THE RELATIONSHIP BETWEEN ELECTRONIC NICOTINE DELIVERY SYSTEM USE AND ALCOHOL CONSUMPTION: A NEUROCOGNITIVE AND BEHAVIORAL INVESTIGATION

by

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I dedicate this to my wonderful daughter, Sam.

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ABSTRACT

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Increasing research shows that the use of electronic nicotine delivery systems (ENDS) is associated with higher rates and quantity of alcohol consumption; however, no research to date experimentally examines the relationship between ENDS use and alcohol use. The present study uses a two-session within-subjects design to examine 1) the relationship between ENDS use prime and attentional bias for alcohol related cues and 2) the relationship between ENDS use and laboratory ad libitum alcohol consumption. A total of N = 31 (mean age = 28.71, SD = 11.17; 45.2% women; 54.8% White/Caucasian) healthy users of ENDS who endorsed liking beer completed the present study, which included 1) a dot-probe and eye-tracking task that assessed attentional bias (reaction time, initial orientation, and delayed disengagement) to alcohol images following ENDS prime or no prime and 2) an ad libitum beer consumption task that assessed mL of beer consumed by the participants when concurrent use of ENDS was allowed or not allowed. All analyses controlled for age, race, and gender. Results of repeated measure ANCOVA's indicate that attentional bias for alcohol does not differ between the ENDS prime or control conditions (F's 0.01 to 0.12, ηp^2's 0.001 to 0.01). There is a large interactive effect of self-reported days of concurrent use of ENDS and alcohol over the last 14 days (ηp^2's 0.35 to 0.85), small to medium effects of alcohol craving preceding eye-tracking (ηp^2's 0.02 to 0.09), and small to medium effects of ENDS craving preceding eye-tracking (ηp^2's 0.06 to 0.13), all of which show increases in attentional bias following the ENDS prime; however, these results were limited by data quality issues that preclude strong support of these effects. Results of repeated measure ANCOVA's demonstrate that amount of beer consumed does not differ by ENDS condition, F (4, 26) = 0.03, p = .86, ηp^2 = 0.001. Results of a hierarchical linear regression show that amount of ENDS weight change (g) is not significantly related to mL of beer consumed in the ENDS session (b = -86.48, t = -0.90, p = 0.38, ΔR^2 = 0.03). Results of linear mixed modeling testing the effect of ENDS puffs on alcohol sips temporally across the ad lib task show puffs are

significantly related to sips (estimate = 0.23, SE = 0.07, p = .002) and number ENDS puffs account for some variability in slope of participant sips across participants. Results of repeated measure ANCOVA's do not demonstrate significant interactions between mL of beer consumed by session and concurrent self-reported ENDS use over the past two weeks ($\eta p^2 = 0.45$), alcohol craving, or ENDS craving (ηp^2's = 0.002). Overall, results indicate that increased frequency of ENDS use is related to an increased frequency of beer consumption in real time. Since ENDS is related to alcohol use in time and place, individuals at risk for alcohol use problems should take care in their ENDS use. This study suggests that research should more fully measure and compare event-level and meta-level data on ENDS and alcohol use and that patterns based in the cigarette literature may not always generalize to ENDS.

INTRODUCTION

Recent estimates indicate approximately 4.5% of adults in the United States age 18 and over regularly use electronic nicotine delivery systems (ENDS; Mirolouk et al., 2018). ENDS, including products such as electronic cigarettes, personal vaporizers, vape-pens, e-cigars, e-hookahs, vaping devices, JUUL, mod systems, or pod systems, are battery powered devices that heat an ENDS liquid (typically containing nicotine). The heated liquid produces an aerosolized mixture of nicotine, flavoring, and other chemicals that the user inhales, similar to inhaling a cigarette. As reviewed by Glasser et al. (2017), ENDS and their refill liquids are heterogeneous between products and users, with refill and aerosol nicotine and other chemical content varying between manufacturers, devices, and by puff (Etter et al., 2012; Geiss et al., 2015; Goniewicz et al., 2014; Lisko et al., 2015; Pagano et al., 2016). Increasing cross-sectional research demonstrates that ENDS use is related to alcohol use (Bartoli et al., 2014; Hefner et al., 2019; Hershberger et al., 2016; Littlefield et al., 2015; Llanes et al., 2019; Saddleson et al., 2015; Tavolacci et al., 2016), based theoretically in the vast research experimentally linking cigarettes to alcohol use (e.g., Drobes et al., 2000; Epstein et al., 2007; Grucza & Bierut, 2006; King & Epstein, 2005; Kouri et al., 2004). A recent meta-analysis shows a strong correlation between ENDS use and alcohol use (Hershberger et al., in preparation); however, no experimental research to date examines this relationship, which is necessary to establish causal links between ENDS use and alcohol use. Additionally, most of this research focuses on the meta-level of behavior (e.g., lifetime use of ENDS; e.g., Cohn et al., 2015; Geidne et al., 2016), which does not provide information on whether the behaviors are occurring at the same time (and, if so, in what sequence) or whether the behaviors appear linked but are not occurring simultaneously.

The overarching goal of the present study is to experimentally examine the effect of ENDS use on alcohol consumption at the event-level and to investigate potential mechanisms of this relationship. Importantly, I will examine the relationship between these behaviors in real time, to establish whether or not the behaviors occur together in time and place. A long-term goal of this work is to better understand the temporal timing between these behaviors, thus providing clinicians and patients accurate and helpful recommendations regarding ENDS use effects on alcohol consumption. This is particularly important for individuals who may be at risk for

alcohol related problems, such as adolescents and individuals diagnosed with or at risk for an alcohol use disorder.

The need for experimental research on concurrent ENDS and alcohol use

Cross-sectional findings: Concurrent ENDS and alcohol use

Overall, an emerging and growing area of cross-sectional research demonstrates a link between ENDS and alcohol use in college students and nationally representative adult samples, with findings remaining fairly robust across varying types of ENDS and alcohol use measures. In college students, life time ENDS use (ever using an ENDS) and past 30-day ENDS use are linked to recent alcohol use, binge drinking (Bartoli et al., 2014; Hefner et al., 2019; Llanes et al., 2019; Littlefield et al., 2015; Saddleson et al., 2015; Tavolacci et al., 2016), and problematic use of alcohol (Tavolacci et al., 2016). In a nationally representative survey of adults, life time ENDS use is related to life time alcohol use (Cohn et al., 2015) and past 30-day ENDS use is related to monthly, weekly, and daily alcohol use. The strongest relationship is between past 30-day ENDS use and daily alcohol use, suggesting a 2.5 increase in the odds of daily use of alcohol among people who report past 30-day ENDS use (OR=2.67; Lee et al., 2016). In a sample of 36,309 adults, both daily and life time ENDS use are related to hazardous drinking, alcohol use disorder diagnosis, and binge drinking frequency (Roberts et al., 2018), although individuals who do not use ENDS daily demonstrate greater alcohol use risk than individuals who use ENDS daily.

A recent meta-analysis of 31 studies (Hershberger et al., in preparation) summarizing effects across 19 adolescent studies and 12 adult studies shows that the relationship between ENDS and alcohol use is most robust in adolescent samples: Adults who use ENDS are 1.76 times more likely to also use alcohol, whereas adolescents who use ENDS are 4.84 times more likely to also use alcohol. In a nationally representative sample of adolescents, life time ENDS use is associated with weekly binge drinking (Hughes et al., 2015) and multiple surveys of high school students document a relationship between both life time and past 30-day ENDS use and past 30-day alcohol use (Camenga et al., 2014; Kong et al., 2016; Morean et al., 2016; Suris et al., 2015), life time alcohol use (Geidne et al., 2016; Kristjansson et al., 2015), and binge

drinking (Camenga et al., 2014; Kaleta et al., 2016). Thus, ENDS and alcohol use appear to be especially linked in adolescents.

Although these data are compelling, these studies have some important limitations. First, these studies use cross-sectional self-report measures. While self-report measurement of substance use serves as a common and useful source of initial data, the validity of self-report substance use measures is uncertain. Importantly, substance use self-reports are often inconsistent with urine drug screen (UDS) results, in that UDS detects substances in one's urine when the individual fails to self-report substance use (Clark et al., 2016). False positives on UDSs can be caused by, for example, energy supplements, anti-depressant medications, and antiretroviral therapy (see Saitman et al., 2014 for a review). While best practices dictate confirmatory lab-tests (i.e., a test with more specificity for the specific substance and levels of the substance) for positive UDS to mitigate false-positives (Nichols et al., 2007), confirmatory tests are expensive, time-consuming, and require access to a laboratory that can conduct these analyses.

Despite some weaknesses with UDS, they are thought to be more valid measures of recent substance use than self-report measures (see Magura & Kang, 1996 for a meta-analysis). There are multiple factors that may explain invalid self-reporting of substance use, including social desirability and difficulty remembering. Social desirability describes someone who may under-report substance use in a situation where it would be socially undesirable to report, such as with parents, (potential) employers, and with individuals who do not use substances. Social desirability is associated with under-reporting of substance use in the context of positive biological assessments for substance use (i.e., urine, saliva, hair; Johnson & Fendrich, 2005). On the other hand, memory difficulties are associated with over-reporting of substance use (Johnson & Fendrich, 2005). Thus, if influenced by social desirability, individuals may under-report their alcohol and ENDS use, thus under-estimating the relationship between use of ENDS and alcohol. If individuals do not recall their recent ENDS and alcohol use, they may over-report their use, thus over-estimating the relationship. Measures of real-time use would overcome such limitations.

Second, most of the previous research focuses on the meta-level of behavior (e.g., lifetime ENDS use; e.g Cohn et al., 2015; Geidne et al., 2016). This does not provide information on whether the behaviors are occurring at the same time (and, if so, in what sequence) or whether

the behaviors appear linked but are not occurring simultaneously. It is often assumed if the behaviors are related on the meta-level that they are occurring together, at least part of the time (i.e., people are drinking alcohol while using their ENDS). However, it is also possible that they are not linked in time and place at all, such as the case where someone might use their ENDS during the day (e.g., at work, school) or during the week, but not drink alcohol during these times. Additionally, individuals may drink alcohol in public places in which ENDS use is banned (Hershberger et al., 2016), further separating these behaviors in time and place. Thus, an important question is if ENDS and alcohol use occur together or if they are only correlated overall, but are mutually exclusive or rarely done at the same time. Real-time data to delineate these patterns would first need to measure ENDS and alcohol use in the same time frame and place, such as during one drinking occasion at a bar or a controlled drinking occasion in the lab. Second, real-time data would need to measure ENDS and alcohol use sequentially across time during the drinking occasion, such as by measuring the number and sequence of sips of alcohol and puffs of ENDS. If such real-time data show that individuals consume more alcohol after an ENDS puff, this would suggest that ENDS use leads to increases in alcohol use. If real-time data show that individuals use ENDS immediately following an alcohol sip, this would suggest that alcohol use leads to increases in ENDS use. Of course, it's also quite possible that such data could show no temporal relationship between ENDS and alcohol use.

There are two primary options to assess and study real-time concurrent ENDS and alcohol use. Ecological Momentary Assessment (EMA; Stone and Shiffman, 1994) is a method of data collection that allows participants to record their daily behavior (e.g., use of alcohol and cigarettes), via electronic device, as it occurs in real-time (Piasecki et al., 2011; Witkiewitz et al., 2012). EMA has the methodological strength of ecological validity (Johnson et al.,2009; Serre et al., 2012; Serre et al., 2015), capturing individuals' substance use in their natural environment. At the same time, EMA is still based on the participants' self-report of substance use, while under the influence of a substance or shortly following the use of a substance, which may be problematic and reduce accuracy. A wealth of research demonstrates the acute impairing effects of alcohol, particularly on working memory (Boha et al., 2009; Cromer et al., 2010; Fillmore et al., 2009; Saults et al., 2007; Schweizer et al., 2006; Tiplady et al., 2009) and response inhibition (i.e., inability to stop an impulsive or habitual response; see Day et al., 2015 for a review; Fillmore & Weafer, 2012; Ostling & Fillmore, 2010; Weafer & Fillmore, 2008). Thus, EMA is

likely biased by impaired working memory, leading to participants having difficulty remembering the amount of alcohol consumed (Johnson & Fendrich, 2005) or forgetting to respond to EMA prompts, and response inhibition, leading to less accurate responses to prompts. Other difficulties with EMA approaches have to do with experimental control, such that participants are engaging in substance use in a wide variety of settings and/or using different types of substances with different levels of brain exposure to the drug, which are difficult to control for across participants and within participants across different substance use occasions. One example of this is two individuals reporting drinking "one beer," when one's beer is a 12oz. "light" beer with a low alcohol content and the other is a 32oz. beer with high alcohol content. Thus, ecological validity is high in EMA approaches, but accuracy and experimental control are sacrificed to some extent.

Another way to examine the relationship between concurrent ENDS and alcohol use experimentally is through the *ad libitum* (ad lib) paradigm (Marlatt et al., 1973). This paradigm was originally developed to examine how much alcohol participants will consume in a controlled laboratory environment by giving participants alcohol and instructing them to drink as much or as little as they would like (Marlatt et al., 1973). The purpose of the task is often concealed by telling the participants they are participating in an alcohol taste test and having them rate the drinks on various qualities (Marlatt et al., 1973). This paradigm is widely used in experimental research to examine alcohol consumption (e.g., Christiansen et al., 2012; Corbin et al., 2008; Sharkansky & Finn, 1998; Van Dyke & Fillmore, 2015; Weafer & Fillmore, 2008). One major limitation of this approach is the potential for limited ecological validity (i.e., consumption of alcohol in a lab setting, compared to a naturalistic setting). Many research laboratories reduce this weakness by creating lab settings that mimic real life drinking settings, such as a bar lab (e.g., Corbin et al., 2006; 2008; Leeman et al., 2009) or apartment/dorm room type settings (Weafer & Fillmore, 2008). Despite such efforts, it is certainly true that lab settings do not likely match real-world drinking settings perfectly. On the other hand, ad lib alcohol paradigms show excellent construct validity (Jones et al., 2016). Ad lib alcohol consumption is related to self-report patterns of alcohol consumption and craving, is not impacted by the time of day or day of the week that the experiment took place or awareness that alcohol use is being examined (Jones et al., 2016), and is impacted (as expected) by experimental manipulations intended to increase consumption (e.g., acute stress, ego depletion, disinhibition; Christiansen et al., 2012; Jones et

al., 2011; Jones et al., 2016; McGrath et al., 2016). The ad lib paradigm is used to examine concurrent use of alcohol and cigarettes, including the ad lib use of cigarettes (Barrett et al., 2006; McKee et al., 2006). Importantly, the exact amount of alcohol consumed and the resulting breath alcohol concentration (BrAC) can be objectively measured in laboratory designs, decreasing self-report inaccuracies. Thus, the ad lib paradigm provides a validated and well-controlled method to obtain objective measurement of concurrent ENDS and alcohol use, although ecological validity is limited to some extent. The present study utilizes the ad lib paradigm in order to retain experimental control and obtain objective measurement of ENDS and alcohol use. Although the present study attempts to increase the ecological validity of the laboratory setting (i.e., the lab was set up to mimic a dorm room or small bedroom/apartment), I acknowledge that ecological validity of the study is limited to some extent.

Potential negative effects of concurrent ENDS and alcohol use

There are multiple potential negative effects of concurrent ENDS and alcohol use, making the current inquiry of high impact. Here I focus on three relevant to the current study: increased use of both when used concurrently, poor alcohol use treatment outcomes, and direct health effects related to use of these substances.

First, one concern of concurrent ENDS and alcohol use is the potential for these substances to be mutually reinforcing (e.g., use of ENDS increases use of alcohol and use of alcohol increases use of ENDS). A bidirectional relationship between cigarette and alcohol use is well documented in research, suggesting viability for the relationship with ENDS. EMA research suggests cigarette use leads to greater alcohol use and alcohol use leads to greater cigarette use, specifically in the same time frame (e.g., within one drinking occasion; Piasecki et al., 2011; Witkiewitz et al., 2012). Ad lib laboratory research shows that alcohol use is associated with increases in cigarette use, even when monetary reward is offered for not smoking (McKee et al., 2006) and cigarette use is associated with more ad lib alcohol use (Barrett et al., 2006).

Second, while a bidirectional relationship between the use of ENDS and alcohol is viable, how ENDS use increases alcohol use is concerning, as it could lead to poor alcohol treatment outcomes. Research examining the impact of smoking cessation in the course of alcohol use treatment helps illustrate this point. A meta-analysis shows that adding a smoking cessation intervention to alcohol use treatment significantly increases the likelihood of maintained alcohol

abstinence six-months post-treatment (Prochaska et al., 2004). Additionally, stopping smoking within one year of substance use treatment significantly predicts successful maintenance of alcohol abstinence over the following nine years (Tsoh, et al., 2011). Finally, quitting smoking post alcohol use treatment decreases risk for re-emergence of alcohol use disorder diagnosis (Cavazos-Rehg et al., 2014). Thus, smoking cessation improves alcohol treatment outcomes, suggesting the effect may hold for ENDS as well. Supporting this idea are data showing that current ENDS use is higher in samples of individuals in substance use treatment (estimates 17.7% to 30.5%) than the general population (Gubner et al., 2016; Guydish et al., 2016; Peters et al., 2015) and that ENDS are often used as a smoking cessation aid (Peters et al., 2015). However, if ENDS use increases alcohol use and reduces the effectiveness of alcohol treatment, ENDS use in individuals with alcohol use disorders may be contraindicated.

Third, concurrent ENDS and alcohol use, particularly if these substances are mutually reinforcing, can lead to increased negative health effects. The negative health effects of problematic levels of alcohol use are extensively documented and include cardiomyopathy, arrhythmias, stroke, high blood pressure, alcoholic hepatitis, cirrhosis of the liver, pancreatitis, and multiple forms of cancer (e.g., liver cancer, colorectal cancer; NIAAA, 2009), although moderate levels of alcohol use are associated with some positive outcomes (e.g., Rimm et al., 1999). While the study of the direct health effects of ENDS is comparably new, there is an emerging literature documenting negative effects, including increases in inflammation in the lungs of both animals and humans (Lerner et al., 2015), decreases in anti-viral and anti-bacterial defenses in the lungs (Sussan et al., 2015), decreases in lung endothelial barrier function (Schweitzer et al., 2015), and impairment in psychomotor performance following ENDS exposure (Valentine et al., 2016). ENDS contain potentially harmful levels of nickel and chromium (Hess et al., 2017) and a recent meta-analysis shows that ENDS exposure is related to higher heart rate, as well as diastolic and systolic blood pressure (Skotsirmara et al., 2019). Notably, there are limited long-term data on the health effects of ENDS.

It is important to state that, from a harm reduction perspective, ENDS have the potential to benefit the health of adult smokers if used to quit smoking cigarettes (CDC, 2019). Increasing experimental research examines the effectiveness of ENDS on smoking cessation (see Rohsenow et al., 2018 for a review), although this research is in its infancy and thus strong conclusions about the usefulness of ENDS for smoking cessation cannot yet be made. However, given the

negative health effects of ENDS, their use should not be considered to be without risk. Perhaps of greatest concern are data suggesting that individuals who use ENDS are at 3.83 times greater odds of initiating cigarette use (Soneji et al., 2017), with 23.2% of ENDS users initiating cigarette use, compared to 7.9% of people who did not use ENDS. Thus, ENDS use may have a gateway effect on the cigarette use, increasing a wide array of health risks secondary to the use of cigarettes (USDHS, 2014). Although there is still debate concerning the safety of ENDS, growing research demonstrates although ENDS may have fewer negative effects than cigarettes, they are not without negative health consequences.

Potential mechanism of concurrent ENDS and alcohol use: Cue-induced attentional bias

While mechanisms underlying concurrent ENDS and alcohol use have not been studied, there is significant research examining the mechanisms underlying concurrent cigarette and alcohol use that informs potential mechanisms to study. Classical conditioning theories of substance use suggest that concurrent cigarette and alcohol use leads to associative learning, whereby alcohol cues become a conditioned stimulus for cigarette use and cigarette cues become a conditioned stimulus for alcohol use (Rohsenow, et al, 1997). This "priming hypothesis" is supported through research, with evidence showing that exposure to an alcohol cue (e.g., odor) leads to increased smoking craving (King & Epstein, 2005; Rohsenow, et al, 1997) and increased smoking (King et al., 2009; Shiffman et al., 1994).

Social learning likely also contributes to the mutually reinforcing relationship between cigarettes and alcohol, based in evidence that individuals develop expectancies of concurrent cigarette and alcohol use, such that individuals expect that they will drink more after they smoke a cigarette (Rohsenow, et al., 2005). These expectancies are then associated with increased substance use (Fearnow-Kenny et al., 2001; Fromme & D'Amico et al., 2000; Goldman, Brown & Christiansen, 1987; Pabst et al., 2014). Recent research suggests that this effect may generalize to ENDS, as positive expectancies of concurrent ENDS and alcohol use are associated with greater self-reported alcohol use (Hershberger et al., 2015).

The present study examines the classical conditioning theory of concurrent use, specifically the "priming hypothesis" (Rohsenow et al, 1997), as one mechanism underlying concurrent ENDS and alcohol use. Testing this hypothesis lends itself well to laboratory investigation via the examination of ENDS cue-induced (primed by using ENDS) alcohol-related

attentional bias. Alcohol-related attentional bias is defined as reactivity to alcohol-related cues (e.g., alcohol images or smells; see Field & Cox, 2008 for a review). Cue-induced attentional bias is the use of a conditioned stimulus (e.g., ENDS use) to increase attentional bias for the unconditioned stimulus (e.g., alcohol). Limited experimental research examines cue-induced attentional bias between cigarettes and alcohol (for a review see McKee & Weinberger, 2013), but recent findings from Oliver & Drobes (2015) show evidence for this priming effect, with smoking cues resulting in alcohol-related attentional bias, as well as alcohol cues resulting in smoking-related attentional bias.

One way that attentional bias is assessed is through the use of the visual dot-probe paradigm. This paradigm was developed by MacLeod et al. (1986) to assess responses to emotionally threatening versus neutral information in anxious, depressed, and clinical control participants. For this paradigm, participants are presented with side-by-side experimental and control images for a brief period (typically 500ms-2000 ms; Field & Cox, 2008), one image is replaced by a probe (e.g., arrow, plus sign), and participants are asked to respond as quickly as possible (via mouse click or key stroke) to indicate if the probe is on the left or right side of the screen. This paradigm is used to assess a variety of cognitively biased responding, including responses to angry and neutral faces (Cooper et al., 2006), pain and non-pain related stimuli (Yang et al., 2012), smoking and non-smoking cues (Ehrman et al., 2002), and alcohol and non-alcohol related stimuli (e.g., Manchery et al., 2017; Noel et al., 2006; Townshend & Duka, 2001). Additionally, this paradigm is used to examine cue-induced attentional bias, including positive and negative internet message cues as primes for positive and negative image related attentional bias (Cheng, 2018), PTSD cues as primes for cocaine related attentional bias (Tull et al., 2011), alcohol odor as a prime for alcohol related attentional bias (Karyadi, 2015; Ramirez et al., 2015), alcohol odor as a prime for food related attentional bias (Karyadi, 2015), and in vivo smoking stimuli as a prime for smoking related attentional bias (Correa & Brandon, 2016).

Alcohol-related attentional bias is examined three ways in the visual dot-probe paradigm: reaction time bias, initial orientation, and delayed disengagement. Reaction-time bias is considered an indirect measure of alcohol-related attentional bias (Field & Cox, 2008), whereby bias is inferred by comparing the time it takes participants to respond to the visual probes (e.g., arrows, plus sign) replacing an experimental (alcohol) versus control image (MacLeod, et al; 1986). Quicker reaction times to visual probes replacing alcohol related images, compared to

control images, is inferred to indicate participant's attention was oriented towards the alcohol image (Posner et al., 1980), and further indicates reaction time attentional bias. Reaction time bias is associated with alcohol craving in social drinkers (Manchery et al., 2017) and heavy drinkers display greater reaction time bias for alcohol-related images than social drinkers (Townshend & Duka, 2001). However, there is evidence to suggest this inferred measure lacks convergent validity with other measures of attentional bias (Miller & Ulrich, 2013; Wachter & Stolz, 2015) and concurrent validity with alcohol-related outcomes (Christiansen et al., 2015).

Initial orientation and delayed disengagement are considered to be more direct measures of attentional bias (Field & Cox, 2008), although they still infer attention indirectly through examining participant eye movement. Both initial orientation and delayed disengagement rely on computer measurements of eye movement, or eye-tracking, whereby a small camera calibrated to a participant's eye records eye movement throughout the time-course of the dot-probe paradigm. The recording of participant eye movement allows data to be examined to determine when and where participants gaze is directed during the experimental task. Initial orientation is calculated by examining the proportion of initial eye movements directed towards alcohol-related stimuli (in %; Field et al., 2005). Initial orientation is thought to assess one's initial and automatic (e.g., outside of conscious awareness) shifting of attention when the stimulus is presented (Field & Cox, 2008). Delayed disengagement is calculated by examining the amount of time one's gaze is focused on alcohol-related stimuli, compared to neutral stimuli (Field et al., 2004; 2005). Delayed disengagement is thought to assess a more conscious orienting of attention than initial orientation (Field & Cox, 2008). Both initial orientation and delayed disengagement measures of attentional bias are related to alcohol craving and perpetuated alcohol use (Field & Cox, 2008; Field & Cox, 2009) and are intercorrelated (r = 0.30; Schoenmakers et al., 2008).

Uniqueness of concurrent ENDS and alcohol use compared to concurrent cigarette and alcohol use

Experimental evidence examining concurrent cigarette and alcohol use provides the rationale and scientific premise to experimentally examine concurrent ENDS and alcohol use. While there are some parallels between cigarettes and ENDS that suggest that they would have similar relationships with alcohol, there are also ways in which ENDS and cigarettes might diverge.

First, ENDS and cigarettes are similar in that they contain nicotine, making it likely nicotine related mechanisms would exist across these products. Nicotine and alcohol may be mutually rewarding via the dopaminergic system, the neurobiological reward system (Ericson et al. 2003; Funk et al., 2006; Soderpalm et al., 2000; Tizabi et al. 2002), whereby concurrent alcohol and nicotine use increase dopamine release more than when either is used alone (Tizabi et al., 2002; Tizabi et al., 2007). Additionally, nicotine and alcohol have additive analgesic effects via the opioid system, which is theorized to contribute to high rates of concurrent use (Campbell et al., 2006; Franklin, 1998). Thus, nicotine found in ENDS may similarly interact with alcohol via the dopaminergic and opioid systems, facilitating concurrent ENDS and alcohol use.

Second, some ENDS products closely resemble cigarettes in shape and size and in the oral inhalation route of nicotine administration, making it likely the conditioning could generalize across these products. Since many ENDS users are current or former cigarette users (Jaber et al., 2018; Levy et al., 2017), conditioned properties (inhalation, shape, size) of cigarettes that cue alcohol use may generalize to ENDS, whereby properties of ENDS cue the use of alcohol. However, few studies examine the cueing potential of cigarettes to alcohol (Oliver & Drobes, 2015), suggesting viability of the relationship, but also the need to examine this further.

On the other hand, there are important differences between ENDS and cigarettes that may that may lead to disparate relationships with alcohol use. ENDS deliver less nicotine than cigarettes (Farsalinos et al., 2017; Hajek et al., 2017). Additionally, while ENDS produce variable plasma nicotine concentrations across individuals, such that those who have used ENDS for longer periods of time achieve significantly higher plasma nicotine concentrations (Hiler et al., 2017), cigarettes produce similar nicotine concentration across individuals (Benowitz & Jacob, 1993; Shiffman et al., 1992). While the reinforcing properties of nicotine and alcohol are implicated in their concurrent use (e.g., Tizabi et al., 2002; Tizabi et al., 2007), no research examines if the significantly smaller and variable dose of nicotine found in ENDS reacts similarly with alcohol. It is thus plausible that ENDS do not reinforce alcohol in the same way cigarettes do, or that ENDS do reinforce alcohol in the same way cigarettes do in a dose dependent way.

Additionally, ENDS are viewed as more socially acceptable than cigarettes (Berg et al., 2015; Gorukanti et al., 2017; Hershberger et al., 2017; Trumbo et al., 2013), likely increasing ones willingness to use ENDS in more situations and settings than cigarettes. Relatedly, many public places ban the use of cigarettes, but fewer places ban the use of ENDS (American Non-Smokers Rights Foundation, 2018), although some legislation banning ENDS use is in its infancy. With fewer social (Lee et al., 2018) or legal barriers to the use of ENDS (American Non-Smokers Rights Foundation, 2018), the likelihood of individuals using ENDS and alcohol together in time and place increases. Individuals living in areas where public ENDS use is not banned report higher problematic alcohol use, average drinks per drinking day, and total drinks consumed over a two-week period (Hershberger et al., 2016). Thus, it is quite possible that while the opportunity for paired associations between cigarettes and alcohol use are on the decline (Picone et al., 2004; Young-Wolff, 2013), opportunities are increasing for paired associations between ENDS and alcohol (Hershberger et al., 2016).

Present Study

The cross-sectional literature suggesting a connection between ENDS and alcohol use provides key rationale and premise to examine real-time pairing of these substances. The present study aims to move the field forward by gathering novel experimental, well-controlled laboratory data on concurrent ENDS and alcohol use. To assess this relationship, I conducted a within-person two-session laboratory study. First, participants completed the dot-probe paradigm (MacLeod et al., 1986) to assess ENDS cue induced attentional bias for alcohol (e.g., Manchery et al., 2017; Noel et al., 2006; Oliver & Drobes, 2015; Townshend & Duka, 2001). Second, participants completed an ad lib alcohol use paradigm (Christiansen et al., 2012; Corbin et al., 2008; Marlatt et al., 1973; Sharkansky & Finn, 1998; Weafer & Fillmore, 2008; Van Dyke & Fillmore, 2015). I examined whether attentional bias for alcohol and ad lib alcohol consumption varied across a session in which an ENDS is used (ENDS condition) or not used (control condition). The present study not only provides the first experimentally controlled evidence on the relationship between ENDS and alcohol use in time and place, but also the first experimental data, to date, examining one potential mechanism underlying concurrent use: attentional bias.

Although previous smoking and nicotine research suggests the viability of a bidirectional effect, whereby ENDS use increases alcohol use and vice versa (see Verplaetse & McKee, 2017

for a review), the present study primarily focuses on the effect of ENDS use on alcohol use, due to the high clinical utility of such a causal direction (Cullen et al., 2018; Gubner et al., 2016; Guydish et al., 2016; Peters et al., 2015). If ENDS use increases alcohol use, assessing for and intervening on ENDS use in high-risk populations (e.g., adolescents and those with alcohol use disorders) may be crucial to mitigating alcohol related negative outcomes. At the same time, the present study will examine both sips of alcohol and puffs of ENDS during the ad lib session; thus, the temporal direction from alcohol to ENDS use can also be approximated.

The specific aims and hypotheses for the present study are:

Aim 1

Examine the relationship between ENDS use and attentional bias for alcohol-related cues in healthy individuals who report regular ENDS and alcohol use.

Hypothesis 1

Individuals primed with ENDS use will display a larger attentional bias towards alcohol cues (reaction time bias, initial orientation bias, and delayed disengagement bias), as assessed with eye-tracking measurement during a dot-probe task, than when there is no ENDS prime.

Hypothesis 2

The strength of the attentional bias for alcohol cues following ENDS prime will be related to self-reported concurrent alcohol and ENDS use, as measured by a timeline follow-back.

Hypothesis 3

The relationship between ENDS and alcohol craving preceding the eye-tracking measurement and alcohol attentional bias will be stronger in the ENDS condition than in the control condition.

Aim 2

Examine the relationship between ENDS use and laboratory ad lib alcohol consumption in healthy individuals who report regular ENDS and alcohol use.

Hypothesis 4

Individuals will consume more alcohol ad lib when allowed to use ENDS during the session than when ENDS use is not allowed.

Hypothesis 5

Alcohol consumed during the ad lib session will be significantly related to ENDS use during the ad lib session.

Hypothesis 6

The effect of ENDS use on alcohol consumption will be related to self-reported concurrent alcohol and ENDS use as measured by a timeline follow-back.

Hypothesis 7

The relationship between ENDS and alcohol craving preceding the ad lib paradigm and amount of beer consumed in the ad lib paradigm will be greater in the ENDS condition than in the control condition.

METHODS

Participants

Thirty-four community-dwelling individuals that use ENDS (Mean age = 28.85, SD = 10.89; 47.1% women, 44.1% non-White) completed the consent process for a two-session, within-participants study. Participants were recruited via advertisements in public spaces, the IUPUI campus, local ENDS stores, and online classifieds (e.g., IU classifieds, Craigslist; see Appendix A). Inclusion criteria (see Appendix B) were: aged 21 and older (legal alcohol drinking age in the United States), alcohol use at least once per week (for safety and generalizability to users of ENDS that consume alcohol), no current or prior diagnosis of alcohol use disorder (for participant safety), ENDS use at least once per day (for safety and generalizability to user of ENDS), report liking beer (alcoholic beverage used in the ad lib paradigm; e.g., Weafer & Fillmore, 2008), and able to understand study questionnaires and procedures in English. Individuals that report liking beer were chosen in order to administer the same beverage (beer) across participants during the ad lib paradigm (Christiansen et al., 2012; Marczinski et al., 2005; Weafer & Fillmore, 2008). Beer was chosen because beer is the most frequently consumed alcoholic beverage among adult drinkers (e.g., McCarthy 2017; Naimi et al., 2007).

Exclusion criteria (see Appendix B) were: pregnant or breast feeding (as verified through urine pregnancy screen for females at session onset; for participant safety); desire to be treated for any substance use disorder (for participant safety); unstable or significant medical/mental disorder that may influence study outcome or participant safety; smoke more than one pack of cigarettes per month (to limit impact of cigarette use on study variables); positive urine drug screen at time of study session for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, cannabinoids, or PCP (as verified through urine drug screen at session onset; for participant safety to prevent adverse interactions with alcohol); symptoms consistent with DSM-5 diagnosis (as self-reported by participant through phone screening, for participant safety), positive BrAC reading at the start of any study visit (as assessed through BrAC at session onset; for participant safety to prevent adverse reactions); court-mandated not to consume alcohol (for participant safety); any condition that could place the participant at risk or affect data validity;

and uncorrected vision (required for eye-tracking). A total of N = 2 participants were excluded for having a positive UDS, and N = 1 participant was excluded for only completing one session, making the final sample N = 31 (mean age = 28.71, 45.2 % women, 47.8 % non-White).

Measures

Table 1 provides the operationalization of study variables.

Demographics

The present study collected information on participant's age, race, gender, brand of ENDS, nicotine content of ENDS refill (mg/mL), and number of months using an ENDS via the Qualtrics online survey system (see Appendix C, Table C.1).

Alcohol Use Disorder Identification Test (AUDIT)

The AUDIT (see Appendix C, Table C.2) (Saunders et al., 1993) is a ten-item scale that measures hazardous alcohol consumption and alcohol related problems. Participants provided data via Qualtrics. The AUDIT has demonstrated high concurrent validity (Donovan et al., 2006) and high test re-test reliability (Shields & Caruso, 2003). Reliability of AUDIT scores in the present sample was good (alpha = 0.72).

Nicotine and Other Substance Interaction Expectancies-E-cig Revised (NOSIE-ER)

The NOSIE-ER (see Appendix C, Table C.3) (Hershberger et al., 2016) is an eight-item true/false self-report measure, adapted from Rohsenow et al., 2005, of expectancies of using ENDS and alcohol together. Participants provided data via Qualtrics. Scores on the NOSIE-ER are significantly related to measures of problematic alcohol use (Hershberger et al., 2016) and discriminate between types of ENDS users (e.g., social users, regular users, dual users of ENDS and cigarettes; Hershberger et al., 2016). Reliability of the NOSIE-ER in the present sample was acceptable (alpha= 0.67).

Concurrent alcohol and ENDS use

The timeline follow-back calendar (TLFB; Sobell & Sobell, 1992) (see Appendix C, Table C.4) is a self-report measure used for assessing participant self-report of recent substance use. Participants provided data via Qualtrics. Participants were presented with an image of a calendar for the last two weeks prior to their session (calendar updated for each participant) and an image depicting the definition of one standard drink. Participants read directions asking them to think about the prior two weeks, using the calendar provided as a guide, and indicate if they consumed alcohol on the specified days and if they used their ENDS while they were consuming alcohol on each alcohol use day. Response options were a dichotomous "yes" or "no" for concurrent ENDS and alcohol use. Participants were also asked to provide the number of drinks they consumed on days that they reported alcohol use, using the image of a standard drink as a guide for approximating the number of drinks consumed.

Craving assessment

Alcohol and ENDS craving were assessed via pen and paper self-report: "On a scale from 0 (not at all) to 10 (very much) how much are you craving ENDS?" and "On a scale from 0 (not at all) to 10 (very much) how much are you craving alcohol?" (Etter et al., 2015; Farsalinos et al., 2014). Participants were presented with a Likert scale with numbers listed from 0-10 and asked to circle the number that best described their current cravings. Single item measures of craving show good correlation with multi-item measures of craving and specificity in detecting problematic alcohol use (see Schlauch et al., 2019 for a review).

Participant ENDS device

Participants brought their own ENDS to both study sessions and were randomized prior to participation to use their ENDS in either session one or session two (see "Procedure" for further details). In order to ensure participants' ENDS did not lose all battery power or run out of refill liquid, participants brought an additional battery or charger and replacement nicotine refill liquid for their ENDS. Given the wide variety of ENDS available (7700 refill liquids, 440 brands; Zhu et al., 2014), providing participants with the same ENDS for the study would provide experimental control (e.g., Dawkins & Corcoran, 2014; King et al 2017; Palmer &

Brandon, 2018; Spindle et al., 2018). However, research also indicates that users of ENDS have specific ENDS device preferences (e.g., tank system versus disposable device, flavor of refill liquid, nicotine strength of refill liquid; Yingst et al., 2015; 2017; see Zare et al., 2018 for a review); thus, providing everyone with the same ENDS would reduce ecological validity and create increased error variance across participants relative to their ENDS preferences in the real world. Therefore, in order to increase ecological validity of the study, participants used their preferred ENDS device.

Alcohol related attentional bias: Visual dot-probe paradigm

The present study utilized the computer-based visual dot-probe paradigm (MacLeod, Matthews, and Tata, 1986) to assess attentional bias for alcohol-related images (e.g., a picture of a bottle of beer, a person holding a beer mug). The visual dot-probe paradigm task was pre-programmed using E-Prime 3.0 (Psychology Software Tools, Pittsburg, PA) and alcohol and matched control images selected for the present study were inserted into the program (see Procedures for a description of the task).

Alcohol related attentional bias: Images

For the present study, seventeen matched (e.g., for color, shape, lighting; Miller & Fillmore, 2010) alcohol and control images were piloted on N = 2 for 80 trials to assess for the average valence and arousal rating and pupil dilation in response to each image. Studies to date have not examined reliability and validity based on the number of matched image pairs, but convention in the literature is around 20 images (e.g., Miller & Fillmore, 2010; Price et al., 2015; Townshend & Duka, 2001). One matched pair differed significantly on valence and was removed from the study (Miller & Fillmore, 2010). The remaining matched image pairs that did not differ significantly in valence, arousal, and pupil dilation were retained for the present study (final N = 16 matched image pairs; see Appendix D).

Alcohol related attentional bias: Reaction time bias

Reaction time bias is a measure of attentional bias calculated by comparing the time it takes participants to respond to visual probes (arrows) replacing the experimental (alcohol) versus control image (Field & Cox, 2008). Reaction time was recorded by E-Prime during the

visual dot-probe paradigm and an average reaction time was computed for each participant for both alcohol and control images. Reaction time bias was calculated by subtracting response time to alcohol images from response time to control images, with positive values indicating faster average reaction time to alcohol images.

Alcohol related attentional bias: Initial orientation

Initial orientation was calculated by dividing the number of trials that a participants eyes were first fixated on the experimental (alcohol) image (versus control image) by the total number of trials that an initial fixation was made on either image (Field & Cox, 2008). Thus, as the proportion increased, so did the participant's inferred attentional bias for alcohol images.

Alcohol related attentional bias: Delayed Disengagement

Delayed disengagement was calculated by dividing the duration of time that a participant spends fixated on the alcohol images by the amount of time that a participants spends fixated on any images, across all 80 trials (Field & Cox, 2008). Thus, as the proportion of the participant's fixation on alcohol images increased, so did the participant's inferred attentional bias for alcohol images.

Procedure

Recruitment and Enrollment

An outline of study procedures is presented in Figure 1. Prospective participants were recruited via flyers, both on the IUPUI campus and in the broader Indianapolis community, including in local bars and restaurants, local ENDS stores, local liquor stores, and online (e.g., Craigslist, IU Classifieds). Interested individuals called the research lab and were screened by a research assistant via telephone for inclusion/exclusion criteria (see Participants and Appendix E). After qualifying for the study, participants were scheduled for two separate study sessions and randomly assigned to session order (ENDS or control). Participants were asked not to schedule any sessions on or the day before they had obligations (e.g., tests, work) in order to help ensure such obligations would not affect their alcohol consumption in session. Research assistants asked participants prior to and after completion of the study if they had any upcoming

obligations. One participant reported that they had to work in the morning (reported at the end of session one), but their session one data were withdrawn due to a positive UDS in session two. Participants were also informed that they must stay for the entire study session (four hours) regardless of how much alcohol they consumed in the session; this was done in order to prevent participants from limiting their alcohol consumption during the study in order to leave early. Prior to their first study session, participants were informed that they would be completing a UDS upon arrival to confirm they were negative for all excluded substances (see Appendix B), a urine pregnancy screen (females only), and a breathalyzer to confirm a BrAC of zero at the beginning of the session. Participants were also told to bring their ENDS, ENDS charger, and nicotine refills to each session.

Session One

Upon arrival for session one, participants completed the informed consent process (see Appendix F) and were told by the research assistant that the study would be 1) assessing cognitive acuity following the use of ENDS or control and 2) examining motor-coordination following beer and the use of ENDS or control. Participants provided a urine sample for a UDS and pregnancy screen (females only) and BrAC was measured with a breathalyzer by a trained research assistant. A total of N = 2 participants had a positive UDS (N = 1 positive screen for cocaine in session two-participant described above in *Recruitment and Enrollment* as having work obligations, N = 1 positive screen for opioids in session two) and were dismissed from the study. The research assistant confirmed the participant brought their ENDS, charger, and nicotine refill to session, and subsequently weighed the ENDS (grams). Participants next completed the first craving assessment and were escorted to a computer where they completed a demographic questionnaire, AUDIT, TLFB, NOSIE-ER, and other self-report measures unrelated to the present study via Qualtrics.

Dot-probe paradigm

For the ENDS session, participants were next instructed by the research assistant to take 10 puffs from their ENDS within a five-minute period while the research assistant observed and recorded their puffs. This served as the ENDS prime for the dot-probe task. Research indicates users of ENDS take puffs at approximately 25 second intervals for 5.35 minutes, across brands

of ENDS, and thus 10 puffs was used to approximate this timing across a five-minute period (Strasser et al., 2016). The research assistant then took the participant's ENDS, weighed the ENDS, and kept it in a separate room for the remainder of the dot-probe task. Participants in the control condition sat for five minutes with a pencil in their hand (similar to ENDS in size and weight). Next, participants (both in the ENDS and control condition) completed the second craving assessment.

All participants then completed the visual dot-probe task with eye tracking, using an Eye-Trac D6 Desktop mounted camera. Participants faced a computer, approximately 24 inches from the computer screen, and placed their head in a chin rest to stabilize their head and minimize movement during the dot-probe task. Participant's eye movements were calibrated to ensure accuracy of eye movement tracking. Next, the research assistant began the dot-probe task, reading the instructions that appeared on the participant's computer out loud. Participants completed 10 practice trails of the dot-probe paradigm followed by 80 experimental trials. For each trial of the dot-probe task, participants were presented with two side-by-side images (5 x 7 inches as used in previous work; e.g., Field & Eastwood, 2005) for 1000 milliseconds, one control and one alcohol-related image, against a black background on the computer screen (Field & Cox, 2008). After picture offset, a visual probe appeared where one of the pictures had previously been presented and participants were instructed to identify the location of the probe as quickly as possible by pressing either the left or right mouse button.

Ad libitum paradigm

Participants were escorted by the research assistant to a separate room to complete the ad lib portion of the study. The room was setup provide a relaxed atmosphere (Weafer & Fillmore, 2008), including a recliner and television. Participants then completed the third craving assessment. The research assistant described the next portion of the study, telling the participants they were completing a beer taste test (e.g., Marlatt et al., 197; Weafer & Fillmore, 2008; Van Dyke & Fillmore, 2016) and would need to rate five beers on various qualities (e.g., taste, aroma, drinkability; see Appendix G). The research assistant went to a separate room where they prepared five cold glasses with 355 mL of beer each: Three beers with similar per volume alcohol content were provided (Bud Light-4.2% alcohol, Miller Light-4.2% alcohol, Sam Adams Light-4.1% alcohol; Van Dyke & Fillmore, 2016), and two non-alcoholic beers, Buckler's and

O'Doul's (both 0% alcohol), were provided in order to limit overall breath alcohol concentration of participants.

For the ENDS session, participants were next instructed by the research assistant to take 10 puffs from their ENDS within a five-minute period while the research assistant observed and tallied their puffs. This served as the ENDS prime for the ad lib task. Research assistants then weighed the ENDS and returned the ENDS to the participant. Participants in the control condition sat for five minutes with a pencil in their hand (similar to ENDS in size and weight). Participants then completed the fourth craving assessment. Participants in the ENDS session were next instructed to use their ENDS throughout the next portion of the study as much or as little as they would like.

Next, the research assistant placed the five beers on a table in front of where the participant was seated in a randomized order from left to right. For both sessions, participants were told to drink as much or as little of each beer as they like and rate each beer on various qualities (e.g., taste, aroma, drinkability), but to at least drink enough to rate each beer. Participants were instructed that they had 60 minutes to complete the taste test. The ad lib alcohol consumption paradigm, using a similar quantity of beer as the present study, ranges in length from 30 (e.g., Field & Jones, 2017; McGrath et al., 2016) to 90 minutes (e.g., Weafer & Fillmore, 2008; 2012). The present study utilized a 60-minute paradigm to insure enough time to allow for variability in alcohol consumption between participants, but also to limit participant fatigue.

Prior to beginning the taste test, participants were reminded that they would be dismissed from the study as scheduled and would have to stay for the entire allotted study time (four hours), regardless of the amount of beer they consumed during the session. Participants were given five beer-rating sheets (see Appendix G) and the research assistant left the room. Participants were not informed that the research assistant, trained in session coding, recorded the timing of ENDS puffs (ENDS session only) and sips of beer temporally, through the use of the lab's one-way mirror. Although the research assistant did not assess if participants were aware that they were being watched, research shows that awareness of being observed in the ad lib task does not impact participant alcohol consumption (Jones et al., 2016). The research assistant used Microsoft Excel to create a time stamp for the start and stop time of each sip and puff taken by the participant. After 60 minutes, participants had their BrAC measured and completed the fifth

craving assessment. The research assistant removed the beer and participant's ENDS from the ad lib room. The amount of alcohol consumed was measured in a separate room and calculated by subtracting the amount of alcohol remaining at the end of the ad libitum session from the total amount of alcohol offered (1775 mL). The amount of ENDS consumed was calculated by taking the ENDS weight prior to the ad lib session and subtracting the ENDS weight immediately following the ad lib session.

Post-experiment

The research assistant offered the participant snacks, water, and movies to watch while they waited until the end of the four-hour session (and BrAC < 0.02). The research assistant continued to breathalyze participants every 20-30 minutes to ensure declining BrAC. All participants reached a BrAC < 0.02 within the allotted four-hour session time. At the end of the four hours, a final BrAC was obtained and participants were given a field sobriety test (see Appendix H). Last, participants were paid $60.00 (approximately $15 per hour), given a parking validation ticket, and a reminder card with their session two date and time. Session two was scheduled for no more than two weeks after session one. Mean days between session one and session two was 9.32 days (range 2-14 days).

Session Two

Upon arrival for session two, participants provided a urine sample for a UDS and pregnancy screen (females only) and BrAC was assessed via breathalyzer by a trained research assistant. The research assistant confirmed the participant brought their ENDS, charger, and nicotine refill to the session, and subsequently weighed the ENDS (grams) in the ENDS condition. Participants next completed the first craving assessment. Session two then proceeded as session one, except that participants completed the condition (ENDS or control) not completed in the first session and did not complete the Qualtrics survey. At the end of session two, participants were debriefed on the true nature of the study and given an opportunity to ask questions and raise concerns. Participants did not report guessing the true nature of the study. Last, participants were paid $40 (session two average time of 2.56 hours; average pay $15 per hour), given a parking validation ticket, and asked to not share the true nature of the study until data collection was complete.

Preliminary Data Screening and Hypothesis Testing Plan

Preliminary data screening was conducted using SPSS Statistics 25.0 software (IBM Corp., 2017). Table 1 presents study variables and their calculation. First, I summed the number of days of self-reported concurrent ENDS and alcohol use from the two-week TLFB calendar. I then computed average AUDIT and total NOSIE-ER scores. Next, I calculated the total number of sips and puffs for each participant for their session one and session two and then computed the number of sips and puffs taken by each participant in each 10 minute segment of the ad lib paradigm. I assessed normality for 1) number of days of self-reported concurrent ENDS and alcohol use, 2) AUDIT, 3) NOSIE-ER 4) in-session ENDS cravings, 5) in-session alcohol cravings, 6) total sips, 7) total puffs, 8) sips per segment, 9) puffs per segment, 10) mL of beer consumed in the ENDS condition, 11) mL of beer consumed in the control condition, 12) pre ad lib ENDS weight, 13) post ad lib ENDS weight, 14) months of ENDS use, and 15) mg/mL of nicotine in participants' ENDS. I assessed normality by examining skewness (> 3) and kurtosis (> 10; Kline, 1998). I examined study variables by gender and calculated the correlation between study variables.

I used a dependent samples t-test to examine the effect of the experimental manipulation (ENDS use or control) on ENDS and alcohol craving at two time-points: 1) before and after 5 minutes of ENDS use prior to eye-tracking and 2) before and after 5 minutes of ENDS use prior to the ad lib paradigm (see Figure 1). I expected a decrease in ENDS craving (Helen et al., 2016) and an increase in alcohol craving (Hershberger et al., 2016).

Data Screening: Attentional Bias

I screened attentional bias data (reaction time, initial orientation, and delayed disengagement) both on the participant and aggregate level.

First, reaction time data for each participant was opened using E-Prime and converted to an SPSS file. Each participant had 80 trials of reaction time data for both the ENDS and control session (total of 160 trials per participant) and each trial was associated with a probe replacing either an alcohol or control image. Individual trials of reaction time data were removed if the reaction time was zero (indicating no response; N = 46 total trials removed across participants). I separated each participant's reaction time data by responses following alcohol or control images,

computed the reliability of reaction time by image type, and assessed for normality (skewness -0.03 to 1.82; kurtosis -0.57 to 4.15). Participant data were removed from reaction time analyses if they did not complete both session one and session two or if reaction time data were not recorded (see *Results, Aim 1*).

Second, I extracted initial orientation and delayed disengagement data for each participant. I opened each participants' eye-tracking data file from session one and session two using ASL Results. I then configured two backgrounds, one background with the alcohol image on the left and one with the alcohol image on the right, and I used the backgrounds to define the area of interest (AOI; i.e., the area of the screen where participants gaze is directed when they are looking at an alcohol or control image from the dot-probe task). Next, I selected the participants eye-tracking data points ("events") that were 1) associated with an XDAT value (each XDAT value was pre-programmed to correspond with a specific trial from the dot-probe paradigm; data without XDAT values corresponded to non-related portions of the task, such as the participant viewing task directions), and 2) within the AOI's that I defined. I also specified the program to select fixations based on guidelines from Komogortsev and colleagues (2010) for high quality eye-tracking data: (1) at least 3 consecutive saccades, (2) within 2 degrees of visual angle, and (3) lasting at least 100ms. I then exported each participant's eye-tracking data to SPSS.

For each participant, I calculated the total amount of time that eye-tracking data were obtained. Each trial (N = 80 total trials) presented images from 1000ms, thus if data were collected for the full time of each trial, participant's would have 80 seconds of eye-tracking data relevant to attentional bias measurement. One recommendation suggests that high quality eye-tracking data includes data from at least 75% of the time in which stimuli was presented (Komogortsev et al., 2010), which for the present study, corresponds to 60 seconds (80 seconds x 75% = 60 seconds). Additionally, I examined the total number of trials that participants had fixations in one of the AOI's, although there are not specific recommendations for data quality based on the number of trials with fixations.

The present study was limited by sample size (N = 31), which was further limited by difficulties calibrating participant eyes for both session one and session two (final N = 24, see *Results, Aim 1*). In order to balance data quality with not removing participant data erroneously, I calculated initial orientation and delayed disengagement for each participant with > 1 fixation in one of the AOI's (and correspondingly, > 0ms with eye-tracking data obtained). Next, I

calculated overall means for initial orientation and delayed disengagement for both the ENDS and control condition at each cut point: 1) > 1 fixation, 2) > 25% of trials with fixations (20 trials) and data collected > 25% of the time (20s), and 3) > 50% of trials with fixations (40 trials) and data collected > 50% of the time (40s). I conducted a one-way ANOVA to examine differences in initial orientation and delayed disengagement for participants excluded versus included at each cut-point. There were no significant differences in initial orientation and delayed disengagement across cut-points (see *Results, Aim 1*); in order to retain power and not erroneously exclude data, Aim 1 analyses were conducted for participants using the least conservative cut point (> 1 fixation).

I examined study variables across eye-tracking cut-points and calculated the correlation between study variables and attentional bias measures.

Hypothesis Testing Plan

Hypotheses were examined using SPSS Statistics 25.0 software (IBM Corp., 2017).

Aim 1

Hypothesis 1: Individuals primed with ENDS use will display a larger attentional bias towards alcohol cues (reaction time bias, initial orientation bias, and delayed disengagement bias), as assessed with eye-tracking measurement during a dot-probe task, than when there is no ENDS prime.

For each of the three conceptualizations of attentional bias, I conducted a repeated measure ANOVA controlling for age, race, and gender. Research indicates younger users of ENDS demonstrate a more robust relationship between ENDS and alcohol use (Hershberger et al., in preparation) and both race and gender account for variation in the relationship between ENDS and alcohol use (Roberts et al., 2018). For each analysis, attentional bias in the ENDS versus control condition was entered as the within-participant repeated factor. *F* statistics with $p < .01$, to correct for multiple comparisons, were deemed significant. For each analysis, a partial eta-squared (ηp^2) was calculated and effect sizes were interpreted in line with Cohen's (1988) guidelines of small (0.01), medium (0.06), and large (0.14) effects.

Hypothesis 2: The strength of the attentional bias for alcohol cues following ENDS prime will be related to self-reported concurrent alcohol and ENDS use, as measured by a timeline follow-back.

For each of the three conceptualizations of attentional bias, I conducted a repeated measure ANOVA using SPSS General Linear Modeling (GLM). For each analysis, attentional bias in the ENDS versus control condition was entered as the within-participant repeated factor. Age, race, and gender were entered as covariates. The number of occasions of self-reported concurrent ENDS and alcohol use over the past 14 days was entered as a between-participant effect. *F* statistics with $p < .01$, to correct for multiple comparisons, were deemed significant. For each analysis, a partial eta-squared (ηp^2) was calculated and effect sizes were interpreted in line with Cohen's (1988) guidelines of small (0.01), medium (0.06), and large (0.14) effects. Analyses were followed up by graphing the interaction.

Hypothesis 3: The relationship between ENDS and alcohol craving preceding the eye-tracking measurement and alcohol attentional bias will be stronger in the ENDS condition than in the control condition.

For each of the three conceptualizations of attentional bias, I conducted a repeated measure MANOVA using SPSS General Linear Modeling (GLM). Alcohol craving and ENDS craving (craving assessment preceding eye-tracking) were run in separate models, for a total of six models. For each analysis, there were two within-participant repeated factors: 1) attentional bias in the ENDS versus control condition and 2) craving preceding eye-tracking in the ENDS versus control condition. Due to the limited sample size, no covariates were included in the models. *F* statistics with $p < .01$, to correct for multiple comparisons, were deemed significant. For each analysis, a partial eta-squared (ηp^2) was calculated and effect sizes were interpreted in line with Cohen's (1988) guidelines of small (0.01), medium (0.06), and large (0.14) effects. Analyses were followed up by graphing the interaction.

Aim two

Hypothesis 4: Individuals will consume more alcohol ad libitum when allowed to use their ENDS during the session than when ENDS use is not allowed.

I conducted a repeated measure ANCOVA with the amount of alcohol consumed in the ENDS versus control condition as the within-participant repeated factor. Age, gender, and race were entered as covariates. An F statistic with $p < .01$, to correct for multiple comparisons, was deemed significant. For each analysis, a partial eta-squared (ηp^2) was calculated and effect sizes were interpreted in line with Cohen's (1988) guidelines of small (0.01), medium (0.06), and large (0.14) effects.

Hypothesis 5: Alcohol consumed during the ad libitum session will be significantly related to ENDS used during the ad libitum session.

Hypothesis 5, analysis 1: Meta effect

I conducted a hierarchical linear regression analysis, controlling for age, race, and gender (step 1), with the amount of ENDS used entered as the independent variable and the amount of alcohol consumed entered as the dependent variable (step 2). An F statistic with $p < .01$ was deemed significant and the effect size (R^2) was interpreted in line with Cohen's (1988) guidelines of small (0.01), medium (0.09), and large (0.25) effects.

Hypothesis 5, analysis 2: Temporal effects

First, data for the number of ENDS puffs and alcohol sips taken during the ENDS ad lib session were divided into six ten-minute segments. Within each of the six segments, an average number of sips and puffs were computed for each participant. I used SPSS hierarchical linear mixed modeling to examine the effect of puffs on sips across segments. I examined two goodness of fit indices: Akaike information criterion (AIC; Akaike, 1974), and Bayes information criterion (BIC; Stone, 1979). AIC estimates the likelihood of a model estimating future models and BIC estimates the likelihood of model fit taking into account the complexity of the model. A decrease in AIC and BIC between models indicates a better fitting model.

Hypothesis 5, analysis 2: Model 1

First, with sips entered as the dependent variable, I modeled the variance of the residuals in sips within each segment (Level 1) and variance of the residuals in the intercept of sips across participants (Level 2) to determine if there was variability that could be accounted for by adding other variables to the model.

Hypothesis 5, analysis 2: Model 2

Next, I added segment as a covariate in order to model the growth trajectories of the participants. I examined segment as a fixed effect and specified segment to randomly vary in order to examine variability in slopes across participants, thus allowing both intercepts and slopes to vary across participants.

Hypothesis 5, analysis 2: Model 3

Last, I added puffs as a time-varying covariate to examine if variability in residuals of participant sips could be accounted for by puffs.

Hypothesis 5, analysis 2: Sensitivity analysis

I used SPSS hierarchical linear mixed modeling to examine the effect of sips on puffs across segments. I examined two goodness of fit indices: AIC and BIC.

Hypothesis 5, analysis 2, Model 1, sensitivity analysis

First, with puffs entered as the dependent variable, I modeled the variance of the residuals in puffs within each segment (Level 1) and variance of the residuals in the intercept of puffs across participants (Level 2) to determine if there was variability that could be accounted for by adding other variables to the model.

Hypothesis 5, analysis 2: Model 2, sensitivity analysis

Next, I added segment as a covariate in order to model the growth trajectories of the participants. I examined segment as a fixed effect and specified segment to randomly vary in

order to examine variability in slopes across participants, thus allowing both intercepts and slopes to vary across participants.

Hypothesis 5, analysis 2: Model 3

Last, I added sips as a time-varying covariate to examine if variability in residuals of participant puffs could be accounted for by sips.

Hypothesis 6: The effect of ENDS use on alcohol consumption will be related to self-report concurrent alcohol and ENDS use as measured by a timeline follow-back.

I conducted a repeated measure ANOVA using SPSS General Linear Modeling (GLM). For the analysis, mL of beer consumed in the ENDS versus control condition was entered as the within-participant repeated factor. Age, race, and gender were entered as covariates. The number of occasions of self-reported concurrent ENDS and alcohol use was entered as a between-participant effect. An F statistic with $p < .01$, to correct for multiple comparisons, was deemed significant. A partial eta-squared (ηp^2) was calculated and effect sizes were interpreted in line with Cohen's (1988) guidelines of small (0.01), medium (0.06), and large (0.14) effects.

Hypothesis 7: The relationship between ENDS and alcohol craving preceding the ad lib paradigm and amount of beer consumed in the ad lib paradigm will be greater in the ENDS condition than in the control condition

I conducted two repeated measure MANOVA's using SPSS General Linear Modeling (GLM). For each analysis, there were two within-participant repeated factors: 1) mL of beer consumed in the ENDS versus control condition, and 2) craving (ENDS and alcohol, run in separate models) preceding the ad lib paradigm in the ENDS versus control condition. Age, race, and gender were entered as covariates. F statistics with $p < .01$, to correct for multiple comparisons, were deemed significant. For each analysis, a partial eta-squared (ηp^2) was calculated and effect sizes were interpreted in line with Cohen's (1988) guidelines of small (0.01), medium (0.06), and large (0.14) effects. Analyses were followed up by graphing the interaction.

RESULTS

Study Sample

Participant data screening

Participants that only completed one study session were excluded from analyses. Participants that completed the study (N = 31) and participants that only completed one session (N = 3) did not differ significantly by age ($t = 0.20$, $p = .84$), gender ($\chi^2 = 0.51$, $p = .59$), race ($\chi^2 = 1.01$, $p = .90$), or AUDIT ($t = 0.35$, $p = .73$). After participant removal, 54.8% (N = 17) of the participants had been randomized to ENDS condition in session one.

Total Sample Characteristics

Table 2 presents characteristics of the total sample and by gender. The final sample had a total of N = 31 participants (mean age = 28.71, SD = 11.17; range 21 - 78; 45.2% women; 54.8% White/Caucasian, 19.4% Black/African American, 12.9% Asian, 6.5% Hispanic or Latino, 6.5% other). Women (mean age = 28.86, SD = 15.71) and men (mean age = 28.59, SD = 5.78) had similar ages ($t = 0.07$, $p = .95$) and race ($\chi^2 = 0.78$, $p = .94$). The majority of participants reported their highest education as some college after high school (N = 12, 38.7%) and income of less than $10,000 annually (N = 8, 25.8%).

Participants reported using an ENDS for an average of 37.10 months (SD = 34.71, range 1 - 175) and reported an average ENDS nicotine liquid level of 7.77 mg/mL (SD = 9.06, range 2 - 36). The most common brand of ENDS were JUUL (N = 5), Smok (N = 5), and blu (N = 3). Other brands included Camel (N = 1), eGO-T (N = 2), Kangertech (N = 1), Limitless (N = 2), Mark 10 (N = 1), NJOY (N = 1), Sigelei 213 (N = 1), Sourin Drop (N = 1), SUBVOD (N = 1), Troll RDA (N = 1), Tsunami (N = 1), and Vibe (N = 1). A total of N = 4 did not provide the brand of their ENDS. The majority of participants reported their ENDS had refillable nicotine liquid tanks (N = 17); N = 14 reported using disposable nicotine liquid cartridges.

ENDS Prime effects check

To verify that the ENDS prime was sufficient to initiate an experimental effect, I examined the effects of ENDS prime on ENDS and alcohol craving. For the ENDS prime prior to eye-tracking, ENDS craving significantly decreased pre- (M = 3.84, SD = 3.09) to post-prime (M = 2.38, SD = 3.04), t (30) = 2.51, p = .009; however, alcohol craving did not significantly change pre- (M = 2.26, SD = 2.49) to post-prime (M = 1.87, SD = 2.17), t (30) = 1.36, p = .18. For the ENDS prime prior to ad lib alcohol consumption, ENDS craving did not significantly change pre- (M = 3.57, SD = 3.06) to post-prime (M = 3.50, SD = 3.24), t (30) = 0.32, p = .75. There was a trend for increases in alcohol craving pre- (M = 2.23, SD = 2.31) to post-prime (M = 2.50, SD = 2.61), t (30) = -2.12, p = .04.

Aim 1

Data cleaning and descriptives for Aim 1

A total of N = 5 were missing one session of eye-tracking and reaction time data due to inability to calibrate participant's eye and their data were removed from Aim 1 analyses. A total of N = 2 participants were missing both sessions of eye-tracking and reaction time data due to inability to calibrate participant's eye and their data were removed from Aim 1 analyses. Participants with and without any eye-tracking and reaction time data did not differ significantly by age (t = 1.49, p = .15), gender (χ^2 = 0.001, p = .98), race (χ^2 = 2.98, p = .56), or AUDIT (t = -1.33, p = .20).

Reaction time data for remaining participants (N = 24; mean age = 28.00, SD = 6.89, range 24 - 48; 43.5% women; 52.2% White/Caucasian, 21.7% Black/African American, 17.4% Asian, 4.3% Hispanic or Latino, 4.3% other; see Table 3) were used to test Aim 1 hypotheses. After examining eye-tracking data for initial orientation and delayed disengagement, a total of N = 8 participants had < 1 fixation and N = 4 participants had corrupted data files that could not be opened (final N = 12; see Table 3). Reaction time bias, initial orientation, and delayed disengagement data for the ENDS and control sessions were normally distributed (skewness -2.23 to 2.05; kurtosis -1.09 to 6.59). Average reaction time bias (control image reaction time minus alcohol image reaction time; positive values indicate quicker responses to probes replacing alcohol images; N = 24) for the control condition was 7.33ms (SD = 35.82; range -

170.82 to 57.83) and average reaction time bias for the ENDS condition was -0.65ms (SD = 36.29; range -45.32 to 152.71). Average initial orientation (number of initial fixations on alcohol images/total fixations on images; > 50% indicates initial orientation towards alcohol images; N = 12) for the control condition was 49.07% (SD = 7.97; range 26.67 to 60.98) and average initial orientation for the ENDS condition was 50.56% (SD = 4.34; range 45.71 to 60.71). Average delayed disengagement (gaze time on alcohol images/total gaze time on images; > 50% indicates delayed disengagement from alcohol images; N = 12) for the control condition was 48.45% (SD = 7.88; range 26.67 to 60.98) and average delayed disengagement for the ENDS condition was 51.82% (SD = 5.77; range 27.55 to 60.10).

Table 3 presents descriptive characteristics for Aim 1 for the full sample (N = 31), participants with reaction time data (N = 24), and initial orientation and delayed disengagement data (N = 12). Table 3 also presents demographic characteristics at more conservative (compared to > 1 fixation) cut-points for initial orientation and delayed disengagement data quality: 1) fixations and gaze time for > 25% of trials (20 trials; N = 9) and 2) fixations and gaze time for > 50% of trials (40 trials; N = 4). I conducted a one-way ANOVA to examine differences in initial orientation and delayed disengagement for those excluded at each eye-tracking data cut-point (> 1 fixation; 25% fixations and gaze time, 50% fixations and gaze time) and there were no significant differences in scores for individuals excluded versus included at each time point (*F*'s 0.15 to 2.56, *p*'s .13 to .87; see note Table 3). Initial orientation and delayed disengagement data were retained for N = 12 participants (mean age = 28.00, SD = 7.10, 41.7% women; 50% White/Caucasian, 25% Black/African American, 25% Asian).

Correlations among study variables for Aim 1 are presented in Table 4. Initial orientation was strongly related to delayed disengagement in both the ENDS session ($r = 0.86$, $p < .001$) and control session ($r = 0.85$, $p < .001$). Reaction time bias was negatively related to initial orientation and delayed disengagement in both the ENDS ($r = -0.33$, $p = .0.29$, $r = -0.22$, $p = .54$, respectively) and control session ($r = -0.17$, $p = .60$, $r = -0.32$, $p = .30$, respectively), indicating that as reaction time bias for probes replacing alcohol images decreased, initial orientation to and delayed disengagement from alcohol images increased.

Hypothesis 1

Individuals primed with ENDS use will display a larger attentional bias towards alcohol cues (reaction time bias, initial orientation bias, and delayed disengagement bias), as assessed with eye-tracking measurement during a dot-probe task, than when there is no ENDS prime (see Table 5).

Reaction time bias

Results of a repeated measure ANCOVA indicated that the effect of ENDS condition on reaction time bias, controlling for age, gender, and race, was not statistically significant, F (1, 23) = 0.12, p = .73, and the effect size was small (η_p^2 = 0.006). There were no significant interactions between reaction time by ENDS condition and age, race, or gender (F's 0.05 - 0.57, p's .46 - .83; see Table 5).

Initial Orientation

Results of a repeated measure ANCOVA indicated that the effect of ENDS condition on initial orientation, controlling for age, gender, and race, was not statistically significant, F (1, 11) = 0.10, p = .76, and the effect size was small (η_p^2 = 0.01). There were no significant interactions between initial orientation by ENDS condition and age, race, or gender (F's 0.01 - 0.15, p's .71 - .92; see Table 5).

Delayed Disengagement

Results of a repeated measure ANOVA indicated that the effect of ENDS condition on delayed disengagement, controlling for age, gender, and race, was not statistically significant, F (1, 11) = 0.01, p = .92, and the effect size was small (η_p^2 = 0.001). There were no significant interactions between delayed disengagement by ENDS condition and age, race, or gender (F's 0.29 - 1.23, p's .30 - .60; see Table 5).

Hypothesis 2

The strength of the attentional bias for alcohol cues following ENDS prime will be related to self-reported concurrent alcohol and ENDS use, as measured by a timeline follow-back (see Table 6).

Concurrent ENDS and alcohol use

Reaction time bias

Results of a repeated measure ANCOVA indicated that the effect of ENDS condition on reaction time bias, controlling for age, gender, and race, was not significantly moderated by concurrent ENDS and alcohol use, F (1, 23) = 0.39, p = .93, but the effect size was large (η_p^2 = 0.35). The interaction was probed and graphed (see Figure 2, graph 1). Patterns showed a positive relationship between concurrent use and reaction time in both the ENDS and control condition, with a more robust relationship in the ENDS condition (slope = 1.28; intercept = -4.29) compared to the control condition (slope = 0.64; intercept = 5.63).

Initial orientation

Results of a repeated measure ANCOVA indicated that the effect of ENDS condition on initial orientation, controlling for age, gender, and race, was not significantly moderated by concurrent ENDS and alcohol use, F (1, 11) = 0.80, p = .70, but the effect size was large (η_p^2 = 0.85). The interaction was probed and graphed (see Figure 2, graph 2). Patterns indicated a positive relationship between concurrent use and initial orientation in the ENDS condition (slope = 0.57, intercept = 47.45), but a small negative relationship between concurrent use and initial orientation in the control condition (slope = -0.17, intercept = 49.98).

Delayed disengagement

Results of a repeated measure ANCOVA indicated that the effect of ENDS condition on delayed disengagement, controlling for age, gender, and race, was not significantly moderated by concurrent ENDS and alcohol use, F (1, 11) = 0.55, p = .78, but the effect size was large (η_p^2 = 0.79). The interaction was graphed (see Figure 2, graph 3). Patterns suggested a positive relationship between concurrent use and delayed disengagement in the ENDS condition (slope =

0.78, intercept = 47.56), but a negative relationship between concurrent use and delayed disengagement in the control condition (slope = -0.61, intercept = 51.82).

Hypothesis 3

The relationship between ENDS and alcohol craving preceding the eye-tracking measurement and alcohol attentional bias will be stronger in the ENDS condition than in the control condition.

Alcohol craving (see Table 7, Figure 3)

Reaction time

Results of a repeated measure MANOVA indicated that there was no significant interaction between reaction time in the ENDS versus control condition and alcohol craving in the ENDS versus control condition, F (1, 23) = 1.60, p = .22, Wilks' λ = 0.93, and the effect size was medium, η_p^2 = 0.07. The interaction was probed and graphed (see Figure 3, graphs 1 and 2). Patterns suggested a positive relationship between alcohol craving and reaction time in the ENDS condition (slope = 0.33, intercept = -2.02), but a negative relationship between alcohol craving and reaction time in the control condition (slope = -1.34, intercept = 10.78).

Initial orientation

Results of a repeated measure MANCOVA indicated that there was no significant interaction between initial orientation in the ENDS versus control condition and alcohol craving in the ENDS versus control condition, F (1, 11) = 0.22, p = .65, Wilks' λ = 0.98, and the effect size was small, η_p^2 = 0.02.

Delayed Disengagement

Results of a repeated measure MANCOVA indicated that there was no significant interaction between delayed disengagement in the ENDS versus control condition and alcohol craving in the ENDS versus control condition, F (1, 11) = 1.02, p = .33, Wilks' λ = 0.92, and the effect size was medium, η_p^2 = 0.09. The interaction was probed and graphed (see Figure 3, graphs 3 and 4). Patterns suggested a positive relationship between alcohol craving and delayed

disengagement in the ENDS condition (slope = 0.60, intercept = 50.18) and the control condition (slope = 0.62, intercept = 46.96).

Ends craving (see Table 8, Figure 4)

Reaction time

Results of a repeated measure MANCOVA indicated that there was no significant interaction between reaction time in the ENDS versus control condition and ENDS craving in the ENDS versus control condition, F (1, 23) = 9.61, p = .08, Wilks' λ = 0.87, and the effect size was medium, η_p^2 = 0.13. The interaction was probed and graphed (see Figure 4, graphs 1 and 2). Patterns suggested a negative relationship between ENDS craving and reaction time in the ENDS condition (slope = -3.34, intercept = 7.84) and the control condition (slope = -0.89, intercept = 11.59), with a more robust relationship in the ENDS condition.

Initial orientation

Results of a repeated measure MANCOVA indicated that that there was no significant interaction between initial orientation in the ENDS versus control condition and ENDS craving in the ENDS versus control condition, F (1, 11) = 0.68, p = .43, Wilks' λ = .97, and the effect size was medium, η_p^2 = 0.06. The interaction was probed and graphed (see Figure 4, graphs 3 and 4). Patterns suggested a positive relationship between ENDS craving and initial orientation in the ENDS condition (slope = 0.31, intercept = 49.67), but a negative relationship between ENDS craving and initial orientation in the control condition (slope = -0.97, intercept = 53.03).

Delayed Disengagement

Results of a repeated measure MANCOVA indicated that that there was no significant interaction between delayed disengagement in the ENDS versus control condition and ENDS craving in the ENDS versus control condition, F (1, 11) = 1.49, p = .25, Wilks' λ = .88, and the effect size was medium, η_p^2 = 0.12. The interaction was probed and graphed (see Figure 4, graphs 5 and 6). Patterns suggested a positive relationship between ENDS craving and delayed disengagement in the ENDS condition (slope = 0.18, intercept = 51.32), but a negative

relationship between ENDS craving and delayed disengagement in the control condition (slope = -1.36, intercept = 53.99).

Aim 2

Participant data for Aim 2 is listed under *Total Sample Characteristics* (see Table 2). Correlations among study variables are presented in Table 9. Other data removal is listed by hypothesis below. Average amount of beer consumed in the ENDS session was 716.39 mL (SD = 447.56) and average amount of beer consumed in the control condition was 683.48 (SD = 453.24; t = 0.51, p = .62, d = 0.09). Average number of beer sips in the ENDS condition was 21.93 (SD = 15.65) and average number of beer sips in the control condition was 23.28 (15.91; t = -0.57, p = .58, d = 0.08). Average number of ENDS puffs in the ENDS condition was 16.28 (SD = 12.93).

Hypothesis 4

Individuals will consume more alcohol ad lib when allowed to use ENDS during the session than when ENDS use is not allowed.

The effect of ENDS condition on amount of beer consumed was not statistically significant, after controlling for age, race, and gender, F (1, 30) = 0.03, p = .86, and the effect size was small, η_p^2 = 0.001. There were no significant interactions between amount of beer consumed by ENDS condition and age, race, or gender (F's 0.06 - 0.33, p's .57 - .82; see Table 10).

Hypothesis 5

Alcohol consumed during the ad lib session will be significantly related to ENDS use during the ad lib session.

Analysis 1

N = 2 participants refilled their ENDS during the ad lib task and pre and post ENDS weight (g) could not be calculated. An additional N = 3 participants' ENDS could not be

weighed as they were too heavy for the scale. The final sample for hypothesis 5, analysis 1 was N = 26. Those with and without pre and post ENDS weight did not differ significantly by age (t = 0.69, p = .52), gender (χ^2 = 2.91, p = .09), or race (χ^2 = 2.55, p = .11). After data removal, N = 15 (57.7%) participants had taken part in the ENDS condition in session one.

Results of a hierarchical linear regression indicated that the amount of ENDS weight change (g) was not significantly related to mL of beer consumed in the ENDS session (b = -81.22, t = -0.84 p = 0.41), after controlling for age, race, and gender (see Table 11), and the effect size was small (ΔR^2 = 0.03).

Analysis 2

I used linear mixed modeling to examine the relationship between ENDS puffs and beer sips across the ad lib paradigm (see Table 12).

Analysis 2, Model 1: Random intercept model

The estimated mean sips with no predictors in the model was 3.11 (SE = 0.44, p < .001). For the level 1 model, there was significant variation in residuals in sips within segments one and four (see Table 12). For the level 2 model, there was variation of the residuals in the intercept across participants that fell just short of significance (estimate = 4.22, SE = 2.25, p = .06), which indicated that adding other predictors to the model could account for variation in the residuals within segment and across intercepts (Goodness of fit: AIC = 874.18, BIC = 910.01; Parameters = 8).

Analysis 2, Model 2: Random intercept + fixed effect and slope

Results indicated that, on average, for every increase in segment across the ad lib paradigm, there was a 0.86 (SE = 0.11, p < .001) decrease in sips taken. For the level 1 model, there was significant variation in residuals in sips within all six segments (see Table 12). For the level 2 model, there was significant variation of the residuals in the intercept across participants (estimate = 3.47, SE = 1.34, p = .01) and non-significant variation in the residuals in the slope across participants (estimate = 0.05, SE = 0.61, p = .41). Similar to model 1, this suggested that adding predictors to the model could account for variation in the residuals across intercepts (Goodness of fit: AIC = 836.79, BIC = 861.69; Parameters = 10). Growth trajectories of

participants (i.e., slope) did not significantly differ between participants, but because of the small sample (i.e., difficulties in detecting significant effects), I proceeded with including slope in level 2 for model 3 below.

Analysis 2, Model 3: Random intercept + fixed effect, time-varying covariate, and slope

Results indicated that, on average, for every increase in segment across the ad lib paradigm, there was a 0.89 (SE = 0.10, $p < .001$) decrease in sips taken. For the time-varying covariate of ENDS puffs, results indicated that, on average, for every average increase in ENDS puffs across segments, there was a 0.23 (SE = 0.07, $p = .002$) increase in sips in the same segment. For the level 1 model, there was significant variation in residuals in sips within all six segments (see Table 12). For the level 2 model, there was significant variation of the residuals in the intercept across participants (estimate = 2.70, SE = 0.99, $p = .007$) and non-significant variation in the residuals in the slope across participants (estimate = 0.001, SE = 0.05, $p = .98$). Adding ENDS puffs to the model as a time-varying covariate of sips accounted for additional variability in slope across participants (model 2 slope estimate = 0.05, model 3 slope estimate = 0.001); however, similar to model 1 and 2, adding predictors to the model could account for variation in the residuals across intercepts (Goodness of fit: AIC = 832.39, BIC = 857.23; Parameters = 11) that could not be accounted for by ENDS puffs.

Sensitivity analysis for analysis 2

I used linear mixed modeling to examine the relationship between beer sips and END puffs across the ad lib paradigm (see Table 13).

Sensitivity analysis, Model 1: Random intercept model

The estimated mean puffs with no predictors in the model was 2.76 (SE = 0.38, $p < .001$). For the level 1 model, there was significant variation in residuals in sips within all six segments (see Table 13). For the level 2 model, there was variation of the residuals in the intercept across participants that fell just short of significance (estimate = 3.31, SE = 1.20, $p = .06$), which indicated that adding other predictors to the model could account for variation in the residuals within segment and across intercepts (Goodness of fit: AIC = 799.11, BIC = 820.93; Parameters = 8).

Sensitivity analysis, Model 2: Random intercept + fixed effect and slope

Results indicated that, on average, for every increase in segment across the ad lib paradigm, there was a 0.28 (SE = 0.11, $p < .001$) increase in puffs taken. For the level 1 model, there was significant variation in residuals in puffs within five segments (see Table 13). For the level 2 model, variation of the residuals in the intercept across participants fell short of significance (estimate = 2.02, SE = 0.94, $p = .03$) and variation in the residuals in the slope across participants fell short of significance (estimate = 0.24, SE = 0.12, $p = .04$). Similar to model 1, this suggested that adding predictors to the model could account for variation in the residuals within segment and across intercepts (Goodness of fit: AIC = 772.06, BIC = 812.96; Parameters = 10).

Sensitivity analysis, Model 3: Random intercept + fixed effect, time-varying covariate, and slope

Results indicated that, on average, for every increase in segment across the ad lib paradigm, there was a 0.35 (SE = 0.13, $p = .01$) increase in ENDS puffs taken. For the time-varying covariate of beer sips, results indicated that, on average, for every average increase in beer sips across segments, there was a 0.09 (SE = 0.06, $p = .08$) increase in ENDS puffs in the same segment, which was not statistically significant. For the level 1 model, there was significant variation in residuals in sips within five segments (see Table 13). For the level 2 model, variation of the residuals in the intercept across participants fell short of significance (estimate = 2.02, SE = 0.94, $p = .03$) and variation in the residuals in the slope across participants fell short of significance (estimate = 0.21, SE = 0.11, $p = .06$). Adding beer sips to the model as a time-varying covariate of sips accounted for additional variability in slope across participants (model 2 slope estimate = 0.24, model 3 slope estimate = 0.21); however, similar to model 1 and 2, this suggested that adding predictors to the model could account for variation in the residuals within segment and across intercepts that could not be accounted for by beer sips. Additionally, goodness of fit estimates increased from model 2 to model 3 (Goodness of fit: AIC = 832.39, BIC = 857.23; Parameters = 11), which suggested adding beer sips as a time varying covariate of ENDS puffs reduced model fit. .

Hypothesis 6

The effect of ENDS use on alcohol consumption will be related to self-reported concurrent alcohol and ENDS use as measured by a timeline follow-back.

Number of days of concurrent ENDS and alcohol use

The effect of ENDS condition on amount of beer consumed was not significantly related to number of days of self-reported concurrent ENDS and alcohol use on the TLFB, F (1, 30) = 1.09 p = .42, but the effect size was large, η_p^2 = 0.45 (see Table 14). The interaction was probed and graphed (see Figure 5). Patterns suggested a positive relationship between concurrent ENDS and alcohol use and mL of beer consumed in the control condition (slope = 35.23, intercept = 528.00), but a small negative relationship between concurrent ENDS and alcohol use and mL of beer consumed in the ENDS condition (slope = -1.37, intercept = 677.20).

Hypothesis 7

The relationship between ENDS and alcohol craving preceding the ad lib paradigm and amount of beer consumed in the ad lib paradigm will be greater in the ENDS condition than in the control condition.

Alcohol Craving

Results of a repeated measure MANCOVA, controlling for age, race, and gender, indicated there was no significant interaction between mL of beer consumed in the ENDS versus control condition and alcohol craving in the ENDS versus control condition, F (1, 30) = 0.03, p = 0.86, Wilks' λ = 0.99, and the effect size was small, η_p^2 = 0.001 (see Table 15).

ENDS Craving

Results of a repeated measure MANCOVA, controlling for age, race, and gender indicated that there was no significant interaction between mL of beer consumed in the ENDS versus control condition and ENDS craving in the ENDS and control condition, F (1, 30) = 0.03, p = .87, Wilks' λ = 0.99, and the effect size was small, η_p^2 = 0.001 (see Table 15).

DISCUSSION

The goal of the present study was to experimentally examine the effect of ENDS use on alcohol consumption and investigate attentional bias for alcohol as a potential mechanism underlying the relationship between ENDS and alcohol use. Research on the relationship between ENDS and alcohol use has been cross-sectional and focused on the meta-level of behavior (e.g., lifetime ends use as related to past 30-day alcohol use; Cohn et al., 2015). The present study is novel in that it is the first, to date, to examine the relationship between ENDS and alcohol use on the event-level, which is necessary to provide information on whether or not ENDS and alcohol use occur together in time and place.. If ENDS and alcohol use occur together in time and place, this provides opportunities for associative learning, whereby ENDS triggers alcohol use and alcohol use triggers ENDS use, potentially increasing both behaviors, which are each associated with negative health effects (Hess et al., 2017; Lerner et al., 2015; NIAAA, 2009; Schweitzer et al., 2015; Sussan et al., 2015; Valentine et al., 2016).
If ENDS use increases alcohol use in time and place, this sequence is particularly informative, as assessing for and intervening on ENDS use in high-risk populations (e.g., adolescents and those with alcohol use disorder) may be crucial to mitigating alcohol related negative outcomes. It should be noted that, as my limited sample size decreased my power to detect significant effects, I chose to examine effect sizes in addition to significance levels.

The relationship between ENDS use and alcohol attentional bias

In the current study, I examined the effect of ENDS prime on alcohol related attentional bias, as a test of one potential mechanism underlying the relationship between ENDS and alcohol use. An important limitation of the attentional bias data was that significant data were lost due to difficulty calibrating participants' eyes and corrupted data files. Further, although there is limited experimental evidence on appropriate cut-points for eye-tracking data, I included participants that had at least one (out of 80) fixations in their eye-tracking data in order to retain the most participants. It is difficult to make generalizations about an individual's attentional bias based on a small number of data points (e.g. at least one fixation), particularly with no information on why data were not collected on other trials and if there are patterns of missing fixations between and

within individuals. For example, it could be that the eye-tracking equipment stopped working in the middle of the trial due to changes in pupil dilation (such as from the brightness of the screen or physiological responses to the images themselves), which I cannot assess. In addition to poor eye-tracking data quality, I only had N = 12 participants included at my least-conservative cut-point, which calls into question the overall validity, replicability, and generalizability of my findings. In this context, I have chosen not to interpret findings related to eye-tracking (initial orientation and delayed disengagement). Here, I focus on reaction time findings, for which I was able to retain a larger sample (N = 24) that had excellent data quality (only N = 40 trials across all participants with missing data).

I did not find on overall effect of ENDS use on reaction time attentional bias. In the cigarette literature, limited research has examined the effect of cigarettes cueing alcohol reaction time bias, although some evidence suggests this effect is present (Oliver & Drobes, 2015). My findings are not in line with this research and suggest that reaction time attentional bias is likely not an explanatory mechanism connecting ENDS and alcohol use. I chose to examine alcohol attentional bias in the present sample because it is a well-studied mechanism in the substance use literature with validated measurement appropriate for experimental manipulation. There are other mechanisms that could be involved in the ENDS and alcohol use relationship that could be examined in future research. For example, research has identified genes that make individuals vulnerable to both alcohol and nicotine use (Grucza & Bierut, 2006), which could explain a relationship found between ENDS and alcohol use. Additionally, research demonstrates that individuals have positive expectancies of concurrent ENDS and alcohol use (Hershberger et al., 2016). Higher expectancies of concurrent use are associated with greater alcohol use; thus, this could be a potential mechanism of ENDS and alcohol use. At the same time, there are methodological reasons in the current study that could explain the null effects of ENDS prime on alcohol reaction time attentional bias. Most notably, ENDS prime did not significantly increase ENDS craving, thus suggesting a failure of the ENDS prime manipulation. It is possible that, with a stronger ENDS prime, one might see a change in reaction time alcohol attentional bias. Also, the images used in the present study were piloted in a small sample and have not been used in previous research. It could be that differences in alcohol and control images were not sufficient to incite attentional bias. Additionally, the small sample size limited my ability to detect the effect (if it does exist).

Importantly, there were important moderators of relationship between ENDS prime and alcohol reaction time attentional bias. First, self-reported concurrent ENDS and alcohol use over the previous 14 days moderated the relationship between ENDS use and alcohol reaction time attentional bias. Following ENDS prime, higher reported concurrent ENDS and alcohol use was related to greater reaction time attentional bias for alcohol related images. This effect was not observed in the control condition. Overall, this suggests that recent pairing of ENDS together with alcohol in time and place may not relate to generally higher alcohol reaction time attentional bias, but rather may strengthen the effect of ENDS prime on alcohol reaction time attentional bias. This finding supports a classical conditioning theory for ENDS and alcohol use, whereby ENDS use is required to draw ones attention to alcohol (Rohsenow, 1997) for those with a learning history of concurrent use. Such a learning history would, in this case, increase the likelihood and strength of conditioning, which makes intuitive sense (i.e., someone with limited learning history pairing these behaviors is not likely to display the behaviors together). This also suggests that in studying the persistence and long term effects of concurrent ENDS and alcohol use in research, the population of interest are individuals who have a recent history of concurrent ENDS and alcohol use, otherwise effects could be masked. This finding is novel as no research, to date, has examined the effect of concurrent use on this relationship in the ENDS or cigarette use literature. Previous research has examined the effect of alcohol dependence and drinks per week on cigarette cued alcohol reaction time attentional bias and found no relationship (Oliver & Drobes, 2015), which could lead to the conclusion that alcohol and cigarette use severity and frequency are unimportant in this relationship; however, the present study illustrates this may be an oversimplification. Future ENDS and alcohol research continue to screen for and examine concurrent use; this may also be an important methodological consideration for cigarette and alcohol use research.

The relationship between ENDS use and alcohol consumption

The most important finding from this project is that, in line with my hypothesis, increases in ENDS puffs were associated with statistically significant increases in beer sips during the alcohol ad lib session. These findings indicate that ENDS and alcohol use are proximally related and suggest the viability of examining classical conditioning models of ENDS and alcohol use.

ENDS and alcohol use are related within the same drinking occasion, which gives opportunity for associative learning and could potentiate increased use. In the present study, ENDS puffs accounted for some variability observed in beer sips across the ad lib session. To determine the robustness of the effect of ENDS puffs on beer sips, I also examined the effect of beer sips on ENDS puffs. Increases in beer sips were associated with a small increase in puffs. Additionally, beer sips did not account for variability observed if ENDS puffs across the ad lib session. Thus, this suggests that ENDS puffs are related to greater alcohol use in time and place, but that alcohol use is not a particularly strong facilitator of ENDS puffs. These are the first data to examine these behaviors at the event-level and are good preliminary data suggesting viability of an ENDS to alcohol use direction. The alcohol to ENDS use direction may be less viable according to these data.

An important question is whether this pattern between ENDS and alcohol use mirrors patterns between cigarettes and alcohol use. If they do, this would be support for the generalization of findings between cigarette and ENDS literatures. However, disparate findings would suggest that ENDS and cigarettes are distinct enough to differentially relate to outcomes of interest. Limited cigarette and alcohol research has examined this effect using real time data, so I cannot determine if the event-level relationship between ENDS and alcohol use is similar to an effect observed with cigarettes and alcohol. A recent review of cigarette and alcohol co-administration laboratory studies (Dermody & Hendershot, 2017) concluded that research has overwhelmingly focused on the direction from alcohol to cigarette use. Additionally, while there are some laboratory studies that have examined event-level data in the form of cigarette puffs (Glautier et al., 1996; McKee et al., 2010), analyses were examined on the meta-level, comparing total puffs between alcohol and placebo conditions (Glautier et al., 1996; McKee et al., 2010). EMA studies have examined the association between cigarette use and alcohol use on the event-level, although these studies also primarily made meta-level comparisons. Jackson & colleagues (2010) examined EMA data across an eight-week period and found that, on any given day, any smoking and number of cigarettes were predictors of any drinking and number of drinks per occasion. Witkiewitz and colleagues (2012) found that any smoking and number of cigarettes were predictors of any drinking and number of drinks per occasion. Most similar to the present analysis, Piasecki & colleagues (2011) asked participants to log a report after each cigarette they smoked and after they finished the first drink of a drinking occasion. The authors then divided

each day into six-hour segments, similar to the segment approach taken in the current study. However, the authors did not examine relationships in a single drinking occasion.

Thus, the present study is not just novel for the ENDS and alcohol use literature, but also expands upon methodologies used in the cigarette and alcohol use literature, showing that there is an observable relationship between ENDS puffs and alcohol sips in a single drinking occasion. I also hypothesized, overall, that ENDS use would increase the amount of beer consumed during the session; importantly, this was not supported. Cigarettes and ENDS have been well-linked to alcohol use using overall measures of consumption, such as frequency of alcohol consumption, drinks consumed per week, packs of cigarettes smoked per week, or daily use of ENDS. However, this study suggests that event-level data may or may not correspond with these overall patterns. My preliminary data here suggest that examining overall amount of ENDS nicotine liquid used or amount of alcohol consumed during a day or drinking period may mask more nuanced event-level patterns of concurrent use of these substances. Such cumulative effects do not correspond with the broader level patterns found in previous cross-sectional studies (e.g., relationship between ENDS use and drinks consumed per week), whereas the event-level data from the current analysis did correspond with such broader level patterns.

This lack of correspondence between these patterns is somewhat surprising, as pairing of behaviors in time and place would seem to suggest that you would also find an overall pattern relationship across a given session or day and patterns between cigarettes and alcohol would intuitively suggest a similar pattern would exist for ENDS. Many things could drive these differences. First, lack of correspondence could be due to differences in the data collection methodology. For example, collecting data over a longer period of time in a naturalistic setting and across multiple drinking occasions (i.e., EMA) enhances the ability to detect an effect, if one is present, compared to a limited one-hour ad lib drinking session. Second, there may be something fundamentally different about the ENDS and alcohol use relationship, compared to cigarettes and alcohol use. For example, it could be that there is a longer learning history for the relationship between cigarette and alcohol use (e.g., through media, home, peers) arguably among the general population, making the classical conditioning process almost pre-programmed between cigarettes and alcohol. ENDS are relatively new and it is possible ENDS users are less likely to have a long learning history between ENDS and alcohol use. Additionally, since cigarette use is being increasingly restricted and ENDS use is comparably more acceptable,

ENDS can be used in many places where cigarettes and alcohol cannot be used, such as at schools, work, and in public places (American Non-Smokers Rights Foundation, 2018). Thus, the paired association between ENDS and alcohol may be weaker than that between cigarettes and alcohol.

Third, statistical power and reliability may be influencing these patterns. Reliability for more general reports of behavior (e.g., how often do you use your ENDS in a typical month?) are traditionally higher than measurement of behavior during a given day or hour. Although behavior is fairly consistent across time, it can vary in any given moment. Thus, although an individual may tend to use their ENDS and drink alcohol, a relationship may be more difficult to pick up with a single measure (e.g., weight of ENDS, mL of beer consumed) of use in a one-hour ad lib session. However, by measuring the behaviors multiple times during the session (e.g., sips, puffs), the reliability of the behavioral measure is increased, and any masking of these more nuanced patterns is revealed. Fourth, if one is using their ENDS frequently during a drinking session, this would impede the amount of time they are drinking alcohol, shortening the length of a sip of alcohol and reducing the overall amount consumed. Looking at an overall measure would thus show no relationship between the behaviors and would mask any temporal pairing, such that people may puff on their ENDS preceding a sip of alcohol.

The present findings indicate ENDS and alcohol are occurring together in time and place, which gives the opportunity for associative learning, as suggested by prior theory (Rohsenow et al., 1997). This has the potential to increase the frequency of both behaviors. The present study indicates that ENDS puffs are related to more beer sips, in line with this theory. Accumulating evidence points to negative health effects associated with ENDS use (Hess et al., 2017; Lerner et al., 2015; Schweitzer et al., 2015; Sussan et al., 2015; Valentine et al., 2016), and a large body of literature demonstrates multiple negative outcomes associated with high levels of alcohol use (NIAAA, 2009). Thus, concurrent use may pose a public health concern for negative outcomes associated with both ENDS and alcohol use, particularly if these behaviors are increasing together. For example, particularly concerning, both alcohol and ENDS use are associated with increased blood pressure (Skotsirmara et al., 2019, NIAAA, 2009), thus concurrent use could have additive negative effects on cardiovascular function leading to cardiomyopathy, arrhythmias, and stroke, which are already prevalent with problematic alcohol use alone (NIAAA, 2009). These combined negative health effects are speculative and beyond the present

data, but illustrate that there is a great public health need for investigation of the negative short-term (e.g., high blood pressure) and long-term (e.g., stroke) consequences of concurrent ENDS and alcohol use.

The present findings also suggest that taking more ENDS puffs while consuming alcohol is related to more frequent sips of alcohol. More sips are likely indicative of greater quantities of alcohol consumed in the long-term, although that should be documented further. In the present study, there was a medium relationship between beer sips and mL of beer consumed in the ENDS condition ($r = 0.41$), suggesting more sips as a behavioral proxy for amount of beer consumed in-the-moment, given enough time to see such an effect. While the current data are not in line with ENDS being a general trigger for alcohol use, concurrent use of ENDS and alcohol may pose a risk for greater alcohol consumption during a drinking occasion. Binge drinking ("a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 g/dL. This typically occurs after 4 drinks for women and 5 drinks for men—in about 2 hours;" NIAAA, 2015) is one problem that could arise from ENDS related increases in alcohol consumption in a single drinking occasion. In the current study, I examined ENDS and alcohol consumption over a one-hour period. One hour is a short amount of time for most people to consume four drinks, which may have limited variability in the mL consumed and my ability to detect overall effects. It's possible that, given enough time, the event-level data connecting puffs and sips would also contribute to an overall increase in alcohol consumed. A prime question here is whether ENDS use increases the *length of time* a person is drinking alcohol, slowing the general rate of consumption, which would be a harm reduction approach, but increasing the overall amount in the long run, which would increase risk. An interesting approach would be to examine the binge drinking window (i.e., 2 hours) in people who report regularly engaging in binge drinking in to examine the influence of ENDS use on binge drinking patterns. As reviewed by Kuntsche and colleagues (2017), there are multiple acute consequences of binge drinking that can occur after a single episode, including permanent and unintentional injury and death (Dawson et al., 2008; Gmel et al., 2011; Hingson & Zha, 2009) and intentional injury (e.g., violence, homicide, suicide, self-harm; Borges & Loera, 2010; Brewer & Swahn, 2005; Norstrom & Rossow, 2016). Thus, if ENDS increases overall quantity of alcohol consumption, this may increase instances of binge drinking and associated negative outcomes. However, the current preliminary data, taken

in isolation, seem to suggest a temporal pairing of puffs and sips, without the concomitant increase in quantity of alcohol consumption.

The present finding that ENDS and alcohol use are occurring together in time and place has important implications for future research examining the relationship between ENDS and alcohol use. Given that the relationship between ENDS and alcohol use was found at the event-level, but not the meta-level, future studies should continue to examine in-the-moment relationships between ENDS and alcohol use. While the present study retained experimental control, studies conducted in a naturalistic setting (i.e., using EMA methodology) would provide information on whether the same event-level pattern of ENDS and alcohol use occurs outside of the lab. It would likely be difficult to get participants to reliably track their ENDS puffs and alcohol sips, but more practical to ask participants to record the timing of when they switched between ENDS and alcohol. For example, instead of tracking each sip and puff, participants could press a button in a smart-phone application when they switch between ENDS and alcohol. This paradigm has not been used in previous literature and would likely require validation, but seems as feasible as participants responding to 30 or more prompts per day, as has been done in other studies (e.g., Delfino et al., 2001; Shiftman et al., 2004). Additionally, the development of ENDS device that track puffs timing would be key to conducting such work in a more ecologically valid setting. There is some current development of similar tracking technology of alcohol sips, wherein the glass is placed on a scale that track when the glass is removed and the change in weight pre and post alcohol sip, although these are still in their infancy. Other tracking, including the use of transdermal alcohol sensing devices, could be used, but similar development would need to occur for tracking nicotine exposure in real time.

The persistence of this temporal relationship between ENDS and alcohol use across drinking occasions should be examined. The present study examined a single drinking occasion, but in order to understand the long-term impact of the pattern found between ENDS and alcohol use, data should be collected across multiple occasions. Participants could be brought into the lab multiple times across one year to complete a paradigm similar to the present study. Perhaps more feasible, participants could track their use with EMA over an extended time period (e.g., 6 months; Epstein et al., 2009). Such long-term data on event-level processes would allow for the examination of changes in patterns over time, such as whether this pattern of use becomes stronger or is predictive of increased quantity of alcohol used over time. For example,

researchers could examine if the relationship between event-level concurrent ENDS and alcohol use is related to increases in concurrent use during future occasions, which would add significant data to support the classical conditioning theory of concurrent use. Further, patterns of event-level use across time could be compared to specific alcohol related outcomes, such as alcohol use disorder symptoms and alcohol related injuries, and health outcomes, such as blood pressure. Such data would provide evidence on whether event-level patterns of ENDS and alcohol use increase the likelihood of negative outcomes across time.

Data on the impact of ENDS on alcohol use within drinking occasions is necessary to inform assessment, prevention, and intervention strategies for health care providers. For example, if subsequent data indicate that ENDS use is related to greater alcohol consumption over time, that this effect becomes stronger over time, and is related to problematic patterns of alcohol use, providers would likely not only want to assess if individuals use ENDS or alcohol, but whether they are using them together frequently in time and place, as this could indicate problematic patterns of alcohol use. Additionally, providers may recommend against ENDS use in high-risk populations (e.g., individuals with alcohol use disorders; adolescents), as it may increase alcohol use. Providers could educate patients or clients on the impact of concurrent use and provide tools, such as daily diary tracking, to help individuals examine behavior patterns to make changes in their concurrent use.

Another important future direction is to examine moderators and mechanisms of the ENDS and alcohol use relationship to better inform intervention and prevention strategies (i.e., where do we intervene and for whom?). In the present study, I examined the effect of self-reported concurrent ENDS and alcohol use (as measured over the past 14 days using the TLFB), and alcohol and ENDS craving preceding the ad lib paradigm on mL of beer consumed. Interestingly, greater concurrent use was related to greater alcohol consumption in the control condition, but not the ENDS condition. It could be that individuals that reported higher concurrent use in the present sample were using their ENDS more as a replacement for drinking. This would be counter to research that has shown that alcohol consumption is lower when ENDS or cigarette use is not allowed (e.g., due to public smoking bans; Hershberger et al., 2016; Young-Wolff et al., 2013). Additionally, the relationship between craving (ENDS and alcohol) and amount of beer consumed did not differ by ENDS condition, which was unexpected. Together, while history of concurrent use and cravings could play a role in the ENDS and

alcohol use relationship, there was not an observable effect in the current study. These moderating factors could be easily incorporated into research on the event-level to determine if there is an observable effect on in-the-moment use patterns.

Limitations

The current study presents the novel finding that ENDS use is temporally linked to alcohol use, but there are limitations to discuss. First, findings are limited by sample size, in that it decreased my ability to detect significant effects, although I examined effect sizes to overcome this issue, and reduced my ability to examine important group differences in behaviors, patterns, and risks. At the same time, with a smaller sample, regardless of examining significance level or effect size, the generalizability of findings becomes more uncertain. Future research should aim to replicate and extend findings in a larger sample. While my sample was largely representative of the US population across gender and race, as data were excluded across analyses (i.e., eye-tracking), data became less representative. For example, there were no participants that identified as Hispanic that had initial orientation or delayed disengagement data. This also limited my ability to examine differences in study variables across race. Although there are mixed findings on whether ENDS use varies by race (e.g., King et al., 2011; Littlefield et al., 2015), alcohol consumption undoubtedly varies by race (NIAAA, 2006) and it is further plausible that race may impact concurrent ENDS and alcohol use that could not be detected in the present study. As ethnic and racial minorities face distinct consequences and problems related to alcohol use (e.g., chronicity of alcohol use disorder; greater alcohol related problems, limited access to treatment, poor health outcomes; NIAAA, 2002; NIAAA, 2006; Wells, et al., 2001), documenting information on negative health consequences of concurrent ENDS and alcohol use in minority populations is an important avenue of future research. In addition to racial minorities being at high-risk for negative alcohol related outcomes, nationally representative data indicate that sexual minorities are also at greater risk for problematic alcohol use and negative outcomes (Schuler et al., 2018). Although ENDS research is relatively in its infancy, future work should aim to examine the potential for negative outcomes of concurrent ENDS and alcohol use in individuals at greatest risk. Another high-risk population is adolescents, and although adolescents demonstrate a stronger relationship between the use of ENDS and alcohol

(Hershberger et al., in preparation), it is not possible to experimentally control the use of ENDS and alcohol in adolescent samples due legal constraints on ENDS (18 years) and alcohol use (21 years) in the United States. Future research should aim to examine this relationship in adolescents, potentially using self-report through EMA.

Second, generalizability of the results of the present study may be limited. I examined only individuals with a preference for beer; although this was chosen to maintain experimental control in the present study, as done in other research (e.g., Weafer & Fillmore, 2008), results might not generalize to other drink preferences. Future research could expand to include other alcohol preferences to examine if these effects vary by beverage type. Also notably, participants in the present sample had low AUDIT scores and those with alcohol use disorders were excluded for participant safety reasons; thus, effects may not generalize to individuals with patterns of problematic alcohol use who may be at particularly high risk for negative effects of concurrent ENDS and alcohol use. Participants self-selected to volunteer to participate in this study, which may limit generalizability. Additionally, ENDS cravings did not significantly change pre- to post-ad lib ENDS prime, thus the prime may not have worked as intended (i.e., to reduce ENDS craving). It could be that more puffs or a longer duration of time would have produced a decrease in ENDS craving and influenced alcohol attentional biases more notably. The present study included participants with varying cigarette use history and excluded those that smoked > 1 pack per month, thus the results may not generalize to dual users (use both cigarettes and ENDS). It could be that dual users show a different pattern of attentional bias and alcohol consumption following ENDS use. Future research should examine risk patterns across cigarette use status of ENDS users.

There are also some limitations in variable measurement and study design in the present study. Participants used their own ENDS in the present sample, which was an intentional choice to increase ecological validity of this lab-based design; however, this did not allow for experimental control of ENDS. Thus, there could be differences between ENDS that confound study findings, such as the amount of nicotine individuals had in their nicotine refill liquid. For example, if the refill liquid had higher nicotine content, individuals may have taken less ENDS puffs. Additionally, the present study confounded drug (i.e., nicotine) and cue (i.e., the act of using ENDS) effects. Future research can address this by providing varying levels of nicotine and non-nicotine refill liquid and examining the effect of ENDS on alcohol use by nicotine

concentration. The present study provided pre-selected beers to participants in order in increase experimental control; however, participants could have specific beer preferences that limited their overall beer consumption during the ad lib task, thus underestimating the amount of alcohol consumed in the ENDS and control session. Time-of-day that participants completed the ad lib task could also have impacted their alcohol consumption. Although the majority of sessions took place after one in the afternoon (N = 56 sessions), thus providing some consistency in time-of-day across participants, those that had evening session could have consumed more beer than those with late morning sessions due to time of day, for example, which could confound the present findings.

Although widely use and validated (see Field & Cox, 2008 for a review) the dot-probe paradigm is limited by inference, in that reaction time bias is inferred to measure alcohol related attentional bias, but not necessarily a direct measure, and findings should be interpreted in this context. Further, the current study had overall poor quality of eye-tracking data, which limited my ability to interpret any findings related to eye-tracking. Poor data quality could be due to individual differences, but may also be due to the eye-tracking equipment. There are more advanced eye-tracking techniques and equipment that could be used to obtain better data in future research than used in the present study. For example, newer eye-tracking devices allow participants to wear eye-tracking glasses over their eyes that can be worn in any environment and collect high-quality eye tracking data (e.g., Raynowska et al., 2018). Some measures in the present study are limited by self-report bias, including concurrent ENDS and alcohol use as assessed with the TLFB, ENDS cravings, and alcohol cravings. Additionally, ENDS and alcohol craving were assessed five time throughout the experiment in both sessions, which may have led to participant fatigue in responding and inaccurate responding. Although research assistants were trained in recording sips and puffs throughout the ad lib portion, there is always room for human error that could have resulted in missed beer sips or puffs. This study was conducted in the laboratory, and may not generalize to real world settings. Although EMA data is limited by self-report, it could be beneficial to compare EMA findings, which have greater ecological validity, to ad lib findings.

Summary and conclusion

The present study is the first to examine the experimental relationship between concurrent ENDS and alcohol use using event-level data. While multiple cross-sectional studies have demonstrated a meta-level relationship between ENDS and alcohol use, current findings provide the first evidence to-date that ENDS and alcohol use are occurring together in time and place. The implications of these findings are multifold and pave way for additional experimental research examining the persistence of these patterns over time and their association with negative outcomes.

First, these findings suggest that meta-level and event-level data can tell different stories about the patterns of ENDS and alcohol use, patterns which may generalize to the research on cigarette and alcohol use as well. I suggest that more event-level evidence on the pairing of these behaviors in time and place would tell a more nuanced story on how individuals co-use these substances. Importantly, although ENDS puffs was related to greater alcohol sips over time, there was no overall effect of ENDS use on amount of alcohol consumed, which may suggest the ENDS use may interrupt alcohol use in the short-term. However, it's unclear if ENDS use is related to greater alcohol use over longer periods of time, as suggested by the cross-sectional literature.

Second, in some ways, ENDS use related to alcohol use as would be expected based on the literature examining cigarette and alcohol use, but in other ways the patterns diverge. This suggest that it's not always valid to generalize the cigarette and alcohol patterns to ENDS and alcohol. They may work through different mechanisms or due to different learning effects. For example, attentional biases have been shown to link cigarettes and alcohol (Oliver & Drobes, 2015), but do not link ENDS and alcohol in the current study. Third, the population of study is an important factor to consider in laboratory-based studies of ENDS and alcohol use. Specifically, it is important to choose individuals with a learning history of concurrent ENDS and alcohol use; this consideration may generalize to cigarette and alcohol research as well.

In the long-term, this research sets the stage to determine how providers and clinicians should communicate with their patients about their ENDS use. The current study provides preliminary supporting data linking ENDS and alcohol use in real-time, but at this point does not suggest that ENDS use is related to increases in the quantity of alcohol consumption, although methodology limits this conclusion only to short time periods of alcohol use. This work does

support examining the co-use of these behaviors more thoroughly and viability of continuing this work. The determination of the pattern of these behaviors suggests, at this time, that greater ENDS use is related to greater alcohol use, but that greater alcohol use does not necessarily relate to greater ENDS use. Until more concrete findings are determined, I suggest that providers should speak to their patients about their ENDS use, paying particular attention to vulnerable populations, such as those with or at risk for alcohol use disorder and adolescents. For now, it's best that individuals at risk should take care in their ENDS use. Future research should seek to identify mediators of the relationship between ENDS and alcohol use that could be used to design and test intervention and prevention strategies to mitigate the effect that ENDS use has on increasing in-the-moment alcohol use.

Table 1. Operationalization of Study Variables

Variable	Description	Assessment
Demographics	Age, race, gender, mg/mL of nicotine in ENDS refill liquid, number of months using ENDS	Qualtrics
Alcohol Use Disorder Identification Test (AUDIT)	10-item multiple choice measure assessing problematic alcohol use, total score computed (range 0-40)	Qualtrics
Nicotine and Other Substance Interaction Expectancies Questionnaire-E-cig Revised (NOSIE-ER)	8-item true/false measure of combined expectancies of ENDS and alcohol use, total score computed (range 0-8)	Qualtrics
Concurrent ENDS and alcohol use	Timeline follow-back (TLFB) calendar of past 14 days, used to aid participants in reporting days that they used their ENDS and consumed alcohol during the same drinking occasion, total days computed	Qualtrics
ENDS craving	Single item Likert scale (0-10) of ENDS craving, assessed at 5 time-points	Paper and pencil
Alcohol craving	Single item Likert scale (0-10) of alcohol craving, assessed at 5 time-points	Paper and pencil
Reaction time bias	Response time (ms) to alcohol images minus response time to control images; positive values indicate alcohol attentional bias	Recorded by E-Prime
Initial orientation	Number of trials where gaze was first oriented at alcohol image divided by total trials, >50% indicates alcohol attentional bias	Recorded by Eye-Trac software
Delayed disengagement	Time gaze was directed at alcohol images divided by total gaze time, >50% indicates alcohol attentional bias	Recorded by Eye-Trac software
mL of beer consumed	Total amount of beer pre-ad lib (1775ml) minus beer remaining post-ad lib	Measured by research assistant using a graduated cylinder
Amount of ENDS used	ENDS weight (g) pre-ad lib minus ENDS weight post-ad lib	Measured by research assistant using scale
Beer sips	Total number sips of beer taken in the ad lib paradigm	Sip start and stop were recorded with a time stamp by research assistant in Excel
ENDS puffs	Total number of ENDS puffs taken in the ad lib paradigm in the ENDS session	Puff start and stop were recorded with a time stamp by research assistant in Excel

Table 2. Descriptive statistics for the total sample (n = 31) and by gender

	Range	Total Sample	Men (N = 17)	Women (N = 14)	Statistic	*p*
Race N (%)					χ^2=0.78	.94
White		17 (54.8%)	7 (23.3%)	9 (30%)		
Black		6 (19.4%)	3 (10%)	3 (10%)		
Asian		4 (12.9%)	1 (3.3%)	3 (10%)		
Other		2 (6.5%)	1 (3.3%	1 (3.3%)		
Hispanic or Latino		2 (6.5%)	1 (3.3%)	1 (3.3%)		
Age mean (SD)	32 to 78	28.71 (11.17)	28.59 (5.78)	28.86 (15.71)	*t*=-0.07	.95
Months of ENDS use	1 to 175	37.10 (34.71)	32.64 (24.89)	42.92 (44.96)	*t*=-0.80	.43
Mg/mL of nicotine in ENDS	0 to 36	7.77 (9.06)	6.88 (9.60)	8.92 (8.55)	*t*=-0.61	.55
NOSIE-ER total	0 to 6	3.32 (1.68)	2.82 (1.77)	3.92 (1.38)	*t*=-1.90	.07
N days concurrent use	0 to 14	4.26 (3.59)	4.00 (3.08)	4.57 (4.22)	*t*=-0.70	.49
AUDIT total	1 to 18	6.45 (3.97)	5.41 (2.37)	7.71 (5.14)	*t*=-1.65	.11
ENDS session						
Pre-ad lib alcohol craving	0 to 6	2.50 (2.61)	2.00 (2.35)	3.14 (2.77)	*t*=-1.25	.22
Post-ad lib alcohol craving	0 to 9	1.74 (2.77)	0.94 (2.30)	2.71 (3.04)	*t*=-1.84	.08
Pre-ad lib ENDS craving	0 to 10	3.57 (3.06)	3.00 (3.00)	3.86 (3.5)	*t*=-0.73	.47
Post-ad lib ENDS craving	0 to 10	2.71 (2.97)	1.76 (2.08)	3.86 (3.52)	*t*=-2.06	.05
Total ENDS puffs	0 to 49	16.28 (12.93)	16.93 (11.80)	15.46 (14.66)	*t*=0.30	.76
Total beer sips	2 to 72	21.93 (15.65)	21.19 (13.55)	22.84 (15.45)	*t*=-0.28	.78
ENDS grams pre to post ad lib*	0 to 4	0.81 (1.08)	0.93 (1.07)	0.69 (1.10)	*t*=0.56	.58
Control session						
Pre-ad lib alcohol craving	0 to 7	1.83 (2.00)	2.12 (2.34)	2.29 (2.46)	*t*=-0.20	.85
Post-ad lib alcohol craving	0 to 9	1.87 (2.80)	1.82 (3.03)	1.93 (2.62)	*t*=-0.10	.92
Pre-ad lib ENDS craving	0 to 10	3.74 (3.12)	3.65 (3.22)	4.21 (3.36)	*t*=-0.47	.63
Post-ad lib ENDS craving	0 to 10	4.52 (3.61)	3.41 (3.47)	5.86 (3.44)	*t*=-1.96	.06
Total beer sips	4 to 64	23.28 (15.91)	23.69 (14.92)	22.14 (17.18)	*t*=0.26	.79
ENDS session mL beer consumed	60 to 1775	716.39 (447.56)	769.76 (410.72)	651.57 (496.38)	*t*=0.73	.47
Control session mL beer consumed	100 to 1775	683.48 (453.24)	764.88 (488.77)	584.64 (401.07)	*t*=1.11	.28

*Note.*Concurrent use = number of days of concurrent ENDS and alcohol use (during the same drinking occasion) over the last 14 days as assessed using the timeline follow-back; * Difference between pre and post ad lib ENDS weight in grams; Statistic = test statistic for mean or frequency comparisons by gender; NOSIE-ER = Nicotine and Other Substance Interaction Expectancies Questionnaire-E-cig Revised; AUDIT = Alcohol Use Disorder Identification Test; ENDS = Electronic Nicotine Delivery System

Table 3. Descriptive statistics for the total sample (N = 31), participants with reaction time data (N = 23), and initial orientation and delayed disengagement data (N = 12)

	Total sample (N = 31)	Reaction time data (N = 23)	Eye-tracking data* (N = 12)	25% Eye-tracking data** (N = 9)	50%* Eye-tracking data*** (N = 4)
Gender (% Women)	17 (54.8%)	10 (43.5%)	5 (41.7%)	4 (44.4%)	2 (50%)
Race N (%)					
White	17 (54.8%)	12 (52.2%)	6 (50%)	5 (55.6%)	2 (50%)
Black	6 (19.4%)	5 (21.7%)	3 (25%)	2 (22.2%)	1 (25%)
Asian	4 (12.9%)	4 (17.4%)	3 (25%)	2 (22.2%)	1 (25%)
Other	2 (6.5%)	1 (4.3%)	-	-	
Hispanic or Latino	2 (6.5%)	1 (4.3%)	-	-	
Age mean (SD)	28.71 (11.17)	28.00 (6.89)	28.00 (7.10)	26.11 (3.76)	27.00 (4.69)
Months of ENDS use	37.10 (34.71)	37.32 (38.92)	28.64 (19.37)	29.88 (19.97)	32.66 (27.54)
Mg/mL of nicotine in ENDS	7.77 (9.06)	8.52 (10.14)	6.17 (7.15)	4.00 (2.60)	5.25 (1.50)
NOSIE-ER total	3.32 (1.68)	3.35 (1.64)	3.75 (1.66)	3.67 (2.44)	4.00 (2.00)
N days concurrent use	4.26 (3.59)	4.52 (3.79)	5.50 (3.99)	4.33 (3.32)	5.75 (4.27)
AUDIT total	6.45 (3.97)	6.52 (4.12)	7.17 (3.38)	6.67 (3.67)	8.25 (5.19)
ENDS session					
Pre-attentional bias ENDS craving	2.38 (3.04)	2.96 (3.14)	2.83 (3.24)	2.67 (2.87)	3.25 (2.50)
Pre-attentional bias alcohol craving	1.87 (2.17)	2.30 (2.29)	2.75 (2.45)	2.11 (2.31)	3.00 (2.58)
Reaction time bias (ms)		-0.65 (36.29)	18.43 (32.25)	18.21 (33.86)	40.87 (20.53)
Initial orientation (%)			50.56 (4.34)[a]	50.24 (4.36)[a]	49.51 (1.21)[a]
Delayed disengagement (%)			51.82 (5.77)[b]	51.27 (5.82)[b]	51.57 (2.64)[b]
Control session					
Pre-attentional bias ENDS craving	3.31 (2.95)	4.14 (2.89)	4.08 (3.18)	2.78 (2.28)	3.25 (2.75)
Pre-attentional bias alcohol craving	1.70 (1.86)	2.05 (2.03)	2.42 (2.27)	2.22 (2.28)	3.50 (2.52)
Reaction time bias (ms)		7.33 (35.82)	19.71 (36.31)	21.46 (39.33)	49.70 (35.37)
Initial orientation (%)			49.07 (7.97)[c]	50.89 (4.21)[c]	50.28 (1.36)[c]
Delayed disengagement (%)			48.45 (7.88)[d]	50.88 (94.90)[d]	48.60 (1.88)[d]

Note. Concurrent use = number of days of concurrent ENDS and alcohol use (during the same drinking occasion) over the last 14 days as assessed using the timeline follow-back; * Eye tracking data = initial orientation and delayed disengagement; ** Eye-tracking data after removing participants with > 25% of gaze dwell time (20s) and fixations (20 fixations); *** Eye-tracking data after removing participants with > 50% of gaze dwell time (40s) and fixations (40 fixations); NOSIE-ER = Nicotine and Other Substance Interaction Expectancies Questionnaire-E-cig Revised; AUDIT = Alcohol Use Disorder Identification Test; ENDS = Electronic Nicotine Delivery System; One-way ANOVA comparing initial orientation and delayed disengagement scores across participants included in the full eye-tracking data (N = 12), at 25%, and 50% cut-points: [a] F (2, 9) = 0.71, p = 0.85; [b] F (2, 9) = 0.96, p = .42; [c] F (2, 9) = 0.15, p = .87; [d] F (2, 9) = 2.56, p = .13

Table 4. Pearson's *r* correlations for Aim 1 variables

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1. Age mean (SD)	-0.01	0.20	0.16	**0.43**	-0.23	-0.29	-0.16	0.10	0.28	0.42	0.14	0.26	0.14	-0.01	-0.05
2. Months of ENDS use	-	-0.08	-0.26	-0.10	-0.21	0.29	-0.24	-0.07	0.07	0.20	0.27	-0.24	-0.02	-0.47	-0.40
3. Mg/mL of nicotine in ENDS	-	-	0.05	-0.09	0.11	0.01	0.03	-0.08	0.29	0.30	0.14	-0.01	-0.16	**-0.87**	**-0.87**
4. N days concurrent use	-	-	-	0.22	**0.54**	0.11	0.44	0.23	0.52	0.54	0.27	0.33	0.11	-0.83	-0.31
5. NOSIE-ER total	-	-	-	-	0.32	0.25	0.14	0.37	-0.58	0.47	0.26	-0.08	0.18	0.01	0.01
6. AUDIT total						0.03	0.43	-0.03	-0.20	-0.25	-0.09	0.38	-0.17	0.10	0.03
ENDS session															
7. ENDS craving*	-	-	-	-	-	-	0.38	-0.31	0.24	0.10	0.39	0.11	-0.16	0.14	-0.08
8. Alcohol craving*	-	-	-	-	-	-	-	0.02	0.32	0.26	0.13	**0.58**	0.05	-0.01	-0.31
9. Reaction time	-	-	-	-	-	-	-	-	-0.33	-0.22	-0.10	-0.01	**0.63**	-0.40	-0.32
10. Initial orientation	-	-	-	-	-	-	-	-	-	**0.86**	0.29	0.26	-0.13	-0.08	-0.31
11. Delayed disengagement	-	-	-	-	-	-	-	-	-	-	0.36	0.30	-0.04	0.03	-0.30
Control session															
12. ENDS craving*	-	-	-	-	-	-	-	-	-	-	-	0.15	-0.08	-0.39	-0.55
13. Alcohol craving*	-	-	-	-	-	-	-	-	-	-	-	-	-0.08	0.43	0.18
14. Reaction time	-	-	-	-	-	-	-	-	-	-	-	-	-	-0.17	-0.32
15. Initial orientation	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**0.85**
16. Delayed disengagement	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note. Bolded values indicate $p < .01$; Concurrent use = number of days of concurrent ENDS and alcohol use (during the same drinking occasion) over the last 14 days as assessed using the timeline follow-back; NOSIE-ER = Nicotine and Other Substance Interaction Expectancies Questionnaire-E-cig Revised; AUDIT = Alcohol Use Disorder Identification Test; ENDS = Electronic Nicotine Delivery System; * Cravings assessed preceding eye-tracking

Table 5. Hypothesis 1: Three repeated measure ANCOVA's with attentional bias measures as the repeated factors

	Sum of squares	*df*	*F*	*p*	*ηp2*
Reaction time	67.42	1	0.12	.73	0.006
Reaction time x age	25.13	1	0.05	.83	0.002
Reaction time x gender	42.97	1	0.08	.78	0.004
Reaction time x race	310.99	1	0.57	.46	0.03
Initial orientation	5.64	1	0.10	.76	0.01
Initial orientation x age	8.82	1	0.15	.71	0.02
Initial orientation x gender	7.61	1	0.13	.73	0.02
Initial orientation x race	0.68	1	0.01	.92	0.001
Delayed disengagement	0.69	1	0.01	.92	0.001
Delayed disengagement x age	28.99	1	0.43	.53	0.05
Delayed disengagement x gender	83.17	1	1.23	.30	0.13
Delayed disengagement x race	19.94	1	0.29	.60	0.04

Note. Attentional bias measures (repeated factors) assessed in the ENDS and control condition.

Table 6. Hypothesis 2: Three repeated measure ANCOVA's with attentional bias measures as the repeated factors and concurrent ENDS and alcohol use as the between-participant factor

	Sum of squares	*df*	*F*	*p*	*ηp2*
Reaction time	1004.95	1	1.19	.31	0.13
Reaction time x age	898.52	1	1.07	.33	0.12
Reaction time x gender	293.82	1	0.35	.57	0.04
Reaction time x race	547.44	1	0.65	.44	0.08
Reaction time x concurrent use	3605.46	1	0.39	.93	0.35
Initial orientation	0.41	1	0.006	.95	0.006
Initial orientation x age	1.65	1	0.02	.90	0.02
Initial orientation x gender	0.83	1	0.01	.93	0.01
Initial orientation x race	24.37	1	0.35	.66	0.25
Initial orientation x concurrent use	392.25	1	0.80	.70	0.85
Delayed disengagement	38.40	1	0.34	.66	0.26
Delayed disengagement x age	38.36	1	0.34	.66	0.25
Delayed disengagement x gender	69.13	1	0.62	.58	0.38
Delayed disengagement x race	0.78	1	0.007	.95	0.007
Delayed disengagement x concurrent use	429.48	1	0.55	.78	0.79

Note. Attentional bias measures (repeated factors) assessed in the ENDS and control condition. Concurrent use = number of days of concurrent ENDS and alcohol use (during the same drinking occasion) over the last 14 days as assessed using the timeline follow-back

Table 7. Hypothesis 3: Three repeated measure MANOVA's with attentional bias measures and alcohol craving as repeated factors

	Sum of squares	*df*	*Wilks'* λ	*F*	*p*	*ηp2*
Reaction time	33.60	1	0.99	0.03	.86	0.001
Alcohol craving	335.17	1	0.00	1.39	.25	0.06
Reaction time x Alcohol craving	399.03	1	0.93	1.60	.22	0.07
Initial orientation	26771.39	1	0.007	1563.01	<.001	0.99
Alcohol craving	9.98	1	0.97	0.36	.56	0.03
Initial orientation x Alcohol craving	4.02	1	0.98	0.22	0.65	0.02
Delayed disengagement	27137.63	1	0.008	1403.72	<.001	0.99
Alcohol craving	41.29	1	0.91	1.15	.31	0.09
Delayed disengagement x Alcohol craving	27.78	1	0.92	1.02	.33	0.09

*Note***.** Attentional bias measures (repeated factors) and alcohol craving (preceding eye-tracking measurement) assessed in the ENDS and control condition.

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Table 8. Hypothesis 3: Three repeated measure MANOVA's with attentional bias measures and ENDS craving as repeated factors

	Sum of squares	*df*	*Wilks'* λ	*F*	*p*	*ηp2*
Reaction time	274.93	1	0.38	35.95	<.001	0.62
ENDS craving	19.001	1	0.95	2.88	.30	0.05
Reaction time x ENDS craving	0.001	1	0.87	9.61	.08	0.13
Initial orientation	25788.69	1	0.01	1043.84	<.001	0.99
ENDS craving	0.17	1	0.99	0.009	.93	0.001
Initial orientation x ENDS craving	22.53	1	0.97	0.68	.43	0.06
Delayed disengagement	26178.17	1	0.01	977.65	<.001	0.98
ENDS craving	13.57	1	0.96	0.51	.49	0.04
Delayed disengagement x ENDS craving	473.45	1	0.88	1.49	.25	0.12

*Note***.** Attentional bias measures (repeated factors) and ENDS craving (preceding eye-tracking measurement) assessed in the ENDS and control condition.

Table 9. Pearson's *r* correlations for Aim 2 variables

	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Age mean (SD)	0.12	-0.07	-0.17	-0.26	-0.16	-0.26	-0.21	-0.22	-0.36	-0.11	-0.06	-0.14	-0.04	-0.01	-0.10	-0.64	0.02
2. Months of ENDS use	-	-0.24	-0.16	-0.23	-0.26	-0.23	0.31	0.18	0.04	-0.13	-0.25	-0.19	0.05	0.05	-0.16	0.16	0.10
3. N days concurrent use	-	-	0.20	**0.57**	**0.57**	0.28	0.16	0.08	-0.14	0.01	**0.40**	0.02	0.36	0.32	0.22	-0.03	0.32
4. NOSIE-ER Total				0.31	0.27	0.32	0.10	0.23	0.08	0.25	0.25	0.13	0.25	0.36	0.32	-0.06	-0.17
5. AUDIT total	-	-	-	-	**0.52**	**0.57**	0.05	0.11	-0.15	0.08	0.31	0.34	-0.03	0.15	0.13	0.19	0.24
ENDS session																	
6. Pre-ad lib alcohol craving	-	-	-	-	-	**0.73**	0.35	0.36	0.22	**0.53**	**0.62**	**0.46**	0.37	**0.46**	**0.60**	0.18	0.15
7. Post-ad lib alcohol craving	-	-	-	-	-	-	**0.46**	**0.60**	0.07	0.34	**0.55**	**0.74**	0.07	0.33	**0.37**	-0.04	-0.13
8. Pre-ad lib ENDS craving	-	-	-	-	-	-	-	**0.66**	0.20	0.16	0.14	0.23	**0.43**	**0.44**	0.16	0.03	-0.15
9. Post-ad lib ENDS craving	-	-	-	-	-	-	-	-	0.06	0.20	0.2	**0.44**	**0.42**	**0.56**	-0.01	0.09	-0.11
10. Total ENDS puffs	-	-	-	-	-	-	-	-	-	0.28	0.04	0.01	0.05	-0.08	**0.44**	0.22	0.15
11. Total beer sips	-	-	-	-	-	-	-	-	-	-	**0.48**	**0.43**	0.19	0.18	**0.81**	**0.41**	0.24
Control session																	
12. Pre-ad lib alcohol craving	-	-	-	-	-	-	-	-	-	-	-	**0.72**	**0.39**	**0.46**	**0.60**	0.01	0.07
13. Post-ad lib alcohol craving	-	-	-	-	-	-	-	-	-	-	-	-	0.14	0.35	**0.37**	0.11	-0.05
14. Pre-ad lib ENDS craving	-	-	-	-	-	-	-	-	-	-	-	-	-	**0.86**	0.20	0.21	0.10
15. Post-ad lib ENDS craving	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.16	0.18	-0.03
16. Total sips	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.13	0.22
17. ENDS session mL beer consumed	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	**0.68**
18. Control session mL beer consumed	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Note. Bolded values indicate $p < .01$; Concurrent use = number of days of concurrent ENDS and alcohol use (during the same drinking occasion) over the last 14 days as assessed using the timeline follow-back; NOSIE-ER = Nicotine and Other Substance Interaction Expectancies Questionnaire-E-cig Revised; AUDIT = Alcohol Use Disorder Identification Test; ENDS = Electronic Nicotine Delivery System

Table 10. Hypothesis 4: Repeated measure ANCOVA with mL of beer consumed as the repeated factor

	Sum of squares	*df*	*F*	*p*	*ηp2*
mL of beer consumed	38885.34	1	0.03	.86	0.001
mL of beer consumed x age	23634.126	1	0.33	.57	0.01
mL of beer consumed x gender	14115.24	1	0.20	.66	0.007
mL of beer consumed x race	3885.34	1	0.06	.82	0.002

*Note***.** mL of beer consumed during the ad lib paradigm assessed in the ENDS and control condition.

Table 11. Hypothesis 5: Hierarchical linear regression examining the relationship between change in ENDS weight pre- to post-ad lib and mL of beer consumed in the ENDS condition

	Unstandardized Beta	*95% CI*	*t*	*p*	ΔR^2
DV: Beer consumed in ENDS condition (mL)					
Step 1					0.10
Age	9.44	-21.14 to 40.02	0.64	.53	
Race	52.34	-81.67 to 186.35	0.81	.43	
Gender	-136.73	-519.41 to 245.96	-0.74	.47	
Step 2					0.03
ENDS weight difference pre- to post-ad lib (g)	-81.22	-281.21 to 118.77	-0.84	.41	

Note. ENDS = Electronic Nicotine Delivery System

Table 12. Hypothesis 5: Linear mixed model with ENDS puffs as a time-varying covariate of beer sips in the ENDS condition

		Model 1		Model 2		Model 3	
		Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*
	DV: N beer sips						
Fixed effects	Intercept	3.11 (0.44)	<.001	5.48 (0.50)	<.001	4.91 (0.52)	<.001
	Segment			-0.86 (0.11)	<.001	-0.89 (0.10)	<.001
	ENDS puffs					0.23 (0.07)	.002
Estimates of σ^2	Level 1: Repeated measures						
	Segment 1	15.18 (5.39)	.005	8.84 (2.75)	.001	10.15 (3.08)	.001
	Segment 2	8.89 (5.08	.08	6.89 (2.23)	.002	7.99 (2.43)	.001
	Segment 3	3.78 (2.76)	.17	4.06 (1.34)	.003	4.60 (1.48)	.002
	Segment 4	21.21 (7.04)	.003	22.64 (6.26)	<.001	22.02 (6.09)	<.001
	Segment 5	4.06 (3.22)	.21	1.73 (0.79)	.03	1.70 (0.72)	.02
	Segment 6	7.41 (4.25)	.08	2.67 (1.04)	.01	2.29 (0.87)	.009
	Level 2						
	Intercept (σ^2 between participants)	4.22 (2.25)	.06	3.47 (1.34)	.01	2.70 (0.99)	.007
	Segment (σ^2 in slope across segment)			0.05 (0.61)	.41	0.001 (.05)	.98
Goodness of fit	AIC	874.18		836.79		832.39	
	BIC	910.01		861.69		857.23	
	Parameters	8		10		11	

Note. AIC = Akaike information criterion; BIC = Bayes information criterion; Segment = Ad lib alcohol task divided into 6 ten-minute segments.

Table 13. Hypothesis 5 (sensitivity analysis): Linear mixed model with beer sips as a time-varying covariate of ENDS puffs in the ENDS condition

		Model 1		Model 2		Model 3	
		Estimate (SE)	*p*	Estimate (SE)	*p*	Estimate (SE)	*p*
	DV: N ENDS puffs						
Fixed effects	Intercept	2.76 (0.38)	<.001	2.12 (0.37)	<.001	1.59 (0.49))	.002
	Segment			0.28 (0.13)	.04	0.35 (0.13)	.01
	Beer sips					0.09 (0.06)	.08
Estimates of σ^2	Level 1: Repeated measures						
	Segment 1	5.15 (1.67)	.002	3.71 (1.32)	.005	4.02 (1.41)	.004
	Segment 2	3.21 (1.20)	.007	2.42 (0.84)	.004	2.69 (0.93)	.004
	Segment 3	5.15 (1.70))	.002	5.34 (1.59)	.001	5.24 (1.57)	.001
	Segment 4	4.33 (1.44)	.003	4.21 (1.32)	.001	3.79 (1.23)	.002
	Segment 5	4.11 (1.40)	.003	2.08 (1.06)	.05	2.23 (1.08)	.04
	Segment 6	4.76 (2.28)	.001	7.49 (2.55)	.003	7.07 (2.41)	.003
	Level 2						
	Intercept (σ^2 between participants)	3.31 (1.20)	.06	2.02 (0.94)	.03	2.02 (0.94)	.03
	Segment (σ^2 in slope across segment)			0.24 (0.12)	.04	0.21 (0.11)	.06
Goodness of fit	AIC	799.11		772.06		773.27	
	BIC	820.93		812.96		814.12	
	Parameters	8		10		11	

Note. AIC = Akaike information criterion; BIC = Bayes information criterion; Segment = Ad lib alcohol task divided into 6 ten-minute segments; ENDS = Electronic Nicotine Delivery System

Table 14. Hypothesis 6: Repeated measures ANCOVA with mL of beer consumed as the repeated factor

	Sum of squares	*df*	*F*	*p*	*ηp2*
mL of beer consumed	3277.101	1	.05	.83	.003
mL of beer consumed x age	10716.967	1	.16	.69	.01
mL of beer consumed x gender	283.951	1	.004	.95	<.001
mL of beer consumed x race	82390.067	1	1.25	.28	.08
mL of beer consumed x concurrent use	796934.960	11	1.09	.42	.45

Note. mL of beer consumed during the ad lib paradigm assessed in the ENDS and control condition; Concurrent use = number of days of concurrent ENDS and alcohol use (during the same drinking occasion) over the last 14 days as assessed using the timeline follow-back

Table 15. Hypothesis 7: Two repeated measure MANOVA's with mL of beer consumed and craving (ENDS and alcohol) as repeated factors

	Sum of squares	*df*	*Wilks'* λ	*F*	*p*	*ηp2*
mL of Beer	530998.54	1	0.90	3.00	.10	0.10
mL of Beer x age	6246.82	1	0.99	0.04	.85	0.001
mL of Beer x gender	193255.80	1	0.96	1.09	.31	0.04
mL of Beer x race	143002.04	1	0.97	0.81	.38	0.03
Alcohol craving	1192.64	1	0.99	0.03	.86	0.001
Alcohol craving x age	12010.64	1	0.99	0.34	.57	0.01
Alcohol craving x gender	7294.72	1	0.99	0.21	.66	0.008
Alcohol craving x race	1890.52	1	0.99	0.05	.82	0.002
mL of Beer x Alcohol Craving	1067.94	1	0.99	0.03	.86	0.001
mL of Beer x Alcohol craving x age	11625.06	1	0.98	0.33	.57	0.01
mL of Beer x Alcohol craving x gender	6824.44	1	0.99	0.19	.67	0.007
mL of Beer x Alcohol craving x race	1995.53	1	0.99	0.06	.82	0.002
mL of Beer	529565.25	1	0.90	2.99	.10	0.10
mL of Beer x age	6170.77	1	0.99	0.04	.85	0.001
mL of Beer x gender	193327.17	1	0.96	1.09	.31	0.04
mL of Beer x race	142117.47	1	0.97	0.80	.38	0.03
ENDS craving	1273.47	1	0.99	0.04	.85	0.001
ENDS craving x age	12118.55	1	0.99	0.34	.57	0.01
ENDS craving x gender	7152.74	1	0.99	0.20	.66	0.007
ENDS craving x race	1761.21	1	0.99	0.05	.83	0.002
mL of Beer x ENDS Craving	994.03	1	0.99	0.03	.87	0.001
mL of Beer x ENDS craving x age	11519.37	1	0.99	0.32	.57	0.01
mL of Beer x ENDS craving x gender	6963.14	1	0.99	0.20	.66	0.007
mL of Beer x ENDS craving x race	2133.02	1	0.99	0.06	.81	0.002

Note. mL of beer consumed during the ad lib paradigm assessed in the ENDS and control condition; ENDS craving and alcohol craving (preceding ad lib paradigm) assessed in the ENDS and control condition.

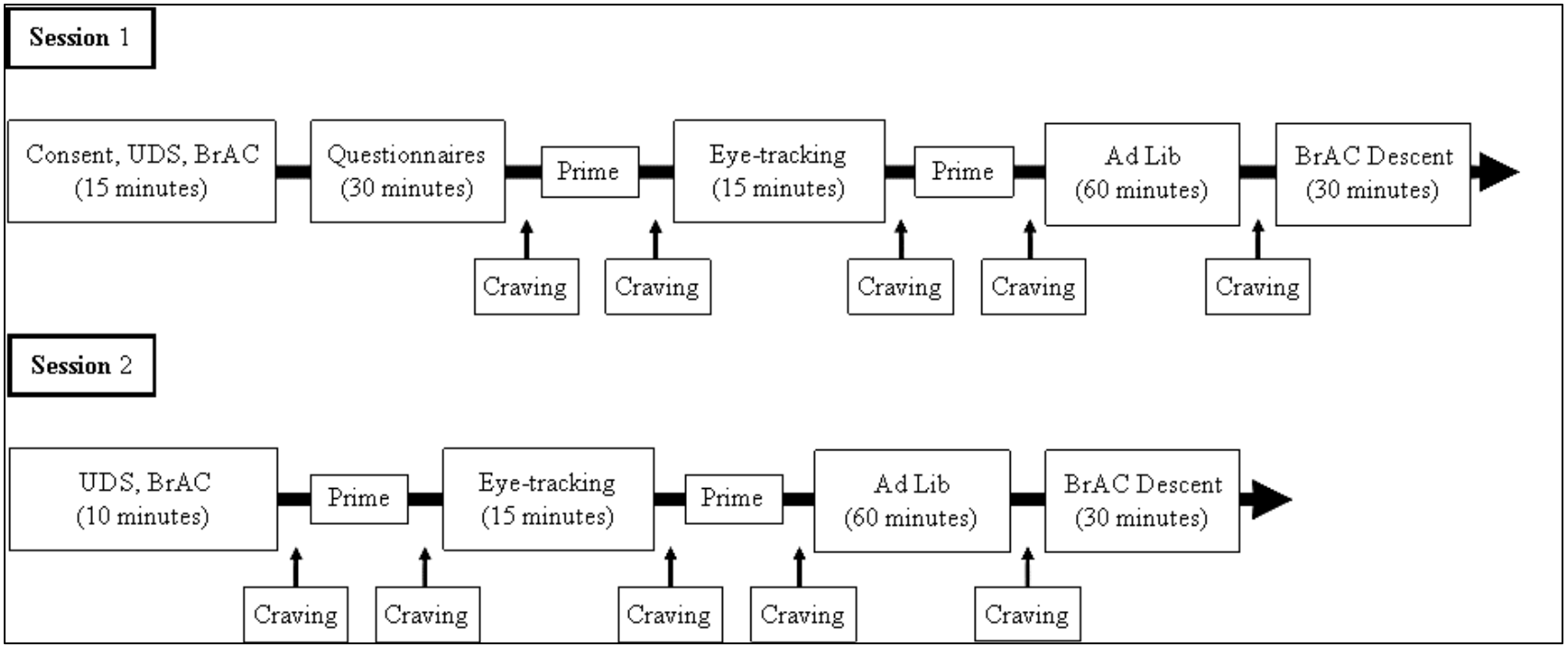

Figure 1. Study Procedures

Note. Two-session, within-participant design; Participants were randomized and counterbalanced to complete either the ENDS or control session first; UDS = Urine drug screen; BrAC = Breath alcohol concentration; Eye-tracking: Portion of study where participants completed the dot-probe paradigm to assess for attentional bias for alcohol related images; Ad lib: Portion of study where participants were given free access to five beers for 60 minutes (and free access to their ENDS in the ENDS condition); Prime: In the ENDS condition, participants took 10 puffs from their ENDS over five minutes, in the control condition participants sat with a pencil in their hand for five minutes; Craving = Participants self-reported their alcohol craving and ENDS craving

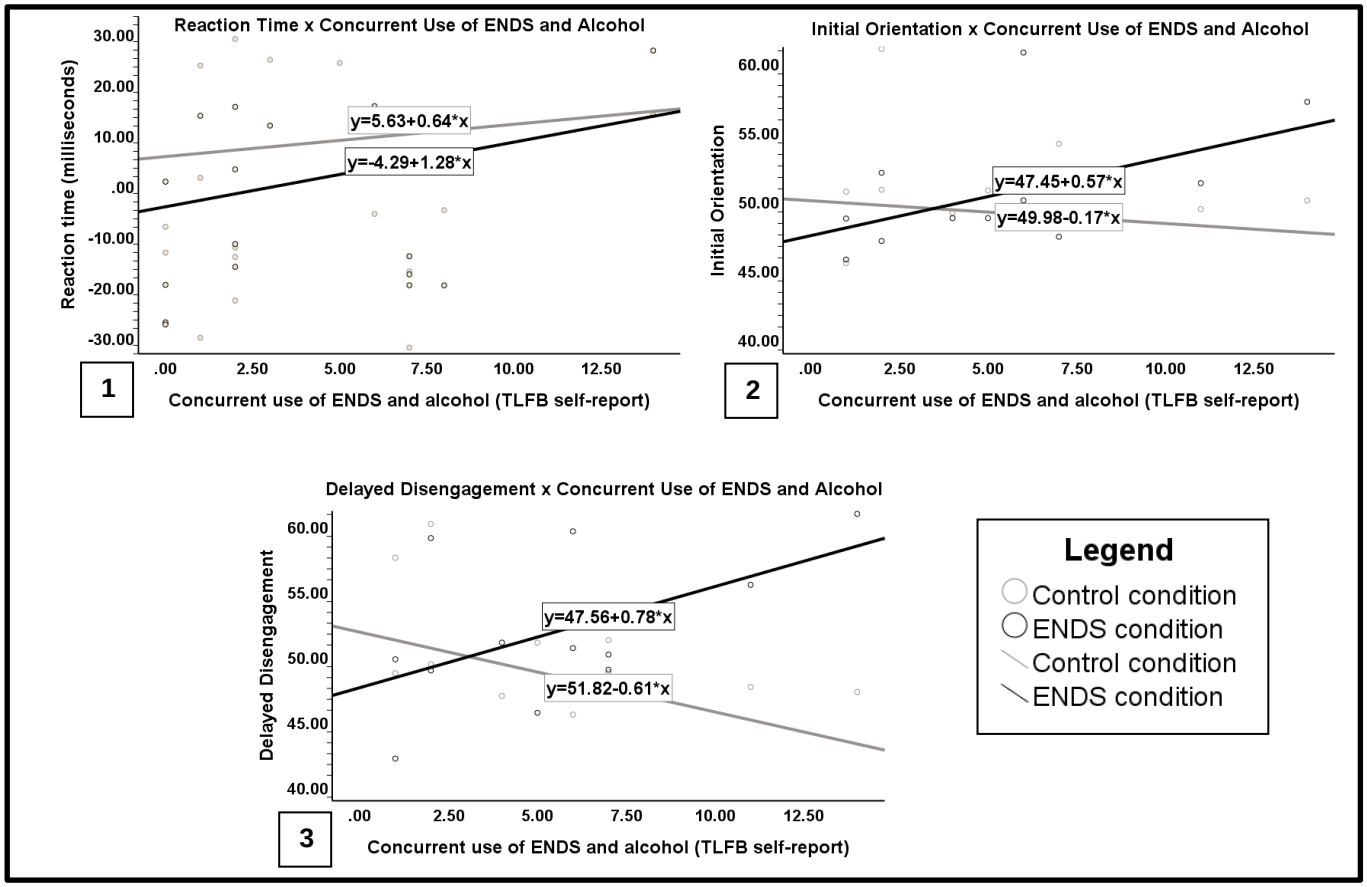

Figure 2. ENDS versus control condition: Attentional bias measures x concurrent ENDS and alcohol use

Note. Reaction time (milliseconds): Response time to control images minus response time to alcohol images, positive values indicate alcohol attentional bias; Initial orientation: Number of trials where gaze was first oriented at alcohol image divided by total trials, >50% indicates alcohol attentional bias; Delayed Disengagement: Time gaze was directed at alcohol images divided by total gaze time, >50% indicates alcohol attentional bias; Equations in black boxes provide the slope and intercept for the ENDS condition; Equations in grey boxes provide the slope and intercept for the control condition; Concurrent use of ENDS and alcohol: participant self-report from a 14-day TLFB calendar of number of days where they used their ENDS and alcohol together; *F*-tests for interactions-Graph 1: F (4, 11) = 0.39, p = .93, $\eta p2$ = 0.35; Graph 2: F (4, 7) = 0.80, p = .70, $\eta p2$ = 0.85; Graph 3: F (4, 7) = 0.55, p = .78, $\eta p2$ = 0.79

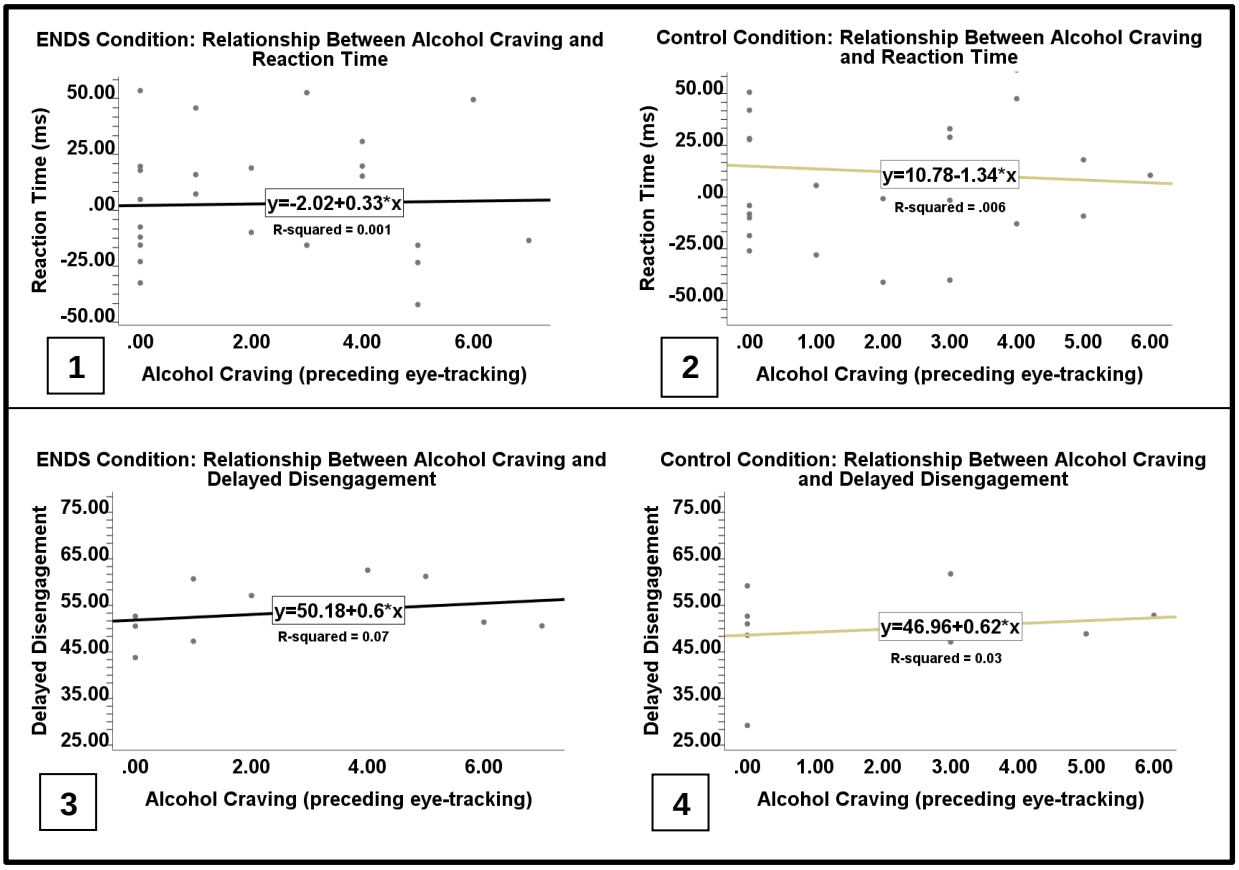

Figure 3. Pre-dot-probe Alcohol craving x Attentional bias measures in the ENDS (left) versus control (right) condition

Note. Reaction time (milliseconds): Response time to control images minus response time to alcohol images, positive values indicate alcohol attentional bias; Delayed Disengagement: Time gaze was directed at alcohol images divided by total gaze time, >50% indicated alcohol attentional bias; Alcohol craving: Participant self-report of alcohol craving following ENDS prime prior to eye-tracking, (scale 0 to10), higher values indicate higher craving; Repeated measure MANOVA Graph 1 and 2: F (1, 22) = 1.60, p = .22, Wilks' λ = 0.93, $\eta p2$ = 0.07; Repeated measure MANOVA Graph 3 and 4: F (1, 11) = 1.02, p = .33, Wilks' λ = 0.92, $\eta p2$ = 0.09

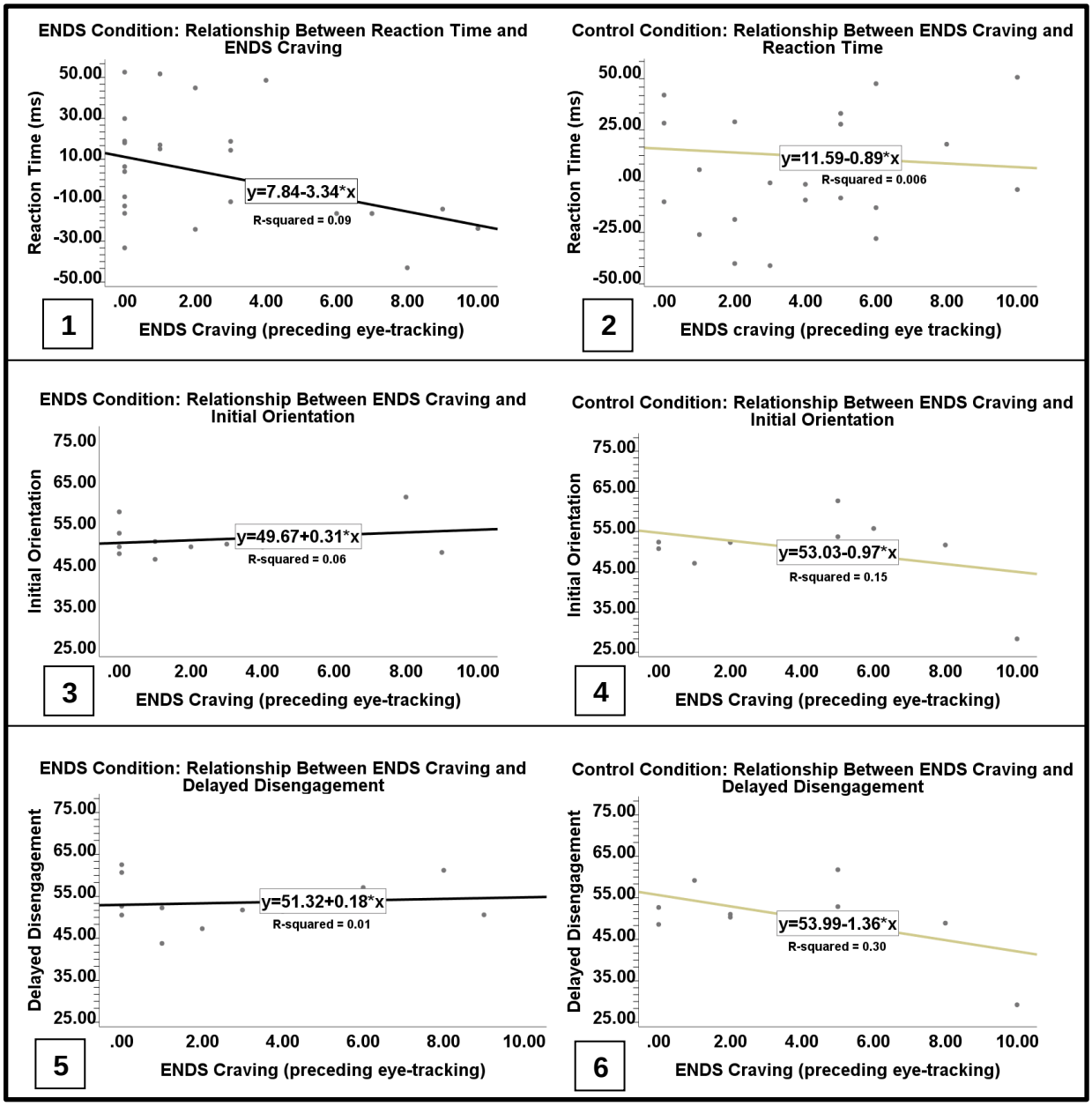

Figure 4. Pre-dot-probe ENDS craving x Attentional bias measures in the ENDS (left) versus no ENDS (right) condition

Note. Reaction time (milliseconds): Response time to control images minus response time to alcohol images, positive values indicate alcohol attentional bias; Initial orientation: Number of trials where gaze was first oriented at alcohol image divided by total trials, >50% indicates alcohol attentional bias; Delayed Disengagement: Time gaze was directed at alcohol images divided by total gaze time, >50% indicated alcohol attentional bias; ENDS craving: Participant self-report of ENDS craving following ENDS prime prior to eye-tracking, (scale 0 to10), higher values indicate higher craving; Repeated measure MANOVA Graph 1 and 2: F (1, 22) = 9.61, p = .08, Wilks' λ = 0.87, $\eta p2$ = 0.13; Repeated measure MANOVA Graph 3 and 4: F (1, 11) = 0.68, p = .43, Wilks' λ = .97, $\eta p2$ = 0.06; Repeated measure MANOVA Graph 5 and 6: F (1, 11) = 1.49, p = .25, Wilks' λ = .88, $\eta p2$ = 0.12

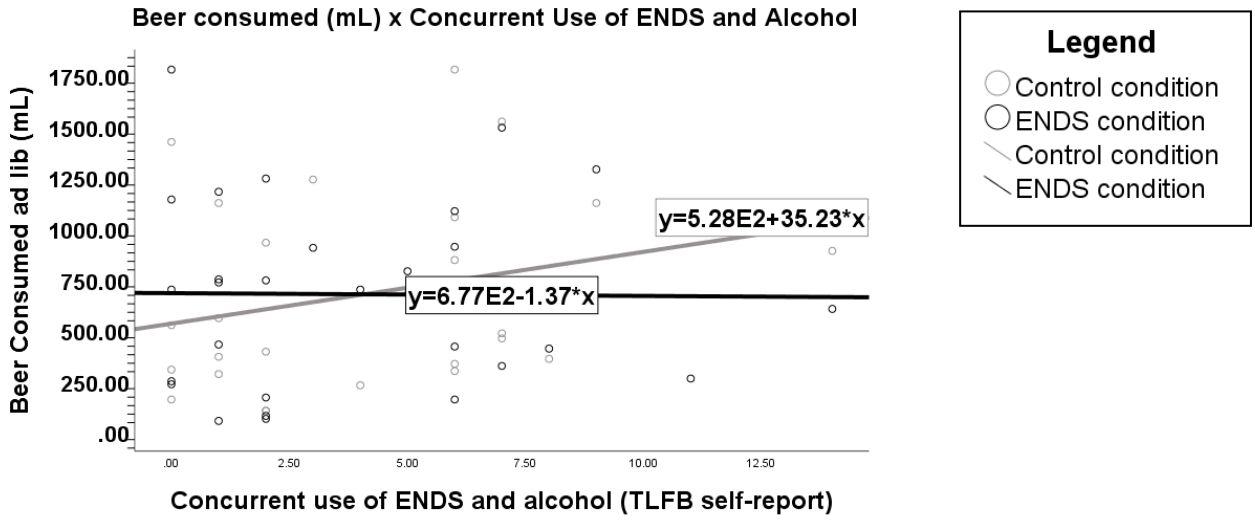

Figure 5. ENDS versus control condition: Beer consumed (mL) ad lib x Concurrent use of ENDS and alcohol

Note. Beer consumed (mL) ad lib: Amount of beer consumed by the participant during the 60 minute ad lib alcohol paradigm; Concurrent use of ENDS and alcohol: participant self-report from a 14-day TLFB calendar of number of days where they used their ENDS and alcohol together; Equation in black box provides the slope and intercept for the ENDS condition; Equation in grey box provides the slope and intercept for the no ENDS condition; *F*-test for interaction F (4, 11) = 0.44 p = .86, η_p^2 = 0.20

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APPENDIX A. RECRUITMENT MATERIALS

DO YOU USE AN E-CIGARETTE?

DO YOU DRINK BEER?

Are you between 21-45 years of age?

Would you like to participate in two research studies rating electronic cigarettes and beer?

After a phone interview, qualified participants visit our lab for two half-day sessions.

You can earn $100 for completing the two studies.

For information, please call

317-278-6761 and refer to the **NBC** study.

Principal Investigator: Melissa Cyders, PhD, HSPP

IUPUI

Department of Psychology

SCHOOL OF SCIENCE

Do you use an electronic-cigarette?

Do you drink beer?

Are you between 21-45 years of age?

Would you like to participate in two research studies rating electronic cigarettes and beer?

After a phone interview, qualified participants visit our lab for two half-day sessions on the IUPUI Campus. You can earn $100 for completing the two sessions.

For information, please call us at 317-278-6761 and refer to the NBC study.

Melissa Cyders, Ph.D., principal investigator.

APPENDIX B. STUDY INCLUSION AND EXCLUSION CRITERIA

Inclusion
 Healthy men and women, 21-45 years of age
 Regular alcohol use (at least once per week)
 No current/prior alcohol use disorder diagnosis
 Current e-cigarette use (at least once per day)
 Able to understand questionnaires/procedures in English
 Reports liking beer

Exclusion
 Pregnant/breast-feeding women
 Desire to be treated for any substance use disorder
 Unstable or significant medical disorders that may influence study outcome or participant safety
 > 1 pack of cigarettes smoked per month
 Positive urine drug screen for amphetamines/methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, or PCP [1- phencyclohexyl piperidine]
 Symptoms consistent with current DSM-5 diagnoses [72]
 Positive BrAC readings at the start of any study visit
 Court-mandated order to not drink alcohol
 Any condition that could place the participant at risk or effect data validity
 Uncorrected vision

APPENDIX C. QUESTIONNAIRES

Table C.1 Demographics

1. How old are you (in years)?
2. What gender do you most identify with or consider yourself to be? Male/Female/Other
3. Which race(s) do you most identify with or consider yourself to be?
    a. White/Caucasian
    b. Black/African American
    c. Asian
    d. Native Hawaiian or Pacific Islander
    e. American Indian/Alaskan native
    f. Hispanic/Latino
4. When did you start using an electronic cigarette? Please give your best estimate.
5. What brand of electronic cigarette do you use?
6. How many mg/ml of nicotine are typically in your nicotine liquid?
    a. 0mg (None)
    b. 6mg (Low)
    c. 12mg (Medium)
    d. 24mg (High)
    e. 36mg (Higher)
    f. Other (please specify)

Table C.2 Alcohol Use Disorder Identification Test (AUDIT)

How often do you have a drink containing alcohol?
(0) Never [Skip to Qs 9-10]
(1) Monthly or less
(2) 2 to 4 times a month
(3) 2 to 3 times a week
(4) 4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?
(0) 1 or 2
(1) 3 or 4
(2) 5 or 6
(3) 7, 8, or 9
(4) 10 or more
3. How often do you have six or more drinks on one occasion?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily
4. How often during the last year have you found that you were not able to stop drinking once you had started?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily
5. How often during the last year have you failed to do what was normally expected from you because of drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily
6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily
7. How often during the last year have you had a feeling of guilt or remorse after drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily
8. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
(0) Never
(1) Less than monthly
(2) Monthly
(3) Weekly
(4) Daily or almost daily

Table C.2 Continued

9. Have you or someone else been injured as a result of your drinking?
(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year
10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?
(0) No
(2) Yes, but not in the last year
(4) Yes, during the last year

Table C.3 NOSIE-ER

NOSIE-ER:
1. It is second nature for me to pick up an e-cig while I am drinking
2. Drinking results in me wanting to use my e-cig more
3. I need to use my e-cig while I am drinking
4. I use my e-cig more while I am having a drink than while I am not actually using
5. I enjoy using my e-cig more after I have had a drink
6. Using my e-cig gives me more desire for alcohol
7. I tend to drink more after I use my e-cig
8. If I could use my e-cig, my urge to drink would increase

(True/False)

Table C.4 Timeline Follow-Back

Try and think about your alcohol use over the last two weeks. Sometimes it is helpful if you identify meaningful days FIRST and then work around that day. For example, if your friend's birthday was last week and you can quickly recall if you consumed alcohol on that date or not, fill that date in first. Then, you can fill in the days around it. It is also helpful to look through your cellphone (text messages, phone calls, your personal calendar) to help you recall your alcohol use.

For each date that has passed, please select how may alcohol drinks you consumed on that date (0-30). Next, please select where you consumed the alcoholic beverages-the choices for the setting in which you consumed alcohol are provided in the drop down menu. If you consumed alcohol at more than one location on a particular date, please select the location where you consumed the majority of your alcohol that day. For each date that you consumed alcohol, please indicate if you smoked cigarettes or an e-cig while drinking. Finally, please select if WHILE DRINKING you smoked cigarettes, an e-cigarette, both, or neither.

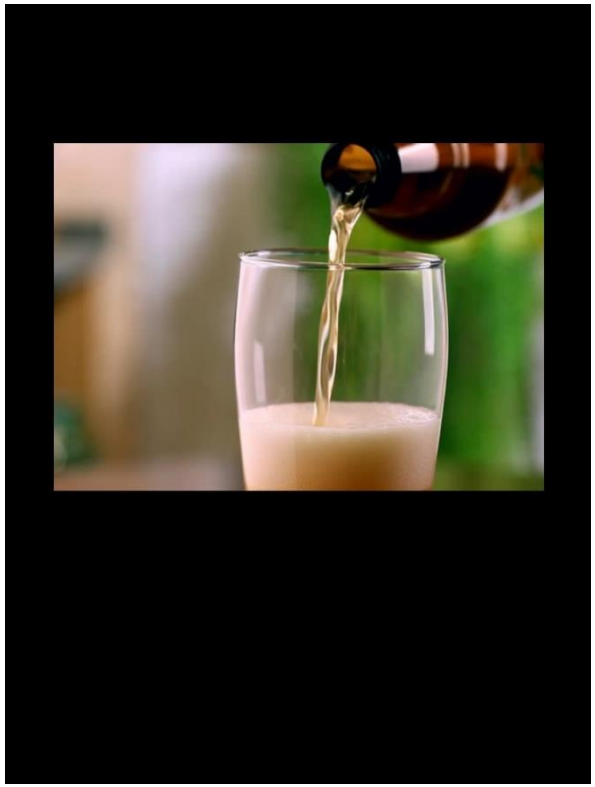
Please fill in the amount of alcohol you drank and in what setting you drank for the following days. Also, indicate if you smoked cigarettes or an e-cigarette WHILE DRINKING.

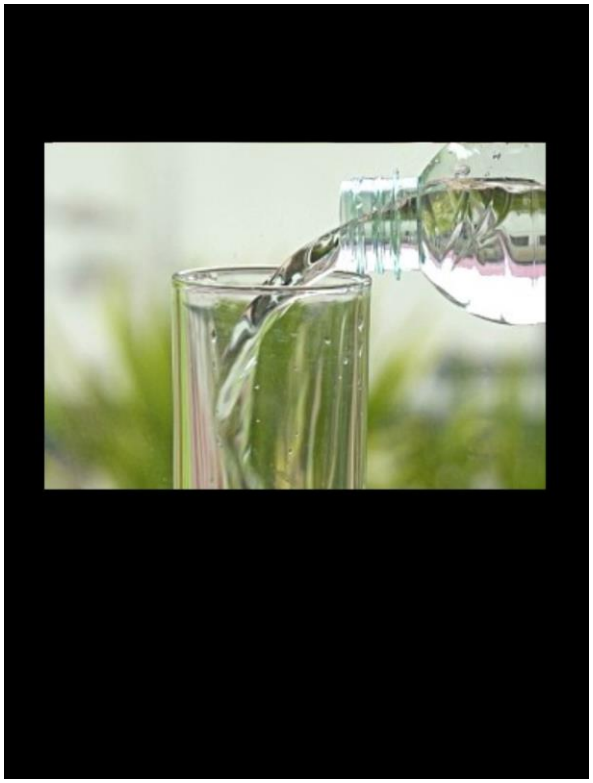
	Alcoholic Drinks Consumed	**Location where alcohol was consumed**	**Smoking and E-cig Use**
Saturday, January 24			

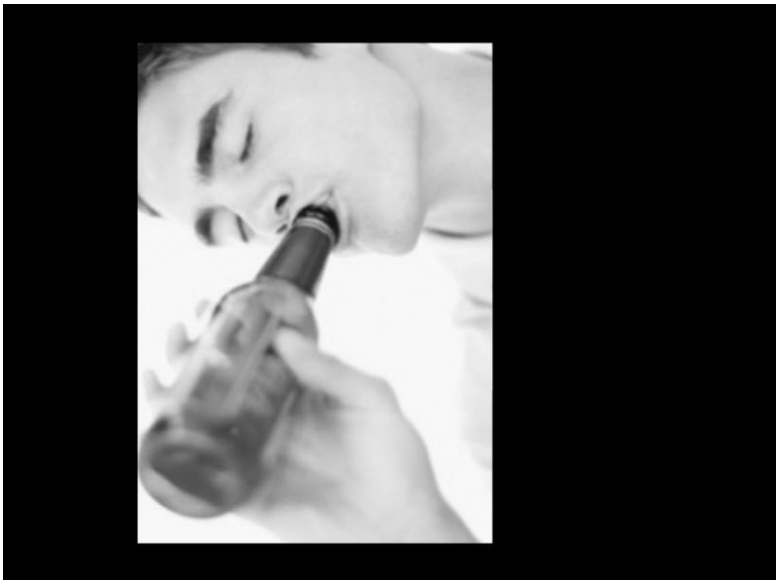
[*The exact days will vary for each participant to reflect the past 14 days of alcohol consumption prior to the date they report to the lab for the study]*

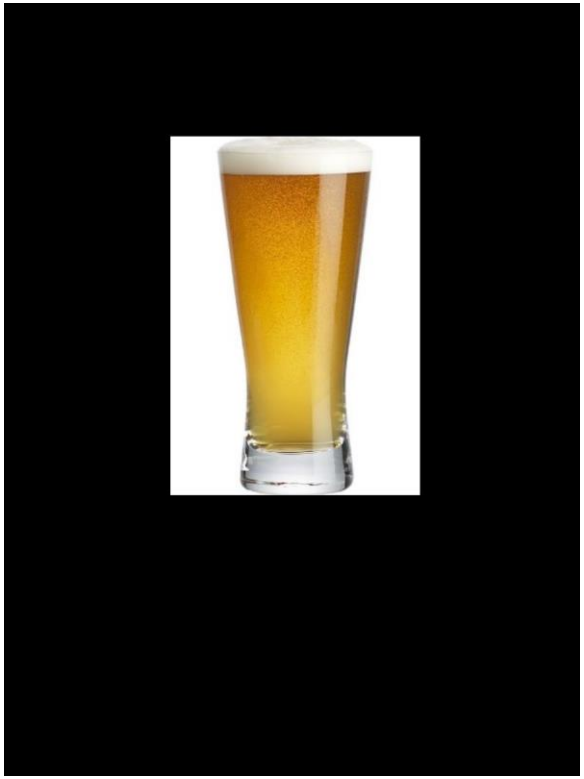
APPENDIX D. IMAGES USED IN THE DOT-PROBE TASK

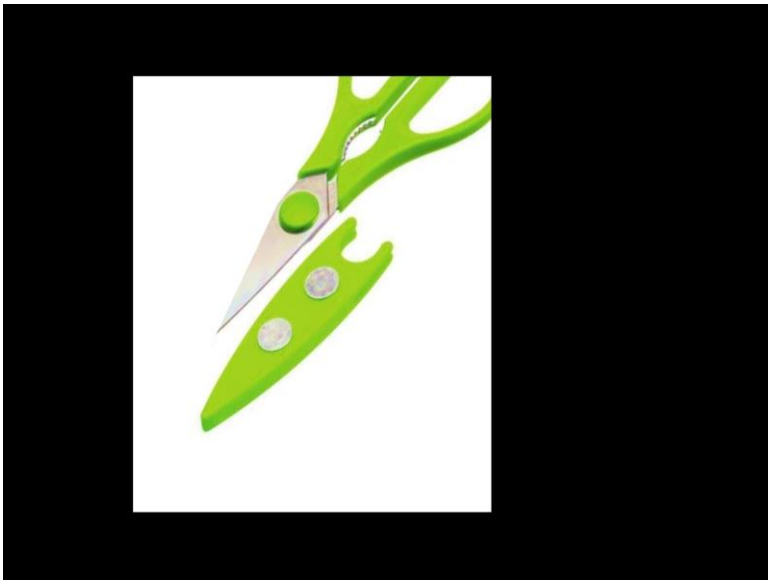
Note: All images were displayed side by side as 5x 7 inches each for the task and appeared in random order. Alcohol and control images were randomly assigned to appear on the left or right.

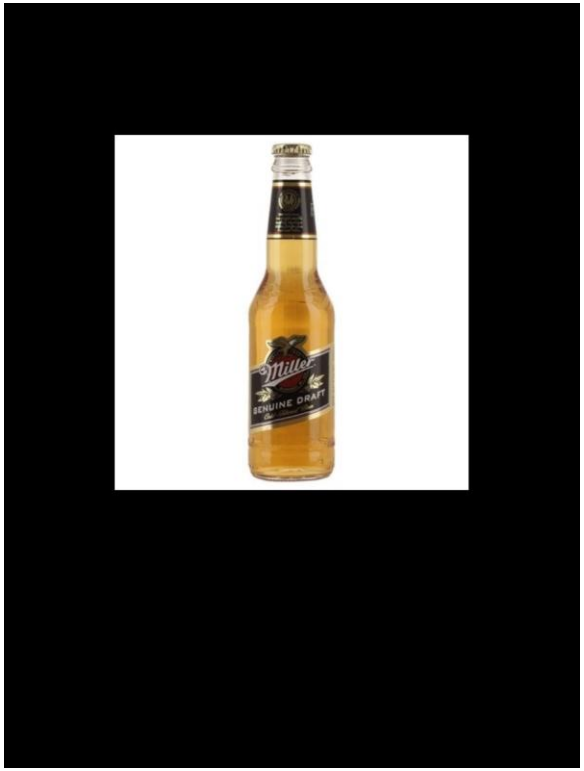




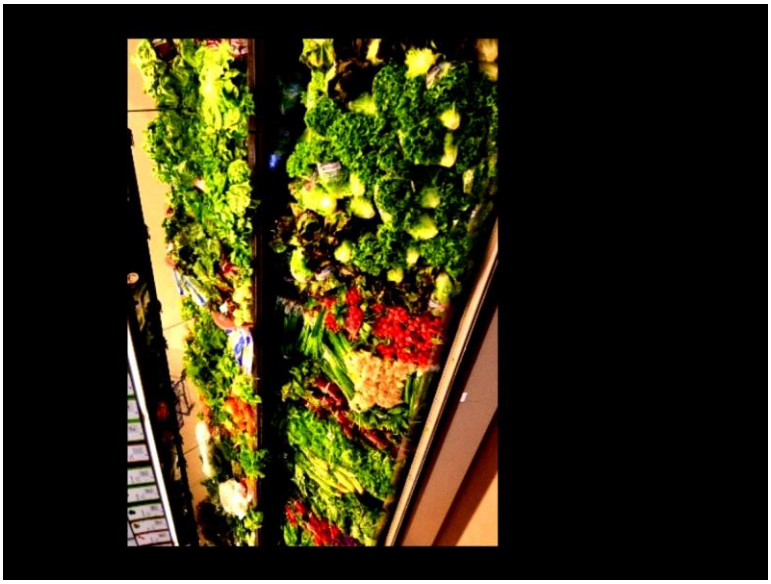


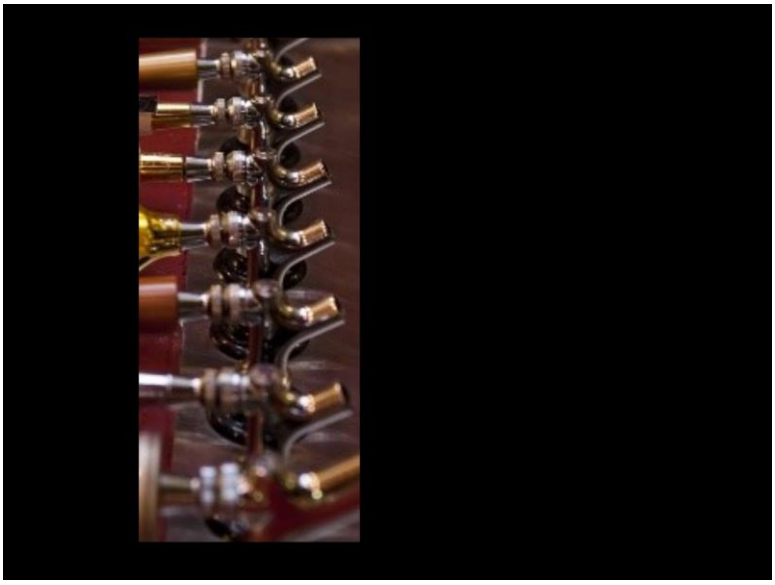





Miller
GENUINE DRAFT

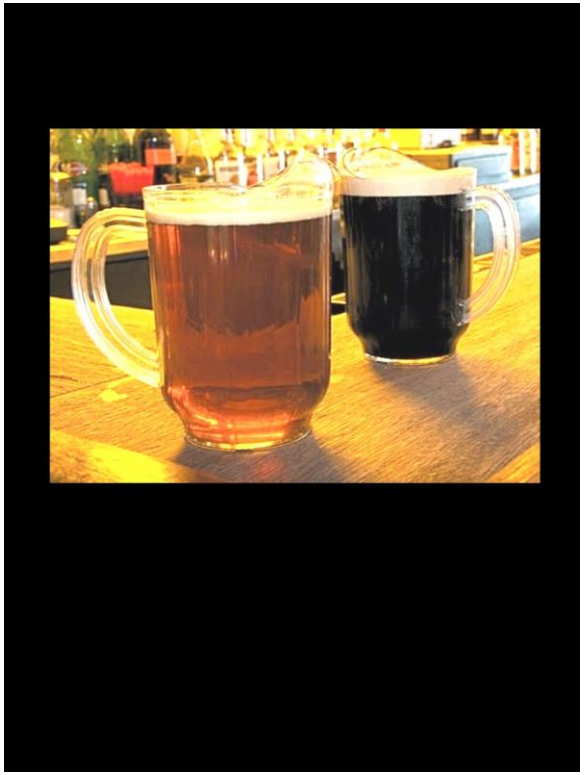

RUST-OLEUM
UNIVERSAL
METALLIC
PAINT & PRIMER IN ONE
PURE GOLD

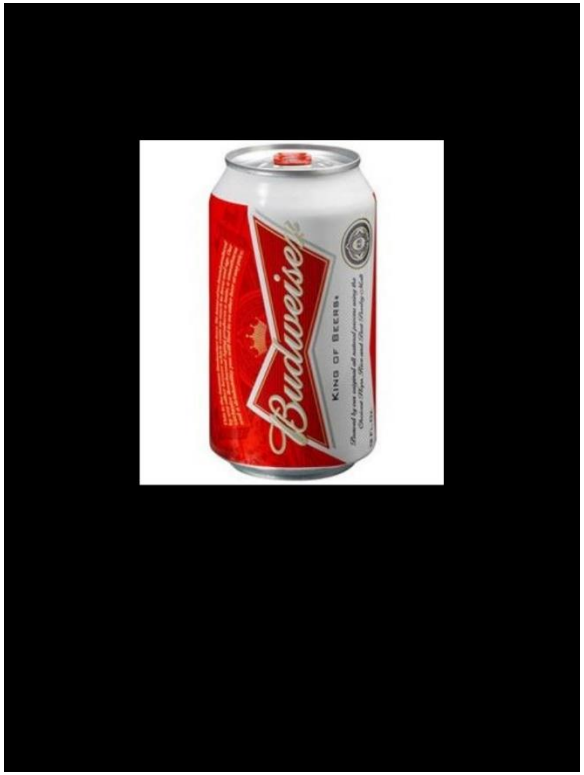




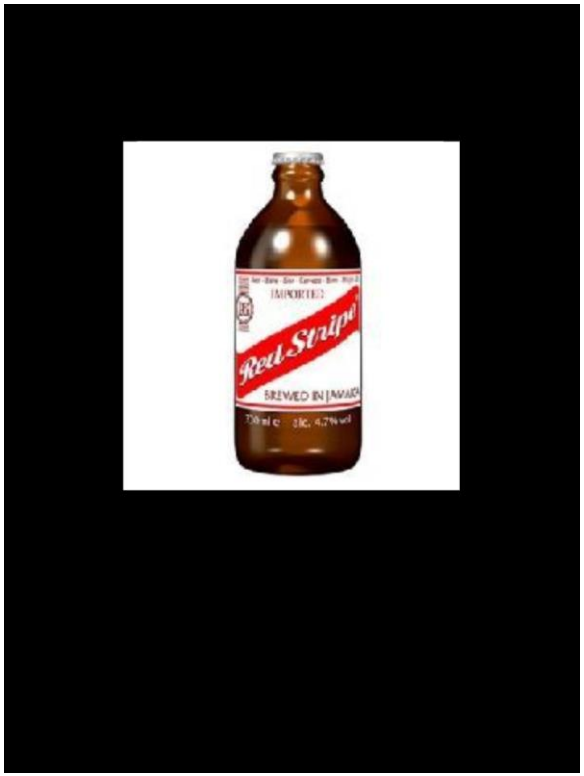

BEER
ON TAP


OPEN
24 HRS

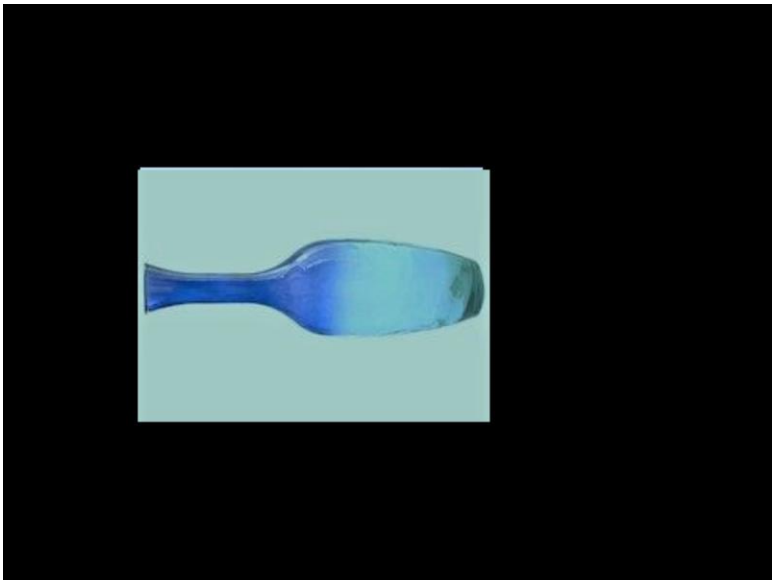


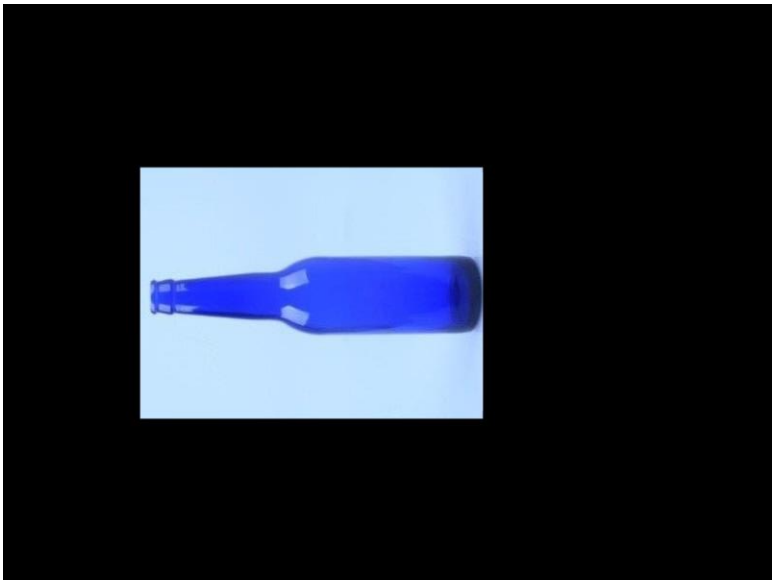

Budweiser
KING OF BEERS

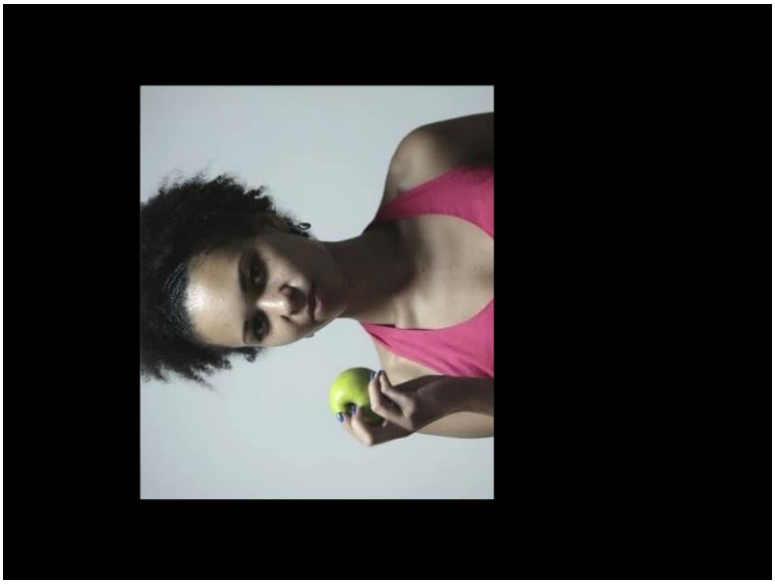

BEHR
PREMIUM PLUS
INTERIOR
FLAT

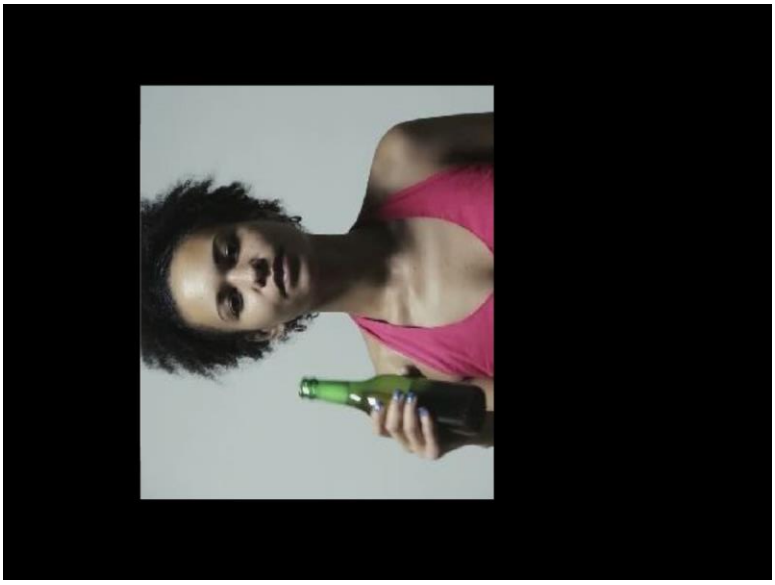

Red Stripe
BREWED IN JAMAICA

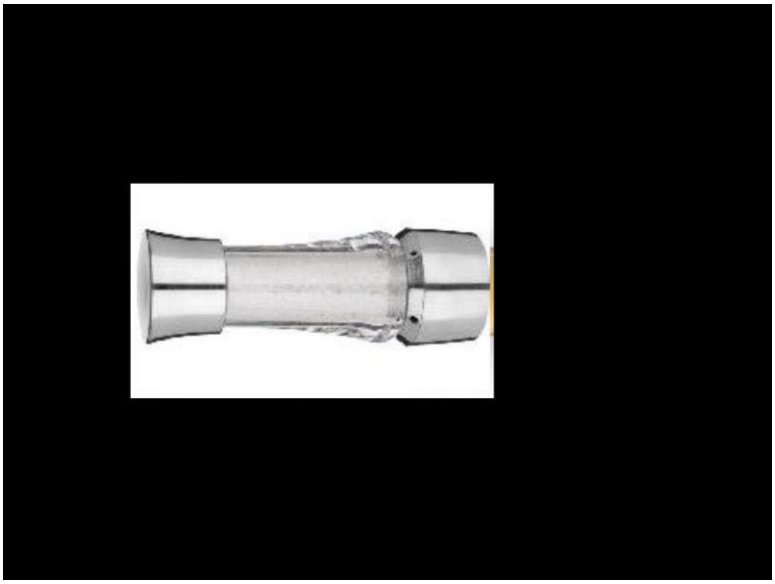

ELMER'S
Rubber Cement

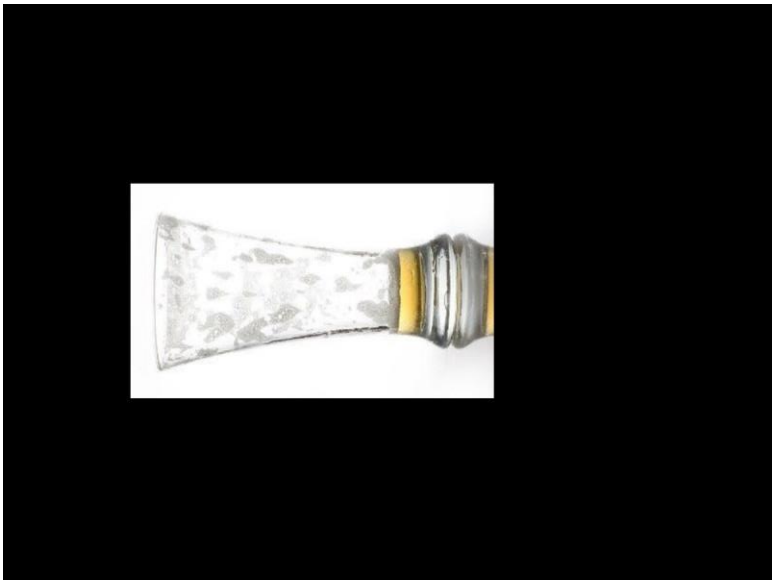


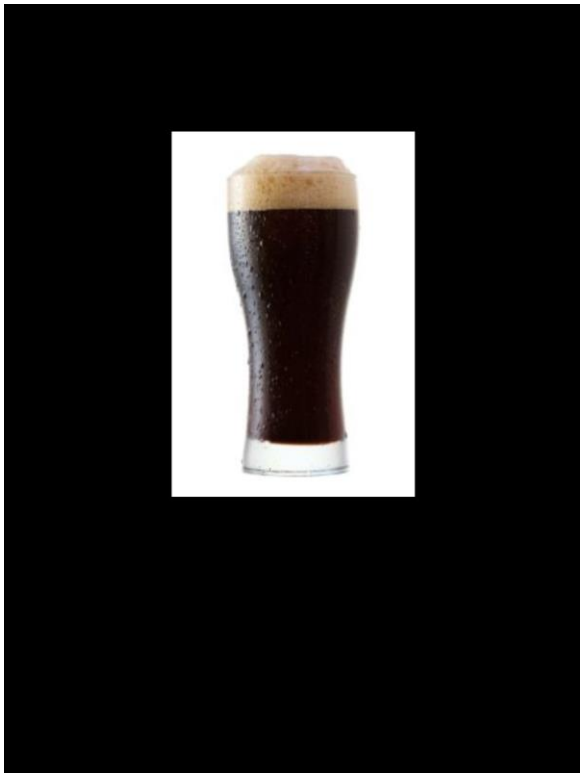


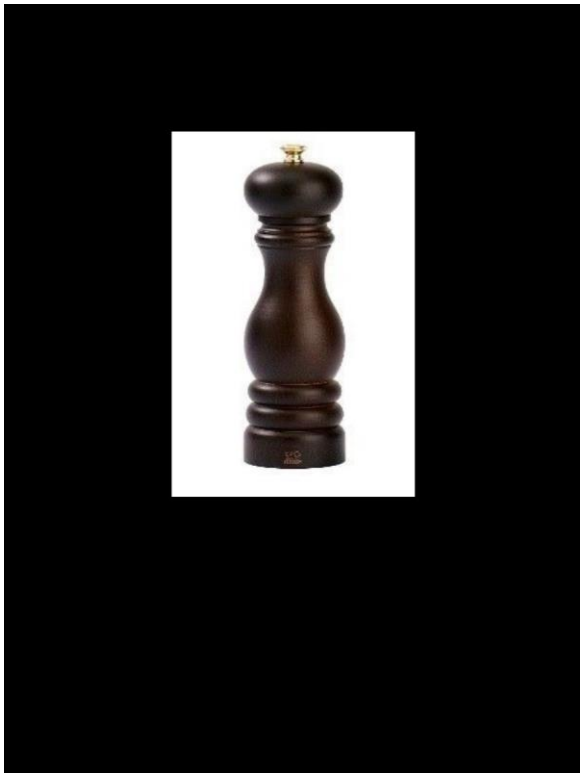


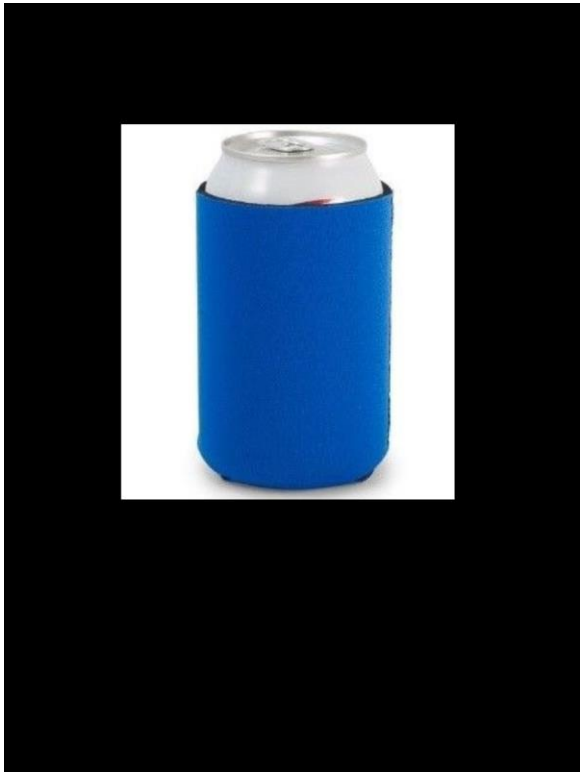












APPENDIX E. TELEPHONE SCREEN

Telephone Screen
Reactions to e-cigs and alcohol

Subject ID Number: _____ Today's Date: ___/___/___ Age: _____ Race:_____

Say to subject, "We would like to know if you are interested in participating in a study that will ask you to participate in e-cig use, beer taste testing, and image viewing. If you qualify and agree to participate, you would come in for two 4-hour sessions, taking about a total of approximately 8 hours, and you would be paid $100 to complete the study. We will hold your car keys during both sessions, verify your age via picture ID at the beginning of each session, and we ask that that you not schedule your sessions before or after any other major obligations. In order to see if you meet requirements for the study, we need to ask you a few questions over the phone, which will take about 5-10 minutes. Some of these questions are about medical and psychological conditions, and some are about drug and alcohol use. Your name will not be kept with your answers. If you do not qualify for this study, based on this conversation, we will destroy all the information you provided us. Would you like to continue?"

Age:
Tell me your birth date: DD/MM/YYYY: ___/___/_____

Weight:
Tell me your approximate weight____lbs and height____ft×12= ____+ ____in =____inches

Are you pregnant or breast feeding? (YES) (NO) **IF YES, EXCLUDE**
Are you trying to become pregnant? (YES) (NO) **IF YES, EXCLUDE**

Smoking History
9. Do you smoke? Yes_____; No_____;
If YES: How many cigarettes/day_____; How many cigarettes/month_____;
cigars/day_____; pipes_____; other_____
IF > 1 PACK PER MONTH, EXCLUDE
Do you use an e-cig? Yes_____; No_____ If yes, what type?
How often do you use an e-cig? _____ (open ended)
IF NO, EXCLUDE

Alcohol and Drugs
10. How many alcoholic drinks (12oz glass of beer, 5oz glass of wine, or 1.5 oz shot of hard liquor) do you drink in a typical week _____.
Do you drink beer? (YES) (NO)
IF DRINK < 1 DRINK WEEKLY OR DOES NOT DRINK BEER, EXCLUDE.

11. Do you use any illicit or recreational drugs? (YES) (NO)
IF YES, EXCLUDE

12. Are you court mandated not to consume alcohol? (YES) (NO)
IF YES, EXCLUDE

Medical History
There are several conditions that might affect our results or your safety. We need to know if any affect you before you visit us. I do not need to know exactly which of these you might have. I will read through one group of conditions and ask you if you think any of those that I have listed affect you. If at any time you become uncomfortable, please just ask me to stop.

Current mental health problem, such as depression, anxiety, posttraumatic stress disorder, bipolar disorder, or schizophrenia
History of or current treatment for alcohol or drug abuse
Any liver conditions, such as Hepatitis C or Pancreatitis
Any longstanding medical issue that requires treatment

(YES) (NO)
IF YES, EXCLUDE

Alcohol/Drug Use history
Please respond yes or no if you currently or have ever experienced the following items either for alcohol or drug use:
I often take alcohol/drugs in larger amounts or over a longer period than was intended. (YES) (NO)
I have a persistent desire or unsuccessful efforts to cut down or control my alcohol/drug use (YES) (NO)
I spend a great deal of time in activities necessary to obtain alcohol/drugs, use alcohol/drugs, or recover from its effects. (YES) (NO)
I have craving, or a strong desire or urge to use alcohol/drugs. (YES) (NO)
My alcohol/drug use has repeatedly caused me to fail to fulfill major role obligations at work, school, or home. (YES) (NO)
I have continued alcohol/drug use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol/drugs. (YES) (NO)
I have given up important social, occupational, or recreational activity because of alcohol/drug use. (YES) (NO)
I have repeatedly used alcohol/drugs in situations in which it is physically hazardous. (YES) (NO)
I have continued to use alcohol/drugs despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol/drugs. (YES) (NO)
I have had to increase the amounts of alcohol/drug to achieve the desired effect or have experienced less than the desired effect with the same amount of alcohol/drug used. (YES) (NO)
I have experience withdrawal when I've reduced or stopped alcohol/drug use (e.g., the shakes, nausea/vomiting, seizures, hallucinations, insomnia). (YES) (NO)
Total out of 11: _____

IF ≥ 6, EXCLUDE

Medications
Can you tell me all of the medications that you take on a regular (daily) basis?

How did you learn about our study?

INCLUDE or EXCLUDE? (circle one)

If EXCLUDE: “Based on the information you have provided in the previous several sections, you do not meet the specific requirements of the study, but thank you for your interest.”

IF INCLUDE: “Based on the information you have provided, you do meet the requirements of this study.” Schedule session 1. Complete next page.

SEPARATE THIS PAGE FROM SUBJECT INFORMATION

- -

Subject ID: _____

Subject Name:_____. DOB____/____/____. Age: ____. Race: _____

Gender: _____.

Telephone Number: ( )_____. Email: _____.

Session 1 Date: ____/____/____.

Administrator signature: _____

APPENDIX F. INFORMED CONSENT

INDIANA UNIVERSITY INFORMED CONSENT STATEMENT FOR

The effect of nicotine on cognitive acuity and motor coordination

You are invited to participate in a research study that involves using your e-cig, assessing cognitive acuity, and testing motor coordination following nicotine and beer consumption. You were selected as a possible subject because you endorsed using electronic-cigarettes and are over 21 years old**.** Please read this form and ask any questions you may have before agreeing to be in the study. You will be asked to use your own e-cig for this study.

These studies are being conducted by Alexandra Hershberger, M.S. and Dr. Melissa Cyders, PhD, HSPP, in the Department of Psychology at Indiana University, Purdue University Indianapolis.

STUDY PURPOSE

The purpose of this study is to 1) examine cognitive acuity following e-cig use (as compared to no e-cig use), 2) examine motor coordination following beer and e-cig use (as compared to beer consumption only). You will use your e-cig in one session and will not use your e-cig in another session.

NUMBER OF PEOPLE TAKING PART IN THE STUDY

If you agree to participate, you will be one of forty subjects who will be participating in this research.

PROCEDURES FOR THE STUDY

If you agree to be in the study, you complete two 4-hour sessions where you will do the following things:

1. You will complete a urine drug screen, pregnancy test (female only), and breathalyzer. If all tests are negative you will be eligible to continue with the study. We will hold your keys during the course of the session (approximately 15 minutes).
2. You will fill out several questionnaires about your electronic-cigarette (e-cig) use, other substance use, beliefs and feelings toward different substances, and personality related items. This should take approximately 45 minutes.
3. You will be asked to puff on your e-cig as you usually do (in one session only) and view pictures. To view these pictures, your chin will be placed on a rest and a camera will be mounted on a computer in front of you. The camera will record your eye and how it responds to the pictures. While viewing these pictures, you will complete a mouse clicking task, in which you will respond with a mouse click to an "x" on the screen. This will take approximately 30 minutes. You will have several practice trials of this task before the study trials begin which will take approximately 3-5 minutes.
4. You will be asked to puff on your e-cig as you usually do (in one session only). You will be given access to 5 beers. You will have 60 minutes to rate the beers on various qualities (examples of ratings: taste, smell). You may drink as much or as little as you would like, but enough to rate your opinions on the beer. At the end of the 60 minutes you will complete a field sobriety task to assess motor coordination.

RISKS OF TAKING PART IN THE STUDY

While in the study, the risks are:
- A risk of being uncomfortable answering questionnaire items.
- A risk of possible loss of confidentiality
- Potential side-effects from using an e-cig, such as throat or nose irritation.
- Fatigue from looking at pictures for twenty minutes.
- There is a possibility that you may become intoxicated or get a headache or become nauseated (sick to your stomach) or even vomit. Additionally, when you are exposed to alcohol, you will have the urge to urinate more often than usual for a few hours
- There also may be other side effects that we cannot predict.

To minimize these risks, we will take the following measures:
- While completing the survey, you can tell the researcher that you feel uncomfortable or do not want to answer a particular question.
- Data will be de-identified and stored securely in our laboratory on a secure server.
- While using an e-cig, you may discontinue at any time if you feel any discomfort with no penalty, and you will be compensated a pro-rated amount for discontinuation. We do not anticipate that you will experience any discomfort different from experiences in everyday life, as you reported regular use of e-cigs. The amount of nicotine to which you will be exposed is well below toxic levels.
- If at any time you are having an aversive reaction to the alcohol consumption or decide to not continue, you may discontinue participation, and you will be compensated a pro-rated amount for discontinuation. There will also be a licensed clinical psychologist, Dr. Melissa Cyders, on call during each study. We do not anticipate that you will experience any discomfort different from experiences in everyday life, as you endorsed drinking beer. Individuals will differ in their risks from alcohol use depending on your drinking history and body habitus (i.e., height/weight). The amount of alcohol to which you will be exposed will place your breath alcohol below driving limits in the state of Indiana.

BENEFITS OF TAKING PART IN THE STUDY

There are no direct benefits to you as a result of participation in this study.

ALTERNATIVES TO TAKING PART IN THE STUDY

Instead of being in the study, your option is to not participate in the study.

CONFIDENTIALITY

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. Your identity will be held in confidence in reports in which the study may be published **a**nd databases in which results may be stored.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the study investigator and his/her research associates, the Indiana University Institutional Review Board or its designees, the study sponsor Indiana University, Purdue University Indianapolis, and (as allowed by law) state or federal agencies, specifically

the Office for Human Research Protections (OHRP) and the National Institutes of Health (NIH) who may need to access your medical and/or research records.

For the protection of your privacy, this research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers may not disclose or use any information, documents, or specimens that could identify you in any civil, criminal, administrative, legislative, or other legal proceeding, unless you consent to it. Information, documents, or specimens protected by this Certificate may be disclosed to someone who is not connected with the research:

(1) If there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases);
(2) If you consent to the disclosure, including for your medical treatment;
(3) If it is used for other scientific research in a way that is allowed by the federal regulations that protect research subjects
(4) For the purpose of auditing or program evaluation by the government or funding agency
(5) [If FDA-regulated] if required by the federal Food and Drug Administration (FDA)
You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

PAYMENT

You will receive payment for taking part in these two studies. Each session will take approximately 4 hours and you will be compensated $60 at the end of session 1 and $40 at the end of session 2. If you chose to discontinue at any point during the study, you will be compensated a prorated amount based on a compensation rate of $11.00 per hour. Compensation will be provided in cash at study completion or time of discontinuation, if this applies.

COMPENSATION FOR INJURY

In the event of physical injury resulting from your participation in this research, necessary medical treatment will be provided to you and billed as part of your medical expenses. Costs not covered by your health care insurer will be your responsibility. Also, it is your responsibility to determine the extent of your health care coverage. There is no program in place for other monetary compensation for such injuries. However, you are not giving up any legal rights or benefits to which you are otherwise entitled. If you are participating in research that is not conducted at a medical facility, you will be responsible for seeking medical care and for the expenses associated with any care received.

CONTACTS FOR QUESTIONS OR PROBLEMS

For questions about the study or a research-related injury, contact the researcher, Melissa A. Cyders at 317-274-6752. If you cannot reach the researcher during regular business hours (i.e., 8 a.m. to 5 p.m.), please call the IU Human Subjects Office at 317-278-3458 or 812-856-4242. After business hours, please call Alexandra Hershberger at 859-221-9070.

In the event of an emergency, you may contact Dr. Melissa Cyders at 317-274-6752.

For questions about your rights as a research participant, to discuss problems, complaints, or concerns about a research study, or to obtain information or offer input, contact the IU Human Subjects Office at 812-856-4242 or by email at irb@iu.edu.

VOLUNTARY NATURE OF THIS STUDY

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision whether or not to participate in this study will not affect your current or future relations with Indianapolis University-Purdue University Indianapolis.

Your participation may be terminated by the investigator without regard to your consent in the following circumstances: you do not cooperate with the study rules, you miss the scheduled session, you show up for a session with a non-zero breath alcohol concentration, testing of your urine sample is positive for any drug of abuse, or, for women, testing of your urine sample indicates that you are pregnant, or if in the clinical judgment of the principal investigator it would not be safe and/or prudent for you to continue participating.

SUBJECT'S CONSENT

In consideration of all of the above, I give my consent to participate in this research study. I will be given a copy of this informed consent document to keep for my records. I agree to take part in this study.

Subject's Printed Name: _____

Subject's Signature: _____**Date _____**
(must be dated by the subject)

Printed Name of Person Obtaining Consent: _____

Signature of Person Obtaining Consent:_____**Date**:_____

APPENDIX G. BEER RATING FORM

Aroma: _____ **(1-10)**

Malty
- Light / moderate / heavy / harsh
- Bread - light / dark
- Cookie
- Grain / Hay / Straw / Cereal
- Toasted / Roasted / Burnt / Nutty
- Molasses / Caramel Chocolate - milk / dark
- Coffee - mild / strong
- Other: _____

Hoppy
- Light / moderate / heavy / harsh
- Flowers / Perfume / Herbs / Grass
- Pine / Spruce / Resin
- Citrus - grapefruit / orange
- Citrus - lemon / lime
- Other: _____

Yeasty
- Light / moderate / heavy / harsh
- Dough / Sweat
- Horse blanket / Barnyard / Leather
- Soap / Cheese
- Earth / Mold / Cobwebs
- Meat / Broth
- Other: _____

Miscellaneous
- Banana / Bubble gum
- Grape / Raisin / Plum / Prune / Date
- Apple / Pear / Peach / Pineapple
- Cherry / Raspberry / Cassis
- Wine - white / red
- Port - tawny / ruby
- Cask wood (e.g., oak)
- Smoke / Tar / Charcoal / Soy sauce
- Toffee / Butter / Butterscotch
- Honey / Brown sugar / Maple syrup
- Coriander / Ginger
- Allspice / Nutmeg / Clove / Cinnamon
- Vanilla / Pepper / Licorice / Cola
- Alcohol
- Dust / Chalk
- Vegetable / Cooked corn
- Cardboard / Paper
- Medicine / Solvent / Band-aid
- Soured milk / Vinegar
- Sulfur / Skunk
- Other: _____

Appearance: _____ **(1-5)**

Head - Initial Appearance
- Size - small / avg / large / huge
- Rocky
- Creamy
- Frothy
- Fizzy
- Virtually none

Head - Color
- White
- Off-white
- Light brown

Head - Lacing
- Excellent
- Good
- Fair
- Virtually none

Head - Longevity
- Fully lasting
- Mostly lasting
- Mostly diminishing
- Fully diminishing

Body - Clarity
- Clear - sparkling / normal / flat
- Cloudy - hazy / murky / muddy

Body - Particles
- Size - Tiny / small / medium / large / huge
- Density - thin / average / thick
- Bottle conditioned

Body - Hue
- Light / medium / dark
- Yellow
- Amber
- Orange
- Red
- Brown
- Black
- Other:_____

Flavor: _____ **(1-10)**

Initial Flavor
- Sweet - light / moderate / heavy / harsh
- Acidic - light / moderate / heavy / harsh
- Bitter - light / moderate / heavy / harsh
- Acetic (vinegar)
- Sour (sour milk)
- Salty

Finish - Flavor
- Sweet - light / moderate / heavy / harsh
- Acidic - light / moderate / heavy / harsh
- Bitter - light / moderate / heavy / harsh
- Acetic (vinegar)
- Sour (sour milk)
- Salty

Finish - Duration
- Short
- Average
- Long

Palate: _____ **(1-5)**

Body
- Light
- Light to medium
- Medium
- Medium to full
- Full

Texture
- Dry
- Watery
- Oily
- Creamy
- Syrupy
- Other: _____

Carbonation
- Fizzy
- Lively
- Soft
- Flat
- Other: _____

Finish - Feel
- Metallic
- Chalky
- Astringent - light / moderate / heavy / harsh
- Alcoholic - light / moderate / heavy / harsh
- Other: _____

Overall Score: _____ **(1-20)**

Comments:

APPENDIX H. STANDARDIZED FIELD SOBRIETY TEST

Horizontal Gaze Nystagmus

"I am going to check your eyes. Keep your head still and follow my finger with your eyes only. Keep following my finger with your eyes until I tell you to stop"

Observe each eye individually while slowly moving pen across face 12-15" away. It should take roughly 2s to move from nose to wide angle, 2s to move back to nose, for each eye. Check appropriate line for presence of each sign:

Lack of smooth pursuit- the person has difficulty smoothly tracking the object.

Left: __ YES __NO Right: __ YES __NO

Distinct nystagmus at maximum deviation- the person has jerking eye movements when holding gaze at maximum angle for more than 4 seconds

Left: __ YES __NO Right: __ YES __NO

Onset of nystagmus prior to 45 degrees- the first jerk is noticed prior to eye moving 45 degrees

Left: __ YES __NO Right: __ YES __NO

NOTE: Participants with 4+ YES are likely (88%) under the influence of a substance

Walk and Turn Test

"Place your left foot on the line. Place your right foot on the line ahead of the left foot, with hell of right foot against toe of left foot. Place your arms down at your sides. Maintain this position until I have completed the instructions. Do not start to walk until told to do so. When I tell you to start, take nine heel-to-toe steps, turn, and take nine heel-to-toe steps back. When you turn, keep the front foot on the line, and turn be taking a series of small steps with the other foot, like this. While you are walking, keep your arms at your sides watch your feet at all times, and count your steps out loud. Once you start walking, don't stop until you have completed the test. Do you understand the instructions? Begin, and count your first step from heel-to-toe position as One."

Demonstrate heel to toe walk

Demonstrate multi-step turn

Check below if any of the following were demonstrated

__ YES __NO **Could not keep balance while listening to the test instructions**

__ YES __NO **Started the test before the instructions were completed**

__ YES __NO **Stopped walking during the test**

__ YES __NO **Did not touch heel-to-toe while walking**

__ YES __NO **Stepped off the line**

__ YES __NO **Used arms to maintain balance**

__ YES __NO **Took the incorrect number of steps (Not 9)**

__ YES __NO **Turned improperly (Not 2 steps to turn)**

NOTE: Participants with 2+ YES are likely (68%) under the influence of a substance

One-Leg Stand Test

"Please stand with your feet together and your arms down at the sides, like this. Do not start to perform the test until I tell you to do so. Do you understand the instructions so far? When I tell you to start, raise one leg, either leg, with the foot approximately six inches off the ground, keeping your raid foot parallel to the ground. You must keep moth legs straight, arms at your side. While holding that position, count out loud in the following manner: one thousand and one, one thousand and two, one thousand and three, until told to stop. Keep your arms at your sides at all times and keep watching the raised foot. Do you understand? Go ahead and perform the test."

Terminate test after 30 seconds.

Check below if any of the following were demonstrated

__ YES __NO **Swaying while balancing on one leg**

__ YES __NO **Using arms to maintain balance**

__ YES __NO **Hopping during test**

__ YES __NO **Putting the raised foot down**

NOTE: Participants with 2+ YES are likely (83%) under the influence of a substance