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The Role of E-Liquid Vegetable Glycerin and Exhaled Aerosol on Cue Reactivity to Tank-Based Electronic Nicotine Delivery Systems (ENDS)

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Abstract

Rationale: Electronic nicotine delivery systems (ENDS or e-cigarettes) share salient features of combustible smoking, such as inhalation and exhalation behaviors, and evidence indicates that first and second-generation ENDS generalize as smoking cues. The present study examined whether newer, tank-based third-generation ENDS (“mods”) also evoke smoking urges, and whether enhancing the visibility of exhaled aerosol clouds - by increasing the e-liquid vegetable glycerin (VG) content - strengthens the cue salience of ENDS.

Objectives: The objective was to assess the role of exhaled aerosol clouds on ENDS cue potency using a standardized laboratory paradigm designed to mimic real-world exposures

Methods: Using a mixed design, young adult smokers (n=50; mean age 26.5 yrs; 5 cigarettes/day) observed a study confederate drinking bottled water (control cue) and vaping an ENDS mod containing e-liquid with either high (73%) or low (0%) VG. Participants completed the Brief Questionnaire on Smoking Urges (BQSU) and visual analog scales (VAS) assessing cigarette and e-cigarette desire pre- and post-cue exposure.

Results: Increasing the e-liquid content of VG enhanced the size and visibility of the exhaled aerosol clouds and evoked a greater increase in smoking desire and a more sustained increase in e-cigarette desire relative to the low VG cue. Both cues elicited increases in smoking urges. These results remained after controlling for sex, prior ENDS experience, recent smoking behavior, and menthol preference.

Conclusions: Observation of tank-based ENDS use generalizes as a smoking cue and its cue salience is strengthened by increasing the e-liquid content of VG to enhance the visibility of the exhaled aerosol cloud.

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Keywords

electronic cigarettes; electronic nicotine delivery systems; urge; cues; vegetable glycerin; mods; vaping

Introduction

The use of electronic nicotine delivery systems (ENDS, also referred to as electronic cigarettes or e-cigarettes) has become globally widespread in the past decade. For example, in the U.S., the prevalence of current e-cigarette use has increased from 0.3% in 2010 (McMillen et al. 2015) to 3.2% in 2016 (Centers for Disease Control, 2017) and in the European Union, adult (≥ 15 years) ever use of e-cigarettes has increased from 29.3 million (~7% of the population) in 2012 (Vardavas et al. 2015), to 48.5 million (11.4% of the population) in 2014 (Farsalinos et al. 2016). Specifically, current tobacco smokers and recent quitters report the greatest use of ENDS (Camenga et al. 2014; McMillen et al. 2015; Coleman et al. 2017). While ENDS may be a harm reduction alternative to combustible cigarettes (Levy et al. 2017; Stratton et al. 2018), concerns remain regarding their public health implications (Rowell and Tarran 2015; Clapp and Jaspers 2017; Rubinstein et al. 2018). One concern is whether they could renormalize smoking behaviors and/or facilitate nicotine use and eventual dependence, particularly among youths and young adults (Choi et al. 2012; Leventhal et al. 2015; Schneider and Diehl 2016; Stratton et al. 2018). Indeed, 2017 data show that nearly one-third of U.S. 12th graders reported any vaping within the past year (Johnston et al. 2018), and in 2016, young adults (aged 18–24 years) showed the highest prevalence of e-cigarette use, with nearly 1 in 4 reporting any use (Schoenborn and Clarke 2017). Emerging evidence suggests that e-cigarette use and receptivity to e-cigarette advertising (Pierce et al. 2018) in adolescence and young adulthood may be associated with a greater risk for subsequent nicotine use, including traditional cigarette smoking (Goldenson et al. 2017; Barrington-Trimis et al. 2016; Soneji et al. 2017; Leventhal et al. 2015; Soneji et al. 2018; Bold et al. 2018).

As ENDS use resembles traditional smoking in hand-to-mouth movements and inhalation and exhalation behaviors, it may generalize as a Pavlovian cue and elicit smoking urges in observers. Indeed, controlled laboratory studies by our group have consistently shown that exposure to in-person or video ENDS cues significantly increases young adult smokers' desire for traditional and electronic cigarettes (King et al. 2015, 2016, 2018). Using online-based data collection, other groups have shown that following exposure to e-cigarette advertisements, observers report smoking urges, thoughts about smoking, interest in ENDS, curiosity about ENDS, and favorable perceptions of e-cigarettes (Maloney and Cappella 2016; Pepper et al. 2014; Kim et al. 2015; Villanti et al. 2016). While these online studies of ENDS video exposures included large sample sizes, participants' immediate environment was not controlled, thus smoking- and vaping-related stimuli and behaviors may have been present during exposure, which would confound cue reactivity.

Across these aforementioned ENDS exposure studies, the e-cigarette products were exclusively first- and/or second-generation products, i.e., “cigalikes” and “vape pens” which

bear close to moderate resemblance to conventional cigarettes. To our knowledge, no studies have examined observers' responses to larger, tank-based third-generation products, i.e., "mods" or "advanced personal vaporizers," which have less resemblance to traditional cigarettes than these earlier ENDS products (Clapp & Jaspers 2017). Mods continue to show increasing preference among vapers due to their customizability (Dawkins et al. 2015; Yingst et al. 2015; Wagener et al. 2017; Clapp and Jaspers 2017). As mods do not include pre-filled e-liquids, users can modify the levels of nicotine, flavoring agents, and other compounds suspended in the solution (Cheng 2014; Herrington and Myers 2015; Clapp and Jaspers 2017), as well as the primary humectant, vegetable glycerin (VG), and solvent, propylene glycol (PG). By increasing the concentration of VG in the e-liquid as well as the wattage of the device, users can enhance their vapor hit and produce larger exhaled aerosol "vape clouds," which is desired by users (Clapp and Jaspers 2017; Baassiri et al. 2017) and emerging as a competitive hobby, particularly among adolescents and young adults (Chu et al. 2016; Mickle 2015; Kim et al. 2017). Adult former smokers who use e-cigarettes daily self-report that modifying ENDS to enhance the "throat hit" and appearance of vape clouds (Etter 2015) provides the greatest cigarette craving relief, suggesting that aerosol visibility may influence subjective responses in users. As larger exhaled aerosols are also more visible to the passive observer (Baassiri et al. 2017), it is possible that they affect the cue salience of ENDS. However, no research to date has examined whether an ENDS mod may serve as a smoking cue or whether higher e-liquid concentrations of VG that enhance the visibility of exhaled "vape clouds" affect their cue strength. Such research may inform the regulation of ENDS products and e-liquids by the Food and Drug Administration (FDA), which could impose restrictions on maximum VG content.

Using a controlled laboratory paradigm, we examined the cue salience of a tank-based ENDS mod on young adult smokers' urge and desire for cigarettes and e-cigarettes. We varied the concentration of VG in the e-liquid and hypothesized that higher (vs. lower) VG would potentiate the cue strength of ENDS exposure.

Methods

Participants

The study was conducted between June and September 2017. The study inclusion criteria were cigarette smoker (≥ 5 cigarettes per day) for at least the past year, age 18–35 years, in good general health, not currently pregnant, and not currently attempting to quit smoking. Candidates were recruited from online advertisements and word-of-mouth referrals. They were instructed to abstain from recreational drugs and alcohol for 24 hours and cigarette smoking for one hour before arrival to the visit. One-hour smoking abstinence was determined via self-report, but ensured through the completion of a one-hour screening process prior to the commencement of the experimental session.

The screening included informed consent and an explanation of study procedures, objective breath tests for alcohol and carbon monoxide levels, self-report surveys, and interviews conducted by a trained research assistant. Breath alcohol readings were required to be 0.003 mg% (Alco-Sensor III, Intoximeter, St. Louis, MO, USA). Current smoking status was biochemically verified via a carbon monoxide breath test. Surveys included the

Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al. 1991), the Beck Depression Inventory (Beck et al. 1961), Spielberger Trait Anxiety Inventory (Spielberger et al. 1983), and general demographic, health, and substance use behaviors, including smoking. The interviews were the Timeline Follow-Back Calendar (Sobell and Sobell 1992) to determine daily estimates of past month cigarette smoking and the research version of the Structured Clinical Interview for DSM-5 (First et al. 1995) with modifications to screen for major psychiatric disorders (schizophrenia, bipolar, etc.). Candidates were excluded if they had survey scores that were outside the standard clinical thresholds for severe depression or anxiety or had a major untreated psychiatric disorder.

Of the 56 in-person candidates screened for this study, three were deemed ineligible (two for prior participation in ENDS cue reactivity studies in our group, and one for a screening breath alcohol reading above 0.003 mg%). All 53 participants deemed eligible from screening completed the study. Data was excluded for three outliers (greater than 2 SD on desire and urge ratings or change scores), therefore yielding in a final sample size of N=50 participants.

Design

The study used a mixed design and each participant was examined in an approximate one-hour experimental session immediately following screening. The experimental session was similar to that employed in our prior studies (King et al. 2015, 2018). Participants were informed they would be involved in two randomly-assigned 5-minute tasks with another participant; the tasks were listed as viewing pictures, eating food, engaging in conversation, drinking a beverage, or smoking. This description was chosen in order to reduce expectancy effects on study measures. Each participant was actually exposed to the study confederate using a control cue (drinking bottled water) as the first task and then randomized to observe the confederate using one of two active ENDS cues (high or low VG e-liquid) as the second task. Randomization was computer generated and stratified by sex and race. The study was fully approved by the University of Chicago Institutional Review Board.

Experimental Session.—Figure 1 depicts the study timeline. All sessions were conducted in a controlled laboratory space that resembled a comfortable living room that did not contain any smoking or vaping-related cues. For standardization purposes, participants were required to store all personal belongings, including cellular phones, in a locked drawer. The experimental session began with the participant completing computerized baseline mood (see Supplementary methods and results) and craving-related measures followed by a five minute rest period. The research assistant then escorted the study confederate, who portrayed the role of being another participant, into the testing room and introduced him/her to the participant. Participant and confederate were each presented with a stack of envelopes and asked to pick one for their first task. Unbeknownst to the participant, the random selection was fixed so that the participant always selected the envelope with *conversation* as his/her task and the confederate always selected the envelope with *drinking bottled water* as his/her first task. The participant was then provided a list of conversation topics to choose from, including: movies and television, places to eat, vacations, pets, weather, or current local activities and events. Both participant and confederate were instructed to focus on their

selected task and give their best effort to have a natural conversation on the chosen topic as it would be videotaped and scored later for social interaction.

After the first 5-minute task period, the participant and confederate were separated for fifteen minutes. The participant completed their computerized mood and craving-related measures (post-water surveys), followed by a short rest period. The confederate then re-joined the participant to engage in a second task with the selection process similar to the first task; the participant again apparently selecting conversation, and this time the confederate seemingly choosing the task of vaping. For half the participants, the confederate vaped a mod with a high VG e-liquid, and for the other half of the participants, the confederate vaped a mod with a low VG e-liquid. After this second 5-minute task, the participant and confederate were again escorted into separate rooms to complete subjective measures (5 min post active cue) followed by fifteen minutes of rest. The participant then completed a final set of mood and craving-related measures (20 min post active cue) and the session concluded with an end of session questionnaire to collect more detailed information regarding recent and past experience with ENDS. To mask the study purpose, a wash-out task, the Digit Symbol Substitution Task (Wechsler 1956), was included after exposure to each cue and additional items were embedded in the subjective measures (e.g. desire for conversation, water, salty foods, etc.). After the entire study was completed, participants were fully debriefed on the deception procedure.

Cues.—All cues were delivered by a trained study confederate, i.e., a 20-year-old Caucasian male or a 24-year-old Middle Eastern female, both of whom were regular smokers with vaping experience. The confederates portrayed the role of being a study participant but their actual objective was to deliver the cues in a natural but standardized fashion, with a goal of 9–10 hand-to-mouth movements for each cue. The sessions were taped and the number of hand-to-mouth movements and the size and visibility of the exhaled vape clouds were later scored by a research assistant.

The non-smoking control cue included the confederate drinking a standard 12 oz. water bottle (Nestle Pure Life®) in the presence of the participant. This was selected because it is neutral in regards to smoking and mimics frequent hand to mouth consummatory behavior (Drobes and Tiffany 1997; Carter and Tiffany 2001). The active vape cues included the confederate using an iStick Pico ENDS mod device that was 12.5cm long, 1.5–4.5cm wide, black with stainless steel band edging, with a 2mL clear MELO III tank, with 1–75 output wattage (set at 40W to enhance the exhaled aerosol cloud while minimizing throat irritation). The e-liquids for use in the ENDS device were prepared by Pace Engineering Concepts (Milwaukee, WI) in accordance with cGMP requirements and ISO9001 manufacturing standards. To provide the confederate with a naturalistic vaping experience, the e-liquids contained 12 mg nicotine (about 1.1% by weight) with either Burley tobacco or menthol flavoring matched to the participants' cigarette preference. The high VG e-liquid was comprised of 73% VG and 17% PG (contents averaged for 2 flavor batches) and the low VG e-liquid was 0% VG and 95.6% PG (averaged for 2 flavor batches). All components in the blend preparation were controlled to exacting tolerances of less than +0.01% by weight for future reproducibility, as typical of research grade materials. No other e-liquid constituents were modified.

Standardization of cue delivery was confirmed by rating each exhaled aerosol cloud on four-point scales for length and width: 0) none/not visible, 1) <30cm, 2) 30–90cm, or 3) >90cm, and on a three-point scale for opacity: 0) none/not visible, 1) visible but translucent, or 2) visible and opaque. These ratings confirmed that the high vs. low VG e-liquid produced significantly larger and more visible aerosol clouds (Figure 2; all $t(48) > 6.93$; $p < 0.001$). Further, exhaled aerosol ratings were similar between the two study confederates ($p = 0.12$). Standardization was also confirmed by videotape review indicating no difference between high and low VG sessions on the number of hand-to-mouth movements [high VG, mean = 10 ± 0.4 SEM; low VG, mean = 9 ± 0.5 ; $t(48) = 1.75$ $p = 0.09$], and on positive valence ratings of the social interaction [Two-Dimensional Social Interaction Scale (Tse and Bond 2001); high VG, mean = 11.8 ± 0.5 ; low VG, mean = 12.5 ± 0.4 ; $t(48) < 0.98$, $p > 0.33$]. The latter also did not differ between the confederates [$t(48) < 0.99$, $p > 0.32$].

Measures

The primary dependent measures were two visual analogue scale (VAS) items, “desire for a regular cigarette (your preferred brand)” and “desire for an electronic cigarette” rated from ‘not at all’ (0) to ‘most ever’ (100) (Heishman et al. 2010) as well as the 10-item Brief Questionnaire of Smoking Urges (BQSU) total score, i.e., the sum of each item rated from 1 (strongly disagree) to 7 (strongly agree) and the two sub-factor scores (Factor 1: smoking for perceived rewarding effects, Factor 2: smoking for relief from negative affect or withdrawal) (Cox et al. 2001). Additional VAS items (e.g., “desire for sweets” and “desire for salty foods”) were included to mask the study purpose.

Statistical Analyses—Participant demographics and smoking characteristics were compared between the high and low VG cue groups using Student’s t-tests and chi-square tests, as appropriate. Time since last cigarette was compared using Wilcoxon Rank Sum test due to non-normal distribution. Expired aerosol clouds were compared between groups via Student’s t-tests or one-way ANOVA, as appropriate. Subjective ratings from the session were summarized as change scores by subtracting baseline scores for each dependent variable from ratings at each time point (5 minutes post-water cue, 5 and 20 minutes post-active ENDS cues). Change scores were then analyzed by Generalized Estimated Equations (GEE) with cue group (high VG and low VG) as the between-subjects factor and time as the within-subjects factor. Post-estimation contrast tests and pairwise comparisons with Bonferroni corrections for multiple comparisons were conducted to determine the source of any significant main effects and interactions. All GEE analyses were conducted with the baseline rating as a covariate as very high or very low baseline ratings can affect outcomes (i.e. floor or ceiling effects). These GEE analyses were repeated with the inclusion of covariates that may affect reactivity to cues including study-specific factors such as confederate, and also participant-specific factors such as sex, smoking level (cigarettes per day), time since last cigarette, preference for menthol cigarettes, and ENDS use [naïve, lifetime (but not past month), or current (*any* past month use)] (Carpenter et al. 2014; Piñeiro et al. 2016; Kim et al. 2015; Heishman et al. 2010). Finally, exploratory analyses were conducted comparing urge and desire ratings in this study to that of our prior studies with similar methodology examining cigarette and first- and second-generation ENDS cue reactivity.

Results

Participant characteristics

Participant demographics are presented in (Table 1). The sample was 62% male with a mean age of 26.3 ± 4.1 (SD) years (range 20–35 years). The sample reported a mean smoking frequency of 6.6 days/week (range 2–7) with an average of 8.6 cigarettes per smoking day (range: 2–21). Menthol cigarettes were preferred by 58% of the sample. While prior ENDS experience was not an eligibility requirement, 84% (42/50) of the sample reported ever ENDS use, 38% (16/42) of which reported current (any past month) use. Among these current users, only 1 person (6%) reported daily use with the majority vaping a few times a month (38%) or less than monthly (31%). Most of the participants who ever vaped primarily use vape pens 37% ($n=6$) or mods 44% ($n=7$), with few preferring cigalikes 19% ($n=3$). Participants in the two cue exposure groups did not significantly differ on any sociodemographic or affective characteristics, smoking behaviors, or prior ENDS use. The low and high VG groups were similar on time since last cigarette (median times 1.8 and 2.6 hours, respectively) and mean baseline CO level (low VG= 10.5 ± 1.5 , high VG= 14.5 ± 1.9), $ps = 0.11$.

Baseline desire and urge ratings

As expected, participants who were moderate/heavy smokers (≥ 10 cigarettes/day, $n=15$) had greater baseline smoking desire than lighter smokers ($n=35$) [mean (SEM): 80.9 (3.1) vs. 62.0 (3.6), $t(48)=3.20$, $p=0.002$], but not BQSU smoking urge scores [47.5 (2.3) vs. 42.6 (1.7), $t(47)=1.74$, $p=0.09$]. Also, past month ENDS users had higher baseline e-cigarette desire than either naïve or lifetime users [31.8 (5.2) vs. 7.9 (4.8) and 13.1 (3.9), respectively, $F(2,45)=5.80$, $ps < 0.01$]. Menthol and non-menthol smokers showed similar baseline smoking urge, cigarette and e-cigarette desire ($ps = 0.64$).

ENDS device effects on desire and urge ratings

Exposure to the use of the tank-based ENDS device produced an immediate and sustained increase in observers' desire for a cigarette (time, Wald $\chi^2(2)=42.6$, $p<0.001$; pairwise comparison, 5 min=20 min post-active cue > water cue, $ps < 0.001$) and an e-cigarette (time, Wald $\chi^2(2)=23.6$, $p<0.001$; 5 min=20 min post-active cue > water cue, $ps < 0.001$). Exposure to the ENDS cue also produced immediate and sustained increases in smoking urge (*total BQSU*: time, Wald $\chi^2(2)=18.8$, $p<0.001$; 5 and 20 min > water cue, 20 min > 5 min, $ps = 0.05$). Both Factor 1 (time, Wald $\chi^2(2)=16.6$, $p<0.001$; 5 min=20 min > water cue, $ps < 0.01$) and Factor 2 BQSU subscores (time, Wald $\chi^2(2)=16.3$, $p<0.001$; 5 min and 20 min > water cue, $p<0.05$; 20 min post-active cue > 5 min, $p<0.05$) increased after the ENDS cue.

VG level effects on desire and urge ratings

Comparisons between the ENDS exposures showed that the high VG e-liquid cue produced more robust increases in cigarette desire relative to the low VG cue (group, Wald $\chi^2(1)=42.6$, $p=0.002$) both immediately and 20 minutes following active cue delivery (group*time, Wald $\chi^2(2)=7.3$, $p=0.026$; pairwise comparison, high > low VG at 5 and 20 min, $ps = 0.008$; Figure 3A). Within the high VG group, the active cue (vs water cue) evoked

significant increases in cigarette desire both immediately and 20 minutes following cue delivery (Table 2; 5 min=20 min > water cue, $p < 0.017$). For e-cigarette desire ratings, the pattern was slightly different, with a marginally significant group*time interaction ($p = 0.054$); both high and low VG cues increased e-cigarette desire immediately after the cue, but this was sustained through 20 minutes only for the high VG cue (high VG at 20 min > water cue, $p < 0.008$; low VG at 20 min=water cue, $p = 0.14$; Figure 3B). The high and low VG cues produced similar increases in BQSU smoking urge (total and sub-factor scores) (group, Wald $\chi^2(1) = 2.3$, $p = 0.13$; time*group, Wald $\chi^2(2) = 1.1$, $p = 0.85$). Finally, the water cue produced minimal change in participants' ratings of cigarette and e-cigarette desire ($p > 0.25$). Table 2 shows the mean urge and desire scores by cue exposure group at each time point.

Notably, results from the aforementioned GEE analyses remained after including smoking and vaping experience (cigarettes/day, time since last cigarette, menthol preference, and past ENDS experience), confederate, and sex as covariates in the model (see Supplementary Tables S2 and S3 for full results of GEE models, including main effects and covariates). In terms of prior ENDS history, the e-cigarette desire response (change scores) to the ENDS cues was directionally higher among those with previous ENDS experience [current and lifetime users, $+8.8 \pm 3.1$ and $+11.7 \pm 3.5$, respectively] vs naïve users [3.1 ± 4.2] with a trend for significance (Wald $\chi^2(2) = 5.40$, $p = 0.07$). Prior ENDS history did not affect cigarette desire or smoking urge response to the ENDS cue. In addition, secondary analyses showed that the social interaction and cue delivery increased observers' positive affect and decreased negative affect with desire for conversation increased throughout the session, suggesting that the paradigm was not stressful or negatively valenced for participants (for more detail, see Supplement).

Exploratory comparisons to combustible cigarette and earlier-generation ENDS cues

Previous work by our group (King et al., 2013, 2015, 2018) assessed the cue salience of combustible cigarettes, cigalikes, and vape pens in a similar controlled laboratory paradigm. The high VG mods cue in the present study produced the most visible exhaled aerosol, as the exhaled smoke from the combustible cigarette [length= 1.5 ± 0.09 , width= 1.0 ± 0.05 , opacity= 0.9 ± 0.03] was intermediate to the aerosol produced by the high and low VG cues [cue: $F(2,71) = 32.6 - 50.4$, $p < 0.001$; pairwise comparisons: length and width, low VG < cigarette = high VG; opacity, low VG < cigarette < high VG, $p < 0.017$]. Exploratory comparisons across all cue conditions showed that the high VG cue produced directionally higher cigarette desire ratings (i.e., baseline corrected change scores) 20 minutes after cue delivery (high VG: $+16.1 \pm 2.2$) than that produced by a combustible cigarette ($+8.5 \pm 2.0$) or ENDS cigalike or vape pen ($+10.6 \pm 2.7$ and $+9.0 \pm 2.4$, respectively).

Discussion

The present study is the first to demonstrate that passive observation of the use of a third-generation ENDS mod acts as a cue and increases the desire for both a cigarette and an e-cigarette in young adult smokers. The present study extends prior work (King et al., 2015, 2016, 2018) by demonstrating that the cue salience of ENDS mods can be strengthened by

increasing the concentration of VG in the e-liquid that produced more visible exhaled aerosol. Higher VG levels enhanced the potency of ENDS both as a smoking cue and also as an e-cigarette cue, with increased desire for both products sustained 20 minutes after cue delivery. These responses were not attributable to subjective changes in affect or social stress (see Supplement). Further, the increase in cigarette desire produced by an ENDS mod with high VG, but not low VG e-liquid, was comparable to, and actually directionally higher than, that elicited by exposure to other smoking and vaping cues in prior studies (combustible cigarette, ENDS cigalike and vape pen) (King et al 2015, 2016, 2018). Thus, the unique customizability of third-generation ENDS, specifically the enhancement of exhaled aerosol clouds, not only enhances the pleasure of vaping to the user (Yingst et al 2015), but also boosts their ability to affect the passive observer.

The present study contributes to a growing body of literature on the impact of ENDS use, which, thus far, has tended to focus on the user's experience rather than the effects on observers. Advanced generation ENDS, as used in the present study, are capable of delivering nicotine in amounts and at a pace similar to that of combustible cigarettes, which may increase their abuse liability (Wagener et al. 2017). Further, the e-liquids used in these devices can adversely affect users by producing airway irritation and activating cellular immune signaling pathways (DeVito and Krishnan-Sarin 2018). There has been speculation that ENDS can affect non-users through an unintended effect of normalizing vaping behavior and undermining social norms about tobacco, which may facilitate nicotine dependence, particularly among youths who are frequently targeted by aggressive e-cigarette advertising (Duke et al. 2014, 2016; Villanti et al. 2016). With the growing prevalence of ENDS use and presence of vaping-related stimuli, identifying the subjective and behavioral effects on passive observers will become increasingly important, particularly among youths and young adults who are especially vulnerable to the motivational salience of such stimuli.

There are many strengths of the current study, including the use of well-controlled laboratory methodology mimicking ecologically-relevant exposure to ENDS use, repeated pre- and post-cue exposure assessments, and utilization of strategies to minimize expectancy and stress effects. Despite these strengths, there are some limitations worth noting. First, the sample size was modest which precluded comprehensive analyses of subgroup effects (i.e. previous ENDS experience), and the sample consisted primarily of young adult smokers. Thus, it remains to be determined if the results generalize to older, heavier, or former smokers. We chose this age range because 18–35 year olds show the highest prevalence of ENDS use among adults (Centers for Disease Control 2017) and therefore may be a priority subpopulation to study for ENDS cue reactivity (Soneji et al. 2017; Barrington-Trimis et al. 2016). Second, only two concentrations of VG (73% and 0%) were examined and while these concentrations produced aerosol clouds that were clearly discernible on measures of visibility, precise quantification of the exhaled aerosols was not possible due to the video technology utilized and the lack of pre-existing standardized scoring metrics. Dose-dependent effects of a larger range of VG levels and the effects of other e-liquid constituents, such as flavorings, solvents, and sweeteners were outside the scope of the present study. Third, cues were presented in a fixed order such that the water cue always preceded the ENDS cue to eliminate potential cue reactivity carryover effects from the active cue. While the water cue served as an appropriate non-smoking control as it included hand-to-mouth

consummatory behavior and evoked little change in smoking desire, future studies with multiple sessions to permit counterbalanced cue delivery are advised to rule out possible temporal effects on craving responses, although for young adult smokers averaging a half a pack of cigarettes a day, a twenty minute time difference likely would not have produced large increases in smoking urge. Fourth, while the high VG cue elicited a greater increase in cigarette desire, it produced comparable increases in smoking urge as the low VG cue. Debate continues in the field (Kozlowski et al. 1996; Cox et al. 2001; West and Ussher 2010) about the advantages of single or multiple items to capture craving, and we may speculate that young adult smokers with relatively low-to-moderate nicotine dependence may be best served with simpler, single-item assessments of cigarette (and e-cigarette) desire because the concept of multi-dimensional smoking urge may not yet be as fully developed as in longer-term and older smokers.

In sum, our results demonstrate that passive exposure to the use of a third-generation, tank-based ENDS stimulates smoking urge and desire, as well as e-cigarette desire. Modification of the e-liquid by increasing the concentration of the humectant VG enhanced the visibility of the exhaled aerosol cloud and strengthened the salience of ENDS as a smoking cue. The present study is especially timely as the FDA continues to evaluate the public health impact of ENDS to determine a regulatory framework of these products. Future work may help discern if the salience of ENDS, and impact on observers, would be diminished by imposing restrictions on VG concentrations in e-liquids. Additional studies are also needed to examine whether exposure to ENDS product constituents that produce more visible aerosol clouds affect perceptions and/or initiation of ENDS use among adolescents, young adults, and middle/older age adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- Baassiri M, Talih S, Salman R, et al. (2017) Clouds and “throat hit”: Effects of liquid composition on nicotine emissions and physical characteristics of electronic cigarette aerosols. *Aerosol Sci Technol* 51:1231–1239. 10.1080/02786826.2017.1341040
- Barrington-Trimis JL, Urman R, Berhane K, et al. (2016) E-Cigarettes and Future Cigarette Use. *Pediatrics* 138:e20160379–e20160379. 10.1542/peds.2016-0379 [PubMed: 27296866]
- Beck AT, Ward CH, Mendelson M, et al. (1961) An Inventory for Measuring Depression. *Arch Gen Psychiatry* 4:561 10.1001/archpsyc.1961.01710120031004 [PubMed: 13688369]

- Bold KW, Kong G, Camenga DR, et al. (2018) Trajectories of E-Cigarette and Conventional Cigarette Use Among Youth. *Pediatrics* 141:e20171832 10.1542/peds.2017-1832 [PubMed: 29203523]
- Camenga DR, Delmerico J, Kong G, et al. (2014) Trends in use of electronic nicotine delivery systems by adolescents. *Addict Behav* 39:338–340. 10.1016/j.addbeh.2013.09.014 [PubMed: 24094920]
- Carpenter MJ, Saladin ME, LaRowe SD, et al. (2014) Craving, Cue Reactivity, and Stimulus Control Among Early-Stage Young Smokers: Effects of Smoking Intensity and Gender. *Nicotine Tob Res* 16:208–215. 10.1093/ntr/ntt147 [PubMed: 24042699]
- Carter BL, Tiffany ST (2001) The cue-availability paradigm: the effects of cigarette availability on cue reactivity in smokers. *Exp Clin Psychopharmacol* 9:183–90 [PubMed: 11518094]
- Centers for Disease Control (2017) QuickStats : Percentage of Adults Who Ever Used an E-cigarette and Percentage Who Currently Use E-cigarettes, by Age Group — National Health Interview Survey, United States, 2016. *MMWR Morb Mortal Wkly Rep* 66:892 10.15585/mmwr.mm6633a6 [PubMed: 28837550]
- Cheng T (2014) Chemical evaluation of electronic cigarettes. *Tob Control* 23:ii11–ii17. 10.1136/tobaccocontrol-2013-051482 [PubMed: 24732157]
- Choi K, Fabian L, Mottey N, et al. (2012) Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: findings from a focus group study. *Am J Public Health* 102:2088–93. 10.2105/AJPH.2011.300525 [PubMed: 22813086]
- Chu K-H, Allem J-P, Cruz TB, Unger JB (2016) Vaping on Instagram: cloud chasing, hand checks and product placement. *Tob Control* 26:575–578. 10.1136/tobaccocontrol-2016-053052 [PubMed: 27660111]
- Clapp PW, Jaspers I (2017) Electronic Cigarettes: Their Constituents and Potential Links to Asthma. *Curr Allergy Asthma Rep* 17:79 10.1007/s11882-017-0747-5 [PubMed: 28983782]
- Coleman BN, Rostron B, Johnson SE, et al. (2017) Electronic cigarette use among US adults in the Population Assessment of Tobacco and Health (PATH) Study, 2013–2014. *Tob Control* tobaccocontrol-2016-053462 10.1136/tobaccocontrol-2016-053462
- Cox LS, Tiffany ST, Christen AG (2001) Evaluation of the brief questionnaire of smoking urges (QSU-brief) in laboratory and clinical settings. *Nicotine Tob Res* 3:7–16. 10.1080/14622200020032051 [PubMed: 11260806]
- Dawkins L, Kimber C, Puwanesarasa Y, Soar K (2015) First- versus second-generation electronic cigarettes: predictors of choice and effects on urge to smoke and withdrawal symptoms. *Addiction* 110:669–77. 10.1111/add.12807 [PubMed: 25407505]
- DeVito EE, Krishnan-Sarin S (2018) E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure. *Curr Neuropharmacol* 16:438–459. 10.2174/1570159X15666171016164430 [PubMed: 29046158]
- Diener E, Emmons RA (1984) The independence of positive and negative affect. *J Pers Soc Psychol* 47:1105–17 [PubMed: 6520704]
- Drobes DJ, Tiffany ST (1997) Induction of smoking urge through imaginal and in vivo procedures: physiological and self-report manifestations. *J Abnorm Psychol* 106:15–25 [PubMed: 9103714]
- Duke JC, Allen JA, Eggers ME, et al. (2016) Exploring Differences in Youth Perceptions of the Effectiveness of Electronic Cigarette Television Advertisements. *Nicotine Tob Res* 18:1382–1386. 10.1093/ntr/ntv264 [PubMed: 26706908]
- Duke JC, Lee YO, Kim AE, et al. (2014) Exposure to electronic cigarette television advertisements among youth and young adults. *Pediatrics* 134:e29–36. 10.1542/peds.2014-0269 [PubMed: 24918224]
- Etter J-F (2015) Explaining the effects of electronic cigarettes on craving for tobacco in recent quitters. *Drug Alcohol Depend* 148:102–108. 10.1016/J.DRUGALCDEP.2014.12.030 [PubMed: 25592454]
- Farsalinos KE, Poulas K, Voudris V, Le Houezec J (2016) Electronic cigarette use in the European Union: analysis of a representative sample of 27?460 Europeans from 28 countries. *Addiction* 111:2032–2040. 10.1111/add.13506 [PubMed: 27338716]
- First M, Spitzer R, Gibbon M, Williams J (1995) Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition (SCID-I/P) Biometrics Research, New York State Psychiatric Institute, New York, NY

- Goldenson NI, Leventhal AM, Stone MD, et al. (2017) Associations of Electronic Cigarette Nicotine Concentration With Subsequent Cigarette Smoking and Vaping Levels in Adolescents. *JAMA Pediatr* 171:1192. 10.1001/jamapediatrics.2017.3209 [PubMed: 29059261]
- Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO (1991) The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *Br J Addict* 86:1119–27 [PubMed: 1932883]
- Heishman SJ, Lee DC, Taylor RC, Singleton EG (2010) Prolonged duration of craving, mood, and autonomic responses elicited by cues and imagery in smokers: Effects of tobacco deprivation and sex. *Exp Clin Psychopharmacol* 18:245–56. 10.1037/a0019401 [PubMed: 20545389]
- Herrington JS, Myers C (2015) Electronic cigarette solutions and resultant aerosol profiles. *J Chromatogr A* 1418:192–9. 10.1016/j.chroma.2015.09.034 [PubMed: 26422308]
- Johnston L, Miech RA, O'Malley P, et al. (2018) Monitoring the Future national survey results on drug use: 1975–2017: Overview, key findings on adolescent drug use. *Ann Arbor*
- Kim AE, Lee YO, Shafer P, et al. (2015) Adult smokers' receptivity to a television advert for electronic nicotine delivery systems. *Tob Control* 24:132–135. 10.1136/tobaccocontrol-2013-051130 [PubMed: 24092599]
- Kim H, Davis AH, Dohack JL, Clark PI (2017) E-Cigarettes Use Behavior and Experience of Adults: Qualitative Research Findings to Inform E-Cigarette Use Measure Development. *Nicotine Tob Res* 19:190–196. 10.1093/ntr/ntw175 [PubMed: 27613944]
- King AC, Smith LJ, Fridberg DJ, et al. (2016) Exposure to electronic nicotine delivery systems (ENDS) visual imagery increases smoking urge and desire. *Psychol Addict Behav* 30:106–12. 10.1037/adb0000123 [PubMed: 26618797]
- King AC, Smith LJ, McNamara PJ, et al. (2015) Passive exposure to electronic cigarette (e-cigarette) use increases desire for combustible and e-cigarettes in young adult smokers. *Tob Control* 24:501–504. 10.1136/tobaccocontrol-2014-051563 [PubMed: 24848637]
- King AC, Smith LJ, McNamara PJ, Cao D (2017) Second Generation Electronic Nicotine Delivery System Vape Pen Exposure Generalizes as a Smoking Cue. *Nicotine Tob Res* ntw327. 10.1093/ntr/ntw327
- Kozlowski LT, Pillitteri JL, Sweeney CT, et al. (1996) Asking Questions About Urges or Cravings for Cigarettes. *Psychol Addict Behav* 10:248–260
- Leventhal AM, Strong DR, Kirkpatrick MG, et al. (2015) Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA* 314:700–7. 10.1001/jama.2015.8950 [PubMed: 26284721]
- Levy DT, Borland R, Lindblom EN, et al. (2017) Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob Control* tobaccocontrol-2017-053759. 10.1136/tobaccocontrol-2017-053759
- Maloney EK, Cappella JN (2016) Does Vaping in E-Cigarette Advertisements Affect Tobacco Smoking Urge, Intentions, and Perceptions in Daily, Intermittent, and Former Smokers? *Health Commun* 31:129–138. 10.1080/10410236.2014.993496 [PubMed: 25758192]
- McMillen RC, Gottlieb MA, Shaefer RMW, et al. (2015) Trends in Electronic Cigarette Use Among U.S. Adults: Use is Increasing in Both Smokers and Nonsmokers. *Nicotine Tob Res* 17:1195–1202. 10.1093/ntr/ntu213 [PubMed: 25381306]
- Mickle T (2015) Take a Deep Breath if You Want to Try Competitive Vaping. *Wall Str. J*
- Pepper JK, Emery SL, Ribisl KM, et al. (2014) Effects of advertisements on smokers' interest in trying e-cigarettes: The roles of product comparison and visual cues. *Tob Control* 23:iii31–iii36. 10.1136/tobaccocontrol-2014-051718 [PubMed: 24935896]
- Pierce JP, Sargent JD, Portnoy DB, et al. (2018) Association Between Receptivity to Tobacco Advertising and Progression to Tobacco Use in Youth and Young Adults in the PATH Study. *JAMA Pediatr* 10.1001/jamapediatrics.2017.5756
- Piñeiro B, Correa JB, Simmons VN, et al. (2016) Gender differences in use and expectancies of e-cigarettes: Online survey results. *Addict Behav* 52:91–97. 10.1016/J.ADDBEH.2015.09.006 [PubMed: 26406973]
- Rowell TR, Tarran R (2015) Will chronic e-cigarette use cause lung disease? *Am J Physiol Lung Cell Mol Physiol* 309:L1398–409. 10.1152/ajplung.00272.2015 [PubMed: 26408554]

- Rubinstein ML, Delucchi K, Benowitz NL, Ramo DE (2018) Adolescent Exposure to Toxic Volatile Organic Chemicals From E-Cigarettes. *Pediatrics* e20173557 10.1542/peds.2017-3557 [PubMed: 29507165]
- Schneider S, Diehl K (2016) Vaping as a Catalyst for Smoking? An Initial Model on the Initiation of Electronic Cigarette Use and the Transition to Tobacco Smoking Among Adolescents. *Nicotine Tob Res* 18:647–53. 10.1093/ntr/ntv193 [PubMed: 26386472]
- Schoenborn CA, Clarke TC (2017) QuickStats: Percentage of Adults Who Ever Used an E-cigarette and Percentage Who Currently Use E-cigarettes, by Age Group. *National Health Interview Survey, United States, 2016*
- Sobell LC, Sobell MB (1992) Timeline Follow-Back. In: Litten RZ, Allen JP (eds) *Measuring Alcohol Consumption* Humana Press, Totowa, NJ, pp 41–72
- Soneji S, Barrington-Trimis JL, Wills TA, et al. (2017) Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults. *JAMA Pediatr* 171:788 10.1001/jamapediatrics.2017.1488 [PubMed: 28654986]
- Soneji SS, Sung H-Y, Primack BA, et al. (2018) Quantifying population-level health benefits and harms of e-cigarette use in the United States. *PLoS One* 13:e0193328 10.1371/journal.pone.0193328 [PubMed: 29538396]
- Spielberger CD, Gorsuch R, Lushene RE, et al. (1983) *Manual for the State-Trait Anxiety Inventory* Consulting Psychologists Press, Inc., Palo Alto, CA
- Stratton K, Kwan LY, Eaton DL (eds) (2018) *Public Health Consequences of E-Cigarettes* National Academies Press, Washington, D.C.
- Tse WS, Bond AJ (2001) Development and validation of the Two-Dimensional Social Interaction Scale (2DSIS). *Psychiatry Res* 103:249–260. 10.1016/S0165-1781(01)00271-2 [PubMed: 11549412]
- Vardavas CI, Filippidis FT, Agaku IT (2015) Determinants and prevalence of e-cigarette use throughout the European union: A secondary analysis of 26 566 youth and adults from 27 countries. *Tob Control* 24:442–448. 10.1136/tobaccocontrol-2013-051394 [PubMed: 24935441]
- Villanti AC, Rath JM, Williams VF, et al. (2016) Impact of Exposure to Electronic Cigarette Advertising on Susceptibility and Trial of Electronic Cigarettes and Cigarettes in US Young Adults: A Randomized Controlled Trial. *Nicotine Tob Res* 10.1093/ntr/ntv235
- Wagener TL, Floyd EL, Stepanov I, et al. (2017) Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tob Control* 26:e23–e28. 10.1136/tobaccocontrol-2016-053041 [PubMed: 27729564]
- Wechsler D (1956) *Manual for the Wechsler Adult Intelligence Scale* Psychological Corporation, New York, NY
- West R, Ussher M (2010) Is the ten-item Questionnaire of Smoking Urges (QSU-brief) more sensitive to abstinence than shorter craving measures? *Psychopharmacology (Berl)* 208:427–432. 10.1007/s00213-009-1742-x [PubMed: 20033133]
- Yingst JM, Veldheer S, Hrabovsky S, et al. (2015) Factors Associated With Electronic Cigarette Users' Device Preferences and Transition From First Generation to Advanced Generation Devices. *Nicotine Tob Res* 17:1242–6. 10.1093/ntr/ntv052 [PubMed: 25744966]

Figure 1: Experimental timeline

Figure shows timeline of experimental session, which began immediately upon completion of screening. X = Visual analog scale items (“Desire for a cigarette,” “Desire for an e-cigarette”), Brief Questionnaire of Smoking Urges (BQSU), and Diener & Emmons Affect Mood Form (Diener and Emmons 1984).

Figure 2: Aerosol cloud dimensions and visibility ratings

Data are Mean $\pm$ SEM. The high VG e-liquid produced more visible aerosol clouds on all rated measures relative to the low VG e-liquid. * p <0.001.

Figure 3: Ratings of traditional cigarette and e-cigarette desire

Data are Mean $\pm$ SEM. Subjective ratings of cigarette desire (A) and e-cigarette desire (B), represented as change scores from the baseline rating. The time points include following delivery of a water cue and 5 and 20 minutes after delivery of the active cue (expired aerosol clouds with high or low VG). ** $p = 0.001$ for high vs low VG

Table 1.**Group Characteristics**

	Low VG (n=25)	High VG (n=25)	P
Demographics and background:			
Age (y)	25.5 (0.8)	27.2 (0.8)	$p = 0.14$
Education (y)	14.0 (0.3)	14.2 (0.4)	$p = 0.60$
Sex (% male)	15 (60%)	16 (64%)	$p = 0.77$
Race:			$p = 0.54$
% <i>Caucasian</i>	12 (48%)	8 (32%)	-
% <i>African American</i>	9 (36%)	10 (40%)	-
% <i>Asian</i>	2 (8%)	2 (8%)	-
% <i>More than one race</i>	2 (8%)	5 (20%)	-
Beck Depression Inventory	9.4 (1.8)	6.9 (1.7)	$p = 0.33$
Spielberger Trait Anxiety (<i>t</i> -score)	56.3 (2.6)	50.2 (2.7)	$p = 0.11$
Alcohol drinks/week	10.1 (2.6)	9.4 (1.8)	$p = 0.82$
Smoking patterns and use:			
Days smoked (of past 28 days)	26.4 (0.9)	26.3 (0.9)	$p = 0.92$
Cigarettes smoked per smoking day	9.1 (1.1)	8.2 (0.8)	$p = 0.51$
FTND (nicotine dependency, 0–10)	3.8 (0.5)	4.2 (0.4)	$p = 0.54$
Previous ENDS use:			$p = 0.82$
Naïve ENDS user (never used ENDS)	4 (16%)	4 (16%)	-
Lifetime ENDS user (no past month use)	14 (56%)	12 (48%)	-
Current ENDS user (past month use)	7 (28%)	9 (36%)	-
Other tobacco use in the past year:			
Hookah	13 (52%)	13 (52%)	$p = 1.00$
Cigars	13 (52%)	15 (60%)	$p = 0.57$
Other (Smokeless, Pipe, Cloves, etc.)	7 (28%)	4 (16%)	$p = 0.50$

Note. Values are Mean (SEM) or $N(\%)$, as indicated. All variables were compared between groups with Student's t test, chi-square, or Fisher's exact test of independence, as appropriate. ENDS = Electronic nicotine delivery systems; FTND = Fagerström Test for Nicotine Dependence.

Table 2.

Mean Urge and Desire Scores

Primary Study Outcomes High VG n=25; Low VG n=25				
Outcome	Baseline	Water Cue	Active Cue	Post Cue
		Score	Score	Score
E-cigarette Desire				
Low VG	17.4 (4.3)	-0.2 (2.2)	+12.2 (5.0) *	+4.8 (1.9)
High VG	19.8 (4.5)	+1.7 (0.9)	+10.2 (2.6) *	+14.2 (3.8) *
BQSU Total				
Low VG	45.9 (2.0)	-0.4 (1.2)	+2.3 (1.4)	+3.5 (1.6) *
High VG	42.5 (2.0)	+0.1 (1.2)	+2.7 (1.4)	+4.6 (1.4) *
Cigarette Desire				
Low VG	77.1 (3.3)	-0.5 (2.0)	+2.7 (1.7)	+5.0 (1.3) *
High VG	59.7 (4.3) ^	+3.7 (1.8)	+12.7 (2.2) *	+16.1 (2.2) *

Note. Data are Mean (SEM). BQSU = Brief Questionnaire of Smoking Urges; Score = Baseline-corrected rating. Significance was determined by post-estimation contrast tests and pairwise comparison (with Bonferroni corrections) after Generalized Estimating Equations modeling.

^
p<0.05 for high vs low VG

*
p<0.017 post-hoc pairwise comparisons of main effects of time when compared to the water cue score.