Study Title: Effects of Dietary Conditions on Drug Response

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Tobacco use remains the leading preventable cause of death in the United States, yet relatively little is known about what variables contribute to differences in subjective response to nicotine, the primary reinforcer in tobacco products. Caffeine is a commonly consumed drug that may contribute to differences in response to nicotine. Our laboratory has demonstrated that relative to placebo, chronic exposure to moderate doses of caffeine increased the reinforcing effects of intravenous nicotine among cigarette smokers. It is presently unknown whether chronic caffeine would similarly predispose individuals who are non-smokers to the reinforcing effects of nicotine. Understanding the reinforcing effects of nicotine among non-smokers is a pressing concern because non-smokers may be drawn to new non-combustible tobacco products such as electronic cigarettes which may be perceived as less harmful than smoking. It is particularly important to examine the effects of chronic caffeine on nicotine reinforcement because caffeine use is common and a potentially modifiable risk factor for nicotine dependence. Therefore, we propose to examine the effects of chronic caffeine on the subjective and reinforcing effects of nicotine in non-smokers under double blind laboratory conditions. The study will administer oral nicotine in capsules during each of two conditions compared within subjects: a caffeine maintenance condition and a placebo maintenance condition, with the order of the conditions counterbalanced across participants. During the caffeine maintenance condition, participants will ingest 200 mg of caffeine orally in capsules three times daily. After being exposed to the caffeine maintenance condition for at least one week, participants will continue daily caffeine administration and will also be exposed to experimental test sessions in a counterbalanced order across approximately 3-4 weeks (one session each for placebo, 1, 2, 3 and 4 mg/70 kg nicotine and 300 mg caffeine; administered orally in capsules). During the placebo maintenance condition, participants will ingest placebo capsules orally three times daily and will be exposed to experimental test sessions as they did during caffeine maintenance. An interim period of one week will separate maintenance conditions, during which participants will continue to ingest study capsules three times daily. Caffeine will be gradually tapered during the one-week interim period following caffeine maintenance to reduce the potential for caffeine withdrawal. After both maintenance conditions, participants will be exposed to one multiple-choice reinforcement session which will reinforce a randomly selected drug vs. money choice made by the participant during prior sessions as a surrogate measure of drug reinforcement. We hypothesize that participants will report greater positive subjective and reinforcing effects of nicotine during the caffeine maintenance condition relative to the placebo maintenance condition. These findings may have important implications for the prevention of tobacco dependence and may lead to recommendations to modify dietary caffeine to reduce susceptibility to nicotine reinforcement.

2. Objectives (include all primary and secondary objectives)

Primary objective: Determine whether chronic exposure to moderate doses of caffeine increases the positive subjective and reinforcing effects of nicotine among healthy volunteers.

Secondary objective: Characterize and compare individuals who show positive subjective and reinforcing effects of nicotine on subject demographics (e.g., age, sex), drug use history, and personality factors relative to individuals who do not demonstrate positive subjective and reinforcing effects of nicotine.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

In spite of tremendous gains in knowledge over the past 50 years, tobacco use remains the leading preventable cause of death in the United States (US DHHS, 2014). In order to prevent tobacco dependence and its long-term detrimental health consequences, it is important to examine factors that may contribute to the initiation of cigarette smoking, including the positive subjective effects of nicotine. Nicotine is a psychoactive drug contained in tobacco products and is considered the primary driver of tobacco dependence (US DHHS, 2014), but individuals who are not smokers vary in their subjective response to nicotine (e.g., Duke et al., 2015). The varied response to nicotine is consistent with the observation that only a subset of individuals who try tobacco products go on to regular smoking (Birge et al., 2018). If individual or environmental variables that enhance the positive subjective response to nicotine can be identified, this information can be used to improve public health recommendations to prevent tobacco dependence. Specifically, this study will focus on the potential effects of chronic caffeine on subjective and reinforcing response to nicotine.

Caffeine is of interest because it is a widely consumed psychoactive drug, and a potentially modifiable risk factor for tobacco dependence. Our laboratory has focused on the potential role of caffeine in vulnerability to drug reinforcement across several ongoing and prior research studies (e.g., IRB00165287; Sigmon & Griffiths, 2011; Jones & Griffiths, 2003; Johnson et al., 2010). For example, research from our laboratory showed that chronic caffeine can enhance the positive subjective effects of nicotine among cigarette smokers (Jones & Griffiths, 2003). Specifically, we demonstrated that relative to placebo, chronic administration of a moderate dose of caffeine (200 mg/70 kg oral three times daily) for ≥12 days significantly increased subjective ratings of drug effect and stimulation, and significantly increased willingness to pay for nicotine after intravenous nicotine (2.0 mg/70 kg) among cigarette smokers. Furthermore, chronic caffeine significantly decreased subjective ratings of bad drug effects during a lower dose of nicotine (1.0 mg/70 kg i.v.), and significantly increased identification of the lower dose as a stimulant. It is not currently known, however, whether chronic caffeine would similarly predispose individuals who are not cigarette smokers to the positive subjective and reinforcing effects of nicotine.

Examining nicotine reinforcement among non-smokers is particularly important given that non-smokers would be able to modify their behavior, including their dietary caffeine consumption, to prevent vulnerability to the effects of nicotine and potentially prevent a transition from preliminary exposure to regular smoking. Further, there is growing concern about the appeal of non-combustible tobacco products, such as electronic cigarettes, to people who would not choose to use combustible tobacco products. This may be due in part to the perception that e-cigarettes are safer than smoking (Bhalerao et al., 2019; Sears et al., 2017; Walley et al., 2019). Therefore, studying nicotine reinforcement among non-smokers is timely and may inform vulnerability to both smoking and novel methods of nicotine self-administration. Our laboratory has experience examining the reinforcing

effects of oral nicotine among non-smokers under rigorous double-blind conditions (i.e., IRB00165287; Duke et al., 2015). Thus, in the present study, we propose to conduct a within-subjects comparison of subjective and reinforcing effects of nicotine following chronic administration of a moderate daily dose of caffeine relative to a placebo maintenance condition. We hypothesize that healthy individuals will report greater positive subjective and reinforcing effects of oral nicotine during chronic caffeine administration relative to the placebo maintenance condition.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures (distinguish research procedures from those that are part of routine care).

Overview. This double-blind, placebo-controlled study will be conducted over a period of approximately 10-12 weeks. Participation may be longer depending on scheduling considerations. The study will assess participants' subjective ratings of the effects of nicotine (one session each for placebo, 1, 2, 3 and 4 mg/70 kg nicotine) and caffeine (one session of 300 mg caffeine) across two conditions compared within-subjects: a caffeine maintenance condition (4-5 weeks) and a placebo maintenance condition (4-5 weeks). The order in which caffeine and placebo maintenance conditions are administered will be counterbalanced across participants. Figure 1 shows a study overview.

Procedural Changes Due to COVID-19. As an effort to protect study participants and study staff, participants will routinely answer questions to determine their risk of exposure and infection with the novel coronavirus known as COVID-19. As described in "Measures" section below, the exact nature of the risk assessment questions may change due to shifting Johns Hopkins institutional guidelines. Some of these screenings will occur remotely via phone or online survey (using HIPAA-compliant Qualtrics surveys), and some will occur during in-person visits. Johns Hopkins Participants who meet the threshold of risk criteria for COVID-19 according the screening questionnaire will be instructed not to come to the laboratory for the in-person visit and are instructed to contact their primary care provider or the Johns Hopkins COVID-19 Response Team. If a person presents with symptoms or provides responses to screening questions above the risk threshold during an in-person visit, we have established a standard operating procedure that states if there is a suspected case of COVID-19, the participant is to be isolated in the session room. Study staff will immediately contact members of the Behavioral Pharmacology Research Unit medical team to notify them that there is a participant in the building with a possible case of the COVID-19 in order to determine safe next steps in order to minimize contact with the participant and provide them with the appropriate recommendations for care.

In line with university guidelines concerning COVID-19, we require all participants to wear a mask when visiting our research unit. Surgical grade or N-95 masks are acceptable. If participants arrive without an appropriate mask, they may not be able to complete their scheduled research session if the study team does not have adequate supply of masks to provide them with one. Study staff will also wear masks and maintain 6 feet of distance whenever possible. Participants may need to remove their mask briefly for parts of the sessions, such as taking a breathalyzer test, providing saliva samples, or swallowing study capsules. The total time within 6 feet should be minimal (i.e., estimated at less than 5 minutes). For example, research assistants may pass briefly within six feet of the participant while leading them through locked doors to the private laboratory space. Research assistants will need to take a blood pressure measurement to determine eligibility, and fitting the cuff will require brief interactions within six feet. Research assistants will also need to do a visual mouth check of the participant to ensure the participant has swallowed the study capsules. This involves no contact but the research assistant may need to be within six feet for a few seconds in order to see under the participant's tongue. Additional personal protective equipment will be used by staff if distancing cannot be maintained during study procedures (gloves, face shields, etc.). The research assistant should be able to conduct all structured interviews/ study measures from six feet away. For example, study staff will set up the

computer/paper measure, and then invite the participant to complete the measure after stepping six feet away. Some study visits may be canceled or rescheduled if participants or study staff report symptoms or risk of COVID-19 or test positive for COVID-19.

Much of these study procedures are already well-suited to minimize risk to research participants and study team members. For example, most study visits are expected to last less than 30 minutes and the research assistant does not need to be within six feet of the participant for any extended period of time. We also previously incorporated JHMI-credentialed Qualtrics surveys that are sent to the participants via email/text message at 1, 2, 3, and 4 hours after administration of the study capsules so that participant in-person burden is limited. Although most brief sessions (typically less than 30 min) are still necessary due to the need to ingest study capsules and collect biospecimens (e.g., urine to check for pregnancy in females), we will allow some flexibility with study sessions that can be conducted remotely via phone or video visits using HIPAA-compliant software (e.g., HIPAA compliant JHMI Zoom instance), such as the last session to pick up final study payment and complete the end-of-study survey. All or part of some visits may occur via telephone or video visits where determined to be appropriate, and where determined by the investigator not to increase participant risks.

Typically only one research staff (a research assistant) will interact with the participant at each visit. It is possible that a member of the BPRU medical staff will join if a medical concern arises or an Investigator if a protocol concern arises, but this will not be routine. If additional study staff (e.g., an investigator) would like to speak with the participant (e.g., to answer participant questions about study procedures), the research assistant may set up a brief video meeting using HIPAA-compliant software (e.g., HIPAA compliant JHMI Zoom instance) on the study computer so that the investigator can speak with the participant without in-person interaction.

Finally, we have moved several of the in-person screening surveys to be administered remotely via JHMI-credentialed Qualtrics links as part of the preliminary screening in order to reduce the amount of time participants are in the laboratory for the in-person screening. We anticipate that the duration of in-person screening may be able to be reduced 30-50%. It is still necessary to have in person screening due to the need for physical evaluation (e.g., blood pressure for eligibility; height/weight for drug dosing; urine drug screen) and because some of the mental health screenings may identify mental health conditions for which clinical action is immediately necessary.

The Behavioral Pharmacology Research Unit has developed a thorough plan to implement physical distancing measures, cleaning protocols, and participant interaction protocols in order to minimize the risk of COVID-19 infection for staff and participants. Adequate personal protective equipment is available to the research unit, and staff are required to undergo PPE training according to School of Medicine guidelines. Research assistants and other study staff will continue to telework where possible to minimize interaction.

Screening. After initial pre-screening conducted via phone, online self-screener or online preliminary screening, individuals will come to the Behavioral Pharmacology Research Unit (BPRU) at the Johns Hopkins University School of Medicine on the Bayview Medical Campus to complete a battery of questionnaires assessing demographic variables and drug use history. They will receive a brief medical screening that will include assessment of blood pressure, urine toxicology, breathalyzer test, pregnancy testing (female volunteers only), medical history, and psychiatric and personality questionnaires. Participants will also provide a saliva sample. In the present study, selected saliva samples will be analyzed for caffeine content. In the written informed consent form, we will also ask participants for permission to store their biospecimens for future research, as it is possible but not certain that future research may include genetic testing (e.g., for markers related to addiction vulnerability) on saliva samples that are not used for caffeine testing.

Dietary restrictions. In order to reduce possible caffeine withdrawal effects on the assessment of the reinforcing effects of caffeine, enrolled subjects will be required to remain caffeine abstinent throughout the study. As in some of our previous studies (e.g., IRB00165287; Sigmon & Griffiths,

Figure 1. Illustrative sequence of study conditions with the Caffeine Maintenance condition first. Caffeine and Placebo Maintenance conditions will be counterbalance across participants.

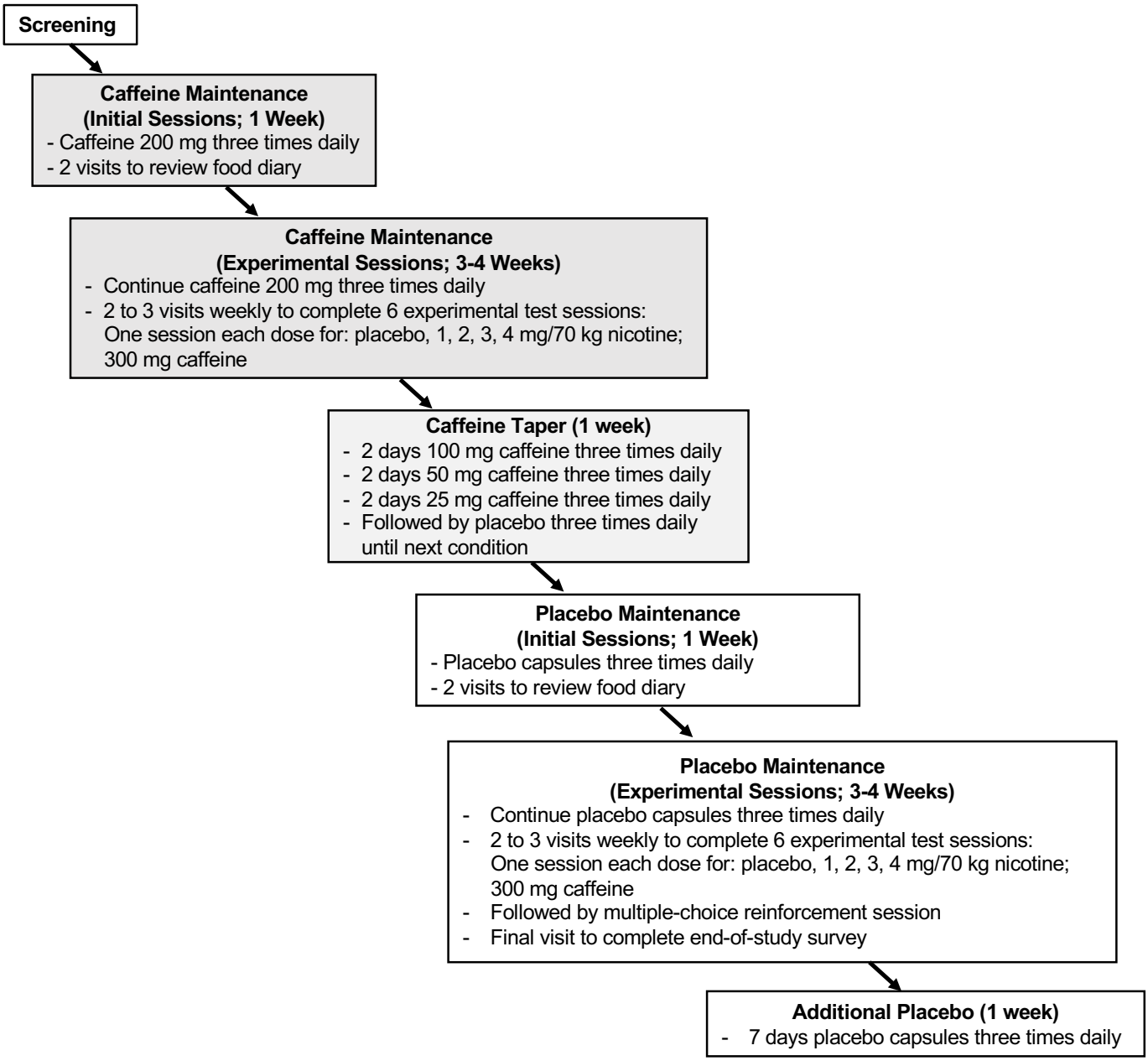

Fig 1. Illustrative participation timeline including screening, caffeine maintenance, and placebo maintenance. All doses of drug and placebo are administered orally in capsules. The order of caffeine maintenance and placebo maintenance will be counterbalanced across participants and the multiple-choice session and end-of-study survey visit will always occur after the second maintenance condition. Total participation will consist of 19 visits including 1 screening visit, 4 food diary visits, 12 experimental sessions, 1 multiple-choice reinforcement session, and 1 final visit to complete the end-of-study survey. We estimate participation will occur across 10-12 weeks. Participation may be longer depending on scheduling considerations.

2011), to control for expectancy effects, participants will not be informed that caffeine is a primary focus of the study and will be asked to eliminate caffeine as well as various other caffeine-free foods and beverages from their diet. Including caffeine-free distractor items on the list of restricted foods and beverages will assist in maintaining participant blindness to the exact drugs under study. Specifically, participants will be asked to eliminate: coffee drinks of any kind (including decaffeinated), drinks/food/gum containing aspartame, energy drinks and supplements, hot chocolate, instant drink mixes, red wine, sodas and carbonated drinks of any type, tea (including decaffeinated), chocolate, coconuts, grapefruit and grapefruit juice, mussels, oysters, poppy seeds, and all prescription and over-the-counter medications. Any participant taking appropriate medical prescriptions that are contraindicated to the study medication will be excluded from participation. Prescription contraceptives will not be exclusionary. Participants will not be asked to forego taking appropriately prescribed medication in order to participate in this study. Caffeine abstinence will be verified by selecting regularly provided saliva samples for analysis. Data from non-compliant subjects may be excluded from analysis. Participants will be told that samples will be analyzed for compounds contained in the restricted foods. Analysis of saliva samples from past research indicates that the majority of subjects who are informed of the dietary restrictions and agree to enroll in the studies are compliant.

Caffeine maintenance. During the caffeine maintenance condition, participants will ingest 200 mg of caffeine orally in capsules three times daily. Study capsules will be prepared by the Pharmacy and Investigational Drug Services (IDS) staff at the Behavioral Pharmacology Research Unit. Capsules will be opaque size 0 capsules.

Initial visits during caffeine maintenance. On their first visit to the laboratory following screening, participants will review food and beverage restrictions, provide a saliva sample, and receive a food diary. The food diary is used to monitor food and beverage consumption during the first week of each condition to assist in adhering to the dietary restrictions. During this visit, participants will also receive study capsules in blister packs and ingest their first dose with water. Participants will receive instructions to take a single dose three times per day at the same times every day. The study team will send reminders to take the study medication at the appropriate time via email or text message or via medication timers supplied to the participant during the study. The times at which participants are instructed to take the study medication will be approximately 2 hours before and 3 and 8 hours after they will attend the laboratory for experimental sessions (see *Experimental Sessions* below). For example, a participant planning to attend experimental sessions at 9 AM would take a study capsule containing 200 mg of caffeine (absolute dose) every day at 0700 h, 1200 h, and 1700 h. This caffeine maintenance schedule is roughly equivalent to 12 oz of brewed coffee three times daily (Sweeney et al., 2018). Given this dosing schedule, experimental sessions will be limited to the morning hours to minimize the sleep disruptive effects of caffeine. Participants will attend a second initial session during the first week of the caffeine maintenance during which they will provide a saliva sample and review their food and beverage diary with study staff.

Experimental sessions during caffeine maintenance. After receiving caffeine maintenance for at least one week, participants will continue daily caffeine administration and will also be exposed to experimental test sessions across approximately 3-4 weeks (one session each for placebo, 1, 2, 3 and 4 mg/70 kg nicotine and 300 mg caffeine). The purpose of the nicotine sessions is to assess the subjective and reinforcing effects of nicotine, whereas the purpose of the caffeine session is as a manipulation check to test tolerance to caffeine during caffeine maintenance relative to placebo maintenance. The order in which the different doses for experimental sessions are received will be counterbalanced across participants. Subjects will report to the laboratory approximately 2-3 times per week, depending on schedule considerations. Sessions will be separated by at least 48 hours (e.g., Monday, Wednesday, Friday sessions). At each visit, participants will provide a saliva sample, complete pre-drug subjective questionnaires, and orally ingest study capsules with water under double-blind conditions. After leaving the laboratory, outcome measures will be assessed at 1, 2, 3, and 4 hours post-capsule administration.

Measures will include subjective ratings of drug effects (e.g., energetic, drowsy/sleepy, elated, jittery/shaky) and surrogate measures of reinforcement such as liking, take again, and the multiple-choice reinforcement procedure, which we have used in previous research. These questionnaires will be completed online using Qualtrics survey technology, including via the Qualtrics App while in the laboratory, or using conventional paper forms. When participants are completing their surveys online, a survey link will be sent to them via email or text message. Paper forms of surveys will be provided as a back-up in the event of technical issues with administering surveys via Qualtrics, in the event of difficulties with participant compliance for online assessments, or in the event the participant does not have a smart phone or computer access. The multiple-choice procedure will assess participant preference for "today's drug" over various amounts of money ranging from -$30 (i.e., forego $30 rather than receive "today's drug") to $30 (i.e., receive $30 rather than receive "today's drug").

Caffeine taper following caffeine maintenance. Caffeine will be gradually tapered after the last experimental session during caffeine maintenance by providing decreasing amounts of caffeine in the thrice daily capsules over six days in order reduce the potential for caffeine withdrawal. Approximately one week will separate caffeine maintenance and placebo maintenance conditions in order to allow for the caffeine taper (or one week of placebo capsules if the placebo maintenance condition occurs first).

Placebo maintenance. The placebo maintenance condition will be identical to the caffeine maintenance condition, with the exception that the thrice daily capsules will contain placebo (microcrystalline cellulose) rather than containing caffeine. The initial sessions during placebo maintenance during which the food diary is provided and reviewed, as well as the experimental test sessions during placebo maintenance will be conducted exactly as they were during the caffeine maintenance condition. To maintain study team and participant blindness, participants will receive at least a week of continued thrice daily placebo administration following the placebo maintenance condition in order to parallel the timeframe of the caffeine taper period following the caffeine maintenance condition.

Multiple-choice reinforcement session. As has been done in previous studies (e.g., Griffiths et al., 1993; Zacny & Gutierrez, 2009), one of the participant's choices during the multiple-choice procedure collected after experimental test sessions during both maintenance conditions will be randomly selected for reinforcement during the final experimental session. If the selected choice was one of the study drugs, then the selected study drug will be administered to the participant under the same conditions as before. If money was selected, then the amount of money chosen by the participant will be added or subtracted from the session payment. In order to make the procedures of choosing drugs or money equivalent, participants who selected money will ingest placebo capsules. Following the multiple-choice reinforcement session, all participants are required to complete subjective effects questionnaires at 1, 2, 3, and 4 hours after capsule administration.

Final visit. Participants will return to the laboratory to receive their bonus payment for study completion so that we have the opportunity to review their subjective drug effects from the multiple-choice reinforcement session and discuss with them if necessary. They will also complete an end-of-study questionnaire which will assess their beliefs about what conditions they may have experienced during the study and any perceived differences between conditions.

Measures

Screening/Descriptive Measures: The following measures will be administered at study screening, the online self-screener or online preliminary screening in order to establish patient eligibility and characterize the sample. Basic demographic information and personality measures will be examined as potential covariates of individual differences in drug response following drug administration. The measures described will be administered via computer or using paper or pencil, and

as such formatting or question wording may change slightly to adjust for computer vs. paper administrations.

COVID-19 Questionnaire. We will administer a survey to assess any symptoms of COVID-19 that participants may be experiencing prior to each session. We will also be asking if participants have had any contact with a person they know has tested positively for COVID-19, or if they live or work in a high-risk facility (e.g., a homeless shelter). These screening questions may be conducted remotely via phone or online survey prior to sessions or in-person. The exact nature of the questions may change due to changing Johns Hopkins institutional guidelines. The current version of the screening questions has been incorporated into the revised telephone screening document uploaded to the eIRB website. Participants who meet the threshold of risk criteria for COVID-19 according the screening questionnaire will be instructed not to come to the laboratory for the in-person visit and are instructed to contact their primary care provider or the Johns Hopkins COVID-19 Response Team. If a person presents with symptoms or provides responses to screening questions above the risk threshold during an in-person visit, we have established a standard operating procedure that states if there is a suspected case of COVID-19, the participant is to be isolated in the session room. Study staff will immediately contact members of the Behavioral Pharmacology Research Unit medical team to notify them that there is a participant in the building with a possible case of the COVID-19 in order to determine safe next steps in order to minimize contact with the participant and provide them with the appropriate recommendations for care.

Medical History and Demographic Questionnaire. We will administer a standardized medical history survey to assess demographic information (e.g., age, sex, marital status, education) and relevant medical history (e.g., medical and psychological conditions, hospitalizations, past drug research participation, prescriptions, allergies, contraception) to probe for contraindications to drug administration. We will also collect the following biometrics data: blood pressure, height, weight, balance, heart rate, and respiration.

Psychiatric Assessment. The MINI International Neuropsychiatric Interview (MINI DSM-5, Lecrubier et al., 1997) will be used to exclude individuals with a current indication of serious psychiatric condition (e.g. schizophrenia, major depression). Current and past psychiatric diagnoses will also be assessed in the medical history and demographic questionnaire. The Beck Depression Inventory II (BDI-II; Beck, Steer, & Brown, 1996) will be used as a secondary assessment of depressive symptoms at screening and to describe the final sample. Participants who demonstrate significant psychiatric distress on either the BDI-II or the MINI DSM-5 will be provided with a list of emergency and treatment resources (e.g., 24-hr crisis response hotlines; local mental health referrals). A member of the study team will discuss the assessment responses with the participant and will encourage the participant to seek treatment, but will note that the study assessments are not considered a formal diagnosis. In the event of severe distress (e.g., suicidal ideation with intent to act, with or without a specific plan), one of the co-investigators or a member of the medical staff will discuss appropriate options for treatment referral, including escort to the emergency room if necessary. The MINI DSM-5 Alcohol Use Disorder and other Substance Use Disorder criteria, combined with the results of urine toxicology and the medical history questionnaire, will be used to exclude participants with evidence of a current substance use disorder (other than caffeine) that may interfere with study participation or increase the risk of study participation. Note: Given the low threshold for meeting DSM-5 criteria for *mild* Alcohol or Substance Use Disorder (i.e., 2-3 symptoms), individuals with a *mild* Alcohol or Substance Use Disorder designation may be included in the study if their alcohol or substance use is judged by the study investigators and medical team to be unlikely to interfere with study participation and unlikely to increase the risk of study participation. Individuals meeting criteria for *Moderate* (4-5 symptoms) or *Severe* Alcohol or Substance Use Disorder according to MINI for DSM-5 will always be excluded.

Additional Drug Use/Prescription History. Internally developed, standardized measures of drug use history including a Prescription and Over-the-Counter Drug Questionnaire and Drug Use History Matrix will determine eligibility based on number of lifetime nonmedical uses (uses without a prescription) and past prescriptions of the administered drugs. Additionally, these questionnaires will give insight into the participant's current drug use and means of administration. Drug use history is assessed across a comprehensive list of drug classes which includes: alcohol, nicotine, cannabis, synthetic marijuana, caffeine, ephedrine, sedatives/hypnotics, opioids, muscle relaxants, GHB, nitrous oxide, inhalants, MDMA, and dissociative anesthetic hallucinogens.

Dietary Questionnaire. We will administer an internally developed, standardized questionnaire to assess typical consumption of the restricted foods and beverages (e.g., coffee, energy drinks, chocolate) to facilitate discussion of the restricted foods and beverages with the participant so they may adhere to the protocol by eliminating the restricted foods. The Dietary Questionnaire is also used to calculate typical caffeine consumption in order to determine eligibility and to describe the sample.

Delay Discounting. Delay discounting describes the loss in subjective value of an outcome when there is a delay to that outcome. Individuals who use drugs tend to discount delayed rewards at a higher rate relative to those who do not use drugs, that is, individuals who use drugs are more likely to choose a smaller sooner reward over a larger delayed reward relative to nonusers. The present study will determine delay discounting of monetary rewards using a 5-trial adjusting delay task (Koffarnus & Bickel, 2014) at screening as a potential covariate of individual differences in drug response.

Personality Measures. Different dimensions of personality (e.g., greater sensation seeking, greater impulsivity) have been linked to patterns of substance use and substance use disorders (e.g., Stanford et al., 2009; Kotov et al., 2010). We will assess different aspects of personality in order to describe the sample and potential covariates of individual differences in drug response. Specifically, we will administer the Big Five Inventory and two measures assessing Sensation Seeking/Impulsiveness. *Big Five Inventory.* The Big Five Inventory is a 44-item self-report instrument based on the Big Five Factors of personality. The Big Five Factors of personality dimensions include: extraversion versus introversion, agreeableness versus antagonism, conscientiousness versus lack of direction, neuroticism versus emotional stability, openness versus closedness to experience (Goldberg, 1992; Goldberg, 1993; John & Srivastava, 1999). *Sensation Seeking/Impulsiveness.* Sensation seeking is a personality dimension that assesses the need for new, intense and varied experiences and the willingness to take risks for such experiences which has been shown to be a dispositional risk factor for drug use. This study will assess sensation seeking and impulsiveness using two personality assessment measures: a) the Brief Sensation Seeking Scale, an 8-item questionnaire assessing dimensions of experience seeking, boredom susceptibility, thrill and adventure seeking, and disinhibition (Hoyle et al., 2002) and b) the Barratt Impulsiveness Scale (BIS-11; Patton, Stanford, & Barret, 1995), a 30-item instrument created to assess across subscales of attention, motor, self-control, cognitive complexity, perseverance and cognitive instability.

Family Tree Questionnaire (FTQ). The Family Tree Questionnaire (FTQ) for Assessing Family History of Alcohol Problems (Mann, Sobell, & Sobell, 1985) is an instrument that allows participants to indicate each of their blood relative's alcohol use and categorize it according to their knowledge of their family members' problematic use (e.g., never drank, social drinker, possible problem drinker, definite problem drinker, don't know/don't remember). We have modified this questionnaire to include two additional modules allowing participants to categorize family members' known history of tobacco use and other drug use. It is possible that participants who show greater positive subjective drug response may have a greater number of relatives with problematic alcohol or drug use.

Experimental Session Measures: The following measures will be administered to participants before capsule administration at experimental test sessions (e.g., pre-drug subjective effects questionnaire) or at 1, 2, 3, or 4 hours after capsule administration. These questionnaires will be completed online using Qualtrics survey technology or using conventional paper forms. When

participants are completing their surveys online, a survey link will be sent to them via email or text message. Paper forms of surveys will be provided as a back-up in the event of technical issues with administering surveys via Qualtrics, in the event of difficulties with participant compliance for online assessments, or in the event the participant does not have a smart phone or computer access. Formatting or question wording may change slightly to adjust for computer vs. paper administrations.

COVID-19 Questionnaire. The same COVID-19 Questionnaire procedure (described above) will be administered prior to every in-person session to ensure safety for participants and research staff.

Subjective Effects Questionnaire. The Subjective Effects Questionnaire (SEQ) is an internally developed measure allowing participants to rate how they feel (e.g., energetic, drowsy/sleepy, elated, jittery/shaky) prior to ingesting the study drug and at 1, 2, 3, and 4 hours after capsule administration. Items on the subjective effects questionnaire were developed to detect effects of caffeine, nicotine, and stimulant drugs and we have successfully used the items in past research to detect significant drug dose effects (Duke et al., 2015; Sigmon & Griffiths, 2011).

Delay Discounting. The same brief delay discounting procedure (described above) may be administered during experimental test sessions at a single time point per session (e.g., 3 hrs after capsule administration) to probe for acute drug effects on decision-making.

Multiple-Choice Procedure. In the multiple-choice procedure, the subjective reinforcing value of the study drug dose is assessed by asking participants to indicate whether they would prefer to repeat "today's drug" or take placebo capsules and receive or lose money at the end of the study. The multiple-choice questionnaire asks participants make repeated choices between "today's drug" over various amounts of money ranging from -$30 (i.e., forego $30 rather than receive "today's drug") to $30 (i.e., receive $30 rather than receive "today's drug"). The multiple-choice questionnaire will only be administered at a single time point per session (e.g., 4 hrs after capsule administration). As has been done in previous studies (e.g., Griffiths et al., 1993; Zacny & Gutierrez, 2009), one of the participant's choices during the multiple-choice procedure will be randomly selected for reinforcement during a multiple-choice reinforcement session. If the selected choice was one of the study drugs, capsules containing selected study drug will be administered to the participant during the multiple-choice reinforcement session using the same procedures as in other experimental test sessions. If money was selected, then the amount of money chosen by the participant will be added or subtracted from the session payment and the participant will receive placebo capsules. Placebo capsules are administered if the choice was for money in order to make the procedures involved in choosing drug or money equivalent. This procedure has been successfully utilized in past research to determine and compare the subjective reinforcing value of administered drugs (Garrett & Griffiths, 1998; Griffiths et al., 1996; Griffiths et al., 1993). We hypothesize that chronic caffeine may increase the subjective monetary value of nicotine.

End-of-study survey: The end-of-study survey will assess what kinds of drug and/or placebo participants believe they may have received during their study participation. This survey will also assess their confidence in their guesses regarding the kinds of drugs and/or placebo received, and will provide open response so they may provide any information they think we may be interested to know about their experiences during the different maintenance conditions and experimental test sessions.

b. Study duration and number of study visits required of research participants.

The duration of participation will be approximately 10-12 weeks, but may be longer in some instances due to participant and laboratory scheduling needs. Participants will be required to attend an in-person screening session, 4 brief sessions to receive instructions and go over the food diary (2 during caffeine maintenance and 2 during placebo maintenance), 12 brief experimental test sessions (6 during caffeine maintenance and 6 during placebo maintenance) and 1 multiple choice reinforcement session following the second maintenance condition. Participants will return to the laboratory for a final session

to complete an end-of-study survey and receive their bonus payment for study completion so that we have the opportunity to review their subjective drug effects from the most recent multiple-choice reinforcement session and discuss with them if necessary. Screening sessions will be approximately 2.5 hours in duration. The first session after screening will be approximately 45 minutes. All other sessions will usually last less than 30 minutes.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

As part of instructions during the informed consent process, volunteers will be given a list of drugs they may receive rather than informing them only of the specific drugs being administered. The list of potential substances provided to the volunteers during written informed consent will include the substances that will be administered (i.e., caffeine and nicotine), but will also contain other mood-altering medications including sedatives, stimulants, and antihistamines that will never be administered. The purpose of this is to increase the degree to which participants are blind to the specific drug being studied and thereby reduce expectancy effects. This is consistent with previous practices in other research studies (e.g., IRB00165287; Sigmon & Griffiths, 2011; Duke et al., 2015). Blindness to the specific study drugs administered will be maintained after the study to present the possible confounding of results that could occur if a past participant informed a current participant of the specific drugs administered. Further, blindness to the specific drugs administered also serves to reduce the likelihood that participants will seek out administered substances, even though the risk of participants seeking out substances after receiving them in a medically monitored setting is judged to be low. The informed consent document will list all potential side effects of the administered medications so that participants may make an informed decision regarding their participation despite not knowing the specific drugs to be administered. The informed consent document will also state that participants will not be debriefed either during or after the study as to which drugs they received. Researchers will be blind to the drug conditions on any given session because a pharmacy member with no participant interaction will assign the randomized dose sequence and prepare the study drugs. Medical staff will be available to address any adverse events or break the medication blind if necessary.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

N/A

e. Justification for inclusion of a placebo or non-treatment group.

A placebo maintenance condition, as well as a placebo experimental test session have been included as a comparison for determining drug-related effects.

f. Definition of treatment failure or participant removal criteria.

Participants may voluntarily withdraw from the study at any time. They may also be removed if they have a significant adverse effect that we judge likely to be a reaction to a study drug, if they are noncompliant with study procedures or restrictions, if they become pregnant, or if new information becomes available that suggests continued study participation would put them at increased risk of adverse events.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

The proposed study is not a treatment study and participants are healthy volunteers. Neither study participation nor its termination will affect the ability of the participants to seek treatment services. Participants may withdraw from the study at any time without loss of benefits.

5. Inclusion/Exclusion Criteria

Inclusion Criteria

1. Participant age is 18-45 years.
2. Participant regularly consumes caffeine (e.g., at least once weekly or at least approximately 3 times per month).
3. Participant has less than 100 lifetime exposures to tobacco or nicotine-containing products (i.e., accepted definition of a never smoker according to the U.S. Centers for Disease Control).
4. Participant has no nicotine use in the last year.
5. The subject must be in good health as determined by medical history and vital signs.
6. Participant Body Mass Index (BMI) must be between 18.5 and 34.9 (BMI<18.5 = Underweight; BMI>34.9 = moderate-to-high-risk Obese).
7. The subject is fluent in English (speaking, writing, and reading) and is capable of understanding and complying with the protocol.
8. Females: Females of childbearing potential must agree to use appropriate birth control (barrier methods, hormonal contraceptives, and/or intrauterine devices) during the entire duration of the study. Females who are not of childbearing potential must be postmenopausal for 2 years or have a history of hysterectomy and/or oophorectomy.

Exclusion Criteria

1. Subjects with known hypersensitivity or medical contraindication to the study drugs.
2. Subjects with a significant current neurological, hepatic, renal, endocrine, cardiovascular, gastrointestinal, pulmonary or metabolic disease for which administration of the study drugs would be contraindicated.
3. Current indication of serious psychiatric condition (e.g. schizophrenia, major depression) according psychiatric assessments (BDI-II; MINI for DSM-5) or medical and psychiatric history questionnaires.
4. Evidence of current substance use disorder (other than caffeine) that may interfere with study participation or increase the risk of study participation. Evidence of substance use disorder is assessed using DSM-5 substance use disorder criteria in the MINI for DSM-5, medical and psychiatric history questionnaires, and urine toxicology. Note: Given the low threshold for meeting DSM-5 criteria for *mild* Alcohol or Substance Use Disorder (i.e., 2-3 symptoms), individuals with a *mild* Alcohol or Substance Use Disorder designation may be included in the study if their alcohol or substance use is judged by the study investigators and medical team to be unlikely to interfere with study participation and unlikely to increase the risk of study participation. Individuals meeting criteria for *Moderate* (4-5 symptoms) or *Severe* Alcohol or Substance Use Disorder according to MINI for DSM-5 will always be excluded.
5. Subjects with a diastolic blood pressure >90 mmHg or a systolic pressure of >140 mmHg.
6. Use of prescription or over-the-counter medications that could interfere with the study. Oral contraceptives and estrogen replacement therapy, vitamins, and periodic use of over-the-counter analgesic medications are acceptable.
7. Subjects unwilling or unable to comply with the protocol or scheduled appointments.
8. Subjects with any other serious disease or condition that might affect life expectancy or make it difficult to successfully manage the subjects according to the protocol.

9. Female participants: Participants who are pregnant, breastfeeding, or planning to become pregnant.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

As discussed previously, we propose to examine the effects of chronic caffeine on the subjective and reinforcing effects of nicotine in non-smokers under double blind laboratory conditions. Nicotine is of interest because it is important to identify potential markers of vulnerability to nicotine use (e.g., tobacco smoking), which remains the single leading preventable cause of death in the United States (US DHHS, 2014). This project will also extend our work examining individual differences in nicotine reinforcement in non-smokers (Duke et al., 2015). Doses and preparations of placebo, nicotine and caffeine have been selected based on prior studies from our laboratory. Specifically, prior research has demonstrated that the proposed oral doses of caffeine and nicotine are well-tolerated in healthy non-smokers, including both the acute (i.e., 300 mg) and chronic doses (i.e., 200 mg three times daily) of caffeine (e.g., IRB00165287; Duke et al., 2015; Evans & Griffiths, 1992; Jones & Griffiths, 2003). Maximum study dose of nicotine is consistent with what is currently available over-the-counter in oral form (e.g., 4 mg lozenges or gum). Nicotine doses are expressed as nicotine base and are prepared from nicotine hydrogen tartrate as in our ongoing study. Caffeine will be administered as caffeine anhydrous. Placebo is microcrystalline cellulose. The formulations of nicotine, caffeine, and placebo are the same as our ongoing laboratory study with healthy volunteers (IRB00165287). So that our results may be compared to prior work from our laboratory, doses of nicotine (1, 2, 3 and 4 mg/70 kg nicotine) are based on participant body weight whereas caffeine will be administered as absolute doses (i.e., 200 mg three times daily; 300 mg acute dose) for each participant regardless of body weight. Individual administrations of nicotine will have an upper limit of 6 mg regardless of body weight in order to reduce the likelihood of adverse effects of nicotine for participants of a higher body weight.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

Both study drugs to be administered are legally marketed in the United States. Further, the study does not involve a route of administration, dose, or patient population that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug. Previous research has demonstrated that caffeine (Sigmon & Griffiths, 2011) and nicotine (Duke et al., 2015) at the proposed doses (or indeed at higher doses) and the proposed route of administration (oral) are well-tolerated in non-drug-abusing volunteers. The maximum study dose of nicotine is consistent with what is currently available over-the-counter in oral form (e.g., 4 mg lozenges or gum). Caffeine is readily available over-the-counter in medications, supplements, beverages, and foods. The study is not intended to be reported to FDA in support of a new indication or to support any other change in labeling of the drugs. The study does not intend to support a significant change in advertising for the drugs, and the investigation is not intended to promote or commercialize the drug products. As such, the proposed investigation is exempt from IND requirements because all of the criteria for an exemption in FDA regulations § 312.2(b) are met.

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.

Primary outcome measures will be participant ratings assessed pre-drug and at 1, 2, 3, and 4 hours post capsule administration during the experimental test sessions examining placebo, nicotine, and caffeine. Primary outcomes include subjective ratings (e.g. Subjective Effects Questionnaire, and surrogate measures of reinforcement such as liking, take again, monetary value). Primary outcomes will be compared within-subjects across the caffeine maintenance condition and the placebo maintenance condition.

b. Secondary outcome variables.

Secondary outcome measures will be subject demographic characteristics, drug use history, personality factors (e.g., sensation seeking), and decision-making factors (i.e., delay discounting) that will be examined as they correlate to positive subjective effects of nicotine during the experimental test sessions.

c. Statistical plan including sample size justification and interim data analysis.

Subjective and reinforcing effects of nicotine (e.g., drug liking, take again, monetary value) will be examined as a function of nicotine dose and caffeine maintenance. Repeated measures ANOVAs will be conducted with caffeine maintenance phase (caffeine vs. placebo), drug dose (placebo and 4 doses of nicotine) and time (1, 2, 3, and 4 hours, as appropriate) as within-subjects factors. It is anticipated that there will be a significant drug dose by maintenance phase interaction such that positive subjective ratings on active nicotine sessions will be greater (and more differentiated from placebo) during the caffeine maintenance phase relative to the placebo maintenance phase. A sample size of 11 was previously sufficient to detect significant differences in nicotine reinforcement within subjects as a function of caffeine maintenance in an inpatient study (Jones & Griffiths, 2003). In order to facilitate the exploration of effects of demographics (e.g., age, sex) and previous caffeine use, and to account for additional variability in an outpatient study, we propose a larger sample size of 36. This sample size is consistent with previous outpatient studies conducted by our laboratory that manipulated caffeine maintenance and examined differences in caffeine subjective effects (Evans & Griffiths, 1992). The appropriateness of the proposed sample size is supported by a formal power analysis for repeated measures ANOVA examining an interaction between drug dose (five observations: placebo and four doses of nicotine) and caffeine maintenance (two levels treated as groups in the power analysis, thus conservatively assuming no correlation for this within-subjects factor) assuming an effect size of .20, correlation among repeated measurements of .5, desired power of .8, and $\alpha = .05$.

It is anticipated that in order to have 36 participants successfully complete the study, approximately 60 participants may have to be enrolled in order to allow for the possibility of participant dropout (i.e., attrition of up to 40% of enrolled participants). In order to obtain 60 enrolled participants, we anticipate that as many as 150 individuals may need to be consented and screened for study eligibility during the in-person Screening session (i.e., a screening failure rate of approximately 60%).

d. Early stopping rules.

There are no early stopping rules in this study.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Risks from behavioral procedures. The behavioral procedures employed in these studies are benign. There are minimal risks related to the behavioral and self-report assessments. Potential risks are that some individuals might feel uncomfortable, tired, or bored in answering some of the questions.

Risks related to breach of confidentiality. Although staff members are highly trained to maintain participant confidentiality, there is always a risk that some of the confidential information collected could be revealed to people who are not involved in the research study.

Risks from caffeine withdrawal. This study involves periods of total abstinence from caffeine. Thus, there is a risk that participants will experience caffeine withdrawal consisting of headache, tiredness/fatigue, decreased energy/activeness, decreased alertness/attentiveness, drowsiness/sleepiness, decreased contentedness/well-being, depressed mood, difficulty concentrating, irritability, muzzy/foggy/not clearheaded, muscle pain/stiffness, flu-like symptoms, or nausea and/or vomiting. This is a transient phenomenon with little medical risk.

Risks from drug administration. Primary medical risks to participants are those related to the effects of the drugs under study. In the proposed research the risks associated with drug administration are expected to be minor. Yet, administration of any drug involves some risks simply because of individual differences in reactions to drugs. The main risk is that subjects will experience side-effects of the drugs which may be unpleasant. Side-effects could include agitation, anxiety, arousal, confusion, decreased appetite, dizziness, dry mouth, excitement, fatigue, flushing, gastrointestinal distress, head rush, headache, hypertension, hypotension, increased energy/activeness, insomnia, irritability, jitteriness, light-headedness, muscle tenseness, nausea, nervousness, pallor, palpitation, quickened respiration, relaxation, restlessness, sensory disturbances, skin rash, sweating, tachycardia, tension, tremors, vigor, and vomiting. Other more unlikely effects could include cardiac arrhythmias (irregular heart beat), pericardial (chest or heart) pain, seizures, convulsions, respiratory depression, and significant allergic reaction; these would constitute grounds for immediate termination from the study. Side-effects of the drugs are temporary, usually dissipating within several minutes to a few hours, and are generally dose-dependent as well. The risk of a serious adverse event is minimal due to the amount of drug participants will receive. Individual administrations of nicotine will have an upper limit of 6 mg regardless of body weight in order to reduce the likelihood of adverse effects of nicotine for participants of a higher body weight. Thus, subjects may only experience side-effects occasionally during the research. It is not anticipated that caffeine or nicotine will be impairing, and both substances are known to have some acute performance-enhancement effects under certain conditions (Heishman et al., 2010; McLellan et al., 2016).

There is a theoretical risk that subjects might choose to seek out licit or illicit sources of drugs they received experimentally and liked. This risk is minimal because drugs are administered under blind conditions, at relatively low dosages, and in a setting that is not conducive to development of dependence. In support of this, several studies have shown that research participation does not increase subsequent drug use (e.g., Pratt & Davidson, 2005; Roux et al., 2012; Sommer et al., 2015; Vadhan et al., 2006). Our administration of substances to naïve individuals is consistent with statements issued by the College on Problems of Drug Dependence that concluded exposure of drug-naïve individuals in a medically monitored setting is unlikely to create addiction or exacerbate pre-existing risk factors for addiction (Adler, 1995).

b. Steps taken to minimize the risks.

Protection against risks associated with behavioral procedures. Before research participation, a detailed consent form is reviewed and explained to potential subjects by one of the project staff who is approved to do so by the IRB. The consent form describes all of the potential risks of participation including the risks associated with behavioral procedures, drug administration, and caffeine withdrawal symptoms that they might experience. Subjects in all studies are informed that participation is strictly voluntary, that they may skip any questions they do not wish to answer, and that they may discontinue their participation at any time.

Protection against risks related to breach of confidentiality. Research staff are highly trained to maintain participant confidentiality. Records and data are maintained on-site and will only be released outside of the study team with written authorization. Study IDs are used on data collection instruments and in electronic data storage wherever possible in place of any personally identifying information. The identity of subjects is not revealed in written records and documents with subjects' names are shredded before disposal.

Protection against risks associated with caffeine withdrawal. Participants will be informed that withdrawal symptoms may be an expected part of this study prior to enrolling in the study as part of the informed consent process. Withdrawal will be assessed during the study and participants will be reminded that they can end study participation at any time if the withdrawal becomes difficult to manage or unexpectedly aversive. We have also included a caffeine taper period (described in Item 4. a., Study design, above) in order to reduce the potential for caffeine withdrawal following the caffeine maintenance condition.

Protection against risks associated with drug administration. As described previously, there is a risk that volunteers may experience transient adverse symptoms associated with caffeine (e.g. restlessness, anxiety, insomnia), or nicotine (e.g., dizziness, nausea, headache). Study staff have extensive experience in the monitoring and response to adverse events. Participants for whom administration of caffeine or nicotine is considered potentially unsafe will not be enrolled into the study. Potential adverse effects of study participation will be queried at each study visit and participants will be able to end participation at any time with no consequence if the caffeine or nicotine administration becomes sufficiently aversive. Research assistants will consult with medical team in order to respond to adverse events as they occur, including termination of study participation and referral to medical treatment if necessary. The proposed study procedures, including allowing participants to leave the laboratory following capsule administration, were successful in our previous studies administering caffeine, *d*-amphetamine, and nicotine (i.e., Duke et al., 2015; Sigmon & Griffiths, 2011). The study physician, Dr. Annie Umbricht, or another member of the medical staff at the Behavioral Pharmacology Research Unit will be available 24 hours if there is an urgent medical problem related to participation in the research. The Principal Investigator (Lee) has multiple years' experience with human laboratory drug administration studies as a key Co-Investigator including studies administering caffeine, tobacco/nicotine, cannabis, and cannabidiol. He also has extensive experience managing randomized controlled clinical trials, including monitoring and reporting adverse events. Dr. Lee has worked closely with Dr. Sweeney (prior PI) and Co-Investigator Griffiths during his transition to PI. Collectively, Dr. Griffiths and other Co-Investigators on this project (e.g., Umbricht) have had extensive experience over the last 40 years administering moderate and high doses of psychoactive drugs, including caffeine and nicotine, to both healthy volunteer and clinical subject populations and have developed an effective screening and drug administration environment that minimizes untoward reactions and ensures participant safety. We anticipate that as in previous research, careful screening of participants prior to enrollment and monitoring of subjects during participation will minimize untoward effects.

c. Plan for reporting unanticipated problems or study deviations.

All unanticipated problems and adverse events will be reported to the IRB and other relevant agencies as required and described in the Data and Safety Monitoring Plan.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Potentially sensitive information (e.g., history of illicit drug use) is collected for this study, which may represent some legal risk. A Certificate of Confidentiality protecting research subjects in this NIH-funded project was automatically issued with the grant award. The Certificate of Confidentiality prohibits the disclosure of identifiable, sensitive research information to anyone not connected to the research except when the subject consents. There remains a theoretical risk that a breach in confidentiality will occur. In order to protect against this risk, research staff are trained in procedures for protecting participant privacy and personal health information. Data are managed to maximally protect participant confidentiality (e.g., in locked rooms, on encrypted computers, using participant ID codes rather than personal information). Records and data are maintained on-site and will only be released outside of the study team with written authorization from the participant. Documents with subjects' names are shredded before disposal.

e. Financial risks to the participants.

There are no financial risks to the participants.

9. Benefits

a. Description of the probable benefits for the participant and for society.

There will be no direct benefit to subjects who participate in this trial. Through the study procedures, volunteers may gain insights into their personal use of drugs (e.g., caffeine) and how drugs affect them. The volunteers may find the behavioral tasks or personality measures interesting and gain insight into their own preferences.

The knowledge to be gained from the present study is important to understanding individual vulnerabilities to nicotine reinforcement. As mentioned previously, nicotine is of interest as the primary reinforcing component of combustible tobacco smoking, which is the leading preventable cause of death in the United States. Further, the changing patterns of nicotine use, including the broader appeal of electronic cigarettes, makes the examination of nicotine reinforcement among non-smokers particularly timely. This study investigates exposure to chronic dietary caffeine as a predictor of abuse potential of nicotine. Data from this project will contribute to a scientific understanding of nicotine reinforcement and will ultimately contribute to the development of improved prevention and treatment procedures. Specifically, data showing that chronic caffeine increases abuse liability of nicotine in non-smokers would suggest that reduction in dietary caffeine could reduce the positive effects of nicotine upon first exposure. Thus, limiting caffeine exposure may reduce the likelihood of liking nicotine and transitioning to regular smoking upon trying a combustible tobacco cigarette or e-cigarette. Overall, the possible risks of participation to subjects appear to be outweighed by the benefits to subjects and to society.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Participants will be paid $35 for screening, $15 per session for initial sessions reviewing the food diary (4 total sessions), $45 per experimental test sessions and multiple-choice reinforcement sessions (13 total sessions), $45 on the final session during which they complete an end-of-study survey and will earn two completion bonuses: $75 for completing all sessions in the first maintenance condition and $200 for completing all sessions in the second maintenance condition. Thus, compensation for participation will be up to $1000. Because a random choice of the participant is selected during the multiple-choice reinforcement session (during the second maintenance condition), participants may receive up to $30 additional or have up to $30 deducted from their final study payment if they indicated they would prefer additional money or to forego money over receiving an additional dose of the specified study drug. If additional screening sessions are necessary, participants will be paid an additional $35, and if additional experimental sessions are necessary, such as in the event of procedural or computer error, participants would be paid at the same per-session rate (i.e., $45 per session). Additional sessions could increase earnings beyond $1000, but study staff will strive to minimize the need for any additional sessions. If a participant is discontinued due to noncompliance, they will not receive the completion bonus. If a participant is discontinued due to adverse effects of the drug they will be considered as completed and will earn a bonus of $10 for each session completed during the first maintenance condition (if they are discharged during the first maintenance condition) and $20 for each session completed during the second maintenance condition (if they are discharged during the second maintenance condition).

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

Costs to participants include travel to and from study sessions. There are no other costs to participants. All other study costs will be paid for by the research project, which is funded by NIH grant R01DA003890.

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