Title: Age-Related Effects of THC (“Effects of drugs on behavior – ART” on the consent form)

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Protocol

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Objectives: **1**) To determine whether adolescents (defined here as ages 18-20) are at greater risk to acute oral 7.5 and 15 mg Δ9-tetrahydrocannabinol (THC) intoxication than adults (defined here as ages 30 to 40), **2**) to develop a sensitive behavioral measure to detect intoxication levels of THC, and **3**) to determine whether age-related drug effects are detectable using electroencephalography (EEG).

Background: Increased accessibility to cannabis and its primary psychoactive constituent THC has raised public health concerns. One major concern surrounds the potential risks associated with acute THC intoxication and who might be most at risk. A second major concern is the need to develop sensitive measures that can detect THC intoxication after recent use and enable robust comparisons of intoxication to determine sources of risk. One potential source of risk is age, specifically during the period of adolescence. Preclinical studies indicate that adolescent rats are more sensitive to the acute effects of THC than adults (Cha et al., 2006; Quinn et al., 2008; Wiley et al., 2007), findings that are related to the brain during adolescence. Specifically, during this critical neurodevelopmental period, expression levels of the receptor that THC activates – the cannabinoid receptor (CB1R) – are more prevalent than any other period of life (Gee et al., 2016; Meyer et al., 2018). Due to this heightened expression of CB1R, the rodent brain is highly receptive to THC effects during adolescence (Heng et al., 2011). Similarly, in humans, CB1R expression peaks at ages 15-17 and declines to base levels near age 35 (Choi et al., 2012; Long et al., 2012), raising the possibility that adolescents are also at risk to heightened THC effects in humans. Notably, a recent report comparing responses to vaporized cannabis in adolescents vs adults indicated that adolescents reported *smaller* effects on certain subjective measures and less performance impairment. However, that study was complicated by possible differences in recent cannabis use and the fact that participants were not completely drug-free at the time of testing (Mokrysz et al., 2016). The purpose of the present study is to determine whether adolescence is a source of risk for THC intoxication in humans and to develop a new, sensitive behavioral assay to detect and compare THC effects. Greater sensitivity to acute THC intoxication may indicate higher potential for abuse, in addition to acute adverse effects including THC-induced psychosis and impairments in behavior and cognition.

Our central hypotheses are 1) that the subjective, behavioral, and physiological responses to acute THC will be greater in adolescents, including reductions in EEG activity during task performance, and 2) that speech and text analyses will be sensitive indices of acute THC intoxication across dose and age. We and others have used analysis of speech production to detect effects of drugs, using measures of both production and content (Baggott et al., 2015; Bedi et al., 2014). To our knowledge, speech and text analyses have not been used to study THC. Our hypotheses will be tested using a well-established regimen of oral 7.5 and 15 mg THC administration in the laboratory (Childs et al., 2017; Pabon and de Wit, 2019; Wardle et al., 2015).

Significance & Innovation: Cannabis use is widespread among adolescents and young adults with over 11 million people ages 18-25 having consumed cannabis in the past year (2015) in the United States (National Institute on Drug Abuse). Furthermore, the average age of onset is 19 years of age (National Survey on Drug Use and Health). Cannabis products are increasingly accessible to young adults in the United States, a trend tied to increased use (Ter Bogt et al., 2014). For example, after cannabis was legalized in Colorado in 2011, past year cannabis use increased from 39% to 49% for ages 18-25 through 2017 (National Survey on Drug Use and Health). The consequences of long-term cannabis use are more severe in adolescents, and there is evidence that chronic use of cannabis in adolescents is associated with impaired neural maturation (Chadwick et al., 2013; Coffey and Patton, 2016). However, it is not established whether adolescents are more or less sensitive to the short-term effects of acute THC intoxication. Preclinical studies consistently show that adolescent rats are more sensitive to the acute effects of THC than adult animals (Cha et al., 2006; Quinn et al., 2008; Wiley et al., 2007). The period of sensitivity coincides with a neurodevelopmental period when cannabinoid receptors are most densely expressed in both rodent and human cortex (Choi et al., 2012; Gee et al., 2016; Heng et al., 2011; Long et al., 2012; Meyer et al., 2018). Therefore, human adolescents may also be more sensitive to the acute effects of THC, and under certain circumstances this may increase their risk for adverse effects such as psychosis and behavioral impairments, or likelihood of abuse.

There is limited knowledge on the effects of THC in adolescents vs adults. One recent report compared responses to vaporized cannabis in heavy adolescent vs adult cannabis users (Mokrysz et al., 2016) and found that the adolescents were less sensitive to the drug on most measures. However, their findings were complicated by several factors: i) the study used vaporized cannabis, which may have other constituents and does not offer full control of the dose, ii) the participants were heavy users, making it difficult to determine the influence of prior drug exposure, and iii) the participants were not drug-free at the time of testing. Prior exposure to THC can lead to tolerance, and adolescents and adults may differ in the rate at which they develop tolerance, consistent with changes in CB1R receptor function (Burston et al., 2010; Cha et al., 2006; Murray, Pabon, de Wit, unpublished finding; Quinn et al., 2008; Wiley et al., 2007). Our study will compare adolescent (here, aged 18 to 20) and adult (here, aged 30 to 40) responses to THC in relatively light cannabis users who are drug-free at the time of testing.

A second goal of this study is to develop a sensitive measure of THC intoxication by analyzing text from samples of subjects' spontaneous speech. We have used analyses of speech production and semantic content to assess changes in mental state during acute intoxication with several other drugs, including MDMA and methamphetamine (Agurto et al., *in press;* Baggott et al., 2015; Bedi et al., 2014; Wardle et al., 2011), but never with THC. The application of speech and text analyses to THC effects is a promising avenue to develop more sensitive behavioral measures of THC intoxication. Importantly, the accurate detection of cannabis intoxication is a major public health concern. Drugs can change a range of features of human speech, including the quantity, speed, fluency, volume, and acoustic features. In addition, drugs can affect many aspects of semantic content including perceived features of drug effects. By applying sensitive quantitative techniques to analysis of speech and text samples, it may be possible to extract features that reflect intoxication with this drug.

A third goal is to determine whether THC alters EEG patterns, and whether this is related to age. THC is known to affect neural responses as measured by EEG from oscillatory power to evoked related potentials (ERP) (Skosnik et al., 2016). (For instance, oral, smoked, and intravenous administration of THC reduce the amplitude of the P300 waveform (D'Souza et al., 2012; Ilan et al.,

2005; Roser et al., 2008; Stadelmann et al., 2011; Theunissen et al., 2012). The P300 is a positive waveform that peaks 300 ms after a stimulus and is related to attention and working memory. Another study showed that vaporized THC (22 mg) reduced the error-related negativity (ERN) in frequent cannabis users. ERN is an ERP with negative polarity that corresponds to a participant's recognition of error during an error-monitoring task (Kowal et al., 2015). Although THC is known to disrupt gamma (30-80 Hz) and theta (4-7 Hz) oscillations (reviewed by Skosnik et al., 2016), in this study, we will focus specifically on the P300 and ERN. Electrophysiological measures are valuable because they provide a sensitive direct measure of neural activity and can be used to examine drug effects, and age-related variations in drug effects, in relation to both mood and cognitive performance.

Research Design: We will use a combined within and between subject design to examine whether healthy, young men and women (aged 18 to 20) are more sensitive than older participants (aged 30 to 40) to the acute effects of THC. Healthy occasional cannabis users in the two age groups will participate in three laboratory-based sessions spaced at least seven days apart, in which they will receive capsules containing placebo, 7.5 mg THC, or 15 mg THC under double-blind conditions. For each session, participants will complete self-report questionnaires of subjective effects, and cardiovascular measures will be obtained at regular intervals. They will complete speech, behavioral, and electroencephalogram (EEG) tasks once each session, at the time of expected peak effect.

Participants. Participants will include 20 healthy male and female volunteers, half of whom will be aged 18-20 and the other half aged 30 to 40. The N of 20 participants is based on a reported effect size *(f* = 0.403; Mokrysz et al., 2016) on our primary outcome measure (group x drug interaction on Drug Effects Questionnaire: "Feel"), which requires a sample size of 16 for at least 80% power at an alpha of 5% (G*Power). The groups will be matched on number of males and females and on body mass index. Subjects will be excluded if they have a history of psychosis, nursing or pregnant, planning to become pregnant, or have a body mass index outside of 19 to 26. Subjects must have at least a high school education and fluency in English. Other criteria include individuals who have used the drug between 1 to 20 times lifetime and 0 times in last 30 days. Qualifying participants will agree to abstain from alcohol for 24 hours and other recreational drugs for at least 2 days before each session. They will be informed that breath and urine samples will be obtained on each session to verify abstinence. Participants will also be asked to fast 4 hours before the behavioral laboratory session.

Drug. THC (Marinol® [dronabinol]; Solvay Pharmaceuticals) will be orally administered in doses of 7.5 mg and 15 mg, in opaque capsules with dextrose filler. Placebo capsules contain only dextrose. The 15 mg dose reflects the amount of THC in one-half of a cannabis cigarette containing 0.2 g of 15% THC. These doses of THC are known to produce performance impairments as well as subjective intoxication (Broyd et al., 2016; Hartman and Huestis, 2013; Pabon and de Wit, 2019).

Orientation Session. During an initial, 30-min orientation session, study procedures will be explained and participants will read and sign a consent form. Participants will then practice the tasks and questionnaires that will be administered during the subsequent study sessions. A urine sample will be obtained to confirm abstinence from cannabis; subjects will be instructed to maintain abstinence from cannabis throughout the study and refrain from any use of drugs or alcohol for 24 before and 6 hours after each drug administration session. Participants will also be told to have a normal night's sleep and to fast 4 hours before the session; a standardized snack will be provided.

Drug Administration Sessions. Three 5-hour drug administration sessions of placebo, 7.5 mg, or 15 mg Δ9-tetrahydrocannabinol (THC) will be separated by at least seven days. Each session will be conducted from 9 am to 1:30 pm in comfortably furnished study rooms that resemble living room settings. Upon arrival at the laboratory, participants will provide breath and urine samples to test for recent drug or alcohol use, and pregnancy (in females). Participants will complete the Addiction Research Center Inventory (ARCI) and Profile of Mood States (POMS) and provide measures for heart rate (HR) and Blood Pressure (BP) to assess their baseline state. Participants will consume a capsule containing 0, 7.5, or 15 mg THC under double-blind conditions. The order will be randomized across subjects. Participants will be provided a snack 30 min after administration. Participants will complete the ARCI, POMS, and Drug Effects Questionnaire (DEQ) 60, 120, 180, and 240 min after taking the capsule; heart rate (HR) and Blood Pressure (BP) will be taken at the same time. During peak drug effects, participants will complete a 10-min written self-report, 5-min monologue speech task and several behavioral tasks, including the Stop Task, N-Back Task, and Time Production Task (TPT) in randomized order. At 130 min post-administration, participants will be accompanied across the hall to the EEG center for two tasks: the Auditory Oddball P300 and Flanker Interference task. After EEG measures, participants will return to the lab and subjects will be given lunch. At 240 min subjects will complete the 5 Dimensions of Altered States of Consciousness (5D-ASC) scale, the State Mindfulness Scale (SMS) and an End of Session Questionnaire before being discharged. In the interest of safety, for subjects who cannot arrange a ride home, we will pay for transportation home. After the final session, participants will be informed of the purpose of the study including the drug that they received and will be allowed to ask any additional questions about the study.

Speech and Text Measures.

1. The monologue speech task (Agurto et al., *in press*; Higgins and Stitzer, 1989; Wardle et al., 2011) measures spontaneous speech, initially developed to determine how the amount of speech may be changed by acute effects of alcohol and amphetamine (Higgins and Stitzer, 1989). The task consists of a 5-min period during peak drug effects in which subjects are allowed to talk while they are alone in a room with a voice recorder. Subjects are told they are allowed to talk as much or as little as they like on any topic. All recorded speech is transcribed by a professional blind to drug condition for analysis. The primary outcome measure is the percent accuracy in classification of drug condition based on frequent word occurrences during the 5-min task.

   Analytic approach

   a. Acoustic features: Acoustic features will be extracted from five categories, including voice stability (jitter, shimmer, and voice breaks), pitch variations, spectral characterization, vowel space, and temporal features. Feature extraction involves the software Praat and Python.
   b. Semantic features: Total number of words and frequency of word occurrences will be used to compare across the drug conditions. Text derived from speech will be preprocessed with the Natural Language Toolkit (NLTK). Words will be counted from a tokenized word list, which is created by use of Treebank tagger, to identify parts of speech, and WordNet, to lemmatize words into tokens.

c. Classification: We will use a machine learning approach to determine the number of word occurrences in text in each drug condition. This approach incorporates Random Forests, which generates decision trees based on individual word predictors.

2. For written self-report, participants will receive the following instructions: "For the next 10 minutes, you are asked to attend to how you are feeling right now. During this time, write down as little or as much as you like about any thoughts or sensations you are having." All writing will be converted into text for analysis. The primary outcome measure is the degree of distinction between drug conditions based on frequent word occurrences, in parallel to the 5-min speech task.

   Analytic approach

   a. Semantic features: Total number of words and frequency of word occurrences will be used to compare across the drug conditions. Text derived from speech will be preprocessed with the Natural Language Toolkit (NLTK). Words will be counted from a tokenized word list, which is created by use of Treebank tagger to identify parts of speech, and WordNet, to lemmatize words into tokens.

   b. Classification: We will use a machine learning approach to classify the number of word occurrences in the written text. This approach incorporates Random Forests, which generates decision trees based on individual word predictors.

Self-Report Measures.

1. The Addiction Research Center Inventory (ARCI; Martin et al., 1971) is a 53-item true/false questionnaire, including a 12-item Marijuana (M) subscale specific to cannabis. We will focus our analyses on the M scale.
2. The Profile of Mood States (POMS; McNair et al., 1971) is a 72-item questionnaire used to assess momentary mood states across 8 subscales: Anxiety, Depression, Anger, Vigor, Fatigue, Confusion, Friendliness, and Elation. Participants will indicate how they feel at that moment in relation to 72 adjectives on a 5-point scale from "Not at all" (0) to "Extremely" (4).
3. The Drug Effects Questionnaire (DEQ; Morean et al., 2013) is comprised of 100 mm visual analog scales (VAS) to provide ratings to five questions: "Do you feel any drug effect?" ("None at all" to "A lot"); "Do you like the effects that you are feeling now?" ("None at all" to "A lot"); "Do you dislike the effects that you are feeling now?" ("None at all" to "A lot"); "Are you high?" ("Not at all" to "Very"); and "Would you like more of what you consumed, right now?" ("Not at all" to "Very much"). The measure of primary interest is the "feel" question.
4. The 5 Dimensions of Altered States of Consciousness (5D-ASC; Studerus et al., 2010) scale consists of 94 statements describing common features of altered states of consciousness (ASC), independent of their means of induction. In developing the scale, 11 ASC induction mechanisms including THC were used. The 5D-ASC contains five dimensions of ASC: Oceanic Boundlessness, Dread of Ego Dissolution, Visionary Restructuralization, Acoustic Alterations, and Vigilance Reduction (Studerus et al., 2010). Subjects respond to statements on a 100 mm visual analog scale indicating how they feel relative to their normal waking consciousness and the degree to which they experienced each item during that day's session. The 5D-ASC is often used in studies of 'classical psychedelics' which bind 5HT-2A serotonin receptors. Although THC was included in the development of this scale, we note that measures of THC effects will

be exploratory. We know of no previous THC studies that have incorporated the 5D-ASC. The 5D-ASC will be administered once at the end of each session.

5. The State Mindfulness Scale (SMS; Tanay and Bernstein, 2013) is comprised of two subscales, including a 15-item mindfulness-of-mind subscale and six-item mindfulness-of-body subscale (sample item: "I clearly physically felt what was going on in my body"). With each item, participants provide ratings on a five-point scale from "Not at all" to "Very much." The SMS will be administered once at the end of each session.

Behavioral Measures.

1. The Simple Reaction Time task (SRT; Leth-Steensen et al., 2000) is used to measure inattention. Participants execute a key press as quickly as possible to a target presented on the computer screen at variable intervals. The difference between a participant's mean and modal reaction time (RT) represents the proportion of unusually long RT's, which are inferred to reflect momentary lapses in attention. Greater deviations of mode scores indicate more lapses in attention (De Wit, 2009; McCloskey et al., 2010). This task takes 2-3 minutes to complete.
2. The Stop Task (Logan et al., 1997) is designed to assess a participant's ability to inhibit a prepotent motor response. Subjects are instructed to respond as quickly as possible when a certain letter (Go signal) is presented visually on a computer screen, and to inhibit (stop) their responses when a tone is presented. The tone is presented on random trials and at different delays following each letter presentation. The delays to the Stop signal are varied systematically according to the participant's performance: the delay to the tone is adjusted until the subject inhibits (stops) his or her responses on approximately 50% of trials. Once the Stop signal delay has been adjusted to this 50% criterion, the time required for the subject to stop the go response is determined. The primary measure of interest is the Stop reaction time (Stop RT), which is calculated by subtracting the final mean delay at which the tone is presented from the mean Go reaction time (Go RT), or the latency to respond to the letter presentation, which is a secondary measure. Both reaction times are measured in milliseconds. This task takes 7 mins.
3. The N-Back Task (Gevins and Cutillo, 1993) assesses executive attention and working memory. Participants respond when the current visual and audio stimulus (a letter) is the same as the one presented *n* trials earlier; where *n* is either 1, 2, or 3. This task takes 10 mins.
4. The Time Production Task (Sewell et al., 2013) assesses the rate of participant's internal clock relative to actual time. Participants will be instructed to press and hold a key for 10, 20, 30, and 40 seconds in a randomized order while attending to distractor stimuli. The ratio of produced time to actual time is the outcome measure of interest. This task takes 3 mins.

Cardiovascular Measures. Blood pressure and heart rate will be monitored every 30 min using portable blood pressure cuffs, to track the cardiovascular effects of the drug, and ensure participant safety.

EEG Measures.

For EEG recordings we will use 128 sintered Ag/AgCl active electrodes (ActiveTwo™ system, BioSemi B.V., Amsterdam). Electrodes will be placed according to equiradial layout on a head cap with snaps. Additional electrodes will be placed at reference locations of the mastoids, and around the eye to exclude data contaminated by eye blink artifacts. The analog-to-digital box receiving the electrode leads is battery-powered, so participants are electrically isolated and multiple safety mechanisms in the

ActiveTwo system limit current flow (http://www.biosemi.com/faq/limit_current.htm) takes about 30-45 minutes for two research staff members to apply the gel and snap on electrodes. EEG data will be acquired continuously, amplified, and digitized using Biosemi ActiveView software. Electrode placement reflecting head shape will be digitized using a Patriot™ Digitizer Stylus (Polhemus Co., Colchester VT) and Locator software (Source Signal Imaging, Inc., San Diego CA). The stylus touches each electrode site until registered by the software (5-10 minutes total). EEG recordings will high pass filtered (0.05 Hz), and low pass filtered (60 Hz, -12 dB/octave) to remove extraneous high and low frequency noise. EEG and EOG signals will be processed by voltage-controlled amplifiers and digitized for storage and analysis. Data will be processed offline based on data stored on computer workstation hard drives using BESA Research signal processing software.

1. The Auditory Oddball P300 Task (Donchin et al., 1978) is an event related potential (ERP) task known to be a valid index of attention and cognition. Subjects will attend to auditory stimuli. Using a classic oddball design, frequent tones will be jittered with rare tones for 1 block in a 3 to 1 ratio. Stimuli will be projected from computer speakers for 1500 ms. The sequence of blocks will be randomized and counterbalanced across subjects. A total of 320 auditory stimuli will be presented. The P300 is detected near the vertex of the scalp electrode array source localized to the right insula at a latency of 450 ms post stimulus. This task takes 15 minutes.
2. The Flanker Interference Task (Endrass et al., 2008; Eriksen and Eriksen, 1974) is an error monitoring task involving visual stimuli. A visual target stimulus is flanked by non-target stimuli that may either be congruent, incongruent, or neutral to the target response. Experimental stimuli will be displayed with Presentation software (Neurobehavioral Systems, San Francisco, CA) on an LCD monitor placed at a comfortable viewing angle. Trials begin with a fixation mark for 1100–1700 ms. 100 ms after onset of Flanker arrows, a central target arrow will appear for 30 ms. Subjects are to indicate the direction of the central target arrow with a button press. 500 trials will be presented, with 150 being compatible trials (with congruent flanker and target errors) and 350 being incompatible trials in pseudo-random order. To maintain time pressure and ensure an adequate number of error trials, subject response times will be recorded and subjects will be prompted to move more quickly based on a moving average of the past 50 correct trials. Error-related negativities (ERNs) will be recorded. This task takes 5 mins.

Timeline:

9:00	-30	Arrival, breath and urine tests
9:15	-15	Subjective and cardiovascular measures (baseline)
9:30	0	Capsule administration
10:00	+30	Standardized snack
10:30	+60	Subjective and cardiovascular measures
10:50	+80	Written self-report
11:00	+90	Subjective and cardiovascular measures, speech and behavioral tasks
11:30	+120	Subjective and cardiovascular measures
11:40	+130	Move to CNPRU and prepare EEG for recording
12:10	+160	EEG: auditory oddball P300 and Flanker task
12:30	+180	Subjective and cardiovascular measures
1:30	+240	Subjective and cardiovascular measures, 5D-ASC, SMS, End of Session Questionnaire

Data Analyses: The effects of the drug on subjective, behavioral, and cardiovascular measures will be assessed with mixed analysis of variance, with the between-subjects factor of group (adolescent, adult) and within-subjects factors of drug (placebo, 7.5 mg, 15 mg THC) and time (within session). Repeated measures ANOVA will compare ERPs including P300 amplitude between THC and placebo sessions.

Human Subjects Information

Recruiting methods: We will place print ads in newspapers and on online job search sites such as craigslist.org, Facebook, and flyers in the Chicago area. Volunteers who respond to our ads are screened using our standard screening protocol for all studies in the Human Behavioral Psychopharmacology Laboratory, which is separately approved by the IRB under Protocol #13681B

Obtaining consent: Consent for the screening session only is obtained at the screening according to procedures outlined in Protocol #13681B. Written informed consent for the study procedures is obtained at the orientation session, after a verbal explanation of study procedures, check of comprehension, and an opportunity for the participant to ask any questions they may have. Consent is verbally re-verified at the beginning of each study session.

Risk to subjects:

1. Diagnostic procedures and questionnaires: Some of the questions asked during the screening may be considered sensitive information, including drug use history and psychiatric history. We have rigorous procedures in place to ensure confidentiality of data, including locked cabinets for confidential files, subject coding, secure computer systems, and rigorous training of personnel. Please see screening protocol #13681B for full information on steps taken to protect information gathered as part of the screening.

2. Study drug: The possible side effects of THC (Marinol® [dronabinol]) include weakness, nausea or vomiting, memory loss, anxiety, confusion, dizziness, lack of balance, feeling like you are outside your body, "high" or elevated mood, hallucinations, sleepiness, and strange or unusual thoughts. Subjects are carefully screened to exclude those who are physically or psychiatrically at risk (e.g., current AXIS I disorders or history of psychosis). The studies are conducted in a hospital, where emergency assistance, including the psychiatry resident on-call, and the psychiatrist connected with the study are close at hand. A research assistant will be present throughout the procedures and will monitor heart rate, blood pressure throughout the sessions. In addition, on-call physicians will be available in the case of medical emergencies. Subjects will be provided with transportation home after the sessions. Subjects will be told that small amounts of the drugs or their metabolites will be detectable in the body for several weeks and to advise the experimenter if they intend to undergo a drug screening within one month of participating in the study.

3. EEG: There are no known side effects or toxicity from EEG recording. Sometimes the sessions can be tedious and subjects may become drowsy during the procedure. This is a temporary state that can usually be addressed by allowing the subject to stand up and stretch. Placement of the electrodes requires the use of a conductive gel and parting of the hair. Therefore, cleanup is needed after each session and this is likely to disturb hairstyle and grooming temporarily.

Subject time commitment and compensation: The study sessions (3 sessions) are estimated to last 5 hrs each, for a total of 15 hours spent in study sessions. Participants will be compensated $50 for each session with a $100 completion bonus for a total of $250.

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