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RESEARCH PROTOCOL

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A. RATIONALE AND OVERVIEW

Since 1996, 20 states (including Rhode Island) and Washington DC have legalized use of marijuana for medical purposes, and Washington and Colorado legalized recreational use of marijuana in 2012 [1]. If these trends in marijuana legislation continue, the production, advertisement, and sale of marijuana are likely to commence across the United States. The relative ease of accessibility to inexpensive marijuana is a considerable risk factor for heavy use, as is the case with alcohol [2], and marijuana legalization may amplify initiation and progression of use [3]. Due to the shift in normative perceptions surrounding marijuana use [4], an approach to analyze the value of this drug is essential. It is not only imperative, but time-sensitive, that we investigate the factors that may influence the behavioral economic demand for marijuana in this novel drug market. The goal of the present study is to develop and validate a refined measure for assessment of demand for marijuana to be used in future investigations.

B.1. SPECIFIC AIMS

The following aims will remedy prior purchase task limitations and will ultimately address important gaps in the drug demand literature:

Aim 1: Validate the Marijuana Purchase Task (MPT) measure via administration to a representative sample of marijuana users and assessment of smoking behavior in the laboratory (n=85). Hypothetical MPT responses (e.g., how many hits of marijuana would you take if they cost $0.25?, $0.50?, etc…) will be compared to responses on an Actual MPT whereby one of the subject's response choices is selected at random to determine the amount of marijuana to be administered. Marijuana smoking topography will be assessed during a subsequent *ad libitum* smoking session.

Aim 1.1: Test the hypothesis that performance on the Hypothetical MPT will be significantly associated with performance on the Actual MPT.

Aim 1.2: Test hypothesis that marijuana craving post-administration will be lower than craving assessed pre-administration.

Aim 1.3: Test the hypothesis that marijuana puff topography from the *ad libitum* marijuana self-administration session will be related to self-reported grams of cannabis used per week.

B.2. SAMPLE DESCRIPTION AND RECRUITMENT

Participants will be recruited from the community via flyers, advertisements, and social media. Potential subjects will be screened via phone and staff will summarize study procedures. Eligible subjects will be scheduled for an initial laboratory visit. Preliminary data suggests that there is much variability in marijuana use practices; therefore, we will include individuals with a range of use practices and patterns to capitalize on variability. During the initial laboratory visit, participants will provide informed consent and will be enrolled in the study using the following inclusion criteria:

Aim 1: a) marijuana use at least 4 times in the past month on average and at least monthly for the past 6 months; b) English-speaking; c) negative urine toxicology screen for drugs other than marijuana; d) no self-report of other illicit drug use in the past 30 days; e) non-treatment seeking; f) purchase of marijuana at least twice in the past 6 months to confirm familiarity with the construct to be measured; g) negative pregnancy test; h) not nursing; i) use of contraception during the study; j) good physical health; k) zero breath alcohol concentration; l) absence of diagnosis of current depression, mania**,** psychosis, and panic disorder; m) no self-report of past serious adverse reaction to marijuana; n) no current psychotropic drug use; o) smoking 0-20 tobacco cigarettes per day; p) ability to abstain from marijuana for 15 hours; and q) body mass index in 18.5-30 kg/m^2 range. In addition, participants must be 18 to 50 years of age. This age range was chosen based on previous marijuana self-administration work [5], [6] to minimize potential cardiovascular risk from smoking marijuana, which increases with age. Participants who test positive for drugs other than marijuana will be given one re-try appointment.

B.3. METHODOLOGY

Aim 1 Approach. *Laboratory Sessions*: one experimental session (Session 1: controlled paced puff smoking procedure). Participants (*n*=85) will complete a baseline session with medical screening and two experimental sessions (Session 1: controlled paced puffing smoking procedure; Session 2: *ad libitum* smoking topography). Following phone screening, subjects will visit the laboratory to provide informed consent. They will be asked to refrain from all marijuana and tobacco smoking for 15 hours, alcohol for 24 hours, and caffeine for 4 hours prior to experimental sessions. Subjects will complete an alcohol breathanalysis, a urine drug screen and pregnancy test (females), and a carbon-monoxide (CO) reading to confirm absence of recent smoking. Subjects with a positive BrAC will be rescheduled. A positive THC screen will be required at this time to confirm marijuana status; however, positive results for other drugs will result in ineligibility. Participants who test positive for drugs other than marijuana will be given one re-try appointment. Participants that do not test positive for marijuana will not be given a re-try appointment. Those with a CO of > 8 ppm will be rescheduled due to the difficulty in confirming overnight marijuana abstinence with higher CO levels [7]–[9]. For those with a CO reading of more than 8ppm during the baseline session, research staff will consult with the PI on a case-by-case basis. PI discretion will be used to ensure the target CO reading of 8ppm is obtained. With respect to the experimental sessions, for those with a CO reading of more than 8ppm at session arrival, PI discretion will be used to ensure the target CO reading of 8ppm will be reached by the onset of marijuana administration. Participants will be allowed one re-test in the event of a CO level above the 8 ppm cut-off when the PI has determined the participant cannot feasibly reach a CO reading of 8ppm in a timely manner on the same date. Tobacco smokers will be allowed to smoke a cigarette following the CO test to prevent nicotine withdrawal. Similar CO-based procedures have been used in marijuana administration studies to avoid the onset of cannabis withdrawal [9]. Subjects will be administered a medical screening questionnaire to rule out history of adverse reaction to marijuana, and a structured clinical interview to rule out Axis I DSM-5 diagnoses. Ineligible subjects will be paid $10 and excluded from further participation. Eligible subjects will complete baseline measures and undergo a medical screening exam to determine medical clearance prior to the marijuana administration sessions.

Drug: Marijuana (**5.9%** Δ^9-tetrahydrocannabinol/THC) cigarettes will be provided by the NIDA Drug Supply Program. This dose was selected because administration of **5.9%** THC will closely model potency of marijuana obtained outside the laboratory as marijuana preparations have increased from 3.4% in 1993 to 8.8% in 2008 [10].

Laboratory Session 1: Controlled Paced Puff Smoking Procedure: Subjects will complete the Hypothetical (not associated with marijuana available to smoke) Marijuana Purchase Task (MPT), Actual MPT (identical to Hypothetical MPT but a response choice will be selected at random to determine amount of marijuana available to be smoked), and self-report measures of craving and subjective effects. A blood pressure cuff will be attached to continuously record heart rate (HR) and blood pressure (BP) during the entire experimental session for safety monitoring. Selection of marijuana amount available to smoke: A response choice corresponding to an item price will be randomly selected from the Actual MPT measure completed during the session. Subjects

will draw a number and will be given a monetary budget based on the maximum price set on the MPT measure ($20) for the marijuana smoking session. Once the response choice/price has been selected, the corresponding number of marijuana hits will be available to smoke, and the subject will receive any remaining money from the monetary budget (e.g., budget=$20, item selected from Actual MPT =$5/unit, subject reported he/she would purchase 3 units at this price, 3 units will be available during the smoking procedure, and subject will receive the remaining $5 from the monetary budget). The controlled paced-puffing procedure [11] includes instructions to "light the cigarette" (30s), "get ready" (5s), "inhale" (5s), "hold smoke in lungs" (10s), and "exhale." The puffing sequence will continue until the subject chooses to cease smoking or the number of available units has been reached (i.e., 20 hits). Subjects are not required to smoke any marijuana as our intention is to assess the relationship between Actual MPT performance and real smoking in the laboratory. Subjects will be informed that the administration session will last 1-hour regardless of number of marijuana hits available. This methodology is based on established procedures that have been successfully used to assess demand for Hypothetical versus Actual alcohol [12]. No more than 20 hits total will be available during the session due to potential safety concerns (e.g., increases in HR which reliably occur [5], [13]).

Laboratory Session 2. *Ad Libitum* Smoking Topography Procedure: Participants will complete baseline measures including the Hypothetical MPT, and will then complete a 1-hour *ad libitum* marijuana self-administration session for assessment of smoking topography. Marijuana cigarettes (5.9% THC) will be smoked through a handheld smoking topography device (CReSSMicro™). The device will include a holder for the cigarette and study staff will place the cigarette in the device. The subject will light the cigarette and each puff will register immediately upon inhalation. Data from the device will be downloaded and indices of topography will be recorded including number of cigarettes, number of puffs, puff volume (ml), puff duration (ms), average puff velocity (ml/s), and time to peak velocity (ms). Logs will also be maintained by the PI and RA documenting number of puffs smoked and each cigarette or partial cigarette smoked ensuring an accurate count of marijuana cigarettes smoked during the session. These procedures have been successfully used to assess marijuana smoking topography [14]. A maximum of two joints will be available during the session.

Sobriety Assessment: Subjects will receive snacks upon the completion of the administration session. Subjects will remain in the laboratory for 3-hours following the smoking procedure (psychotropic effects of smoked marijuana taper off within 2-3 hours [15]), and will subsequently be evaluated for motor signs of intoxication. Following completion of a field sobriety test [16], subjects will be transported home in a taxi.

Compensation: Participants will be paid $20 for the baseline session, $10 for the physical exam, and $50 for each experimental session (and amount remaining from $20 tab) for a total of at least $130 and up to $150.

Security and Regulatory Aspects for Marijuana: Marijuana cigarettes will be provided by NIDA and will be stored frozen in an airtight container in a locked refrigerator safe located in a cement block room without windows and one door that is locked with code-protected card-key access at 121 South Main Street on the 3rd floor. Only DEA designated individuals will have access to this room (located in the same building and floor as the location of marijuana administration). Thus, the cigarettes will remain secure at all times. Dr. Aston will retrieve a designated number of marijuana cigarettes prior to a scheduled experimental session, humidify them at room temperature for 24 hours before use (per NIDA's instructions) in the same cement block room, and transfer them directly to the laboratory following the start of the session.

Statistical Analysis Plan: The primary aim of this investigation is to confirm the validity of the Marijuana Purchase Task (MPT; primary outcome measure). A linear regression will be performed with marijuana hits purchased on the Actual MPT predicting marijuana hits actually purchased and smoked in the laboratory; baseline total individual income will be included as a covariate. The first secondary aim includes change in marijuana craving pre- and post-marijuana smoking during the experimental session (secondary outcome measure). A two-sided t-test will be conducted to compare craving pre- and post-marijuana smoking. The second secondary aim includes correlation between puffs on the topography device during *ad libitum* marijuana administration and self-reported grams of marijuana used per week (secondary outcome measure).

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