Document Coversheet

Study Title: Neural Mechanisms of Cannabinoid-impaired Decision-Making in Emerging Adults

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	10/13/23 (protocol); 7/10/23 (consent)
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Which IRB

- ◉ Medical ○ NonMedical

Protocol Process Type

- ○ Exemption
- ○ Expedited (Must be risk level 1)
- ◉ Full

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

Which IRB

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

Note: Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

Which Protocol Process Type

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Neural Mechanisms of Decision-Making in Emerging Adult Cannabis Users

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

TMS in Emerging Adults with CUD

Anticipated Ending Date of Research Project: 6/30/2024

Maximum number of human subjects (or records/specimens to be reviewed) 80

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? (•) Yes ( ) No

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

The landscape surrounding cannabis use in the US is changing dramatically (Pew Research Center, 2015). From 2002-2014, daily or near daily cannabis use steadily increased in young adults (Compton et al., 2016) and further escalation is expected due to decreasing perceptions that use is harmful (Johnston et al., 2014). The concentration of delta-9-tetrahydrocannabinol (THC), the main psychoactive chemical in cannabis, has also risen (Mehmedic et al., 2010), which is thought to add to the risk for addiction and other negative outcomes (NIDA, 2015; Niesink & van Laar, 2013; Sarne et al., 2011). Adolescence and young adulthood are critical neurodevelopment periods, and importantly, the endogenous cannabinoid system plays a central role in neurodevelopment (Lubman et al., 2015). Data from preclinical (Rubino et al., 2015; Verrico et al., 2014; Zamberletti et al., 2014) and human studies (Camchong et al., 2016; Churchwell et al., 2010; Lopez-Larson et al., 2011) suggest that cannabis use alters neurodevelopmental trajectories. For example, habitual use in young adults was linked to prefrontal cortex (PFC) abnormalities (Churchwell et al., 2010; Lopez-Larson et al., 2011; Shollenbarger et al., 2015) and adverse neurocognitive outcomes, including suboptimal decision-making (Meier et al., 2012; Volkow et al., 2016) and decreased attention and motivation (Volkow et al., 2014, 2016). These findings indicate that young adults are particularly vulnerable to the negative consequences of cannabis use. Accordingly, NIDA has predicted that cannabis use disorder (CUD) will soon escalate in this group (Volkow et al., 2016).

CUD is largely defined by maladaptive decision-making, including the choice to use cannabis instead of fulfilling role obligations, more frequently/longer than intended, and despite negative consequences. Decision-making in habitual users often occurs while intoxicated, which is problematic because cannabis/THC impairs decision-making processes. Acute cannabis/THC administration increased risky decision-making (Lane et al., 2005; Liguori et al., 1998; Ramaekers et al., 2000) and impaired working memory and attention (Greenwald & Stitzer, 2000; Ilan et al., 2004; Kelly et al., 1990; Lane et al., 2005), and dysfunction in these processes is predictive of problematic drug use. For example, a positive correlation between impaired decision-making and cannabis use amount and use-related problems was found in young adults (Gonzalez et al., 2012). Although impaired decision-making may precede cannabis intake, these data suggest that cannabis intoxication exacerbates suboptimal decision-making, thereby promoting the continued expression of CUD (Loughead et al., 2015). Further, individual differences in susceptibility to the impairing effects of cannabis/THC on decision-making processes and their underlying neural substrates likely contributes to the differential development of CUD (Sagheddu & Melis, 2015). Lastly, sensitivity to the acute reinforcing and positive subjective effects of cannabis/THC also likely contributes to the decision to use cannabis and the development of CUD (Sagheddu & Melis, 2015; Fischman & Foltin, 1991). These data demonstrate the need to understand the mechanisms of acute cannabinoid effects on decision-making and associated neurocognitive processes that confer increased CUD risk (Volkow et al., 2016).

The PFC, which underlies higher-order cognitive functions and interoception (Lau & Rosenthal, 2011), undergoes experience-dependent synaptogenesis and pruning throughout young adulthood (Lubman et al., 2015). The dorsal lateral prefrontal cortex (DLPFC) is hypothesized to monitor and direct task-relevant information, and to evaluate costs and benefits of choice alternatives (Davidson & Irwin, 1999). Previous magnetic resonance imaging (MRI) studies, including our own (Wesley & Bickel, 2014), demonstrated that the left DLPFC is critically involved in decision-making, working memory, and attention processes (Wesley & Bickel, 2014; Rossi et al., 2009a), and has been linked to cannabis vs. money choices (Bedi et al., 2015). Of particular relevance are the direct anatomical links between the DLPFC and the medial orbital (OFC) and ventral medial (vmPFC) prefrontal cortices. We previously demonstrated that abnormal function in these ROIs is associated with impaired decision-making (Wesley et al., 2011a) and emotional evaluation (Wesley et al., 2011b) in heavy cannabis users. Activity and connectivity of these ROIs might be especially important in the cognitive control of decision-making and affective states related to drug use. For example, age-related increases in their connectivity improves behavioral control (Steinbeis et al., 2016) and their connectivity increased when choosing long-term rewards (Hare et al., 2014). Increasing PFC functionality could lead to "healthier" decision-making in drug abusers (Gorelick et al., 2014a).

Clinical pharmacology studies are able to establish causal links between specific neurotransmitter systems and behavior, but are limited in their ability to determine the causal role of specific and interconnected ROI function on behavior. Non-invasive brain stimulation has emerged as a safe means to test causal relationships between neural function and behavior by temporarily raising or lowering intrinsic activity in targeted brain regions. The combination of non-invasive brain stimulation with drugs having preferential activity at specific neurotransmitter sites and neuroimaging techniques is being used in other research fields to uncover mechanisms of behavior (Liebetanz et al., 2002; Paulus et al., 2008; Ziemann, 2013; Ziemann et al., 2014; Nardone et al., 2015; Korchounov &

Ziemann, 2011). In particular, transcranial magnetic stimulation (TMS) holds promise for combatting reductions in cognitive functions observed with chronic cannabis use. TMS directly modulates neuronal transmission by passing a magnetic field through the skull to subsequently initiate action potentials through electromagnetic induction (Rossini et al., 2015). TMS applied to the DLPFC reduced craving for nicotine, cocaine and alcohol (Gorelick et al., 2014b) and has been approved as a treatment for major depressive disorder by the FDA since 2008. Thus, TMS is a safe and effective means to test direct relationships between neural structure/function and behavior by temporarily raising or lowering intrinsic functionality in the DLPFC. This prefrontal modulation approach to treatment is consistent with central theories of addiction (Bickel et al., 2007; Bechara and Damasio, 2005). Importantly, non-invasive stimulation of the DLPFC with TMS has been shown to positively impact outcomes that are compromised by acute cannabis or THC exposure (subjective state, risky choice, working memory; see Coles et al., 2018 for a thorough review), making it a likely candidate for blocking the acute effects of cannabis and THC.

This double-blind, placebo- and sham-controlled study will determine how increasing and decreasing neuronal activity via TMS influences the effects of THC in young adults. More specifically, it will assess the impact of excitatory and inhibitory TMS (real and sham) of the DLPFC on decision-making and working memory as well as the subjective and physiological effects of oral THC (0, 10, and 30 mg). The MagVenture TMS brain stimulation devices have previously been approved by the FDA (See FDA letters at the end of Form S under Additional Information/Materials). THC (Marinol) is FDA approved for use as an appetite stimulant in AIDS patients and as an anti-emetic for patients undergoing chemotherapy for cancer. The product information for Marinol (dronabinol) and the MagVenture TMS devices are provided in Form S.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

The present study will test the ability of excitatory and inhibitory DLPFC TMS (real and sham) to block the subjective and cognitive impairing effects of oral THC (0, 10, and 30 mg), thus examining its potential as an intervention for the treatment of CUD. This study will also determine the degree to which functional activity and connectivity of PFC ROIs during baseline cognitive task performance is associated with the response to DLPFC TMS and THC, alone and in combination, using functional magnetic resonance imaging (fMRI) techniques.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

A double-blind, sham- and placebo-controlled, 2x2x3 mixed-factorial design will be used to assess the impact of excitatory and inhibitory TMS (real and sham) of the DLPFC on decision-making, working memory, subjective drug effects, and physiology following acute administration of oral THC (0, 10, and 30 mg) in two experiments. Each experiment will consist of one training and six experimental sessions. Subjects in Experiment 1 will receive real and sham excitatory intermittent theta-burst stimulation (iTBS) in combination with each dose of oral THC. In Experiment 2, subjects will receive real and sham inhibitory continuous theta-burst stimulation (cTBS) combined with each dose of oral THC. Under this arrangement, TMS Protocol (iTBS or cTBS) is a between-subjects factor whereas TMS Type (real and sham) and THC dose (0, 10, and 30 mg) are within-subjects factors. Figure 1a (attached) shows a diagram of the experimental design.

Attachments

Attach Type	File Name
StudyDesign	Figure1.pdf

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

Subjects are recruited primarily through formal advertisement (i.e., newspaper advertisements), local flyers posted in public areas (e.g., bars, marketplaces), online classifieds (e.g., craigslist) and by word-of-mouth. These advertisements have been approved by UK PR and are provided under our screening protocol (IRB#: 43686). Briefly, during this screening subjects will initially contact the laboratory by calling the telephone number or writing to the laboratory's official, university-issued email address (nsl@uky.edu) that are provided on the approved advertisements. Whenever possible, email will be used as the preferred means to communicate with potential research participants regarding the procedures and process for determining whether they might qualify to participate in the study (e.g., provision of secure links to complete REDCap surveys) and to schedule in-person appointments. However, email will not be used as a means to collect sensitive information (e.g., protected health information) that will be used to determine eligibility for study participation. All information used to determine eligibility will be collected via secure REDCap surveys completed prior to and/or during in-person appointments at the laboratory. All screening procedures are described in detail in our screening protocol (IRB#: 43686). Screening is coordinated by research staff who have completed the required research training and HIPAA compliance web-based teaching modules and conducted remotely (online) and/or in-person at one of the Neurobehavioral Systems Lab (NSL) facilities. All screening information is collected electronically and securely stored via UK's REDCap system. Study investigators may interact with subjects during screening and appropriate cautions are in place to ensure privacy during the intake process.

Screening procedures for all subjects will include a medical history questionnaire, lifetime drug use history, lab chemistries (blood chemistry screen, complete blood count, urinalysis and ECG) and a brief psychiatric examination. These procedures will be conducted under our screening protocol (IRB#: 43686). During screening, potential subjects will be asked to provide a urine specimen that will be screened for the presence of recent use of amphetamines, benzodiazepines, barbiturates, cocaine, cannabis and opioids. Urine samples from females will also be tested for pregnancy; women who test positive for pregnancy will be notified and discontinued from the screening process for this protocol. Of note, relevant inclusion/exclusion criteria involving neuroimaging scanning are consistent with those involving brain stimulation and as such are accounted for in our research protocols. All participants will be judged to be healthy by the study physician, Lon R. Hays, MD, prior to being enrolled in the study.

Important to note is that HIPAA-regulated PHI will NOT be accessed as part of this study. HIPAA-protected PHI is only accessed during screenings that are conducted under our approved screening protocol (IRB#: 43686) prior to enrollment in this study.
All advertising procedures are described in our screening protocol (IRB#: 43686). A copy of the fliers and social media ads pertinent to this protocol are attached.

Attachments

Attach Type	File Name
Advertising	nsl_cannabis_flier_APPROVED.pdf
Advertising	nsl_cannabis_social_media_ad_3_APPROVED.pdf
Advertising	nsl_cannabis_social_media_ad_4_APPROVED.pdf
Advertising	nsl_cannabis_social_media_ad_4.pdf
Advertising	nsl_cannabis_flier.pdf
Advertising	nsl_cannabis_social_media_ad_3.pdf

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

See Table 1 (attached) for a list of study visits and Figure 1b for a schematic of the procedures during experimental sessions. Excluding approximately two screening visits prior to study enrollment (carried out under our screening protocol IRB#: 43686), the study proper will consist of seven (7) outpatient visits: 1 training session (Visit 1) and 6 brain stimulation (TMS) and drug administration experimental sessions (Visits 2-7) taking place over approximately 3-5 weeks. Experimental sessions (Visits 2-7) will last for approximately 7 hours and will be separated by at least 48 hours.

Check-in/Check-out Procedures and Verifying Compliance with Restrictions (All Visits):
Monitoring and check-in and check-out procedures for all sessions will be the standard for behavioral pharmacology studies conducted in the NSL. Upon arrival, subjects will relinquish their keys, watch and mobile phone, which will be stored securely until the end of the session. Next, a field sobriety test will be conducted and an expired-breath sample will be collected to detect recent alcohol use. A urine sample will also be collected to screen for illicit drug use and pregnancy using standard (i.e., qualitative) commercially-available, urine toxicology cassettes (e.g., CLIA-RDDT-52, CLIA-RDDT-88, CLIA-02-2479; CLIAwaived, San Diego, CA, USA). Subjects must agree to abstain from using illicit drugs other than cannabis for the duration of the study. Subjects must also agree to refrain from using cannabis and alcohol for 12 hours prior to each experimental session. Breath samples positive for alcohol or a urine sample positive for drugs of abuse other than cannabis will preclude the subject from participation in that experimental session, and an additional visit will be scheduled. Repeated violations will result in dismissal from the study. Female subjects who test positive for pregnancy will be notified and discontinued from participation. Subjects who smoke tobacco cigarettes will then be escorted by research staff to smoke a single cigarette. Subjects will not be allowed to smoke again until the session has ended. Previous research that has required subjects to abstain from using tobacco products over the course of a 6- to 7-hour session has been successful and appears acceptable. Nonetheless, all subjects will be closely monitored for signs of nicotine withdrawal. Subjects must also agree to abstain from solid food and caffeine for 4 hours before each experimental session, and will be provided with a standard, fat- and caffeine-free snack after completing all check-in procedures.

Prior to being discharged at the end of each session, subjects will provide an expired-breath sample, perform a field sobriety test, and sign a release form stating their vital signs and breathalyzer balance at the time of their release. The release form includes statements for the subject to acknowledge that they may still be impaired by the capsules that they received during the session and that they have been advised not to drive a motor vehicle or operate heavy machinery and that they agree to abide by those instructions (see Release Form attachment).

Training Session: Baseline Tasks and MRI Scans (Visit 1)
During the Training Session, subjects will be familiarized with the experimental tasks and procedures of the experimental sessions. Subjects will be familiarized with TMS during the training session using a single-pulse TMS procedure that will be used to determine resting motor threshold (rMT) during experimental sessions. Briefly, the volunteer will be seated in a chair and the MagVenture C-B60 TMS coil will be positioned against the subject's scalp over the primary motor cortex. Single magnetic pulses from the TMS coil will be used to locate the region of the primary motor cortex that controls the hand and fingers, with the goal of limiting TMS-pulse-induced motor responses to the thumb and first finger. Single TMS pulses will then be administered and the stimulation output intensity will be adjusted using either the adaptive PEST algorithm for non-parametrically estimating TMS motor thresholds (http://www.clinicalresearcher.org/software.htm) and/or the Rossini-Rothwell method using electromyographic (EMG) recording equipment. The Rossini-Rothwell method determines the minimum single-pulse intensity necessary to produce motor evoked potentials (MEPs) of at least 50 microvolts (uV) peak-to-peak amplitude in at least 50% of pursued trials (e.g., 5 or more of 10 trials).

Subjects will also be escorted to the Magnetic Resonance Imaging and Spectroscopy Center (MRISC) at the UK Medical Center to perform the battery of cognitive assessments (described under Data Collection) while in the MRI scanner during the training session. Neuroimaging data will be acquired using a Siemens 3-Tesla (3T) PRISMA scanner as described under Data Collection below. Subjects will not undergo MRI scanning during the 6 experimental sessions.

Brain Stimulation and Drug Administration Experimental Sessions (Visits 2-7):
Experimental sessions during Experiments 1 and 2 will last approximately 7 hours and test 6 combinations of TMS and THC on relevant outcome measures (Visits 2-7; Figure 1). Subjects in Experiment 1 will receive real and sham excitatory iTBS of the left DLPFC. Subjects in Experiment 2 will receive real and sham inhibitory cTBS of the left DLPFC. A single bout of iTBS or cTBS (real or sham) TMS will be delivered at a single time point (approximately 3 hours after capsule administration) during each experimental session. Subjects will receive the 6 experimental conditions in random order except that the combination of 30 mg THC + active TMS condition (iTBS or cTBS) will not be administered prior to the administration of 30 mg THC + sham TMS.

Drug Administration: THC (10 and 30 mg) and placebo will be administered orally under double-blind conditions. The oral route was chosen to maintain subject and research staff blindness and to eliminate any expectations that may accompany other routes of drug administration (i.e., smoking). Subjects will ingest capsules with approximately 150 mL of water. Research staff will conduct a mouth check to ensure that the subject swallowed the capsules. Placebo will also be tested and capsules will be filled with a behaviorally inert substance (e.g., corn starch). If heart rate is above 100 bpm before dose administration, the dose will be withheld and heart rate reassessed every 15 minutes for 1 hour. If heart rate has not fallen below 100 bpm after 1 hour, the study physician will be consulted regarding the subject's continued participation in the study.

The doses of THC will be 10 and 30 mg. Capsules will contain commercially available delta-9-THC (Marinol; dronabinol). This active dose was chosen based on our previous laboratory research with THC in humans (Lile et al., 2009, 2010a, 2010b, 2011, 2012a, 2012b, 2013, 2014, 2015). For comparison, the therapeutic dose range indicated for antiemesis is 5-20 mg administered 4-6 times per day. The starting therapeutic dose range indicated for appetite stimulation is 2.5-10 mg administered prior to lunch and dinner, but this can be increased up to 20 mg. We have previously administered up to 90 mg THC acutely (Lile et al., 2013) in individuals with less cannabis experience than proposed in the present study. Plasma concentrations for oral THC peak from 2-4 hours, which is consistent with the proposed experimental procedures (Hollister et al., 1981). The half-life of THC is 19-36 hours, but the duration of the psychoactive effects last only 4-6 hours (Hollister et al., 1981; Lemberger et al., 1972).

TMS Coil Placement and Stimulation Parameters: For real and sham sessions in both experiments, rMT will be determined before the delivery of iTBS (Exp. 1) and cTBS (Exp. 2) using standard single-pulse motor mapping procedures (described above) during each experimental session. Determination of rMT before delivery of TMS (i.e., iTBS or cTBS) during each session is necessary because rMT varies across individuals and in response to various environmental and individual factors (e.g., across days and times of day, amount of sleep) and ensures that the minimum necessary stimulation intensity is used during the TMS protocol during each experimental session. rMT will be determined after check-in procedures have been completed, prior to capsule administration.

A two-sided, MagVenture Cool-B65 active/placebo coil will be used to deliver active (real) and sham TMS during experimental sessions. This coil is specifically designed to facilitate double-blind research experiments in that the administrator does not know which side of the coil is active. Instead, the administrator relies on protocol numbers and a gyrometer internal to the coil to determine the appropriate coil orientation for a given session. Standard 10-20 international EEG coordinates and neuronavigation technology will be used to place the TMS coil over the left DLPFC. The international 10-20 EEG coordinate system will be used to locate the F3 region (corresponding with the DLPFC) and each subject's structural MRI scan, collected during the training session, will be uploaded into functional neuronavigation software (Brainsight; Rogue Research Inc., Montreal, Quebec, Canada) that is integrated with real-time, infrared tracking equipment. The neuronavigation system will be used to refine the position of the TMS coil to minimize the distance between the center of the coil and the subject's cortical tissue.

Theta-burst stimulation (TBS) protocols deliver 3-pulse bursts of TMS at a frequency 50 Hz, repeated every 200 milliseconds (i.e., 5 Hz), and differentially modulate neuronal activity depending on whether bursts of pulses are delivered intermittently (i.e., iTBS; excitatory) or continuously (i.e., cTBS; inhibitory). These TBS parameters mimic endogenous theta rhythms that are associated with the induction of long-term potentiation (LTP) and long-term depression (LTD) mechanisms implicated in learning and memory (Huang et al., 2005).

Subjects will receive a single bout of real or sham TBS during each experimental session that will occur approximately three hours after THC administration (see Figure 1). This time point coincides with the approximate time at which THC concentration in plasma reaches its peak. During each session involving real, excitatory iTBS sessions in Experiment 1, the active side of the coil will face inward directly over the stimulation target (left DLPFC) and the iTBS600 stimulation protocol will be delivered. The excitatory iTBS600 protocol consists of twenty, 2-second trains (10 TBS bursts; 30 pulses/train) repeated every 10 seconds (8 second inter-train interval) across a total of 190 seconds (Huang et al., 2005; Wischnewski and Schutter, 2015). This iTBS protocol recently received FDA approval for the treatment of medication resistant major depressive disorder (FDA 510(k): K173620). During each session involving real, inhibitory cTBS in Experiment 2, the active side of the coil will face inward directly over the stimulation target (left DLPFC) and the cTBS600 stimulation protocol will be administered. The cTBS600 protocol consists of one, uninterrupted, 40-second train of 3-pulse bursts presented at 5 Hz, for a total of 600 pulses (Huang et al., 2005). Comparable TBS parameters have been used previously to modulate executive functioning and motor cortex excitability (see Chung et al., 2016 and Lowe et al., 2018 for reviews). The effects of TBS on executive function last approximately 50-60 minutes after stimulation (Huang et al., 2005; Wischnewski and Schutter, 2015). During all TMS sessions, the target amplified iTBS and cTBS pulse outputs will be 120% of rMT. Importantly, this output intensity setting is the same as that in the FDA-approved iTBS protocol used clinically and we have successfully delivered TMS at 120% of rMT in another IRB-approved protocol (IRB: 44178) without untoward effects. However, the final amplifier output intensity setting for each subject may be reduced from 120% of rMT (final pulse output intensity range of 80-120% of rMT) to increase tolerability, minimize subject discomfort, and improve subject satisfaction with study procedures. To further promote subject comfort and satisfaction with study procedures, a ramp-up procedure that gradually increases the amplifier output intensity from 80% of the target stimulation intensity up to the final pulse output intensity (maximum: 120% of rMT) will be used. The ramp-up procedure will consist of an additional 300 pulses following the same pulse sequence parameters described above (adding approximately 20 or 100 seconds to the total stimulation period length for cTBS and iTBS, respectively) that immediately precede the 600 pulses delivered for iTBS600 and cTBS600. Thus, subjects will receive a total of 900 TMS pulses in each real/active TBS session, 600 of which will be delivered at the target pulse output intensity. Although we do not have other IRB-approved protocols that have used a ramp-up procedure, they are commonly used to enhance the tolerability of TMS procedures (e.g., Hanlon et al., 2017; Kearney-Ramos et al., 2018).

During all sham TMS sessions, the placebo side of the coil will be positioned over the left DLPFC as described above, however the active side of the coil faces outward and a magnetic field does not pass through the skull. For both real and sham sessions, small electrodes are placed approximately 4 to 5 cm apart on the forehead on either side of the TMS target location. These electrodes pass small electrical currents subcutaneously (under the skin but not through the skull) in synchronization with the pulse sequence of the TMS procedure. This allows subjects to experience skin sensations akin to the real TMS protocol (e.g., slight tingling and/or itching and

twitching) during the sham session to facilitate experimental blinding.

Attachments

Attach Type	File Name
ResearchProcedures	07_release_form.doc

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Neuroimaging data will be acquired on a Siemens 3-Tesla (3T) PRISMA scanner. A high-resolution (1 cubic millimeter voxels) T1-weighted MP-RAGE structural image will be acquired for each subject. Functional images will be acquired using echo-planar imaging. Hyper-angulated volumes will be acquired with 37 ascending and interleaved slices at an angle 30-degrees to the anterior-posterior commissure to prevent OFC washout. Additional parameters will be similar to those used in other approved neuroimaging protocols in our lab (e.g., a repetition time (TR) of 2 seconds, echo time (TE) of 25 ms, a flip angle of 90 degrees, and functional voxels of size 3.4mm x 3.4mm x 4.0mm). Image preprocessing will be performed in statistical parametric mapping (SPM) 12 software using standard procedures (see Wesley et al., 2014). Data from functional scans will be treated similarly to fMRI data in previous studies (e.g., slice-timing corrected, head-motion corrected, warped into MNI standard space, re-sliced to 4 cubic millimeter voxels and smoothed with an 8mm full-width, half-maximum (FWHM) Gaussian kernel).

Experimental Session Outcomes: Physiological outcomes will include measurements of heart rate and blood pressure collected at hourly intervals throughout the session before each block of experimental tasks. Performance will be measured on 4 experimental tasks at baseline (approximately 30 minutes after arrival; 1 hour before THC administration) and immediately following TMS (approximately 4.5 hours after arrival; 3 hours after THC administration) (Figure 1).

Task 1: The visual analog scale (VAS) task consists of 24 items used previously to assess the subjective effects of THC (cf. Lile et al., 2015). Briefly, it measures positive (e.g., like drug), negative (e.g., nauseated) and cannabis-specific (e.g., high) subjective outcomes. Items are presented individually and measured by marking a 100-unit line anchored on the extremes by “Not At All” and “Extremely”.

Task 2: A Probabilistic Reinforcement-Learning Choice (PRLC) task (cf. Rutledge et al., 2009). During this task, subjects complete two types of trials, control trials and choice trials. Control trials are inserted at the beginning and end of the task, in which subjects will be instructed to select a randomly scheduled option and will be provided feedback that is visually similar to that in choice trials. Control trials will permit neural activity related to decision-making to be isolated from activity associated with performing the task (e.g., visual, motor). During choice trials, subjects choose one of two options, signaled by visual cues (e.g., blue and green boxes). When reinforcement is scheduled for the chosen option, subjects are notified that they have earned money (e.g., $1.00); or are informed that they did not earn money. Four probability ratios for the two options are used (e.g., 6:1, 2:1, 1:2, and 1:6). Trials are divided into un-signaled blocks, in which the identity of the higher reward probability option is reversed. Once a reinforcer is scheduled for an option, it remains available until that option is chosen, so that the longer an option remains un-chosen, the greater the probability that a reinforcer will be delivered by choosing it. Subjects will complete the task using an MRI-compatible keypad and visual display during the training session. During experimental sessions (Visits 2-7), subjects will complete the PRLC task on a laptop computer outside of the MRI scanner (no scanning occurs during experimental sessions). The PRLC task will end when a maximum number of reinforcers (e.g., 50) associated with one of the two options have been delivered, a fixed number of trials (e.g., 480) have been completed, or after exceeding a predetermined time limit (e.g., 45 minutes), whichever occurs first.

Task 3: The N-Back (N-Back) task is a validated working memory task (Jaeggi et al., 2010). Subjects are presented with a sequence of letters and must indicate when the letter currently being viewed matches the one from N steps earlier in the sequence. The load factor “N” is adjusted to make the task more or less difficult. Adjusted accuracy and reaction times on rounds of, 0-, 1-, 2-, and 3-Back are the primary outcomes.

Task 4: The Cannabis Purchasing Task (CPT) is an adaptation an established hypothetical alcohol purchasing task (Amlung et al., 2015). Subjects are asked how many puffs of their preferred cannabis they would consume at 21 prices, ranging from free to $20/unit. Primary outcomes of this task include elasticity of demand (a or “alpha”) and intensity of demand (Q(0) or “Q naught”). These values are derived using nonlinear regression with the exponential demand equation (Hursh & Silberberg, 2008): Log(10)Q = log(10)(Q(0)) + k(e^[-a*Q(0)*C]-1), where Q = consumption at a price; Q(0) = derived intensity of demand (consumption at zero price); k = a constant that denotes the range of consumption values in log(10) units; C = the price of the commodity; and a = derived essential value (a measure of elasticity of demand). Greater values of Q(0) indicate greater consumption at unconstrained price (i.e., a theoretical price of zero). Greater values of a indicate a higher elasticity of demand or change in consumption with change in unit price.

Behavioral Data Analyses: Analysis of variance (ANOVA) will be used to compare group demographic data, data from primary outcome measures (above), and the primary molar PRLC task outcome, amount of money earned on the task. Data from the cannabis purchasing task (CPT) will be analyzed using the exponential demand equation (Hursh & Silberberg, 2008) described above. Molecular PRLC results will be analyzed using RL modeling of trial-by-trial data (Sutton & Barto, 1998), which uses the history of reinforcement for each choice, expressed as an expected value, to predict future choices. The value of the chosen option (option A) is updated via the outcome of the trial according to Equation 1 (see Figures attachment), where the updated value of option A is

determined by its current value and delta, the reward prediction error, defined in Equation 2 as the difference between the obtained or omitted reinforcer minus the outcome expectation that is determined by the reinforcement history for that option. The learning rate parameter (alpha) then determines the magnitude of expected value updating for option A. Finally, the probability of choosing A is determined via a softmax decision rule according to Equation 3, where the probability of choosing option A is a function of the difference between the values for A and B, multiplied by beta, a "temperature" parameter that alters the likelihood of the differential values between the alternatives dictating the predicted choice. Finally, A and B choices from the previous trial (C[a](t-1) and C[b](t-1)) are multiplied by a perseveration parameter ("c"; the propensity of the individual to make the same choice on the current trial, regardless of reinforcement history). The free parameters alpha, beta, and c will be estimated using maximum likelihood estimation and differences (delta) in model fits estimated using Akaike's Information Criterion (AIC) and pseudo r-squared, with parameters compared by model comparison and linear mixed modeling (Burnham & Anderson, 2002; Gelman & Hill 2006; McFadden 1974). Importantly, the RL modeling framework is flexible, and further decision-making complexities (e.g., outcome-specific learning rates or differential future-reward discounting) can be included when warranted. The alpha level will be set at the $p<0.05$ for all analyses.

Neuroimaging Data Analyses: Brain activity and functional connectivity patterns will be associated with PRLC task outcomes and cannabis use demographics. For traditional analyses, separate first-level fixed-effects general linear models (GLMs) will be performed for each subject using SPM12 (Friston et al., 2007; Wesley et al., 2016). For molar analyses, blood-oxygen-level dependent (BOLD) signals associated with each condition of interest (selection and feedback event times for each choice alternative and control trials) will be convolved with the hemodynamic response function (HRF) and contrasted (choice events > control) to produce activity maps of each choice of interest. For molecular analyses, trial-by-trial RL modeling parameters (learning rate a and reward prediction error delta, and the perseveration parameter "c") will be parametrically regressed against the observed BOLD signal for events of interest (choice and feedback times for each choice option). Similarly, connectivity analyses will be performed using the psychophysiological interaction (PPI) method for both molar and molecular analyses (see Figure 2). In this case, first-level GLMs will contain interaction terms generated from primary eigenvariate timecourses extracted from corticostriatal ROIs and the aforementioned conditional and parametric event times of interest. All first-level outputs will be moved forward to second-level random effects GLM analyses examining activity and connectivity between groups and correlating demographic variables with brain maps. Analyses will be performed with the hypothesis-driven corticostriatal ROIs and a whole-brain mask for exploratory analyses. Voxel-wise statistical thresholds will be set to $p<0.001$ with contiguous voxel extent thresholds set to 5 and 20 for ROI and whole-brain analyses, respectively. Small volume family-wise error correction for multiple comparisons will be applied.

Attachments

Attach Type	File Name
DataCollection	N-Back Instructions and Worksheet.pdf
DataCollection	PRLC Envelope Instructions.pdf
DataCollection	Cannabis Purchase Task Instructions.pdf
DataCollection	Specific Items on the VAS.pdf

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

This study will take place at the NSL and MRISC, which contain all the necessary physiologic, computer, brain stimulation, and imaging equipment for the study. Dr. Hays is an adult psychiatrist who has worked extensively with individuals with substance use disorders in both the clinical and research setting and he is the responsible medical investigator for this study. He will be available to attend to medical problems as well as any psychological or psychiatric issues that may arise. Dr. Wesley (PI), Dr. Lile (Co-I), and their investigator-level colleagues will provide scientific oversight for the study and have safely completed numerous human behavioral pharmacology studies. Overall, the study team and resources described above are well equipped to protect participants and successfully implement, carry out and complete this study protocol.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

The behavioral, subjective and physiological assessment procedures employed in these experiments are benign. Adverse events identified as possible risks in this study include:
1. The risk that the subject's protected health information (PHI) may be viewed by others not directly involved in the conduct of the proposed research.

2. Possible embarrassment in disclosing sensitive personal information.

3. Possible discomfort due to study procedures.

4. Possible dissatisfaction with the study procedures.

5. Side effects associated with the physiological and behavioral effects of the study drug.

With respect to side effects, the dose of THC to be administered in the proposed research has been administered safely to human subjects under controlled laboratory and medical conditions. The relative safety, as well as the contraindications and possible side effects of THC are well known and documented. However, the administration of any drug involves some risks simply because individuals differ in their reactions to drugs.

Common side effects of cannabinoid agonists such as cannabis and THC include anxiety, asthenia, ataxia, myalgia, akathisia, tachycardia, palpitations, arrhythmias, hypotension, flushing, abdominal pain, nausea, vomiting, diarrhea, constipation, dry mouth, headache, change in appetite, cognitive and mood disturbances (e.g., euphoria, paranoia, depersonalization, amnesia, confusion and memory impairment), sleep disturbances and nightmares, speech difficulty, dizziness, sedation, somnolence, hypothermia and shortness of breath. It is likely that subjects will experience one or more of these side effects. In addition, these drugs may exacerbate psychiatric symptoms in individuals with certain mental health disorders (i.e., mania, depression or schizophrenia). Unsupervised self-administration of higher doses of cannabis has resulted in more serious side effects such as psychotic episodes and panic attacks. It is unlikely that subjects will experience these more serious side effects. In addition, seizures can occur in subjects with existing seizure disorders. The occurrence of seizures appears to be related to the presence of certain predisposing factors including histories of head trauma, CNS tumors and previous incidence of seizures. Individuals reporting any of these predisposing factors will be excluded from participation, so the risk of seizure is extremely low. In addition, cannabis interacts with other licit and illicit drugs and alcohol. All subjects will be monitored for use of unauthorized drugs throughout the study and will be appropriately cautioned about their activities before and after their participation, so the risk of interactions with other drugs is also low.

6. Side effects associated with brain stimulation.
There are no known health risks associated with TMS at the output intensities and duration of stimulation proposed in this application (Huang et al., 2005; Chung et al., 2016; Lowe et al., 2018). It is not uncommon, however, for some subjects to experience skin sensations under the stimulation coil (e.g., itching, tingling, twitching). These sensations typically occur immediately after stimulation begins and subside shortly thereafter as the skin desensitizes. Participants will be made aware of this possibility prior to stimulation and asked to report any such sensations if they occur. If sensations occur that are irritating to subjects, stimulation will be paused and adjustments will be made to the stimulation equipment to help alleviate irritation (e.g., repositioning the coil, scratching the skin to alleviate an itch). Another side effect that has been reported with TMS is a tension-type headache, which can be treated with over-the-counter (OTC) pain relievers and tend to resolve naturally over time (Rossi et al., 2009). Subjects will be informed of this possibility and asked to report any headaches that occur following TMS during experimental sessions. Subjects who report headache following TMS will be advised on what OTC pain relievers (and what doses) are approved for use by the study physician without special permission. The study physician will be consulted in the event that a subject reports severe and/or persistent headaches and a determination will be made regarding their continued participation in the study. Although not expected, we will ask subjects to report any burning sensations that may be indicative of physical burns. If a subject reports a burning sensation under a TMS coil, then stimulation will be stopped immediately and the skin will be examined for redness and soreness. If a subject's skin appears to be abnormally irritated and/or if a subject continues to report a burning sensation, then the protocol will be halted and they will be withdrawn.

The current study uses MagVenture stimulation devices, coils, and stimulation protocols that are cleared by the FDA and/or are within the safety limits for the use of TMS in humans. TMS delivery has been associated with an increased risk of seizure, we therefore exclude individuals who report a history of seizures and/or epilepsy. Although the occurrence of TMS-induced seizures is rare and unexpected given the stimulation parameters and procedures used, should a participant experience a TMS-induced seizure, the TMS protocol will immediately be stopped and the participant will be monitored until the event resolves (Rossi et al., 2009b). Additionally, the participant will be moved to the floor and oxygen will be administered via a bag valve mask once the seizure passes. The study physician will be contacted and available should further medical intervention be necessary. If the seizure is deemed serious enough by the study physician, an ambulance will be called to provide medical assistance to the participant if they agree to it. It is also possible that participants could experience syncope (i.e., fainting) during the TMS session. Should a participant experience a syncopal event, the TMS protocol will immediately be stopped, the participant will be moved to the floor, and monitored until they regain consciousness. Syncopal events are more common than seizures in the context of TMS but tend to resolve naturally very quickly (Rossi et al., 2009b). In the event of any SAEs (seizures or syncopal events), the NSL staff recommend the participant does not drive themselves home. An emergency contact number provided at screening will be contacted to pick the participant up. The safety profile

of TBS protocols is comparable to that of other repetitive TMS protocols (Oberman et al., 2011). Of note, in a clinical setting, patients receive an FDA-approved TMS protocol (e.g., iTBS or 10 Hz repetitive TMS) once daily for 4 to 5 days a week for 5 to 6 weeks. In addition, the FDA-approved 10 Hz repetitive TMS protocol that is used clinically delivers a total of 3000 pulses across a 19-minute period whereas the TBS protocols used in this study will deliver a total of 900 pulses during one, approximately 4-minute and 40-second (iTBS) or 60-second (cTBS) bout of stimulation during each session. Our research study will test a single bout of TMS per session, approximately 3 hours after capsule administration, across three real and three sham stimulation sessions of equivalent duration (each separated by at least 48 hours) in cannabis users.

7. Side effects associated with the neuroimaging.
The neuroimaging protocol is considered a minimal risk procedure, and Dr. Wesley has performed neuroimaging studies involving Magnetic Resonance Imaging (MRI) for more than 15 years (Wesley et al., 2011, 2014a, 2014b, 2016). In studies involving MRI, movement or heating of metallic implants is a potential risk; therefore, subjects will be carefully screened to exclude individuals with metallic implants, fragments, or pacemakers. Some individuals may experience mild discomfort or anxiety in the scanner, and all subjects will be informed of this possibility prior to the study. Throughout scanning procedures subjects will be able to communicate with the investigators via intercom, and any subject reporting discomfort will be removed from the MRI scanner immediately.

The 3.0 Tesla (T) scanner used at the MRISC has been FDA approved. However, there may be additional risks associated with scanning at 3.0 T compared to the conventional clinical scanners at 1.5 or 2.0 T. There is risk associated with exposure to the static magnetic field. Although there is no conclusive evidence for irreversible or hazardous effects to acute, short-term exposure to a 1.5 T magnetic field, side effects reported at 4.0 T have included nausea, vertigo, and metallic taste. There is no evidence, however, that these effects are irreversible or harmful. There is also risk of exposure to the gradient magnetic field. MRI operates by rapidly changing small magnetic fields, called gradients, within the larger static field. This process can induce small electrical currents in any conductor. Thus, MRI could theoretically induce mild peripheral nerve stimulation. This risk is not substantially different at higher magnetic fields, however, because gradients are distinct from the larger static magnetic field. There is no evidence that gradients at 3.0 T are different than those at 1.5 or 2.0 T. Lastly, there is risk associated with radio frequency (RF) electromagnetic field pulses used for functional MRI (fMRI). Higher static field strengths require higher RF pulses in order to excite protons in the brain. The FDA has defined the limits of RF energy that can be safely given to humans, and the MRISC adheres to these FDA recommendations by limiting the maximum RF power level. If subjects experience unusual sensations and/or peripheral nerve stimulation resulting in nerve tingling or twitching, they will be withdrawn.
The direct benefit to be gained by subjects from participation in the studies is the medical evaluation, which could reveal a disease or illness that needs further treatment (incidental finding). For example, the MRI could reveal unknown structural abnormalities or masses in the brain. The degree of risk to which individual study subjects are exposed as a consequence of their research participation is low. There is a theoretical risk that subjects might choose to seek out illicit sources of drugs they received experimentally and liked. However, this risk is minimal since all drugs are administered under blind conditions, and in a setting that is not conducive to the development of dependence. Also, the subjects included are current daily cannabis users. Therefore, it is unlikely that the oral doses of THC administered will be perceived as desirable, relative to their current habitual cannabis use. The potential and probable benefits to be derived by society appear to be considerable. The major benefits of these studies are scientific and clinical ones related to the knowledge gained concerning potential treatments for CUD. The data from this project will contribute to a better understanding of drug abuse and may ultimately contribute to the development of improved treatment procedures.

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

There are no available alternative treatments as this is not a treatment study. If subjects express the desire for treatment they will be given referrals for treatment and not be allowed to participate in this study.

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Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies

FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

Information about the potential subject's drug history and physical/mental health will be collected for the purpose of selecting subjects for approved research protocols under our screening protocol (IRB: 43686). Similarly, urine and blood samples will be collected at screening prior to a subject's participation in the experimental protocol. These urine samples will be tested for the presence of a full range of drugs of abuse. Blood and urine samples will be used for the laboratory chemistries. Females will also be given a pregnancy test at the time of screening (via the urine sample). During the experiment proper, urine drug and pregnancy tests will be conducted prior to the conduct of each experimental session. Expired breath samples will be used to test for the presence of alcohol prior to the conduct of each experimental session. Other data obtained from the subjects will include computerized performance and physiological measures described above, and non-intrusive observations and ratings. Collection of these materials should not impact subject privacy in that the environment in which these materials will be obtained is not associated specifically with drug abuse research and all personal health information will be kept confidential.
All subjects will be assigned a unique identifying number. The master file linking the subject name to the identifying number will be encrypted and only the PI and key personnel will have access. Data will be collected in both paper and electronic form. Initial screening materials will contain protected health information (PHI), but will be de-identified once data collection for the study is complete. Electronic versions of informed consent documents will be stored in a HIPAA-compliant archive on UK's REDCap system and paper records will be stored in locked cabinets in the NSL. Access to the NSL is restricted with keyed and magnetic locks. Electronic data files will be stored on a password-protected computer protected from outside access by a two-tiered firewall system: the UK firewall system and Macintosh OS Server firewall system. Key and password access will be limited to the PI and key personnel. Confidentiality of all personal health information will be maintained according to HIPAA guidelines. Forms containing subject identifying information (e.g., consent forms, payment receipts) will be removed from the subject records and stored separately upon study completion, and master files will be destroyed, so that all PHI and study data will be de-identified. Urine specimens collected for urine drug and pregnancy (female subjects only) screening at the beginning of all sessions will be disposed of (i.e., flushed) immediately following testing. Materials used in the urine drug screening process (i.e., the specimen cup) will be marked with a randomly determined number at the outset of the session to allow research staff to correctly identify a subject's urine sample but this number will not be linked with the subject's identity or study subject number. Specimen cups and urine test cassettes will be discarded into a trash receptacle at the NSL or MRISC, to which there is no public access.
The standard safety precautions used for behavioral pharmacology studies in the NSL (similar to those in use at the UK Laboratory of Human Behavioral Pharmacology) will be used for the present experiment.

1. Possible violation of confidentiality.
All research information concerning study subjects is confidential and will be appropriately protected as outlined by the HIPAA guidelines. No identifying patient information will be revealed without the study subjects' written authorization. The confidentiality of the subjects will be safeguarded by storing documents containing subject identification information (e.g., consent forms, initial contact forms, subject-ID number files, payment receipts) under double lock in a secure area accessible only to staff personnel. Any material disseminated in research reports will identify the subjects by numbers only. Information identifying the subjects' participation in a drug study and information from selection questionnaires or interviews would be made available to any other parties (e.g., employers) only with the written consent of the subject.

2. Possible embarrassment in disclosing sensitive personal information.
The risk is minimized through the use of confidentiality safeguards described above. The study will be fully de-identified upon completion of the data collection phase of the study so that this risk is limited in duration.

3. Possible discomfort due to study procedures.
Subjects are informed that they have the right to withdraw from study protocols at any time. A research staff member will always be available to answer questions, and the study subjects have telephone contact information to reach both the PI and the study physician. If individuals become overly distressed or distraught, participation in the study is discontinued immediately, and private consultation with the study physician and/or PI is offered immediately.

4. Possible dissatisfaction with the study procedures.
Protocol management forms will include prompts to record any protocol anomalies, data collection problems, concerns with study subjects, or any unusual events that could impact the safety of the subjects or the integrity of the protocol. In addition, the PI, as well as the study physician or an appointed representative, are available at all times by telephone to respond to any questions or concerns that occur during the study. Furthermore, the PI meets with the project staff regularly to review the study activities. Every employee or volunteer at the research lab is required to participate in the mandatory training program on human subjects protection provided by UK. Research staff also receive training specific to the use of technology, implementation materials and subject safety assessment used in the protocol.

5. Physiological and behavioral effects of the study drugs.
The procedures for minimizing the risks associated with drug administration consist of a) careful medical and psychological screening with an extensive battery of screening tests, including psychometric evaluations, interview assessments, and medical lab testing in order to provide as much information as possible upon which to base subject selection, b) the exclusion of subjects with physical and psychiatric conditions which would increase the risk of study participation or obscure interpretation of study results, c) recruiting subjects who report daily use of cannabis, d) continuous monitoring of the subjects for adverse drug reactions following dose administration with an attending physician available on call for emergencies at all times, e) urine testing to ensure the absence of pregnancy or the occurrence of drug use outside of what was administered in the study, and f) use of behavioral assessments during intake and discharge to assure the absence of residual impairment associated with dose administration. Furthermore, while the dosing

conditions are blinded, the dose schedules for each subject are always available in written form in the event that the information is needed in a timely manner.

Dose levels were selected to balance experimentally desired effects and side effects. It is anticipated that careful subject selection, dose selection and subject monitoring by the investigators and medical staff on this project will greatly reduce, if not eliminate, the occurrence of serious side effects. The study physician will screen all potential subjects for physical and psychiatric contraindications to participation and drug administration. Urine samples will be monitored prior to each experimental session to ensure that female subjects are not pregnant and that all subjects are adhering to the drug use restrictions. Subjects will undergo thorough medical evaluations to determine that they are healthy and to minimize the likelihood that the drugs will produce undesirable effects. All subjects will be thoroughly informed of the various drug side effects that they might experience and will be appropriately cautioned concerning their activities in the hours after drug administration.

Subject monitoring following drug administration during sessions will consist of, at minimum, regularly timed subjective effects questionnaires, cardiovascular assessments, staff observations and spontaneous subject reports.

A field sobriety test (walk and turn, one-leg balance [timed], finger-to-nose and backwards-counting tasks) will be used to assess psychophysical performance when subjects arrive for each session and before they are discharged. Performance on this battery prior to drug administration is designed to ensure the absence of any performance impairment prior to the session and to serve as a pre-drug baseline from which to compare performance on the same battery at the end of the day during discharge assessment. If drug effects are evident at the end of the experimental session, or if subjects report any subjective drug effects, they must remain onsite until these effects dissipate. Previous research indicates that by comparing pre- and post-drug performance on the experimental tasks and the field sobriety test, subtle levels of impairment can be detected.

There are risks associated with leaving the lab following drug administration, if subjects choose to withdraw from a study. Subjects must interact with staff prior to leaving the facility. They will be required to remain in the lab until the staff determines that they are no longer affected by the drug, based on self-report as well as the assessment battery described above; however, they are free to spend their time engaged in activities which are not part of the study. If they choose to leave before the investigators are satisfied that they are no longer affected by the drug, they receive no financial compensation, their study participation is cancelled, they are asked to sign a form that they are leaving against medical advice, and they are required to have someone pick them up at the lab and take responsibility for their safety.

6. Effects of brain stimulation.
As noted above, the risks associated with the proposed TMS protocols are small. The iTBS protocol is an FDA-approved treatment for major depressive disorder and the inhibitory cTBS protocol has been used safely in human subjects without untoward effects (e.g., Huang et al., 2005; Chung et al., 2016; Lowe et al., 2018; Wischnewski and Schutter, 2015). The TMS device, coils and excitatory stimulation protocol (i.e., iTBS) are all FDA cleared. In addition, the TMS device monitors heat and energy output of the coil and will turn off before reaching an unsafe level. During the stimulation session if there is an indication of TMS coil malfunction, which might also contribute to skin irritation, steps will be taken to increase stimulation quality and reduce the likelihood of irritation (e.g. slight repositioning of TMS coil).

7. Effects of neuroimaging.
As noted above, physical risk to subjects during MRI sessions is very low, and Dr. Wesley has extensive experience conducting research using MRI methods (Wesley et al., 2011, 2014a, 2014b, 2016). In addition to the measures to ensure the safety and comfort of subjects noted above, every effort will be made to provide information and support to subjects to minimize discomfort during brain scanning sessions. Specifically, the following will be carefully explained prior to participation, and will be included in our consent form:

"While in the MRI scanner you may become too hot or too cold, in which case you may ask for an adjustment of room temperature or a blanket. Some people may become nervous or feel claustrophobic while in the scanner. If this happens, you may ask to be withdrawn and will be withdrawn from the scanner immediately. A small number of people experience a sense of dizziness or vertigo while in the scanner due to the magnetic field. If this occurs and disturbs you, you may ask to be withdrawn and you will be withdrawn immediately. You will be instructed to remove all jewelry and other metal-containing objects. Because the magnetic field will affect any metallic object, you should not participate if you have any type of metallic implant in your body, including pacemakers, aneurysm clips, shrapnel, metal fragments, orthopedic pins, screws, or plates, IUDs, or piercings that you cannot remove."

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?

◉ Yes ○ No

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

Subjects will receive a Base Visit Compensation (BVC) of $40 for completing the training session (Visit 1) and $50 per session for completing each of the 6 experimental sessions (Visits 2-7), for a total BVC of $340. Subjects will receive three forms of a bonus compensation: (1) an Ascending Participation Bonus (APB); (2) a Study Completion Bonus (SCB); and (3) a Task Performance Bonus (TPB) based on experimental task performance. The APB for completion of each of the 6 experimental sessions is as follows: Visit 2 APB = $10; Visit 3 APB = $15; Visit 4 APB = $20; Visit 5 APB = $25; Visit 6 APB = $30; Visit 7 APB = $50, for a total APB of $150.

The SCB will be a maximum of $50. The TPB will range from $0 to $50 depending on the overall performance on the experimental cognitive tasks. Therefore, if a subject successfully completes the 1 practice and 6 experimental sessions and earns all available bonus compensation, the total compensation for this study is $590 (BVC $340 + APB $150 + SCB $50 + TPB $50 = $590: range of $540 to $590). Depending on the needs and/or availability of the subjects, additional follow-up visits interspersed with experimental sessions may be required. In this instance, subjects will be asked follow-up questions, provide a urine specimen for screening, and will be compensated $20 and released similar to procedures described in our screening protocol (IRB: 43686).

If a subject decides to discontinue their participation or is discharged for noncompliance issues before fully completing the study, they will not receive the completion bonus. If a subject is terminated for medical reasons, they will receive all of the money that they have earned up to that point, including the completion bonus money earned at the time of their termination.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

There will be no cost to the subject for participating.

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

The purpose of this project is to understand the neural mechanisms of cannabinoid-impaired decision-making and associated neurocognitive processes. Randomized, double-blind, placebo-controlled (for drug), sham-controlled (for brain stimulation), within-subjects designs will be employed. Subjects will be forty (N = 40) men and women of various race/ethnicity, aged 18-34, who report daily or near-daily cannabis use (i.e., at least 20 days in the last month) and meet criteria for cannabis use disorder but are not seeking treatment for their drug use. All subjects must provide informed consent to participate. This sample will be recruited from the local community and will participate as outpatients at the NSL and MRISC.

The proposed experiments will examine the ability of non-invasive brain stimulation (TMS) to impact the acute effects of THC on specific neurocognitive outcomes. These experiments will also use neuroimaging to model the regional and interconnected functional brain profiles that predict individual differences in the specific and combined effects of THC and/or brain stimulation on experimental outcomes. Together, the proposed studies will advance the understanding of neural mechanisms contributing to maladaptive decision-making that promotes habitual cannabis use and the development of cannabis use disorder in young adults.

The PI will be responsible for monitoring the safety and efficacy of this trial, executing the DSMP, and complying with the reporting requirements. The PI will provide a summary of the DSM report to the funding agency (e.g., NIDA) on an annual basis as part of the progress report. The DSM report will include the subject sociodemographic characteristics, expected versus actual recruitment rates, retention rates, any quality assurance or regulatory issues that occurred during the past year, summary of serious adverse events (SAEs), and any substantial actions or changes with respect to the protocol. The DSM report to NIDA will also include, if applicable, the results of any data analysis conducted. There are no conflicts of interest.

Data Monitoring Plan:
Data from experimental sessions will be collected using a computerized data collection and management system. This system automates the collection of the behavioral and physiological data, which ensures the accuracy and completeness of data collection. The data are stored in a unique file on the hard-drive of the computer and are electronically backed-up at the end of each session. In all instances, the data files do not contain the name of the subject; but instead, each subject is identified by a unique four-digit number. The computer file linking subject names and numbers will be encrypted and only key personnel will have access. Data files for experimental tasks and physiological measures from each experimental session will be managed and combined into a single electronic spreadsheet by automated macros. Data will then be combined into a single electronic spreadsheet and separated by experimental measure for statistical analysis using SPSS (Statistical Package for the Social Sciences, IBM Corp.) software. Neuroimaging data will be stored and backed-up on encrypted and secure servers at the MRISC according to existing and approved UK protocols. Secure copies of structural and functional neuroimaging data sets will be securely routed to the PI's office computer via encrypted network protocols occurring behind by the UK firewall. These data will be analyzed using customized Matlab (MATrix LABoratory) scripts and an array of neuroimaging software packages, including but not limited to SPM and FSL primary platforms and their associated neuroimaging toolboxes.

The primary outcomes for both experiments are those from neurocognitive tasks measuring decision-making and working memory. Subjective drug effects will also be measured. Changes in outcome variables following active drug and placebo administration will be compared between real and sham transcranial magnetic stimulation (TMS) to determine if excitatory iTBS600 (Exp.1) or inhibitory cTBS600 (Exp. 2) delivered to the left dorsal lateral prefrontal cortex (DLPFC) alters the effects of THC on study outcomes. Data will

be analyzed using ANOVA with alpha set at 5%. Additionally, functional neuroimaging data from Training Sessions in each experiment will be modeled using traditional mass-univariate approaches (e.g., general linear models and statistical parametric mapping) and newer multivariate pattern analysis (i.e., support vector machine learning) to classify the brain profiles that predict the ability of THC and brain stimulation to impact neurocognitive outcomes.

The quality of manipulated data and data analyses will be monitored by random inspection by the PI and/or other key personnel. Preprocessing and analysis of subject-specific behavior and brain data will begin as individual data are collected. Interim analysis of group data will begin once 25% of the sample is accrued.

Safety Monitoring Plan:
Potential subjects will provide information regarding their drug use history and undergo an extensive physical and psychiatric health screening to determine their eligibility and the safety of their participation. Any individual with a past or current serious physical or mental health condition, other than drug use disorder, that, in the opinion of the study physician would be contraindicated for study participation, or who have metallic implants, fragments or pacemakers, will be excluded from research participation. Individuals who report a first-degree family history of cardiovascular disease that resulted in premature death or seizures will also be excluded from research participation. Female subjects must be using an effective form of birth control and test negative for pregnancy prior to each experimental session. Potential subjects who report regular use of any psychotropic medication, or illicit drug other than cannabis, will be excluded. All study subjects will be judged by the medical staff to be psychiatrically and physically healthy. Methods for monitoring adverse events (AEs) will include unobtrusive observations by medical and research staff, spontaneous report by the subjects, regular measurement of physiological indices, subjective-effects questionnaires, and performance on experimental tasks. Subjects will not receive study drug if they have any signs or symptoms that may contraindicate its administration (e.g., HR outside of predetermined range).

All AEs occurring during the course of the study will be collected, documented, and reported to the PI and the Study Physician following each occurrence. The occurrence of AEs will be assessed daily for the duration of participation and as needed in follow-up visits as appropriate. The PI and Study Physician will follow all AEs to the point of a satisfactory resolution. Subjects may be withdrawn from the study if the investigators determine it is the best decision in order to protect the safety of the subject. All AEs will be assessed to determine if they meet criteria for a serious adverse event (SAE).

Serious adverse events, as defined by the FDA, will be systematically evaluated daily for the duration of participation, and as needed in follow-up visits as appropriate. Any SAE, whether or not related to brain stimulation, drug administration, or neuroimaging will be reported to the IRB, NIDA and the FDA. In the event that a subject either withdraws from the study or the investigator decides to discontinue a subject due to an SAE, the subject will have appropriate follow-up medical monitoring. Monitoring will continue until the problem has resolved or stabilized with no further change expected, is clearly unrelated to the study drugs, or results in death. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NIDA.

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Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

De-identified information will be securely stored at the University of Kentucky NSL indefinitely. De-identified data may be used for future research or shared with other researchers. Those data may include demographic, physical, mental health, medical history, and/or drug use history information that can be used to describe the study population and facilitate experimental analyses of neurobehavioral outcomes related to the study population. There is a risk that someone could get access to the information in spite of the security measures and safeguards. There may also be risks that at this time are unknown. A researcher from another institution may request to receive de-identified information by contacting the study PI, that request will also be reviewed by the IRB. Information will not be shared with researchers in other countries.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.

When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

KEY INFORMATION FOR
Neural Mechanisms of Decision-Making in Emerging Adult Cannabis Users

We are asking you to choose whether or not to take part in a research study about the effects of non-invasive, transcranial magnetic stimulation (TMS) on the effects of Marinol®, an FDA-approved drug that contains the psychoactive chemical Δ^9-tetrahydrocannabinol (THC) that is also found naturally in cannabis/marijuana. You are being asked to participate because you are 18-34 years old with a history of non-medical cannabis use. You are also being asked to participate because you have expressed interest in participating in this study, and because you passed the medical screen. If you choose to take part in this study, you will be one of about 40 people to do so over the next five years. You must be at least 18 years of age to participate in this study and you will be asked to provide legal proof of age.

WHAT IS THE PURPOSE, PROCEDURES, AND DURATION OF THIS STUDY?

The purpose of this study is to learn more about how non-invasive brain stimulation (TMS) affects the brain's response to THC. Specifically, we are interested in how brain stimulation and drug effects influence: (a) a person's mood and state of mind (subjective effects); (b) a person's ability to perform laboratory tasks, and (c) a person's physiology (e.g., heart rate and blood pressure). The study will take place over the course of seven (7) in-person appointments that will last approximately 7 hours each. The general study procedures are summarized briefly below.

Summary of General Study Procedures

1. Pass a breathalyzer test and a field sobriety test (all study sessions).
2. Give a urine sample for drug and pregnancy (for females) tests (all study sessions).
3. Complete experimental questionnaires and tasks that measure how you think, feel, and perform.
4. Have your blood pressure and pulse rate taken at regular intervals.
5. Perform computer tasks in a magnetic resonance imaging (MRI) scanner.
6. Receive a type of non-invasive brain stimulation called transcranial magnetic stimulation (TMS).
7. Ingest capsules that contain either Marinol® or placebo (a blank or no drug).

WHAT ARE KEY REASONS THAT YOU MIGHT CHOOSE TO VOLUNTEER FOR THIS STUDY?

You are genuinely interested in participating in a research study at the Neurobehavioral Systems Lab (NSL) on the effects of non-invasive brain stimulation (TMS) and Marinol®, a drug that contains the primary psychoactive ingredient in cannabis (THC). For a complete description of the potential benefits, refer to the Detailed Consent.

WHAT ARE KEY REASONS THAT YOU MIGHT *NOT* CHOOSE TO VOLUNTEER FOR THIS STUDY?

You may not want to swallow capsules that contain Marinol® or placebo. Having THC in your system may potentially affect your ability to get or keep a job. You may not want to have an MRI of your brain or receive TMS. You may not want to fill out questionnaires or complete study tasks. You may decide that you do not have time to commit to participating in research. For a complete description of risks, please refer to the Detailed Consent.

This is a research project, not a treatment program. The procedures of the study are designed to provide scientific information in a way that is relatively safe and comfortable for you, but not to provide benefits. ***If you are seeking treatment for your drug use, do not agree to participate in the study.*** This study is not intended to help you stop using drugs. The investigators can arrange for referral to an appropriate treatment program, if desired.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in this study, it should be because you really want to volunteer to participate in a research study on the effects of non-invasive brain stimulation (TMS) and oral THC. You will not lose any services, benefits, or rights that you would normally have if you choose not to volunteer. You can discontinue your participation in the study at any time and still keep the services, benefits, and rights you had before volunteering.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS, OR CONCERNS?

The person in charge of this research study is Michael J. Wesley, Ph.D. of the University of Kentucky College of Medicine, Department of Behavioral Science. If you have questions, suggestions, or concerns regarding this study or you want to withdraw from the study, you may contact the NSL at (859) 323-0579 or Dr. Wesley at (859) 323-1332. You can also contact the laboratory via email at nsl@uky.edu. If you have any questions, suggestions or concerns about your rights as a volunteer in this research, contact staff in the University of Kentucky (UK) Office of Research Integrity (ORI) between the business hours of 8am and 5pm EST, Monday-Friday at 859-257-9428 or toll free at 1-866-400-9428.

DETAILED CONSENT:

ARE THERE REASONS WHY YOU MIGHT NOT QUALIFY FOR THIS STUDY?

You should not participate if you have a history of serious physical disease, current physical disease (including, but not limited to, impaired heart functioning, high blood pressure, chronic obstructive pulmonary disease (COPD), eating disorder or diabetes), history of epilepsy or seizure, current or past histories of serious psychiatric disorder, or metal implants in your head. If you have any non-removable, metallic objects or implants in your head or body that you have not told us about, you should not participate in this study. If you have any allergies, please report them to the research staff.

If you have ever been addicted to drugs other than cannabis, including alcohol, you should discuss this with the research staff before agreeing to participate. You should not participate if you are currently seeking/wanting treatment for your drug use, currently in treatment for your drug use, or have successfully quit using drugs.

If you are a female, you should not participate if you are pregnant or plan on becoming pregnant during your participation in this study. You must be using an effective form of birth control (e.g. birth control pills, be surgically sterilized, cervical cap with a spermicide, or abstinence; ***please tell the investigator if you have an IUD***), and you must be willing to take a pregnancy test before being accepted into the research study. You will also be required to provide a urine sample for a pregnancy test prior to each experimental session. Should one of these tests show that you are pregnant, you will be discharged from the study immediately. If you are female, you should not participate if you are breast feeding a baby.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

This study will be conducted at the facilities of the Neurobehavioral Systems Lab (NSL) and the Magnetic Resonance Imaging and Spectroscopy Center (MRISC) at the University of Kentucky Medical Center. The study will consist of a total of 7 in-person sessions: 1 training session and 6 brain stimulation (TMS) and drug administration experimental sessions. Each experimental session will last approximately 7 hours. These sessions must be separated by at least 48 hours. In total, we expect the study to take approximately 3-5 weeks to complete.

WHAT WILL YOU BE ASKED TO DO?

If you agree to participate today, you will be asked to come to the laboratory up to seven (7) times to complete one (1) training session and six (6) experimental sessions, across a 3- to 5-week period (excluding weekends). The following table summarizes the research study:

Daily Compensation	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Training	Experimental Session 1	Experimental Session 2	Experimental Session 3	Experimental Session 4	Experimental Session 5	Experimental Session 6
Base Visit Compensation	$40.00	$50.00	$50.00	$50.00	$50.00	$50.00	$50.00
Ascending Participation Bonus		$10.00	$15.00	$20.00	$25.00	$30.00	$50.00
Study Completion Bonus							$50.00
Task Performance Bonus							$0.00 - $50.00
Total	$40.00	$60.00	$65.00	$70.00	$75.00	$80.00	$150 - $200

*This is an approximation based on expected procedure times. **The maximum total possible (not including follow-up visits) is **$590**

The schedule is provided above as an example. It includes the general procedures for each session, the expected length of each visit, and the compensation you will receive at the end of each session. Additionally, if you complete all procedures in the whole study, then you will receive a completion bonus that will range in value according to your experimental task performance during the sessions.

Intake Procedures (all visits to the Lab):

Each laboratory visit will involve taking urine samples and breath screens to test for drug use. If you are female, this urine sample will also be tested to ensure that you do not continue in the experiment if you are pregnant. We will tell you if the result of the urine pregnancy test is positive, and your participation in the study will be discontinued. *Importantly, you must refrain from using cannabis, nicotine, alcohol, and other drugs starting at midnight the night before all laboratory visits.* Because there is a small risk that the drugs in this study could interfere with your ability to perform various activities, you must agree to notify the investigators if your lifestyle, daily activities, or job status changes during your participation.

Training Session (Visit 1):

The training session will last approximately 3-4 hours and will involve introducing you to the procedures that will be used in experimental sessions. You will not receive any capsules to swallow during the training session but you will be introduced to the procedure for taking capsules. During this session, you will perform the main experimental tasks in a magnetic resonance imaging (MRI) scanner. These tasks will be conducted on a computer and will measure how you are feeling and various aspects of behavioral performance.

MRI uses magnetic fields to measure brain structure and brain activity. It involves lying down on a padded platform that is loaded into the cylindrical (tube-shaped) center of the MRI machine. During the scan, you will be asked to remain still as images of your brain are acquired. While in the MRI scanner you may become too hot or too cold, in which case you may ask for an adjustment of room temperature or a blanket. Some people may become nervous or feel claustrophobic while in the MRI scanner. If this happens, you may ask to be withdrawn and will be removed from the scanner immediately. A small number of people experience a sense of dizziness or vertigo while in the scanner due to the magnetic field. If this occurs and disturbs you, you may ask to be withdrawn and you will be removed immediately. Before the scan, you will be instructed to remove all jewelry and other metal-containing objects. Because the magnetic field will affect any metallic object, you should not participate if you have any type of metallic implant in your body, including pacemakers, aneurysm clips, shrapnel, metal fragments, orthopedic pins, screws, or plates, IUDs, or piercings that you cannot remove.

You will receive transcranial magnetic stimulation (TMS) during the training session to show you what TMS feels like. To do this, we will place a stimulation coil on your head, which may potentially involve moving hair on the head and/or wearing a cap or wrap on the head. TMS works by passing a focused magnetic field across your skull to temporarily change the activity of nerve cells in a small area of the tissue that covers the outer surface of your brain (called the cortex) directly below the stimulation coil. For example, if we deliver one pulse of TMS to the area of the cortex that controls the movement of your index finger, that finger will twitch once. This type of TMS procedure ("single-pulse TMS") will be used during each experimental session to determine the stimulation intensity setting that will be used during the TMS treatment for that particular session. In other words, we will determine the minimum amount of energy needed to make your index finger twitch when a TMS pulse is delivered (called resting motor threshold or rMT). The rMT is what is used to set the intensity of the TMS protocol for each day. Although you will experience single-pulse TMS during the training session, you will not receive the specific TMS protocol that will be used during experimental sessions until later during those sessions.

Experimental Sessions (Visits 2-7):

Experimental sessions will involve capsule administration, non-invasive brain stimulation (TMS), and performing experimental tasks and will be separated by at least 48 hours. During experimental sessions, you will ingest capsules that could contain Marinol®, an FDA-approved medication that is used to treat anorexia, nausea, and vomiting in some clinical conditions. Later in each session you will receive a

specific TMS protocol (explained below). The active ingredient in Marinol® is Δ^9-tetrahydrocannabinol (THC), which is also a naturally-occurring chemical in cannabis/marijuana. The capsules could also contain placebo (a blank, no drug). Capsules will be swallowed with the aid of water.

Experimental sessions will also involve receiving a form of non-invasive brain stimulation called TMS. As described above, TMS is a method for administering a low magnetic field to the brain. You will be randomly assigned (by chance) to receive **one of two** types of TMS to the left side of your head throughout your participation in the study: an intermittent theta-burst stimulation (iTBS) ***OR*** continuous theta-burst stimulation (cTBS) protocol. These stimulation protocols can temporarily increase or decrease your intrinsic (i.e., normal) brain activity. The iTBS protocol that you could receive lasts approximately 3 minutes and is FDA-approved for the treatment of medication resistant major depressive disorder. The cTBS protocol you could receive lasts approximately 40 seconds and has been used safely in previous research studies without any significant negative effects.

During each experimental session, you will receive either real or sham (fake) iTBS or cTBS one (1) time approximately 3 hours after taking capsules. The study staff will find the best place on the left side of your head to apply the stimulation. An FDA-approved magnetic coil will be placed on your scalp and held in place with an articulating supporting arm. Two small electrodes will also be placed on your skin near the stimulation site to deliver a small electrical current into your skin. This electrical current does not cross the skull. At the beginning of TMS, it is common to feel slight tingling on the surface of the skin just under the stimulation coil and electrodes. You should not feel any pain during TMS, but if you become uncomfortable, stimulation will be stopped. During the stimulation protocol, you will be asked to remain still and awake.

For all experimental sessions, you must agree not to eat or drink anything except water for at least four (4) hours before each visit to the laboratory. You must also agree not to take other drugs during your participation in the experiment unless approved by the study doctors. This includes prescription and over-the-counter medication, as well as illicit drugs. Pain relievers containing only ibuprofen or acetaminophen are acceptable for normal use without special permission. If your urine or breath screening reveals that you have used drugs other than cannabis or the drug administered to you during the study, you could be removed from the study. A list of the participation requirements for each study visit is at the end of this consent form.

We expect most experimental session to last approximately 7 hours. However, you must remain in the laboratory at the end of each session until you and the research staff are reasonably certain that the study drugs no longer affect you and the investigators determine that your performance is normal. This may require that you remain in the laboratory beyond 7 hours. Before the experimental session begins, you will be required to give your watch, keys, and mobile phone to the study staff. They will be returned to you at the end of the session. At the beginning of the session, you will complete the intake procedures described above. We will then use single-pulse TMS (explained above) to determine your resting motor threshold (rMT). After completing the intake procedures, you will then be required to eat a standardized breakfast snack. *If you smoke tobacco cigarettes, you will be allowed to smoke one (1) cigarette (of your usual brand, provided by you) during the intake process. You will not be permitted to smoke again until after the session has ended.*

After completing the intake procedures, we will take your blood pressure and then you will complete the main experimental tasks. You will later receive capsules to swallow that could contain Marinol® or placebo (a blank, no drug). We will take your vital signs (i.e., blood pressure and heart rate) to monitor safety and ask you to complete an experimental task that asks about the way you are feeling at regular intervals until the end of the session. Approximately 2 hours and 45 minutes after swallowing the capsules, we will position the TMS coil over the appropriate area of your head and you will receive the real or sham (fake) TMS protocol (iTBS or cTBS) that you have been randomly (by chance) assigned for that day. Immediately after the TMS protocol has ended, you will complete the main experimental tasks again. After receiving TMS and all behavioral tasks are finished, you will be allowed to eat a standardized

lunch and request snacks. You will not be permitted to eat chocolate or drink caffeinated beverages during the session. When you are not completing study activities, you will be permitted to watch movies, listen to music, and/or play video games until it is time for the next set of study activities.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

The laboratory tasks and questionnaires present no risks that exceed those of everyday experience. The primary risks of participation are those specifically related to the ingestion of the study drug, delivery of TMS, and MRI scanning. The tables below provide a list of possible risks and side effects, the expected frequency of occurrence, the seriousness of the risk or side effect, and whether it can be corrected.

There is a chance that information could be learned during the MRI scan that potentially impact your health. These procedures are not intended to detect or diagnose a medical condition and you are not a patient receiving medical treatment. We will notify you if something is found during the MRI scan that looks abnormal and advise you regarding consultation with a physician. If you decide to consult with a physician, the University of Kentucky has no way to provide funds for this consultation. In other words, if you decide to consult a physician, any charges for treatment will be your responsibility.

The drugs you will receive are known to interact with other medications, including over-the-counter medications. It is important that you tell us about any medications that you are taking. If you need to take any other medications during the time you are participating, you will need to call us so that we can determine if it is safe for you to continue in the study. The drugs you will receive are detectible in the urine for days to weeks after administration. Therefore, if you are required to take a urine drug test during screening for employment, for example, there is the risk that it will be positive.

There is the rare but serious possibility that TMS can induce a syncopal event (fainting) or a seizure. In the instance that a serious adverse event occurs, we will immediately stop the stimulation, move you to the floor, administer oxygen (if needed), and wait for you to regain consciousness. An ambulance will be called if the adverse event is deemed serious enough by the study physician, and you agree to immediate medical treatment. We strongly recommend you do not drive or operate heavy machinery after fainting or a seizure. We will contact your emergency contact you provided at screening to pick you up from the lab.

There is always a chance that any drug or medical procedure can harm you. The research treatments/procedures in this study are no different. In addition to risks described in this consent, you may experience a previously unknown risk or side effect. You should tell the research staff about all the medications, vitamins, and supplements you take, as well as any medical conditions you have. This may help avoid side effects, interactions, and other risks.

Side Effects of MRI (Relevant to the Training Session only)

Possible Risk or Side Effect	**Expected frequency of occurrence.**	**How serious is it?**	**Can it be corrected?**
dizziness or vertigo	These are unexpected	Not serious	Effects typically go away within minutes.
becoming too hot or too cold	These are unexpected	Not serious	Adjust room temperature or provide a blanket.

Side Effects of TMS (Relevant to Experimental Sessions)

Possible Risk or Side Effect	**Expected frequency of occurrence.**	**How serious is it?**	**Can it be corrected?**
tingling or itchy skin	Likely to occur at the beginning of stimulation sessions	Not serious	Effects typically go away within a couple of minutes.
Seizure	These are unexpected	Somewhat serious	Seizure resolves naturally.*
Syncopal Event (Fainting)	These are unexpected	Not serious	Fainting resolves naturally.

* symptoms after a seizure may include muscle soreness, loss of coordination, mood changes, and fatigue that could last hours to days.

Side Effects of Marinol® (Relevant to Experimental Sessions)

Possible Risk or Side Effect	**Expected frequency of occurrence.**	**How serious is it?**	**Can it be corrected?**
anxiety, restlessness, amnesia, confusion, abnormal thinking, paranoia, depersonalization, dizziness, nightmares, sleep disturbances, speech difficulty, headache, abdominal pain, nausea, vomiting, diarrhea, changes in performance, loss of strength, decreased movement, muscle soreness, sedation, flushing, change in appetite, heart palpitations or arrhythmias, increase in heart rate, decrease in blood pressure, chills/cold sensations, dry mouth, shortness of breath, feeling tired	You could experience one or more of these side effects	Somewhat serious	These side effects are likely to decrease over time as the drug clears from your system.
panic attack psychotic episodes, unconsciousness	These are unexpected	Very Serious	These side effects are likely to decrease over time as the drug clears from your system.

WILL I BENEFIT FROM TAKING PART IN THIS STUDY?

There is no guarantee that you will receive any direct benefits from taking part in this study. However, the knowledge gained may contribute to a better understanding of the nature of effects of these drugs and may result in improved treatments. If you are seeking treatment, please notify the investigator now and he/she will make the necessary referral.

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to take part in the study, there are no other choices except not the take part in the study.

WHAT WILL IT COST YOU TO PARTICIPATE?

Participating in this study will not cost you anything and you will be compensated for your time after completing each in-person session. The MRI scan and laboratory tasks performed as part of the study procedures will be paid for by funds awarded to the investigators to perform research studies.

Please note that you and/or your insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that you receive during this study that you would normally receive for your condition. These are costs that are considered medically necessary and will be part of the care that you would normally receive even if you did not take part in this study.

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

Your information will be used to ensure that the research meets legal, institutional, and accreditation requirements. Every effort will be made to maintain the confidentiality of your study records. We will make every effort to prevent anyone who is not on the research staff from knowing that you gave us information, or what that information is.

The information collected during this study may also be published. However, when we write about or share results from the study, we will write about the combined information. ***We will keep your name and other identifying information private. Any identifiers will be removed from identifiable private information or identifiable biological specimens if that information or specimen could be used for future research studies or distributed to another investigator for future research studies without additional informed consent.***

You should know that there are some circumstances in which we may have to show your information to other people. For example, the law may require that we share your information with a court or agencies if you have a reportable disease/condition. We may also be required to share your information with authorities if you report information about a child being abused; or if you pose a danger to yourself or someone else.

The researchers conducting this study may need to access or disclose certain health information about you that we will collect as part of the study. This includes your demographic information, urine pregnancy tests, urine drug testing, and other information or results of the medical screening that you underwent during the screening process for this study. ***Any urine specimens or other biological specimen that was collected during the screening for this study or will be collected during this study will be properly disposed of in a way that makes every attempt to maintain your privacy and confidentiality and will not be shared for commercial use or profit.***

Your identity will remain confidential, unless you give prior written approval or unless it is required by law. For example, other than the research staff, officials at the Food and Drug Administration (FDA), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), and the University of Kentucky may look at or copy pertinent portions of records that identify you. Your name, address, and social security number will also be listed on the receipt for payment that you receive, as required by the Internal Revenue Service (IRS); but no information about your participation in this research study that identifies you will be released.

THIS RESEARCH IS COVERED BY A CERTIFICATE OF CONFIDENTIALITY from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or specimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or specimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects.

The Certificate cannot be used to refuse a request for information from personnel of the United States federal or state government agency sponsoring the project that is needed for auditing or program evaluation by the National Institute on Drug Abuse (NIDA) which is funding this project or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it.

CAN YOU CHOOSE TO WITHDRAW FROM THE STUDY EARLY?

You can stop your participation in this study at any time. You will not be treated differently if you decide to stop taking part in this study.

If you choose to leave the study, you may not receive the compensation and/or completion bonus described below. If you decide to leave the study early, the data collected until that point will remain in the study database and may not be removed.

The investigators conducting this research may need to remove you from the study. This may occur for many reasons. You may be removed from the study if:

- Your participation in the study is more of a risk than benefit to you
- You fail to adhere to the patient rules for the NSL or MRISC
- You verbally or physically assault another volunteer, patient, or staff member at the NSL or MRISC
- Your behavior is disruptive to other ongoing studies that are conducted at the NSL or MRISC
- Your behavior is disruptive to the other volunteers, patients, research staff, or medical staff at the NSL or MRISC
- You do not comply with the alcohol, drug, and food restrictions
- You fail to attend and/or successfully complete a scheduled visit
- You do not follow directions and/or perform the study tasks to the best of your ability
- The agency paying for the study (NIDA) chooses to stop the study early for a number of scientific reasons

******If you are withdrawn from the study by the investigators for any of the above reasons, you may not receive the compensation described below******

ARE YOU PARTICIPATING, OR CAN YOU PARTICIPATE, IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may potentially take part in this study if you are currently involved in another research study. *It is important to let the investigator know if you are currently in or considering participating in another research study.* Because this study involves the administration of an FDA-approved drug and non-invasive brain stimulation, it is possible that participating in other studies (especially those that involve you receiving/taking study drugs or other medications) could endanger your safety and well-being. You should discuss this with the investigator ***before*** you agree to participate in another study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study procedures, you should call Lon R. Hays, M.D. at (859) 323-6021, extension 79015. After business hours, please call the Psychiatry Department On-Call Group at (859) 226-7063 and explain to the physician that you are a study participant. The physician will determine what type of treatment, if any, is best for you at that time.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study. This means that while all investigators will do everything possible in providing careful medical care and safeguards in conducting this research, there is no way in which the institution can pay for the unlikely occurrence of injury resulting solely from the research itself. ***Medical costs related to your care and treatment because of study-related harm will be your responsibility.***

You do not give up your legal rights by signing this form.

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?

You will be paid $40 for completing the Training Session and you will earn $50 for completing each of six (6) experimental sessions. Depending on your performance on tasks during experimental sessions, you could earn a completion bonus of $150-$250. You may also complete follow-up visits on an as-needed basis. You will be paid $20 for each follow-up visit. If you successfully complete all sessions and earn all of the bonus money possible, you could earn a maximum total of $590 in this study, not including optional follow-up visits.

With a few exceptions, study payments are considered taxable income reportable to the Internal Revenue Service (IRS). A form 1099 will be sent to you if your total payments for research participation are $600 or more in a calendar year. It is your responsibility to determine how these earnings might affect your personal financial situation.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

You will be informed if the investigators learn new information that could change your mind about participating in this study. You may be asked to sign a new informed consent form if the information is provided to you after you have started the study. At that time, you will be allowed to decide if you wish to continue in the study.

WILL YOU BE GIVEN INDIVIDUAL RESULTS FROM THE RESEARCH TESTS?

Generally, the tests and procedures that will be done during the study are not meant to provide clinical information and will not be shared with you.

As noted above, there is a slight possibility that during a research project, an investigator could discover something that could affect the health of you or your family. If this occurs, the finding will be reviewed by the investigators and study physician to determine if it is in your best interest to contact you.

If so, the investigators will contact you using the information you provided. With the help of the study physician, they will present possible risks or benefits of receiving the information. At that time, you can choose to receive or refuse the result or finding. You will be asked to provide your expressed, written consent for us to provide you with a copy of any result or finding that may impact the health of you or your family. If you would like more information about this, call the Neurobehavioral Systems Lab (NSL) at (859) 323-0579 or email us at nsl@uky.edu.

WILL WE CONTACT YOU WITH INFORMATION ABOUT PARTICIPATING IN FUTURE STUDIES?

The research staff would like to contact you in the future with information about participating in additional studies. Before signing this consent document, you will be given the opportunity to give your permission for the research staff to contact you about participating in studies in the future. *This is optional; you are not required to permit the research staff to contact you about participating in future studies.*

WHAT ELSE DO YOU NEED TO KNOW?

If you choose to take part in this study, you will be one of about 40 people to do so over the next five years.

Research in the Neurobehavioral Systems Lab (NSL) is supported by funding from the National Institute on Drug Abuse (NIDA; Grant: DA043652) of the National Institutes of Health (NIH), as well as internal funds from the University of Kentucky.

The information that you are providing will no longer belong to you. The research may lead to new clinical or educational knowledge, tests, treatments, or products. These products could have some financial value. There are no plans to provide financial payment to you or your relatives if this occurs.

This study is being conducted under the scientific and administrative supervision of Michael J. Wesley, Ph.D and Joshua A. Lile, Ph.D., of the University of Kentucky College of Medicine, Department of Behavioral Science. This study is under the medical supervision of Lon R. Hays, MD. There may be other people on the research team assisting at different times during the study.

Telephone contact information for each of the investigators is provided below. You may also contact the laboratory via email at nsl@uky.edu.

STORING AND SHARING YOUR INFORMATION FOR FUTURE USE:

We would like to store, use, and potentially share the information collected during this study, for future research. Having information from many people helps researchers identify trends and discover better ways to diagnose, prevent, and treat many conditions. Researchers can use the stored information to learn more about clinical conditions that produce neurobehavioral dysfunction (like substance use disorders, stroke, and post-traumatic stress disorder) or research additional scientific questions. ***Your information will be stored at the facilities of the Neurobehavioral Systems Lab (NSL) forever.*** There is risk that someone could get access to your information. In spite of security measures and safeguards we will use (e.g., de-identifying your data, storing identifiable information in locked cabinets behind locked doors and/or on password and firewall protected computers), we cannot guarantee that your identity will never become known. There may be risks that at this time are unknown. As technology advances, there may be new ways of linking information back to you that we cannot foresee now.

Identifiable information such as your name, medical record number, or date of birth may be removed from the information collected in this study. ***After removal of information that identifies you, your information may be used for future research or shared with other researchers without your additional informed consent.***

INVESTIGATOR CONTACT INFORMATION:

Michael J. Wesley, Ph.D.	(859) 323-1332
Joshua A. Lile, Ph.D.	(859) 323-6034
Lon R. Hays, M.D.	(859) 323-6021 x79015

Neurobehavioral Systems Lab (NSL) E-mail Address: nsl@uky.edu

PLEASE REVIEW THIS IMPORTANT INFORMATION ABOUT RESTRICTIONS YOU ARE REQUIRED TO FOLLOW BEFORE A SESSION

Requirements for Study Visits:

Before all visits:

(1) Do not take other drugs or medications unless approved by the study doctors
(2) Do not use cannabis, alcohol, nicotine, or other drugs starting at midnight the night before your visit.
(3) Do not eat or drink anything (except water) for at least 4 hours before your appointment. You will be provided with food at different times during the session.
(4) Refrain from drinking caffeinated beverages or consuming caffeine containing foods or medications after midnight the night before your appointment.
(5) Do not smoke or use tobacco products/nicotine after midnight the night before your appointment. You will be given an opportunity to smoke after you arrive.
(6) Be prepared to give your urine sample when you arrive or shortly thereafter.

*** If procedural screens and/or study personnel determine that these requirements have been violated you may be disqualified from participation in the screening and/or future studies.