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Protocol Title: Eye-tracking as a Biomarker of Cannabis Effects
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Lay Summary

Biomarkers of recent drug use and intoxication have societal relevance, in that they are used by law enforcement and other agencies to detect drug impairment. For instance, a breathalyzer can quickly and accurately detect blood alcohol content (BAC) to indicate if a person is under the influence of alcohol; however, there is currently no similar way to quickly detect if a person is under the influence of cannabis. In light of increasing cannabis use, it is important to define a quantitative, objective method of determining recent use and intoxication.

The link between changes in eye characteristics (e.g. movement, pupil dilation) and cannabis use is documented (Peragallo et al. 2013), but insufficiently characterized. Certain outcomes of eye behavior are known to be affected by recent cannabis use (e.g. the eyes' ability to converge on a target; Stapleton et al 1986), while findings are mixed regarding other outcomes (e.g. the eyes' ability to smoothly follow a target; Fant et al. 1998). Thus, the goal of this study is to identify a characteristic pattern of eye behavior, defined by performance on a battery of four eye tasks, as a function of recent cannabis use (7% vs. 0% THC).

Using 30 healthy cannabis users (15 men, 15 women), this study will be one of the first to assess changes in eye behavior as a function of recent cannabis use within a quantified virtual reality (VR) environment. We will examine the effect of smoked cannabis (7% vs. 0% THC) on individual eye movements, with the goal of defining the utility of the eyes as potential objective indicators of cannabis use and intoxication. Four eye tests (nystagmus, smooth pursuit, convergence, and pupillary light response; outlined below), which previous literature has defined as effective in detecting recent drug use (including opioids and alcohol; Murillo et al. 2004), have been compiled into a 5-minute task battery using a VR headset environment equipped with high frequency infrared eye trackers (the HTC Vive with Pupil Labs Tracking). This 5-minute VR battery of four eye tests will be administered prior to cannabis consumption as a baseline, and then at 0, 15, 30, 45, 60, 75, 90, 105**,** 120, and 165 min after cannabis, with the goal of comparing baseline values to the ten post-cannabis timepoints to detect changes in eye behavior as a function of cannabis intoxication. We will also administer a battery of subjective-effects and mood visual analogue scales (0-100 mm; e.g. 'Good Drug Effect') prior to the eye test battery at each timepoint, allowing us to correlate each outcome of the eye tasks to subjectively reported cannabis impairment and mood.

In addition to measuring eye behavior as a function of cannabis use, we will utilize the training session of this study to collect exploratory data on the relationship between pupil dilation and experimental pain. There is a small literature suggesting that changes in pupil size can be used as an objective biomarker of pain perception (Wildemeersch, 2018); thus, we would like to collect preliminary data on changes in pupil dilation as a function of pain induction. Using Quantitative Sensory Testing (Medoc TSA-II NeuroSensory Analyzer), we will induce thermal pain threshold and tolerance using a cold stimulus (4.0°C; induced with a 30 x 30 mm Peltier thermode, which is 1.5" square metal applicator that is connected to the TSA-II NeuroSensory Analyzer device and software, and produces an ongoing cold sensation applied to the lower palm of the participant's non-dominant hand). Participants will indicate when they first feel pain (pain threshold), and when the pain becomes too much to bear (pain tolerance) by pressing a button on a controller connected to the TSA-II. As the HTC Vive collects

data on pupil size at a frequency of 120 times per second, throughout exposure to the cold stimulus we will be able to measure and correlate potential changes in pupil size to the patient's subjectively reported pain latencies.

The findings of this study may: 1) characterize the validity of eye tests as an objective measure of cannabis use and intoxication; 2) provide pilot data on the relationship between pupillary changes and pain response.

Background, Significance, and Rationale

Significant legislative changes regarding cannabis are rapidly occurring, with 33 states legalizing medical cannabis and 11 states legalizing recreational use (ProCon.org, 2019). With this spreading legalization and changing social attitudes towards cannabis, rates of cannabis use and use disorders are rising (Compton, 2017), with 22.4 million adults over the age of 18 reporting past month use in the United States (GHSA, 2018). These changes also correlate with an increase in the use of cannabis while driving (NHTSA, 2017). A survey conducted by the National Highway Traffic Safety Administration in 2013 and 2014 found that the number of weekend evening drivers with cannabis in their system increased by nearly 50% since 2007. Of 11,100 participants in the survey, nearly 13% tested positive for cannabis based on oral fluid and/or blood tests (Berning et al. 2015). In 2016, 41.1% of drug-positive fatally injured drivers were positive for cannabis (GHSA, 2018).

Importantly, the interaction between cannabis and driving skills has not yet been fully defined by well-controlled research, but previous research highlights the negative effects of driving under the influence of any substance. Driving is a complex task that involves the integration of many skills and functions related to attention and perception of one's environment, including information sampling, judgement, decision-making and motor performance (Stapleton et al. 1986). The psychoactive ingredient of cannabis, delta-9-tetrahydrocannabinol (THC), has been shown to impair attention, memory formation, perception of object sizes, passage of time and sedative effects, all of which negatively impact one's ability to drive (Compton, 2017).

Despite increases in recreational and medicinal cannabis use, research is limited due to the controversial Schedule 1 classification of the drug (indicating that it has no medical utility and a high potential for abuse). Finding a standardized test that can detect cannabis impairment is a public health and traffic safety necessity.

Current Research

The current method used to detect cannabis impairment road-side is based on the Standardized Field Sobriety Test (SFST), which was developed in the 1970s to detect alcohol-impaired driving (Compton, 2017). In this case, a breathalyzer can accurately detect blood alcohol content (BAC) to establish whether an individual is driving over the legal limit (NHTSA, 2017). However, with cannabis, THC blood levels and degree of impairment are not correlated. Whereas alcohol metabolizes at a steady rate and can be detected accurately by a breathalyzer, THC blood concentration levels decline exponentially and there is no existing roadside device that can quickly detect THC levels (Compton, 2017). Furthermore, depending on individual differences in tolerance to the effects of THC, drivers with low THC blood levels may be functionally unsafe behind the wheel, while others with higher THC blood concentration levels may be functionally safe (Compton, 2017). During the process of evaluating alcohol or drug use during a traffic stop, if a BAC test is negative, additional evidence to support a drug impaired driving charge must be collected. This often includes a drug influence evaluation conducted by a drug recognition expert, in which the driver gives a biological sample (blood or urine) to be analyzed. Yet, these experts are not always available and are rarely present at the scene of the incident. All fifty states and the District of Columbia follow this process (Compton, 2017).

Currently, blood sampling is considered by law enforcement officials to be the most effective way to establish recent cannabis use in drivers suspected to be under the influence (Bondallaz et al., 2016). The process involves asking a suspect for consent to withdraw blood, and subsequently bringing the suspect into a police department to conduct a blood draw. However, based on the pharmacokinetics of cannabis, blood sampling is not an ideal method to determine impaired driving, as there is no correlation between impairment and the level of THC in the blood (Compton, 2017). In addition, blood sampling to determine cannabis-impaired driving is not ideal based

on the pharmacodynamics of cannabis, as the time between ingestion and blood sampling may be lengthy and THC blood levels reach their peak within 10 minutes of ingestion before dropping and remaining detectable in low amounts (Fant et al. 1998; Compton, 2017). Furthermore, THC is fat soluble, meaning that it can be stored in fatty tissues and released back into the blood long after ingestion; some studies detect that this may occur up to twenty days post-ingestion (Huestis, 2007), while the psychoactive effects of THC last only 3-4 hours after ingestion. In Colorado, when THC is identified in the driver's blood at a concentration equal to or above the legal limit of 5ng/ml, the driver is considered to be "under the influence." Yet, unintoxicated chronic cannabis users, including medical users, may have elevated blood levels of THC which can be above specified legal limits in many states, 18 of which have zero tolerance or non-zero per se laws for cannabis (Teigen, 2012). Therefore, blood sampling is not a reliable indicator of impairment, and additionally is a highly invasive, costly and lengthy process. Saliva testing for THC is another method that has become popular, yet with limited practical application due to a high number of false negatives as well as low reliability and low sensitivity (Bosker et al. 2012). Saliva testing presents a problem in distinguishing between personal use and environmental exposure, as exposure to second hand cannabis smoke can cause a person to test positive for THC (Compton, 2017; Herrmann et al. 2015; Moore et al. 2007).

The Current Road-side Approach

The Standardized Field Sobriety Test (SFST), consists of three holistic tests of sobriety: 1) the horizontal gaze nystagmus (HGN) to look for the presence or absence of nystagmus, 2) the "walk and turn", and 3) the one leg stand test. The outcomes of these three tests are combined to determine an individual's level of intoxication. There is the possibility of human error and biases when conducting these tests, particularly with the horizontal gaze nystagmus test and other eye tests, as eye movements are subtle. Observing nystagmus with the bare eye requires extensive training that is typically not provided to officers performing traffic stops. Yet, of the three tests in the SFST, the HGN test has been shown to be the most accurate measure of alcohol impairment. In previous research on alcohol-impaired driving, the HGN test correctly classified approximately 88% of participants as impaired (Stuster et al. 1998), highlighting the value of this test in identifying drug-impaired drivers. Accordingly, assessing nystagmus as a metric for recent cannabis use is of interest.

A Proposed Objective Ocular Approach

Utilizing the eyes as biomarkers for drug impairment requires further study before it may be implemented into the legal system. The eyes can be a neurobiological indicator of impairment (Jones et al. 2003), as observed abnormalities in ocular motility can provide diagnostic clues about drug use (Leigh, 2011). Many abnormal eye movements are distinctive and point to specific attributes related to impairment, making them extremely useful in systematic examination (Leigh, 2011). Eye movement patterns that are believed to have a connection to cannabis use and may act as a sign of impairment include lack of smooth eye pursuit, presence of nystagmus at maximum deviation and prior to 45 degrees, lack of convergence and pupil dilation (Compton, 2017).

This study uses a virtual reality high-frequency eye tracker (VR HTC Vive with Pupil Labs Eye Tracking) in a standardized, quantified environment to conduct an eye test battery. Participants will wear the VR headset and be instructed to follow a stimulus with their eyes. The eye battery takes approximately 5 minutes to conduct, and consists of the following four tests:

1) Smooth pursuit: This refers to the eyes' ability to fixate on and track a moving target smoothly, without saccades (Hartman et al. 2016). Some studies indicate that smooth eye pursuit may vary as a function of cannabis use, with chronic users displaying less of a deficit in this task vs. less habitual users (Firth, 2006). Central nervous system depressants and cannabis significantly increase the chance of lack of smooth pursuit and distinct nystagmus at maximum deviation (Porath-Waller et al. 2013). This study will measure the number of saccadic eye movements as the stimulus moves across the screen.
2) Nystagmus (horizontal, vertical, resting): This characteristic is an involuntary jerking of the eye, and is a common effect of many drugs of abuse including cannabis, but also opioids and barbiturates (Peragallo et al. 2013). Tests of nystagmus tend to correlate with impairment. Nystagmus at maximum deviation occurs when a participant is able to hold their eyes steady on a non-moving target without a nystagmus (Hartman et al. 2016). In this study, the stimulus will appear at the edges of the visual field both

horizontally and vertically, referred to as HGN and VGN respectively. We will assess the number and amplitude of jerky eye movements when the stimulus is at an extreme.

3) Convergence: This refers to the eyes' ability to converge, or cross, while a participant focuses on a target that is moved slowly towards the bridge of their nose (Hartman et al. 2016). If a participant is unable to converge on a target a minimum of 2 inches from the bridge of the nose, lack of convergence is established and considered to be a sign of impairment (Stapleton et al. 1986). This study will measure maximum binocular adduction (both pupils moving inward) to quantify participants' ability to converge.
4) Pupil dilation: Pupillary Light Reflex (PLR): In this test, the eye tracking environment will go from dark to bright light instantly and pupil size will be tracked. There is some controversy about the impact of cannabis on pupil diameter, hence the need for further research to characterize the relationship between cannabis intoxication and pupil diameter. Some studies have shown pupil constriction (miosis), some have shown no change in pupillary size, and some have reported dilated pupils (Bramness et al., 2010). Yet, the majority of research shows some relationship between cannabis intoxication and pupil dilation. Pupillary reaction to light tends to be slow when a participant is under the influence of cannabis within the first few hours following consumption (Bramness et al., 2010), suggesting a potential method of testing recent cannabis use amongst drivers. Rebound dilation has been shown to be related to cannabis use in a study in which the pupil diameter at the end of the presentation of a bright stimulus was significantly affected by cannabis (Fant et al. 1998).

In this study, the following latent features related to pupil behavior (not directly observable but calculated later in a Principal Component Analysis and Factor Analysis) will also be analyzed:

1. Rebound dilation: a period of pupillary constriction that is immediately succeeded by a period of pupillary dilation. The light level tests allow for the assessment of rebound dilation when the lights engage, as the pupils constrict in response.
2. Maximum constriction velocity (MCV): a measure of the most extreme rate of change in pupil size during a constriction event. These data are collected during the light level tests as the pupils constrict in response to the light's engagement.
3. Response Latency: the time it takes for the pupil to begin constricting after the light stimulus is turned on. Response latency refers to the biological lag in the pupillary light reflex.
4. Max/Min Pupil Size: Miosis (1.5-2mm)/Mydriasis (7.5-8mm)

State of the field and current limitations: Previous research on the effects of cannabis on the eyes has been conducted, yet most of this research is decades old and used outdated technology that cannot accurately or frequently measure eye movements and pupil dilation. The literature also presents contradicting results on correlations between cannabis and certain eye movements, specifically regarding nystagmus and smooth pursuit. Despite these studies and the fact that eye movements are currently used in the field to detect drug intoxication, little is known about the causal relationship, if any, between cannabis, eye movements and pupil dilation. To date, no published studies have used modern VR eye trackers and data analysis to build a predictive model of cannabis intoxication. The current study seeks to explore the effects of cannabis on eye movements using a sophisticated eye tracking software to provide an objective, accurate measure of cannabis impairment.

Specific Aims and Hypotheses

Aim 1: Examine the relationship between cannabis intoxication and eye behavior.
Hypotheses: (a) Active cannabis (7% THC) will have an effect on eye behavior, evidenced by lack of convergence, lack of smooth pursuit, presence of nystagmus and pupil dilation when compared to inactive placebo cannabis (0% THC).
Exploratory Aim: Examine the relationship between experimental pain and pupil size.
Hypotheses: (a) Changes in pupil size will correlate with subjective reports of experimental pain threshold and tolerance using Quantitative Sensory Testing thermal pain.

Inclusion/Exclusion Criteria

Description of Subject Population:
Non-treatment seeking cannabis smokers.

CRITERION	METHOD OF ASCERTAINMENT
Inclusion:	
1. Males/non-pregnant females aged 21-55 years	Age verified via identification/Non-pregnancy confirmed via urine toxicology
2. Report smoking cannabis ≥1 day per week, and ≥1 joint (~0.5 grams) per smoking day, during the 4 weeks prior to screening	Self-report during clinical interview
3. Urine test positive for recent cannabis use	Urine toxicology
4. Body Mass Index from 18.5-34 kg/m2	Physical examination
5. Not currently seeking treatment for their cannabis use	Self-report during clinical interview
6. Able to perform all study procedures (i.e., does not experience discomfort or nausea from VR headset, can perform computer tasks)	Training session
7. For women, not pregnant, lactating, or breast-feeding and currently practicing an effective form of birth control (double-barrier methods, hormonal birth control pills, hormonal implants, or IUDs)	Self-report during clinical interview, blood, and urine pregnancy test (7091R), physical examination
Exclusion:	
1. Meeting the DSM-V criteria for Severe Cannabis Use Disorder or any other Use Disorder other than for Cannabis, Nicotine, or Caffeine; any other psychiatric disorder	Clinical interview
2. Report using other illicit drugs ≥1 day/week in the prior 4 weeks; positive for anything other than THC > 1x during screening	Clinical interview, urine toxicology
3. Abnormality with the eyes which may affect the eye tracking technology such	Physical examination, training/calibration session with VR eye-tracking device

as color blindness, naturally occurring nystagmus, amblyopia, strabismus, age-related macular degeneration (AMD), cataract, diabetic eye disease, glaucoma, dry eye, extreme refractive error, bacterial or viral infections of the eye.	
4. If medical history, physical and psychiatric examination, or laboratory tests performed during the screening process revealed any significant illness (e.g., diabetes, cardiovascular disease, hypertension (BP >140/90), hepatitis, clinically significant laboratory abnormalities, chronic obstructive pulmonary disease, Parkinson's disease, dementia, cognitive impairment, history of a seizure disorder, history of traumatic brain injury, any immunocompromising conditions such as HIV/AIDS, cancer, or diabetes, or LFTs > 3x upper limit of normal)	Medical history, physical examination, laboratory tests, ECG
5. Current licit use of medical cannabis	Self-report, physical examination
6. Current pain	Self-report during clinical interview, physical examination, medical history
7. User of supplemental oxygen	Medical history, physical examination

Study Procedures

General Overview

This study will examine the effects of cannabis intoxication on eye behavior. Eleven eye-task batteries will be conducted with a VR HTC Vive with Pupil Labs Eye Tracking headset. Healthy cannabis users (N=30, 15M, 15F) will complete a training session followed by two counterbalanced outpatient laboratory sessions in a randomized, double-blind, placebo-controlled (0% vs. 7% THC) design.

In each session, the participant will smoke two-thirds of one cannabis cigarette according to our paced-puff procedure (Foltin et al. 1987). They will complete an eye task battery (5 minutes per battery) 15 minutes prior to smoking as a baseline measure in each session, and again at the following timepoints: 0, 15, 30, 45, 60, 75, 90, 105, 120, and 165 minutes post-cannabis. Baseline assessments will be compared to those at post-cannabis timepoints.

In order to collect exploratory data, we will also conduct one pain assessment during the training session (described below).

Screening:

Initial telephone interviews will be carried out by research assistants who have been trained by Dr. Arout, during which time potential participants will be asked about their current and past drug use and general health. To conduct this telephone interview, we are requesting a waiver of consent.

After initial determinations of eligibility over the phone, volunteers will come into the Cannabis Laboratory for two screening visits. At the first screening visit, they will be asked to sign our currently approved outpatient screening consent form (#7091R), allowing us to collect questionnaire data, conduct interviews, obtain medical information including a medical history and bloodwork (including blood pregnancy test for women at screening), and do an ECG. Potential participants will be told that they will be taking part in a study investigating the effects of smoked cannabis and eye movements. After the general screening process, a study psychologist (Caroline Arout, PhD, Margaret Haney, PhD, Tonisha Kearney-Ramos, PhD) will explain the details of the study procedure and confirm that the volunteer understands what participation entails, after which they will sign the study-specific consent form (#7844).

At the second screening visit, conducted under the study-specific consent form (#7844), study physicians will then conduct a medical exam that includes a physical exam and a psychiatric evaluation (if needed), review medical results, and review study inclusion/exclusion criteria. At screening, the study physician and study PI will explain that the cannabis in this study could be harmful to a developing fetus or young infant, and we will confirm via self-report that women are using and will continue to use a birth control method (double-barrier protection, hormonal birth control pills, hormonal implants, or IUDs) and are not breast-feeding while in the study. The study physician will also explain that birth control methods must be used properly and consistently in order to most effectively avoid pregnancy, that even still they could become pregnant, and thus they should inform research staff immediately if they think they might be pregnant. If a participant becomes pregnant during study participation, they will be discontinued from the study, and we will provide referrals for obstetrical follow-up.

Both screening sessions will be conducted in the Cannabis Laboratory of the Substance Use Research Center (SURC), located on the 3rd floor of the NYS Psychiatric Institute.

Laboratory Facility:
All experimental sessions will be conducted in the Substance Use Research Center (SURC) located on the 3rd floor of the NYS Psychiatric Institute. The outpatient laboratory sessions described in this protocol will be conducted in the Outpatient Cannabis Laboratory. The laboratory has 2 testing rooms that are adjacent to a control room. The testing rooms are equipped with a workstation consisting of a worktable, a comfortable chair, and a Windows computer networked with computers located in the adjacent control room used to collect data. The test rooms are also equipped with automatic sphygmomanometers, electrocardiography systems, CPT apparatus, a VR headset (the HTC Vive with Pupil Labs Eye Tracking), two tripod mounted infrared headset position trackers, a mini refrigerator, and microwave. The control room oversees the test rooms via one-way mirror. It contains office and storage space and Windows computer systems with a Hewlett Packard Laser Jet printer. Windows computers in the control room are used to run sessions and to automate data collection. Participants are continuously monitored through one-way glass and are able to communicate with the investigators via an intercom. The control room also houses ancillary computer equipment and physiological monitoring equipment (heart rate, blood pressure monitor, pulse oximeter unit). Participants will sit in a comfortable task chair in front of a Windows computer. A response manipulandum (“mouse”) will be used for completion of pain rating scales and subjective-effects questionnaires.

Training Session 1: VR headset + QST-TP + Paced-puff procedure description
Volunteers who meet the inclusion/exclusion criteria will complete a training session outlined below.

Participants will wear a VR headset and be asked to follow a virtually projected fixation point (target) in an environment that is identical to the test environment. Participants will be told to follow the fixation point with only their eyes. Participants will be asked if they feel claustrophobic or experience cyber-sickness (a feeling similar to motion sickness) due to incongruence of sensory inputs from the visual and vestibular system. They will spend

a minimum of 10 minutes wearing the headset following a variety of stimuli and adjusting to the virtual environment after which they will report any discomfort verbally and through a feedback form.

In order to collect exploratory data on the potential utility of pupil dilation as a biomarker of pain response, participants will undergo Quantitative Sensory Testing (QST) to induce cold pain threshold and tolerance latencies. We will conduct this assessment during training rather than within the laboratory sessions to avoid the potential confound this task may have on measuring cannabis' effects on eye-tracking and pupil dilation. Further, cannabis administration would also affect our ability to detect changes in pupil dilation as a result of exclusively experimental pain induction. For QST, a thermal testing analyzer (Medoc TSA-II NeuroSensory Analyzer) with a 30 x 30 mm Peltier thermode is used to apply a cold stimulus on the thenar eminence of the palm. The temperature is set to 4.0°C. Using a computerized response button, participants will note the time (in seconds) at which they begin to perceive the cold as painful, and when it becomes too painful to continue. At this latter point, the program will discontinue the cold stimulus and return to baseline temperature. They will also continuously rate the magnitude of perceived pain using a computerized VAS (Co-VAS, 0-100) throughout stimulation. Throughout this assessment, changes in pupil dilation will be measured using the eye-tracking headset and correlated to their subjective Co-VAS pain responses. If participants exceed the 3-minute cut-off, the task will be discontinued in order to avoid tissue damage.

We will also describe the paced-puff procedure of cannabis administration (Foltin et al., 1987) during the training session. We will inform participants that during the two laboratory sessions, we will be directing them through smoking a cannabis cigarette, and that we do this in attempt to standardize the amount of cannabis that each person is getting. We will inform them that this procedure "involves cues to prepare to inhale (5 sec), inhale (5 sec), hold the inhalation (10 sec), and exhale, with 40 seconds in between each puff". Participants will smoke two-thirds of the cigarette using this procedure.

Laboratory Sessions:

There will be two counterbalanced, within-subjects laboratory sessions, which can occur with no wash-out period in between if scheduling permits. Participants will abstain from alcohol and cannabis use 15 hours prior to each laboratory session.

Participants will arrive at NYSPI at 9 am and be given a light breakfast. Vitals (blood pressure/heart rate) will be performed prior to initiating each session. Participants will complete two baseline eye-tracking batteries prior to cannabis administration at each of the two sessions (7% or 0%). Participants will be seated and asked to wear a VR headset connected to the host PC. The headset will be placed on the participant's head and the tracker will be calibrated in a standard calibration. A research assistant may help the participant adjust the headset so that their pupils are centered, and so that the headset is securely placed on their head.

The 5-minute battery of four eye tasks will be administered through the VR headset at 0, 15, 30, 45, 60, 75, 90, 105, 120, and 165 mins after cannabis smoking over the time course of cannabis intoxication. Before each eye test, there will be a calibration which takes between one to three minutes. Vitals (heart rate, blood pressure) will be measured at the end of each of these timepoints throughout the session.

Prior to each eye test at 0, 15, 30, 45, 60, 75, 90, 105, 120, and 165 minutes post-cannabis, the participant will also complete a 3-minute subjective-effects battery, consisting of a series of VAS in which participants indicate how they are feeling at that moment. The 44-item VAS includes mood, physical symptom and drug effect descriptors. Based on a cluster analysis, we employed arithmetic means of individual item scores to reduce 34 of the 44 items into eight subscales: good drug effect; miserable; irritable; anxious; bad effect; social and confused. We also analyze individual VAS drug craving ratings. These subjective measures may detect changes in abuse-related effects as well as changes in mood (miserable, irritable, anxious, cannabis craving) as a function of cannabis condition, and will be correlated to changes in the eye-tracking battery.

The order of the eye tests within the battery will be standardized and will not change across timepoints or sessions. The eye tests are conducted in a VR environment where a fixation point (target) in the shape of a cross – the stimulus – is virtually projected 12 inches in front of the participant. The participant will be asked to follow the center of the target without moving their head. The fixation point's movements are based upon the tests below:

1. Nystagmus:
    - Horizontal Gaze Nystagmus (HGN): The stimulus (a fixation cross) moves from the center of the visual field to 45 visual degrees to the right and left and is held at each extreme for 10 seconds.
    - Vertical Gaze Nystagmus (VGN): The stimulus (a fixation cross) moves from the center of the visual field to 40 visual degrees up and down and is held at each extreme for 10 seconds.
2. Smooth Pursuit (SP): The stimulus (a fixation cross) moves from each extreme of the visual field at a speed of 40 degrees/second. This test measures the tracking ability of the eyes. The smooth pursuit test is embedded in the nystagmus tests; it takes place in between the HGN/VGN tests as the stimulus moves from the horizontal/vertical extremes. Horizontal smooth pursuit is assessed as the stimulus moves from one side of the visual field to the other, while vertical smooth pursuit is assessed when the stimulus moves from the upper extreme of the visual field to the lower extreme, or vice versa.
2. Convergence: The stimulus (a fixation cross) moves from 12 inches to 2 inches away from the participant's nose at a continuous speed over 5 seconds, then is held at that point for 10 seconds.
3. Pupil response: For both pupil tests, participants are asked to stare directly at the stimulus (a large grey fixation cross) to minimize eye movement.
    - Pupillary Light Reflex (PLR): Bright light is presented in a previously dark setting for 10 seconds followed by 30 seconds of no light for pupil adjustment.
    - Pupillary Light Flash Reflex (PLFR): Light is flashed once for one second followed by an observation period of 5 seconds. During the observation period, no lights flash and the participant's reaction to darkness is assessed.

Tests conducted:

Test	Time (sec)
Horizontal Smooth Pursuit x 4	9.2
HGN Hold x 4	40
Vertical Smooth Pursuit x 4	9.2
VGN Hold x 4	40
Convergence In x 3	4.89
Convergence x 3	30
Darkness	30
PLR – Both Eyes	10
Darkness	30
PLR – Right Eye	5
Darkness	30
PLR – Left Eye	5
Darkness	15

PLFR	1
Darkness (observation)	5
Total time:	264.29 sec/ 4.40 min

Session Time		
TIME (hours)	***Cannabis admin (mins)***	**Study procedures and assessments**
0900	-60	Participant arrives
0915	-45	Urine, vitals (BP and HR), breath CO and EtOH, TLFB, breakfast
0930	-30	***Baseline assessment:*** Subjective-effects Battery (SEB), Eye-tracking Battery (ETB)
1000	**0**	***Cannabis administration:*** (**7%** or **0%**)
1000	0	***Post-cannabis 1:*** SEB, ETB, vitals
1015	15	***Post-cannabis 2:*** SEB, ETB, vitals
1030	30	***Post-cannabis 3:*** SEB, ETB, vitals
1045	45	***Post-cannabis 4:*** SEB, ETB, vitals
1100	60	***Post-cannabis 5:*** SEB, ETB, vitals
1115	75	***Post-cannabis 6:*** SEB, ETB, vitals
1130	90	***Post-cannabis 7:*** SEB, ETB, vitals
1145	105	***Post-cannabis 8:*** SEB, ETB, vitals
1200	120	***Post-cannabis 9:*** SEB, ETB, vitals
1245	165	***Post-cannabis 10:*** SEB, ETB, vitals
1300	180	Field sobriety test, vitals, MMSE, discharge

The total time for each trial, including calibration, the eye tracking battery, and the subjective-effects battery is approximately 10 minutes.

At 180 minutes after cannabis administration participants will complete field sobriety tests, vital signs, and a Mini-Mental State exam, and will be permitted to leave once they meet discharge criteria. Criteria for discharge will be met when participants report no ongoing subjective drug effects and have no signs of impairment or intoxication, pass the field sobriety test, have normal vitals, and a normal mental status score as assessed by the Mini-Mental State Exam (MMSE). Dr. Arout, Dr. Haney, or a study physician will make the final determination that the patient is sober and medically stable and can leave the facility. In the rare event the participant is still impaired they will be paid an extra $10 for every hour they stay. They will be instructed not to drive a car after administration of cannabis; therefore, participants will be required to take public transportation (i.e., bus or subway) both to and from the laboratory each session, for which they will be reimbursed.

Video recordings of the eyes will be taken using Pupil Labs at each timepoint during both sessions. These videos will make calibration more accurate; research staff will be able confirm correct pupil calibration after the session is complete. These videos will be available only to research staff (investigators and assistants), will not be used for educational purposes, and will be deidentified and stored by patient study identification number on an encrypted computer in the Cannabis Laboratory. We will destroy these videos at the conclusion of data analysis (approximately 3 years after study initiation).

Criteria for Early Discontinuation

If a woman becomes pregnant during study participation (confirmed via urine pregnancy test), her participation in the study will be discontinued.

Blood and other Biological Samples

Bloodwork to determine eligibility and pregnancy status for this study is conducted under screening protocol #7091R, prior to any screening or study procedures for this study.

Assessment Instruments

Screening Assessments (conducted under #7091R):
1) Telephone Interview: 20min
2) Structured Clinical Interview for DSM-5: variable; relevant sections are performed if participant endorses any of the SCID screening instrument questions
3) Timeline Follow-Back interview for substance use: 10min
4) Beck Depression Inventory: 5min
5) General Health Questionnaire: 5min
6) The Short Form Health Survey: 5min
7) Medical History Questionnaire: 5min
8) General Pain Index Questionnaire: 5min
9) 12-lead electrocardiogram: 15min
10) Blood count with differential, chemistry profile, liver enzymes, and GGTP
11) Urinalysis with 12-panel urine drug testing
12) Physical and Psychiatric Examination: 30min

Behavioral Performance Tasks during Sessions:
1) Quantitative Sensory Testing thermal pain (QST-TP; at training session only): Using a thermal testing analyzer (Medoc TSA-II NeuroSensory Analyzer) with a 30 x 30 mm Peltier thermode is used to apply a cold stimulus on the thenar eminence of the palm. 5 min

2) ETB (Eye Test Battery): Participants will complete four eye tracking tasks in a VR environment. Participants will follow a target with their eyes as it moves up, down, left, right, forwards, and backwards. 5 min.
3) SEB-VAS (Subjective Effects Battery-Visual Analogue Scale): Participants will rate the extent to which they are experiencing 44 different positive (e.g., 'Mellow') and negative (e.g., 'Anxious') mood states, physical symptoms (e.g., 'Muscle Pain') and drug effects (e.g., 'High') at that moment: 2min

Physiological Measures during Laboratory Sessions:
1) Quantitative Urinalysis: Samples analyzed daily
2) Heart Rate and Blood Pressure: 1min
3) Carbon monoxide expiration: 30 sec
4) Breath alcohol concentration: 30 sec

Research Related Delay to Treatment

Research procedures will not result in a delay to treatment since participants are not seeking treatment for cannabis use. Nonetheless, all will be informed of cannabis treatment at STARS in case they change their minds in the future.

Clinical Treatment Alternatives

Participants are not seeking treatment. The alternative is to not participate in this study.

Risks/Discomforts/Inconveniences

Medications:

1) Cannabis: Participants will be administered active cannabis (7% THC) during the training session and on 1/2 laboratory session days, and inactive cannabis (0% THC) in the other laboratory session. The most frequently reported adverse experiences associated with cannabis administration are increased appetite, sleepiness, concentration difficulties, dependence, faintness, restlessness, confusion, lightheadedness, loss of coordination, clumsiness, shakiness, dizziness, stomach upset, headache, paleness, flushing, sweating, dry mouth, slurred speech, fatigue, heart pounding, and changes in the pattern of heart beats. Additionally, cannabis use during pregnancy increases the risk for premature birth, low birthweight, neural tube defects, anemia, and stillbirth (Gunn et al., 2016; Varner et al., 2014).

Procedures:

1) Virtual Reality Headset: Participants may experience dizziness or discomfort from the virtual reality headset. Motion sickness and pressure applied to the face from the headset may lead to clumsiness, shakiness, dizziness, or stomach upset.
2) Quantitative Sensory Testing – thermal pain: the nature of this test is to induce moderate pain and discomfort through the application of a cold stimulus, similar to holding an ice cube. However, the participant controls the amount of pain and amount of time exposed to the painful stimulus by clicking a button on the QST apparatus to indicate their pain threshold, and the designated temperature of 4 degrees Celsius in conjunction with a cut-off time of 3 minutes will ensure that this stimulus does not result in tissue damage.
3) Confidentiality: Potential participants divulge information that is sensitive and may have adverse social consequences if released. This would include information released to insurance companies, health care agencies, family members, or made public in any way.

Describe procedures for minimizing risks:

1) All participants are fully informed of cannabis' side effects, and because all currently smoke cannabis, these effects should be familiar to them. Regardless, we will assess vital signs (blood pressure and heart rate) after patients smoke cannabis to ensure safety. As the medical director of the marijuana laboratory,

Dr. Adam Bisaga will oversee any medical components of the study. In addition to Dr. Adam Bisaga, Dr. Jeanne Manubay, Janet Murray RN, Claudia Tindell, RN, or one of the Medical Fellows (Dr. Jeremy Kidd, Dr. Shulman, Dr. Wai, Dr. Blevins, Dr. Iqbal, Dr. Srivastava, Dr. Castillo) will be available in the case of an emergency. Women who are pregnant or breast-feeding will not be eligible for study participation. If a woman becomes pregnant during study participation, she will be discontinued from the study and referred to obstetrical treatment.

2) During the Training Session, if a participant indicates any discomfort or nausea from the VR headset, the patient, study PI, and the study physician will make the determination together as to whether or not the patient should be enrolled in the study. If a patient experiences nausea or discomfort during either of the laboratory sessions, they can opt to discontinue their study participation and will be observed until the discomfort passes and they can be discharged. If a patient vomits at any point during the Training or Laboratory Sessions, their participation will be discontinued, and they will be observed by study staff until the sensation passes and they can be discharged.
3) The QST computerized program utilizes a temperature of 4 degrees Celsius and a cut-off time of 3 minutes to avoid tissue damage.

Definition and Reporting of Adverse Events:
An adverse event is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (21 CFR 312.32(a)) and a serious adverse event is an adverse events that, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect (21 CFR 312.32(a)). Adverse events will be reported as required in IND safety reporting requirements (21 CFR 312.32).

Methods to Protect Confidentiality

All data records containing identifying information will be kept in locked files and on password-protected computers. Only the principal investigator and other core study staff will have access to identifiable information, which will be maintained on site under lock and key. All computer data is stored without names or other identifiers. Participants will be identified only through a numerical code in all electronic databases. This study will be covered by a Federal Certificate of Confidentiality issued by the Department of Health and Human Services (DHHS).

Direct Benefits to Subjects

There are no direct benefits to research volunteers in the proposed studies. Prior to study acceptance, all volunteers will have an extensive medical and psychiatric work-up. We offer all participants the option of obtaining help to abstain from drug taking. Volunteers understand that they can obtain a referral for drug treatment at any stage of their research participation. We repeat our offer for treatment referral at screening and at discharge from the study. We will attempt to obtain a placement in a drug abuse clinic for those people who indicate a desire for help and will inform all volunteers of our ongoing marijuana-treatment studies conducted within the Division of Substance Abuse.

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NYSPI IRB Approved
7844
8/20/2020 -> 8/18/2021

RESEARCH VOLUNTEERS: Healthy male and female MARIJUANA SMOKERS (age 21-55) needed to study the effects of marijuana on eye behavior. Requires two visits (4 hours each) at the NYS Psychiatric Institute. Compensation for time: $215. Call (646) 774-7777 for more information.

SUMMARY SHEET

Title of Project: Effects of Cannabis on Eye Behavior

This page is a summary of the study you are being asked to participate in. The following outline is meant to serve as a guide to help you learn about this research study and decide whether or not you want to take part. It does not replace the consent form that you will be asked to read and sign. The consent form includes much more information that you will need to make an informed decision. Please read the consent form carefully, ask questions, and take your time or speak to others if you want to before you make your choice. Remember, even if you agree to take part in research you can change your mind at any time.

Purpose: You are being asked to participate in a research study called *Effects of Cannabis on Eye Behavior*. The goal of this study is to examine the effects of a range of marijuana doses on eye behavior. The test will occur in a virtual reality (VR) environment. Your eyes will be tracked and recorded as you complete various eye tests. These tests include tasks in which you are asked to follow a target with your eyes as well as tasks in which the light level of the headset will change.

Alternatives: This is not a treatment study for marijuana use; data are being collected for research purposes. If you are interested in treatment for your marijuana use, we will refer you to a treatment program.

Participation is Voluntary: Your participation is voluntary—it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no," your decision will not affect any of your rights or benefits or your access to care.

Procedures:

- This study includes 2 laboratory sessions that can be completed within one week. You will need to arrive at the laboratory in the morning and stay for approximately 4 hours for each session.
- You will inhale marijuana cigarettes and will complete eye tests in a virtual reality (VR) environment in every session.
- We will collect data concerning your response to a painful cold stimulus called Quantitative Sensory Testing, and take your heart rate, blood pressure, and ask you questions about your mood during each session.
- This is not a treatment study; data are being collected for research purposes. If you are interested in treatment, we will give you a referral to a treatment program.

Risks: There are risks and discomforts associated with participating in this study (please refer to the consent form for further details and explanations of these risks). These include:

1. *Marijuana:* You may experience side effects from the marijuana, such as increased appetite, sleepiness, concentration difficulties, faintness, restlessness, confusion, lightheadedness, paranoia, loss of coordination, clumsiness, shakiness, dizziness, stomach upset, headache, paleness, flushing, sweating, dry mouth, slurred speech, fatigue, itching, heart pounding, and changes in the pattern of heart beats. Marijuana use during pregnancy increases the risk for premature birth, low birthweight, neural tube defects, anemia, and stillbirth.
2. *Virtual Reality Headset*: You may experience dizziness or discomfort from the virtual reality headset. Motion sickness and pressure applied to the face from the headset may lead to clumsiness, shakiness, dizziness, or stomach upset.
3. *Quantitative Sensory Testing:* Another risk of research participation is related to the pain test. You will experience temporary moderate pain as a result of this task. The pain you will experience will feel similar to holding an ice cube, but you will control when it stops.

Benefits: This study was not designed to benefit you directly. Your participation may help scientists learn more about marijuana's effects on eye behavior and performance in a virtual reality environment.

Questions: Please contact Dr. Caroline Arout, who is in charge of the study, with questions at 646-774-6167.

New York State Psychiatric Institute
Columbia University Department of Psychiatry

Informed Consent for Participation in Research

Title of Project: Effects of Cannabis on Eye Behavior

Purpose and Overview

The purpose of this research is to study how marijuana affects eye behavior. Various eye tests, including tasks in which you are asked to follow a target and tasks in which the light level of the headset changes, will be conducted. You are being asked to participate because you have experience with marijuana.

Participation is Voluntary

Participation in this project is voluntary. If you decide not to participate or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision to not participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University. You will be informed of any new findings or risks that arise that may affect your willingness to continue in this study. The investigator may also decide that your participation should be discontinued, if she thinks that this is better for you.

Alternative to Study Participation

This is not a treatment study for marijuana use or for pain; data are being collected for research purposes. If you are interested in treatment for your marijuana use, we will give you a referral to a treatment program.

Medications

As part of this study you will be asked to inhale marijuana that will vary in strength from session to session. Neither you nor the research staff will know what strength of marijuana you are given on any particular day, but the investigators can find out in an emergency by contacting Dr. Arout.

Procedures

If you are breast-feeding or if you think you might be pregnant, please tell the investigator. Breast-feeding and pregnant women may not participate in this research because the marijuana used in this study may cause damage to a developing fetus or young infant. Marijuana use during pregnancy increases the risk for premature birth, low birthweight, neural tube defects, anemia, and stillbirth. Therefore, you should not participate in this research if you are pregnant or breast-feeding. To determine your eligibility for this study, a urine pregnancy test will be conducted before you start. If the tests are positive, you will not be able to participate in the study. If you are not pregnant and enroll in the study, urine pregnancy tests will be repeated every time you visit the lab. It is important to understand that even if a pregnancy test is negative, you could still be pregnant, because these tests cannot detect very early pregnancies (that is, within the first few days). If you are sexually active, it is very

important that you use a highly effective form of birth control throughout your study participation. Methods of birth control considered to be highly effective include oral contraceptives, double barrier methods (condom and spermicide), hormonal implants, and intrauterine devices. It is important to understand that even if you use one of these birth control methods, there is still a chance you could become pregnant. Also, if you do not use the birth control method consistently (for example, if you don't take your birth control pills at approximately the same time every day) you may become pregnant. By signing this consent form, you are agreeing to practice a highly effective method of birth control (e.g., oral contraceptives, double barrier protection, hormonal implant, intrauterine device) until the end of the study. If you think you might be pregnant, it is important to let the study team know right away. The study team will conduct a pregnancy test and help you decide what to do next.

You have completed bloodwork and a blood pregnancy test (for women only) to determine initial eligibility under our screening protocol (#7091R). Now that you have completed the screening process, you will participate in 1 training session to familiarize you with the various questionnaires and tasks, we will describe how you will smoke marijuana cigarettes during the two laboratory sessions, and you will also take part in a task that induces moderate pain. After these sessions, we will tell you if you have been selected to participate in the study sessions.

Training session: During the training session, we will complete three tasks.

First, we will show and describe to you how the virtual reality headset works, and you will try it on to see how it feels on your head, and we will also make sure that the virtual reality environment does not cause you any discomfort. If you experience any discomfort (for example, if the headset hurts your head, or if the virtual reality experience causes any nausea or upset stomach), please tell us immediately. The headset is a wearable pair of goggles which rests on the bridge of your nose, similar to a pair of glasses. Adjustable foam straps will be fitted around your head to support the goggles and make them more comfortable. To put the headset on, we will wrap the straps to fit around your head and adjust the tightness to a comfortable level. Once you, along with the research staff, have determined that the headset is on tight enough and is comfortable, we will calibrate it to make sure that it is properly detecting your eyes and your eye movement. If the headset is too loose, tight, or off-center, a research assistant may further assist in successful and comfortable placement. Once you indicate that the headset is comfortable and the placement is sufficient for the cameras to consistently detect and read your eyes, we will have you perform a sample task similar to the tasks you will complete during the laboratory sessions to make sure that the virtual reality environment doesn't cause you any discomfort (such as nausea or upset stomach).

Second, we will also collect data on how your eyes react to a painful stimulus during this session. We will use a procedure called Quantitative Sensory Testing – thermal pain (QST-TP), using a small thermode, which is 1.5" square metal applicator that is connected to a computer and produces an ongoing cold sensation. The thermode will be attached to the lower palm of your hand using a Velcro strip, and you will be given a handheld controller in your other hand that will allow you to control the cold sensation. This thermode will produce a cold stimulus (4

degrees Celsius); we will ask you to let us know by clicking the controller when this cold first starts to feel painful (pain threshold), and when it becomes too painful to bear (pain tolerance). When you click the controller to indicate that the cold sensation is too painful, the cold stimulus will stop and return to room temperature. Please note that the nature of this task is to produce moderate pain, but you control when it stops, and we will use a cut-off time of 3 minutes so that the cold stimulus will not produce any damage to your skin. At the same time that you are doing this pain test, we will have you wear the virtual reality headset which will measure how your pupil size changes while you are feeling pain from the QST-TP.

Finally, during this session we will also describe how you will be asked to smoke marijuana during the laboratory sessions according to our standard paced-puff procedure.

Laboratory sessions: A total of 2 laboratory sessions will be conducted that will require 1 to 2 visits per week for one to two weeks (you can complete both sessions in one week, or you can choose to complete one session per week over a two-week period). You will need to arrive at the laboratory in the morning and stay for approximately 4 hours.

Before you smoke marijuana, you will be fitted into the virtual reality headset in the same way that you were at the training session. You will then complete a 5-minute battery of baseline eye tests, where you will be instructed to follow the center of a target with only your eyes as it moves left, right, up, down, forwards, or backwards. When you can no longer see the target, you should stare straight forward. The light level and position of the target may change. The target may move from left to right, up or down, or closer or farther from you. As it moves, it is important that you follow the center of the target with only your eyes. These tasks will be completed a total of 11 times over the 4-hour period that you are in the laboratory (once before smoking marijuana, and then 10 times after smoking marijuana). We will also ask you how the marijuana makes you feel at the same timepoints as the eye tasks.

During each of the two sessions, you will receive a marijuana cigarette to smoke according to our standardized paced-puff procedure. Using this procedure, we will instruct you to ‘prepare’ to inhale (5 seconds), ‘inhale’ (5 seconds), ‘hold’ the smoke in your lungs (10 seconds), and ‘exhale’, with 40 seconds in between each puff. We will continue this process until you smoke two-thirds of the cigarette. This procedure helps us make sure that everyone gets about the same amount of marijuana in each session.

It is important that you do not smoke marijuana for 15 hours before the start of each session. Thus, if you smoke marijuana the evening before a session, you must stop smoking by 6 PM on the day before the session, so that there will be at least 15 hours between your marijuana use at home and in the laboratory. We will provide a standard light breakfast (including coffee, tea or soda) at the start of each laboratory session; therefore, we do not want you to have anything to eat or drink before arriving at the laboratory. Before each session you will need to provide a urine sample that may be screened for drug use and for pregnancy if you are a woman. You will also have your breath alcohol and carbon monoxide measured in order to verify that you haven’t ingested alcohol

or smoked recently. In each session you will also be provided with snacks and lunch. We ask that you try to complete the questionnaires at the scheduled times, since the assessments are time-sensitive. When you are not filling out questionnaires or doing the eye tasks, you may engage in activities (such as reading) as long as these activities do not interfere with the study.

At the end of the session, the research staff will evaluate you and determine that you are not still feeling marijuana effects and are able to leave. If you are still having a marijuana effect, you may be asked to stay longer until the drug effect wears off; you will be paid at a rate of $10/hour for any extra time. We may also arrange for a taxi to take you to your destination, and we will pay for these expenses when the taxi picks you up from the laboratory. In addition, you must agree to not drive a car for 8 hours after you leave the laboratory, so you need to be picked up by a relative or friend, or you will need to take a bus, subway, or taxi to your destination. We will also pay for mass transit expenses in cash during each visit in a total of $5.50 per visit (to cover up to $2.75 subway fare to and from the laboratory).

Video Consent

The virtual reality headset that we will be using will record a video (it will not include audio) of your eyes at each timepoint during both of the sessions. These videos will be used to help us make sure that we recorded your pupil correctly, or in other words, to ensure data quality. The videos are only available to the investigators on this study and their research assistants, will not be used for professional or educational purposes (e.g. meetings, presentations), and will be de-identified (they will not be saved with any of your personal information such as your name or birth date) and stored on an encrypted computer in our laboratory. They will be discarded at the end of the study after we finish analyzing the data (approximately 3 years from the start of this study). Though these videos are a required part of study participation, please remember that your study participation consent may be withdrawn at any time and that these videos can be erased either during or after the eye-tracking assessment is complete if you change your mind.

Risks and Inconveniences

Marijuana: You may experience side effects from the marijuana, which could include increased appetite, sleepiness, concentration difficulties, dependence, faintness, restlessness, confusion, lightheadedness, loss of coordination, clumsiness, shakiness, dizziness, stomach upset, headache, paleness, flushing, sweating, dry mouth, slurred speech, fatigue, paranoia, itching, heart pounding, and changes in the pattern of heart beats. Marijuana use during pregnancy increases the risk for premature birth, low birthweight, neural tube defects, anemia, and stillbirth, so you may not participate in this study if you are pregnant or think you might be pregnant.

Virtual Reality Headset: You may experience dizziness or discomfort from the virtual reality headset. Motion sickness and pressure applied to the face from the headset may lead to headache, confusion, restlessness, clumsiness, shakiness, dizziness, or stomach upset. If you experience any of these effects, please let us know.

Quantitative Sensory Testing: Another risk of research participation is related to the pain test. You will experience painfully cold temperatures (4 degrees Celsius) due to the nature of this test; the cold pain will feel similar to holding an ice cube, but you control when we stop applying the cold stimulus. We also use a cut-off time of 3 minutes so that there is no damage to your skin as a result of the cold temperature of the stimulus.

Benefits

This study was not designed to benefit you directly. Your participation may help scientists better understand how marijuana changes performance on virtual reality eye behavior tasks, and how pupil size changes when people experience pain.

Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Records will be available to research staff, and to Federal, State, and Institutional regulatory personnel such as the DHHS and Food and Drug Administration (FDA), who may review records as part of routine audits. 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.

All records, including signed consent forms, will be kept in a locked file, and your name will never be used in publications or presentations. Your name and other identifying information will be stored in an electronically

secure database at New York Psychiatric Institute. All of our computers that contain participant-related information are password protected and only the study personnel have access to the passwords. Once you are enrolled into the study, only your initials and your assigned number will be used to identify you on all documents, including electronic documents that may be used for storage. Your private information, urine samples or other biospecimens will not be used for future research studies, distributed to other investigators for future research studies, used for whole genome sequencing, or used for commercial profit. All research records and data will be kept for at least three years after this study is completed. Research records and data will be deleted and/or destroyed once the study is completed and the PI has determined that it is no longer necessary to retain the data collected under this protocol.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Study Compensation

For participating in this research study, you will receive $25 for each of two screening sessions, and $25 for the training session prior to being accepted into the study. This money will be paid to you in cash at the time of each visit. You will earn $35 for each session, and if you complete the entire study you will get an additional $35 bonus for each of the two sessions. Session pay will be given in cash at the end of the second session if all the sessions are completed. If you withdraw from the study, you will be given cash for the sessions completed at the time that you would have finished the second session. If you do not follow the study instructions, you may be removed from the study. Thus, the total pay for screening, participating and completing this study will be $215. Each session's pay includes $5.50 subway fare to cover transportation expenses.

In Case of Injury: Federal regulations require that we inform you about our institution's policy with regard to compensation and payment for treatment of research-related injuries. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator, Dr. Caroline Arout, at (646) 774-6167 so that you can review the matter and identify the medical resources that may be available to you.

In case of injury, New York State Psychiatric Institute will provide short-term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances. New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

Questions

The investigators will answer, to the best of their ability, any questions you may have now or in the future regarding study procedures or your response to them. If you have any questions, you can call the principal investigator, Dr. Caroline Arout at (646) 774-6167 or the study physician, Dr. Jeanne Manubay at (646) 774-8016. You will be informed of any new findings or risks that arise that may affect your willingness to continue in this study. If you have any questions about your rights as a research participant, want to provide feedback, or have a complaint, you may call the NYSPI Institutional Review Board (IRB; an IRB is a committee that protects the rights of human subjects in research studies). You may call the IRB Main Office at (646) 774-7155 during regular office hours.

You will be given a copy of this consent form to take with you.

Documentation of consent

I have discussed this study with _____ to my satisfaction. To the best of my knowledge, I am not pregnant. I understand that my participation is voluntary, and that I can withdraw from the study at any time without prejudice. Signing this form does not waive any of my legal rights.

I have read the above, and I voluntarily agree to enter this research study.

Signature of Subject Date

Printed Name of Subject

Statement of the Investigator Obtaining Consent

I have discussed the proposed research with this subject and, in my opinion, this subject understands the benefits, risks and alternatives (including the alternative of not participating in the research) and in my opinion is capable of freely consenting to participate in this research.

Signature of Investigator Obtaining Consent Date

Printed Name of Investigator

Statement of Study Physician

I have discussed the proposed research with this participant including the risks, benefits, and alternatives to participation (including the alternative of not participating in the research.) The participant has had an opportunity to ask questions and in my opinion is capable of freely consenting to participate in this research.

Signature of Study Physician Obtaining Consent Date

Printed Name of Study Physician

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SUMMARY SHEET

Title of Project: Effects of Cannabis on Eye Behavior

This page is a summary of the study you are being asked to participate in. The following outline is meant to serve as a guide to help you learn about this research study and decide whether or not you want to take part. It does not replace the consent form that you will be asked to read and sign. The consent form includes much more information that you will need to make an informed decision. Please read the consent form carefully, ask questions, and take your time or speak to others if you want to before you make your choice. Remember, even if you agree to take part in research you can change your mind at any time.

Purpose: You are being asked to participate in a research study called *Effects of Cannabis on Eye Behavior*. The goal of this study is to examine the effects of a range of marijuana doses on eye behavior. The test will occur in a virtual reality (VR) environment. Your eyes will be tracked and recorded as you complete various eye tests. These tests include tasks in which you are asked to follow a target with your eyes as well as tasks in which the light level of the headset will change.

Alternatives: This is not a treatment study for marijuana use; data are being collected for research purposes. If you are interested in treatment for your marijuana use, we will refer you to a treatment program.

Participation is Voluntary: Your participation is voluntary—it is up to you whether you would like to participate. It is fine to say "no" now or at any time after you have started the study. If you say "no," your decision will not affect any of your rights or benefits or your access to care.

Procedures:

- This study includes 2 laboratory sessions that can be completed within one week. You will need to arrive at the laboratory in the morning and stay for approximately 4 hours for each session.
- You will inhale marijuana cigarettes and will complete eye tests in a virtual reality (VR) environment in every session.
- We will collect data concerning your response to a painful cold stimulus called Quantitative Sensory Testing, and take your heart rate, blood pressure, and ask you questions about your mood during each session.
- This is not a treatment study; data are being collected for research purposes. If you are interested in treatment, we will give you a referral to a treatment program.

Risks: There are risks and discomforts associated with participating in this study (please refer to the consent form for further details and explanations of these risks). These include:

1. *Marijuana:* You may experience side effects from the marijuana, such as increased appetite, sleepiness, concentration difficulties, faintness, restlessness, confusion, lightheadedness, paranoia, loss of coordination, clumsiness, shakiness, dizziness, stomach upset, headache, paleness, flushing, sweating, dry mouth, slurred speech, fatigue, itching, heart pounding, and changes in the pattern of heart beats. Marijuana use during pregnancy increases the risk for premature birth, low birthweight, neural tube defects, anemia, and stillbirth.
2. *Virtual Reality Headset*: You may experience dizziness or discomfort from the virtual reality headset. Motion sickness and pressure applied to the face from the headset may lead to clumsiness, shakiness, dizziness, or stomach upset.
3. *Quantitative Sensory Testing:* Another risk of research participation is related to the pain test. You will experience temporary moderate pain as a result of this task. The pain you will experience will feel similar to holding an ice cube, but you will control when it stops.

Benefits: This study was not designed to benefit you directly. Your participation may help scientists learn more about marijuana's effects on eye behavior and performance in a virtual reality environment.

Questions: Please contact Dr. Caroline Arout, who is in charge of the study, with questions at 646-774-6167.

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New York State Psychiatric Institute
Columbia University Department of Psychiatry

Informed Consent for Participation in Research

Title of Project: Effects of Cannabis on Eye Behavior

Purpose and Overview

The purpose of this research is to study how marijuana affects eye behavior. Various eye tests, including tasks in which you are asked to follow a target and tasks in which the light level of the headset changes, will be conducted. You are being asked to participate because you have experience with marijuana.

Participation is Voluntary

Participation in this project is voluntary. If you decide not to participate or if you later decide to stop participating, you will not lose any benefits to which you are otherwise entitled. A decision to not participate or withdraw your participation will not affect your current or future treatment at the New York State Psychiatric Institute or Columbia University. You will be informed of any new findings or risks that arise that may affect your willingness to continue in this study. The investigator may also decide that your participation should be discontinued, if she thinks that this is better for you.

Alternative to Study Participation

This is not a treatment study for marijuana use or for pain; data are being collected for research purposes. If you are interested in treatment for your marijuana use, we will give you a referral to a treatment program.

Medications

As part of this study you will be asked to inhale marijuana that will vary in strength from session to session. Neither you nor the research staff will know what strength of marijuana you are given on any particular day, but the investigators can find out in an emergency by contacting Dr. Arout.

Procedures

If you are breast-feeding or if you think you might be pregnant, please tell the investigator. Breast-feeding and pregnant women may not participate in this research because the marijuana used in this study may cause damage to a developing fetus or young infant. Marijuana use during pregnancy increases the risk for premature birth, low birthweight, neural tube defects, anemia, and stillbirth. Therefore, you should not participate in this research if you are pregnant or breast-feeding. To determine your eligibility for this study, a urine pregnancy test will be conducted before you start. If the tests are positive, you will not be able to participate in the study. If you are not pregnant and enroll in the study, urine pregnancy tests will be repeated every time you visit the lab. It is important to understand that even if a pregnancy test is negative, you could still be pregnant, because these tests cannot detect very early pregnancies (that is, within the first few days). If you are sexually active, it is very

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important that you use a highly effective form of birth control throughout your study participation. Methods of birth control considered to be highly effective include oral contraceptives, double barrier methods (condom and spermicide), hormonal implants, and intrauterine devices. It is important to understand that even if you use one of these birth control methods, there is still a chance you could become pregnant. Also, if you do not use the birth control method consistently (for example, if you don't take your birth control pills at approximately the same time every day) you may become pregnant. By signing this consent form, you are agreeing to practice a highly effective method of birth control (e.g., oral contraceptives, double barrier protection, hormonal implant, intrauterine device) until the end of the study. If you think you might be pregnant, it is important to let the study team know right away. The study team will conduct a pregnancy test and help you decide what to do next.

You have completed bloodwork and a blood pregnancy test (for women only) to determine initial eligibility under our screening protocol (#7091R). Now that you have completed the screening process, you will participate in 1 training session to familiarize you with the various questionnaires and tasks, we will describe how you will smoke marijuana cigarettes during the two laboratory sessions, and you will also take part in a task that induces moderate pain. After these sessions, we will tell you if you have been selected to participate in the study sessions.

Training session: During the training session, we will complete three tasks.

First, we will show and describe to you how the virtual reality headset works, and you will try it on to see how it feels on your head, and we will also make sure that the virtual reality environment does not cause you any discomfort. If you experience any discomfort (for example, if the headset hurts your head, or if the virtual reality experience causes any nausea or upset stomach), please tell us immediately. The headset is a wearable pair of goggles which rests on the bridge of your nose, similar to a pair of glasses. Adjustable foam straps will be fitted around your head to support the goggles and make them more comfortable. To put the headset on, we will wrap the straps to fit around your head and adjust the tightness to a comfortable level. Once you, along with the research staff, have determined that the headset is on tight enough and is comfortable, we will calibrate it to make sure that it is properly detecting your eyes and your eye movement. If the headset is too loose, tight, or off-center, a research assistant may further assist in successful and comfortable placement. Once you indicate that the headset is comfortable and the placement is sufficient for the cameras to consistently detect and read your eyes, we will have you perform a sample task similar to the tasks you will complete during the laboratory sessions to make sure that the virtual reality environment doesn't cause you any discomfort (such as nausea or upset stomach).

Second, we will also collect data on how your eyes react to a painful stimulus during this session. We will use a procedure called Quantitative Sensory Testing – thermal pain (QST-TP), using a small thermode, which is 1.5" square metal applicator that is connected to a computer and produces an ongoing cold sensation. The thermode will be attached to the lower palm of your hand using a Velcro strip, and you will be given a handheld controller in your other hand that will allow you to control the cold sensation. This thermode will produce a cold stimulus (4

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degrees Celsius); we will ask you to let us know by clicking the controller when this cold first starts to feel painful (pain threshold), and when it becomes too painful to bear (pain tolerance). When you click the controller to indicate that the cold sensation is too painful, the cold stimulus will stop and return to room temperature. Please note that the nature of this task is to produce moderate pain, but you control when it stops, and we will use a cut-off time of 3 minutes so that the cold stimulus will not produce any damage to your skin. At the same time that you are doing this pain test, we will have you wear the virtual reality headset which will measure how your pupil size changes while you are feeling pain from the QST-TP.

Finally, during this session we will also describe how you will be asked to smoke marijuana during the laboratory sessions according to our standard paced-puff procedure.

Laboratory sessions: A total of 2 laboratory sessions will be conducted that will require 1 to 2 visits per week for one to two weeks (you can complete both sessions in one week, or you can choose to complete one session per week over a two-week period). You will need to arrive at the laboratory in the morning and stay for approximately 4 hours.

Before you smoke marijuana, you will be fitted into the virtual reality headset in the same way that you were at the training session. You will then complete a 5-minute battery of baseline eye tests, where you will be instructed to follow the center of a target with only your eyes as it moves left, right, up, down, forwards, or backwards. When you can no longer see the target, you should stare straight forward. The light level and position of the target may change. The target may move from left to right, up or down, or closer or farther from you. As it moves, it is important that you follow the center of the target with only your eyes. These tasks will be completed a total of 11 times over the 4-hour period that you are in the laboratory (once before smoking marijuana, and then 10 times after smoking marijuana). We will also ask you how the marijuana makes you feel at the same timepoints as the eye tasks.

During each of the two sessions, you will receive a marijuana cigarette to smoke according to our standardized paced-puff procedure. Using this procedure, we will instruct you to ‘prepare’ to inhale (5 seconds), ‘inhale’ (5 seconds), ‘hold’ the smoke in your lungs (10 seconds), and ‘exhale’, with 40 seconds in between each puff. We will continue this process until you smoke two-thirds of the cigarette. This procedure helps us make sure that everyone gets about the same amount of marijuana in each session.

It is important that you do not smoke marijuana for 15 hours before the start of each session. Thus, if you smoke marijuana the evening before a session, you must stop smoking by 6 PM on the day before the session, so that there will be at least 15 hours between your marijuana use at home and in the laboratory. We will provide a standard light breakfast (including coffee, tea or soda) at the start of each laboratory session; therefore, we do not want you to have anything to eat or drink before arriving at the laboratory. Before each session you will need to provide a urine sample that may be screened for drug use and for pregnancy if you are a woman. You will also have your breath alcohol and carbon monoxide measured in order to verify that you haven’t ingested alcohol

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or smoked recently. In each session you will also be provided with snacks and lunch. We ask that you try to complete the questionnaires at the scheduled times, since the assessments are time-sensitive. When you are not filling out questionnaires or doing the eye tasks, you may engage in activities (such as reading) as long as these activities do not interfere with the study.

At the end of the session, the research staff will evaluate you and determine that you are not still feeling marijuana effects and are able to leave. If you are still having a marijuana effect, you may be asked to stay longer until the drug effect wears off; you will be paid at a rate of $10/hour for any extra time. We may also arrange for a taxi to take you to your destination, and we will pay for these expenses when the taxi picks you up from the laboratory. In addition, you must agree to not drive a car for 8 hours after you leave the laboratory, so you need to be picked up by a relative or friend, or you will need to take a bus, subway, or taxi to your destination. We will also pay for mass transit expenses in cash during each visit in a total of $5.50 per visit (to cover up to $2.75 subway fare to and from the laboratory).

Video Consent

The virtual reality headset that we will be using will record a video (it will not include audio) of your eyes at each timepoint during both of the sessions. These videos will be used to help us make sure that we recorded your pupil correctly, or in other words, to ensure data quality. The videos are only available to the investigators on this study and their research assistants, will not be used for professional or educational purposes (e.g. meetings, presentations), and will be de-identified (they will not be saved with any of your personal information such as your name or birth date) and stored on an encrypted computer in our laboratory. They will be discarded at the end of the study after we finish analyzing the data (approximately 3 years from the start of this study). Though these videos are a required part of study participation, please remember that your study participation consent may be withdrawn at any time and that these videos can be erased either during or after the eye-tracking assessment is complete if you change your mind.

Risks and Inconveniences

Marijuana: You may experience side effects from the marijuana, which could include increased appetite, sleepiness, concentration difficulties, dependence, faintness, restlessness, confusion, lightheadedness, loss of coordination, clumsiness, shakiness, dizziness, stomach upset, headache, paleness, flushing, sweating, dry mouth, slurred speech, fatigue, paranoia, itching, heart pounding, and changes in the pattern of heart beats. Marijuana use during pregnancy increases the risk for premature birth, low birthweight, neural tube defects, anemia, and stillbirth, so you may not participate in this study if you are pregnant or think you might be pregnant.

Virtual Reality Headset: You may experience dizziness or discomfort from the virtual reality headset. Motion sickness and pressure applied to the face from the headset may lead to headache, confusion, restlessness, clumsiness, shakiness, dizziness, or stomach upset. If you experience any of these effects, please let us know.

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Quantitative Sensory Testing: Another risk of research participation is related to the pain test. You will experience painfully cold temperatures (4 degrees Celsius) due to the nature of this test; the cold pain will feel similar to holding an ice cube, but you control when we stop applying the cold stimulus. We also use a cut-off time of 3 minutes so that there is no damage to your skin as a result of the cold temperature of the stimulus.

Benefits

This study was not designed to benefit you directly. Your participation may help scientists better understand how marijuana changes performance on virtual reality eye behavior tasks, and how pupil size changes when people experience pain.

Confidentiality

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. This means that the researchers cannot release or use information, documents, or samples that may identify you in any action or suit unless you say it is okay. They also cannot provide them as evidence unless you have agreed. This protection includes federal, state, or local civil, criminal, administrative, legislative, or other proceedings. An example would be a court subpoena.

There are some important things that you need to know. The Certificate DOES NOT stop reporting that federal, state or local laws require. Some examples are laws that require reporting of child or elder abuse, some communicable diseases, and threats to harm yourself or others. The Certificate CANNOT BE USED to stop a sponsoring United States federal or state government agency from checking records or evaluating programs. The Certificate DOES NOT stop disclosures required by the federal Food and Drug Administration (FDA). The Certificate also DOES NOT prevent your information from being used for other research if allowed by federal regulations.

Researchers may release information about you when you say it is okay. For example, you may give them permission to release information to insurers, medical providers or any other persons not connected with the research. The Certificate of Confidentiality does not stop you from willingly releasing information about your involvement in this research. It also does not prevent you from having access to your own information.

Records will be available to research staff, and to Federal, State, and Institutional regulatory personnel such as the DHHS and Food and Drug Administration (FDA), who may review records as part of routine audits. 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.

All records, including signed consent forms, will be kept in a locked file, and your name will never be used in publications or presentations. Your name and other identifying information will be stored in an electronically

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secure database at New York Psychiatric Institute. All of our computers that contain participant-related information are password protected and only the study personnel have access to the passwords. Once you are enrolled into the study, only your initials and your assigned number will be used to identify you on all documents, including electronic documents that may be used for storage. Your private information, urine samples or other biospecimens will not be used for future research studies, distributed to other investigators for future research studies, used for whole genome sequencing, or used for commercial profit. All research records and data will be kept for at least three years after this study is completed. Research records and data will be deleted and/or destroyed once the study is completed and the PI has determined that it is no longer necessary to retain the data collected under this protocol.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

Study Compensation

For participating in this research study, you will receive $25 for each of two screening sessions, and $25 for the training session prior to being accepted into the study. This money will be paid to you in cash at the time of each visit. You will earn $35 for each session, and if you complete the entire study you will get an additional $35 bonus for each of the two sessions. Session pay will be given in cash at the end of the second session if all the sessions are completed. If you withdraw from the study, you will be given cash for the sessions completed at the time that you would have finished the second session. If you do not follow the study instructions, you may be removed from the study. Thus, the total pay for screening, participating and completing this study will be $215. Each session's pay includes $5.50 subway fare to cover transportation expenses.

In Case of Injury: Federal regulations require that we inform you about our institution's policy with regard to compensation and payment for treatment of research-related injuries. If you believe that you have sustained an injury as a result of participating in a research study, you may contact the Principal Investigator, Dr. Caroline Arout, at (646) 774-6167 so that you can review the matter and identify the medical resources that may be available to you.

In case of injury, New York State Psychiatric Institute will provide short-term emergency medical treatment, which has been determined to be necessary by New York State Psychiatric Institute's doctors, and which is within the capability of New York State Psychiatric Institute to provide. In addition, we will provide assistance in arranging follow up care in such instances. New York State Psychiatric Institute and Research Foundation for Mental Hygiene do not provide compensation or payment for treatment of research related injuries. However, you should be aware that you do not give up your legal right to seek such compensation through the court by participating in this research.

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Questions

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You will be given a copy of this consent form to take with you.