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Impact of Smoked Cannabis on Tobacco Cigarette Smoking Intensity and Subjective Effects: A Placebo-Controlled, Double-Blind, Within-Subjects Human Laboratory Study

Erica N. Peters, Ph.D.[1,*], **Evan S. Herrmann, Ph.D.**[1], **Carson Smith, MPA, MPH**[1], **Jess Alan Wilhelm, Ph.D.**[1], **Bartosz Koszowski, Ph.D.**[1], **Matthew Halquist, Ph.D.**[2], **Leon Kosmider, Ph.D.**[2], **Justin Poklis, B.S.**[2], **Sage Roth, B.S.**[1], **Stephan Bart, M.D.**[1], **Wallace B. Pickworth, Ph.D.**[1]

[1]Battelle, Baltimore, MD

[2]Virginia Commonwealth University, Richmond, VA

Abstract

Co-users of cannabis and tobacco frequently use cannabis, then tobacco cigarettes, in a sequential pattern within an occasion, i.e., they “chase” smoked cannabis with a tobacco cigarette. The objective of this placebo-controlled, double-blind, within-subjects human laboratory study was to gather preliminary data on how smoking active vs. placebo cannabis impacts tobacco cigarette smoking behavior, craving, and subjective effects. Adult daily cannabis and tobacco co-users (*N*=9) were randomly assigned to two experimental visit orders (i.e., active cannabis (5.2% THC) first visit and placebo cannabis second visit, or vice versa). Participants smoked one cannabis cigarette, and approximately 30 minutes later were given a 5-minute *ad libitum* period to smoke one of their own brand of tobacco cigarette. As expected, boost in plasma THC levels and cannabis-related subjective effects differed between active and placebo cannabis conditions. Tobacco cigarette puff topography measures and tobacco craving did not differ between cannabis conditions, but there appeared to be between-participant heterogeneity in cumulative total puff volume. After smoking active vs. placebo cannabis, the changes in subjective effects of tobacco smoking after adjusting for pre-tobacco smoking levels were not significant. Results do not support the notion that immediate effects of smoked cannabis change the behavior of tobacco smoking. The strong overlap between cannabis and tobacco smoking may not be explained by primarily pharmacological factors, but may be driven by more nuanced and complex mechanisms involving pharmacological processes as well as learning factors.

Keywords

cannabis; marijuana; tobacco; nicotine; smoking

[*]Corresponding Author: Erica N. Peters, Ph.D. Battelle, 6115 Falls Road, Suite 200, Baltimore, MD 21209, P: (802) 598-9997, epetie@gmail.com.

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Introduction

The majority of US adults who use cannabis also smoke tobacco cigarettes (Schauer et al., 2015; Pacek et al., 2018), and almost half of adults who use cannabis daily or near daily are also daily tobacco cigarette smokers (Goodwin et al., 2018). The prevalence of daily/near daily cannabis and tobacco cigarette co-use has approximately doubled in the past decade; approximately 3 million US adults and approximately 10% of all adult daily cigarette smokers also use cannabis daily or near daily (Goodwin et al., 2018). Cross-sectional and longitudinal studies indicate that heavy cannabis users have higher rates of tobacco cigarette smoking initiation, faster progression to daily cigarette smoking, fewer cigarette smoking quit attempts, and lower rates of success quitting tobacco cigarette smoking (Agrawal et al., 2008; Becker et al., 2015; Gourlay et al., 1994; Patton et al., 2005; Stapleton et al., 2009; Timberlake et al., 2007). These associations persist after controlling for known covariates, suggesting that frequent cannabis use may promote tobacco cigarette smoking via causal mechanisms.

Additional support for relations between heavy cannabis use and daily tobacco cigarette smoking are garnered from studies characterizing cannabis and tobacco co-use as a behavioral phenomenon. One reliable finding is that co-users frequently use cannabis, then tobacco cigarettes, in a sequential pattern in close temporal proximity, i.e., they “chase” smoked cannabis with a tobacco cigarette (Ream et al., 2008; Wilhelm et al., 2020). Co-users often report having regularly engaged in this pattern of behavior since first initiating use of cannabis and tobacco, and that they believe that smoking a tobacco cigarette after cannabis will increase the positive subjective effects (“high”) from cannabis (Lipperman-Kreda & Lee, 2011). These observations coincide with other findings demonstrating that “chasing” behavior appears to be a unique correlate of smoking more tobacco cigarettes per day and greater nicotine dependence scores (Akbar et al., 2019). These findings are important to the present study because they provide insight as to how to develop the types of ecologically-valid laboratory models best able to examine potential causal mechanisms under controlled conditions.

We are aware of four controlled human laboratory studies that examined the acute effects of cannabis exposure on tobacco cigarette smoking behavior. The first two were long-term residential laboratory studies that examined relations between *ad libitum* cannabis smoking and *ad libitum* tobacco smoking during multi-day periods of cannabis self-administration vs. controlled cannabis abstinence (Mello et al., 1980; Mello & Mendelson, 1985). No changes in the total daily number of tobacco cigarettes smoked were observed, but the authors noted close hourly concordance between *ad libitum* cannabis smoking and *ad libitum* tobacco cigarette smoking in a pattern reflective of “chasing” behavior (Mello et al., 1980; Mello & Mendelson, 1985). The third was an outpatient laboratory study where participants received experimentally-administered inhalations from several different potencies of smoked active cannabis (1.29%, 2.84%, 4.00% Δ9-tetrahydrocannabinol (THC)) and placebo cannabis (0.0% THC) 15 minutes prior to 90-minute periods of *ad libitum* tobacco cigarette self-administration (Nemeth-Coslett et al., 1986). This study did not observe any effects of cannabis potency on the number of tobacco cigarettes smoked or the topographical dimensions of cigarette smoking. In the fourth of these studies (Kelly et al., 1990),

participants smoked active and placebo cannabis cigarettes four times each day during 10–15 day residential periods. Participants were administered active or placebo cannabis in 2–5 consecutive-day intervals by the experimenter, using a procedure similar to the one used by Nemeth-Coslett et al. (1986). In the Kelly et al. (1990) study, active cannabis 1) significantly decreased the number of tobacco cigarettes smoked per day by delaying the initiation of *ad libitum* tobacco smoking immediately following experimenter-administered cannabis, and 2) significantly decreased tobacco cigarette inter-puff intervals in a manner unrelated to the timing of tobacco cigarette smoking relative to cannabis administration.

Synthesis of findings across these four studies suggests that relations between cannabis use and tobacco cigarette smoking may be nuanced. First, the results observed by studies examining relations between *ad libitum* cannabis self-administration and *ad libitum* tobacco self-administration (Mello et al., 1980; Mello & Mendelson, 1985) differed substantially from those of studies examining relations between experimenter-administered cannabis and *ad libitum* tobacco self-administration (Nemeth-Coslett et al., 1986; Kelly et al., 1990). This contrasts with studies examining the effects of other drug of abuse (e.g., alcohol, amphetamine, cocaine, opioid agonists) on cigarette smoking; namely, these other drugs increase *ad libitum* cigarette smoking when self-administered and also when experimenter-administered (Henningfield & Griffiths, 1981; Chait & Griffiths, 1983; Mello et al., 1980; Mello & Mendelson, 1985; Roll et al., 1997; Tidey et al., 2000). Taken together, these four studies may suggest that mechanistic relations between cannabis use and tobacco smoking are not driven by innate pharmacological interactions between Δ9-tetrahydrocannabinol (THC; the active psychoactive ingredient in cannabis) and nicotine (the active psychoactive ingredient in tobacco), but by more complex mechanisms involving learning as well as pharmacological processes (Henningfield et al., 1983). This is also reflected in the results of Kelly et al. (1990); i.e., experimenter-administration of active cannabis reduced tobacco cigarette smoking severity according to one metric (number of cigarettes per day) but increased severity according to a different metric (length of inter-puff interval).

Another interpretation is that these studies may have limited applicability to current co-users of cannabis and tobacco for three reasons. First, participants in one of these studies smoked an average of ~30 cigarettes/day. Cigarette consumption has declined significantly since the study was conducted, and as of 2016 only 7% of US adult daily tobacco smokers consume 30 or more cigarettes per day (Jamal et al., 2018). Smoking behavior in heavier vs. lighter smokers may be less sensitive to external variables, in part because such behavior reflects more severe aspects of nicotine dependence, such as continuity and stereotypy (Shiffman & Sayette, 2015). Second, in two of these studies, only men were included. Relative to men, women may be more sensitive to subjective effects related to cannabis (Cooper & Haney, 2014), although they appear to have less pronounced subjective effects related to cannabis after exposure to transdermal nicotine (Penetar et al., 2005). Third, participants in the three studies were not frequent cannabis users. Epidemiological trends indicate that daily cannabis users represent a growing proportion of US adults and of US adult cigarette smokers (Azofeifa et al., 2016; Goodwin et al., 2018). Thus, data are needed on how cannabis smoking affects tobacco smoking from a sample of adult co-users with cannabis and tobacco use characteristics that are associated with both 1) disproportionately high rates of tobacco cigarette smoking and poor tobacco cessation outcomes, and 2) patterns of use,

i.e., frequent “chasing” suggestive of mechanistic relations. Given this is a fairly substantial proportion of all adult co-users in the US, the recruitment of these individuals and testing using a controlled laboratory model designed to capture these specific patterns of behavior (“chasing” cannabis with a tobacco cigarette following overnight abstinence) is a promising approach.

The objective of this placebo-controlled, double-blind, within-subjects human laboratory study was to gather preliminary data on how smoking active vs. placebo cannabis impacts tobacco cigarette smoking behavior, craving, and subjective effects among a participant sample with co-use patterns that are both suggestive of mechanistic relations and associated with poor tobacco cessation outcomes. In light of the studies reviewed above, we hypothesized that active, relative to placebo, cannabis use would increase: (1) intensity of tobacco cigarette smoking, as measured by tobacco cigarette puff topography; (2) tobacco craving prior to cigarette smoking, and (3) positive tobacco subjective effects.

Methods

Participants.

Participants were healthy adults (ages 18–55) living in the Baltimore, Maryland area and recruited through online advertisements (e.g., Facebook; Craigslist) and word-of-mouth referrals between May 2018 and April 2019. Eligibility criteria were chosen with the goals of (1) sampling from a group representative of cannabis and tobacco co-users with use patterns associated with poor tobacco cessation outcomes, and (2) reducing between-subjects variability in dose-response to experimentally-administered cannabis. In addition to having a positive urine test for cannabis use (THC ≥ 50 ng/mL) at the in-person screening visit, participants had to self-report use of cannabis that met the following criteria: (a) using ≥ 20 days in the past 30 days as determined by Timeline Follow-Back (TLFB) interview (Robinson et al., 2014); (b) using at least 2 days per month for the past 12 months; and (c) had not experienced excessive intoxication or other negative effects from cannabis use in the past 4 weeks. In addition to having a positive urine test for tobacco use (cotinine > 200 ng/mL) at the in-person screening visit, participants had to self-report smoking of an average of ≥5 tobacco cigarettes per day for the past 4 weeks as determined by TLFB, and daily or near-daily tobacco cigarette smoking for the past 12 months. Eligibility was restricted to those who used cannabis ≥ 20 days in the past 30 days (approximately 5–7 days/week) because studies over the past two decades examining changes in tobacco and cannabis co-use patterns demonstrate that approximately 60% of co-users who smoke tobacco cigarettes daily also smoke cannabis 5–7 days/week, and more than half of those who do not use 5–7 days/week cluster into a second discrete group that only uses cannabis 1 day/week or less (Goodwin et al., 2018). Individuals could not have experienced excessive intoxication or other negative effects from cannabis to ensure participant safety during the study. Eligibility was restricted to adults smoking an average of ≥5 tobacco cigarettes per day because lighter smokers (<5 cigarettes per day) are generally not nicotine dependent, and thus would likely not reliably show overnight abstinence effects on motivation to smoke tobacco cigarettes. In general, inclusion criteria are consistent with studies examining cannabis and tobacco co-use among heavy or problematic cannabis users (e.g., Herrmann et al., 2019).

Individuals were excluded if they: (a) met DSM-5 criteria for current or lifetime severe Cannabis Use Disorder or any other current Axis I disorder; (b) self-reported current desire to stop cannabis or tobacco use, defined as 7 or greater on 0–10 scale of Contemplation Ladder assessments; (c) self-reported daily use of non-cigarette tobacco or nicotine products or use of smoking cessation medication; (d) self-reported asthma, chronic obstructive pulmonary disease, hypertension, cardiovascular disease, or any other medical illness that precluded safe participation; (e) self-reported use of medical cannabis or using cannabis for self-medication that precluded participation; (f) had positive urine drug screen for substances other than cannabis; and (g) among females, had a positive urinary pregnancy test, self-reported lactation, or reported being sexually active with a male partner without using a reliable form of contraception.

Study Products.

Cannabis cigarettes were provided by the National Institute on Drug Abuse; active [5.6% tetrahydrocannabinol (THC)] and placebo (<0.01 THC) cigarettes appeared identical. In a US Drug Enforcement Administration-approved storage vault, cannabis cigarettes were stored frozen in an airtight container. Cannabis cigarettes were humidified at room temperature for approximately 24 hours prior to the session. Tobacco cigarettes were participants' self-reported own brand of cigarettes, and were purchased by the experimenter.

Procedures.

The study was approved by the Battelle Institutional Review Board, US Drug Enforcement Administration, US Food and Drug Administration, and National Institute on Drug Abuse Drug Supply Program. The study was registered on clinicaltrials.gov.

Screening.

Following a brief telephone screening to determine initial eligibility, participants completed an in-person screening visit. Participants first provided informed consent to participate in the research and completed a brief consent quiz to ensure they understood study procedures. To maintain the experimental blind, participants were informed that they would be smoking two different strengths of cannabis but were not informed about the specific potencies being tested. The screening included a medical evaluation, a mental health evaluation of Axis I disorders using the Structured Clinical Interview Diagnostic – 5 (First et al., 2015); a comprehensive substance use history [i.e., TLFB assessments of use of marijuana, tobacco and nicotine products, alcohol, and other substances in the past 30 days, plus urinary tests of cotinine and illicit drugs and breath tests of carbon monoxide and alcohol (BAL<0.020%)]; a urinary pregnancy test for females; and self-report assessments (see Measures). Individuals who provided informed consent and were found eligible were enrolled into the study. Enrolled participants were randomly assigned to two possible experimental visit orders (i.e., active cannabis first visit and placebo cannabis second visit, or vice versa). Participants were informed that they had to abstain from cannabis and all products containing tobacco or nicotine for at least 10 hours prior to the 9am start time of the experimental visits, and had to abstain from illicit use of substances other than cannabis for the duration of their study participation.

Experimental Visits.

Participants attended two 5-hour experimental visits that were separated by at least 48 hours to eliminate any possible carryover effects of cannabis exposure. Participants were transported to and from the clinical research facility via taxi so that they were not at risk of driving while intoxicated after completing study procedures. Upon arrival at the clinical research facility, participants were assessed for compliance with study requirements, including a reading of exhaled carbon monoxide (CO)<=10 parts per million (ppm) to ensure recent smoking abstinence, continued eligibility with inclusion/exclusion criteria, and any adverse events (AEs) that occurred since the preceding visit.

Approximately 20 minutes prior to cannabis administration, pre-cannabis smoking measures were collected, including blood pressure and heart rate, a blood sample, and self-report measures (see Measures). A line was drawn on the cannabis cigarette (containing ~800mg of cannabis) at the estimated 50% mark using a fine-tip black marker. Cannabis cigarettes were smoked by participants using a Paced Inhalation Procedure: 5 seconds to prepare for inhalation, 5 seconds to inhale, 10 seconds to hold smoke in the lungs, followed by exhalation, and a 40 second interval prior to the next prepare/inhale/hold cycle, until the 50% mark was reached (Foltin et al., 1987). Each cigarette was weighed before and after the Paced Inhalation Procedure to quantify the total amount of cannabis cigarette smoked. Beginning approximately 10 minutes after the initiation of cannabis smoking, post-cannabis smoking measures were collected, including blood pressure and heart rate, exhaled carbon monoxide, a blood sample, and self-report measures.

Approximately 30 minutes after the initiation of cannabis smoking, participants were given a 5-minute *ad libitum* period to smoke one of their own brand of tobacco cigarette that was placed in the mouthpiece of a portable Clinical Research Support System (CReSS; Borgwaldt KC, Inc; North Chesterfield, VA) puff topography device. Immediately after tobacco cigarette smoking, post-tobacco cigarette smoking measures were collected, including blood pressure and heart rate, exhaled CO, a blood sample, and self-report measures. Each tobacco cigarette was weighed before and after *ad libitum* smoking.

At approximately 30-minute intervals for the next 2.5 hours after tobacco cigarette smoking, blood pressure and heart rate, exhaled CO, and self-report measures were collected. Approximately 3 hours after cannabis administration, participants were evaluated for discharge. Participants who did not show evidence of significant intoxication via the Field Sobriety Assessment and did not have abnormal vitals were sent home via taxi.

Compensation.

Participants received $50 for the in-person screening visit, $100 for completing the first experimental visit, and $150 for completing the second experimental visit. The total amount of possible compensation was $300.

Measures

Measures to Characterize the Sample.: At the screening visit, participants completed self-report measures on demographics, tobacco and cannabis use history and current use

patterns, and nicotine dependence via the Fagerström Test of Nicotine Dependence (FTND) (Heatherton et al., 1991). Participants' past-month cannabis and tobacco cigarette use frequency and quantity, and use of other substances (non-cigarette tobacco, alcohol, non-cannabis illicit and prescription drugs) were assessed via the TLFB method.

Outcome Measures

Tobacco Cigarette Puff Topography.—The CReSS puff topography device recorded the number of puffs taken, puff volume (ml), puff duration (sec), maximum puff velocity (ml/sec), and inter-puff-interval (sec) for one of the participants' own brand of tobacco cigarette smoked at each experimental visit. Total puff volume was calculated from the sum of puff volume over all puffs of the one cigarette, and was *a priori* defined as the primary outcome measure.

Exhaled CO.—Exhaled CO was used as a measure of inhalation of tobacco (and cannabis) smoke, collected via a Vitalograph CO detector (Lenexa, KS), and measured in parts per million (ppm). CO was measured before and after smoking of each product and at 30-minute intervals, until 150 minutes after tobacco cigarette smoking ended.

Plasma Nicotine and THC.—Three blood samples (approximately 7 mL each) were collected approximately 20 minutes prior to cannabis administration, approximately 5 minutes after cannabis smoking ended, and immediately after tobacco cigarette smoking. Samples were analyzed for plasma nicotine and THC. Briefly, sample levels of nicotine were determined using liquid chromatography tandem mass spectrometry (LC-MS/MS) preceded by a validated extraction method in plasma (Cappendijk et al., 2010; Spindle et al., 2018). THC was determined using 0.250 mL aliquot that was subjected to a protein precipitation extraction with cold acetonitrile. Following vortex mixing and centrifugation, the supernatant was then transferred, evaporated in a Speedvac and reconstituted with acetonitrile prior to LC-MS/MS analysis (Poklis et al., 2010). The linear range for nicotine and THC was 2–75 ng/mL and 1–100 ng/mL, respectively.

Tobacco Smoking Craving.—The 10 items of the Questionnaire of Smoking Urge – Brief version (QSU-Brief) (Cox et al., 2001) were scored on a 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree), and were averaged to yield two subscale scores (Desire to Smoke and Relief from Negative Affect) and a total score. The QSU was administered pre- and post- cannabis smoking, immediately following tobacco cigarette smoking, and post-tobacco cigarette smoking at 30-minute intervals, until 150 minutes after tobacco cigarette smoking ended.

Cannabis and Tobacco Cigarette Subjective Effects.—Immediately before and after cannabis smoking, a 6-item questionnaire assessed subjective effects related to cannabis. At the top of the questionnaire were instructions for participants to rate the "marijuana you just smoked" and items of "I feel strong drug effects," "I like the drug effects," "I want to smoke more of the marijuana I just smoked," "I feel good drug effects," "I feel bad drug effects," and "Do you think the marijuana you just smoked was strong or weak marijuana?" rated on a 100mm visual analog scale. Immediately before and after

tobacco cigarette smoking, a 6-item questionnaire assessed tobacco cigarette subjective effects. At the top of the questionnaire were instructions for participants to rate the “tobacco cigarette you just smoked” and items of “I feel the drug effects,” “I like the drug effects,” “I am content,” “I want to smoke more cigarettes,” “I feel good drug effects,” and “I feel bad drug effects” rated on a 100mm visual analog scale. Subjective effects related to nicotine and to cannabis were assessed at 30-minute intervals, until 150 minutes after tobacco cigarette smoking ended. Instructions differed by timing of assessment (e.g., before smoking of either substance, participants were instructed to rate how they were feeling “right now”) and by substance (e.g., after tobacco cigarette smoking, participants were instructed to rate how they were feeling about the tobacco cigarette they just smoked). Immediately after tobacco cigarette smoking, the Duke Sensory Questionnaire (DSQ; Behm & Rose, 1994) and Cigarette Evaluation Scale (CES; Westman et al., 1992) also assessed tobacco cigarette subjective effects.

Data Analysis.—Puff topography data were cleaned according to manufacturer guidelines: puffs shorter than 200 milliseconds or less than 15mL in volume were removed. Total puff volume, the primary outcome of the trial, was calculated from the sum of the volumes of all cigarette puffs taken by participants during each experimental visit. As normality cannot reliably be assumed, a non-parametric Wilcoxon signed-rank test was used to test differences in total puff volume from smoking the single tobacco cigarette after smoking active vs. placebo marijuana.

Other puff topography measures (e.g., number of puffs, puff duration, mean puff velocity) as well as change in exhaled CO, plasma nicotine concentration, tobacco craving, and subjective effects were considered secondary outcomes. Secondary outcomes were also analyzed using paired T-tests and Wilcoxon signed rank tests. For measures with pre-smoking assessments, we analyze the change in post-smoking values from pre-smoking (i.e., cannabis or tobacco smoking, depending on the measure). We used an alpha of 0.05 for all hypothesis tests. Due to the exploratory nature of this study and the small sample size, we do not address the multiplicity issue in secondary analyses. As in most clinical trials, we did not power for all secondary outcomes, including correction for multiple comparisons. Statistical significance of findings on secondary outcomes should be considered as suggestive, rather than confirmation, of an effect. Analysis was conducted in Stata version 15 (Stata Statistical Software: Release 15, 2017).

Results

Participants.

Of 160 individuals who were screened by telephone for inclusion into the study, 123 (77%) were ineligible and two were eligible but not interested in participating. The most common reasons for ineligibility were smoking an average of < 5 tobacco cigarettes per day, smoking marijuana < 19 days/month, and planning to quit tobacco smoking. Of the 35 individuals who were eligible and interested in participating, 23 (66%) were determined to be not eligible at in-person screening or did not show for the screening visit. Twelve participants enrolled in the study, of whom 3 did not complete because of positive urine drug test for

non-cannabis illicit drugs, exhaled CO > 10 ppm, or BAC > 0.020% at the start of scheduled experimental visits.

Table 1 presents the characteristics of the nine participants who completed the study. The sample was mostly African American and relatively evenly split with regard to sex (5/9 male); the mean age was approximately 35 years [standard deviation (SD) = 8.5]. Participants used cannabis daily, used a mean of 2.2 grams (SD=1.2) of cannabis per day, and 5/9 participants reported smoking cannabis within 30 minutes of waking. All participants reported that smoking was their primary mode of cannabis use, although other modes of use in the past 30 days included vaporizing (3/9 participants), eating (2/9), and dabbing (1/9). Participants were daily cigarette smokers who smoked approximately 14 cigarettes per day (SD=8.2) and had a mean FTND score of 4.9 (SD=2.8); 7 of 9 participants smoked menthol cigarettes.

Cannabis Administration.

The pre-post difference in the weight of the cannabis cigarette was 0.43 g in the active condition and 0.38 g in the placebo condition. As expected, cannabis-related outcomes differed between active and placebo cannabis conditions, including boost in plasma THC levels (difference between pre- and post-cannabis smoking) (active boost: mean (M)= 57.4 ng/mL; SD=35.5 vs. placebo boost: mean = 0.01 ng/mL; SD=0.77), and cannabis-related subjective effects immediately after cannabis smoking, such as “Do you think the marijuana you just smoked was strong or weak marijuana?” (active: mean (*M*) = 58.3; SD=30.4 vs. placebo: *M*=27.6; SD=23.3), “I feel strong drug effects” (active: mean (*M*) = 64.7; SD=29.4 vs. placebo: *M*=36.7; SD=32.2), “I like the drug effects” (active: mean (*M*) = 77.7; SD=26.6 vs. placebo: *M*=35.8; SD=27.1), and “I feel good drug effects” (active: mean (*M*) = 76.9; SD=25.2 vs. placebo: *M*=39.0; SD=32.2).

Intensity of Tobacco Cigarette Smoking.

Figure 1 presents each individual participant’s cumulative total puff volume (primary outcome) over the 5-minute *ad libitum* period of smoking one of his/her own brand of tobacco cigarette. As can be seen in Figure 1, every possible permutation of outcomes was observed; that is, some participants appeared to have no difference in cumulative total puff volume of the tobacco cigarette between the two cannabis conditions, some appeared to show that cumulative total puff volume was greater in the active cannabis condition, and others appeared to show that it was lower in the placebo cannabis condition. Thus, there was substantial inter-individual heterogeneity in cumulative total puff volume, and consistent with this heterogeneity, there was no significant difference in this primary outcome measure between active and placebo conditions, and there were high standard deviations of the mean values (Table 2). There were no significant differences between the active and placebo cannabis conditions in other cigarette puff topography measures, biomarkers of tobacco-related exposure (i.e., exhaled carbon monoxide and plasma nicotine), or weight of the cigarette smoked for participants’ own brand of tobacco cigarette (Table 2).

Tobacco Craving.

QSU-Brief scores after cannabis smoking did not differ between active and placebo cannabis conditions, nor did they differ between condition at any timepoint after tobacco cigarette smoking (results not shown).

Tobacco Cigarette Subjective Effects.

There were significant unadjusted differences between active and placebo cannabis conditions for two subjective effects ("liking" and "feeling good effects") related to the tobacco cigarette. However, after adjusting for pre-tobacco smoking levels, the changes in subjective effects of tobacco smoking after cannabis smoking were not significant. Scores on the DSQ and CES-D immediately after tobacco cigarette smoking did not differ between active and placebo cannabis conditions (results not shown).

Discussion

The overall finding of this placebo-controlled, double-blind, within-subjects human laboratory study was that tobacco cigarette smoking behavior and subjective effects associated with tobacco cigarette smoking did not differ after smoking active vs. placebo cannabis.

Analysis of tobacco cigarette smoking topography data demonstrated no significant overall differences in common topography-related measures of the reinforcing effects of cigarette smoking. However, cursory analysis of aggregate differences between active and placebo conditions suggests numerically large effects on several metrics, as well as substantial between-participant variability, as indicated by high standard deviations of the means (Table 2). Visual analysis of individual participant-level data on tobacco cigarette smoking topography, as displayed in Figure 1, illustrate that the lack of overall differences in puff topography may be the result of variations in tobacco cigarette smoking behavior between active and placebo conditions. Puff topography measures during *ad libitum* tobacco cigarette smoking are highly reliable (Perkins et al., 2012), and given the rigorous experimental control established in this study, these data suggest smoked cannabis produces a potentially genuine but variable effect on tobacco smoking. The observed variability in the effect of smoked cannabis on smoked tobacco could indicate that such effects may not be primarily pharmacological in nature, but may be driven by more nuanced and complex mechanisms involving learning as well as pharmacological processes (Henningfield et al., 1983).

The overall lack of change in intensity of smoking behavior is consistent with similar prior studies that found that smoked cannabis had no significant effect on indices of tobacco cigarette smoking intensity, such as quantity of cigarettes smoked or the topographical dimensions of cigarette smoking (Mello et al., 1980; Mello & Mendelson, 1985; Nemeth-Coslett et al., 1986). However, they are not consistent with the prior study by Kelly et al. (1990) that showed that smoked cannabis 1) significantly decreased the number of tobacco cigarettes smoked per day by delaying the initiation of *ad libitum* tobacco smoking immediately following experimenter-administered cannabis, and 2) significantly decreased tobacco cigarette inter-puff intervals in a manner unrelated to the timing of tobacco cigarette

smoking relative to cannabis administration. This inconsistency may be because participants in the Kelly et al. (1990) study smoked active and placebo cannabis cigarettes four times each day during 10–15 day residential periods, while participants in the current study smoked a single active or placebo cannabis cigarette in one session in each experimental condition.

Co-users of cannabis and tobacco frequently use cannabis, then tobacco cigarettes, in a sequential pattern within an occasion, i.e., they "chase" smoked cannabis with a tobacco cigarette (Ream et al., 2008), perhaps because smoking tobacco after cannabis may increase the positive subjective effects ("high") from cannabis (Lipperman-Kreda & Lee, 2011). To our knowledge, no research has examined a different aspect of this behavioral phenomenon of "chasing" – whether smoking tobacco after cannabis can affect the subjective effects from tobacco. Results showed that, at some timepoints, the item for "liking" the effect of the tobacco cigarette, and the item for "feeling good effects" of the tobacco cigarette, appeared higher after smoking active vs. placebo cannabis, but were not significantly different after adjusting for pre-tobacco smoking levels. Given our study's small sample size, however, future clinical studies may test other subjective effects (e.g., mood) and may test subjective effects through more objective means, such as choice tasks. As one prior study revealed sex differences in nicotine's enhancement of cannabis-related subjective effects (Penetar et al., 2005), future research may investigate potential sex differences in the impact of cannabis on tobacco-related abuse liability. In this study, we chose to assess the subjective effects associated with the more proximal substance smoked, as participants with regular use of both cannabis and tobacco were thought to be experienced in distinguishing the effects of each. It is possible, though, that the effects of the tobacco cigarette might have been conflated with the effects of cannabis, and the tendency to use both simultaneously or in close proximity might actually impede the ability to distinguish the effects of each. Also tempering this finding is that study questionnaires were not reviewed with participants prior to the first session; thus, participants may not have understood the questionnaire items. Although the study design aimed to maximize both experimental control and real-world validity in a parsimonious design, a placebo control for nicotine exposure would have helped clarify the time course of the subjective effects of cannabis alone vs. cannabis plus tobacco.

Smoking of cannabis and of tobacco was the focus of the present investigation because smoking remains the most common mode of using both substances (Agaku et al., 2014; Schauer et al., 2016), and smoking is the most common mode of cannabis use among tobacco smokers (Singh et al., 2016). Nonetheless, other modes of cannabis use (e.g., vaporized; edible) are proliferating, perhaps due to the evolution of state-based cannabis policy in the US, in which 11 states and the District of Columbia have voted to allow adult legal use of cannabis, and 33 states and the District of Columbia have voted to allow medical use of cannabis. Future studies are needed to examine the relative impact of different modes of cannabis use on tobacco-related outcomes. At the same time that state-based cannabis policy is changing in the US, the US Food and Drug Administration intends to set product standards to reduce the nicotine content in cigarettes to a minimally- or non-addictive level, with the goals of promoting smoking cessation and preventing smoking initiation (Gottlieb & Zeller, 2017). One future study could test the impact of cannabis on smoking of very low nicotine content cigarettes, and vice versa, as a way of modeling the predicted reciprocal

impact of changing policies for both cannabis and nicotine. Finally, increased understanding of the mechanisms explaining how cannabis may impede tobacco cessation are needed to inform future smoking cessation interventions.

Strengths of the current study include its placebo-controlled within-subject design that confers experimental rigor, its assessment of both objective and subjective measures of tobacco-related outcomes, its inclusion of female participants, and its examination of adult daily co-users of cannabis and tobacco, a subpopulation that is growing in the US (Goodwin et al. 2018). The most significant limitation is its small sample size. Another limitation is the strength of THC in the active cannabis condition. The THC content in this study (5.2% THC) was higher than in previous similar studies (Mello et al., 1980; Nemeth-Coslett et al., 1986; Kelly et al., 1990), and did elicit robust effects on cannabis-related outcomes, but it is lower than the average potency of THC in recreational cannabis in the US (~12% THC) (ElSohly et al., 2016). Our study entailed *ad libitum* smoking of one tobacco cigarette and did not examine how active cannabis might exert an effect on quantity of cigarettes smoked, an index of smoking intensity positively associated with adverse health effects. Participants' smoking of the tobacco cigarette via the puff topography device, i.e., smoking the cigarette differently than they would in their usual environments, may have affected study outcomes. Co-administration of tobacco and cannabis via blunts and/or spliffs was common in this sample, and results may not be replicated in a sample that does not frequently co-administer cannabis and tobacco. The study was predicated on the notion that the association between cannabis smoking and tobacco smoking is driven by THC delivery, but other cannabinoids or components of cannabis smoke could be involved. Finally, our results capture only the very next tobacco cigarette after cannabis smoking; there may be more prolonged effects of cannabis smoking that impact tobacco smoking.

Daily cannabis users represent a growing proportion of US adult tobacco cigarette smokers (Goodwin et al., 2018). In this study of adult daily co-users of cannabis and tobacco cigarettes, smoked cannabis did not change the intensity of tobacco cigarette smoking or subjective effects associated with tobacco cigarette smoking. In light of observed between-participant heterogeneity in the tobacco cigarette smoking behavior after smoking active cannabis, future studies may further examine the complexity in factors explaining the strong overlap between cannabis and tobacco smoking.

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Public Health Statements:

This study adds to a limited literature on how cannabis use impacts tobacco smoking outcomes. This clinical study shows that there may be variability between people in the way that smoked cannabis affects tobacco cigarette smoking.

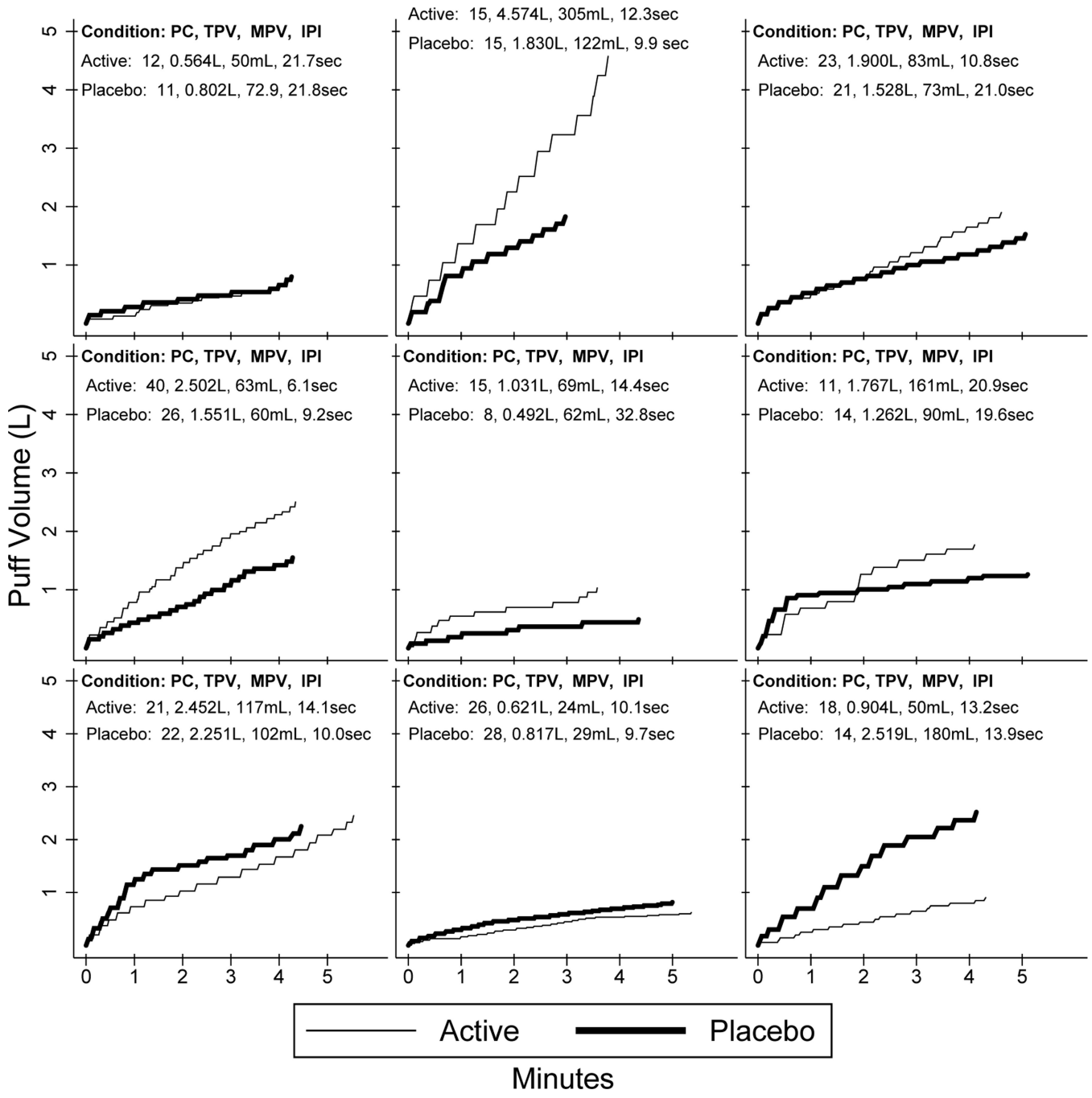

Figure 1.

Per-Participant Cumulative Puff Volume of the Tobacco Cigarette, Active vs. Placebo Cannabis. Each panel represents each participant's cumulative puff volume of the tobacco cigarette over the 5minute *ad libitum* period. PC=puff count, TPV=total puff volume, MPV=mean puff volume, IPI=inter-puff-interval.

Table 1.

Participant Characteristics (*N*=9).

Characteristic	Frequency or Mean (Standard Deviation)
Sex (Male)	5/9
Age (years)	35.2 (8.5)
Race	
White Only	1/9
African American Only	6/9
Other/More than One Race	2/9
Ethnicity (Frequency Non-Hispanic)	9/9
Education (Frequency High School Diploma/GED or higher)	9/9
Employment (Frequency Full-Time)	3/9
Tobacco Cigarette Smoking (Frequency Menthol)	7/9
Tobacco Cigarettes per Day	14.1 (8.2)
Fagerström Test of Nicotine Dependence Score	4.9 (2.8)
Cannabis Use	
Days of Use [a]	29.9 (0.3)
Grams of Cannabis per Day [a]	2.2 (1.2)
Primary mode of consumption (Frequency Smoke)	9/9
Co-administer cannabis and tobacco (e.g., blunt; spliff) (Frequency)[a]	9/9

Note.

[a]Within past 30 days.

Table 2.

Intensity of Tobacco Cigarette Smoking, Active vs. Placebo Cannabis (*N*=9).

Outcome	Active Cannabis M (SD)	Placebo Cannabis M (SD)	Difference M (SD)	Wilcoxon Signed-Rank Test p-value
Total puff volume (mL)	1817 (1267)	1450 (682)	367 (384)	0.21
Total puff duration (sec)	34.3 (12.0)	36.3 (15.2)	−2.0 (3.3)	0.86
Mean puff velocity (mL/sec)	50.3 (23.7)	40.4 (8.2)	10.4 (6.5)	0.11
Mean puff volume (mL)	102.3 (86.2)	87.8 (43.7)	14.4 (27.5)	0.44
Number of puffs	20.1 (9.0)	17.7 (6.9)	2.4 (1.8)	0.29
Mean inter-puff interval	13.7 (5.0)	16.4 (8.0)	−2.7 (2.4)	0.59
Time to first puff (sec)	17.6 (10.0)	27.7 (58.8)	−10.1 (19.3)	0.14
Boost in exhaled carbon monoxide (ppm)[a]	5.1 (5.3)	5.1 (3.3)	0.0 (4.0)	0.91
Boost in plasma nicotine (ng/mL)[b]	5.07 (2.73)	6.26 (1.71)	−1.19 (3.77)	0.35
Weight of tobacco cigarette smoked (g)	0.55 (0.05)	0.56 (0.08)	0.00 (0.07)	0.86
Change in heart rate (BPM) after cannabis smoking	10.4	0.9	9.6	0.998
Change in heart rate (BPM) after tobacco cigarette smoking[a]	1.8	3.3	−1.5	0.64
Change in MAP (mmHg) after cannabis smoking	1.8	3.3	−1.5	0.68
Change in MAP (mmHg) after tobacco smoking[a]	4.5	0.7	3.7	0.26

Note. There were no significant differences between active and placebo cannabis conditions. BPM=beats per minute; M=mean; MAP=mean arterial pressure (1/3*Systolic + 2/3*Dyastolic), mmHg=millimeters of mercury, SD=standard deviation.

[a]Change in heart rate, MAP, and carbon monoxide boost was calculated as the difference between pre- and post-tobacco cigarette smoking levels..

[b]Boost was calculated as the difference between pre- and post-tobacco cigarette smoking levels. Nicotine boost was based on 5 participants that had plasma nicotine before and after smoking the tobacco cigarette for both active and placebo cannabis.