The Effect of High-Potency Acute Cannabis Use on Prospective Memory

by

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ABSTRACT

An important facet of daily memory function is prospective memory, which is one's ability to complete established intentions in the appropriate temporal and spatial context. Many factors contribute to impairments in prospective memory, such as limited cognitive resources or aging. A factor that has been subject to recent investigation is how cannabis use may have an impact on the mechanisms that contribute to prospective memory. Cannabis use has been on the rise across the world, and in the United States more states are pushing to legalize its recreational use, if they haven't already. As this substance becomes more easily accessible, akin to alcohol use, the necessity to investigate its potential consequences on cognition is needed now more than ever. Prospective memory is an appropriate measure cannabis-induced deficits due to the wide literature looking at neural correlates of the component mechanisms that contribute to successful prospective memory, attentional and memory processes. The current study employed two experiments to measure this argued claim. Experiment 1 replicated well-defined effects from the prospective memory literature by measuring task accuracy (memory), response times (attention), and pupillary dynamics (attention). Informed by the research looking at the brain regions suspected of experiencing the most functional impairment, Experiment 2 aimed to extend these findings with a sample of participants following acute cannabis administration, however, results indicated cannabis group performance was similar in accuracy and showed faster mean latencies to that of the control group.

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Prospective Memory (PM)

Standard Mean Difference (SMD)

Locus Coeruleus (LC)

Functional Magnetic Resonance Imaging (fMRI)

Cannabinoid$_1$ Receptor (CB1)

Δ^9-tetrahydrocannabinol (THC)

Time point 1 (TP1)

Time point 2 (TP2)

Time point 3 (TP3)

Cannabidiol (CBD)

Institutional Review Board (IRB)

Versus (Vs)

Standard Deviation (S

LITERATURE REVIEW – EXPERIMENT 1

Prospective Memory Theory & Background

Individuals form intentions to complete activities in the future whenever contextual factors prevent them from doing so in the moment. Prospective memory broadly refers to forming intentions, maintaining intentions, remembering intentions, and executing intentions at the appropriate time in the future (Einstein et al., 2005). Completing intentions has potentially significant implications for an individual's well-being and daily functioning. For instance, an older adult forgetting to take medication with a meal may hinder their ability to live independently as this prospective memory failure could have devastating health effects. The overarching goal of the current study is to investigate the effects of acute cannabis intoxication on event-based prospective memory. In the first experiment, we validated behavioral and pupillary correlates of event-based prospective memory. In the second experiment, we investigated the effects of acute cannabis intoxication on these correlates.

Event-based prospective memory refers to how environmental events serve as cues to activate intentions from memory (Einstein et al., 1997, Marsh & Hicks, 1998). Two primary theories have been proposed to explain how event-based prospective memory cues initiate the retrieval of intentions. The preparatory attention and memory processes (PAM) theory suggests that individuals must allocate some limited capacity resources to detecting cues associated with their intention (Smith, 2003). Based on this theory, conscious and subconscious monitoring processes are required to detect a cue and retrieve the cue-action response plan. Alternatively, the Multi-Process View (MPV) posits that cue detection

relies on multiple coordinated processes, including effortful strategic monitoring processes as well as less effortful and sometimes automatic detection and retrieval processes (Einstein et al., 2005).

Einstein and McDaniel (2000) have suggested that several factors influence prospective memory performance, including individual differences in cognitive ability (Brewer et al., 2010), the importance of the intention (Cook et al., 2015, Walter & Meier, 2014;), the demands of the ongoing task (Marsh & Hicks, 1998), the context surrounding the cue (Marsh & Cook Cites; Smith & Loft, 2014), the difficulty of cue detection (Einstein et al, 2005, Ball, Vogel, & Brewer, 2019, Scullin et al., 2010), and the difficulty of intention retrieval (Guynn, 2003, Guynn & McDaniel, 2007). In many of these instances, differences in successful prospective memory are driven by its demand on effortful cognitive processes.

Regarding the difficulty of prospective memory cue detection, cue focality has been shown to be a critical factor contributing to whether the intention is recognized and subsequently fulfilled. Focality refers to the extent to which ongoing activities in the future lend themselves to effective (focal) processing of potential prospective memory cues (McDaniel & Einstein, 2000). For example, Einstein and McDaniel (2005) observed differences in performance as a function of cue focality by having participants complete a category identification task where a pair of words was displayed on the screen. Participants were instructed to determine if the lowercase word on the right was a category member of the capitalized word on the left. After completing a block of trials, participants were randomly assigned to one of two conditions. In the Focal condition, participants had a prospective memory intention to make a special response when a specific word occurred in the category judgment

task (e.g., tortoise). In the Nonfocal condition, participants had a prospective memory intention to make a special response when they encountered a word with a specific syllable (e.g., TOR; tortoise). The cues (or prospective memory targets) were the same across both conditions. However, participants' prospective memory accuracy significantly differed as a function of how they were instructed to process the cue (Focal = 93% versus Nonfocal = 61%).

This substantial difference in prospective memory accuracy suggests that when a prospective memory cue is less semantically demanding to process, detecting it as an important event is seemingly automatic (i.e., spontaneous detection). To evaluate this hypothesis, Einstein and McDaniel (2005) also investigated reaction times in the ongoing category identification task as a function of intention (control versus intention) and cue focality (focal versus nonfocal). After controlling for no intention baseline response times, the reaction times in the focal versus nonfocal conditions were substantially different, with individuals in the focal condition being faster than those in the nonfocal condition (i.e., task interference). This finding supports the claim that attentional mechanisms were not utilized to the same degree in the focal condition as in the nonfocal condition. Based on many replications of this effect, the claim is often made in the literature that participants in nonfocal prospective memory conditions are required to employ more conscious effort and semantic processing to detect specified prospective memory cues at the cost of slower reaction times on the category-identified task (Smith, 2003, Hicks, Marsh, & Cook, 2005, Brewer, 2015).

Physiological Correlates of Prospective Memory

The literature on prospective memory has established clear behavioral measures for assessing important aspects of performance (prospective memory accuracy and task interference), but there is a growing interest in utilizing physiological techniques. One such technique is pupillometry (Moyes, Sari-Sarraf, Gilbert, 2019, Koslov, Bulls, & Lewis-Peacock, 2022), which involves using an eye tracker to measure changes in pupil size during the completion of behavioral tasks. Pupillometry has a higher temporal resolution than behavior and allows for the measurement of cognitive processes that are not directly tied to action. Furthermore, research has shown that the cognitive demand on effortful processes while completing an experimental task results in pupillary dynamics such as dilation. Previous studies from the 1960s have reported an increase in pupil diameter as arithmetic difficulty increases (Hess and Polt, 1964) and when working memory task demands increase (Kahneman and Beatty, 1966). More recent research has replicated these results and looked more deeply into changes in pupil size across time during cognitive tasks (Robison & Unsworth, 2016).

A pupillary measurement of particular interest to those investigating their correlates with cognitive demand is pretrial pupil. Literature in sustained attention has shown that when a participant's pretrial pupil diameter is smaller than baseline measures, participants reported that their mental state was off-task and behavioral measures mirrored this claim with slower response times (Unsworth & Robison, 2016). This is thought to occur due to anticipatory processes where the participants know their attention is required soon so the eye dilates, letting more light through the retina allowing them to process and respond efficiently. The neural basis for this

claim suggests that the locus coeruleus in the brainstem which produces and projects norepinephrine throughout the neocortex increases the firing rate for salient events (Aston-Jones & Cohen, 2005) Meaning when a participant is on task and focused, their pretrial pupils are significantly larger than the baseline pupil diameter.

Although pupillometry has been used to measure various cognitive abilities, it has rarely been used to assess physiological responses during prospective memory. One notable exception is the work by Boyer, Sari-Sarrah, and Gilbert (2018) who sought to investigate this relation to better understand how participants engage in effortful cognitive processes to strategically monitor for prospective memory cues. In this study, participants completed a lexical decision task where they were instructed to indicate whether or not a string of letters was a valid English word (two-alternative forced choice ongoing task). They then completed blocks of the ongoing task with varying levels of effortful prospective memory cue detection, such as responding with a special key when they saw a single word (e.g., TOWER) or when they saw a word belonging to a category (e.g., METAL; iron, steel). The authors used the ongoing task to calculate baseline measurements of reaction time and pupil diameter for later assessment of difficulty. The data showed that during ongoing trials without a prospective memory target, pupillary response was greatest during the category prospective memory block relative to the single-word prospective memory target and ongoing task only blocks (Boyer, Sarri-Sarraf, & Gilbert, 2019). Additionally, relative to the single-item condition, the category condition showed lower prospective memory accuracy and a greater task interference effect. These findings support the notion that cognitive demands during prospective memory

tasks are observable by utilizing pupillometry in addition to behavioral measurements.

CURRENT STUDY – EXPERIMENT 1

In the current study we aimed to replicate the cue focality effect, which was first observed by Einstein and McDaniel (2005) and documented support for the Multiprocess view of prospective memory that posits multiple mechanisms contribute to prospective memory cue detection. In addition, we measured pupil size during the completion of the task in which participants had either a focal or nonfocal prospective memory intention. The Multiprocess framework suggests that relatively automatic cue detection processes can support performance in the focal condition, but that relatively effortful cue detection processes are required for the nonfocal condition.

METHODS & PROCEDURE

Participants

We collected a sample size of 91 participants from Arizona State University who completed the study in exchange for partial course credit. Due to missing pupillary data greater than 40%, n = 12 participants were removed from analysis. Before completing the study, all participants read and signed an informed consent document. The experimental protocol was approved by the Institutional Review

Board at Arizona State University. Participants were required to be at least 18 years old and have English as their primary language.

Prospective Memory

Participants arrived at the laboratory and were asked to review and sign the informed consent document. They were then escorted to an individual testing room, where they were instructed to silence or turn off their cell phones and adjust the chinrest to a comfortable height. Research assistants then used a calibration procedure to validate the pupillary measurements and ensure that the eye tracker could accurately track their eyes. If validation failed, participants were given half of a research credit and informed that they could not continue with the study. There were four participants whose pupils were not readable and therefore were not able to participate in the study.

After completing the eye-tracking calibration process, participants were informed that they would perform a task requiring them to make judgments on strings of letters and would receive instructions on how to respond as well as complete practice trials to become familiar with the task. During the task, participants were instructed to decide whether a string of letters was a valid English word or not, with two response options: the "Z" key for non-words (e.g., SPANGE) and the "/" key for valid English words (e.g., SPONGE). Participants were instructed to make their decision and respond as quickly and accurately as possible. Participants completed 10 practice trials with feedback to ensure they understood the task. All participants then completed 98 trials of the task without a prospective memory intention, followed by counterbalanced blocks of focal and nonfocal prospective memory conditions.

Participants in the focal condition were instructed to respond with the "shift" key (right or left) if they saw the words ``TORTOISE" or "BTORQ," instead of using "Z" or "/" to make their word versus nonword response. Participants in the nonfocal condition were instructed to respond with the "shift" key (right or left) if they saw any word with the syllable "TOR" (e.g., TORONTO or HTORQ), instead of using "Z" or "/" to make their word versus nonword response. Both the focal and nonfocal intention blocks had 192 letter strings, with 96 being non-words and the other 96 being valid English words. There were eight prospective memory cues in each block, with four being valid words and four being non-word letter strings. All non-word stimuli were pronounceable letter strings (e.g., DEAG, FUDNET). The stimuli presentation consisted of a fixation cross that appeared in the center of the screen for 1000 milliseconds, followed by a letter string presented for 500 milliseconds, and lastly, a blank screen displayed while the participant responded to the word for 2000 milliseconds. After completing the first condition, participants were then given instructions for the second condition, where a new set of 192 letter strings were presented following the same procedure as the first. If the participant did not respond to a trial, it was marked as incorrect. All participants completed both the nonfocal and focal conditions.

Pupillometry

The pupil data was collected using a Gazepoint GP3 eye tracker. Before starting the task, the Gazepoint Control program was used to confirm that the participant's pupils were readable and valid using the calibration module. The calibration process required the participants to track a white dot on a black screen that moved to five locations with their eyes, enabling the Gazepoint to measure

pupil diameter and gaze location on the screen. The Gazepoint GP3 collected the pupil diameter of both eyes as well as gaze location at a sampling rate of 60 Hz. Later, measurements from the right eye were analyzed, as there was little variability between the left and right eye's diameter. A pipeline was used to clean the eye data, starting by filtering out eye measurements outside the range of 2 millimeters to 8 millimeters. Additionally, participants with more than 40% missing eye observations were excluded from the analysis. To assess pretrial pupillary dynamics, the diameters of the right pupil were averaged when the fixation screen was presented for each trial.

ANALYSES

Data Processing

Prospective memory accuracy was computed as the proportion of cues successfully detected and responded to as a function of condition. Task interference was computed as the average reaction time to accurate ongoing task trials subtracted by the average response time of the ongoing lexical judgement task for each group. All reaction times greater than 2.5 SD from the participant's mean reaction time were excluded from analyses (Brewer, 2015). All analyses were tested at $p = .05$. Participants with <40% missing pupil data were removed from the analyses ($n = 12$).

Behavioral Hypotheses & Analyses.

1a. We predicted that prospective memory accuracy would be higher in the focal condition compared to the nonfocal condition.

1b. We predicted that participants would respond faster to prospective memory cues in the focal condition compared to the nonfocal condition. Results will provide evidence for both spontaneous retrieval of prospective memory cues as well as strategic monitoring.

1c. We predicted that participants would show greater task interference in the nonfocal condition compared to the focal condition.

All participants completed both experimental conditions, so a series of matched pair t-tests assessed the behavioral analysis of the experimental design. 1a investigated the memory retrieval component of prospective memory and the spontaneous retrieval aspect of MPV. Analyses 1b and 1c assessed the attentional aspects of prospective memory detection and strategic monitoring outlined in the MPV.

Pupillary Hypotheses & Analyses.

2a. We predicted that participants would exhibit a larger pretrial pupil during the nonfocal condition compared to the focal condition.

In order to assess pretrial pupil size as a function of task difficulty, analysis of 2a will use matched pairs t-test. Results will provide additional support for evidence of the neural correlates of attention.

RESULTS – EXPERIMENT 1

Across all dependent measures of interest, counterbalancing had no effect, and the subsequent results were derived from pooled data. All reported analyses had a p-value less than .05, unless otherwise specified.

The proportion of prospective memory target-cues detected during the focal and nonfocal blocks was entered into a paired t-test. The analysis replicated previous work (Brewer et al., 2010; Einstein et al., 2005) showing that participants in the focal block detected more target-cues than in the nonfocal block [$t(78) = 9.87$, $p < .0001$]. Additionally, the time to respond to prospective memory target-cues showed a similar pattern, with participants in the focal block responding faster than those in the nonfocal block [$t(78) = 3.22$, $p < .01$].

Response times for the ongoing lexical decision task were analyzed to investigate task interference and how attentional processes were utilized during the prospective memory task. Response times were partitioned into baseline, focal, and nonfocal conditions, and each participant's baseline response time was subtracted from their focal and nonfocal response times. The results revealed a significant difference in the interference induced by the prospective memory intention, where participants in the nonfocal condition experienced more interference to making decisions in the ongoing lexical decision task than those in the focal condition [$t(78) = 2.21$, $p > .05$, $d = 0.24$].

When investigating the physiological measures of prospective memory, participants in the nonfocal block exhibited a greater standardized pretrial pupil diameter than when completing the focal block. However, this difference was not statistically significant [$t(75) = 1.02$, $p = 0.311$, $d = -0.153$].

DISCUSSION – EXPERIMENT 1

This experiment produced two sets of results: behavioral and pupillary. In terms of the behavioral measures, we tested cue detection accuracy, response time for successful prospective memory target cues, and task interference. We observed support for all three hypotheses, with significantly superior performance during the focal block compared with the nonfocal block. Focal target accuracy was higher, and the time to detect and respond to the prospective memory cue was faster than in the nonfocal condition. Furthermore, both groups experienced a mean response time latency due to the prospective memory intention, but task interference was significantly greater in the nonfocal block compared to the focal block. Regarding the pupillary data, we found that participants had a greater pretrial pupil during the nonfocal block than during the focal block. This finding supports our hypothesis that nonfocal cue detection is more difficult, leading to physiological markers of increased cognitive demand such as the eye letting more light into the eye.

LITERATURE REVIEW – EXPERIMENT 2

Cannabis & Prospective Memory Background

Researchers are interested in how pharmacological interventions, specifically cannabis, can impact the various processes required to complete a pre-established intention. Research investigating the effects of cannabis on cognition is ever-growing, but the field still requires more clarification, at present results tend to skew toward general impairments but in the context of prospective memory, the drawn conclusions tend to range from an impairment, no impairment, and some

improvement. We set out to shed some light on this discrepancy in hopes to provide a clearer picture.

Cannabis Use Background

According to the World Health Organization, cannabis is the most widely cultivated and abused illicit drug on Earth (World Health Organization, 2023). As of 2021 in the United States alone, approximately 17% (55 million) of adults regularly use cannabis, and 45% have tried it at least once in their lives (National Institute of Drug Abuse, 2023). In terms of economics, legal sales in the United States reached a market cap of $33 million and are expected to reach $52 billion by the end of 2025 (Forbes Insights, 2020). Cannabis was first legalized for medical use in California in 1996, and since then, 21 states and the District of Columbia have passed laws making recreational cannabis use legal, with another 17 states legalizing medical use. As more states press for recreational legalization, the need to define the effects of cannabis on cognition grows more important than ever.

The effects of cannabis mainly stem from the key active component, Δ-9-tetrahydrocannabinol (THC), which acts as an agonist in the endocannabinoid system via the Cannabinoid Receptor Type 1 (CB1) (Dellazizzo et al., 2022). Research has indicated that THC acts on CB1 receptors by mediating the effect of how various neuromodulators such as dopamine, serotonin, acetylcholine, norepinephrine, and glutamate are released from axon terminals (Iverson, 2003). Regions of the brain such as the hippocampus, basal ganglia, brainstem, anterior cingulate cortex, and neocortex are thought to be highly localized with CB1 receptor concentrations, which may cause the impairment of psychomotor and cognitive function (Egertová & Elphick, 2000, Burns et al, 2007). The degree to which

cannabis dysfunction affects these areas is under continued investigation and requires more rigor to define these parameters clearly. Regarding the suspected areas affected following acute cannabis use, the hippocampus has been implicated as the area of the brain responsible for memory and learning (Burgess et al., 1994). The basal ganglia are a group of connected structures primarily implicated in the regulation of movement, specifically the selection, initiation, and termination of movement, in addition to learning motor skills and automaticity of learned motor ability (de Fonseca et al., 1998, Graybiel, 2000). The brainstem, which connects the spinal cord to the brain, is responsible for vital life functions such as breathing regulation, heart rate, blood pressure, and digestion (Grotenherman, 2003, Mattes et al., 1994). The function of the anterior cingulate cortex is thought to play a role in attention, specifically facilitating error correction and monitoring processes (Carter et al., 1998).

Lastly, the neocortex is involved in higher-order cognition, such as decision-making, spatial reasoning, and language comprehension (Penfield & Rasmussen, 1950, Herkenham et al., 1991, Kovacs et al., 2012). The effects of long-term cannabis use or chronic use have provided evidence that both structural and functional changes to the brain may occur.

Cannabis and How it Affects Cognition

Although the field of cannabis and cognition has a ways to go before being well-defined, studies have found dose-dependent impairments in a range of cognitive abilities, such as learning and memory, attention, inhibition, decision-making, and working memory (Kroon, Kuhns, & Cousijn, 2021). To provide a background on the suspected impairments, I will first cover review papers and meta-analyses, followed

by empirical data investigating acute cannabis use on cognitive ability generally, and specifically, episodic memory and attention control abilities. In 2021, Dellazizzo and colleagues conducted a meta-review of meta-analyses investigating the growing evidence of the neurocognitive effects of cannabis use. The authors analyzed the findings of 10 meta-analyses, with an aggregate sample size of 43,761 participants and 71 effect sizes, and classified the results into various cognitive domains, including executive functioning, attention, processing speed, language, and memory (Dellazizzo et al., 2021).

Starting with executive functions and some of its facets, they observed a small to moderate effect of acute cannabis use relative to placebo controls. Cannabis had a small but significant effect on response inhibition, and for working memory, there was also a small to moderate negative effect of cannabis intoxication (Zhornitsky et al., 2021). The residual effects on executive function showed a small impairment in task performance for regular cannabis users relative to individuals who do not use cannabis (Scott et al., 2018). However, the effect increased for participants who reported an earlier age of first cannabis use.

For learning and memory, the authors found little to no effect of acute cannabis use on visual learning and visual memory. Researchers observed a small effect on verbal learning and memory for both acute and chronic cannabis use (Schoeler et al., 2016). For attention ability, Zhornitsky and colleagues (2021) found small but significant effects of cannabis use on the performance of sustained and divided attention tasks, as well as more commission errors on a continuous performance task relative to a placebo control group. Investigation into processing speed found small to moderate effects. There was no residual effect on chronic

cannabis users observed in the attention and processing speed domains (Schoeler et al., 2016).

Lastly, for perceptual motor function and language, only a small effect on motor function was observed (McCartney et al., 2021). No acute cannabis effect on language, and no chronic effect of cannabis use on either perceptual-motor function or language. It should be noted that the effect sizes have a range of quality ratings, with worse quality being attributed to variability in the type of cannabis administered, THC concentration, the ratio of CBD and THC, dosage, type of administration (smoking, vaporized, or oral), duration of abstinence, and measures of tolerance and dependency, all of which may impact participants' performance on various tasks. In addition, Dellazizzo and colleagues (2021) observed wide heterogeneity when looking at how researchers classified the intensity of use relative to non-cannabis users. Some studies may investigate nonusers compared to heavy users, while others may look at individuals with minimal lifetime use (less than 50 individual uses), age of onset of use, where adult onset has been shown to have varying effects relative to those who start to use cannabis in their teenage years.

Cannabis and How it Affects the Brain

In a literature review conducted by Iverson (2002), research articles examining the effects of cannabis on the brain were analyzed. Iverson's analysis focused on the cognitive neuro-perspective of these effects. The review first delved into the literature on the distribution of cannabinoid receptors in the rat brain, where CB1 mapping was first conducted (Herkenham et al, 1991). Herkenham found that the majority of CB1 receptors were located in axons and nerve terminals, which

suggests that cannabinoid agonists, such as THC, have a modulating effect on neurotransmitters due to their presynaptic location relative to post-synaptic. As previously mentioned, CB1 receptors are most abundant in the cerebral cortex, basal ganglia and cerebellum, anterior cingulate cortex, and hippocampus in both animals and humans. Studies have shown that the effects of CB1 receptors in the basal ganglia and cerebellum can cause a range of effects on psychomotor function.

The impact of cannabinoids on the hippocampus and their effect on various aspects of memory have been studied more extensively (Hampson & Deadwyler, 1999, Jager et al., 2007, Atakan, 2012, Blest-Hopley et al, 2021). Iverson notes that cannabis impairment in short-term memory tasks is the most widely documented, particularly in cases where attentional ability is heavily required. In a study of rats, researchers observed that the impairment was similar to the after-effects of surgical removal of the hippocampus, rendering the animals completely unable to organize information from one trial to another (Hampson & Deadwyler, 1999). One theory for this effect stems from electrophysiological studies that suggest cannabinoids reduce glutamate in the hippocampus, which impairs the ability to consolidate events (long-term potentiation) and prune no longer relevant information (long-term depression; Stella, Schweitzer, & Piomelli, 1997, Hoffman et al., 2007).

Like other illicit substances, cannabis has been shown to have a range of effects on the cerebral cortex, also known as the neocortex due to its development relative to other animals (Eggan & Lewis, 2007). Although the cannabis and cognition literature has extensively explored higher-order effects, the complexity of these processes makes it challenging to clarify the inconsistent effects observed by researchers. For instance, a study on delayed discounting found that participants

who used cannabis showed a positive relationship between their reported frequency of use and their tendency to choose smaller, immediate rewards over larger, delayed rewards (Sofis et al., 2020). Several areas are thought to be necessary for delayed discounting, the prefrontal cortex in the neocortex has been implicated in the valuation of a delayed gain specifically, the portion of the task that is seemingly most affected by cannabis use (McClure et al, 2007, Frost & McNaughton, 2017). However, further research is needed to fully understand the effects of cannabis on the neocortex, as this area has been inadequately studied thus far.

The anterior cingulate cortex (ACC) is of particular interest in the context of cannabis and cognition due to its role in attention and motivation. A frequent claim of cannabis users is that they seem to lack motivation to do things and an inability to focus, perhaps due in part to the high density of CB1 receptors in the area. While the literature on acute cannabis use and ACC function is sparse, a study conducted by Hester and colleagues (2009) used functional magnetic resonance imaging to investigate the ACC during a Go/No-Go task that looks at control of inhibition and error awareness in chronic cannabis users. For behavioral measures, the authors found that cannabis users showed similar rates of inhibition, however active cannabis users had significantly more commission errors in the task. The imaging data provides preliminary support where they observed hypoactivity in the ACC's of cannabis users but not in participants in the control group.

Lastly, there is limited research on the effects of cannabis use on the brain stem due to the challenges of imaging and measuring function in this area. One attempt to investigate this area used structural magnetic resonance imaging to compare cannabis users to a control group of non-users. The results showed that

cannabis users exhibited significantly lower white matter clustering in the brainstem (Matochik et al., 2005). In a pilot study, Roitman and colleagues (2014) found that THC administration reduced symptoms of post-traumatic stress disorder, such as hyperarousal, providing support for the involvement of cannabinoid receptors in the locus coeruleus, which is the primary source of norepinephrine in the brain and located in the brainstem.

Cannabis and Prospective Memory

While the present review mostly focuses on the effects of cannabis use on memory and attention, a small subset of studies have also investigated prospective memory. The conclusions drawn from these studies unfortunately leave us with more questions than answers. Bartholomew and colleagues (2014) compared regular cannabis users and non-users on self-reported prospective memory ability and a video-based prospective memory task. The results showed no difference in self-reported measures of prospective memory between cannabis users and non-users, but cannabis users recalled fewer location-based intentions in the video-based task. Braidwood and colleagues (2018) examined time-based and event-based prospective memory ability in cannabis non-users, dependent cannabis users, and nondependent cannabis users, as measured by the Severity of Dependence Scale. The results showed no significant difference in prospective memory performance for either task across the three groups.

Platt and colleagues (2019) conducted a meta-analytic review of the effect of illicit and licit chronic drug use on prospective memory. They assessed six articles that looked at event-based prospective memory ability and observed an average standard mean difference (SMD) of -0.69 (confidence interval: -1.09, -0.30) for

chronic cannabis use, indicating a medium-to-large effect. While the average effect is sizable, some studies showed large, medium, small, or no impairment. However, further investigation into the studies that contributed to this value found two sources of wide variability. First, the effect sizes varied widely from study to study, with the greatest absolute SMD being -1.37 and the smallest effect of 0.10 SMD, which is interpreted as a small improvement in ability. Second, within each study, the confidence intervals also varied in range. For example, Bartholomew's (2010) study exhibited an effect size of -0.67 with a confidence interval ranging from -0.76 to -0.57. In contrast, Hadjiefthyvoulou's (2011b) study had an SMD of -0.42, but the confidence interval ranged from -0.81 to -0.03, indicating that the mean difference from the control group may range from a moderate-to-large effect all the way to virtually no effect of cannabis use. Overall, the literature on chronic cannabis use and prospective memory is somewhat varied but cannabis use has a deleterious effect on prospective memory when using a meta-analysis to combine these studies.

Cutter and colleagues (2021) conducted one of the few studies that investigated acute cannabis administration and prospective memory which is the goal of the current experiment. Participants were placed into one of four administration groups (one of which was a placebo condition), and the study collected data on several cognitive abilities, including prospective memory. The results showed no significant difference in prospective memory performance between the four groups. The results from this investigation of acute cannabis use on prospective memory is in contrast to the effects of chronic cannabis usage.

Cannabis and Pupillometry

Studies have provided evidence linking the locus coeruleus, also known as "the blue spot," to an individual's pupillary dynamics through the use of mice, monkey, functional magnetic resonance imaging (fMRI), and other methods (Gilzenrat et al., 2010, Murphy et al., 2014, Joshi, Kalwani, Gold, 2016, Liu et al., 2017). The locus coeruleus (LC) is located in the brainstem and is responsible for creating and projecting norepinephrine throughout the brain (Sara, 2009). As previously mentioned, the brainstem is a region of the brain that is suspected to be altered following acute cannabis use due to the high concentration of CB1 receptors (Wyrofsky et al., 2017). Pupillometry may be a tool for researchers to measure the effect of cannabis use on the LC. In 2006, Mutoni and colleagues measured single-unit extracellular recordings in the locus coeruleus of mice to investigate the effect of THC on neural firing. The study found that THC caused an increase in LC firing rate in a dose-dependent fashion relative to baseline measurements. In addition, THC increased the activity of noradrenergic LC neurons which decreased the suppression from the medulla, providing evidence that THC can regulate norepinephrine projections in other parts of the brain. In humans, Stark and colleagues (2003) found that participants in high and low THC dose groups both showed more pupillary increases relative to a placebo group. Contrary to other research, a study investigating human pupil size and cannabis intoxication saw an immediate and significant decrease in pupil size following acute cannabis use, which did not return to baseline until 180 minutes after smoking (Coucke et al., 2016). Lastly, Mewmeyer and colleagues assessed pupil size as a function of different types of cannabis administration including placebo, oral, smoking, and vaporization, in

different settings of light (2016). They found that pupil sizes were significantly larger after oral dosing relative to placebo at 1.5 and 3.5 hours after administration, and general increases in THC concentration in participants' blood were related to larger pupil sizes across all light settings to a significant degree.

THE CURRENT STUDY - EXPERIMENT 2

Although conclusions on cannabis-induced impairments are occasionally mixed, but overall, the evidence suggests that acute cannabis intoxication can lead to a decline in cognitive abilities such as memory, attention, decision-making, and other constructs in a dose-dependent manner. Considering various factors that may contribute to acute use deficits, such as dose and timing, the effects of cannabis use on cognition have the potential to significantly interfere with daily functioning, including work, driving ability, school, and relationships, particularly in regular users. In this experiment, we aimed to clarify the effects of acute high-potency cannabis use on prospective memory by testing cannabis users following cannabis intoxication in comparison to a control group not under the influence. Specifically, we planned to use the nonfocal event-based prospective memory task from Experiment 1 and measure pupillary diameter during the task.

Given the literature on acute cannabis effects on cognitive ability and specifically prospective memory, our primary behavioral hypothesis predicts that when given a nonfocal cue, individuals in the control group will have superior performance compared to their acute cannabis use counterparts. Using the same metrics from Experiment 1, we predicted that those in the cannabis use group compared to controls would not only be (1a) less accurate in prospective memory

detection, but also (1b) slower to detect prospective memory targets and (1c) show a greater task interference effect.

The literature investigating the effects of cannabis on the brainstem and subsequently, participants' pupillary dynamics provide conflicting interpretations which allow the present paradigm to propose multiple predictions based on these mixed results. Some evidence suggests that CB1 receptors increase the rate of basal firing in the brainstem which lead us to have conflicting hypotheses (Muntoni et al., 2006). One theory is that pretrial pupil size may be larger, but not due to increased cognitive demands, but a physiological reaction to the acute cannabis administration. The other theory is that since we expect the cannabis group to exhibit cognitive impairment following acute administration, they will require increased cognitive effort in order to adequately perform the task, leading to a larger pretrial pupil diameter. Other research has shown that pupil size decreased after cannabis use which generates alternative hypotheses regarding pretrial pupil size, however, that study did not employ a cognitive task before or after cannabis administration so it cannot inform us what to infer from the data looking at task-evoked pupillary responses.

METHODS AND PROCEDURE - EXPERIMENT 2

Participants. There were two sources of participants in Experiment 2. The control group was sourced from ASU's psychology 101 courses where they received partial credit for participating in research studies. Due to constraints given the legal nature of the study, the experimental cannabis group was recruited using advertisements (recruitment specifics below).

Control Group. The participants from Experiment 1 will serve as the control group in Experiment 2.

Cannabis-Use Group (Recruitment and Inclusion/Exclusion Criteria

Participants in the cannabis group were recruited through online advertisements, in newspapers, as well as physical flyers posted in public places such as smoke shops, dispensaries around the area, and the Arizona State University campus. Additionally, recruitment was also completed by word of mouth and snowball recruitment. Participants who complete the study are suggested to tell their friends and colleagues who may also be interested in participating. The recruitment advertisement asked potential participants to call or email to receive more study information and determine eligibility. All participation was voluntary and participants were told they could withdrawal at any point. Participants were compensated with a $20 Amazon gift card for completion of the online survey and another $40 Amazon gift card for completion of the in-home visit.

All participants in the Cannabis-Use group were legal recreational cannabis users (at least 21 years of age), had reported the use of high-potency cannabis flower (=>20% THC Concentration) in the past month with no prior history of experiencing any adverse reactions, and a willingness to purchase cannabis flower with at least 20% THC from a local dispensary. Regarding the testing environment, participants were required to have access to a private, enclosed room for smoking marijuana away from research assistants, and are not living on a property owned or controlled by Arizona State University. Other exclusion criteria include the participant being free of any substance disorder for the past year, not currently being treated for cannabis use disorder, having no illicit drug use for the past 60 days not including

cannabis, and having no serious mental illness, neurological, or medical incidents. During a telephone screening, we confirm with the participants that they have previously used cannabis with at least 20% THC concentration and that they are not pregnant.

PROSPECTIVE MEMORY MATERIALS

Control Group

Since the control group consists of the participants from Experiment 1, the materials and procedure for this group of participants are identical to that of Experiment 1.

Cannabis Group

The cannabis portion of the study was completed as part of a larger study, specifics regarding the assessments and measurement can be found in Appendix A. The materials for the cannabis group were nearly identical to that of Experiment 1 with some alterations to the design due in part to the data being collected as part of a larger study, the differences are explained below.

Similar to Experiment 1, following the eye-tracking calibration participants were given the ongoing task instructions, complete ten practice trials with feedback, fifteen trials of the ongoing task with no prospective memory intention, and were then given the experimental instructions. Due to our hypothesis looking exclusively at the nonfocal condition, the cannabis group only completed the nonfocal condition. All participants in the cannabis use group were given 132 letter strings where 66 of the letter strings were valid English words and the other 66 letter strings were pronounceable nonwords. Eight of the letter strings were prospective

memory targets, four valid words and four nonwords. The letter string list that stimuli are sampled from was the same as Experiment 1, and stimuli were presented on an identical design and timescale. Once the task was completed, the research assistant asked the participant if they remembered the secondary instruction to ensure the prospective memory instructions were understood. Participants who did not remember the prospective memory instructions were excluded from the analysis. The data from six participants were removed due to an inability to remember the prospective memory instructions.

PUPILLOMETRY MATERIALS

Control Group

Pupillometry materials and procedures were the same as in Experiment 1.

Cannabis Group

Alterations to the pupillometry materials and procedure were required because the testing of participants occurred in their own homes. When administering this task, researcher materials included a table (28in x 14in), laptop with windows operating system, additional response keyboard, Gazepoint GP3 eye tracker with tripod mount, chinrest, fiduciary marker glasses and dongle for cords (Set-up can be seen

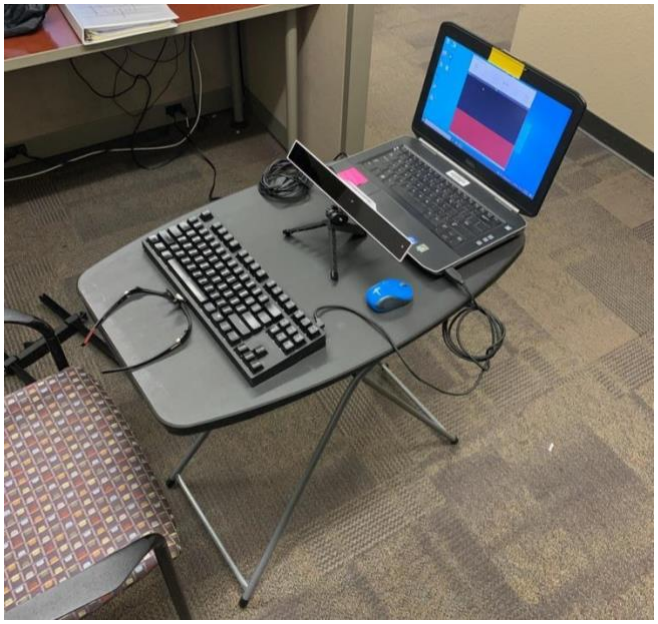

Figure 1: Depicts a standard behavioral and pupillometry setup for cannabis home visits.

in Figure 1). The research assistant would set up the equipment in a dim corner of the testing location. Before pupil calibration and validation, the research assistant would minimize room lighting, ask participants to put on the fiducial marker glasses, and adjust the chinrest to a suitable height for the participant. The fiducial marker is a small symbol placed in the center of a pair of sunglasses with the lenses removed. The symbol is used to minimize data loss by being a specific predetermined size the eye tracker can recognize and use as a reference measurement, such that if a participant moves the Gazepoint Eye Tracker knows what the size of the marker and can maintain the relative size of their pupil diameter. Following setup, the Gazepoint Control module validates and calibrates the participant's pupils to ensure they are readable and measurable. The remainder of the pupillometry parameters, procedure, and processing pipeline are identical to that of Experiment 1.

Home Visit Covariate Measures

Age. Participants age in years.

Sex. Participants sex at birth. Females are coded as 0 and Males are coded as 1.

Height. Participants current height on an arbitrary scale where the higher values indicate the participant is relatively taller in height and lower values indicate the participant is relatively shorter in height.

Weight. Participants current weight in pounds.

Years of cannabis use. The number of years a participants has been using cannabis since their first reported use.

Money spent on cannabis per week. The typical amount of money spent on cannabis per week in US dollars.

Age of first cannabis use. The age in years at which the participant first used cannabis.

Joint length. In millimeters, the length of the participants cannabis joint before and after acute cannabis administration. For analyses, a difference score is computed where joint length after administration is subtracted from the joint length before administration. Values indicate how much of the joint the participant smoked during acute administration.

Joint weight. In grams, the weight of the participants cannabis joint averaged over three measurements before and after acute cannabis administration. For correlational analyses, a difference score was computed where joint weight after administration is subtracted from the joint weight before administration. Values indicate how much of the joint the participant smoked during acute administration.

THC concentration. The percent of THC concentration in the participants cannabis joint. Measurements were taken from the label on the joint container provided by the dispensary. An additional measurement of THC concentration was taken using Purpl Pro which uses near-infrared spectroscopy on a small portion of the cannabis from the joint to provide a measure of THC concentration. For correlational analyses, a difference score was computed where the Purpl Pro concentration is subtracted from the concentration listed on the dispensary provided joint container. Positive values indicate the dispensary listed value was greater than Purpl Pro provided concentration. Negative values indicate Purpl Pro concentration was greater than dispensary provided and labeled concentration.

Heart rate. Measured in beats per minute and collected at all three time points. For correlational analyses, a difference score was computed where the time point

one values were subtracted from the average of time points two and three. Positive values indicate greater heart rate following acute cannabis administration. Negative values indicate greater heart rate before acute cannabis administration.

Blood pressure. Two measurements of blood pressure were taken at all three time points. Systolic blood pressure measures the pressure inside one's arteries when the heart beats. Diastolic blood pressure measures pressure inside the arteries as the heart rests between beats. For correlational analyses, a difference score was computed for both systolic and diastolic measurements where the time point one values were subtracted from the average of time points two and three. Positive values indicate greater blood pressure following acute cannabis administration. Negative values indicate greater blood pressure before acute cannabis administration.

DRUID. A mobile application that assesses participants level of cognitive and motor impairment, measured at all three time points. Higher scores indicate more impairment. For correlational analyses, a difference score was computed for the DRUID where the time point one scores were subtracted from the average score of time points two and three. Positive values indicate greater cognitive and motor impairment following acute cannabis administration. Negative values indicate greater cognitive and motor impairment before acute cannabis administration.

Subjective cognitive function - ability. Self-report items from *PROMIS Adult v2.0 – Cognitive Function Abilities Subset 8a* where participants indicate how much they agree with a statement describing their current cognitive function ability on a scale of 1 (Not at all) – 5 (Very much), measured at all three time points. Statements such as "My mind is sharp as usual" or "My memory is good as usual". Higher scores

indicate better subjective cognitive function ability. For correlational analyses, a difference score was computed for the cognitive function ability items where the time point one scores were subtracted from the average score of time points two and three. Positive values indicate greater subjective cognitive function ability following acute cannabis administration. Negative values indicate less subjective cognitive function ability before acute cannabis administration.

Subjective cognitive function impairment. Self-report items from *PROMIS Adult v2.0 – Cognitive Function Concerns Subset 8a* where participants indicate how frequently they think about a statement describing concerns regarding their current cognitive function on a scale of 5 (Never) – 1 (Very often), measured at all three time points. Statements such as "My thinking is slow" or "It seems like my brain is not working as well as usual". Following data collection, scores were reverse coded so higher scores indicate less subjective cognitive function impairment. For correlational analyses, a difference score was computed for the recoded cognitive function impairment items where the time point one scores were subtracted from the average score of time points two and three. Positive values indicate less subjective cognitive function impairment following acute cannabis administration. Negative values indicate more subjective cognitive function impairment before acute cannabis administration.

Subjective feeling of being high. Single item question that asks about the participants subjective rating of how intoxicated they are by cannabis on a scale of 1 (Not high at all) – 10 (Extremely high), measured at all three time points. For correlational analyses, a difference score was computed for subjective intoxication where the time point one values were subtracted from the average score of time

points two and three. Positive values indicate a greater subjective feeling of intoxication following acute cannabis administration. Negative values indicate more subjective feeling of intoxication before acute cannabis administration.

Home Visit Procedure

Approximately 24 hours prior to the home visit, research assistants called the participants to remind them of the visit and confirm that they have purchased the correct type of cannabis. They also remind them to abstain from cannabis, alcohol, and nicotine/tobacco for at least 24 hours before the scheduled home visit. Upon arrival, two research assistants administered informed consent and ask the participant to take an illicit drug urine test to confirm that no substances other than cannabis are in their system. Women are also asked to take a pregnancy test to ensure that they are not pregnant. If either test comes out positive, the research assistant cancels the home visit. If the participants appear to be already intoxicated, the home visit is rescheduled.

Once the research assistants confirmed that the participants have met the criteria for the home visit (not pregnant, no illicit drug use, at least 21 years of age, and have purchased the correct cannabis product), the assessment begins. Generally, there are three timepoints at which measurements were taken; before acute cannabis administration (TP1 – "Pre"), after acute cannabis administration (TP2 – "Post"), and approximately one hour after acute cannabis administration (TP3 – "1-Hour Post"). Among other tests and assessments (see Appendix A), research assistants collected data on various covariates that were included in supplemental analyses for Experiment 2 such as: age, sex, height, weight, years of

cannabis use, money spent on cannabis per week, age of first cannabis use, THC concentration, and joint length and weight before and after acute administration. Additionally, blood pressure, heart rate, subjective feeling of being high, DRUID, subjective cognitive function ability, and subjective cognitive function impairment were measured at all three timepoints (scoring scales for each covariate provided in previous section). Roughly 60 minutes after cannabis consumption, participants were asked to complete a task that investigates prospective memory using a Gazepoint eye-tracker to assess their pupillary dynamics during the completion of this task. The entire home visit takes approximately three to four hours to complete, six hour including the online prescreening and phone screening prior to the home visit.

Cannabis Consumption

Participants were requested to purchase a pre-rolled cannabis cigarette from a local dispensary, which contains at least approximately 20% THC and less than 1% CBD. During the prescreening process, participants are asked to confirm that they were willing to leave the testing area to smoke their cannabis product. After completing all the baseline/pretest assessments, the length and weight of the joint were measured, and participants were then instructed self-titrate, or smoke as much as they normally would when using cannabis. Following the participants cannabis administration, the weight (measured in grams three times and then averaged) and length (in millimeters) are recorded and logged. All team members abstain from touching any cannabis product, as per IRB approval parameters.

ANALYSES

Data Processing

Prospective memory accuracy was computed as the proportion of cues successfully detected as a function of experimental group (Control vs Cannabis). Task interference was computed as the average reaction time to accurate ongoing task trials as a function of experimental group. All reaction times greater than 2.5 SD from the participant's mean reaction time were excluded from analyses (Brewer, 2015). All analyses were tested at $p = .05$.

Behavioral Analyses & Hypotheses

1a. We predicted that prospective memory accuracy would be higher for participants in the control group compared to the accuracy of participants in the cannabis use group.

1b. We predicted that participants in the control group would respond faster to prospective memory cues compared to participants in the cannabis-use group.

1c. We predicted that participants in the cannabis use group would shower a greater task-evoked pupillary response compared to participants in the control group.

A series of t-tests was conducted to investigate group differences in various metrics of performance described above. Analyses were similar to that of Experiment 1, however in the context of acute cannabis effects instead of cue focality. Analysis 1a investigated the memory retrieval component of prospective memory and the spontaneous retrieval aspect of MPV. Results supporting hypothesis 1a would provide evidence for cannabis-induced memory processes

impairment. Analyses 1b and 1c assessed the attentional aspects of prospective memory detection and strategic monitoring outlined in the MPV. Results supporting hypothesis 1b and 1c would provide evidence for cannabis-induced attention impairment.

Pupillary Analyses & Hypotheses

2a. We predicted that participants in the cannabis group will exhibit a larger pretrial pupil size compared to participants in the control group.

To assess differences in pretrial pupil size as a function of acute cannabis administration, analysis for 2a will use two-sample t-tests to assess group differences. Results supporting hypothesis 2a would provide additional support for evidence of dysfunction in the neural correlates of attentional processes caused by acute cannabis use.

RESULTS – EXPERIMENT 2

All participants accurately completed the lexical decision task in both groups, with a mean accuracy rate of 0.75. We conducted a paired t-test to analyze the proportion of prospective memory target-cues detected between the control and cannabis groups. Results showed that participants in the cannabis group ($M = 0.50$) detected fewer target-cues than those in the control group ($M = 0.56$), but the difference was not statistically significant [$t(103) = 1.03$, $p = 0.308$, $d = 0.235$]. Contrary to hypothesis 1b, participants in the cannabis group ($M = 881.30$) responded significantly faster to prospective memory target-cues than those in the control group ($M = 978.97$) [$t(103) = 2.08$, $p > 0.05$, $d = 0.239$].

Next, we analyzed response times from the ongoing lexical decision task to investigate task interference and attentional processes during the prospective memory task. Response times were partitioned by group (control vs. cannabis) into baseline and nonfocal conditions. We then subtracted each participant's baseline response time from their respective nonfocal response time. Results showed a significant difference in the interference induced by the prospective memory intention between the two groups, with participants in the control condition experiencing more intention induced interference than those in the cannabis group [$t\ (111) = 2.76$, $p > 0.05$, $d = 0.602$].

In terms of physiological measures, when investigating the standardized pretrial pupil diameter during prospective memory task, participants in the control group exhibited a larger pupil diameter than their counterparts in the cannabis group, but this difference was not statistically significant [$t\ (107) = 0.63$, $p = 0.533$, $d = 0.155$]. A post-hoc analysis was conducted on the intra-subject coefficient of variation, which was subsequently aggregated by group and analyzed via independent sample t-test. The analysis observed a statistically significant difference, where the variation in participants pretrial pupil diameter in the control group was greater than the pretrial pupil diameter variation of the participants of the cannabis group [$t\ (108) = -5.93$, $p > .0001$, $d = 0.329$].

Supplemental post-hoc analyses investigated how covariate measures may have impacted the dependent measures of interest. For each of the dependent measures, correlations were analyzed for various demographic variables such as sex, age, height, and weight. Additionally, measures such as years of cannabis use, age of first cannabis use, and difference scores for heart rate, blood pressure, joint

length, joint weight, THC content, subjective feeling of being high, DRUID, subjective cognitive function ability, and subjective cognitive function impairment. For both prospective memory cue-detection accuracy and prospective memory target response times there were no significant correlation with any of the specified covariates. Correlational analyses of task interference observed significant effects for age of first cannabis use ($r(27) = 0.40$, $p = 0.038$), heart rate ($r(27) = 0.49$, $p = 0.011$), druid ($r(27) = 0.53$, $p = 0.001$), systolic blood pressure ($r(27) = 0.52$, $p = 0.006$), subjective cognitive function ability ($r(27) = 0.48$, $p = 0.011$), and subjective cognitive function impairment ($r(27) = 0.65$, $p = 0.0002$). Pretrial pupil diameter was only significantly correlated with the participant weight ($r(27) = -0.47$, $p = 0.031$).

DISCUSSION – EXPERIEMENT 2

Results from Experiment 2 were generally inconsistent with our hypotheses. We observed significant differences for three of the four dependent measures; however, the differences were in the opposite direction as expected. In terms of behavioral data, while cue detection accuracy was slightly higher for the control group, the difference between the two groups was not statistically significant as the accuracy means were relatively similar. Surprisingly, participants in the cannabis group responded significantly faster to nonfocal prospective memory target cues than those in the control group, which was opposite to our hypothesis. Both groups exhibited task interference, but the effect was significantly greater in the control group, again, contrary to what we expected.

The pupillary data also followed this antithetical pattern, with the control group showing a significantly larger pretrial pupil diameter than the cannabis group, which goes against our hypothesis that the cannabis group would exhibit a greater physiological reaction to the cognitively demanding block. Additionally, a post-hoc analysis where the variation of the pretrial pupil was computed at the trial level in order to investigate if the variability in pretrial pupil may explain behavioral differences were observed. If pupil size is a metric of cognitive demand placed on the participant, perhaps the variability in this diameter may be able to clarify why we are seeing the cannabis group exhibit smaller pretrial pupil diameters. The analysis indicates that the cannabis group had significantly less pretrial diameter variability, meaning their physiological indicator of demand was relatively stable compared to their control group counterparts. This is rather surprising, authors thought the results would show an opposite pattern, such that the cannabis group would show great variability meaning while their mean pretrial diameter was smaller they had more difficulty preparing for the demands of the task. The present results seem to indicate the not only did of the cognitive group show less of a physiological response to the demands of the task, but the response was also stable, showing little signs of grander correction after the task had begun and they were used to the paradigm.

The significant correlation between task interference and age of first cannabis use indicates that the later in life participants started to use cannabis, the more task interference they experienced. Significant correlation of heart rate and blood pressure indicated that an increase to the participants physiology also increased task interference. For both measures of cognitive function higher scores

generally indicate better subjective cognitive function. Both significant correlations are positive which means as participants rated themselves as having higher cognitive function, the more task interference they tended to experience.

There is no previous research to indicate why the correlation between pupil diameter and weight was significant. A subsidiary post-hoc correlational analysis between standardized pupil diameter and weight was conducted and observed the relation between pretrial pupil diameter and the weight of the participant was no longer significant ($r(27) = -0.13$, $p = 0.586$).

GENERAL DISCUSSION

The current study aimed to determine the extent to which acute cannabis administration affects prospective memory performance. Specifically, we investigated prospective memory performance by assessing both behavioral and physiological measures using a computerized event-based prospective memory task. Furthermore, we analyzed this unique data collected in the context of a high-potency THC exposure to gain insight into the extent of psychomotor and cognitive impairments after cannabis administration. There were two main findings in this study. First, Experiment 1 replicated previous work that investigated how cue focality impacts prospective memory performance. Second, Experiment 2 did not exhibit any of the hypothesized trends that were anticipated such that there was either no group difference between controls and cannabis or the cannabis group performed significantly better.

In Experiment 1, all hypotheses were supported, and the results replicated a robust finding in the prospective memory literature. The performance difference for focal and nonfocal cues provides support for the multiprocess view, as the context of

established intentions impacts how participants complete both the ongoing task and the prospective memory task. We observed a significant difference in cue detection for focal and nonfocal cues, as well as response times, which concur with the assessment that focality alters the degree to which semantic processing is required to recognize and detect a string as a target, inhibit the standard lexical judgment, and subsequently retrieve the intention for how to respond uniquely to the prospective memory target. The discrepancy in target detection accuracy and response times indicated that strategic monitoring varies from less effortful to relatively demanding, in line with theory outlined in the MPV of prospective memory.

In order to dig deeper into this concept, mean response times were further analyzed. The latencies for each participant were broken up by block (Ongoing task baseline vs. focal vs. nonfocal) and further manipulated. Two sets of difference scores were calculated: the mean ongoing task response time served as a baseline and was subtracted from the participant's mean response time for the ongoing lexical decision task during the focal block as well as the nonfocal block to derive a task interference metric (Brewer, 2015). By averaging the response time before participants received the prospective memory intention, we could look at the discrepancy cognitive demand caused by each intention for both focal and nonfocal blocks. Our results showed that the nonfocal block was more cognitively demanding, providing support that the context of the intention changes the effort required to detect targets, again, in line with MVP of prospective memory.

A possible confound while looking at task interference is that the baseline is always the first block participants are given. This means that they may require time

to get accustomed to the task beyond that of the practice trials (Smith et al., 2007). Additionally, this difference in cognitive effort is observed in the pupillary pretrial analysis where the diameter in the nonfocal condition was non-significantly greater than the pretrial diameter during the focal block. Research has shown that pupil diameter increases as relevant task difficulty increases (Hess and Polt, 1964, Kahneman and Beatty, 1966). This physiological reaction is hypothesized to occurs in order to let more light into the eye, allowing for more information accumulation and in the context of this study, as a preparatory mechanism where subconscious thought indicates the degree to which a participant will have difficulty on a task and makes a proactive response that varies for focal vs nonfocal blocks.

The results of Experiment 2 did not provide evidence for the expected impairments of THC intoxication; in fact, accuracy trends were in the opposite direction of our a priori hypotheses. While cue detection for the control group was better than that of the cannabis group, the difference was not significant (accuracy difference score = .06). The cannabis group exhibited a faster mean response time for cue detection and showed less task interference than the control group, both to a significant degree. These results are dissimilar to the acute cannabis use effects on cognition reported in the literature.

From a neurobiological perspective, the dense concentration of cannabinoid receptors in the hippocampus would lead us to predict impairments in memory ability (Hampson & Deadwyler, 1999; Jager et al., 2007; Atakan, 2012; Blest-Hopley et al., 2021). Behavioral studies in both mice and humans have suggested that acute cannabis use may impair memory processes (Hampson & Deadwyler, 1999; Hunault et al., 2009). Furthermore, this impairment has been observed in the prospective

memory of chronic cannabis users (Bartholomew et al., 2014; Platt et al., 2019; Levent & Davelaar, 2018, 2021). However, some studies have observed little to no effect (Gallagher et al., 2014; Cutter et al., 2021), and one study even showed cannabis users performing better than controls (Cutter et al., 2012).

Regarding attentional processes, a meta-analysis by Zhornitsky and colleagues examining the acute effects of CB1 receptor partial agonists (such as cannabis) indicated small to moderate effects on attention and speed of processing (2021). Imaging studies have shown structural changes in brain regions thought to be implicated in attention control, such as hypoactivity in the anterior cingulate cortex with increased commission errors (Hester et al., 2009) and in the brainstem, where Matochik (2015) and colleagues observed significantly less white matter clustering relative to individuals who do not use cannabis. Therefore, we anticipated nonfocal prospective memory deficits due to the tasks demands on both memory and attention functions (Ball et al., 2021).

The pupillary results showed that cannabis users had a significantly smaller pretrial pupil diameter than the control group. This result was surprising because several studies suggest that acute cannabis use increases the pupil diameter in humans following intoxication (Mutoni et al., 2006; Stark et al., 2003; Coucke et al., 2016; Mewmeyer et al., 2016). A possible explanation for why the cannabis group's pretrial pupil may be smaller than the control group's is a difference in the perceived difficulty of the task. Cannabis users frequently report feeling more relaxed after smoking, which may cause less of a physiological preparatory response. However, they were still able to maintain cognitive function to a similar degree as their control counterparts. In line with this idea, the Yerkes-Dodson performance-arousal curve

suggests that when people are over- or under-aroused, performance tends to be suboptimal (Teigen, 1994). It may be the case that acute cannabis use is modulating arousal, considering that the participants self-titrated their cannabis use to reach their desired high, it is possible that they reached a preferred state of arousal and subsequently performed optimally.

The present study may have observed the results it did for several reasons. Firstly, the nature of the at-home visits altered the study design between the two experiments and subsequently the experimental sample groups in the second experiment. Additionally, due to time constraints, the task completed by the cannabis group had fewer trials of the baseline ongoing task as well as the nonfocal condition. Within the task, cannabis participants may not experience as much resource depletion. However, the entire home visit ranges from 3-4 hours, and by the time participants get to the prospective memory task, they have been in the study substantially longer than the control group. In terms of compensation, the control group received partial credit in the Psychology 101 course, whereas the cannabis users received $60 in Amazon gift cards, which may have motivated the participants to perform better.

Apart from differences in study and task design, there is the pressing issue of more global environmental differences. The participants in the control group were tested in the laboratory on campus, where the parameters of their participation were different on several metrics relative to the cannabis group who participated in their own homes. A difference in task administration is the presence of a researcher in the testing location. For experiment 1, the researcher takes the participant to one of four individual testing rooms, goes through the instructions, and after completion of the

practice trials, the researcher leaves the room in order to set up another participant in one of the remaining testing rooms. In the cannabis group, data collection occurred in a single room (participants living room, kitchen, bedroom, etc.) where the present researcher was also present for the duration of the assessment after walking through the instructions and practice trials. Perhaps the presence of the task administrator may implicitly cause the participant to perform better, although during the task's completion, there is no way to know if they are doing well or not.

Regarding factors that the environment may contribute, the cannabis group completed the task in the comfort of their own homes, as opposed to a collection room they are not familiar with. In the context of experiment 2, this may not be such a bad thing. While the difference in environment may reduce the internal validity between the control and cannabis group, testing cannabis users in their homes provides increased external validity due in part to most cannabis users tend to use and stay in their homes while intoxicated. In which case, testing in their homes provides an advantage over having participants come to the laboratory and acutely administer cannabis because when people smoke cannabis, chances are it is not in a psychology laboratory.

The lack of expected findings in Experiment 2 may be explained by the role of tolerance. Participants in the cannabis group had experience smoking cannabis flower with THC concentration >20% without any adverse reactions, and while they varied in tolerance, they were able to communicate fluently and complete goal-directed behavior while under the influence. This prior experience may have mitigated the expected impairments, resulting in similar scores to the control group.

The parent study Experiment 2 collected a host of covariate measures beyond the scope of this project, such as age, weight, sex, income, age of first use, motor function, heart rate, blood pressure, and subjective cognitive function. However, these measures did not correlate significantly with the dependent measures. More complex analyses may be able to uncover possible effects lacking in the data.

Several limitations should be explicitly stated. First, the small sample size for the cannabis group limits the ability to generalize the findings and casts doubt on the differences between the cannabis group and the control group. Second, delays in the timing of the prospective memory task ranging from 45-90 minutes following acute cannabis administration were frequently out of researcher control, but post-hoc examination of the self-report measure of being high revealed significant differences between timepoints. Lastly, differences in testing environment, compensation between groups, task design, and researcher presence are limitations.

Future research should aim to reduce these limitations, such as testing non-cannabis users in their homes and/or testing cannabis participants in a laboratory setting to balance internal and external validity. Investigating the effects of alternative forms of cannabis administration, such as edibles and vaporizers, on prospective memory performance is another direction this line of work could take.

The present and ongoing results suggest that prospective memory performance for the control group and cannabis users following acute high-potency cannabis administration are similar for the memory component of prospective memory and that the cannabis group performs better at the attentional component of cue detection.

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APPENDIX A

ASSESSMENTS FROM THE LARGER STUDY EXPERIMENT 2 ORIGINATES FROM.

Informed Consent and Release of Liability
Drug and Pregnancy Test (if applicable)
Alcohol and Tobacco Use 30-Day TLFB
Cannabis Use 30-Day TLFB
NART
REY
Druid Balance Test
REY Recall
Measure Blood Pressure
Psychomotor Vigilance Task
SDMT
Smoking Measurements & Administration
REY 2nd Administration
Measure Blood Pressure (#2)
Druid Balance Test - 2nd Administration
Psychomotor Vigilance Task - 2nd Administration
REY Recall (#2)
SDMT - 2nd Administration
Measure Blood Pressure (#3)
REY - 3rd Administration
Druid Balance Test - 3rd Administration
Psychomotor Vigilance Task - 3rd Administration
Prospective Memory Task

REY Recall (#3)
SDMT - 3rd Administration
Resource List

APPENDIX B

APPROVED INSTITUTIONAL REVIEW BOARD DOCUMENT

	PREPARED BY: IRB Staff	APPROVED BY: Heather Clark
DOCUMENT TITLE: HRP 503 A Social Behavioral Protocol	DEPARTMENT: Office of Research Integrity and Assurance (ORIA)	EFFECTIVE DATE: [3/26/2020]

INSTRUCTIONS

Complete each section of the application. Based on the nature of the research being proposed some sections may not apply. Those sections can be marked as N/A. Remember that the IRB is concerned with risks and benefits to the research participant and your responses should clearly reflect these issues. You (the PI) need to retain the most recent protocol document for future revisions. Questions can be addressed to research.integrity@asu.edu. **PIs are strongly encouraged to complete this application with words and terms used to describe the protocol is geared towards someone not specialized in the PI's area of expertise.**

IRB: 1. Protocol Title: Effects of Cannabis Use on Cognition, Affect, and Pain in Older and Younger Adults

2. Background and Objectives

1 List the specific aims or research questions in 300 words or less.

2 Refer to findings relevant to the risks and benefits to participants in the proposed research.

3 Identify any past studies by ID number that are related to this study. If the work was done elsewhere, indicate the location.

for streamlining the review time:

- Two paragraphs or less is recommended.
- Do not submit sections of funded grants or similar. The IRB will request additional information, if needed.

Response:

The proposed study addresses fundamental gaps in knowledge about the acute effects of cannabis use in older adulthood. Relative to younger adults, older adults have shown large increases in cannabis use in recent years. This is concerning because older adults may be more vulnerable to cannabis's acute intoxicating and impairing effects than younger adults, due to aging-related changes in drug metabolism. The proposed study is a naturalistic study comparing the acute effects of *ad libitum legal recreational* cannabis use on cognition, pain, and affect in older (ages 50+) and younger (ages 21-30) adult cannabis users in Arizona. (Cannabis use is legal in the state of Arizona for adults ages 21+ years.)

The study involves visiting legal cannabis users in their homes and observing them both before and after their customary cannabis use. Like other similar studies in US states where adult cannabis use is legal (Bidwell et al., 2020; Cuttler et al.; 2021), participants will be asked to purchase a specific cannabis product at a local dispensary, to standardize the product across participants. The product is marijuana flower with ~20% THC and <1% CBD, selected because this is the average cannabinoid content of marijuana advertised in cannabis dispensaries (Cash et al., 2020). All participants must have experience smoking marijuana with ~20% THC or higher to be eligible for the study. Participants will be observed before and after they smoke marijuana. Smoking will occur away from research assistants in a private enclosed room.

Aims are to test the hypotheses that:

1. Cannabis use is associated with acute cognitive and motor impairment, more strongly for older adults than for younger adults.
2. Cannabis use is associated with acute changes in affect, more so for older adults than younger adults.
3. Cannabis use is associated with reductions in pain, more so for older adults than younger adults.

References

Bidwell, L. C., Ellingson, J. M., Karoly, H. C., York Williams, S. L., Hitchcock, L. N., Tracy, B. L., ... & Hutchison, K. E. (2020). Association of naturalistic administration of cannabis flower and concentrates with intoxication and impairment. JAMA Psychiatry, 77(8), 787-796.

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3. Data Use - What are the intended uses of the data generated from this project?
Examples include: Dissertation, thesis, undergraduate project, publication/journal article, conferences/presentations, results released to agency, organization, employer, or school. If other, then describe.

Response:
Data will be used for undergraduate and graduate research projects, publication in journal articles, and conferences.

4. **Inclusion and Exclusion Criteria**

4.1 List criteria that define who will be included or excluded in your final sample.

Indicate if each of the following special (vulnerable/protected) populations is included or excluded:

- Minors (under 18)
- Adults who are unable to consent (impaired decision-making capacity)
- Prisoners
- Economically or educationally disadvantaged individuals

not obvious, what is the rationale for the exclusion of special populations?
hat procedures will be used to determine inclusion/exclusion of special populations?

for streamlining the review time.

- Research involving only data analyses should only describe variables included in the dataset that will be used.
- For any research which includes or may likely include children/minors or adults unable to consent, review content [here]
- For research targeting Native Americans or populations with a high Native American demographic, or on or near tribal lands, review content [here]

rch involving minors on campus, review content [here]

Response:

Participants will be legal (i.e., age 21+) cannabis users residing in the Phoenix metro area. Two groups of legal cannabis users will be eligible: young adults (ages 21-30 years) and older adults (age 50+ years). Inclusion/exclusion criteria are: fluent in English; inhalation of marijuana with THC concentration of at least 20% (determined based on self-reported THC content on the dispensary product labels of recent purchases) in the past month with no history of adverse reaction; willingness to purchase marijuana with 20% THC and <1% CBD from a local dispensary for use during the home visit (confirmed via receipt during the study visit); access to a private, enclosed room (away from research assistants) for smoking marijuana; not living on property owned or controlled by ASU (self-reported and independently confirmed by our team); free of any past-year substance use disorder besides cannabis use disorder; not interested in, or currently receiving, treatment for cannabis use disorder; no illicit drug use in past 60 days (based on combination of self-reported illicit drug use, self-reported prescription medication, and urine dip test); no current daily tobacco use; no current heavy alcohol use (<15 drinks per week for men; <8 drinks per week for women); no serious mental illness (psychosis, bipolar disorder); free of serious neurologic (e.g., brain injury, stroke, dementia) and medical (e.g., cancer, heart attack) conditions; not pregnant or lactating (based on pregnancy test); and report any COVID symptoms prior to visit (if showing symptoms, the visit will be rescheduled).

On the telephone screening, participants will self-report whether they have used marijuana with ~20% THC and will self-report if they are pregnant. At the beginning of the home visit, prior to cannabis use, women of childbearing age will take a pregnancy test. The test must be negative to continue the home visit.

Participants will self-report illicit drug use, and will take a urine dip test for drug use at the beginning of the home visit. The dip test cannot distinguish between licit and illicit use, so we will rely on the combination of self-reported illicit drug use, self-reported prescription medication use, and dip test results to ascertain illicit drug use. If the dip test shows use of drugs other than cannabis and prescription medications, the visit will be discontinued. Participants will show the receipt for their marijuana purchase. If the correct marijuana was not purchased, the visit will be rescheduled. All participants will be advised to stay within legal limits for the amount of marijuana purchased/possessed. If a participant is already in possession of marijuana at the time of screening, the home visit will be scheduled for a time when the participant judges that they can purchase marijuana for the study while staying within legal limits. It is the responsibility of the participant to stay within legal limits.

5. Number of Participants

Indicate the total number of individuals you expect to recruit and enroll. For secondary data analyses, the response should reflect the number of cases in the dataset.

Response:

50 young-adult cannabis users (ages 21-30)
50 older-adult cannabis users (ages 50+)

6. Recruitment Methods

fy who will be doing the recruitment and consenting of participants.
fy when, where, and how potential participants will be identified, recruited, and nsented.
materials that will be used (e.g., recruitment materials such as emails, flyers, vertisements, etc.) Please upload each recruitment material as a separate cument, Name the document: recruitment_methods_email/flyer/advertisement_dd-m-yyyy
ibe the procedures relevant to using materials (e.g., consent form).

Response:

PI Meier and her research assistants (RAs) will be responsible for participant recruitment in the fall of 2022 and spring of 2023. Participants will be recruited via advertisements online (e.g., Craigslist and Reddit) and in newspapers, and physical flyers posted in public places, including cannabis dispensaries, smoke/head shops in Phoenix that sell cannabis paraphernalia, and ASU's campus. We will also recruit via our lab website operated by the ASU Department of Psychology and by word-of-mouth. Ads will ask interested potential participants to call or email us for more information about the study and to determine eligibility (see "Recruitment_methods_flyer_7.29.22"). Participation is voluntary.

7. Study Procedures

7.1 List research procedure step by step (e.g., interventions, surveys, focus groups, observations, lab procedures, secondary data collection, accessing student or other records for research purposes, and follow-ups). Upload one attachment, dated, with all the materials relevant to this section. Name the document: supporting documents dd-mm-yyyy

7.2 For each procedure listed, describe **who** will be conducting it, **where** it will be performed, **how long** is participation in each procedure, and **how/what data** will be collected in each procedure.
t the total period and span of time for the procedures (if applicable the timeline for low ups).
condary data analyses, identify if it is a public dataset (please include a weblink here the data will be accessed from, if applicable). If not, describe the contents of the taset, how it will be accessed, and attach data use agreement(s) if relevant.

for streamlining the review time.

- Ensure that research materials and procedures are explicitly connected to the articulated aims or research questions (from section 2 above).
- In some cases, a table enumerating the name of the measures, corresponding citation (if any), number of items, sources of data, time/wave if a repeated measures design can help the IRB streamline the review time.

Response:

Potential participants who see our ad and call or email us will complete a telephone screening for eligibility. Screening will take 15-30 minutes. Eligible participants will then complete an online survey and a home visit. The questionnaires/surveys for each procedure (screening, online survey, and home visits) are shown in the table below. Overall, participation should take 5-6 hours over a period of a few weeks.

Home Visits

Two RAs will visit participants' homes and assess participants' blood pressure and heart rate, subjective mood state, cognitive function, pain, pupillometry, and balance both before and after participants' customary cannabis use. Participants will be asked to (i) buy a particular brand of marijuana with ~20% THC and <1% CBD from a local cannabis dispensary (to standardize the cannabis product across participants), and save the receipt; (ii) abstain from cannabis use the day before the visit (i.e., ~24 hours and at least 8 hours before the visit) to reduce any residual effects of recent cannabis; and (iii) abstain from tobacco/nicotine and alcohol the day before the visit (and at least 8 hours before the visit).

Participants will be asked to purchase marijuana with ~20% THC and <1% CBD from a local dispensary. All products are labeled with THC and CBD content, by law. Marijuana with ~20% THC and <1% CBD was selected because this is the average THC and CBD content of marijuana sold in cannabis dispensaries. Dispensaries track legal purchase limits for medical users using a statewide tracking system operated by the Department of Health Services, and legal purchase limits for adult recreational use for purchases made at their dispensaries.

Approximately 24 hours before the home visit, RAs will call participants to remind them of the visit; confirm purchase of the correct cannabis brand marijuana; remind participants to abstain from cannabis, alcohol, and tobacco/nicotine; and

screen participants for CDC symptoms of COVID (https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html). If participants did not purchase the correct cannabis, or report symptoms of COVID, the visit will be rescheduled. On arrival to participants' home, if the participant is already intoxicated, the visit will be rescheduled (see "Procedure for Intoxicated Participant"). Participants will complete informed consent; show their driver's license to confirm age eligibility; take an illicit drug urine dip test to confirm abstention from illicit drugs; and women of childbearing age will be asked to take a pregnancy test to confirm they are not pregnant. If the person does not meet eligibility criteria at this time (age, no illicit drug use, not pregnant), the visit will be cancelled. Participants will show the receipt of the marijuana they purchased. If the incorrect marijuana was purchased the visit will be rescheduled. RAs will administer a series of baseline surveys and tests. Next, RAs will ask participants to go to a private, enclosed room in the house to inhale marijuana as they customarily would (ad libitum use). Before participants go to the private room, RAs will train participants to use a handheld device to test the cannabinoid content (THC, CBD) of their cannabis (Purpl device; https://www.purplscientific.com/) because THC and CBD content could vary somewhat from the product label; RAs will also train participants to weigh their cannabis on a portable scale before and after use as a means of ascertaining the quantity of cannabis used. Notably, RAs will not handle the participant's cannabis, nor will they be exposed to secondary smoke. Participants will then smoke cannabis in their private and enclosed room as they customarily would (i.e., amount used will be decided by the participant), and then return to the main room for completion of outcome measures immediately following use (~5 minutes) and 1 hour following use.

After the home visit, the study is over. There will be no long-term follow-up.

3. Compensation

8.1 Report the amount and timing of any compensation or credit to participants.
8.2 Identify the source of the funds to compensate participants.
8.3 Justify that the compensation to participants to indicate it is reasonable and/or how the compensation amount was determined.
8.4 Describe the procedures for distributing the compensation or assigning the credit to participants.

for streamlining the review time.

- **If partial compensation or credit will be given or if completion of all elements is required, explain the rationale or a plan to avoid coercion.**
- **For extra or course credit guidance, see "Research on educational programs or in classrooms" on the following page: https://researchintegrity.asu.edu/human-subjects/special-considerations.**
- **For compensation over $100.00, review "Research Subject Compensation" at: https://researchintegrity.asu.edu/human-subjects/special-considerations for more information.**

Response:

Participants will be responsible for the costs of cannabis ($8 for one gram). Participants will be compensated as follows: $15 20 Amazon gift card for the online survey, $40 Amazon gift card for the home visit.

). Risk to Participants

List the reasonably foreseeable risks, discomforts, or inconveniences related to participation in the research.

for streamlining the review time.

- Consider the broad definition of "minimal risk" as the probability and magnitude of harm or discomfort anticipated in the research that are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- Consider physical, psychological, social, legal, and economic risks.
- If there are risks, clearly describe the plan for mitigating the identified risks.

Response:

Participants will be legal cannabis users. (Adult recreational cannabis was legalized in AZ in 2020, and recreational cannabis sales began in January 2021.) A possible risk of participation involves breach of confidentiality. Participants will provide private information, and it is possible that the information they provide could be linked to the identifying information that we collect from them. We will take steps to mitigate this (described below). It may also be distressing to some participants to answer some of the study questions. Some participants might also experience some discomfort from abstaining from cannabis the day before the study, but this is expected to be mild and temporary. COVID-19 is a risk of in-person interactions. Mitigation measures involve cancelling home visits if the research assistant or participant is showing symptoms of COVID-19. The home visit will be rescheduled for at least 10 days after symptoms have subsided.

10. Potential Direct Benefits to Participants

List the potential direct benefits to research participants. If there are risks noted in 9 (above), articulated benefits should outweigh such risks. These benefits are not to society or others not considered participants in the proposed research. Indicate if there is no direct benefit. A direct benefit comes as a direct result of the subject's participation in the research. An indirect benefit may be incidental to the subject's participation. Do not include compensation as a benefit.

Response:

There is no direct benefit to participants.

11. Privacy and Confidentiality

Indicate the steps that will be taken to protect the participant's privacy.

11.1 Identify who will have **access to the data**.
11.2 Identify where, how, and how long data will be **stored** (e.g. ASU secure server, ASU cloud storage,
filing cabinets).
11.3 Describe the procedures for **sharing, managing and destroying data**.

4 Describe any special measures to **protect** any extremely sensitive data (e.g. password protection, encryption, certificates of confidentiality, separation of identifiers and data, secured storage, etc.).
5 Describe how any **audio or video recordings** will be managed, secured, and/or de-identified.
6 Describe how will any signed consent, assent, and/or parental permission forms be secured and how long they will be maintained. These forms should separate from the rest of the study data.
7 Describe how any data will be **de-identified**, linked or tracked (e.g. master-list, contact list, reproducible participant ID, randomized ID, etc.). Outline the specific procedures and processes that will be followed.
8 Describe any and all identifying or contact information that will be collected for any reason during the course of the study and how it will be secured or protected. This includes contact information collected for follow-up, compensation, linking data, or recruitment.
9 For studies accessing existing data sets, clearly describe whether or not the data requires a Data Use Agreement or any other contracts/agreements to access it for research purposes.
10 For any data that may be covered under FERPA (student grades, etc.) additional information and requirements is available at https://researchintegrity.asu.edu/human-subjects/special-considerations.

Response:

All data in this study will be maintained confidentially but will not be anonymous. Risks to confidentiality will be minimized in a number of ways. First, data will not contain personally identifying information. We will assign each screened potential participant a study ID number, which will be used on data collected online, via telephone, on paper, and in person as an external reference. The master file linking study IDs to identifying information will be kept separate from the data on an encrypted and password protected computer. For online data collection, we will use Qualtrics secure online software, and we will disable the automatic collection of IP addresses in Qualtrics. Second, we will obtain a certificate of confidentiality. Third, paper and pencil data will be transferred to an encrypted and password protected computer and/or on secure online survey software (Qualtrics). Paper and pencil data will be destroyed immediately upon transfer. Qualtrics has security features which allow administrators to control who has access and ensure only senior research staff have access to the data (https://www.qualtrics.com/security-statement/). Fourth, written consent forms will be stored in locked file cabinets. Fifth, no results for individual participants will be published or released. The master list linking study IDs to identifying information will be destroyed upon completion of the study. Only the PIs and students in the laboratory will have access to the deidentified data. In accordance with the American Psychological Association standards, all data, including screening data, will be retained for five years after publishing. Screening data for all participants, including ineligible participants, will be retained as a means of estimating, for a future grant proposal, what % of participants are eligible for the study and reasons for ineligibility. No individual results will be published, and personally identifiable information will not be used in any publications. All project

personnel undergo CITI human subjects training prior to participating in research.

Procedures to help prevent distress related to research participation include disclosure in consent forms about the purpose of the study, the nature and content of the data collection instruments, and participants' rights to refuse to answer questions or withdraw from the study at any time without penalty. Despite these safeguards, it is possible that some participants may have concerns raised as a result of their participation. General procedures to help participants reduce and cope with distress include providing all participants with contact information for the PI and contact information for counseling centers in the Phoenix metropolitan area (see "Participant Resource List"). Risks of distress in the surveys will be minimized by informing participants that they are free to skip any question and to discontinue participation.

2. Consent

Describe the procedures that will be used to obtain consent or assent (and/or parental permission).

Who will be responsible for consenting participants?
Where will the consent process take place?
How will the consent be obtained (e.g., verbal, digital signature)?

for streamlining the review time.

- If participants who do not speak English will be enrolled, describe the process to ensure that the oral and/or written information provided to those participants will be in their preferred language. Indicate the language that will be used by those obtaining consent. For translation requirements, see Translating documents and materials under https://researchintegrity.asu.edu/human-subjects/protocol-submission
- Translated consent forms should be submitted after the English is version of all relevant materials are approved. Alternatively, submit translation certification letter.
- **If a waiver for the informed consent process is requested, justify the waiver in terms of each of the following: (a) The research involves no more than minimal risk to the subjects; (b) The waiver or alteration will not adversely affect the rights and welfare of the subjects; (c) The research could not practicably be carried out without the waiver or alteration; and (d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.** Studies involving confidential, one time, or anonymous data need not justify a waiver. A verbal consent or implied consent after reading a cover letter is sufficient.
- ASU consent templates are [here].
- Consents and related materials need to be congruent with the content of the application.

Response:

Written consent will be obtained for online surveys and home visits. Oral consent will be obtained for telephone screening. Research assistants will obtain consent.

The consent form is attached ("Consent Form 7.29.229.20.22"). For the online survey, the attached consent form will be shown, and participants will be asked to click the button saying "I consent to participate in this research." For the home visit, this consent form will be shown, and participants will be asked to sign this form.

3. Site(s) or locations where research will be conducted.

List the sites or locations where interactions with participants will occur-

- Identify where research procedures will be performed.
- For research conducted outside of the ASU describe:
  - Site-specific regulations or customs affecting the research.
  - Local scientific and ethical review structures in place.
- For research conducted outside of the United States/United States Territories describe:
  - Safeguards to ensure participants are protected.
- For information on international research, review the content [here].

search conducted with secondary data (archived data):

- List what data will be collected and from where.
- Describe whether or not the data requires a Data Use Agreement or any other contracts/agreements to access it for research purposes.
- For any data that may be covered under FERPA (student grades, etc.) additional information and requirements is available [here].
- For any data that may be covered under FERPA (student grades, homework assignments, student ID numbers etc.), additional information and requirements is available [here].

nse:

ipant interactions will occur remotely (via telephone and online) from Tempe Campus (Schwada Classroom Building – Meier's research suite), and will occur at participants' homes in the Phoenix metro area. To ensure research assistant's safety during home visits, two research assistants will be required to go to each home visit. Research assistants will be trained to scan the participants' neighborhoods/home environments prior to entering the participants' homes. If research assistants feel unsafe either before or after entering participants' home, they should leave the premises and consult with PI Meier, via telephone, to determine if any additional steps should be taken.

4. Human Subjects Certification from Training.

ovide the names of the members of the research team.

ASU affiliated individuals do not need attach Certificates. Non-ASU investigators and research team members anticipated to manage data and/or interact with participants, need to provide the most recent CITI training for human participants available at www.citiprogram.org. Certificates are valid for 4 years.

for streamlining the review time.

- If any of the study team members have not completed training through ASU's CITI training (i.e. they completed training at another university), copies of their completion reports will need to be uploaded when you submit.
- For any team members who are affiliated with another institution, please see "Collaborating with other institutions" [here]
- The IRB will verify that team members have completed IRB training. Details on how to complete IRB CITI training through ASU are [here]

Response:
Madeline Meier
Eve Barton
Gray Harris
Jaiden Stepnowsky
Jade Debuhr
Benjamin Roman
Jack Waddell
Allison Hays
Gene Brewer
Xavier Celaya
Sofia Wernik
Haley Hummel
Katrina Ager
Kaleigh Andres
Joseph Lucero
Megan Silva
Savannah Poling

PROCEDURES FOR THE REVIEW OF HUMAN SUBJECTS RESEARCH

General Tips:

- Have all members of the research team complete IRB training before submitting.
- Ensure that all your instruments, recruitment materials, study instruments, and consent forms are submitted via ERA when you submit your protocol document. Templates are [here]
- Submit a complete protocol. Don't ask questions in the protocol – submit with your best option and, if not appropriate, revisions will be requested.
- If your study has undeveloped phases, clearly indicate in the protocol document that the details and materials for those phases will be submitted via a modification when ready.
- Review all materials for consistency. Ensure that the procedures, lengths of participation, dates, etc., are consistent across all the materials you submit for review.
- Only ASU faculty, full time staff may serve as the PI. Students may prepare the submission by listing the faculty member as the PI. The submit button will only be visible to the PI.

- Information on how and what to submit with your study in ERA is [here]. Note that if you are a student, you will need to have your Principal Investigator submit.
- For details on how to submit this document as part of a study for review and approval by the ASU IRB, visit https://researchintegrity.asu.edu/human-subjects/protocol-submission.