# Study Title: Effect of Commonly Used Medications on Mood and Choice

## NCT # 03652740

## February 25, 2021

# JHM IRB - eForm A – Protocol

- **Use the section headings to write the JHM IRB eForm A, inserting the appropriate material in each. If a section is not applicable, leave heading in and insert N/A.**
- **When submitting JHM IRB eForm A (new or revised), enter the date submitted to the field at the top of JHM IRB eForm A.**

**********

## 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.

This study will examine caffeine reinforcement as a prospective predictor of positive subjective and behavioral choice effects of commonly used drugs. Caffeine is a widely consumed psychoactive drug with mild psychomotor stimulant effects that has served as a useful model system for understanding drug reinforcement. Earlier data from our laboratory demonstrated that caffeine choosers showed higher ratings of pleasant effects and lower ratings of unpleasant effects when administered *d*-amphetamine relative to nonchoosers. It remains unknown, however, whether this effect is specific to *d*-amphetamine, which shares a dopaminergic mechanism of action with caffeine, or whether it reflects a broader dispositional vulnerability to drug reinforcement. Thus, the proposed study will systematically replicate our previous study with *d*-amphetamine to determine whether individual differences in caffeine choice predicts increases in surrogate measures of reinforcing effects (e.g., ratings of liking, take again, monetary value) of methylphenidate and nicotine. Eligible participants (desired $n = 36$ completers) will complete the study in three phases. In Phase 1 (initial abstinence), abstinence from caffeine will be established one week prior to drug-administration in order to reduce the impact of withdrawal from caffeine on subsequent experimental phases. Other dietary restrictions will also be implemented in Phase 1 to reduce caffeine-related expectancy. During Phase 1, participants will report to the laboratory to review their food and beverage intake up to three times per week and will provide saliva samples to be analyzed for caffeine content (3 sessions). During Phases 2 and 3, participants will be administered placebo or drug-containing capsules under double-blind conditions. To facilitate blindness to the study drugs being administered, caffeine, nicotine, and methylphenidate are disclosed to participants during consent among a longer list of potential drugs they may receive including other prescription and over-the-counter stimulant, sedative, and antihistamine medications. During Phase 2 (choice phase), participants will choose between caffeine (200 mg/70 kg) and placebo across 10 choice sequences. Each choice sequence consists of two exposure sessions (i.e., one session each of caffeine or placebo, order counterbalanced) and one choice session (i.e., choice between caffeine or placebo) for a total of 30 sessions in Phase 2. Following the choice phase, participants will complete the dose-effect phase (Phase 3) to measure the subjective reinforcing effects of methylphenidate (10, 20, and 40 mg/70 kg) and nicotine (1, 2, 3 and 4 mg/70 kg) under double-blind conditions. Phase 3 will consist of 13 total sessions including one session per drug/dose condition plus placebo (8 sessions), a replication of the four nicotine doses (4 sessions), and a final multiple-choice reinforcement session (1 session). During the multiple-choice reinforcement session, we will reinforce a randomly selected choice (i.e., drug vs. money) made by the participant after previous sessions as a surrogate measure of drug reinforcement. The identification of behavioral and pharmacological markers of vulnerability to the effects of drugs of abuse is important in order to inform future substance use disorder prevention and regulatory efforts.

**2. Objectives** (include all primary and secondary objectives)

Primary objective: Determine whether caffeine choice prospectively predicts positive subjective response to methylphenidate and nicotine.

Secondary objective: Characterize and compare caffeine choosers and nonchoosers on subject demographics (e.g., age, sex), drug use history, and personality factors that may co-vary with caffeine choice and subjective drug response.

**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)

Despite the known reinforcing effects of nicotine (Duke et al., 2015) and stimulants such as amphetamine or methylphenidate (Rush et al., 2001), only a small number of individuals who try these substances develop problematic use (de Wit, 1998). Therefore, it is important to identify individuals who are vulnerable to the reinforcing effects of different drugs. One possible predictor of substance use vulnerability may be caffeine reinforcement. Our laboratory has conducted extensive research examining caffeine as a model system for understanding substance use phenomena including reinforcement, tolerance, withdrawal, and continued use in spite of substance-related problems (e.g., Evans & Griffiths, 1992; Griffiths & Woodson, 1988; Griffiths, Bigelow, & Liebson, 1989; Juliano & Griffiths, 2004; Meredith et al., 2013). Prior work in our laboratory using a repeated choice procedure, which we have used to study reinforcing effects of caffeine and nicotine (e.g., Griffiths & Woodson, 1988; Duke et al., 2015), has demonstrated that caffeine choice predicts positive subjective response to *d*-amphetamine (Sigmon & Griffiths, 2011). The proposed research tests the generality of our previous finding to drugs with more diverse pharmacological mechanisms, namely methylphenidate and nicotine. The data collected will determine whether caffeine reinforcement is a marker for a general vulnerability to the subjective positive effects of drugs of abuse, which may ultimately inform substance use disorder prevention efforts.

In the present study, we hypothesize that individual differences in caffeine reinforcement may predict vulnerabilities to the reinforcing effects of other drugs of abuse. In support of this hypothesis, research from our laboratory demonstrated that caffeine reinforcement predicts individual differences in the subjective and reinforcing effects of *d*-amphetamine (Sigmon & Griffiths, 2011). Using a repeated choice procedure developed to distinguish between caffeine choosers and caffeine avoiders (Griffiths & Woodson, 1988), we showed that caffeine choice prospectively predicts positive subjective response to *d*-amphetamine (Sigmon & Griffiths, 2011). In that study, choosers and nonchoosers of caffeine were identified using 10 independent choice trials in which subjects, who were blind to the dose conditions, repeatedly chose between caffeine (200 mg/70 kg) and placebo. Choosers of caffeine subsequently showed higher ratings of pleasant subjective effects and lower ratings of unpleasant subjective effects after receiving *d*-amphetamine. These data suggest that caffeine choice may be a clinically useful predictor of vulnerability to *d*-amphetamine abuse.

It is unknown, however, whether this effect is specific to *d*-amphetamine, which shares a dopaminergic mechanism of action with caffeine, or whether it reflects a broader dispositional vulnerability to drug reinforcement. Thus, in the present study, we propose to systematically replicate our previous study to determine whether individual differences in caffeine choice predict increases in surrogate measures of reinforcing effects (e.g., ratings of liking, take again, monetary value) of more pharmacologically diverse drugs: methylphenidate and nicotine. Methylphenidate is of interest because it is a widely used dopaminergic stimulant having significant neuropharmacological differences from *d*-amphetamine.

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 (DHHS, 2014). This project will also extend our work examining individual differences in nicotine reinforcement in never-smokers (Duke et al., 2015).

We hypothesize that caffeine choosers will show more positive subjective response to methylphenidate and nicotine relative to nonchoosers. Data showing that caffeine choice predicts abuse liability of other commonly used drugs would suggest caffeine use may be an early marker of vulnerability to substance use disorders, which would have important implications for education and prevention. For example, caffeine preferers (e.g., heavy caffeine consumers) could be identified as a high risk group for liking the effects of nicotine or stimulant drugs and potentially targeted for nicotine or drug use prevention interventions.

## 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).

After screening for eligibility, this double-blind, placebo controlled study will be conducted over a period of approximately 14-17 weeks across three phases, including an initial abstinence phase (Phase 1), a choice phase (Phase 2), and a dose-effect phase (Phase 3). Our goal is to have $n = 36$ participants complete the study.

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 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 gene sequencing (e.g., for markers related to addiction vulnerability) on saliva samples that are not used for caffeine testing.

Phase 1: Initial Abstinence Phase (Week 1). 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 beginning one week before the initial choice session. As in some of our previous studies (e.g., Sigmon & Griffiths, 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 receiving 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 appropriate prescription medication in order to participate in this study.

To ensure participants understand and comply with the dietary restrictions, participants will be asked to record the amounts and types of all foods, drinks, and medications they consume and the time of day the items are consumed during the first week of the study (Phase 1). During Phase 1 (i.e., initial abstinence phase), participants will come to the laboratory to provide a saliva sample, review food restrictions and food diaries up to three times per week (e.g., Monday, Wednesday, and Friday). Caffeine abstinence will be verified by randomly 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.

Phase 2: Choice Phase (Weeks 2-8). During the choice phase (Phase 2), participants will report to the laboratory approximately 3-5 times per week, Monday through Friday, for brief visits. On each of these experimental days, subjects will provide a saliva sample, complete pre-drug subjective questionnaires, and ingest p.o. 2 identical, opaque size 0 color-coded capsules with water under double-blind conditions. To facilitate blindness, the drugs to be administered are disclosed to participants during consent among a longer list of potential drugs including other prescription and over-the-counter stimulant, sedative, and antihistamine medications. Thus, participants are aware that they may receive caffeine, nicotine, methylphenidate, or placebo and aware of the possible risks, but expectancy regarding the effects of study drugs is reduced. This strategy has been used successfully in past research (see section c. below for further information regarding justification for blinding procedures).

Phase 2 will consist of ten test sequences of three experimental sessions per sequence. Each test sequence begins with two “no-choice” forced exposure days during which subjects will receive two different types of color-coded capsules on each day (e.g., 2 red capsules on Monday and 2 green capsules on Tuesday). Subjects will always receive placebo (e.g., microcrystalline cellulose) on one forced exposure day and caffeine anhydrous (200 mg/70 kg) on the other forced exposure day, with the order of exposure to caffeine and placebo counterbalanced across the trials. After leaving the laboratory, subjects will be required to complete subjective effects questionnaires at 1, 2, 3, and 4 hours after capsule ingestion. Measures will include subjective ratings of subjective drug effects (e.g., energetic, drowsy/sleepy, elated, jittery/shaky) and surrogate measures of reinforcement such as liking, take again, and monetary value, that we have used in previous research. 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. On the subsequent "choice session" day, subjects will be shown their self-report data from the previous two exposure days to help them recall the specific drug effects (e.g., drug liking) associated with each color-coded capsule. Subjects will then choose one of the two types of color-coded capsules (e.g., 2 red capsules or 2 green capsules) and report the reason for their choice. They will then ingest the capsules they chose. After leaving the laboratory, subjects will again be required to complete subjective drug effect questionnaires at 1, 2, 3, and 4 hours after capsule ingestion. This 3-day test sequence (2 no-choice days followed by 1 choice day) will be repeated for a total of 10 consecutive test sequences (30 total sessions). For each subject, each 3-day choice sequence will be experimentally independent (e.g., each sequence will involve exposure and choice between novel color-coded capsules).

Phase 3: Dose-Effect Phase (Weeks 9-14). After completing the choice phase, participants begin the acute dose-effect phase (Phase 3). During Phase 3, subjects will report to the laboratory approximately 2-3 times per week, depending on schedule considerations. At least 48 hours will occur between completing the caffeine choice phase and beginning the dose-effect phase. Sessions during this phase will be separated by at least 48 hours (e.g., Monday, Wednesday, Friday sessions). These sessions will be similar to the forced exposure sessions during the Phase 2 except there will not be an opportunity to choose between capsules and capsules color will not change across sessions. At each visit, participants will have their blood pressure taken to ensure that it is $\leq$ 140 systolic and $\leq$ 90 diastolic prior to capsule administration, provide a saliva sample, complete pre-drug subjective questionnaires, and ingest p.o. 2 identical capsules with water under double-blind conditions. After leaving the laboratory, outcome measures will be assessed pre-capsule and at 1, 2, 3, and 4 hours post-capsule using the same measures as the Phase 2 (choice phase), with the addition of the multiple-choice procedure. 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"). 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 the final session of Phase 3 (see below).

The acute effects of placebo and the two test drugs will be evaluated using a double-blind, cross-over design in which each participant will be tested under each of 8 drug conditions: methylphenidate hydrochloride (10, 20, and 40 mg/70 kg; 60 mg is the maximum allowable dose of methylphenidate any individual would receive regardless of body weight) and nicotine base (prepared from nicotine hydrogen tartrate; 1, 2, 3 and 4 mg/70 kg; 6 mg is the maximum allowable dose of nicotine any individual would receive regardless of body weight) across one session per drug/dose condition plus placebo. Doses have been selected based on prior studies from our laboratory and others (e.g., Duke et al., 2015; Kollins et al., 2009; Rush et al., 1998, 2001). Due to the fact that there was considerable variability in the positive subjective and discriminative stimulus effects of nicotine among never-smokers in our previously published study (Duke et al., 2015), the four nicotine doses will be replicated once within each subject. Dose conditions will be presented in ascending order for both methylphenidate and nicotine, but whether methylphenidate or nicotine are presented first will be counterbalanced. We will conduct one final administration session during which a prior choice made by the participant as a part of the multiple-choice procedure will be randomly selected and reinforced. If the selected choice was one of the study drugs, then the selected study drug will be administered to the participant on the final session using the same procedures as the rest of Phase 3. 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. The addition of the multiple-choice reinforcement session results in a total of 13 sessions during Phase 3. 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.

## 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 used to explore possible differences between caffeine choosers and non-choosers and 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.

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 to compare choosers and non-choosers of caffeine on their decision-making.

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 to determine whether choosers of caffeine differ from nonchoosers. 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, Stephenson, Palmgreen, Lorch, & Donohew, 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 choose caffeine (or who show greater positive subjective response to other drugs) 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 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 show significant differences between choosers/nonchoosers and to detect significant drug dose effects (Duke, Johnson, Reissig, & Griffiths, 2015; Sigmon & Griffiths, 2011).

Delay Discounting. The same brief delay discounting procedure (described above) may be administered during Phase 3 (acute dose-effect phase) at a single time point (e.g., 3 hr) per Phase 3 session following 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 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 (e.g., 4 hr) per session during all sessions of Phase 3. 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 the final session of Phase 3. If the selected choice was one of the study drugs, then capsules containing selected study drug will be administered to the participant on the final session using the same procedures as the rest of Phase 3. 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 a placebo capsule. A placebo capsule is 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, Rush, & Puhala, 1996; Griffiths, Troisi, Silverman, & Mumford, 1993). We hypothesize that choosers of caffeine may show greater subjective monetary value of the administered drugs.

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

The duration of participation will be approximately 14-17 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, 3 brief sessions during Phase 1 (initial abstinence), 30 brief sessions during Phase 2 (i.e., two exposure sessions followed by one choice session for a total of ten choice sequences), and 13 brief sessions during the during Phase 3 (dose-effect phase). 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. Screening sessions will be approximately 2 hours in duration. 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, methylphenidate, 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., 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 the 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 condition has 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 18-65 years.
2. Participant has a history of regular or intermittent caffeine use.
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 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 caffeine, psychomotor stimulants, or nicotine.
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. A past prescription of methylphenidate which exceeded two weeks or occurred within the past year.
8. Subjects unwilling or unable to comply with the protocol or scheduled appointments.
9. 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.
10. 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, this study will administer oral caffeine, methylphenidate, and nicotine in order to determine whether individual differences in caffeine choice predicts increases in surrogate measures of reinforcing effects (e.g., ratings of liking, take again, monetary value) of methylphenidate and nicotine. Data showing that caffeine choice predicts abuse liability of other commonly used drugs would suggest caffeine use may be an early marker of vulnerability to use of methylphenidate and/or nicotine. Specifically, methylphenidate is of interest because it is a widely used dopaminergic stimulant having significant neuropharmacological differences from *d*-amphetamine, which was used in our previous study (Sigmon & Griffiths, 2011). 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 death in the United States (DHHS, 2014). This project will also extend our work examining individual differences in nicotine reinforcement in never-smokers (Duke et al., 2015). Drugs and doses to be administered in different study sessions as described in Study Procedures include: placebo (e.g., microcrystalline cellulose), caffeine anhydrous (200 mg/70 kg), nicotine base (1, 2, 3 and 4 mg/70 kg; 6 mg is the maximum allowable dose of nicotine any individual would receive regardless of body weight in order to reduce the likelihood of adverse effects for participants of a higher body weight), and methylphenidate hydrochloride (10, 20 and 40 mg/70 kg; 60 mg is the maximum allowable dose of methylphenidate any individual would receive regardless of body weight). The doses of nicotine base will be prepared from nicotine hydrogen tartrate. Doses have been selected based on prior studies from our laboratory and others which have used the proposed doses (or higher doses) and found them to be well-tolerated in non-drug abusing volunteers (e.g., Duke et al., 2015; Kollins et al., 2009; Rush et al., 1998, 2001; Sigmon & Griffiths, 2011). 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). Maximum study doses of oral methylphenidate are well-within the practice parameters for the use of stimulant medications (i.e., up to 60 mg per day; Greenhill et al., 2002).

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.

All the 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), nicotine (Duke et al., 2015), and methylphenidate

(Kollins et al., 2009; Rush et al., 1998, 2001) at the proposed doses (or indeed at higher doses) and the proposed route of administration (oral) are well-tolerated in non-drug-abusing volunteers. 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). Maximum study doses of oral methylphenidate are well-within the practice parameters for the use of stimulant medications (i.e., up to 60 mg per day; Greenhill et al., 2002). 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-administration during the Phase 3 (dose effect phase). 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 between caffeine choosers and nonchoosers. Caffeine choosers and nonchoosers are individuals who choose caffeine or placebo, respectively, 7 or more times during Phase 2.

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 relate to caffeine choice.

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

Our goal is to have 36 participants complete the study. Sample sizes from our previous research with caffeine choice and *d*-amphetamine ($n$ = 19 included in analysis) supports the appropriateness of the proposed sample size. The somewhat larger group size will permit a more complete characterization of subject demographics (e.g., age, sex), drug use history, and personality factors that may co-vary with caffeine choice. Based on our previous study with caffeine choice and *d*-amphetamine, the dichotomous measure of caffeine reinforcement should provide approximately equal numbers of choosers and nonchoosers (about N=15 each) for this analysis (with about 6 volunteers failing to meet the criteria for either chooser or non-chooser). Repeated measures ANOVAs will be conducted with caffeine choice (chooser vs. nonchooser, drug dose (placebo & 2 doses of each drug) and time (1, 2, 3, and 4 hours, as appropriate) as factors. Planned comparisons will be conducted between caffeine choosers and nonchoosers at each drug dose. We will conduct correlational analyses between number of caffeine choices and peak effects for the drug conditions, subject demographics, drug use history, and personality factors. Significant effects will be $p$-value $\leq .05$. Appropriateness of a sample size of N=15 per group was also supported by a power analysis for repeated measures ANOVA examining an interaction of the between-subjects factor of caffeine choice (2 groups) and within subjects factor of drug dose (4 observations; placebo and minimum

of three doses for each drug) using an effect size of .25, correlation among repeated measurements of .5, desired power of .90, 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.

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.

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.

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 the participants will receive. Thus, subjects may only experience side-effects occasionally during the research. It is not anticipated that caffeine, methylphenidate, or nicotine will be impairing, and all three substances are known to have some acute performance-enhancement effects under certain conditions (Heishman et al., 2010; Linssen et al., 2014; McClellan 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 since 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.

All participants in the drug studies will be thoroughly informed of the various drug side-effects (including possible caffeine withdrawal symptoms) that they might experience. Since participation is voluntary, subjects can withdraw at any time if they find the behavioral procedures or drug effects undesirable. A member of the medical staff reviews information from Screening to determine medical eligibility. All women will receive a pregnancy test at screening. Pregnancy testing will be repeated every other week throughout the duration of study participation. Participant blood pressure will be confirmed to be ≤ 140 systolic and ≤ 90 diastolic at the screening visit and also prior to capsule administration during Phase 3 of the study as a precaution against the potential hypertensive effects of methylphenidate.

We anticipate that careful subject selection, careful dose selection, and careful subject monitoring will, as in the past, prevent any potential problems. The investigators on this project have had extensive experience over the last 40 years administering moderate and high doses of psychoactive drugs to healthy volunteer subjects and have rarely experienced any untoward reactions. Examples of our prior research with these compounds include: caffeine (e.g., Evans & Griffiths, 1992; Sigmon & Griffiths, 2011; Sweeney et al., 2017; Griffiths et al., 1989); nicotine (e.g., Duke et al., 2015; Jones & Griffiths, 2003; Johnson et al., 2010; Sobel et al., 2004; Nemeth-Coslett et al., 1987; Chausmer et al., 2003); and methylphenidate (e.g., Griffiths et al., 2006). Again, the doses examined in the present study have been selected based on prior studies from our laboratory and others which have used the proposed doses (or higher doses) and found them to be well-tolerated in non-drug abusing volunteers (e.g., Duke et al., 2015; Kollins et al., 2009; Rush et al., 1998, 2001; Sigmon & Griffiths, 2011). 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 proposed doses of methylphenidate are generally comparable to the doses of *d*-amphetamine (Rush et al., 1998, 2001) used in our prior study (Sigmon & Griffiths, 2011) and should not represent additional risk. Further, the use of a conservative ascending dose exposure for both drugs will be used to initially expose the volunteers to the effects of the study drugs to minimize unpleasant or adverse effects. 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.

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.

There is 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.

The identity of subjects is not revealed in written records and documents with subjects' names are shredded before disposal.

e. Financial risks to the participants.

There are no financial risks to the participants in this study.

**9. Benefits**

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

Although not considered a direct benefit, participants in all of the proposed studies will be paid for their research participation. 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 substance use. This study investigates caffeine choice as a predictor of abuse potential pharmacologically diverse drugs nicotine and methylphenidate, which are of particular interest as abused drugs. Data from this project will contribute to a scientific understanding of drug abuse and will ultimately contribute to the development of improved prevention and treatment procedures. Specifically, data showing that caffeine choice predicts abuse liability of other abused drugs would suggest that caffeine use is an early marker of vulnerability to some substance use disorders. For example, study findings regarding caffeine choosers vs. nonchoosers may inform physicians that caffeine choosers are a potentially higher risk group for developing problematic substance use related to certain prescribed drugs. Overall, the possible risks to subjects of participation 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 during Phase 1 (3 sessions), $20 per session (30 sessions) during the Phase 2, $40 per session (13 sessions) during Phase 3, and will earn an $800 bonus for completing all the study sessions. Thus, compensation for participation will be up to $2000. Because a random choice of the participant is selected during the multiple-choice reinforcement session (final session of Phase 3), 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., $20 per session during the Phase 2 and $40 per session during Phase 3). Additional sessions could increase earnings beyond $2000, 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 $18 for each session completed during Phases 2 and 3.

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

## References

Adler MW. Human subject issues in drug abuse research. College on Problems of Drug Dependence. *Drug Alcohol Depend.* 1995 Feb; 37(2): 167-175.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Chausmer AL, Smith BJ, Kelly RY, Griffiths RR. Cocaine-like subjective effects of nicotine are not blocked by the D1 selective antagonist ecopipam (SCH 39166). *Behav Pharmacol.* 2003 Mar; 14(2): 111-120.

de Wit H. Individual differences in acute effects of drugs in humans: Their relevance to risk for abuse. *NIDA Res Monogr.* 1998 Mar; 169: 176-187.

Duke, A. N., Johnson, M. W., Reissig, C. J., & Griffiths, R. R. (2015). Nicotine reinforcement in never-smokers. *Psychopharmacology*, *232*(23), 4243-4252.

Evans SM, Griffiths RR. Caffeine tolerance and choice in humans. *Psychopharmacology (Berl).* 1992; 108(1-2): 51-59.

Garrett, B.E., & Griffiths, R.R. (1998). Physical dependence increases the relative reinforcing effects of caffeine versus placebo. *Psychopharmacology*, 139, 195-202.

Goldberg, L.R. (1992). The development of markers for the Big-Five factor structure. *Psychological Assessment*, 4(1), 26-42. doi: 10.1037//1040-3590.4.1.26

Goldberg, L.R. (1993). The structure of phenotypic personality traits. *American Psychologist*, 48(1), 26-34. doi:10.1037/0003-66X.48.1.26

Greenhill, L. L., Pliszka, S., & Dulcan, M. K. (2002). Practice parameter for the use of stimulant medications in the treatment of children, adolescents, and adults. *Journal of the American Academy of Child & Adolescent Psychiatry*, *41*(2), 26S-49S.

Griffiths RR, Bigelow GE, Liebson IA. Reinforcing effects of caffeine in coffee and capsules. *J Exp Anal Behav.* 1989 Sep; 52(2): 127-140. PMCID: PMC1338955.

Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl).* 2006 Aug; 187(3): 268-83.

Griffiths, R.R., Rush, C.R., & Puhala, K.A. (1996). Validation of the multiple-choice procedure for investigating drug reinforcement in humans. *Experimental and Clinical Psychopharmacology*, 4(1), 97-106. doi: 10.1037/1064-1297.4.1.97

Griffiths RR, Woodson PP. Reinforcing effects of caffeine in humans. *J Pharmacol Exp Ther.* 1988 Jul; 246(1): 21-29.

Griffiths, R. R., JR Troisi, I. I., Silverman, K., & Miumford, G. K. (1993). Multiple-choice procedure: an efficient approach for investigating drug reinforcement in humans. *Behavioural pharmacology*, *4*(1), 3-14.

Heishman, S. J., Kleykamp, B. A., & Singleton, E. G. (2010). Meta-analysis of the acute effects of nicotine and smoking on human performance. *Psychopharmacology*, *210*(4), 453-469.

Hoyle, R. H., Stephenson, M. T., Palmgreen, P., Lorch, E. P., & Donohew, R. L. (2002). Reliability and validity of a brief measure of sensation seeking. *Personality and Individual Differences*, *32*(3), 401-414.

John, O.P., & Srivastava, S. (1999). The Big-Five trait taxonomy: History, measurement, and theoretical perspectives. In L.A. Pervin & O.P. John (Eds.), Handbook of personality: Theory and research (Vol. 2, pp. 102-138). New York: Guilford Press.

Johnson MW, Strain EC, Griffiths RR. Effects of oral caffeine pretreatment on response to intravenous nicotine and cocaine. *Exp Clin Psychopharmacol.* 2010 Aug; 18(4): 305-315. PMCID: PMC3528786.

Jones HE, Griffiths RR. Oral caffeine maintenance potentiates the reinforcing and stimulant subjective effects of intravenous nicotine in cigarette smokers. *Psychopharmacology (Berl).* 2003 Jan; 165(3): 280-290.

Juliano LM, Griffiths RR. A critical review of caffeine withdrawal: Empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology (Berl).* 2004 Oct; 176(1): 1-29.

Koffarnus, M. N., & Bickel, W. K. (2014). A 5-trial adjusting delay discounting task: accurate discount rates in less than one minute. *Experimental and clinical psychopharmacology*, 22(3), 222.

Kollins, S. H., English, J., Robinson, R., Hallyburton, M., & Chrisman, A. K. (2009). Reinforcing and subjective effects of methylphenidate in adults with and without attention deficit hyperactivity disorder (ADHD). *Psychopharmacology*, *204*(1), 73-83.

Kotov, R., Gamez, W., Schmidt, F., & Watson, D. (2010). Linking "big" personality traits to anxiety, depressive, and substance use disorders: A meta-analysis. *Psychological Bulletin*, *136*(5), 768.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H., ... & Dunbar, G. C. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry*, *12*(5), 224-231.

Linssen, A. M. W., Sambeth, A., Vuurman, E. F. P. M., & Riedel, W. J. (2014). Cognitive effects of methylphenidate in healthy volunteers: a review of single dose studies. *International Journal of Neuropsychopharmacology*, *17*(6), 961-977.

Mann, R. E., Sobell, L. C., Sobell, M. B., & D., P. (1985). Reliability of a family tree questionnaire for assessing family history of alcohol problems. *Drug and Alcohol Dependence*, *15*, 61-67.

McLellan, T. M., Caldwell, J. A., & Lieberman, H. R. (2016). A review of caffeine's effects on cognitive, physical and occupational performance. *Neuroscience & Biobehavioral Reviews*, *71*, 294-312.

Meredith SE, Juliano LM, Hughes JR, Griffiths RR. Caffeine use disorder: A comprehensive review and research agenda. *J Caffeine Res.* 2013 Sep; 3(3): 114-130. PMCID: PMC3777290.

Nemeth-Coslett R, Henningfield JE, O'Keeffe MK, Griffiths RR. Nicotine gum: Dose-related effects on cigarette smoking and subjective ratings. *Psychopharmacology (Berl).* 1987; 92(4): 424-430.

Patton, J.H., Stanford, M.S., & Barratt, E.S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*(6), 768-774.

Pratt, W. M., & Davidson, D. (2005). Does participation in an alcohol administration study increase risk for excessive drinking? *Alcohol*, *37*(3), 135-141.

Roux, P., Tindall, C., Fugon, L., Murray, J., Vosburg, S. K., Saccone, P., ... & Foltin, R. W. (2012). Impact of in‐patient research participation on subsequent heroin use patterns: Implications for ethics and public health. *Addiction*, *107*(3), 642-649.

Rush CR, Essman WD, Simpson CA, Baker RW. Reinforcing and subject-rated effects of methylphenidate and d-amphetamine in non-drug-abusing humans. *J Clin Psychopharmacol.* 2001 Jun; 21(3): 273-286.

Rush, C. R., Kollins, S. H., & Pazzaglia, P. J. (1998). Discriminative-stimulus and participant-rated effects of methylphenidate, bupropion, and triazolam in d-amphetamine-trained humans. *Experimental and Clinical Psychopharmacology*, *6*(1), 32-44.

Sigmon SC, Griffiths RR. Caffeine choice prospectively predicts positive subjective effects of caffeine and d-amphetamine. *Drug Alcohol Depend.* 2011 Nov 1; 118(2-3): 341-348. PMCID: PMC3188327.

Sobel BF, Sigmon SC, Griffiths RR. Transdermal nicotine maintenance attenuates the subjective and reinforcing effects of intravenous nicotine, but not cocaine or caffeine, in cigarette-smoking stimulant abusers. *Neuropsychopharmacology.* 2004 May; 29(5): 991-1003.

Sommer, C., Seipt, C., Spreer, M., Blümke, T., Markovic, A., Jünger, E., ... & Zimmermann, U. S. (2015). Laboratory alcohol self-administration experiments do not increase subsequent real-life drinking in young adult social drinkers. *Alcoholism: Clinical and Experimental Research*, *39*(6), 1057-1063.

Stanford, M. S., Mathias, C. W., Dougherty, D. M., Lake, S. L., Anderson, N. E., & Patton, J. H. (2009). Fifty years of the Barratt Impulsiveness Scale: An update and review. *Personality and Individual Differences*, *47*(5), 385-395.

Sweeney MM, Meredith SE, Evatt DP, Griffiths RR. Effects of caffeine on alcohol reinforcement: Beverage choice, self-administration, and subjective ratings. *Psychopharmacology (Berl ).* 2017; 234(5): 877-888.

United States Department of Health and Human Services (DHHS). The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

Vadhan, N. P., Hart, C. L., Roe, B., Colley, J., Haney, M., & Foltin, R. W. (2006). Substance use and psychosocial outcomes following participation in residential laboratory studies of marijuana,

methamphetamine and zolpidem. *The American Journal of Drug and Alcohol Abuse*, *32*(4), 589-597.

Zacny, J. P., & Gutierrez, S. (2009). Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers. *Drug & Alcohol Dependence*, *101*(1), 107-114