Am I Stoned? Developing a field sobriety test for cannabis use.
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The rapid increase in use of cannabis across the US has raised public health concerns about safety related to the drug, especially risks related to impairments in cognitive performance and judgment. There is evidence from controlled studies that marijuana and its active ingredient delta-9-tetrahydrocannabinol (THC) can impair memory, reaction time and attention. However, it is not clear to what extent these impairments are manifested in naturalistic, non-laboratory settings, and importantly, it is not clear to what extent users are aware of their impairments after drug use. A lack of awareness of impaired performance would pose an especially great risk to public safety compared to deficits that are clearly apparent to the user.

We have developed a prototype for an app called *Am I Stoned?* that could be used by marijuana users in the non-laboratory setting to assess their level of impairment relative to their non-intoxicated state. Information about impairments and awareness of impairment would be of value to researchers studying the safety of the drug, as well as to users who are concerned about their ability to function safely. In the ultimate version of this app, users would engage in a baseline determination phase and then a drug utilization phase. The baseline determination phase would require them to complete simple tasks on a hand-held device (e.g., phone) on 6 occasions when they have not used any drugs, and on 6 occasions when they have used, provide personalized data about their performance with and without the drug. Then in the drug utilization phase, users would use the app to estimate their own level of impairment with a quick phone-based assessment. Importantly, users would also be asked to estimate their level of performance to obtain an indicator of how aware they are of their intoxicated state. The data would be stored in a coded form for use by researchers and by users themselves.

A critical first step in developing this app is to conduct a controlled, laboratory-based study with known doses of THC to determine the sensitivity and time course of the impairments in app-based task performance. Therefore our Specific Aims for this administrative supplement are as follows:

Aim 1: To determine the sensitivity of our app-based tests of memory, reaction time and attention in experienced marijuana users using known doses of THC (7.5, 15 mg oral) and placebo. Fifty-six volunteers will participate in three 4-hour sessions, separated by one week. They will be required to be drug-free at these sessions. On each session they will ingest a single dose of THC (7.5 or 15 mg) or placebo, and complete both the computer and app-based tasks two hours after consumption. Subjects will also complete brief performance tasks and mood questionnaires on a desktop computer at 0, 1.5, 1, 1.5, 2, 2.5, and 4 hours after consumption.

Aim 2: To assess participants' ability to predict and estimate their performance impairment. The participants described in Aim 1 will predict and estimate their level of performance on each task (i.e., better than normal, about normal, poorer than normal). These ratings will be examined in relation to participants' actual performance, and subjects will be provided with feedback – relative to their non-drug performance. Awareness of impaired performance is a critical step in preventing accidents and minimizing risk.

This proposal will establish the sensitivity of the tasks to be used by testing participants under controlled conditions. The project will provide initial information about the participants' ability to judge their own performance, about sensitivity of the tasks, and about inter-individual variability in performance and in drug effects. Once we have established the sensitivity of the app tasks to detect THC-induced impairment we will be ready to deploy the app *Am I Stoned?* to a more naturalistic setting. Overall, the long-term benefits of this app would be to: 1) improve the safety of marijuana use by making individual users more aware of their impairment, and 2) contribute to our knowledge of marijuana use by gathering data from users in the field. This laboratory study is a first step to achieving these goals.

Significance.
This project will develop a methodology for assessing, and ultimately reducing harm from accidents related to marijuana use. First, it will allow both researchers and drug users to assess the level of impairment after marijuana use using convenient, portable devices in the users' own naturalistic setting. Second, it will allow both researchers and users to determine the users' own ability to judge their level of impairment. And relatedly, the project will provide information about the relationship between subjective intoxication and impaired performance. The information obtained will be valuable to researchers and users alike, and lead to ways to reduce risks from marijuana use.

Marijuana is among the most widely used recreational drugs in the world, and its use in the US is increasing rapidly as laws controlling availability become more lenient. Frequent marijuana use is associated with numerous adverse outcomes, including impairments in cognitive functions such as reaction time and short term memory (e.g., Sewell et al, 2009; Desrosiers et al, 2015; Broyd et al, 2016). A recent comprehensive review of the adverse effects of marijuana by Broyd et al (2016) concludes that marijuana impairs psychomotor function, memory and attention. However, most studies assessing cognitive impairments have been assessed under highly controlled laboratory conditions, and it is not known whether these problems accurately reflect the impairments that occur in the drug users' natural environment. Performance assessments under controlled laboratory assessments may either overestimate the degree of impairment, or underestimate their severity in the more complex real-world setting. It is difficult to assess users' performance in the field because we lack data on users' baseline drug-free performance. We also lack information about the dose they ingested, the purity of the drug or the time since dosing, and about the users' psychological state and activities at the time of testing, and about the presence of other drugs. The lack of knowledge about participants' drug-free performance makes it especially difficult to know whether a user is impaired by a drug, relative to his or her own baseline performance. Ultimately, we propose to develop an app to assess participants' performance on simple cognitive tasks in their natural environments, both under the influence of the drug and in a drug-free state. As a first step to achieve this goal, and the plan for this administrative supplement, we plan to validate the sensitivity of our app under controlled conditions. We will administer known doses of pure THC or placebo to participants who are drug-free, and assess their performance and performance awareness under controlled conditions. Performance will be assessed both on tasks administered on a phone (to be used in the final app), and on standardized computer tasks typically used in laboratory studies. Our goal is to identify phone tasks that are equally sensitive to the computer tasks, and to show that both are sensitive to THC administration.

An important feature of our to-be-developed app ***Am I Stoned?*** is that it will provide feedback on users' perceptions of impairment, relative to their actual impairment. Drug users are not always able to judge their own level of performance under the influence of a drug (Goldstein et al, 2009). Importantly, this lack of knowledge greatly heightens the risk for engaging in unsafe behaviors. Indeed, drugs themselves may have direct effects on cognitive judgment, which may impair the users' ability to detect degradation in their performance. Evidence from controlled studies indicates that drug users often underestimate the extent to which drugs impair their performance. For example Brumbeck et al (2007) reported dissociations between perceived and actual impairment after an acute dose of alcohol among light and heavy drinkers. Both light and heavy drinkers were equally impaired by objective tests, but the heavy drinkers underestimated their level of impairment, compared to the light drinkers. It is not known whether marijuana users are able to estimate their own level of impairment. A lack of awareness between perceived and actual performance impairment has important consequences for safety of drug use.

This project will also address a related question: Are the user's feelings of intoxication related to his or her impaired performance? In general, feelings of intoxication are related to performance impairments and both are related to the dose of drug. However, tolerance can develop to either the subjective or objective effects, and tolerance to the subjective intoxicating effects may develop more rapidly than tolerance to drug effects on psychomotor performance. This discordance is an especially dangerous combination for the safe use of drugs. Moreover, as noted above, drugs that produce feelings of euphoria may also impair judgment and cognitive function. Assuming that users are more aware of their subjective state of feeling 'high' than their level of impairment, this is important information to obtain, and provide directly to the users.

Innovation. This project is highly innovative in several respects. The ultimate goal is to develop an app that will enable users' to assess their level of impairment in the own natural environments. The app-based tasks will be brief, simple and sensitive, and relate to impairments that may affect the user's functioning. The app will also provide unique new information about the extent to which users are aware of their impairments in performance. The project outlined here is the first step to developing this app, by testing it in a controlled setting.

Approach.
This is a proposal for an administrative supplement to obtain preliminary, proof-of-concept data to **develop an app for self-assessment of cannabis-induced impairment**. Marijuana use, for both recreational and therapeutic purposes, is becoming increasingly common as states remove restrictions on use. The increased use raises new concern about the safety of this drug, including its ability to impair basic cognitive and psychomotor tasks, and whether the users are aware of their impairment.

We propose to design a simple performance test that users can use in the field, using a cell phone, to assess their level of impairment *relative to their own drug-free state.* In this preliminary study we will compare participants' simple task performance after a known dose of delta-9-tetrahydrocannabinol (THC), or placebo, administered under double blind conditions. In our app the participants will be asked to gauge their own perceived level of impairment (as determined by self-ratings and judgments of impairment) as well as their actual impairment (as gauged by the app) , providing important feedback and training about their ability to detect impairment. In the ultimate version of the app (though not in this task development study) we will provide participants with feedback about their performance, including both their objective performance and their perceptions of the performance. It will be valuable for users to know that their drug use leads to decrements in performance, and it would be especially informative if we can demonstrate their inability to gauge their own impairment. These features will be part of the final app, when we get to the point of administering it repeatedly in the non-laboratory setting.

THC, the primary psychoactive ingredient of marijuana, is known to impair short-term memory, increase reaction time and impair attention. We will examine four tasks sensitive to the effects of THC using a simple app in a controlled setting (memory task, motor tapping task, reaction time and addition; Broyd et al, 2016; Desrosiers et al, 2015). The data obtained in the controlled setting will provide the basis for future testing in the naturalistic, field setting. Fifty-six healthy experienced but non-daily marijuana users will be recruited for a three-session laboratory study, in which they receive oral doses of THC (7.5 and 15 mg oral) and placebo under double blind conditions. They will be required to be THC-free at the beginning of the 4-hour sessions. During the sessions subjects will ingest the drugs and complete the app tasks two hours after ingestion, as well as standardized laboratory measures of performance and mood states at half hour intervals. Subjects will be asked to estimate their level of performance before and after each app task completion, without feedback on their actual performance. Cardiovascular measures (heart rate and blood pressure) will be obtained at regular intervals. The primary goal is to develop app tasks that are sensitive to the drug's effects and the drug dose on performance, as a model for future field testing.

We would like to expand on several methodological considerations and our responses to them.

1. Why use THC instead of marijuana? We have chosen to develop the app tasks with THC because the drug is readily available and because it has a known pharmacology, time course and dose effects. We recognize that we propose to use the app in a naturalistic setting where users will be using marijuana, and not THC, and where we have little control of the composition of the marijuana they will be using. However, to develop a task sensitive to the primary psychoactive ingredient of marijuana, we feel that oral THC is the drug with which we have the most control.
2. Why not obtain plasma samples of THC and its metabolites during each session, to link impairments to plasma levels of THC and its metabolites? This would be extremely valuable, and we have given careful consideration to the possibility of obtaining plasma samples. It would help to account for individual differences in absorption and metabolism, and to serve as a comparison to drug levels

detected in the field, where there is no control over how much people use. However, obtaining plasma samples in our hospital would entail a significant investment of time and money because we would need to have a nurse present to insert indwelling catheters and take the blood draws for repeated samples. Nurses charge about $50 per hour, and with fringe this would require $25,000 additional costs, plus the cost of the assays. An even greater expense would be the assays for both THC and its metabolites in repeated samples. One less costly alternative would be to obtain a single blood sample at the expected time of peak levels, but a single sample would not provide information about peak or time course.

3. Why not obtain saliva samples to monitor THC levels? Most commercially available salivary THC kits test only presence or absence of THC. The quantitative assays that do exist measure only THC and not its metabolites, and because the metabolites form quickly and contribute to the behavioral effects, the simple THC level would provide little useful information.

Thus, we believe that for this purpose it would be best to administer oral THC. We do not feel that the plasma level data are essential for our purpose, as we plan to administer fixed doses of oral THC to participants who are known to be drug-free at the beginning of the sessions. We recognize that marijuana contains many other constituents than THC, and that the pharmacokinetic profile of oral THC is very different from smoked marijuana (Milman et al, 2014; Wachtel et al 2002). Yet, THC (and its metabolites; Huestis, 2007) seems to be the primary active ingredient responsible for the behavioral and subjective effects of marijuana (Wachtel et al, 2002). Although the pharmacokinetic information would be of value in a future study, we feel that in this study, where we have full control over the dose and time course of the drug effects, we can accomplish our primary goals without THC assays

EXPERIMENTAL METHODS.

Participants. Healthy experienced but nondaily marijuana users (N=56 obtain, 48 completers; 24 men, 24 women 18-35 years) will be recruited with print and internet ads. Our ultimate target population in the future naturalistic phase of this project will be users who use occasionally but not daily, in order to obtain information about both drug-free and post-drug performance. We are not targeting daily users for this project because we wish to obtain baseline data from drug-free days as well as data from smoking days, to provide users with accurate feedback on their performance. Thus, only experienced, non-daily users will be recruited in this preliminary study. Participants will be screened according to Protocol 13681B, and accordingly must have at least a high school education, BMI 19-26, no current physical or psychiatric health problems determined by a physical examination, an electrocardiogram and an in-person psychiatric screening interview (SCID; First et al, 2015), no current medications, and no current substance use problems, based on the interview and a time-line followback. We will exclude women who are pregnant or planning to become pregnant. We will obtain detailed information about participants' drug use history, including their use of cannabis. Participants who meet criteria for Moderate or Severe Cannabis Dependence will be excluded (First et al, 2015), and subjects must agree to abstain from marijuana use to test negative for recent cannabis use at each session. For this protocol we will obtain information about habitual cannabis use (age at first use, period of heaviest use, past year use and current use over the past month), so that we may use level of use as a covariate in the analysis. We will also collect data on sex, age, height and weight to conduct exploratory analyses on these variables. Women will be tested any phase of the cycle except women who report serious premenstrual dysphoria will be tested during the follicular phase. We will record whether women are users of oral contraception and the phase of their menstrual cycle at each session.

Sample Size and Power: We will test 48 subjects in this within-subject study. No previous studies have assessed the sensitivity of phone-based tasks to detect drug effects. We based the sample size on our own previous studies and other published reports using laboratory-based studies. Desrosiers et al (2015) detected effects of smoked marijuana (6.8% THC) on cognitive and psychomotor performance using a critical tracking task and a divided attention task using samples of 11 and 14 participants. We have found in a previous study (Ballard et al., 2013) that THC significantly impaired memory accuracy (relative to placebo) for positive and negative affective images, with large effect sizes in each case (partial eta squared = .20 and .13 respectively).

Orientation session. Subjects will first participate in a 1-hour orientation session to provide informed consent, agree to the study conditions described above, and practice the performance tasks. They will be instructed to refrain from any use of drugs or alcohol for 24 before the sessions and 6 hours after the sessions.

Participants will be advised that they must pass urine tests for recent drug use including marijuana, and to pass these tests they should abstain from use for one week if they are light users (1-2 times per week) and for two weeks if they are heavier users (e.g., daily). They will be instructed to abstain from smoking marijuana for the entire study. They will be told to have a normal night's sleep before the session, and a small breakfast before the sessions. Subjects will then practice the app tasks and the computer tasks to be used in the three sessions to minimize practice effects across the three study sessions.

Experimental protocol. Each subject will participate in three sessions (0, 7.5 mg and 15 mg THC) in counterbalanced order, separated by at least one week. The sessions will be conducted from 9 am to 1 pm. Upon arrival in the laboratory for each session subjects will provide urine samples to rule out recent use of opiates, stimulants, sedatives, cannabinoids, and breath samples for recent alcohol use and urine samples to test for pregnancy (women). Those who test positive for any drugs will be rescheduled and pregnant women will be dropped. Participants will then complete pre-drug mood questionnaires and their heart rate and blood pressure will be measured. They will then ingest a capsule containing 0, 7.5 or 15 mg Dronabinol with 100 ml water. One drug condition will be administered on each of the three days, in mixed order and under double-blind conditions. Subjects will complete the tasks 2 hours after ingesting the capsule, and heart rate and blood pressure, as well as mood questionnaires, will be measured at half hour intervals. At times when no experimental events are scheduled subjects will be free to relax, read or watch tv. Following the sessions subjects will be escorted to public transportation or provided with transportation home.

Drug. THC (Marinol® [dronabinol]; Solvay Pharmaceuticals) will be orally administered in doses of 7.5 mg and 15 mg, in opaque capsules with dextrose filler. Placebo capsules contain only dextrose. These doses of THC are known to produce performance impairments as well as subjective intoxication (Broyd et al, 2016; Hartman and Huestis, 2013).

Dependent measures.

Selection of tasks: We have selected five app tasks from ResearchKit [http://www.researchkit.org/docs/docs/ActiveTasks/ActiveTasks.html] that are likely to be affected by marijuana (Broyd et al, 2016; Hartman and Huestis, 2013). These are spatial-span memory), finger tapping, reaction time, mental addition, and time perception/estimation. These tasks assess basic motor, psychological and cognitive function that THC and marijuana are known to affect (Broyd et al, 2016; Hartman and Huestis, 2013; Sewell et al. 2013). The tasks are relevant to everyday activities including safe operation of machines and accurate decision-making in a job setting. Note that the App to be used in the future naturalistic study will include additional features related to consent, demographic characteristics and data collection and management. However, for the present, laboratory-based study we will only use the App to administer the tasks and collect data on the hand-held device. We have selected four tasks from ResearchKit for initial testing, with the goal of selecting the three most sensitive tasks for the next stage of the project. The working software operates on a mobile device using Apple's ResearchKit framework. For the purpose of this laboratory-based preliminary study we will distribute the app to iOS devices we provide through the Apple "B2B" (business-to-business) distribution system. Reviewers wishing to examine the app should ask us for a redemption code that will give them access. Task performance and questionnaire data collected on the app will be transferred to an Access database on our main computer system.

The four tasks will be presented in mixed order at each hourly administration of the task. From these four tasks we propose to select the three tasks that are most sensitive to the effects of THC, and show the least change in learning across sessions.

- Spatial Memory (forward and reverse): In this memory task participants are asked to observe and then recall pattern sequences of increasing length in a game-like environment. The span is automatically varied during the task, increasing after successful completion of a sequence, and decreasing after failures, in a range from 3 to 9. The play speed is set at 1.0 second and the custom target image is the flower. The game finishes when either 7 tests have been completed, or the participant has made two consecutive failures in a row. In the reverse portion of the task participants must recall pattern sequences in reverse order.
- Finger-tapping: In this measure of psychomotor performance and coordination, the participant rapidly alternates between tapping to targets on the touch screen using the non-dominant hand for 20 seconds.
- Reaction time: In this reaction time task, the user is asked to shake the device in response to a visual

clue on the device's screen. The user makes three attempts, in which he or she must shake or move the device with an acceleration that is greater than the value of the thresholdAcceleration property within the given time. The task finishes when the user successfully completes the attempts as instructed in the task. Data collected by this task is in the form of ORKReactionTimeResult objects. Each of these objects contain a timestamp representing the delivery of the stimulus and an ORKFileResult object that references the motion data collected during an attempt.

- Paced Visual Serial Addition Task (PVSAT). The PVSAT measures cognitive function that assesses visual information processing speed, flexibility, and the calculation ability of the user. Single digits are presented every 2 or 3 seconds and the user must add each new digit to the one immediately before. The score for the PSAT task is the total number correct answers out of the number of possible correct answers.
- Time Perception/Estimation Task. The time perception/estimation task measures two components of time perception, time estimation as well as time production. The user must estimate the amount of time elapsed during a certain visual distraction for several trials and then the user must hold down a button for a defined period of seconds without seeing a timer.

Self-evaluations of performance on the app tasks. Subjects will be asked to estimate their performance on the tasks immediately before and following each task. They will indicate on a 5-point scale whether they think their performance will be or was poorer than normal (1-2), about the same as normal (3) or better than normal (4-5). They will not be provided with feedback on their estimates, relative to their actual performance, until the end of the study. The apps are currently being developed.

Computer-based tasks. Participants will also complete standardized psychomotor tasks on a desktop computer 1.5 hours after drug administration. We will be converting all the ResearchKit tasks into computer-based tasks. This will allow us to compare performance decrements using the hand-held device to impairments seen with typical laboratory tasks.

Self-report rating questionnaires. Prior to performing the tasks as well as after completing the tasks, they will also complete questionnaires regarding the mood and intoxication states 0, 1.5, 1, 1.5, 2, 2.5, and 4 hours after consumption. They will complete the Drug Effects Questionnaire (Morean et al 2013), asking whether they feel a drug effect, whether they like or dislike it and whether they feel high. They will also complete a shortened version of the Marijuana scale of the Addiction Research Center Inventory (Chait et al 1994) to detect marijuana-specific mood effects.

Data analysis and timeline. The primary outcome measures are i) actual performance on the app tasks:; ii) actual performance on the desktop tasks. iii) predicted and perceived performance on each task, and iv) ratings of how "high" the subject feels. First we will examine the quality of the data to exclude grossly inappropriate responses (e.g., all minimum or all maximum values). Then we will determine whether there are orderly changes in task performance (i.e., improvement or decline) across the 3 sessions, and co-vary for session order if necessary. Then we will assess the effects of the drug on performance on each task and on the mood questionnaires using linear mixed models for repeated measures (Hedeker & Gibbons, 2006) with factors of drug condition and session time point, and random subject intercept and session effects. For drug condition, we will treat placebo as the reference cell and make comparisons of each drug level to placebo. We expect that the effects of THC on both subjective state and performance will peak two hours after drug ingestion. Finally, we will examine relationships across variables. We will examine the concordance in impairment using the desktop administered tasks and the tasks administered with hand-held devices. We will also examine the relationship between participants' estimates of the impairment and their actual impairment by calculating a ratio between the two (drug minus placebo for estimates: drug minus placebo for actual impairment). We expect that it will take one year to complete testing of 48 participants in the three sessions, and to conduct the analyses of the findings. Our goal is to have a fully functional and sensitive app ready to test in a non-laboratory, naturalistic setting.

Possible pitfalls. It is possible that the tasks, either app-based on computer based, will fail to detect THC-induced impairments. We will examine data from completed subjects as we go, and if we fail to see

performance effects in the first 8 participants, we will try to increase the difficulty of the tasks. We will also consider including tasks other than the four we have proposed here, and we have the capacity to create new tasks using ResearchKit. Another possibility is that performance on the app tasks differs from performance o the computer based tasks. If the app tasks are more sensitive (to time or dose effects), we will continue to use these. If they less sensitive we will again review the difficulty level of the app tasks, and attempt to harmonize the app tasks with the computer-based tasks.

Next steps. Once we have demonstrated that the app is sensitive to the effects of THC, we will be ready to test it in a non-laboratory setting. The ResearchKit apps are designed for use in real-world settings, and we expect to be able to proceed to the next phase with little further technical development. In the next phase, we will invite occasional marijuana users (N=20) to participate in a feasibility study, in which they agree to complete the tasks on 6 occasions when they have not used marijuana for at least 3 days to allow a reasonable time for the performance-impairing effects to return to normal and on 6 occasions when they have used the drug in the past 3 hours. (In the present project we will wait one week between sessions to allow full clearance of THC between sessions.) Subjects will provide informed consent, demographic information (age, sex, education), and information about their current habitual drug use. We will collect the data in a coded form, and compare the performance and performance evaluations to the findings from our laboratory study. Once we determine the sensitivity of the app to detect impairments when used outside the laboratory, we can proceed to offer the app on a larger scale to marijuana users who are interested in obtaining objective feedback on their level of impairment.

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