (both $p$s $\leq .02$). A one-point increase in Satisfaction subscale difference scores predicted a 7% increase in responding for the 15.8 mg/g cigarette relative to the reduced nicotine content cigarettes. Conversely, a one-point increase in Aversion subscale difference scores was associated with a 10% decrease in responses made for the 15.8 mg/g cigarette relative to the reduced nicotine cigarettes (see Figure 1). The interaction between dose comparison and mCEQ subscale difference scores was not significant, suggesting that the slopes across the three dose comparisons were similar (see Figure 1). Difference scores on the remaining three mCEQ subscales, Psychological Reward, Enjoyment of Respiratory Tract Sensations, and Craving Reduction, were not significantly associated with nicotine choice (all $p$s $> .21$).

A second model with Satisfaction and Aversion subscales entered simultaneously revealed that both subscales significantly predicted unique variance in nicotine choice (both $p$s $\leq .01$). The proportion of variance explained by the Satisfaction and Aversion subscales was similar to when each subscale was modeled separately and the interaction between dose comparison and each of these mCEQ subscales remained nonsignificant.

## Discussion

To our knowledge, this is the first systematic investigation examining the validity of a smoking self-report measure for predicting behavioral preference for cigarettes varying in nicotine content. Results indicate that the Satisfaction and Aversion sub-

Table 2
*Mean ± SE (Range) mCEQ Subscale Difference Scores by Dose Comparison*

| Measure | Dose comparison | | |
|---|---|---|---|
| | 15.8 vs. .4 mg/g | 15.8 vs. 2.4 mg/g | 15.8 vs. 5.2 mg/g |
| Satisfaction | .88 ± .40 (−1.6 to 4.3) | .48 ± .20 (−1.3 to 2.6) | .39 ± .23 (−1.3 to 3.0) |
| Psychological reward | .34 ± .26 (−2.2 to 3.4) | .40 ± .23 (−1.6 to 2.4) | .28 ± .23 (−2.0 to 3.6) |
| Enjoyment of respiratory tract sensations | .57 ± .35 (−3.0 to 4.0) | .34 ± .30 (−3.0 to 3.0) | .42 ± .22 (−2.0 to 3.0) |
| Craving reduction | .30 ± .41 (−5.0 to 4.0) | .34 ± .35 (−4.0 to 5.0) | .73 ± .28 (−3.0 to 4.0) |
| Aversion | .44 ± .28 (−2.0 to 3.5) | .15 ± .17 (−1.5 to 2.5) | .42 ± .21 (−1.0 to 3.5) |

*Note.* mCEQ = modified Cigarette Evaluation Questionnaire.

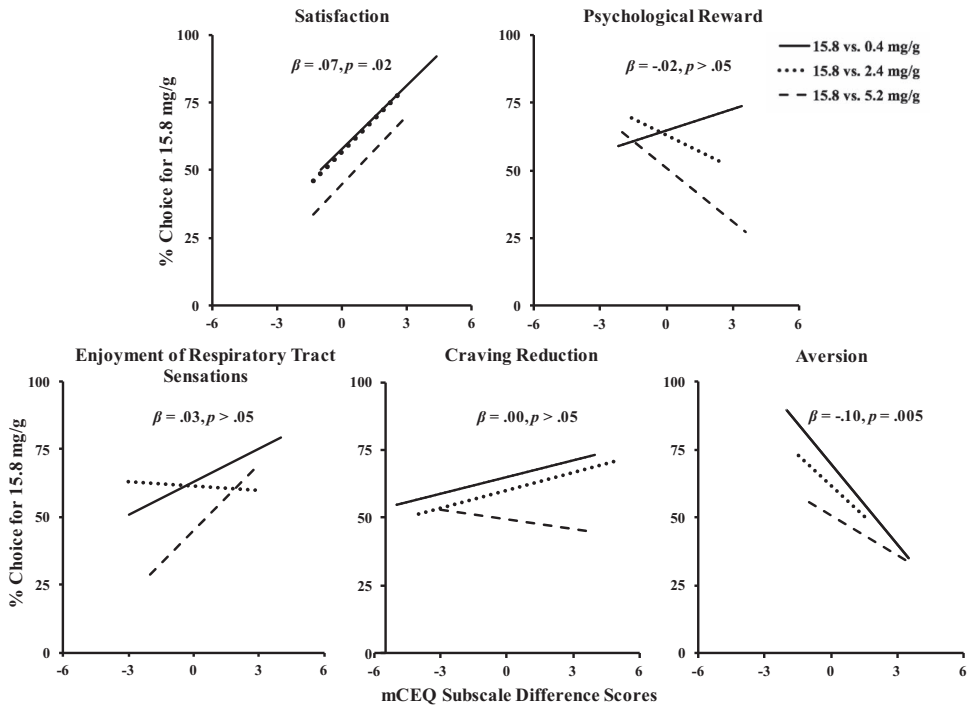


*Figure 1.* Panels show Satisfaction, Psychological Reward, Enjoyment of Respiratory Tract Sensations, Craving Reduction, and Aversion subscale difference scores predicting nicotine choice within the 15.8 mg/g vs. 0.4 mg/g, 15.8 mg/g vs. 2.4 mg/g, 15.8 mg/g vs. 5.2 mg/g dose comparison. The interaction between dose comparison and modified Cigarette Evaluation Questionnaire (mCEQ) subscale difference scores was not significant. β = the fixed effect estimate of the strength of the association between mCEQ subscale difference scores and nicotine choice across dose comparisons.

scales independently predicted the behavioral preference for a NNC research cigarette versus multiple reduced nicotine content cigarettes. The observation that Satisfaction subscale difference scores were associated with choice proportions is consistent with Hatsukami et al. (2013b), who found that scores on the Satisfaction subscale predicted both oral tobacco product choice as well as the amount of use of the chosen product during a subsequent 14-day trial period. Positive subjective experiences derived from tobacco products are believed in part to be the result of pharmacodynamic effects of nicotine on the central nervous system. Subscales such as satisfaction, liking, and enjoyment may provide an approximation of the influence of nicotine on neurobiological reward pathways and associated reinforcing properties that may underpin nicotine dependence (Shiffman & Kirchner, 2009).

The observation that Aversion subscale difference scores were associated with response allocation in the choice arrangement is consistent with Hatsukami et al. (2013b) and suggests that aversive effects such as dizziness, light headedness, and nausea, in combination with positive subjective effects likely play independent roles in determining the relative reinforcing effects of tobacco products varying in nicotine content. Conversely, Psychological Reward and Craving Reduction subscales that assess symptoms consistent with nicotine withdrawal were not associated with nicotine dose preference during choice tests. This suggests that these subscales are limited in their capacity to predict the relative reinforcing effects of varying nicotine dose cigarettes and perhaps other products. Both VLNC and NNC cigarettes have been shown to alleviate withdrawal symptoms such as irritability and anxiety following acute smoking abstinence, which may be the result of conditioned effects of smoking (Butschky, Bailey, Henningfield, & Pickworth, 1995).

These results should be considered in the light of some limitations. The sample comprised three vulnerable subpopulations of smokers. Although disadvantaged populations make up an increasingly large proportion of current smokers, future studies conducted among the general smoking population are warranted. Additionally, we intend to replicate this analysis among a larger sample which will allow assessment of subjective and reinforcing effects across all dose combinations. This study has several strengths that are worthy of note. First, to our knowledge, this is the first examination of the parametric relationship between subjective and reinforcing effects across a range of nicotine doses. Given that low and intermediate content cigarettes have only recently become available to the research community, several previous studies (Donny & Jones, 2009; Perkins et al., 1996; Rukstalis et al., 2005) evaluating subjective and reinforcing effects only compared NNC cigarettes with VLNC cigarettes and other studies administered cigarettes that differed in physical characteristics and non-nicotine tobacco constituents (Perkins et al., 1996; Rose, 2006; Rose, & Behm, 2004). Overall, the present study illustrates the importance of considering both positive and aversive subjective effects when evaluating the relative reinforcing effects and abuse potential of

tobacco and nicotine delivery products. Hence, it seems prudent for future studies to consider results across the Satisfaction and Aversion subscales to capture distinct and independent subjective effects likely to influence product choice and associated abuse potential.

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