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Assessing the Impacts of Sensorimotor Stimuli and Nicotine Content on Cravings and Other Outcomes of E-Cigarette Use

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by

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DEDICATION

To Dad: Wish you were here to say “I don’t understand any of this, but I’m proud of you.”

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ABSTRACT

As use rates of e-cigarettes continue to rise, especially among cigarette smokers, there remains concern that "dual use" may lead to increased dependence and hinder smoking cessation efforts. At the same time, emerging evidence suggests clinical efficacy of e-cigarettes. The role of nicotine must be considered, in addition to non-pharmacologic influences, such as expectancies or conditioned reinforcers. Sensorimotor stimuli associated with drug delivery have been demonstrated to produce cigarette and e-cigarette craving reduction, even without the nicotine. The purpose of the present study was to parse the influences of nicotine and sensorimotor delivery on various outcomes of e-cigarette use, including craving reduction. In this design, drug dosage (open label nicotine vs non-nicotine e-cigarettes) was crossed with sensorimotor manipulation (sensorimotor deprivation vs natural). Participants (N=127 dual users) completed an experimental visit that included an ad-lib vaping session with either a standard e-cigarette or a modified stationary apparatus (sensorimotor deprivation). It was hypothesized that the sensorimotor manipulation would primarily affect subjective, psychosocial outcomes, and nicotine would primarily influence objective, physiological outcomes. However, results showed main effects of both nicotine (ps<.01) and delivery (ps<.05) on both cravings to smoke and cravings to vape, with greater craving reduction among participants receiving nicotine as well as those in the sensorimotor deprivation condition. A nicotine X delivery interaction was found on negative affect (p<.05), such that only within the natural delivery condition was negative affect lower among those who received nicotine than those who did not. There were main effects of nicotine on satisfaction and reward (ps<.05), such that ratings were higher among those receiving

nicotine. Results were similar when controlling for baseline withdrawal. Positive reinforcement expectancies significantly moderated delivery effects on satisfaction ($p < .01$). In summary, inconsistent with the hypotheses, nicotine was implicated as the main driver of various subjective outcomes. Additionally, it may be that the novelty of our apparatus in the sensorimotor deprivation condition reduced cravings to smoke and vape via distraction. Clinical implications are discussed.

INTRODUCTION

Cigarette smoking is at an all-time low in the United States, which likely is a combined result of years of policy changes, intervention developments, and the more recent introduction of alternative nicotine delivery products, such as electronic (e-)cigarettes (Zhu, Zhuang, Wong, Cummins, & Tedeschi, 2017). E-cigarette use rates, on the other hand, have fluctuated since their introduction: Amounts of those reporting "ever use" are increasing within the general adult population (12.6% in 2014 to 15.3% in 2016; Bao, Xu, Lu, Snetselaar, & Wallace, 2018), whereas current use in the general adult population appears to be decreasing (3.7% in 2014 to 3.2% in 2018; Dai & Leventhal, 2019). Current use tends to be concentrated among former smokers as well as current smokers, referred to as "dual users" of both cigarettes and e-cigarettes (Coleman et al., 2019). E-cigarettes have generated a great deal of debate within the realm of tobacco control (Fagerström, Etter, & Unger, 2015). Newer products, such as JUUL® ("pod-mods"; device with a nicotine-salt based solution), continue to dramatically shift the landscape of vaping patterns and the impact of electronic nicotine delivery devices (ENDS; Huang et al., 2019).

Electronic Cigarettes

Traditional e-cigarettes are battery-powered devices that contain a heating coil and liquid solution containing propylene glycol, vegetable glycerin, free-base nicotine, and flavoring (Ebbert, Agunwamba, & Rutten, 2015). More contemporary devices, such as pod mods, instead utilize a protonated nicotine ("nicotine salts") solution within a smaller, sleeker device (Patel et al., 2019). ENDS products are not combustible, thus reducing much of the risk typically

associated with cigarette smoking (Glasser et al., 2017). However, e-cigarettes carry other potential risks, such as the availability of flavors that may be attractive to youth, or additional constituents in the solutions that have limited safety data to date (Farsalinos & Polosa, 2014; Glasser et al., 2017). Proponents of e-cigarettes are optimistic that these products will contribute to significant harm reduction if cigarette smokers are able to quit smoking via e-cigarettes (Abrams et al., 2018). However, others are concerned that e-cigarettes could facilitate nicotine addiction for those already smoking, and that those who have never smoked could potentially initiate e-cigarette use that could progress to other products (i.e. cigarettes), which is especially concerning among youth (Glantz & Bareham, 2018). Following an extensive literature review, the National Academies of Sciences and Medicine (2018) released a report that supported the health benefits of vaping over smoking, but also emphasized the risks of increases in cigarette smoking among those who otherwise would not smoke. Thus, more research within both of these domains was suggested.

As with the popularity of the devices, e-cigarette research has expanded, utilizing a variety of methods to assess the impact of e-cigarettes on smoking, including surveys, laboratory paradigms, and intervention trials. Survey results suggest that a majority of individuals initiate e-cigarette use as a means to quit smoking, or as an alternative to cigarettes (Glasser et al., 2017; Pepper, Ribisl, Emery, & Brewer, 2014). Several early cross-sectional studies suggested that e-cigarettes may facilitate smoking cessation (Brown, Beard, Kotz, Michie, & West, 2014; Popova & Ling, 2013; Rutten et al., 2015; Zhu,Gamst, Lee, Cummins, Yin, & Zoref, 2013), whereas other earlier research suggested the opposite, in that e-cigarette use is associated with continued smoking (e.g., Al-Delaimy, Myers, Leas, Strong, & Hofstetter, 2015; Grana, Popova, & Ling, 2014). More recent evidence suggests that higher rates of e-cigarette use (e.g., daily), as opposed

to non-daily use, are associated with a higher probability of quitting smoking (Coleman et al., 2019).

Additional concern has been raised in regards to the remaining individuals labeled as "dual users;" individuals who continue using both cigarettes and e-cigarettes simultaneously (Wills & Sargent, 2017). Consistent with previously mentioned studies, evidence suggests that dual use is associated with a reduction in cigarette use, which aids cessation attempts (Brose, Hitchman, Brown, West, & McNeill, 2015). Indeed, many individual, environmental, and social influences may impact the e-cigarette use trajectories and outcomes of smokers and vapers during and after a quit attempt.

Clinical Utility of E-cigarettes

Thus, a general consensus is growing among public health agencies as evidence increasingly suggests that e-cigarettes aid cessation (National Academies of Sciences & Medicine, 2018; Royal College of Physicians, 2016). The first two published clinical trials to evaluate the potential of e-cigarettes for cessation had limitations (Bullen et al., 2013; Caponnetto et al., 2013), but a Cochrane review meta-analyses showed that there was indeed a promising effect of e-cigarettes on smoking cessation, perhaps beyond that of nicotine replacement therapy (NRT; e.g. patch; McRobbie, Bullen, Hartmann-Boyce, & Hajek, 2014). A secondary analysis of the Bullen et al., 2013 trial showed efficacy of e-cigarettes within their subsample of participants diagnosed with a mental illness (O'Brien, Knight-West, Walker, Parag, & Bullen, 2015). Interestingly, the trials that compared nicotine e-cigarettes to non-nicotine e-cigarettes showed only a slight advantage of nicotine over placebo (McRobbie et al., 2014, *Cochrane Review*); thus, nicotine content may not be critical, and smoking reduction may occur regardless of nicotine content.. Following these trials, other smaller, less-controlled studies

provided additional promising evidence of the clinical efficacy of e-cigarettes (Adriaens, Van Gucht, Declerck, & Baevens, 2014; Tseng et al., 2016). Finally, the most recent RCTs conducted directly testing e-cigarettes to NRT in treatment-seeking smokers concluded that e-cigarettes are effective and well-received, and could also be successfully utilized in conjunction with "gold standard" treatments, like NRT (Hajek et al., 2019; Walker et al., 2020).

Another review evaluated the preliminary evidence from the clinical trials as well as prospective cohort studies comparing the efficacy of e-cigarettes with versus without nicotine to standard smoking cessation treatments (e.g. NRT, buproprion, varenicline; El Dib et al., 2017). The authors concluded that e-cigarettes containing nicotine showed higher rates for smoking cessation without elevated risk for adverse events associated with the treatment, which is consistent to the results found by Hajek et al., 2019. Overall, results from these two reviews suggest that e-cigarette specific factors as well as nicotine may contribute to smoking cessation outcomes observed in clinical trials (Glasser et al., 2017), but more research is needed to determine the extent of these effects.

Nicotine

The mechanisms by which e-cigarettes may be able to reduce cigarette smoking are still under investigation, but preliminary evidence suggests a number of pathways. One factor to consider is the delivery of nicotine via e-cigarettes. Nicotine is the primary psychoactive ingredient in cigarettes, and is considered be the "addictive" component that drives continued smoking (Benowitz, 1988). Due to its pharmacologic effects, nicotine is the primary reinforcer of cigarette smoking, but nicotine also reinforces some of the secondary components related to smoking (Caggiula et al., 2009). That is, nicotine maintains smoking behavior through direct drug administration as well as the conditioned response to stimuli and cues related to smoking.

This being stated, the standard recommended treatment for smoking cessation includes utilizing nicotine replacement therapy (NRT) to alleviate withdrawal symptoms and cigarette cravings during the quit attempt (Fiore et al., 2000). With a physical withdrawal aid, it is suggested that other habitual aspects of cigarette smoking can be addressed through behavioral and psychological means, such as those delivered via counseling.

Considering that e-cigarettes also deliver nicotine, some proponents view these devices as an updated version of NRT (Elam, 2015). First-generation, primitive models of e-cigarettes showed the ability to suppress cigarette withdrawal symptoms during periods of abstinence (Bullen et al., 2010). More recent laboratory-based studies utilizing more advanced models have continued to show that e-cigarette use can reduce symptoms of smoking withdrawal (Dawkins & Corcoran, 2014; Farsalinos et al., 2014; Jorenby, Smith, Fiore, & Baker, 2017; Vansickel & Eissenberg, 2013). Outside of the laboratory, e-cigarette users often self-report that vaping can alleviate cravings and other symptoms of nicotine withdrawal (Etter & Bullen, 2011).

Given that nicotine plays a powerful pharmacologic role in smoking behaviors (Robinson & Pritchard, 1992), e-cigarette use is likely influenced by nicotine as well. There is evidence to support that e-cigarette use can lead to dependence; however measurement of vaping-induced nicotine dependence can be difficult to capture due to the heterogeneity of devices and use patterns (Bold et al., 2018; Piper, Baker, Benowitz, Smith, & Jorenby, 2019; Martínez et al., 2019). Indeed, regular e-cigarette users report experiencing withdrawal symptoms when abstaining from vaping (Hughes & Callas, 2019), and neuroimaging studies demonstrate these effects are similar to cigarette withdrawal (Hobkirk et al., 2018). Overall, the mentioned research on the role of nicotine in e-cigarette use suggests that effects of nicotine impact outcomes of both e-cigarette use distinctly, and the combined dual use of cigarettes and e-cigarettes.

Non-nicotine Aspects

Non-pharmacologic factors separate from and/or enhanced by the effects of nicotine also drive smoking behaviors (Robinson & Pritchard, 1992). One explanation of this phenomena lies within expectancy theory, which posits that beliefs about a drug learned through biological, social, and experiential means can contribute to the outcome of drug use (Goldman, Brown, & Christiansen, 1987). Expectancies regarding smoking include a number of factors that are secondary to the drug, such as sensorimotor stimulation, social facilitation, affective regulation, and craving reduction (Brandon, Juliano, & Copeland, 1999; Copeland, Brandon, & Quinn, 1995). Expectancies about nicotine content have been shown in placebo laboratory paradigms to influence various outcomes of smoking (Juliano & Brandon, 2002) and, more recently, e-cigarette use (Copp, Collins, Dar, & Barrett, 2015; Palmer & Brandon, 2018; 2019).

Given the evidence of non-pharmacolgic influcenes that enhance effects of nicotine from cigarette smoking, it seems likely that similar features maintain e-cigarette use as well. Palmer and Brandon (2018) utilized a balanced-placebo design to parse effects of drug content (nicotine, non-nicotine) from information about the drug (told receiving nicotine, told not receiving nicotine) among dual users and former smokers who vaped. Results showed that among dual users, cravings for cigarettes declined when the participants were told they were receiving nicotine, regardless of the actual drug content. In other words, expectancies about nicotine drove craving reduction effects to a greater degree than the drug itself. In terms of cravings to vape and other outcomes, drug X instruction interactions were observed, illustrating the impact of expectancies in addition to drug effects (Palmer & Brandon, 2019). As beliefs about receiving nicotine appear to drive many of the reported effects of vaping, other non-pharmacologic

influences associated with nicotine should also be evaluated to assess their contribution to e-cigarette use experience.

In line with known tobacco expectancies, sensory factors have long been thought to be a major contributor to smoking behaviors above and beyond the effects of nicotine. For example, the administration of non-nicotine smoke, the pace at which one inhales and exhales, the physical anesthetic sensations of smoking, and the tactile manipulation of cigarettes have all been manipulated in laboratory studies to show their contributions to the satiating outcomes of smoking beyond the effects of nicotine (Rose, Behm, Westman, & Johnson, 2000). In essence, all of these elements can be considered as cues that are associated with nicotine delivery and strengthened by the nicotine itself. Rose (2006) suggested that these could be utilized as targets for future research and treatment development in conjunction with a NRT. In another study, Rose, Behm, Westman, Bates, and Salley (2003) designed a paradigm in which participants received intravenous (IV) nicotine or saline, either alone or with a cigarette (usual brand or denicotinized). Whereas IV nicotine produced some satisfaction, the addition of a denicotinized cigarette increased satisfaction levels to the same degree as smoking a usual brand cigarette without IV nicotine. Therefore, nicotine itself was insufficient to produce satiation, and instead required the addition of a sensorimotor component (denicotinized cigarettes). Thus, the factors secondary to the direct administration of nicotine produced similar responses as if one was receiving nicotine. The mechanisms by which this is possible can be explained within the context of theories of learning.

Theories of Learning

Behavioral theories of drug use behaviors incorporate theories of learning such as classical conditioning, operant conditioning, and social learning theory (Bandura, 1977; Pavlov,

2010; Siegel, 1983; Tolman, 1948). In short, drug administration can produce a rewarding effect that is desired by an organism. As drug administration continues, secondary and/or environmental cues may become associated with the anticipated receipt of the drug. Additionally, behaviors to obtain the drug are positively reinforced through appetitive drug effects and negatively reinforced through avoidance of aversive withdrawal symptoms. Indeed, pharmacologic effects of the drug may strengthen these reinforced associations, as appears to be the case with nicotine.

To begin, it is important to understand the neurological mechanisms of nicotine as a reward. Nicotine acts in a biphasic manner, in that it activates cortical structures within the brain (e.g. those associated with attention and speed) as well as reducing activity in the limbic system, which may be responsible for the reported affective alterations associated with smoking (Lujic, Reuter, & Netter, 2005). Thus, nicotine produces multiple dimensions of reward within these brain structures, aiding the positive and negative reinforcement (Watkins, Koob, & Markou, 2000). Nicotine appears to strongly impact the mesolimbic dopamine system, which is implicated in the learning of rewards and strengthening of these relationships (Corrigall, Franklin, Coen, & Clarke, 1992). Thus, continuation of nicotine administration not only strengthens the brain's pharmacologic response to the drug, but it reinforces the repeated administration within a variety of domains of secondary reinforcers.

Therefore, the strong effects resulting from sensorimotor aspects of smoking are considered a result of the synergistic interactions of conditioned learning, and nicotine effects within related brain regions (Lujic et al., 2005). In addition to Rose et al. (2003), several other studies have parsed the sensorimotor aspects of smoking from those associated with nicotine (e.g., Brauer et al., 2001; Guillot et al., 2015; Levin, Rose, Behm, & Caskey, 1991; Perkins,

Karelitz, Conklin, Sayette, & Giedgowd, 2010; Rose, Behm, & Levin, 1993; Westman, Levin, & Rose, 1992), all of which have produced similar effects on affect regulation, satisfaction, and satiations. That is, the sensorimotor component enhanced these experiences above and beyond simple nicotine administration. Interestingly, however, smokers tend not to rate the sensorimotor aspects of smoking very highly when answering questions measuring motives for smoking (Russell, 1974; Tate & Stanton, 1990).

Altogether, this evidence suggests that sensorimotor aspects of smoking are learned, secondary reinforcers paired with the reinforcing effects of nicotine delivery. At the same time, the sensorimotor aspects of smoking may activate expectancy effects, and in turn, could be a primary reinforcer through related means (such as relaxation or distraction). Sensorimotor stimuli play an important, albeit unconscious, role in smoking behaviors, and therefore should be understood in the context of e-cigarette use.

Sensorimotor Aspects of Vaping

E-cigarettes, especially earlier generations, mirror aspects of reinforced sensorimotor factors of smoking, which may very well have been the primary motive behind the design. Indeed, early generations of e-cigarettes mimicked the size and shape of cigarettes, and some even glowed on the end. Some research has suggested that these aspects may be attractive to individuals considering quitting smoking and can aid reductions in cravings to smoke (Dawkins, Munafò, Christoforou, Olumegbon, & Soar, 2016). Newer designs have deviated from the original aesthetic presentation, but they still provide the imitation of the physical movements of smoking. In contrast to motives reported for smoking, many vapors actually describe this replication of sensorimotor aspects of smoking to be a primary motivator for using e-cigarettes for smoking cessation (Caponnetto, Polosa, Russo, Leotta, & Campagna, 2011). One study found

that just holding an e-cigarette was insufficient to reduce desire to smoke; however allowing the use of placebo or nicotine e-cigarettes produced reductions in desire to smoke. (Dawkins, Turner, Hasna, & Soar, 2012). Thus, the sensorimotor manipulation, even without nicotine, was sufficient to produce changes beyond those elicited from the cue of just holding the e-cigarette.

The conditioned effects of the sensorimotor aspects of vaping in contrast to the receipt of nicotine was parsed by Van Heel, Van Gucht, Vanbrabant, and Baeyens (2017). In this study, the researchers crossed e-cigarette nicotine content (nicotine or placebo), flavor (tobacco or apple), sensorimotor manipulation (using hand or attached to a unipod) and visual aspect (eyes open or blindfolded) in abstinent smokers with minimal e-cigarette experience. Participants were given one week to test an e-cigarette, and then participated in an ad-lib vaping lab session and answered questions regarding cravings. Results showed that the sensorimotor aspect of vaping had the most robust effect on craving reduction, especially when nicotine was not present. However, a major limitation of this study was the use of participants inexperienced with vaping, which the authors understood could have confounded responses through the novelty of e-cigarettes generally, as well as the flavor, sensory, and visual components that differ from combustible cigarettes. Additionally, the study was underpowered to assess the many factors (N = 81, 16 condition groups). However, these results suggest that the non-nicotine, sensorimotor aspects of e-cigarette use can have effects on outcomes of use, regardless of nicotine content.

The Present Study

The purpose of the present study was to parse the influences of nicotine and sensorimotor manipulation on the reported outcomes of e-cigarette use, with a particular emphasis on those that may maintain vaping behavior, such as cravings. Evaluating these mechanisms contributes to the understanding of dual use trajectories of cigarettes and e-cigarettes, but also provides

insight into the addictive liability of e-cigarettes via habitual motor actions. In the present study, participants were randomized to receive an e-cigarette that either contained nicotine or did not contain nicotine, and at the same time were randomized to a naturalistic motor delivery or a stationary delivery mechanism that minimized the sensorimotor aspects of vaping (sensorimotor deprivation). Thus, four experimental conditions emerged: 1) given nicotine/normal delivery; 2) given nicotine/stationary delivery; 3) given no nicotine/normal delivery; and 4) given no nicotine/stationary delivery. From this, the independent influences of drug and sensorimotor agency, as well as their synergistic interactions, were evaluated on the outcome variables related to use motivation. A similar approach to Palmer and Brandon (2018, 2019) was utilized, which allows for the simultaneous evaluation of multiple outcome variables in addition to the aforementioned foci. However, the present study did not include an expectancy manipulation. That is, participants were told the actual drug dosage to be received (i.e., open label), which likely activated consistent expectancies. Whereas this did not allow for the evaluation of pure drug effects absent of expectancies, it represents the "real world" effects of drug delivery in conjunction with accompanying expectancies. Furthermore, this study addresses the limitation of novelty that occurred in previous sensorimotor evaluations of e-cigarettes by using a sample of daily e-cigarette users who were also currently smoking (i.e. "dual users"). With this sample, the clinical utility of e-cigarettes is assessed alongside the addictive liability.

Primary Aims and Hypotheses

Primary Aim 1: Test the main effect of delivery mechanism on outcomes

In line with previous research, it was predicted that there would be a main effect of delivery mechanism on subjective, psychosocial primary outcomes such that the normal delivery condition would produce different responses on the outcome variables than in the sensorimotor

deprivation condition. Specifically, it was predicted that those in the natural delivery condition would show reduced cravings to smoke, cravings to vape, and negative affect, and increased satisfaction, reward, and enjoyment of use. These predictions are consistent with previous studies evaluating the effects of non-nicotine manipulation on such outcomes (Dawkins et al., 2012; Palmer & Brandon, 2018, 2019; Rose, 2006; Van Heel et al., 2017).

Primary Aim 2: Assess the main effects of nicotine on outcomes

It was hypothesized that there would also be a main effect of drug content, in that participants who received nicotine would exhibit different levels in the outcome variables than those who did not receive nicotine. More specifically, those participants who received an e-cigarette containing nicotine would show greater attention, lower appetite, lower aversion and greater respiratory tract sensations. Once again, it was predicted that these effects would be observed regardless of the delivery mechanism (sensorimotor deprivation or natural delivery). This prediction is consistent with known effects of nicotine and previous balanced-placebo studies of nicotine and alcohol (L. Dawkins & Corcoran, 2014; Harrell & Juliano, 2012; Hull & Bond, 1986; Palmer & Brandon, 2018; 2019).

Secondary Aim 1: Explore condition interactions

Beyond main effects that are posited to emerge, there is potential for drug X sensorimotor manipulation interactions which could reveal moderation effects of nicotine and delivery mechanism. For instance, nicotine may enhance some rewarding qualities of the natural delivery method, as nicotine is strongly associated with the learned secondary reinforcers (Corrigall et al., 1992; Lujic et al., 2005). However, the craving reduction effects of nicotine may only be present within the sensorimotor deprivation condition, as has been observed in previous research (Rose et al., 2003; Van Heel et al., 2017). If this effect was replicated in the present study, it would

further illustrate the significance of sensorimotor conditioned reinforcers on craving reduction motivations of e-cigarette use.

Secondary Aim 2: Explore participant characteristics as moderators of nicotine and sensorimotor delivery manipulation

Participant characteristics, baseline expectancies about e-cigarettes, and e-cigarette dependence were explored as moderator variables, as previous research and theory indicates that these factors may influence response to e-cigarette use. In particular, craving reduction expectancies, sensorimotor expectancies, dependence, and gender were tested as moderators of sensorimotor and/or drug manipulation.

Gender differences in smoking and vaping outcomes have been observed in previous cigarette and e-cigarette research (Copp et al., 2015; Piñeiro et al., 2016; Smith, Bessette, Weinberger, Sheffer, & McKee, 2016), therefore, it was hypothesized that gender would emerge as a moderator of outcomes in the present study. For example, some evidence suggests males may be more sensitive to nicotine itself, whereas females could be more influenced by psychosocial aspects of smoking (Benowitz & Hatsukami, 1998). Therefore, differences could have emerged in gender moderations of main effects of drug and main effects of delivery mechanism. Additionally, it was possible that expectancies would moderate the effects of delivery mechanism, as expectancies are developed and strengthened from continued e-cigarette use experience. Thus, expectancies might have been activated by the sensorimotor aspects of vaping. Specific expectancies (negative consequences, negative reinforcement, positive reinforcement, appetite/weight control, smoking expectanices, and vaping expectancies) were therefore tested as moderators. Finally, the degree to which the drug produces outcome effects may be related to level of dependence; therefore, dependence was tested as a moderator of drug

effects. Specifically, that those with higher dependence would show a greater effect of drug on outcomes hypothesized to be most influenced by drug (e.g. attention, appetite, aversion, respiratory tract sensations).

METHOD

Sample Size

Sample size analyses were conducted using G-power (Faul, Erdfelder, Lang, & Buchner, 2007). The 2x2 study was powered for the primary aim of assessing the main effects of drug and sensorimotor manipulation on cravings to smoke and cravings to vape. Thus, secondary, exploratory aims (secondary outcome variables) may be somewhat underpowered. In Palmer and Brandon (2018), the effect size for the main effect of instructions on cravings to smoke was f = .31, and for the interaction of drug X expectancy effects, f = .21. Thus, it was determined that a sample size of 128 (32 per group) was required for the analysis to achieve power of .80 for detecting main effects, with a medium sized effect and a two-tailed alpha level of .05.

Participants

Participants were recruited through flyers at local vape shops and community locations (e.g., gas stations, convenience stores, grocery stores, restaurants, laundromats, salons/barbershops, libraries, colleges and universities), online advertisements (e.g., Craigslist, Indeed, online forums), and the undergraduate psychology participant pool (SONA).

Participants were screened over the phone for the following eligibility criteria: 1) At least 18 years old; 2) Current daily e-cigarette users (use at least once per day for the past 30 days, must use nicotine solutions, must like tobacco, menthol, fruit, or dessert flavor); 3) Smoking history of at least 100 lifetime cigarettes; 4) Current smoking rate of at least 1 cigarette per week

for at least 30 days[1]; 5) No current engagement in an *e-cigarette* cessation attempt; and 6) Not currently pregnant, attempting to get pregnant, or nursing (by self-report). A study flow diagram detailing participant recruitment and randomization can be seen in Figure 1. Randomization was stratified by gender and flavor using an 8-block system. This was done to account for gender differences in response to nicotine (Benowitz and Hatsukami, 1998) as well as differences in nicotine absorption between various flavor constituents, as suggested by prior literature (Helen, Dempsey, Havel, Jacob, and Benowitz, 2017).

Baseline Measures

Baseline measures were assessed to describe sample characteristics, including potential moderator variables.

Baseline and Demographic Questionnaire

Participants reported time since last meal, time since last cigarette, and time since last e-cigarette use. A research assistant collected a carbon monoxide (CO) reading upon arrival. Participants then completed questionnaires capturing basic demographic information, smoking history, and vaping history. (See Appendix C, D, E, and F). Smoking and Vaping histories included collection of number of cigarettes smoked/number of vaping sessions per day, typical brands/devices used, and readiness to quit, among other variables.

[1] Prior to 2/21/19, participant eligibility criteria stated that eligible individuals would smoke at least one cigarette per day. However, due to difficulties in recruiting this population, the authors and committee members agreed to change the criteria to match that of Palmer & Brandon (2018). Prior to this change, 49 participants were recruited under the previous criteria and completed the study. Previously ineligible participants who now met criteria were contacted to assess interest in re-screening for the study.

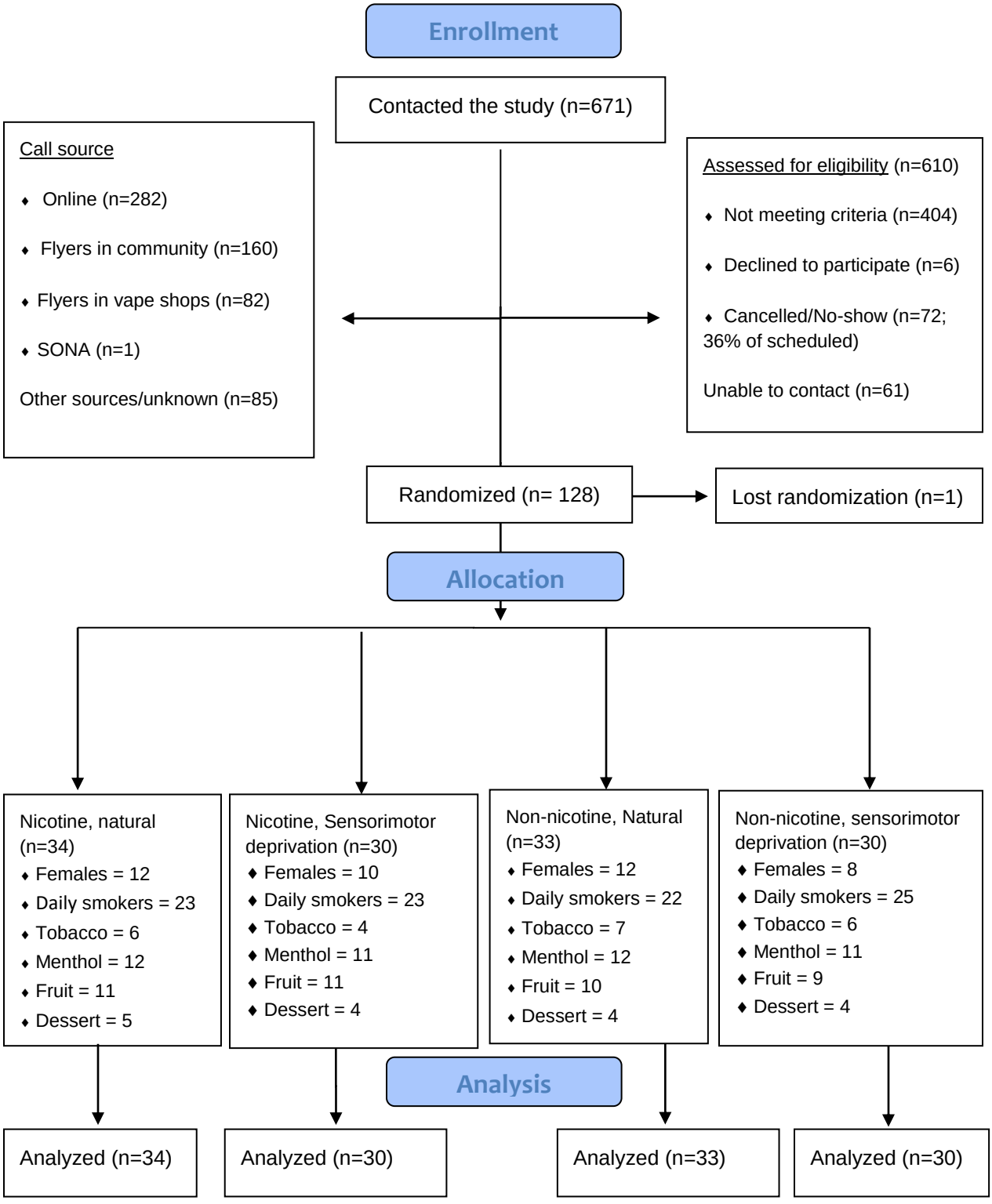


Figure 1. Study flow

Expectancies about E-cigarettes

Participants' expectancies about the effects of e-cigarette use was measured using the Short Form Vaping Consequences Questionnaire (S-VCQ; Morean & L'Insalata, 2017). Participants are asked to rate the likelihood of different outcomes on a on a scale of "0 / completely unlikely" to "9 / completely likely." The items in this measure load onto four factors: Negative consequences, negative reinforcement, positive reinforcement, and appetite/weight control. In addition, several items modified from the Smoking Consequences Questionnaire (SCQ; Brandon & Baker, 1991; SCQ-A; Copeland et al., 1995) were added to assess craving-related expectancies more directly for both cigarette and e-cigarette cravings. (α=.91; See Appendix G). For analyses, two scores were created: Smoking craving expectancies and vaping craving expectancies. These scores were composed of items related to general nicotine craving expectancies as well as specific items related to craving expectancies for each product type.

Dependence

Dependence on e-cigarettes was measured using the Penn State Electronic Cigarette Dependence Index (ECDI; Foulds et al., 2014; (α=.695). This questionnaire was derived from the Cigarette Dependence Index, which determined cigarette dependence using items and constructs found to be the most predictive of future smoking. The questionnaire was modified and tested on e-cigarette users to assess levels of e-cigarette dependence as compared to cigarette dependence. Scores range from 0-20, with higher scores indicating higher dependence. This measure has been shown to be highly correlated with other measures of e-cigarette dependence, as well as self-reported addiction (Piper et al., 2019). Additionally, cigarette dependence was measured with the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerström, 1991; α=.11 among daily smokers, α=.36 among non-daily smokers). Scores on this

measure range from 0-10, with higher scores indicating greater dependence. (See Appendix D, H).

Withdrawal

To assess the effects of nicotine withdrawal upon arrival to the study session, the Minnesota Nicotine Withdrawal Scale was be administered (MNWS; Hughes & Hatsukami, 1986; α=.78). This measure was designed to be sensitive to acute changes in nicotine withdrawal, as well as map onto DSM diagnostic criteria for tobacco withdrawal. Participants rated the extent to which they have experienced the 7 symptoms over the past 3 hours on a five-point Likert scale, with "0" indicating "strongly disagree" and "4" indicating "strongly agree," for a score range of 0 – 28. (See Appendix I).

Dependent Variables

The following were assessed before and after the ad-lib "vaping" session, with the exception of the measures of attention and subjective effects of vaping, which was only administered after.

Cravings to Smoke and Use E-cigarettes

The desire to smoke and the desire to use e-cigarettes was measured both pre- and post-ad-lib session using a 3-item adaptation of the Questionnaire of Smoking Urges-Brief (QSU; αs=.90-.94). The QSU is a 10-item questionnaire that measures desire and intentions to smoke (Cox, Tiffany, & Christen, 2001; Tiffany & Drobes, 1991); however, a briefer, 3-item adaptation assessing urge to smoke (Kozlowski, Pillitteri, Sweeney, Whitfield, & Graham, 1996) was utilized to assess both cigarette and e-cigarette urges, as was administered by Palmer and Brandon (2018; αs=.90-.92). On each item, participants are asked to report the degree to which

they agree with a particular statement from "0 – strongly disagree" to "6 – strongly agree," for a score range of 0-24. (See Appendix J, K).

Mood

Changes in self-reported mood as a result of cigarette smoking are a result of conditioning effects, as well as the effects of nicotine withdrawal (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Brandon, Herzog, Irvin, & Gwaltney, 2004), and thus, may be related to other non-pharmacologic stimuli. To assess changes in mood state pre- and post- ad-lib session in the present study, The Positive and Negative Affect Scale (PANAS; Watson, Clark, & Tellegen, 1988; αs=.79-.84) was administered. Participants rate the degree to which they are experiencing different mood states on a scale of 1-5, which then creates two combined scores for both positive and negative affect (range 10-50). In the first balanced-placebo design with cigarettes, it was found that both nicotine and expectancies impacted the reduction of a negative mood state following a mood manipulation (Juliano & Brandon, 2002). In contrast, Palmer and Brandon (2019) did not observe significant changes in affect in a balanced-placebo design. Nevertheless, it is possible that the sensorimotor stimuli may better activate expectancies related to affect regulation. (See Appendix L).

Appetite

Nicotine has a suppressive metabolic effect on appetite (Winders & Grunberg, 1990). Many smokers, especially females, report expectancies that smoking reduces appetite and aids in weight loss (Brandon et al., 1999). Changes in appetite were assessed pre- and post- ad-lib session using a Visual Analogue Scale (VAS; Flint, Raben, Blundell, & Astrup, 2000; αs=.76-.85), which utilizes a tick mark system for participants to rate their degree of hunger. This scale has been validated to assess appetite changes in smokers in previous research (Jessen, Buemann,

Toubro, Skovgaard, & Astrup, 2005). Scores range from 0-285, with higher scores indicative of increased appetite. (See Appendix M). Once again, Palmer and Brandon (2019) were unable to show evidence of this effect for e-cigarettes, but conditioned learning of these expectancies should continue to be evaluated.

Reinforcement from E-cigarettes

Following the ad-lib session, participants completed the Modified Cigarette Evaluation Questionnaire (mCEQ; Cappelleri et al., 2007) which has been further modified to measure subjective immediate effects of e-cigarette use (as used in Palmer & Brandon, 2019; α=.895). These effects include Satisfaction (3 items), Psychological Reward (5 items), Aversion (2 items), Enjoyment of Respiratory Tract Sensations (1 item), and Craving (1 item). Scores for each item range from "1 – not at all" to "7 – extremely." (See Appendix N).

Sustained Attention

Nicotine has been shown to have beneficial effects on short-term sustained attention (Heishman, Kleykamp, & Singleton, 2010), as evidenced by performance on tasks such as the Rapid Visual Information Processing Task (RVIP; Harrell & Juliano, 2012; Wesnes & Warburton, 1983). Palmer and Brandon (2019) found effects of drug on sustained attention, in that those who received nicotine performed better on this task. The task was administered via E-Prime (Psychology Software Tools, Inc.).

Participants viewed a series of single digits presented at a rate of 100 digits per minute for approximately 4 minutes, which is sufficient time to detect effects due to nicotine withdrawal (Hendricks et al., 2006). Participants were told to respond (pressing the spacebar) to a specific target series of three consecutive odd or three consecutive even digits. Reaction time was recorded, with a "hit" defined as correctly identifying the target within 1,500ms. Targets appear

8 times per minute with 8-36 digits appearing between each target. Response sensitivity was calculated using the individual's hit rate (hr; correct responses) and false alarm rate (far; incorrect responses) in the formula $0.5 + [(hr - far) + (hr - far)^2] / 4*hr*(1 - far)$ (Sahgal, 1987), which has been utilized by several studies assessing the effect of nicotine on cognitive performance (e.g. Harrell & Juliano, 2012). For the final analysis, 14 participants were removed (6 = missing data, 8 = outliers/invalid) and a reciprocal transformation was performed on the data to reduce negative skew.

Nicotine Dosing Estimate

Participants completed a brief questionnaire post ad-lib session asking various questions about the e-cigarette provided in the study, including an estimate of the nicotine dose provided (0mg/ml, 6mg/ml, 12 mg/ml, 18 mg/ml, 24mg/ml). (See Appendix O).

Number of E-cigarette Puffs

Number of e-cigarette puffs was confirmed through observation and the reading on the apparatus.

Apparatus

The basic components of the apparatus chosen closely replicates that used in Palmer and Brandon (2018, 2019). (See Appendix P).

E-cigarette

The e-cigarette provided to participants was an "eGo LCD MEGA" 3.6-4.2 Volt, 1100 mAh battery with a 1ml "eGo+" 2.8-Ohm, 510-style clearomizer (transparent tank for the liquid solution that is connected to a heating coil), modified for delivery condition (appendix P). This type of e-cigarette is a second generation device, which consists of a battery attached to a refillable tank, thus allowing for customization of the nicotine solution per randomization and

flavor preference. Because the heating coils in the tanks wane in power over time, and for sanitation purposes, a new tank and mouthpiece was used for each participant. This style is beneficial for several reasons; one being that is better reflects the devices used by participants than first generation "cig-a-like" styles (Bullen et al., 2010), especially among those attempting to quit smoking or who have successfully transitioned to e-cigarettes exclusively (Chen, Zhuang, & Zhu, 2016). Additionally, because of the more advanced heating characteristics, these devices are superior in delivering nicotine compared to disposable styles (Farsalinos et al., 2014; Yingst et al., 2019).

Solution

It is important in drug administration studies that the drug utilized is acceptable and satisfactory for experienced users. Therefore, careful consideration is required when selecting an e-cigarette solution for an experimental study (Blank et al., 2016). The liquid nicotine solution used was a 75% vegetable glycerin (VG), 25% propylene glycol (PG) liquid. This ratio is similar to what many vapers utilize in their typical e-cigarette. In addition, four flavor options were presented to participants: tobacco, menthol, fruit, and dessert. Tobacco and menthol were offered as many dual users prefer tobacco flavors, whereas the other options are preferred by adult e-cigarette users in general (Zare, Nemati, & Zheng, 2018). Finally, a dose of 12mg/ml was used as it replicates that which would be found in a cigarette, but is mid-range in terms of e-cigarette concentration values (Lopez et al., 2016; Ramôa et al., 2015).

The e-liquid used was tested by both the manufacturing vendor and secondarily by Moffitt Cancer Center's Proteomics Core to verify nicotine content. Tested nicotine solutions contained the following contents: Tobacco = 1.6 mg/ml; Menthol = 1.5 mg/ml; Fruit = 1.5 mg/ml; and Dessert = 1.4 mg/ml. Non-nicotine solutions were verified to be nicotine-free.

Delivery Mechanism

Participants randomized to receive their e-cigarette with the stationary delivery (sensorimotor deprivation) mechanism faced a table with a large box containing the e-cigarette. The e-cigarette was held on a stand inside the box, allowing only the mouthpiece to protrude from a designated section of the box. The e-cigarette battery was attached to a foot pedal; when the foot pedal was pressed, the battery was activated, much like the button operates on a typical e-cigarette battery. With this configuration, a majority of visual cues are eliminated as well as any hand motions associated with vaping. Participants used the foot pedal to activate the battery in order to take puffs. (See Appendix P).

Participants randomized to naturalistic movements were presented with the second-generation e-cigarette in its original form. Participants were told to use the e-cigarette as they normally would to take puffs. (See Appendix P).

Procedure

Telephone Screening

All individuals were screened via telephone for eligibility criteria. Qualified, scheduled participants were asked to abstain from using e-cigarettes and combustible cigarettes for three hours prior to the session. Participants were offered a text reminder for these instructions. As an attempt to increase adherence, participants were notified that a breath CO reading would be administered upon arrival. At this time, participants also indicated their flavor preference (tobacco, menthol, fruit, or dessert) for the session. Participants were notified of compensation for the study ($30 or 3 SONA points).

Consent

The experimenter provided the participant with a copy of the consent form, including a brief description of the study, and explained the purpose, risks, benefits, rights, and confidentiality of the study. To mask true intent of the study, participants were told the study was evaluating the different effects from using an e-cigarette. (See Appendix B).

Qualification and Randomization

After signing consent, participants confirmed self-reported abstinence verbally (i.e., "When was your last cigarette/e-cigarette?") and via a CO test. The CO test was administered with no cutoff. Upon qualification, participants were randomized using an 8-block pattern with stratification based on gender (male or female) and flavor preference (tobacco, menthol, fruit, or dessert).

Administration of Baseline Questionnaires

Participants completed demographic and baseline measures as follows: Demographic and Smoking/Vaping History Questionnaire, modified SCQ-A, and Penn State Electronic Cigarette Dependence Scale.

Ad-lib Vaping Session

Participants completed the first administration of dependent measures (QSU and modified QSU, PANAS, and VAS). Participants were then instructed to try an e-cigarette provided by the experimenter, either in natural or stationary (sensorimotor deprivation) configuration. Participants were told whether or not their e-cigarette contained nicotine, according to the randomization. Thus, corresponding expectancies about nicotine content were likely activated, consistent with what participants experience outside of the lab. A timer was presented on a laptop that counted down in 30 second intervals. Participants were instructed to

take 15 puffs from the provided e-cigarette following the sound of a tone set at every 30 seconds (consistent with Ramôa et al., 2015). Participants were monitored (but not recorded) via video to validate compliance. After 15 puffs, the research assistant informed the participant that the session was complete and they could stop vaping. Number of puffs was confirmed and recorded from the puff counter on the device.

Post-Vaping Session Measures

After the ad-lib session, the following dependent measures were administered: Modified mCEQ, QSU and modified QSU, PANAS, VAS, RVIP, and Nicotine Dosing Estimate Form.

Compensation and Debriefing

Participants were debriefed and compensated for their time and travel. (See Appendix Q).

Data Analysis Plan

To test group equivalence on demographic characteristics and nicotine dependence, a series of chi-squares or analyses of variance (ANOVAs) were conducted comparing the conditions. If a main effect was found, this variable was entered as a covariate in the subsequent analyses for that specific main effect.

Next, to test the hypotheses in Aims 1 and 2, condition groups were compared using factorial ANOVA or analysis of covariance (ANCOVA; if a baseline characteristic is used as a covariate). ANOVAS were 2 X 2: Drug (nicotine/non-nicotine) by delivery (sensorimotor deprivation/natural motor). ANOVAs were run on each outcome variable of interest within the predicted main effect domain: Sensorimotor manipulation effects were tested on the primary outcomes of cravings to smoke and cravings to vape, and the secondary outcomes of positive/negative affect, satisfaction, reward, and enjoyment. Drug manipulation was tested on secondary outcomes of attention, appetite, aversion, respiratory tract sensations. As the primary

variable of interest is cravings, and previous research has demonstrated consistent effects within this domain, alpha was set at .05. Since the secondary variables are ancillary, the Holm method was used to correct alpha and reduce chance for Type I error for each of these tests. If significant main effects or interactions were found, post-hoc t-tests evaluated the directionality of the results, with alpha set at .05.

Some research supports distinct gender differences in response to nicotine; thus, to test this influence, the previous analyses were re-analyzed as 2x2x2 ANOVAs, with gender as the third factor. This is consistent with Palmer and Brandon (2018). Additionally, analyses were re-analyzed using withdrawal (MNWS) as a covariate to control for baseline withdrawal. Finally, other moderator variables were evaluated using hierarchical regression, which essentially tests to see if a significant moderator X effect (drug or sensorimotor manipulation) interaction arose. The covariate (if applicable) was entered as the first step, with main effects following, the moderator as the next step, and the final step as a main effect X moderator interaction term. If this interaction was significant, post-hoc simple effects analyses evaluated the directions of these effects. Alpha was set at .05.

RESULTS

Participant characteristics

One participant was removed from analyses (randomization was mistakenly not recorded) for a final sample size of 127. Participant demographic and characteristic information are presented in Tables 1 and 2, respectively. Daily dual users were defined as those who vaped at least once daily and smoked at least one cigarette per day over the past month, and daily vaping non-daily smokers were defined as those vaping every day and smoking at least one cigarette per week over the past month. Overall, the sample was diverse and representative of the geographic area of recruitment. It should be noted that there was a great deal of variability in reported e-cigarette use patterns. Daily dual users and daily vaping non-daily smokers were compared across characteristics (Table 2), with differences found in cigarettes smoked per day, type of device used, and e-cigarette dependence. Results from chi-squared tests and ANOVAs did not show any significant differences between conditions on any demographic or pre-test variables, *ps* > .05.

Table 1. *Participant demographics (N=127)*

Variable	Description	Mean or N	% or SD
Age	(range 18-66)	33.64	12.12
Gender	Male	85	66.9%
	Female	41 (42*)	32.28% (33.1%*)
	Transgender*	1	<1%
Race	American Indian / Alaska Native	1	<1%
	Asian	5	3.9 %
	Native Hawaiian / Pacific Islander	0	0%
	Black / African American	42	33.1%
	White / European Origin	75	59.1%
	Did not report	4	3.1%
Ethnicity	Hispanic / Latino	23	18.1%
	Non-Hispanic	105	81.9%
Marital Status	Single	95	74.8%
	Married	10	7.9%
	Separated	9	7.1%
	Divorced	10	7.9%
	Widowed	3	2.4%
	Did not report	0	0%
Sexual Orientation	Identify as LGBT+	19	14.9%
	Heterosexual	106	83.5%
	Did not report	2	1.6%
Education	Less than high school	14	10.9%
	High School	32	25.2%
	Some College	40	31.5%
	Tech School / Associate's	19	15%
	4-year College Degree	11	8.7%
	Beyond 4-year Degree / Professional Degree	8	6.2%
Income	Under $10,000	31	24.6%
	$10,000 - $29,999	46	36.2%
	$30,000 - $49,999	28	22.0%
	$50,000 - $69,999	12	9.4%
	Above $70,000	9	7.1%
	Did not report	1	<1%

Note: No significant differences between conditions were found for any of the variables.
*Participants that identified as transgender were asked their gender preference on the day of the session, and were coded as such throughout the remainder of the analyses.

Table 2. *Participant smoking and vaping characteristics*

	Full sample (N=127) #, mean (%, SD)	**Daily dual users (n=93) #, mean (%, SD)**	**Daily vapers, non-daily smokers (n=34) #, mean (%, SD)**
Cigarettes per day: <10	62 (48.8%)	**32 (34.4%)****	**29 (85.3%)****
11-20	41 (32.3%)	**40 (43%)****	**2 (5.9%)****
>20	24 (18.9%)	**22 (23.6%)****	**2 (5.9%)****
Number of daily e-cigarette uses	20.17 (27.49)	**14.7 (19.5)***	**35.8 (39.3)***
Minutes per e-cigarette use session	10.39 (17.75)	12.1 (19.7)	5.1 (4.8)
Puffs per e-cigarette use session	26.65 (122.24)	31.7 (140.3)	11.1 (10.7)
Report vaping continuously all day	59 (46.5%)	**36 (38.7%)****	**23 (67.6%)****
Currently using: 1st generation devices	39 (30.7%)	**32 (34.4%)****	**7 (20.6%)****
2nd generation "pen" devices	11 (8.6%)	**10 (10.8%)****	**1 (2.9%)****
3rd generation "mod" devices	29 (22.8%)	**23 (24.7.6%)****	**6 (17.6%)****
pod-mod/JUUL® devices	36 (28.3%)	**19 (20.4%) ****	**17 (50%)****
Multiple types	9 (7.1%)	**7 (7.5%)****	**2 (5.9%)****
Typical nicotine content: mg/ml	18.41 (9.84)	18.63 (9.84)	17.31 (10.18)
% (nicotine salts)	5 (0)	5 (0)	5 (0)
Flavor used most often: Tobacco	19 (15%)	17 (18.2%)	2 (5.9%)
Menthol	45 (35.4%)	32 (34.4%)	14 (41.2%)
Fruit	40 (31.5)	27 (29%)	13 (33.2%)
Other	15 (11.8%)	14 (15.1%)	1 (2.9%)
E-cigarette initiation to quit/reduce smoking	67 (52.8%)	48 (51.6%)	19 (55.9%)
Reported past e-cigarette cessation attempt	39 (30.7%)	28 (30.1%)	11 (32.3%)
Reported no plans to quit smoking	8 (6.3%)	6 (6.4%)	2 (5.8%)
Reported no plans to reduce vaping	44 (34.6%)	34 (36.6%)	10 (29.4%)
Flavor requested for ad-lib session: Tobacco	23 (18.1%)	20 (21.5%)	3 (8.8%)
Menthol	46 (36.2%)	34 (36.6%)	12 (35.2%)
Fruit	41 (32.3%)	25 (26.7%)	16 (47%)
Dessert	17 (13.4%)	14 (15%)	3 (8.8%)
Mean EDCI (range: 0-20)	9.75 (4.85)	**8.8 (4.6)***	**12.1 (4.9)***
Mean FTND (range: 0-10)	4.1 (1.79)	4.1 (1.7)	4.1 (1.9)

Note: In comparing daily dual users versus daily vaping non-daily smokers, * $p < .05$, ** $p < .01$.

Manipulation effects: Drug X Sensorimotor Manipulation

The independent and interaction effects of both nicotine content and sensorimotor manipulation on the hypothesized dependent variables were tested with 2 (drug) X 2 (delivery) ANOVAs, or ANCOVAs, if controlling for pre-ad-lib session scores. Results are shown in Table 3.

Primary Aim 1

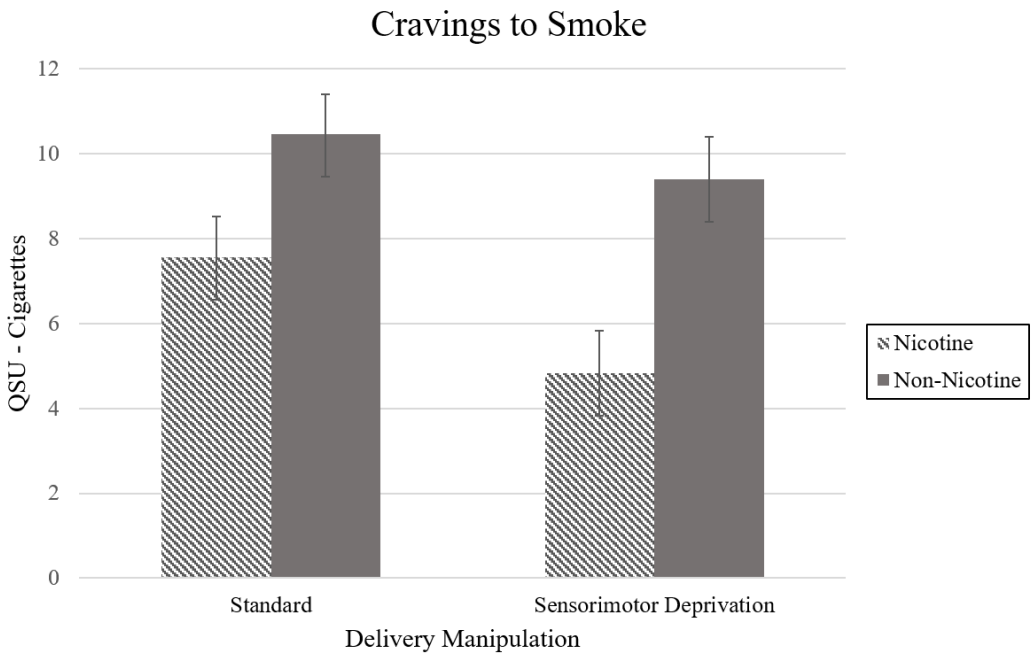
First tested were the variables hypothesized to be affected primarily by sensorimotor manipulation (cravings to smoke and vape, affect, psychological reward, and satisfaction).

Cravings to Smoke. A 2 X 2 (drug x sensorimotor manipulation) ANCOVA (using pre-test QSU scores as a covariate) showed both a significant effect of drug (F [1, 120] = 14.23, $p <$ .001, $\eta^2 = 0.11$) and a nearly significant effect of sensorimotor manipulation (F [1, 120] = 3.77, p =.055, $\eta^2 = 0.03$) on reducing craving to smoke as measured by the QSU. Covariate-adjusted post-test scores were lower among those who received nicotine (M = 6.19) than those who did not receive nicotine (M = 9.92). In addition, covariate-adjusted post-test scores were lower among those who received the sensorimotor deprivation apparatus (M = 7.10) than those who received the standard delivery (M = 9.01). See Figure 2.

Table 3. *Manipulation effects: Drug X sensorimotor manipulation*

	Adjusted (post-measure) means				Marginal means: Drug		Marginal means: Delivery				
Variable	**Nicotine, natural**	**Nicotine, Sensorimotor deprivation**	**Non-nicotine, natural**	**Non-nicotine, Sensorimotor deprivation**	**Nicotine**	**No Nicotine**	**Natural**	**Sensorimotor Deprivation**	**F (Nicotine)**	**F (Sensorimotor)**	**F (Nicotine X Sensorimotor)**
Subjective, psychosocial variables											
QSU- smoke	7.56	4.82	10.45	9.39	6.19	9.92	9.01	7.10	**14.23****	**3.77**†	0.73
Modified QSU-vape	8.28	5.25	10.51	9.34	6.76	9.93	9.40	7.29	**12.01****	**5.21***	1.04
PANAS- positive	30.62	30.33	27.26	30.42	30.47	28.84	28.94	30.37	2.38	1.83	2.64
PANAS- negative	12.37	13.40	14.97	13.12	12.89	14.04	13.67	13.26	3.66†	0.48	**5.79***
Modified mCEQ-Psychological reward	19.91	20.33	15.42	15.40	20.12	15.41	17.67	17.87	**9.54****	0.02	0.02
Modified mCEQ-Satisfaction	14.82	14.23	12.39	12.47	14.53	12.43	13.61	13.35	**6.49***	0.10	0.16
Objective, physiological variables											
VAS - hunger	130.52	130.20	158.25	136.58	130.35	147.41	144.38	133.39	2.91†	1.20	1.14
RVIP sensitivity	1.49	1.54	1.54	1.54	1.52	1.54	1.52	1.54	0.68	0.54	0.33
Modified mCEQ-Enjoyment of respiratory tract sensations	4.41	4.03	4.36	4.17	4.22	4.27	4.38	4.10	0.01	0.62	0.06
Modified mCEQ-Aversion	3.47	4.33	3.30	3.23	3.90	3.27	3.39	3.78	2.36	0.93	1.28

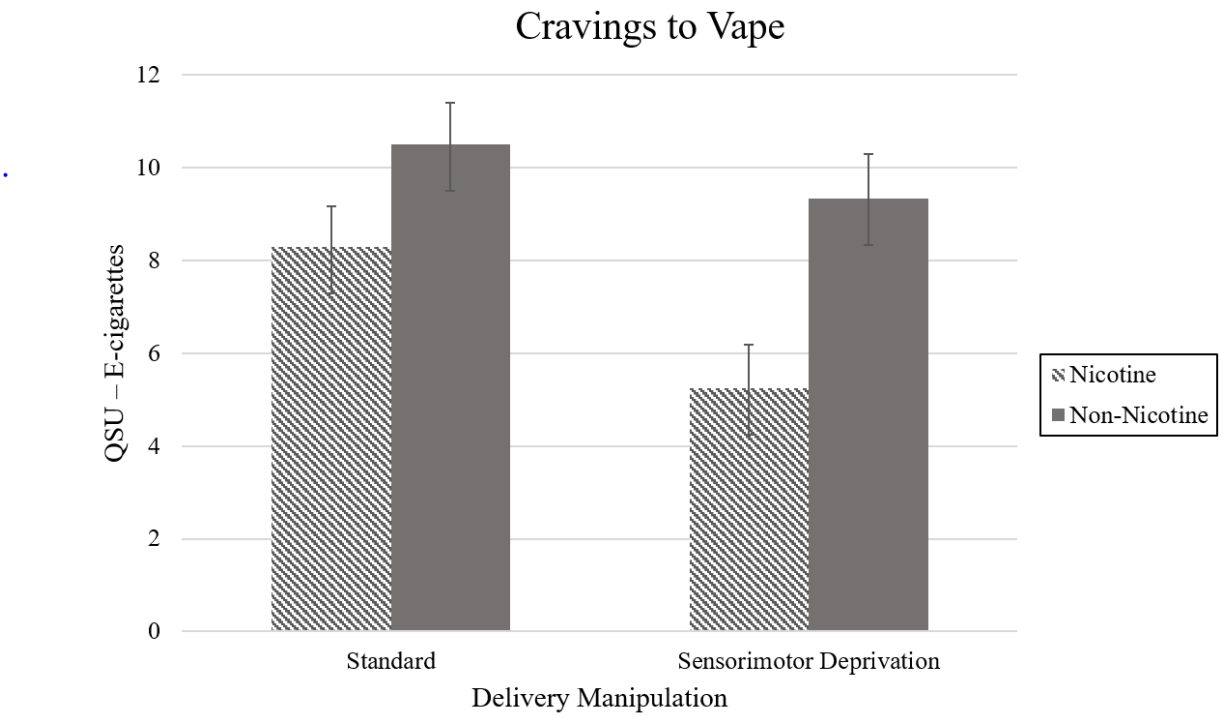
Note: † $p < .10$, * $p < .05$, ** $p < .01$. Modified mCEQ = modified Cigarette Evaluation Questionnaire, modified for e-cigarettes. RVIP = Rapid Visual Information Processing task. VAS = Visual Analogue Scale. QSU = Questionnaire of Smoking Urges-Brief- Urge factor. PANAS = Positive and Negative Affect Scale.



Note: QSU represents post-test score controlling for pre-test score. Main effect of nicotine $p < .01$, delivery $p = .055$. Error bars are standard error of the mean.

Figure 2. *Manipulation effects on cravings to smoke*

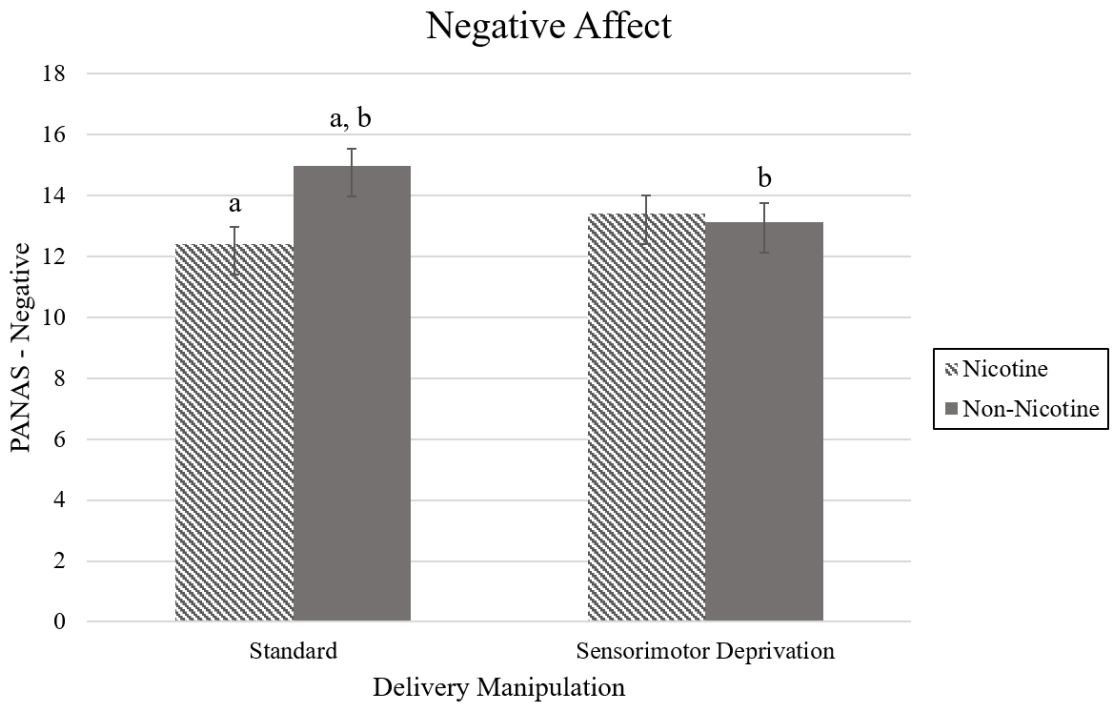
Cravings to Vape. A 2 X 2 (drug x sensorimotor manipulation) ANCOVA (using pre-test QSU scores as a covariate) showed both a significant effect of drug (F [1, 122] = 12.01, $p < .01$, $\eta^2 = 0.09$) and a significant effect of sensorimotor manipulation (F [1, 122] = 5.22, $p < .05$, $\eta^2 = 0.04$) on reducing craving to vape as measured by the QSU. Covariate-adjusted post-test scores were lower among those who received nicotine (M = 6.76) than those who did not receive nicotine (M = 9.93). In addition, covariate-adjusted post-test scores were lower among those who received the sensorimotor deprivation apparatus (M = 7.29) than those who received the standard delivery (M = 9.40). See Figure 3.



Note: QSU represents post-test score controlling for pre-test score. Main effect of nicotine $p < .01$, delivery $p < .05$. Error bars are standard error of the mean.

Figure 3. *Manipulation effects on cravings to vape*

Negative Affect. A 2 X 2 (drug x sensorimotor manipulation) ANCOVA (using pre-test PANAS-Negative scores as a covariate) failed to show either a significant effect of drug or sensorimotor manipulation on negative affect as measured by the PANAS-Negative subscale. However, a significant drug X delivery interaction emerged (F [1, 121] = 5.79, $p < .05$, η^2 = 0.05). Post-hoc comparisons showed significant differences in nicotine dose within the standard condition (nicotine M = 12.38, non-nicotine M = 15.06; F [1, 64] = 12.88, $p < .01$). At the same time, significant differences were observed among the sensorimotor factor in the non-nicotine condition, (natural M = 14.50, sensorimotor deprivation M = 12.73; F [1, 59] = 4.44, $p < .05$). See Figure 4.



Note: PANAS represents post-test score controlling for pre-test score. Interaction $p < .05$. Bars with same subscripts represent paired comparison differences at $p < .05$. Error bars are standard error of the mean.

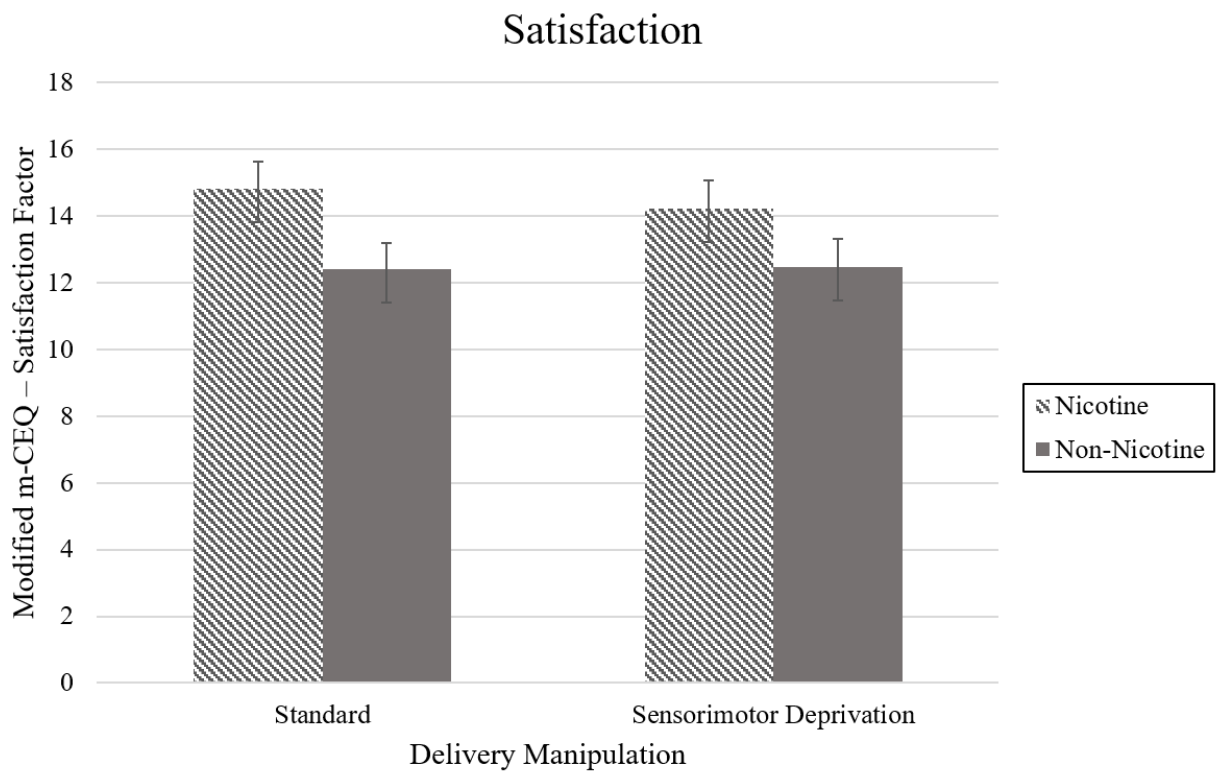
Figure 4. *Manipulation effects on negative affect*

Reward. A 2 X 2 (drug x sensorimotor manipulation) ANOVA showed a significant effect of drug (F [1, 122] = 9.54, $p < .01$, $\eta^2 = 0.07$) on the Reward factor of the modified m-CEQ. Post-test scores were higher among those who received nicotine (M = 20.12) than who did not receive nicotine (M = 15.41). See Figure 5.

Note: Main effect of nicotine, $p < .01$. Error bars are standard error of the mean.

Figure 5. *Manipulation effects on psychological reward*

Satisfaction. A 2 X 2 (drug x sensorimotor manipulation) ANOVA showed a significant effect of drug (F [1, 122] = 6.49, $p < .05$, $\eta^2 = 0.05$) on the Satisfaction factor of the modified m-CEQ. Post-test scores were higher among those who received nicotine (M = 14.53) than who did not receive nicotine (M = 12.43). See Figure 6.



Note: Main effect of nicotine, $p < .05$. Error bars are standard error of the mean.

Figure 6. *Manipulation effects on satisfaction*

Positive affect. No significant main effects or interactions were found on positive affect.

Primary Aim 2

Next tested were the variables hypothesized to be primarily affected by nicotine (appetite, attention, enjoyment of respiratory tract sensations, aversion).

No significant main effects or interactions were found on attention (RVIP sensitivity), appetite, enjoyment of respiratory tract sensations (modified m-CEQ factor) or aversion (modified m-CEQ factor).

Holm Correction.

Given the large number of tests, a Holm-Bonferroni correction was used, with each outcome variable considered one test. Outcomes were first ranked in order of *p*-values from

lowest to highest: Reward (p = .002), Satisfaction (p = .012), Negative Affect (p = .019). Per Holm method, alpha = .05 is then divided by N-R+1, where N = number of tests performed (8 secondary outcomes), R = ranking of variable. If the p-value of original test is less than the new alpha suggested by the Holm calculation, it may be considered a significant finding. The Holm-correct alpha for Reward = .006, Satisfaction = .007, and Negative Affect = .008. Given this correction, the interpretation of results for psychological reward remain as stated, whereas the outcomes for negative affect and satisfaction should be interpreted with caution in order to control Type I error.

Exploratory Aim: Gender Moderator

The independent and interaction effects of both nicotine content, sensorimotor manipulation, and gender on the hypothesized dependent variables were tested with 2 (drug) X 2 (delivery) X 2 (sex) ANOVAs, or ANCOVAs, if controlling for pre-ad-lib session scores.

No main effects of gender were found. With gender as an included factor, the pattern of results reported above remained the same, with the exception of cravings to smoke. A 2 X 2 X 2 (drug x sensorimotor manipulation x gender) ANCOVA (using pre-test QSU scores as a covariate) continued to show a significant effect of drug (F [1, 120] = 12.06, $p < .01$, $\eta^2 = 0.09$) and an emerged significant effect of sensorimotor manipulation (F [1, 120] = 4.79, $p < .05$, $\eta^2 = 0.04$) on reductions in craving to smoke as measured by the QSU.

Exploratory Aim: Other Moderators

Specific expectancies and dependence were tested as moderators of main effects using hierarchical regression; essentially, assessing if a moderator X effect (drug or sensorimotor manipulation) interaction term significantly impacts outcomes when added to the full model. Specifically, the effect of psychosocial expectancies moderating the effects of delivery

mechanism, as well as physiological expectancies and dependence tested as moderators of drug effects. Craving expectancies were tested as moderators of both delivery and nicotine mechanisms.

Positive reinforcement expectancies (VCQ factor) significantly moderated delivery effects on satisfaction (modified mCEQ factor) outcomes (β=1.23, F [4,122] = 3.95, $p < .01$). Post-hoc simple effects analyses showed that among participants receiving the sensorimotor deprivation apparatus, higher positive reinforcement expectancies were associated with higher ratings of satisfaction (β=.350, F [1,57] = 7.82, $p < .01$), whereas these expectancies had no such effect on participants receiving natural, standard delivery.

E-cigarette craving reduction expectancies (modified score from VCQ) significantly moderated nicotine effects on cravings to vape (β=1.08, F [5,125] = 13.93, $p < .01$). Post-hoc simple effects analyses showed that among participants who received nicotine, higher e-cigarette craving reduction expectancies were associated with lower cravings to vape (β= -0.32, F [2, 62] = 10.05, $p < .05$), whereas these expectancies had no such effect on those not receiving nicotine.

To assess their impact on craving, various measures of nicotine dependence (ECDI, FTND, and MNWS) were tested as moderators of the drug manipulation, with the first two using hierarchical regression, and the last as a baseline covariate. The FTND and ECDI did not produce significant interaction effects on craving outcomes. When including the MNWS as a covariate in the full model, a nearly identical pattern of results was produced.

DISCUSSION

E-cigarettes have grown to become an increasingly popular and equally controversial product, prompting the initiative to investigate their addictive liability and clinical potential. In the present study, a 2 X 2 design was utilized to assess the independent and interactive effects of both nicotine content and sensorimotor stimuli on acute outcomes of e-cigarette use in a sample of duals users. Specifically, cigarette and e-cigarette craving reductions were of particular interest, as cravings are a primary driver of drug use behavior, and can hinder cessation attempts. Previous literature suggests that both pharmacologic and non-pharmacologic properties of e-cigarettes influence outcomes (Palmer & Brandon, 2018; 2019). Therefore, delivery mechanism (natural e-cigarette use or a sensorimotor deprivation apparatus) was hypothesized to affect psychosocial and subjective outcomes, such as cravings, whereas nicotine would impact objective and physiological outcomes. In fact, a main effect of delivery mechanism was observed on cravings to smoke and cravings to vape, although in the opposite direction than hypothesized. Also, in contrast to the original hypothesis, there were several significant main effects of nicotine on the craving variables, as well other subjective variables (reward and satisfaction). Finally, a nicotine X delivery interaction was observed on negative affect. To reduce Type I error, only reward should be considered a significant secondary finding.

Cravings to Smoke and Vape

Cravings to use a drug are thought to be a result of both cue-elicited urges and physical withdrawal symptoms, with the latter often thought to be the primary motivator for drug use behaviors (Hughes et al., 1984). Indeed, alcohol and tobacco literature suggest that expectancies

about cravings may impact the experience, and subsequent relief, of cravings (Brandon et al, 1999; Palmer & Brandon, 2018; Goldman et al., 1987). The results of the present study continue to support these theories of cravings. To begin, participants in the sensorimotor deprivation condition, who used the stationary apparatus, reported lower cravings than those who were assigned to use an e-cigarette as normal. Although this result is in the opposite direction of that which was predicted, this finding still provides insight into possible mechanisms, including sensorimotor stimuli that influence e-cigarette use outcomes. In this study, the novelty of the stimuli may have been more powerful (perhaps via distraction) than the replication of sensorimotor actions (i.e., e-cigarettes are handled in a similar way as cigarettes), in mitigating cravings to smoke or vape. Certainly, the apparatus utilized was unique and activated a different set of sensorimotor stimuli than those typically paired with smoking or vaping.

On the other hand, stronger nicotine effects were observed on the reduction of cravings to smoke and vape. Participants who received nicotine reported lower urges to smoke or vape, regardless of what type of e-cigarette was used. These results provide further support of pharmacological theories of cravings (Hughes et al., 1984), consistent with relief of withdrawal symptoms as a strong reinforcer of continued smoking and vaping. Indeed, previous reviews suggest that sensorimotor stimuli generally enhance the effects of nicotine, contributing fewer effects on their own (Przulj, McRobbie, & Hajek, 2012). This explanation, however, contrasts with the findings of Palmer and Brandon (2018), which showed stronger non-pharmacologic influences on craving reduction. However, there were several differences between the two studies that may have led to this discrepancy. First, participants in the present study were limited in the frequency and number of puffs that could be taken during the vaping session, whereas in Palmer and Brandon (2018) participants could puff ad lib. Although this change was instituted to

improve standardization of nicotine intake, it may have also unintentionally interfered with naturally-occurring nonpharmacological effects.

This being stated, these results should also be considered within the context of nicotine effects compounded with expectancy effects. To begin, participants in the present study were entirely dual users, unlike the Palmer and Brandon (2018) study with a smaller dual use sample. Emerging evidence suggests an increase in nicotine dependence among initiating dual use of cigarettes and e-cigarettes (Martínez et al., 2019). This is also indicative of well-developed expectancies emerging from experiential learning across both products. The present study had an "open-label" drug delivery experience, whereas in Palmer and Brandon (2018), drug delivery was blinded and at times inconsistent with labeling. This was done to keep expectancies consistent with the drug delivery, as is experienced by vapers outside of the laboratory, which increases the generalizability of our findings. Nicotine delivery, in combination with matching expectations, was found to produce the strongest reductions in cravings in the Palmer and Brandon (2018) study. The results of the present study could be interpreted in the context of these prior findings, as expectations for the drug were consistent with the delivery. This mimics the "real life" generalized experiences of e-cigarette users, as they engage in a conscious choice to use nicotine solutions based on expectations about the effects of nicotine. Indeed, e-cigarette craving reduction expectancies moderated the effects of nicotine on craving to vape, showing further support for the role of expectancies. Together, these effects of nicotine may have overshowed the observation of any stimulus effects. Future research can continue to assess the effects of blinded and open-lab nicotine delivery within the context of other manipulations.

Psychological Reward, Negative Affect, and Satisfaction.

In line with the strong effects of nicotine on cravings, strong effects of nicotine were observed on the Psychological Reward and Satisfaction factors of the modified m-CEQ, in that those who received nicotine reported higher subjective ratings of reward and satisfaction. Additionally, there was drug X delivery interaction on negative affect, with post-hoc analyses providing some insight into the nature of this interaction. However, as these are secondary outcome variables, the results of satisfaction and negative affect should be interpreted with caution as significance levels did not meet Holm criteria. Once again, it may be that expectancies about reward and satisfaction are more strongly tied to nicotine, and not as consciously associated with sensorimotor stimuli. Indeed, expectancies for positive reinforcement from e-cigarettes moderated the effects of delivery mechanism on satisfaction, but this moderation was not observed for psychological reward. In regards to mood, another psychosocial construct not hypothesized to be affected by nicotine, nicotine appeared to reduce negative affect among those who received the standard device (natural delivery). On the other hand, negative affect was reduced by the stationary apparatus when participants did not receive nicotine. This is suggestive that again, sensorimotor stimuli produce strongest effects when in the presence of nicotine (Przulj et al., 2012). Altogether, these results provide further evidence to support that the synergistic relationships between nicotine, expectancies, and associated stimuli (such as sensorimotor actions) produce reinforcing outcomes of e-cigarette use.

Clinical Implications

E-cigarettes have been argued to be both a threat to public health progress as well as a beacon of hope for smoking cessation efforts. This study provides further insight into mechanisms that maintain the dual use of cigarettes and e-cigarettes, which is a phenomenon that

has received a great deal of concern and attention among tobacco control experts. Indeed, results suggest that nicotine plays an important role in maintaining e-cigarette use behavior through craving reduction, feelings of satisfaction, and subjective reward. Craving reduction, which is a construct of great importance in regards to the clinical utility and addictive liability of e-cigarettes, was also influenced by the sensorimotor manipulation. These results suggest that e-cigarettes may be perceived as a novel and efficacious means by which to deliver nicotine. Traditional smoking cessation methods utilizing nicotine replacement therapy (NRT; i.e., patch, gum) have demonstrated empirical efficacy (Stead et al., 2012) but may not be as well received for a variety of reasons. E-cigarettes, on the other hand, have been reported to be a better accepted method for smoking cessation, and smokers perceive them to be more efficacious than NRT (Dawkins, 2012; Harrell et al., 2014). This could very well be related to the replication of sensorimotor movements; however, our results suggest that perhaps the novelty, or ability to distract through a new engaging activity also provides smokers some relief in cravings. Indeed, it could be that these features work together: the sensorimotor replication provides a consistent, familiar benefit to craving reduction, whereas the novelty of the device produces more immediate and short-term benefits through means of distraction. Interventions should capitalize on this novelty effect, as well as other unique aspects of e-cigarette use, such as the ability to customize the device and liquid used. This may improve treatment engagement and acceptability, thus improving outcomes.

Results should also be considered in the context of expectancy results (e.g., Palmer and Brandon, 2018; 2019). To reiterate, the previously mentioned studies have shown beliefs about nicotine influence both cigarette and e-cigarette craving reduction following the use of an e-cigarette, regardless of the nicotine content. However, participants in the “true positive”

condition, in which their beliefs matched the nicotine delivery, experienced higher levels of craving reductions and psychological reinforcement. This is consistent with the results of the present study, and demonstrates the importance of expectancies on drug effects. Individuals' beliefs about nicotine, whether conscious or unperceived, shape experiences of e-cigarette use. When utilizing e-cigarettes for smoking cessation, clinicians can capitalize on these expectancy effects by identifying those which are held by the individual and shaping them to produce the most efficacious outcomes. Expectancies can also be challenged, either cognitively or in-vivo, to produce alterations that can have lasting clinical effects, as has been observed in studies of alcohol use among college students (Wiers et al., 2003).

Limitations

There are several factors to consider as limitations for the present study. First, the null findings within nicotine manipulation, including attention, appetite, aversion, and enjoyment of respiratory tract sensations, should be considered. One explanation for these may be that the outcomes were measured through subjective self-report questionnaires, with the exception of sustained attention. The reliability and validity of self-reports of these physical sensations may be limited, and these null findings were generally consistent with previous research, although nicotine effects on attention have been demonstrated previously (Palmer & Brandon, 2019). Null findings within the delivery manipulation, such as positive affect, should also be considered. It should be noted that, with the exception of short-term nicotine abstinence, we did not induce states (e.g., negative affect, hunger) that might have revealed larger effects of the manipulation. Finally, we failed to show main or interactive effects of gender. However, the literature on gender differences in responses to nicotine is mixed (Smith et al., 2016), and this warrants further research within the context of e-cigarettes.

Additional error and variability may be attributed to the heterogeneity of available e-cigarette devices, solutions, and flavors available to participants, thus reducing the generalizability of the results. The present study utilized a second-generation device; however, a majority of our participants endorsed using a first generation "cig-a-like" or pod-mod style device (e.g., JUUL®), which differ from the experimental apparatus in the mechanisms of delivery (our device used a button, other devices only require inhalation to activate), aesthetic style, and e-juice constituents (our device used a free-base nicotine, JUUL® uses a nicotine salt). Our sample was limited to dual users, yet there was a great deal of heterogeneity in participant characteristics as well. Specifically, there were highly varying ranges of smoking and e-cigarette use patterns. Although we were able to maintain consistency between participants in e-cigarette experience during the ad-lib session by controlling for device and number of puffs, for a majority of our participants this session was dissimilar to their typical use, which may have influenced results.

Another limitation of the present study is that with the aforementioned stationary delivery system in the sensorimotor deprivation condition, there remained some sensorimotor stimuli associated with vaping (e.g., the mouthpiece on the lips, inhalation of vaping aerosol) that was not controlled for. Thus, we did not completely eliminate the sensorimotor experience of vaping. However, a majority of the important stimuli were able to be removed while maintaining vaping experience integrity. Future research could test other ways to remove additional stimuli, which may demonstrate different results.

Finally, statistical and methodological considerations are warranted. A large number of tests were conducted, which may increase Type I error. The Holm correction should alleviate this risk; however, as e-cigarettes are novel products, a cautious exploratory review of the other

results remains appropriate. Next, many of the measures utilized were validated for cigarettes and modified for e-cigarettes, but have not been psychometrically validated for this purpose.

Conclusions and Future Directions

E-cigarettes remain a controversial, challenging, and yet engaging and exciting field of study. In particular, the potential for e-cigarettes to create positive health outcomes is driving many clinical intervention researchers to seek ways in which to improve current smoking cessation treatments by incorporating e-cigarettes. At the same time, tobacco control proponents are cautiously monitoring the addictive liability and other potential harmful effects of e-cigarettes as to maintain the progress made on reducing the rates of smoking-related deaths and illnesses. The present study utilized a 2 X 2 design to parse the influences of nicotine content and sensorimotor stimuli on various outcomes of e-cigarette use that may be ultimately related to their potential for health or harm. Results showed strong effects of nicotine on craving reduction as well as other psychosocial outcomes not hypothesized to be related to nicotine. However, our results also suggested the effects of the delivery manipulation (normal e-cigarette or sensorimotor deprivation) reduced cravings for cigarettes and e-cigarettes. Specifically, cravings were reduced when receiving the manipulated delivery mechanism. In combination with other results, it appears that expectancies, the novelty of the apparatus, and specific characteristics of dual users may have interacted with our manipulation to produce observed outcomes. Therefore, harm reduction proponents should consider these factors synergistically when developing interventions for e-cigarettes as a means for smoking cessation. At the same time, those aiming to control the addictive, and "gateway" potential for e-cigarettes may also considering the results of the study. Further research can test these interactions to elucidate the nuances of novelty,

distraction, and sensorimotor manipulation effects on craving reductions following e-cigarette use.

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