# ASSESSMENT OF THE ACUTE PSYCHOACTIVE EFFECTS OF NATURALISTIC CANNABIS USE: A VALIDATION OF THE NATURALISTIC CANNABIS ADMINISTRATION PROTOCOL (NCAP)

by

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## Abstract

Concerns about the impact of acute cannabis use on cognition are significant and widespread. Following legalization in 2018, Canadian federal health messaging emphasized the cognitive impacts of cannabis use and extrapolated from research that was conducted in a laboratory-based setting. These settings have long been recognized as producing measurable changes in physiology (e.g., white coat hypertension), emotionality (e.g., increased anxiety), and cognition (e.g., decreased cognitive performance). Drug use is particularly sensitive to the contextual cues present in lab-based studies. Moreover, among people who use drugs, these settings are often associated with higher levels of perceived stigma. Taken together, these factors question the generalizability of extant findings on cannabis and cognition. This apparent disconnect mandates the development of new research paradigms. The Naturalistic Cannabis Administration Protocol (NCAP) is an attempt to develop a more ecologically valid methodology to study acute effects of cannabis. In the present study, participants (*N* = 28; *M* age = 21.82, *SD* = 2.26**)** self-administered cannabis via inhalation and underwent a cognitive assessment via video conference. Within-subject assessment of cognitive function during a no-cannabis control versus directly following cannabis use revealed no differences in immediate verbal recall ($F(1, 27) = .28$, $p = .60$), delayed verbal memory ($F(1, 27) = 2.73$, $p = .11$), working memory and attention ($F(1, 27) = .60$, $p = .45$), processing speed ($F(1, 27) = .88$, $p = .36$), or verbal fluency ($F(1, 27) = 1.62$, $p = .22$). Results demonstrated support for the feasibility and acceptability of the NCAP in a sample of adult cannabis users. When given an option, participants predicted that they would prefer the at-home administration of cannabis over a lab-based administration. Findings suggest that when cannabis is used by regular cannabis users in a naturalistic setting cognitive function is equivalent to their no-cannabis baseline.

## Lay Summary

The cognitive effects of acute cannabis use are a primary concern for public health and patients. Research on the acute effects of cannabis have long-been conducted in lab-based settings which differ substantially from typical drug use contexts. Drug effects are sensitive to individual, contextual, and environmental factors present during substance use. Previous research has demonstrated that the context of clinical settings can produce measurable changes in emotionality and cognition. Among people who use drugs, these settings can be associated with higher levels of perceived stigma which might confound the effects of acute cannabis use and cognition. The Naturalistic Cannabis Administration Protocol is an attempt to develop a more ecologically valid methodology to study acute effects of cannabis. Cannabis users self-administered their cannabis of choice in their home environment and demonstrated equivalent cognitive performance across assessments (no-cannabis vs. cannabis). Findings support the use of naturalistic cannabis use paradigms in future research.

## Preface

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# CHAPTER 1 Introduction

The relationship between cannabis and humans is long and curious. This green leafy plant has been an important source of fiber, food, and medicine for thousands of years. Indeed, it is among the first of our cultivated plants (Clarke & Merlin, 2013). Different medical texts document the use of cannabis for therapeutic purposes (CTP) for a wide range of indications across many cultures and times (Aggarwal, 2013; Russo, 2015, 2017). Discoveries over the last 80 years have helped us understand why humans have such an affinity for cannabis. The isolation and synthesis of the primary cannabinoids, tetrahydrocannabinol (THC; Gaoni & Mechoulam, 1964) and cannabidiol (CBD; Adams et al., 1940), and identification of the endocannabinoid system (ECS; Devane et al., 1988) have resulted in increased interest in cannabis.

Growing interest in cannabis is reflected in the increasingly wide-spread commercialization and use. Cannabis is among the most widely used, cultivated, and trafficked psychoactive substances in the world (World Health Organization, 2016). By 2017, more than 1 in 10 Canadians reported using cannabis in the last month (Pham et al., 2022). These high rates of use occurred despite the illegal status of non-therapeutic cannabis use.

The Government of Canada legalized non-therapeutic cannabis use in October 2018. The introduction of a new legal psychoactive substance saw the government disseminate health warning messages about the harms of cannabis. These messages were centered around the cognitive harms such as cannabis can "lower your ability to pay attention... impair your thinking, concentration, memory and decision-making, and can impact your ability to perform well on the job or at school (Health Canada, 2018, para. 2)." The association between cannabis use and cognition appears nuanced and complicated.

Experimental research examining the effects of cannabis administration on human behavior has largely been conducted in laboratory settings for the past 40 years. The highly controlled laboratory environment enables researchers to isolate drug effects from other contextual and individual variables and protects participants from the stigma and potential legal consequences of documented ingestion of a controlled substance (Pertwee, 2014). This approach has been useful for elucidating the pharmacodynamics and pharmacokinetics of cannabis use in humans.

The laboratory setting is distinct from the typical settings in which people use drugs such as in their home or in nature. To increase our confidence in the research findings on cannabis and cognition, we need to consider if data generated in the lab can be generalized to the real-world. Lab-based approaches might compromise ecological validity by failing to account for the influence of factors which have been shown to relate to the subjective effects of cannabis use on human behavior. This is a longstanding concern that has been recognized for decades. Clinical Psychologist Harry Klonoff argued that assessing the impact of cannabis use on human behavior in "a rigid and sterile lab environment would result in artefact" (Klonoff, 1974, p. 8). Due to the influence of contextual factors, research should strive to create a setting that is socially and clinically relevant to cannabis use.

## 1.1 Cannabis and Cognition

### *Cannabinoid Receptors and Cognition*

Cannabinoid-1 (CB-1) receptors are unevenly distributed throughout the brain. Regions implicated in learning and memory are the areas with the highest densities of receptors including the hippocampus, cerebellum, cortex, amygdala, and basal ganglia (Ameri et al., 1999; Herkenham et al., 1990). CB-1 receptors can suppress neurotransmission which allows

endogenous and exogenous cannabinoids to impact neuronal communication and provides another avenue for impacting learning and memory (Hampson & Deadwyler, 1999; Lichtman et al., 1995; Varvel et al., 2001). Studies in rodents demonstrate persistent and profound alterations in cognition and memory following THC administration (Basavarajappa et al., 2014; Heyser et al., 1993). Similar effects have not been consistently demonstrated in humans.

*Acute, Residual, and Long-Term Effects*

Over the last 50 years there has been concerted public health interest and scientific effort directed towards understanding the cognitive impact of cannabis use. Paracelsus' observation that the *dose makes the poison* cautions us from generalizing about the effects of psychoactive substances without considering the dose. Therefore, to characterize the effects of cannabis use more accurately we should understand these effects in temporally discrete categories: acute, residual, and long-term.

A helpful analogy to support this distinction can be seen in the case of nicotine use. Nicotine exhibits an inverted J dose-response with low dose or brief exposure leading to appealing cognitive-enhancing effects in the domains of attention, working memory, fine motor skills and episodic memory. Higher doses and long-term use are associated with impaired cognitive functioning (Valentine & Sofuoglu, 2018). It is therefore critical to frame the consequences of use in temporal terms.

*Acute Effects of Cannabis on Cognition*

Daily cannabis users, such as those using CTP, need to know how acute cannabis use (ACU) affects cognition. If ACU was found to be impairing, it could have a significant effect on the quality of life of those using CTP and result in serious public health consequences. Indeed, there are documented concerns regarding safe and effective parenting (Daniels, 2019), driving

ability (Grotenhermen et al., 2007), and the impact of ACU on workplace safety (Hazle et al., 2020).

A recently published systematic review and meta-analysis examined the magnitude and duration of cognitive impairment following ACU (McCartney et al., 2021). Across 80 studies, with mixed routes of administration and dosing, meta-analyses revealed detrimental effects ($p <$ .05) of THC on tracking performance ($g$ = -0.42), information processing ($g$ = -0.38), fluid intelligence ($g$ = -0.37), fine motor function ($g$ = -0.36), working memory ($g$ = -0.36), conflict control ($g$ = -0.34), reaction time ($g$ = -0.28), divided attention ($g$ = -0.28), and sustained attention ($g$ = -0.23). Neither sensory discrimination nor time perception demonstrated impairment. Importantly, when data were limited to “regular users" (i.e., used cannabis weekly or more) many of these effects were no longer present. This review highlights an important factor when predicting the magnitude of impairment that one might experience following cannabis use. The findings suggest that effects of ACU are less pronounced in individuals that use cannabis often. A finding that is especially relevant for therapeutic users.

A recent scoping review identified and summarized studies that investigated the duration and degree of acute neurocognitive impairment for medical cannabis use and compared to non-therapeutic use literature (Eadie et al., 2021b). Forty studies were assessed for eligibility and twelve studies (six randomized control trials (RCTs), one observational clinical trial, and five systematic reviews) met criteria to be included. Four of the seven RCTs required participants to be abstinent from cannabis for at least 30 days prior to the experimental session. The review noted that neurocognitive testing varied significantly between studies both in terms of tests administered and in the timing of assessment following cannabis use. Unsurprisingly, there was a lack of consistent impairment effects across neuropsychological measures and time-points.

However, acute impairment was demonstrated in the following domains: immediate and delayed verbal recall, processing speed, task switching, visual attention, fine motor coordination, and working memory. There were no differences on any neurocognitive test between placebo and active conditions at the four-hour mark (Wallace et al., 2015). Impairment appeared to be dose-dependent such that higher doses of THC were generally more impairing than low doses although there was considerable variability. In fact, some studies demonstrated improved neurocognitive performance following cannabis use (e.g., Gruber et al., 2016; Rekand, 2014).

A sample of near-daily cannabis users demonstrated improved performance on a task of divided attention (higher maximum speed entering patterns and improved accuracy) on cannabis administration days relative to abstinent days (Haney et al., 1999). Another study demonstrated that performance on a decision-making task that measures executive functioning and planning (i.e., Tower of London; Shallice, 1982) was unaffected by cannabis administration across frequent and occasional cannabis users (Ramaekers et al., 2009).

Gruber and colleagues (2016) assessed the impact of three months of CTP on executive functioning in 11 patients ($n$ = 5 females). Patients used cannabis on average 5 days/week. Compared to a non-using baseline, CTP patients demonstrated improved executive functioning measured with the Stroop Color Word Test (color naming time 59.55 seconds vs. 56.91 seconds, $p$ = .01) and the Trail Making Test (Trails A time 26.91 seconds vs 22.91 seconds, $p$ = .02). Patients also reported reductions in depression (18.18 vs. 13.64, $p$ = 0.04), and improvements on a scale measuring energy/fatigue (35.45 vs. 45.91, $p$ = .02).

Recently, Sagar and colleagues (Sagar et al., 2021) expanded on Gruber's pilot by more closely examining the relationship between clinical improvements and improved cognitive performance following the initiation of CTP. Over the course of the 12-month study, 54 cannabis

using participants exhibited changes on several measures of executive functioning and various aspects of their clinical state (e.g., depression and anxiety). Results suggested that observed cognitive improvements were not associated with acute cannabis effects (e.g., CTP use episodes/week, THC mg/week, CBD mg/week) but instead were correlated with clinical improvements. Reductions in depression, anxiety, and improved sleep were associated with improved executive function and stable verbal learning and memory over time.

The following study (Olla et al., 2019) examined the acute effects of cannabis use in CTP patients. Participants ($N$ = 22) were administered the same brief neurocognitive battery three times during a six-hour period: at baseline, 30 minutes after they inhaled one gram of cannabis via vapes, joints, and dabs (20% THC), and once more three hours later. Patient performance was compared to a normative sample supplied by the test producer and compared to an undergraduate student sample ($N$ = 40) who had not used cannabis prior to completing the battery.

Patients outperformed both the normative sample ($d$ = 0.39) and the student sample ($d$ = 0.72) on a test of language (i.e., Boston Naming Test; Kaplan et al., 1983). A large effect was also observed on the animal fluency test where patients outperformed the normative sample during the last two administrations ($d$ = 0.50 - 0.70). Patients also outperformed the normative sample on a test of simple attention and processing speed (i.e., Digit Span; Wechsler, 1997). These findings are complicated by practice effects which may have been a major experimental confound. Despite this limitation, the findings are consistent with Gruber and Sagar's studies (Gruber et al., 2016; Sagar et al., 2021) and suggest that tolerance may develop to the neurocognitive effects of cannabis such that frequent users may perform in ways that are indistinguishable from non-using controls. Notably, tolerance does not extend to tachyphylaxis

or loss of efficacy with respect to therapeutic benefits (e.g., Johnson et al., 2013; Russo & Hohmann, 2013)

*Residual Effects*

The acute subjective effects of cannabis begin to diminish within hours after the initial exposure. However, it takes the body additional days to weeks to rid itself of remaining cannabis metabolites that are stored in body fat. Elucidating the association between residual cannabis use and cognitive effects will help individuals make informed decisions about their use. Further, policy makers and safety-sensitive workplaces across Canada may rely on this information when assessing when someone is deemed fit for work following cannabis use. For example, Transport Canada requires airline crew to be abstinent from cannabis for 28 days prior to working as do all active members of the Royal Canadian Mounted Police (Government of Canada, 2018).

Studies vary in terms of how they define residual effects with some assessing 12 hours following cannabis exposure to over a year since last use. A recent study looking at residual effects included results from five meta-analyses with data from more than 8000 cannabis users and non-users (Bourque & Potvin, 2021). Small deficits in attention, executive functioning, and processing speed were reported (Cohen's $d$ ~0.2 - 0.3). The authors note the relative risk to be lower than that of other substances. For example, the residual effects of alcohol on cognition are generally categorized as moderate (Cohen's $d$ ~0.4 - 0.6; Bourque & Potvin, 2021). Despite evidence of persisting mild cognitive impairment among some individuals, abstinence of longer than 72 hours appeared to diminish the cognitive deficits associated with cannabis use (Scott et al., 2018).

*Long-Term Cannabis Use Effects on Cognition*

The long-term effects of cannabis use on cognition are defined as those effects which are demonstrated long after the acute use and residual phase have passed. Extant findings on the association between long-term cannabis use and cognitive deficits demonstrated modest cognitive declines. A meta-analysis, performed on 13 studies between 2010-2019, examined cognition in chronic cannabis users compared with non-using controls (Figueiredo et al., 2020). The largest effect sizes were seen in short-term ($d$ = .48) and long-term ($d$ = .43) memory deficits. The deficits were dose-dependent in a manner that was sensitive to frequency of use. Those with the heaviest cannabis use were the only ones to demonstrate a deficit. Of note, effect sizes were rarely greater than .5 standard deviations and were often no longer significant after controlling for potentially confounding variables (Gonzalez et al., 2017).

*Adolescent Cannabis Use and Cognition*

Numerous studies have reported a relationship between the early initiation of cannabis use and subsequent negative impacts on intelligence (e.g., Fried et al., 2002). An oft-cited study by Meier reported that individuals who met criteria for cannabis dependence at age 18 had greater cognitive decline than those meeting criteria for dependence after age 18 (Meier et al., 2012). This study and others are complicated by the plethora of potential confounding factors that are difficult to control for such as cognitive ability prior to cannabis initiation, psychiatric concerns, comorbid substance use, and lifestyle factors. Indeed, poor cognitive function is predictive of later substance use (Ridenour et al., 2009).

Quasi-experimental twin studies can help researchers approximate causal relationships. A recent study examined cognitive ability, executive function, and substance use among same-sex monozygotic twins ($N$ = 856; Ross et al., 2020). Findings were consistent with previous twin-

controlled studies and reported minimal evidence for a causal relationship between prior cannabis use and cognitive decline. The authors argued that the association between cannabis use and cognitive deficits was better explained by genetic and/or environmental factors present in both siblings rather than from cannabis use alone.

*Sex Differences*

Preclinical and clinical studies suggest that males and females may be differentially affected by cannabis use. Observed differences in behavioral effects and the development of tolerance may be due to sex-dependent differences in cannabinoid metabolism and influence of sex-specific hormones and/or endocannabinoids (Castelli et al., 2014; Fattore & Fratta, 2010; Fratta & Fattore, 2013; Ketcherside et al., 2016; Nia et al., 2018; Prashad et al., 2020). Study of the interaction of biological sex, cannabis use, and cognition is in its infancy. Of the extant studies, some have failed to find a sex difference on cognitive measures of selective and divided attention, cognitive flexibility, or time estimation (Anderson et al., 2010; McDonald et al., 2003). Other studies have revealed women to be more sensitive to the acute effects of cannabis use on psychomotor function (Roser et al., 2009) and enhancement in spatial working memory (Makela et al., 2006).

A recent study examined 40 cannabis users (55% female) and 40 healthy controls (58% female). Participants were asked to abstain from cannabis use from the evening prior to their test day (~12 hours). On a measure of intellectual function (i.e., Wechsler Abbreviated Scale of Intelligence-II; Wechsler, 2011), male cannabis users performed worse than non-using male controls ($d$ = 1.18). There were no differences between the female groups. Psychomotor function performance differed such that non-using males performed better than cannabis-using males ($d$ = 0.68) whereas cannabis-using females performed better than non-using females ($d$ = 0.50). There

were no observable differences on digit span, total immediate recall, or total delayed free recall (i.e., Hopkins Verbal Learning Test - Revised; Benedict et al., 1998). The study also examined the association of sex with cognitive dysfunction from residual cannabis use. The only observed significant correlation was a negative association between digit symbol and total lifetime cannabis exposure ($r = .44$, $p < .01$). These findings demonstrated that cannabis using males, but not females, had worse performance on measures of intelligence, psychomotor speed, and immediate and delayed verbal recall when compared to same-sex non-using peers. It appeared that cannabis using females performed better on measures of psychomotor function and immediate verbal recall when compared to their non-using same-sex peers. These findings suggest that there may be sex-dependent cognitive effects associated with cannabis use.

*Cannabidiol and Cognition*

The study of cannabis effects on cognition becomes more nuanced when examining the association between individual cannabinoids. The psychoactive qualities of THC appear to be attenuated by the presence of CBD. At the same fixed concentration of THC, cannabis with modest levels of CBD (> 0.75%) was associated with less pronounced verbal memory impairments compared to low-CBD cannabis (<0.14%; Schacht et al., 2012; Taurisano et al., 2021). A second naturalistic study found similar results. Subjects using a high-CBD chemovar had better recognition memory when compared to individuals using low-CBD cannabis. Importantly, daily cannabis use was associated with impairments in verbal and episodic memory only when individuals consumed high THC chemovars (Morgan et al., 2012).

There is no question that the research on cannabis and cognition is nuanced and at times contradictory. A recent Special Issue from the Journal of the International Neuropsychological Society concluded that the neurocognitive outcomes linked with regular cannabis use are in the

small-to-medium effect size range and a statistically significant effect did not always indicate a clinical impairment (Lisdahl et al., 2021).

Nevertheless, the impact of cannabis use on cognition is a primary concern. Indeed, some experts have questioned a patient's ability to adhere to treatment plans and medical advice due to the purported effects of sustained use of cannabis on cognition (Crean et al., 2011). As seen above, several different methodologies have been used to elucidate the impact of cannabis use on cognition. Study methodology differs widely in terms of the route of administration (e.g., oral ingestion vs. smoked cannabis), constituents ingested (e.g., whole plant cannabis versus isolated cannabinoids), time of cognitive assessment post-administration, and differences in individual tolerance to acute cannabis effects (e.g., frequent users versus naive users). These factors not only contribute to a mixed pattern of results across people, but they also make it difficult to draw general conclusions about the impact of cannabis use on cognition. Communicating these findings also takes many different forms and the effects of *long-term use* with *acute use* of cannabis can often be conflated (Colizzi & Bhattacharyya, 2018a).

The variability of effects supports the idea that other factors are present which modulate the cognitive effects of cannabis use. Eadie and colleagues proposed several modifiable and non-modifiable factors that influence the degree and duration of impairment (Eadie et al., 2021a). Modifiable factors included route of administration, tolerance, dose, alcohol use and other sedating substances, drug interactions, CBD content, and chemovars. Non-modifiable factors included sex, genetics and metabolism, personal/family mental health history, comorbidities, and differences in the endocannabinoid system (e.g., Schacht et al., 2012; Taurisano et al., 2021). Moreover, other research has found that higher aerobic fitness levels moderated the impact of cannabis use on visual memory, executive function and psychomotor speed relative to low-fit

users (Sullivan et al., 2021). Attention should be given to these factors when designing studies and contextualizing results.

### 1.2 Research Paradigms

Cannabis is unlike most other drugs studied in the laboratory. First, aside from tobacco, few other widely studied drugs are primarily inhaled. Administration protocols are therefore deemed necessary to help standardize the amount of cannabis consumed across participants. These protocols can go as far to instruct the participant on how to smoke a joint and how long they have to finish consuming a full joint (e.g., Foltin et al., 1988; Huestis et al., 2005). These administration protocols can therefore result in the participant consuming more cannabis in a shorter timeframe than they otherwise would. This can be problematic if the study is purporting to characterize the acute effects of cannabis in a way that is generalizable outside of the study. In pursuit of standardization, these protocols often significantly deviate from typical naturalistic cannabis administration.

Second, regular cannabis users purport anecdotally that there are differences in subjective effects between cannabis products. Indeed, research findings suggest that subjective effects of cannabis use can vary between products due to the sheer diversity of chemical varieties each with their own unique profiles (Lewis et al., 2018). Therefore, the degree to which a participant is familiar with a particular cannabis product might impact the outcome of acute cannabis use.

Experimental cannabis administration typically follows a standard protocol where the participant is instructed to inhale for five seconds, hold their breath for 10 seconds, and wait 45 seconds between inhalations; this procedure is repeated for 5 inhalations (i.e., *Foltin uniform puff procedure*; Abrams et al., 2007; Foltin et al., 1988; Ogourtsova et al., 2018). Recently, researchers have chosen to use a less rigid method demarcated by finishing an allotted cannabis

dose or joint within a 7-to-10-minute window (Spindle et al., 2018; Swortwood et al., 2017; van de Donk et al., 2019). In all cases discussed above, cannabis was provided by the researcher and unfamiliar to the participant.

In recent years, researchers in a state with legal cannabis devised a protocol that allowed them to study the effects of commercially available cannabis rather than lower quality federally sanctioned research cannabis. In this protocol, participants familiarized themselves with the research cannabis during a few days of ad libitum use prior to the experiment. On the day of the experiment, participants consumed the same cannabis in their own residence, and then presented outside to undergo assessment in the researcher's vehicle which was retrofitted with a mobile laboratory (e.g., Bidwell et al., 2020). This protocol allowed participants to use semi-familiar cannabis in a way that was more typical for them. In doing so, the methodology might have reduced some of the extrapharmacological factors that would have been present in the lab. Therefore, participants might have initially experienced acute effects which more closely resembled that of which they would achieve naturalistically. It is unclear if subsequently presenting to a novel experimental setting in the mobile laboratory interacted with the acute effects of cannabis such that outcomes of interest were impacted.

### 1.3 Extra-Pharmacological Effects

The impact of non-drug, or extrapharmacological factors on the acute drug experience cannot be underestimated. Attempts to account for them in clinical research are a defining feature of placebo-controlled studies. Blinding participants to their assigned experimental condition ensure an equal distribution of positive expectancy effects (i.e., placebo) across both active and control groups and reduces possible bias introduced by study personnel. In a case when the study drug is markedly psychoactive, it becomes exceedingly difficult to blind

participants and research personnel (Burke & Blumberger, 2021). Such is the case for cannabis. If extrapharmacological factors are difficult to separate from actual drug effects, then perhaps the goal should shift from isolating these different elements to instead recognizing that drug effects are a combination of both psychoactive components and extrapharmacological elements. Recognizing this interaction might lead to a greater understanding of the intimate interaction between brain, behavior, and psychoactive substances.

*Set and Setting*

The ancient and sacramental use of drugs has long recognized the influence of context and intention in shaping the drug experience. Indeed, Indigenous cultures around the world traditionally used psychoactive substances within ceremony and on select occasions such as during a rite-of-passage or for healing (Labate, 2011). These experiences were typically supervised by a distinguished person such as a shaman who performed different rituals to shape the user experience (e.g., a shaman singing *icaros* during an ayahuasca ceremony; Tupper, 2009). Centuries after colonization drove the majority of ritual plant use underground, efforts to establish contexts that would enhance the drug experience remained. For example, psychiatrist Jacques-Joseph Moreau wrote about Middle Eastern hashish eaters who made efforts to create a pleasant and inspiring environment "surrounded by their women under the spell of music" while using hashish (Moreau, 1973, p.35).

More recently, the phrase "set and setting" has been used to describe the extrapharmacological factors that influence the drug experience. Set commonly includes mindset, personality, attitudes, motivation, and learned skills for modifying the drug experience. Set may also interact with setting such that an individual feels and behaves differently according to the setting such as at school versus at home. These person-environment interactions include

the environmental, social, cultural, and racial factors that influence substance use and psychoactive effects (Neitzke-Spruill, 2020). The phrase is commonly credited to Timothy Leary and his colleagues at Harvard who were among the first and arguably most controversial to study psychedelics in the 1960s.

Leary's controversy was due in part to his enthusiasm for his unconventional research methods. He viewed psychedelics as *nonspecific catalysts* in which "set and suggestive contexts account[ed] for ninety-nine percent of the specific response to the drug" (Eisner, 1997, p. 214). Leary believed that prior research on psychedelics that had reported negative outcomes, such as symptoms of psychosis, were likely due to the "psychiatric situations where set and setting were purposely psychotogenetic [*sic*]" (Leary & Alpert, 1962, para. 6).

In recognizing that drug effects were sensitive to contextual factors such as set and setting, which differed substantially between hospital, laboratory and typical self-administration contexts, Leary designed the 1962 *Naturalistic Study of Psilocybin* ($N$ = 167). Novel parameters for the research were established such as letting participants determine an appropriate dose for themselves and conducting the study in "a comfortable, homelike environment...the sterile impersonality of the laboratory was avoided (Leary, 1961, para. 64)". By conducting research in a naturalistic environment, Leary felt he was better positioned to capture the effects of psilocybin in a socially and culturally relevant setting which more closely resembled real-world drug effects.

The setting can also interact with the pharmacodynamics of a substance which can alter the acute effects. Although an individual can develop a reduced reaction to a drug following repeated use, research has demonstrated a difference in tolerance between familiar and unfamiliar environments. Indeed, drug tolerance is dependent on environmental cues (e.g., Siegel

et al., 1982), and a failure of tolerance can occur if the drug is administered in a novel environment not already associated with the drug.

Alcohol research paradigms have accounted for the influence of contextual factors for over 40 years (Marlatt & Rohsenow, 1981). Simulated bars in research institutions, colloquially known as bar labs, were designed to evaluate alcohol use in a context far more analogous to a drinking environment than a sterile lab. However, in recent years researchers have argued that observing substance use in an *actual substance-using situation*, such as at a real bar or in a private home, has higher ecological validity than a contrived substance use setting and better accounts for the effects of Pavlovian conditioning on tolerance (Clapp et al., 2008).

In addition to the influence of set and setting on acute drug effects, there are three related phenomena which impact physiological and psychological variables that are relevant to the study of acute cannabis effects and cognition. The *white coat effect, memory self-efficacy,* and *stereotype threat* have all demonstrated pronounced acute effects on cognitive ability. The addition of a non-specific mood amplifier such as cannabis might arguably exacerbate these effects.

*White Coat Effect*

The type of setting and who is present can affect an individual on a physiological and psychological level. These changes are seen across a variety of clinical and research settings. The influence of medical professionals and clinical settings on these domains has been coined the "white coat effect." The white coat effect was initially observed when patients showed marked elevations in blood pressure while in a physician's office. When the same patients were sent home with a blood pressure monitor, they were no longer hypertensive. The phenomenon was also affected by the type of medical professional present. Patients were less likely to be hypertensive when blood pressure was measured by a technician than by a physician (Pickering

et al., 1988). Ironically, the white coat effect is thought to be caused by anxiety over being classified as a hypertensive, which results in inaccurate readings and ensuing misclassification of patients as hypertensive. Since Pickering's seminal study (1988), several others have demonstrated a similar effect on mood and memory (e.g., Schlemmer & Desrichard, 2018; Spruill et al., 2007).

*Memory Self-Efficacy*

Memory is sensitive to context (e.g., context-dependent learning) and can be moderated by one's belief about their capability to use memory effectively. Indeed, individuals with low memory-self efficacy (MSE; Hertzog et al., 1989) performed worse on memory tests in a simulated-neuropsychological environment than in a neutral control environment (Schlemmer & Desrichard, 2018). Interestingly, individuals with high-MSE demonstrated a stereotype lift in the proxy-medical environment where they performed better than in the control environment. This effect further exacerbated differences in performance between low-MSE patients and high-MSE patients. MSE can interact with task instruction such that individuals with low-MSE perform worse on a memory emphasizing task than on the same task with neutral instructions (Desrichard & Köpetz, 2005).

*Stereotype Threat*

Stereotype threat is a type of self-evaluative threat whereby individuals internalize negative stereotypes about the group they belong to and as a result experience performance-disrupting anxiety about behaving consistently with the stereotype (Steele & Aronson, 1995). This belief can result in impaired performance not because a true deficit exists, but because the person is cognitively burdened with knowledge of the stereotype and the anxiety of confirming it (Looby & Earleywine, 2010). Numerous studies provide evidence for the impact of stereotype

threat on performance in African Americans (Steele & Aronson, 1995), women (Spencer et al., 1999), and the elderly (Levy, 1996).

The detrimental effects of cannabis on cognition are proselytized by the media and public health messaging. Indeed, official cannabis health warnings from Health Canada purport that "THC can cause anxiety and impair memory and concentration." Therefore, it is unsurprising that a cannabis user stereotype, which exaggerates the memory impairing effects of cannabis use, may be particularly salient to cannabis users. Looby and Earleywine (2010) demonstrated the effect of stereotype threat (ST) on cognitive performance in frequent cannabis users, an effect that was moderated by gender. Male participants assigned to a ST condition read a summary asserting that there was strong evidence that cannabis use leads to cognitive deficits, even beyond acute cannabis effects. Following the ST, they performed worse on all indices of cognitive ability (i.e., verbal learning and memory, immediate and delayed memory, verbal fluency, working memory and attention span, information processing, sustained attention, and visuomotor concentration). Women exposed to the same ST showed an opposite pattern. The researchers argued that previous research demonstrating cannabis-related cognitive deficits may be overstated and better explained by stereotype threat.

Cannabis stereotypes are not a new phenomenon. For many decades, cannabis use has been associated with stigma. This belief appears to be moderated by drug policy. In a study of European countries, self-stigma was higher in countries with more conservative cannabis policies (Skliamis et al., 2020). Unsurprisingly, the most prominent dimension of stigma reported was "perceived devaluation" which occurs when people who use drugs (PWUDS) believe that the general public endorses common negative stereotypes about them (Ahern et al., 2007). Nearly half of the cannabis users in the study agreed that cannabis users were "unreliable." Other

research found that the terms "irresponsible" and "lazy" are among the five characteristics that are most highly associated with cannabis users (Mikos & Kam, 2019). Cannabis user's self-stigma may influence their behaviour and performance in a way that diminishes their cognitive ability in a test environment.

Curran and colleagues examined subjective cognitive ability across three oral cannabis conditions (i.e., placebo, 7.5mg THC, 15mg THC; Curran et al., 2002). Participants ($N$ = 15) used cannabis less than once per week. Cognitive function was measured over an 8-hour period and residual effects were examined at 24 and 48 hours later. Findings revealed that participants across all three conditions, including the placebo condition, rated subjective memory problems for several hours post-drug administration. It may be that participants held the expectation that cannabis use would result in impaired cognition and behaved in a way consistent with that belief.

*Response Expectancy Effect*

It is human nature to make a prediction about how we will react to certain stimuli. This cognitive event, termed *response expectancy,* can have a direct, unmediated effect on nonvolitional responses and is the core psychological mechanism of placebo-like effects. The anticipation of one's own automatic reactions to various situations and behaviors (e.g., how impaired you expect to feel after using cannabis) are also directly self-confirming (Kirsch, 1997).

There are several complex neurobiological mechanisms (e.g., endorphins, endocannabinoids, and dopamine) and activation of distinct brain regions (e.g., prefrontal cortex and amygdala; Finniss et al., 2010) which underlie the placebo effect, and which share pathways with many common medications (Kaptchuk & Miller, 2015). Literature on the placebo response to anti-depressant and anxiolytic medication provides a model for other studies examining placebo responses of other substances (Kirsch, 2019). A seminal meta-analysis of conventional

double-blind studies indicated that 75% of the anti-depressant response was due to extrapharmacological effects including an expectancy of therapeutic benefit (i.e., placebo; Kirsch, 2019; Kirsch & Sapirstein, 1998).

Expectancy theory was first applied to substance use by Marlatt and Rohsenow (Marlatt & Rohsenow, 1981) in their seminal balanced-placebo design study. In this study participants were assigned to one of four conditions: (1) received active drug and told that they received active drug, (2) received active drug and told that they received placebo, (3) received placebo and told that they received active drug, and (4) received placebo and told that they received placebo. Individuals who expected to consume the active drug behaved as if they were intoxicated under the placebo alcohol condition. We can infer from the results of this study that an individual's expectancy beliefs mediate the effect a substance can have on subsequent behavior. Findings from Marlatt and Rohsenow's study demonstrate that the greatest effects are due to the expectancy rather than the chemical composition of the substance.

It is possible that cannabis users' beliefs about the acute effects of cannabis, which might be influenced by stigma, could lead to an expectation that cannabis use will be impairing. This may then contribute to the impairment that they experience thus inflating our estimation of the impairing effects of cannabis use. Research that considers the set (e.g., stigma, MSE, expectancies) and setting, including how the researcher presents themselves and the task will likely produce a more valid assessment of the cognitive effects of ACU.

### 1.4 Barriers to Research

Policy and institutional barriers to cannabis research have led to a vast knowledge gap as cannabis access and use has far outpaced research (Hutchison et al., 2019). Prior to the Canadian legalization of non-therapeutic cannabis use in 2018, cannabis was a Schedule 4 substance under

the *Controlled Drugs and Substances Act* (CDSA). Researchers were required to apply for a CDSA Section 56 exemption which allowed them to obtain, store, and administer cannabis to study the effects in human subjects.

When Canada became the first G20 country to legalize adult cannabis use, researchers envisioned a new era. There was a potential that legal cannabis would lead to a framework that was analogous to the research framework for tobacco and alcohol. For instance, researchers can purchase commercially available nicotine and alcohol products, obtain research ethics approval, and administer these products to humans for research purposes. Curiously, researching legal cannabis is not subject to the same regulations. Researchers cannot purchase commercially available cannabis and administer it. Instead, industry is required to produce cannabis for research purposes which requires collaboration with a corporate cannabis producer (Rueda et al., 2022).

Another reported barrier is that most non-therapeutic research with cannabis meets the definition of a clinical trial. Clinical trials must be approved by Health Canada. The licensing process to conduct cannabis research with humans in Canada has been described by researchers "onerous" and "preventing us from rapidly getting research conducted" (Geary, 2019). A June 2022 search of Canada's clinical trial registry (clinicaltrials.gov) for cannabis interventions lists seven completed clinical trials since the registry went online in 1997.

The Canadian government recently began a consultation process following concerted effort from cannabis researchers advocating for revised policies (Canadian Researchers, 2021). In March 2022, the federal government released *Proposed implementation approach for non-therapeutic research on cannabis in humans* (Health Canada, 2022). The proposed legislation admits to the existing barriers to research and tries to reduce them with a new set of proposals.

Within the proposal are three levels of risk that studies will be categorized by. Researchers are incentivized by streamlined application processes to conduct their research in a way that keeps risk levels low. The proposal favors studies in which (a) the dose administered does not exceed what a participant would typically consume in a session, (b) the form of cannabis is typical of what the participant usually consumes, and (c) the route of administration is typical to the participant. This proposal is an opportunity to expand research studies across Canada.

Existing limitations of conventional cannabis administration paradigms are particularly salient in light of the profound expansion of access to legal cannabis for adults across North America. The landscape of cannabis use and access has changed dramatically over the past decade while human research paradigms have remained largely static. The disconnect mandates the development of new research paradigms for studying the acute effects of cannabis administration.

*Barriers to Recruiting Representative Samples*

It is essential that recruited participants are representative of the group that the findings are generalized to. Unfortunately, this is a common issue with research and one that limits the usefulness of findings. Bringing studies of cannabis use outside of the physical lab may enhance research validity by facilitating access to participation by more representative populations. Prior studies on the effects of cannabis on human behaviour have largely relied on samples in close proximity to the research centre, that is, student samples and/or individuals recruited from urban centers. These strategies facilitate recruitment and are often at lower cost to researchers (Hanel & Vione, 2016). Relying on these samples provoke concerns about the generalizability of findings (e.g., age, gender, ethnicity, education level). Indeed, marginalized groups (e.g., Black, Indigenous, People of Color) and PWUDS are often underrepresented in research that

may directly affect them. Recommendations to improve participation by these individuals that are germane to lab-based research include flexibility when scheduling appointments and reducing travel to a study sites, and addressing such factors has been deemed important for improving the equity and diversity related disparities in research (Batista et al., 2016). Enhancing efforts to recruit from populations that have been underrepresented can help address disparities and bring benefits to the larger community.

# CHAPTER 2 Cannabis and Cannabinoids

## 2.1 Pharmacokinetics of Cannabis Use

The ECS encompasses endocannabinoids and cannabinoid receptors (i.e., cannabinoid 1 and cannabinoid 2). The primary role of the ECS is to maintain homeostasis and it has been referred to as the "master regulator" for its role in the body's drive to "relax, eat, sleep, forget and protect (Di Marzo et al., 1998)." Plant-based and endogenous cannabinoids act as neuromodulators that alter the strength of signal transmissions between neurons (Marsicano & Lutz, 2006).

The cannabinoid THC is one of the primary active ingredients in cannabis and largely responsible for the pronounced psychoactive effects of the plant. Cannabinoids are lipid soluble and when taken orally are absorbed by the digestive system slowly. Although absorption can be facilitated by adding oil to the plant material before consumption, there is a considerable first-pass metabolism (Mattes et al., 1993). First-pass metabolism occurs when a drug gets metabolised at a specific location in the body that results in a reduced concentration of the active drug upon reaching its site of action (Herman & Santos, 2020). In most instances, this leads to abbreviation of therapeutic efficacy, but with THC conversion to 11-OH-THC, it seems to be equally or even more potent as a $CB_1$ agonist (E. Russo, personal communication, October 27, 2022). The effects of oral cannabis peak approximately one-and-a-half to three hours following ingestion and may last six to eight hours (Vandrey et al., 2017). Smoking or vaporizing cannabis is a much more efficient route of administration than oral ingestion. THC is absorbed through the lungs resulting in a rise in blood THC concentration that reaches maximum levels 10 minutes following inhalation (Spindle et al., 2019). The psychoactive effects may be felt within minutes and peak 30-to-60-minutes later.

Once cannabinoids enter the body, the metabolic process begins. THC is diffused into body fat which can accumulate from multiple use sessions and where it will remain for days to weeks until it is fully metabolized out of the body. In a study of frequent long-term cannabis users ($N$ = 25), researchers reported median plasma THC levels were <2mg/mL from day one through seven during seven days of monitored abstinence (Karschner et al., 2009). Trace amounts of THC can be found in the body for weeks to months following cessation of use. The excretion time is mediated by body fat content, and frequency and quantity of use prior to abstinence.

**2.2 Tolerance**

Prolonged exposure to cannabinoid agonists is associated with the development of tolerance. In animal studies, there is evidence of tolerance to the effects of euphoria, analgesia, motor inhibition, memory impairment, anxiety, increased appetite, and physiological effects such as tachycardia (González et al., 2005). Tolerance is also demonstrated in humans. Studies comparing types of cannabis users have demonstrated that frequent cannabis users tend to show less impairment when compared to infrequent users. Haney and colleagues have suggested that cannabis users may already be tolerant to the behavioral effects of cannabis prior to starting experiments and this may explain why cannabis administration sometimes demonstrates a minor effect on task performance (Haney et al., 1999). Indeed, frequent cannabis use (4x/week) was not associated with significant impairment in neurocognitive function or motor side-effects compared to infrequent users at the same dose (Desrosiers et al., 2015a; Ramaekers et al., 2009).

Tolerance is caused by neuroadaptive changes to the ECS in which $CB_1$ receptors are downregulated. This degree of change moderates the impairing effects of cannabis. Tolerance varies across domains, however the domains most impacted are some of the most clinically

relevant such as cognition and anxiety (Colizzi & Bhattacharyya, 2018b). Frequent users have demonstrated tolerance to increases in heart rate relative to occasional users, and occasional users reported increased ratings of anxiety while frequent users did not. Relative to occasional users, frequent users also demonstrated tolerance to the impairing qualities of cannabis administration on a task of divided attention and a critical tracking test (Ramaekers et al., 2009).

Tolerance is promptly lost upon cessation of cannabis use. Indeed, markers of tolerance disappear in the subsequent days to weeks. One study did not find any cortical indicators of tolerance after just two days of abstinence (D'Souza et al., 2016). However, other findings suggest that it may take two-to-four weeks of abstinence for the complete reversal and normalization of the ECS to occur (Hirvonen et al., 2012; Sim-Selley, 2003).

Published studies on the acute cognitive effects of cannabis use rarely distinguish between occasional and frequent users - those with and without tolerance to the impairing effects of cannabis. In a study of 11 occasional users (i.e., weekly use or less) and 14 frequent users (i.e., smoking more than 4 days/week), occasional users reported longer, and more intense subjective effects of smoked cannabis (6.8% THC) than frequent users did. Failing to account for tolerance is more than a methodological quirk. This decision may have serious implications for accurately assessing the impact of cannabis use.

The issue of tolerance also appears in studies of frequent users. In oft-employed study designs a prolonged washout period (i.e., 30 days) is required before participating. In such studies, participants recruited as frequent users will no longer rightly represent this group and may be more representative of occasional users. The theoretical rationale for a prolonged washout period is unclear and thus this research area lacks an agreed upon standard for the length of time a participant should remain abstinent before participating in cannabis research.

Although relatively benign and analogous to caffeine withdrawal, cannabis withdrawal symptoms (CWS) may begin to emerge within hours after last use (Jones et al., 1981a) and peak by three to four days following abstinence (Haney et al., 1999). Research designs may inadvertently be provoking CWS such as stomach pain, insomnia, and irritability (Bonnet et al., 2017). Indeed, prolonged abstinence from cannabis may represent a different cognitive state altogether when compared to regular, recent use (Martin et al., 2021).

Importantly, not all studies demonstrate tolerance to the effects of cannabis use among frequent users. This may be explained by differences in individual tolerable dose (Bhattacharyya & Sendt, 2012; Grotenhermen et al., 2007) such that some research protocols ask participants to administer more and/or different cannabinoid preparations than they are familiar with. This unfortunately may result in experienced users experiencing greater acute effects than they usually would in a typical use session.

### 2.3 Cannabis Chemovars

Studies examining the effects of cannabis use on human behavior should consider that characteristics of the cannabis plant itself can also impact the drug experience (Eadie et al., 2021b). The category of cannabis contains hundreds of biochemically diverse chemical varieties or *chemovars* with distinct cannabinoid profiles and concentrations (Piomelli & Russo, 2016). A given chemovar administered in a laboratory may vary considerably with regard to its similarity to the chemovar typically used by a given participant. The effects of cannabis are altered by factors beyond cannabinoid content (e.g., levels of THC and CBD). For example, aromatic chemical compounds called terpenoids may interact with cannabinoid content to alter the effects of cannabis and modify specific effects. The sheer diversity of cannabis available on the market reflects the diversity of product preference among consumers today. This is in stark contrast to

limited range of cannabinoid products typical of scientific studies (Bloor et al., 2008; E. Russo et al., 2002; Schwabe et al., 2019; Vergara et al., 2017).

### 2.4 Summary and Aims

In sum, there has been extensive research examining the association between cannabis use and cognition. Previous research has demonstrated a small-to-medium effect of ACU on cognition in naive users. These findings are often generalized to all cannabis users. However, the extent to which these findings appropriately generalize to naturalistic cannabis use among regular users is less clear. A myriad of methodological issues obscures the findings.

Individual factors such as tolerance, self-titration, preference for cannabis products and route of administration modify acute cannabis effects. If the most important question is to understand the acute cannabis effects on the individual, then it would be more appropriate to measure an individual's reaction to familiar cannabis used in a typical way. Using the individual as their own control could help to account for the many individual factors that can arise when studying a substance with diverse psychoactive effects.

Moreover, the contextual factors of set and setting produce extrapharmacological effects which might meaningfully interact with outcomes of interest. Research on the validity of cognitive assessments done in laboratory and clinical settings has identified marked increases in anxiety and internalized stigma which have shown to impair cognition. Taken together, the laboratory might be particularly ill-suited to capture the relationship between cannabis and cognition.

The present study sought to examine the association between naturalistic acute cannabis use and cognition in frequent cannabis users. A within-subject designs helped to account for the influence of individual differences and helped us to better approximate the impact of cannabis

use on each individual. This study extends previous lab-based studies on cannabis use and cognition by using the novel Naturalistic Cannabis Administration Protocol (NCAP). The NCAP is a low-barrier, easily adoptable and ecologically valid methodology to study acute cannabis effects. Participants self-administer their typical cannabinoid preparation via inhalation in a familiar environment and undergo a research paradigm.

*Feasibility and Acceptability*

When developing a novel methodology, it is important to assess the feasibility and acceptability of the methodology for its intended use. Feasibility is demonstrated when a project can practically achieve its desired aims (Rajadhyaksha, 2010b). Some aspects to assess for feasibility include regulatory and ethical challenges, the ability to recruit the desired target number of participants, and rate of attrition. Feasibility can be difficult to achieve in studies that include a cannabis administration component. As detailed above, researchers experience significant barriers obtaining approval for cannabis studies. Further, it may be difficult to incentivize participants in a region with easy access to cannabis in addition to requiring those individuals to use their own cannabis for the study. It is therefore critical to determine to what extent the NCAP was feasibly implemented before one can argue for broader adoption by other researchers for other outcomes of interest.

Feasibility is necessary but not sufficient when assessing whether a novel methodology should be implemented. Acceptability reflects the extent to which people administering or participating in the methodology consider it to be appropriate. Some metrics of acceptability include participant and researcher burden, reasons for discontinuation, perceived effectiveness, ethicality, and self-efficacy (Sekhon et al., 2017). The present study assesses the degree to which the NCAP was deemed acceptable by the research team and participants.

Finally, while there exists a large body of experimental research on ACU and cognition, few studies have examined naturalistic cannabis use on cognition. This project produced findings which may be more generalizable than typical lab-based approaches. Moreover, demonstrating the feasibility and acceptability of the NCAP will equip researchers with methodology designed to produce an ecologically valid assessment of acute cannabis effects across a range of outcomes. The study has the following aims:

**Primary aim:** To assess the impact of naturalistic cannabis use on cognition among frequent users.

**Hypothesis 1.** Acute cannabis effects will produce a difference in an individual's immediate and delayed verbal recall memory when compared to a no-cannabis condition.

**Hypothesis 2.** Acute cannabis effects will produce a difference in an individual's processing speed when compared to a no-cannabis condition.

**Hypothesis 3.** Acute cannabis effects will produce a difference in an individual's verbal fluency when compared to a no-cannabis condition.

**Hypothesis 4.** Acute cannabis effects will produce a difference in an individual's working memory and attention when compared to a no-cannabis condition.

**Secondary aim:** Exploratory supplementary analyses will characterize the feasibility and acceptability of the NCAP.

# CHAPTER 3 Methods

## 3.1 Participants

A power analysis was conducted using G*Power to identify the appropriate sample size for the present study. Prior studies evaluating the relationship between cannabis and cognition generally reported small-to-medium effects ($d$ = 0.20 - 0.50). The analysis suggested that to observe an effect in this range, a sample of 30 participants would provide sufficient power to find a within-subjects effect (Wolf et al., 2013).

The study was approved by the University of British Columbia Institutional Review Board (H20:01443). Participants were recruited from a listserv of students that indicated they used cannabis at least weekly and were interested in participating in psychological research. Participants were emailed an invitation to participate in the current study and provided informed consent during the first meeting. They were compensated $20 (CAD) for their time after their final appointment.

The criteria for inclusion were:

1. Between 19 and 50 years old.
2. Used cannabis on average at least 3 times per week in the past month.
3. No daily nicotine used in the past 3 months.
4. Not pregnant.
5. Not receiving treatment for psychotic disorder or bipolar disorder.
6. Proficient at reading and speaking English.
7. Ability to consume cannabis via inhalation for the study appointment.

### 3.2 Procedure

Participants were scheduled via email and provided the consent form to review so that they could provide verbal consent during the video session. To maintain typical levels of tolerance, participants were asked to book their appointment at the time when they typically first use cannabis during the day and to refrain from cannabis use only prior to the appointment time during the day of the appointment. Upon presenting to the appointment, the research assistant instructed the participant to consume their own cannabis in the same quantity as during a typical use session in non-technical terms, i.e., "get as high as you would normally get." Cameras were turned off for five minutes to allow for a naturalistic administration and reduce psychological factors (e.g., anxiety) that may be present when being observed. After five minutes had passed, cameras were turned back on and the session resumed with a brief survey querying demographics such as age, gender, and education level as well as characteristics of the participant's cannabis use including amount, chemovar, and method of consumption. These questions were then followed by a battery of cognitive tasks.

A within-subjects design was used to help control for individual differences. The appointments were counterbalanced (cannabis use during first session vs. cannabis use during second session). Both appointments, scheduled one month apart, occurred at the same time of day to account possible for diurnal effects (i.e., morning, afternoon, or evening). See the Appendix for the detailed Naturalistic Cannabis Administration Protocol.

### 3.3 Cognitive Outcomes

A graduate research assistant administered a cognitive battery that assessed across five cognitive domains that have been associated with cannabis use (e.g., Eadie et al., 2021). These domains were: learning, verbal recall, processing speed, working memory, and verbal fluency.

**California Verbal Learning Test-3 (CVLT-3; Delis et al., 2017).** The CVLT-3 evaluates learning of 16 words over five trials as well as long-term retention and retrieval following a 20-minute delay. The words can be organized into four categories to aid in learning and recall. An interference trial of 16 words is administered directly following the five learning trials. An Alternate Form mirrors the CVLT-3 Standard Form and can be used during repeat assessments to reduce practice effects. An estimation of an individual's immediate verbal recall was assessed with the Trials 1-5 Sum of Scaled Score. I supplemented the analyses with the secondary, more conservative, index of learning based on the Trial 5 Scaled Score. Delayed verbal recall memory was assessed with Delayed Recall Correct Sum of Scaled Scores.

**Symbol Digit Modalities Test (SDMT; Smith, 1991).** The SDMT involves a substitution task in which an individual is given 90 seconds to pair specific numbers with corresponding geometric figures according to a reference key. The results provide an estimation of an individual's processing speed.

**Auditory Consonant Trigrams (CCC; Peterson & Peterson, 1959).** The CCC involves verbally presenting three consonants and then asking the individual to recall the sequence following a delay (e.g., 3, 9, 18 seconds). During the delay, the individual performs a distractor task where they count backwards from a specific number by threes. The results provide an estimation of an individual's working memory ability.

**Controlled Oral Word Association Test (COWAT; Spreen & Benton, 1977).** The COWAT, also known as the F-A-S, consists of three conditions in which an individual is required to provide as many words as possible for a specific letter (i.e., F, A, or S) within a 1-minute period. Individuals are instructed to exclude proper nouns, numbers, and the same word with a different suffix. There is an optional trial assessing the generation of a list of animals within a one-minute

period. The results provide an estimation of an individual's phonetic and categorical verbal fluency.

The order of tests in the battery remained the same for both sessions. An alternate version of the CVLT-3 was used during Session Two. The test battery was administered by two doctoral students in clinical psychology who recorded the participants verbal responses. Participants worked with the same research assistant across their appointments.

Cognitive assessments have traditionally been administered face-to-face with pencil-and-paper tests. However, over the last four decades, computerized cognitive assessment tools increased in popularity (Sternin et al., 2019). These tools reduced administration time and errors and thereby increased the validity of the assessment. With the proliferation of personal computers over the last two decades, it became possible for patients to complete these assessments from home. Concerns about responding to crises and issues with security and confidentiality limited widespread adoption (Sampaio et al., 2021). When COVID-19 reduced contact between psychologists and clients, advancements in virtual neuropsychological assessments occurred and confidence in this alternative mode of delivery increased (Watt et al., 2021).

### 3.4 Feasibility and Acceptability

There are a broad range of factors that can be assessed to determine the feasibility of a study (Rajadhyaksha, 2010a) and studies vary widely in their assessment of feasibility. For example, one recent study simply assessed feasibility with patient-rated subjective intensity of drug effects on a 0–1 scale (Carhart-Harris et al., 2016). The present study attempted to comprehensively examine feasibility across two broad domains which contained seven different aspects.

The feasibility of the NCAP was measured across two domains: *Protocol* and *Participant.* In order to characterize the feasibility of the NCAP, descriptive statistics and frequencies were conducted. The four aspects measured within the Protocol domain included: whether the target number of participants was recruited (yes/no) and if not, how close did the study get to achieving the recruitment goal (%), ability to schedule all participants during a time when they typically first used cannabis (%), number of deviations from the protocol as documented by research staff, and the nature of any ethical and/or regulatory challenges.

The three aspects measured in the Participant domain included: number of participants declining to participate due to requirement they administer cannabis via inhalation, percentage of participants that brought their own cannabis to the session, and adherence to cannabis administration instructions measured with responses to “How high are you compared to when you usually get high?” on a three-point Likert scale from "less high than usual" to "higher than usual."

Acceptability was measured by determining if the rate of attrition was acceptable and determining if the reasons for discontinuing were due to the study methodology or an unrelated factor. Following both experimental sessions, participants rated the acceptability of the home-based administration by rating if they would have felt "more comfortable," "the same," or "less comfortable" had they completed the study in a traditional laboratory setting. Participants were initially permitted 5-minutes to ad libitum cannabis and were instructed they could take longer if needed.

### 3.5 Missing Data

Five participants completed only their first appointment and were excluded from all analyses.

### 3.6 Analytic Plan

Repeated-measures analysis of variance (ANOVA) was used to examine differences between the two experimental conditions (i.e., cannabis use versus no cannabis use) and normative data. ANOVA was used to assess for differences which could be due to the order of sessions. Repeated-measures multivariate analysis of variance (MANOVA) were conducted to derive an omnibus statistic on the relationship between cannabis use and the combined cognitive domains. Results were examined across gender. Frequency distributions and descriptive statistics were used to characterize participants. Binary logistic regression was used to determine if subjective performance appraisal (worse vs. same/better) was predictive of objective assessment results for each cognitive test following acute cannabis use.

### 3.7 Hypothesis Testing

#### Primary aim

**Hypothesis 1** Repeated-measures ANOVA was used to determine if acute cannabis effects were associated with a difference on a measure of immediate and delayed verbal recall memory when compared to a no-cannabis condition. Gender and was included to examine possible interaction effects.

**Hypothesis 2** Repeated-measures ANOVA was used to determine if acute cannabis effects were associated with a difference on a measure of processing speed when compared to a no-cannabis condition. Gender was included to examine possible interaction effects.

**Hypothesis 3** Repeated-measures ANOVA was used to determine if acute cannabis effects were associated with a difference on a measure of verbal fluency when compared to a no-cannabis condition. Gender was included to examine possible interaction effects.

**Hypothesis 4** Repeated-measures ANOVA was used to determine if acute cannabis effects were associated with a difference on a measure of working memory and attention when compared to a no-cannabis condition. Gender was included to examine possible interaction effects.

**Secondary aim** Feasibility was assessed by examining frequency distributions for the aspects captured within the Protocol and Participant domains and then comparing to the protocol. Acceptability was assessed by examining frequency distributions and any participant or researcher comments about the study protocol.

# CHAPTER 4 Results

## 4.1 Sample

Assumptions for repeated-measures ANOVA were examined. Data from the cognitive assessment met assumption of independence. Shapiro-Wilk test showed that during the cannabis use appointment the CCC departed from normality $W(28) = 0.92$, $p = .03$. All other data were normally distributed.

A university sample of 252 participants were contacted for the study. Thirty-three cannabis users (i.e., use at least 3 times per week) completed Session One. Five participants failed to complete Session Two. One participant discontinued due to poor internet connection, and another travelled to their home country where cannabis use was prohibited. Three participants failed to present to their second session without explanation therefore a rate 10% of attrition was observed. Analyses were conducted with the remaining 28 participants ($M_{age}$ = 21.82, $SD$ = 2.26) for which complete data were available. Most participants (57.2%) reported using cannabis five or more days per week (see Table 1). Participants were queried regarding their subjective high, chemovar familiarity, and point of access for cannabis used for the study (Figure 1). Logistic regression did not reveal any effect of chemovar familiarity on cognitive outcomes (Table 2).

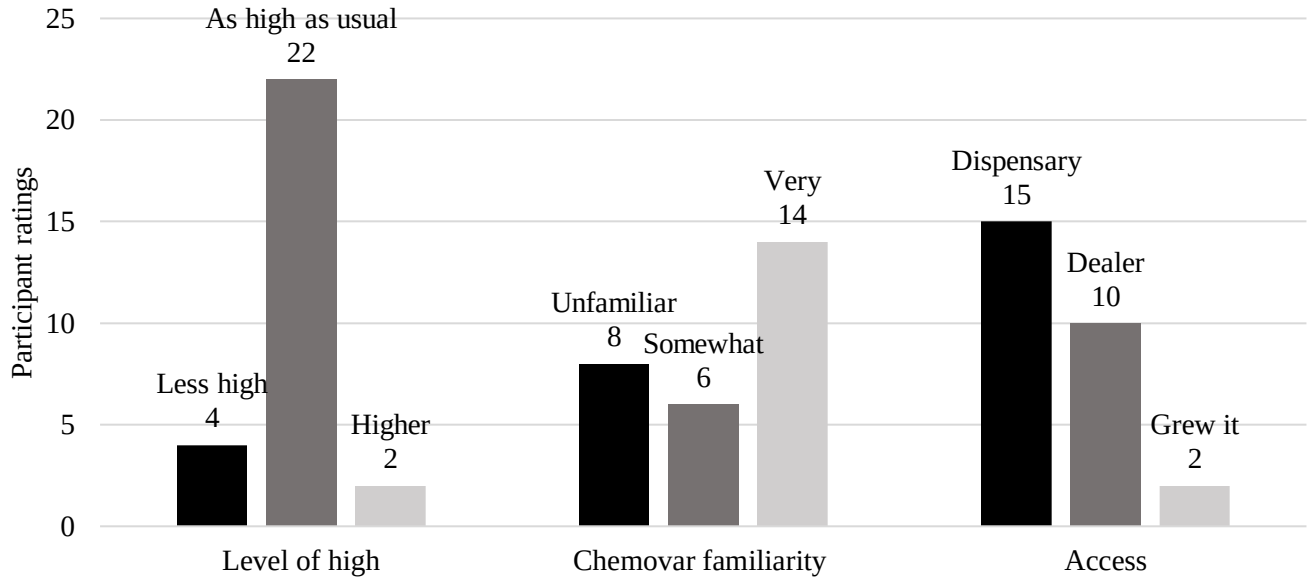
**Table 1**

*Sample Characteristics*

| | % (*n*) |
|---|---|
| Full sample | 100 (28) |
| Female | 53.6 (15) |
| Ethnicity | |
| White | 71.4 (20) |
| Asian | 14.3 (4) |
| Indigenous | 7.1 (2) |
| Latinx | 3.6 (1) |
| Quantity of cannabis used per week | |
| <3.5 grams | 71.4 (20) |
| >3.5 grams | 21.5 (6) |
| Primary method of use | |
| Pipe/Bong | 42.9 (12) |
| Joints | 32.1 (9) |
| Vaporizer | 25 (7) |
| Years of education | *M* = 15.79, *SD* = 1.33 |
| Age first used cannabis | *M* = 16.21, *SD* = 2.04 |

**Figure 1**

*Cannabis Characteristics*



*Note.* Level of high = "How high are you compared to when you usually get high?" Chemovar familiarity = "How familiar are you with the cannabis you used?" Access = "Where did you get the cannabis from?"

**Table 2**

*Logistic Regression Examining Chemovar Familiarity and Cognitive Outcomes*

| Domain | *OR* | *SE* | *p* |
|---|---|---|---|
| Immediate Verbal Recall | .94 | .04 | .13 |
| Delayed Verbal Recall | .98 | .05 | .57 |
| Processing Speed | .99 | .02 | .72 |
| Working Memory | 1.05 | .12 | .70 |
| Verbal Fluency | 1.06 | .04 | .13 |
| Categorical Verbal Fluency | 1.07 | .19 | .55 |

*Note.* Chemovar familiarity dichotomized and included as the dependent variable.

### 4.2 Cognitive Assessment

Most participants ($n$ = 21; 75%) felt that cannabis affected their cognitive assessment performance (see Figure 2). Many participants ($n$ = 13) reported that acute cannabis effects resulted in performing worse than they would have if they had not used cannabis. Among those that felt their performance was negatively impacted, eight used cannabis during their first appointment and five used cannabis during their second appointment. Binary logistic regression did not reveal any association between subjective performance appraisal (worse vs. same/better) and objective assessment results following acute cannabis use (Table 3). MANOVA results revealed equivalent cognitive performance between sessions ($F(1, 5) = .91$, $p = .35$, $\eta_p = .03$).

**Figure 2**

*Subjective Performance Appraisal*

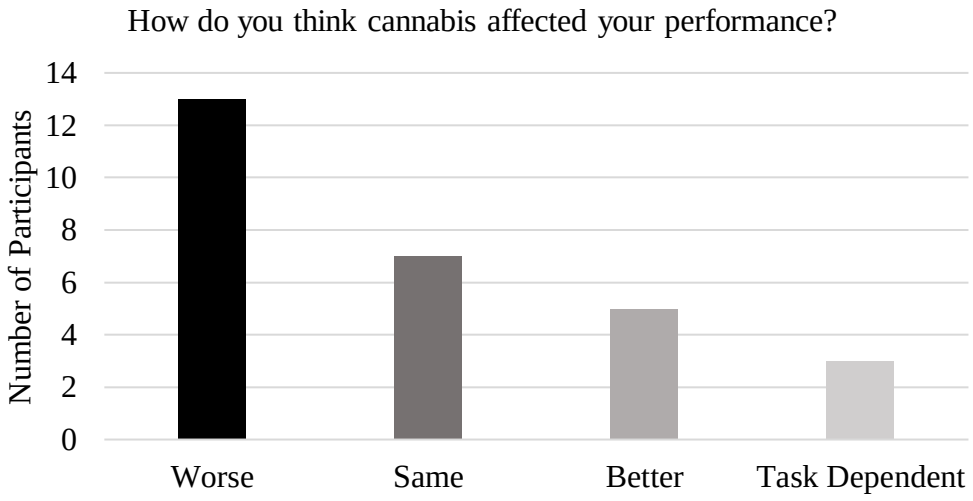



**Table 3**

*Relationship Between Subjective Performance and Cognitive Outcomes*

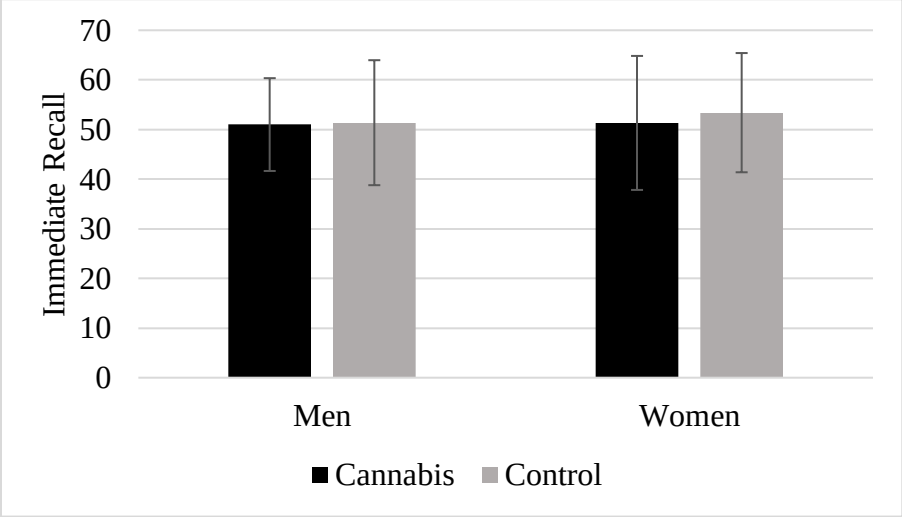
| Domain | *OR* | *SE* | *p* |
|---|---|---|---|
| Immediate Verbal Recall | 1.05 | .04 | .21 |
| Delayed Verbal Recall | 1.00 | .04 | .98 |
| Processing Speed | 1.08 | .04 | .06 |
| Working Memory | 1.08 | .12 | .51 |
| Verbal Fluency | 1.02 | .04 | .57 |
| Categorical Verbal Fluency | 1.10 | .13 | .46 |

**Hypothesis 1.** Acute cannabis effects were not associated with a difference on a measure of immediate verbal recall ($F(1, 27) = .28$, $p = .60$, $\eta_p^2 = .01$; see Figure 3) or delayed verbal recall ($F(1, 27) = 2.73$, $p = .11$, $\eta_p^2 = .10$; see Figure 4). There were no gender differences (Table 5).

Although a normative dataset was not available from the test publisher, raw scores were scaled and did not differ from the mean. There was no evidence of an order effect for immediate verbal recall ($F(1, 27) = .83$, $p = .37$) or delayed verbal recall ($F(1, 27) = .07$, $p = .79$).

**Figure 3**

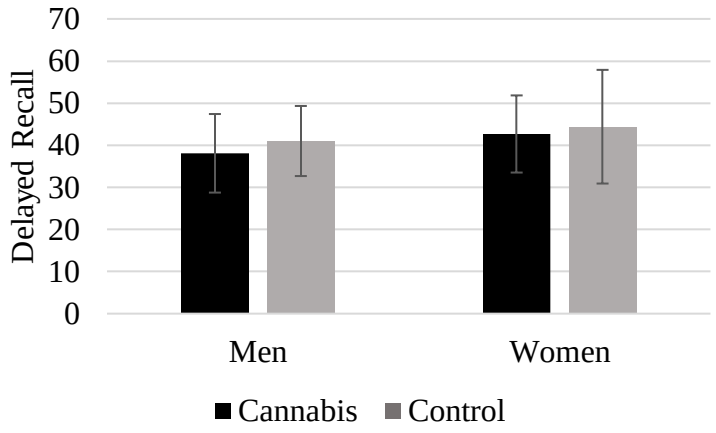
*Immediate Verbal Recall Scores by Gender and Condition*




*Note.* Immediate verbal recall = CVLT-3 Trials 1-5 Correct Sum of Scaled Scores.

**Figure 4**

*Delayed Verbal Recall Scores by Gender and Condition*

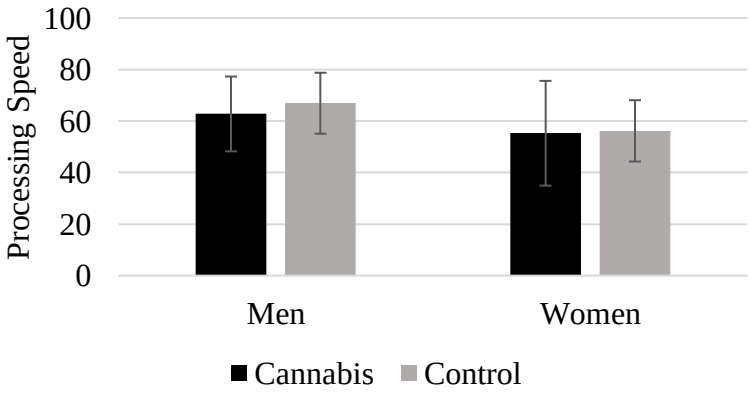



*Note.* Delayed verbal recall = CVLT-3 Delayed Recall Correct Sum of Scales Scores.

**Hypothesis 2.** Acute cannabis effects were not associated with a difference on a measure of processing speed $F(1, 27) = .88$, $p = .36$, $\eta_p^2 = .03$ (See Figure 5). There were no gender differences (Table 5). There was no evidence of an order effect ($F(1, 27) = .63$, $p = .44$).

**Figure 5**

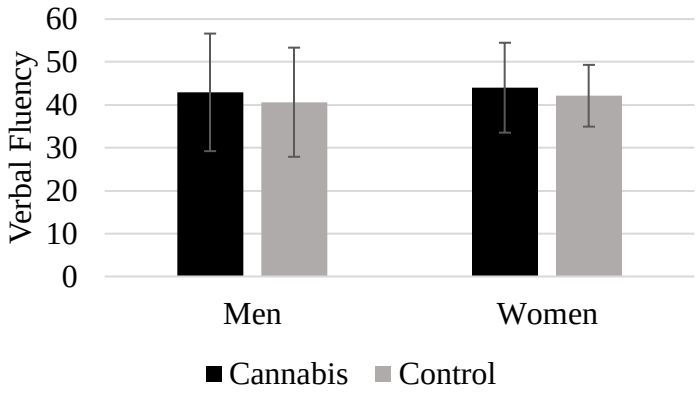
*Processing Speed Scores by Gender and Condition*



**Hypothesis 3.** Acute cannabis effects were not associated with a difference on measures of verbal fluency (phonemic verbal fluency $F(1, 27) = 1.62$, $p = .22$, $\eta_p^2 = .06$ or categorical verbal fluency $F(1, 27) = 1.34$, $p = .26$, $\eta_p^2 = .05$; See Figures 6 and 7). There were no gender differences (Table 5). There was no evidence of an order effect for phonemic verbal fluency ($F(1, 27) = .04$, $p = .84$) or categorical verbal fluency ($F(1, 27) = .00$, $p = .99$).

**Figure 6**

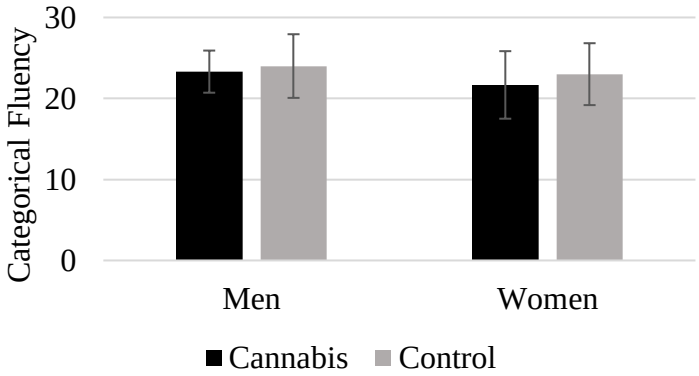
*Phonetic Verbal Fluency Scores by Gender and Condition*




*Note.* Phonetic verbal fluency = sum of F-A-S trials.

**Figure 7**

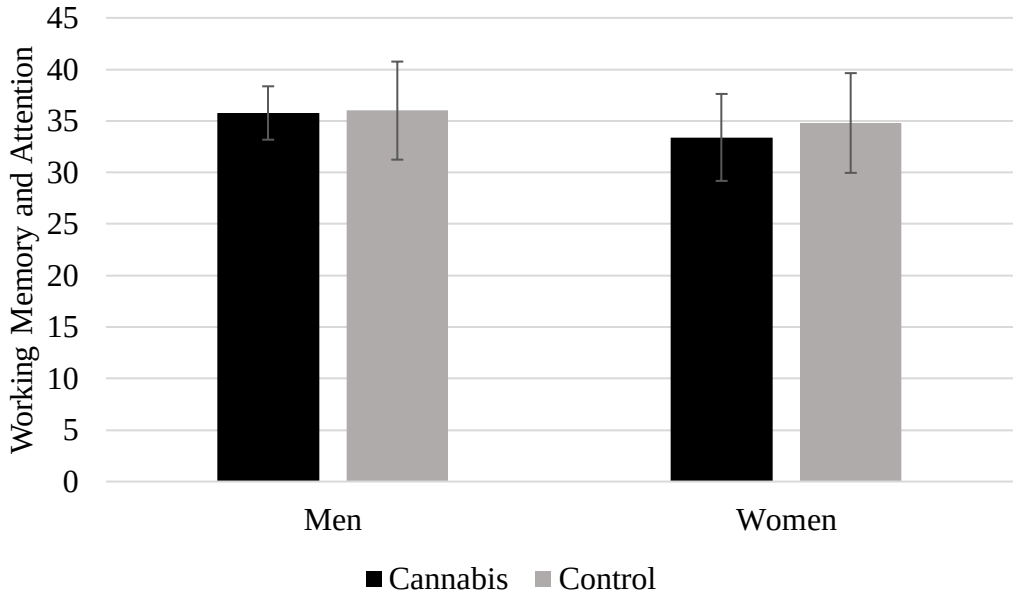
*Categorical Verbal Fluency Scores by Gender and Condition*



**Hypothesis 4.** Acute cannabis effects were not associated with a difference on a measure of working memory and attention $F(1, 27) = .60$, $p = .45$, $\eta_p^2 = .02$ (See Figure 6). There were no gender differences (Table 5). There was no evidence of an order effect ($F(1, 27) = 1.50$, $p = .23$).

**Figure 8**

*Working Memory and Attention Scores by Gender and Condition*




*Note.* Score is the sum of CCC [3-,9-, and 18-second delay] trials.

**Table 4**

*Comparing Means Between Conditions and Normative Data*

| | Control | Cannabis | Normative Data | | |
|---|---|---|---|---|---|
| | *M (SD)* | | *N* | *M* (*SD*) | *F*(1, 27) |
| CVLT-3 Recall | 52.46 (12.09) | 51.29 (11.55) | - | 50 (15.0) | - |
| CVLT-3 Trial 5 | 11.07 (2.68) | 9.75 (3.17) | - | 10 (3.0) | - |
| CVLT-3 Delay | 42.82 (8.12) | 40.54 (9.36) | - | 40 (12.0) | - |
| CVLT-3 LDFR | 10.25 (2.37) | 10.61 (2.64) | - | 10 (3.0) | - |
| CCC 3 | 13.32 (1.56) | 12.96 (1.73) | - | - | - |
| CCC[a] 9 | 11.40 (2.19) | 11.46 (2.12) | - | 12 (2.2) | 0.65, $p = .53$ |
| CCC[a] 18 | 10.68 (2.42) | 10.07 (1.74) | - | 11.4 (2.8) | 2.23, $p = .11$ |
| CCC[a] Total | 35.36 (4.75) | 34.50 (3.70) | - | - | - |
| SDMT[b] | 61.17 (14.03) | 58.75 (17.05) | 1241 | 64.90 (9.89) | 1.34, $p = .26$ |
| FAS[c] | 41.43 (9.97) | 43.50 (11.86) | 242 | 44.7 (11.2) | 0.63, $p = .54$ |
| Animals | 23.46 (3.83) | 22.43 (3.56) | 78 | 21.9 (5.4) | 0.94, $p = .40$ |

*Note.* CVLT-3 Recall = Trials 1-5 Correct Sum of Scaled Scores; CVLT-3 Delay = Delayed Recall Correct Sum of Scales Scores; CVLT-3 LDFR = CVLT-3 Long Delay Free Recall; Normative Data for CVLT derived from Scaled Scores; CCC = Auditory Consonant Trigrams; CCC Total = sum of 3-,9-, and 18-second delay trials; SDMT = Symbol Digit Modalities Test; a = Ages 16-29 from Stuss et al., 1988; b = Ages 20-24 from Jorm et al., 2004; c = Ages 16-59 with 13-21 years of education from Tombaugh et al., 1999.

**Table 5**

*Repeated-Measures ANOVA Examining Differential Gender Effects*

| | Male Control | Male Cannabis | Female Control | Female Cannabis | Main Effect | Interaction |
|---|---|---|---|---|---|---|
| | *M (SD)* | | | | *F*(2, 26) | *F*(2, 26) |
| CVLT Recall | 51.38 (12.59) | 51.00 (9.35) | 53.40 (12.01) | 51.33 (13.50) | 0.28, $p = .60$ | 0.12, $p = .73$ |
| CVLT-3 Trial 5 | 10.69 (2.81) | 10.76 (2.74) | 11.40 (2.61) | 8.87 (3.34) | 2.84, $p = .10$ | 3.21, $p = .09$ |
| CVLT Delay | 41.00 (8.32) | 38.08 (9.33) | 44.40 (7.87) | 42.67 (9.16) | 2.73, $p = .11$ | 0.18, $p = .68$ |
| CVLT-3 LDFR | 9.54 (2.37) | 10.00 (2.16) | 10.87 (2.26) | 11.13 (2.97) | 0.74, $p = .40$ | 0.05, $p = .82$ |
| CCC Total | 36.00 (4.76) | 35.77 (2.59) | 34.80 (4.84) | 33.40 (4.22) | 0.60, $p = .45$ | 0.31, $p = .58$ |
| SDMT | 66.92 (14.52) | 62.77 (11.82) | 56.20 (11.90) | 55.27 (20.32) | 0.88, $p = .36$ | 0.35, $p = .56$ |
| FAS | 40.62 (12.72) | 42.92 (13.70) | 42.13 (7.20) | 44.00 (10.48) | 1.62, $p = .22$ | 0.02, $p = .89$ |
| Animals | 24.00 (3.93) | 23.31 (2.60) | 23.00 (3.82) | 21.67 (4.17) | 1.34, $p = .26$ | 0.13, $p = 72$ |

*Note.* CVLT Recall = Trials 1-5 Sum of Scaled Score; CVLT Delay = Delayed Recall Correct Sum of scaled scores; CVLT-3 LDFR = CVLT-3 Long Delay Free Recall; CCC = Auditory Consonant Trigrams; SDMT = Symbol Digit Modalities Test.

### 4.4 Feasibility

In terms of feasibility within the Protocol domain, the recruitment target was initially met with 33 participants. Despite achieving the recruitment target of 30 participants, five failed to complete the second session. All participants were successfully scheduled during a time when they typically first used cannabis. Most participants used cannabis in the evening and the study accommodated these individuals by scheduling appointments as late as 8:30pm. Consistent with the protocol, research assistants and participants met from their respective homes for the study. There were three documented instances of poor internet connection, and this led one participant to drop out due to technical issues which they attributed to sharing internet bandwidth with roommates. The neuropsychological testing conducted included some timed tests sensitive to disruption or delay, however only 1% of administered measures were invalidated because of connection issues. All participants consented prior to participating and were able to accept payment for participation via e-transfer.

Within the Participant domain, only one prospective participant declined to participate due to the requirement they administer cannabis via inhalation. All participants presented to the cannabis session with their cannabis prepared in their typical way. The majority (79%) of participants indicated that they experienced typical acute cannabis effects following cannabis administration.

### 4.5 Acceptability

In terms of acceptability, only four participants reported that they would have been more comfortable completing the session at the university laboratory and reasons included discomfort using cannabis in proximity to parents and distractions in their home environment. Both psychological comfort (i.e., not comfortable being high on campus or in a research lab) and

physical comfort (i.e., comfortable clothing, furniture, and blankets) were identified as factors preferring a home environment. Eight participants reported equivalent comfort level conducting the study at-home and in-person in a laboratory. The majority ($n$ = 16) preferred the NCAP which allowed them to participate in the study from home. A five-minute cannabis self-administration window was well tolerated by participants and only one participant asked for more time so that they could walk to and from an outdoor smoking section.

# CHAPTER 5 Discussion

## 5.1 Discussion of Cannabis Use and Cognition Findings

The primary aim of the current study was to assess for differences in cognitive performance across five domains following naturalistic cannabis administration. Specifically, whether measures of learning, verbal recall, processing speed, working memory, and verbal fluency were affected by ACU in a sample of frequent users. Individuals that reported using cannabis at least three times a week produced equivalent results across two cognitive assessments. Moreover, the results were within normal limits when compared to the available normative data.

While there is a fairly consistent trend demonstrating a small-to-medium effect of ACU on cognition among naive users, the present study suggests that results may not generalize to frequent users. This sub-group of near daily users were characterized by patterns of greater quantity and frequency of use. If cannabis use was associated with marked cognitive impairment, this group would likely experience the most significant negative consequences due to these patterns.

One possible explanation for these divergent findings is that cannabis users develop tolerance to the cognitive impairing effects of cannabis (Haney et al., 1999; Jones et al., 1981). Findings from the present study are consistent with results from a recent meta-analysis that examined differences between naive and frequent users. Alterations in cognitive performance following ACU were no longer present when data were limited to individuals that used cannabis weekly or more (McCartney et al., 2021).

The present study's cannabis administration protocol diverges in important ways from other cannabis administration paradigms. Participants are often required to consume a standardized dose of cannabis regardless of whether it differs from their usual dose. Findings from the present study suggest that when users ad libitum cannabis, they are experienced enough to titrate their dose in a way that enables them to perform equivalent to a no-cannabis assessment. Indeed, recent research using a similar ad libitum instruction ("smoke as you would at home to get high") found no differences in driving performance or THC blood concentration between a 5.9% THC joint and a 13.4% THC joint. These findings support the hypothesis that experienced users can self-titrate to achieve familiar impairment levels (Marcotte et al., 2022).

Another possible reason for the surprising findings may be explained by the setting in which the study was conducted. Although some lab-based studies have demonstrated that cannabis use is associated with cognitive impairment, these environments are known to produce extrapharmacological effects that can alter cognition via factors such as anxiety, expectancy, and self-stigma. Previous research by Looby and Earlywine (2010) suggested that the link between ACU and cognitive impairment is more easily attributed to psychological factors such as stereotype threat. Cannabis users may assume that others believe they will be impaired by ACU and this in turn causes them to perform in a way that is consistent with this belief. To reduce stereotype threat in the present study, research assistants used colloquial language, such as “get as high as you would normally get,” and adopted language used by each respective participant (e.g., referring to their cannabis dose as a "hit" or "bowl").

Interestingly, the majority of participants reported a perceived difference in performance between conditions. A small number of participants felt that cannabis had improved their performance whereas most reported that cannabis use had impaired their performance. Despite

the presence of perceived deficits, analyses did not reveal a difference across any outcome. This phenomenon was also unaffected by the order of appointments. One possible interpretation of this finding is that participants experienced self-stigma regarding their cannabis use and consistent with prior research viewed themselves more negatively as a result of their cannabis use (Mikos & Kam, 2019) rather than due to their objective cognitive performance.

Some studies have suggested that the subjective effects of cannabis differ between chemovars. In the present study, nearly 30% of participants indicated that they were unfamiliar with the chemovar they chose to use. Interestingly, chemovar familiarity was not associated with differences in cognitive performance. Questions remain as to whether different cannabis chemovars produce divergent effects on cognition.

*Implications of Cognitive Results*

These findings are especially important for individuals using cannabis daily for therapeutic purposes. Patients are regularly assessed for their capacity to complete instrumental activities of daily living (IADLs), such as managing medicine, transportation needs, preparing meals, and managing finances. Commonly prescribed medications such as benzodiazepines have been shown to limit IADLs (Carrière et al., 2015). As such, physicians have questioned whether cannabis might also impair a patients' capacity to meet their IADLs (Crean et al., 2011). The present findings may help to relieve the concerns of patients and health care providers. Cognitive domains associated with memory, communication, and processing speed were unaffected by ACU.

Other studies have claimed that long-term cannabis use is associated with modest cognitive declines (Figueiredo et al., 2020). However, in the present study among educated young adults no deficits were demonstrated between the no-cannabis cognitive assessment and

normative data. This has increased implications given the high rate of cannabis use among university-aged individuals and the significant cognitive demands of university coursework.

Findings from the present study do not support the hypothesis that ACU leads to cognitive impairment in frequent users with established tolerance. Rather it calls into question previous research that has found such a link. Lab-based research works under the assumption that it is necessary and possible to eliminate variance in the data by creating a sterile environment in which to collect data. Thus, in an attempt to increase internal validity, external validity is compromised. A growing body of research suggests that this paradigm is inappropriate when it is applied to the clinical use and research of psychoactive drugs due to the influence of extrapharmacological effects on the drug experience. Paradoxically, past research has potentially introduced a confound to ecologically validity by researching cannabis in the laboratory.

### 5.2 Discussion of Feasibility and Acceptability Findings

The secondary aim of this study was to assess the feasibility and acceptability of a novel cannabis administration methodology in a university sample. Results from this study indicated that the NCAP was feasible for both the research team and participants. Study recruitment occurred during a time when in-person research activities were suspended due to COVID-19. Despite various waves of lockdowns due to the pandemic, NCAP research activities were unaffected. Participants demonstrated adequate technological literacy and bandwidth to complete the study virtually. Participants were more comfortable completing this study in a home environment versus a laboratory-based cannabis administration setting. Cannabis is most commonly used via inhalation, and this was deemed an accepted route of administration by all participants.

*Implications of NCAP*

The NCAP reduces temporal, logistic, and financial barriers to conducting cannabis research by eliminating the need for researchers to apply for federal licenses to access, store, and subsequently destroy cannabis. Participant barriers were reduced while increasing factors that encourage participation such as comfort, familiarity, and convenience. Reducing these barriers provides access to potential participants in any location and increases the likelihood of participation from underrepresented rural and remote populations. Asking participants to self-administer cannabis in their own home addresses the often-cited safety concerns of driving after cannabis consumption (Ogourtsova et al., 2018). Finally, the required research equipment is minimal and limited to a private space, a computer, and reliable internet connection and thus reduces experimenter barriers. Equipping researchers with improved methodology will help to combat stigma or other extrapharmacological factors that are inaccurately attributed to cannabis use. This finding has important implications for studies assessing the impacts of cannabis use on human behavior. Given the robust effect of factors such as the white-coat effect, anxiety, and stereotype threat on performance, future studies must consider the impact of their respective cannabis administration protocols on research findings and ultimately on the participant experience.

In recent years, there has been increased attention given to designing studies that are participant centred. Factors which centred participants in research include, increased flexibility with protocols, accommodating appointments outside of regular business hours and engaging with groups of interest to develop research measures that accurately capture outcomes of interest (Gross & Fogg, 2001). Participant centred research has many benefits. Improved external validity will lead to findings with greater clinical significance and ultimately improved

generalizability to real-world contexts. Moreover, participation from individuals outside of academic institutions may be more interested in participating thus increasing representation from often more difficult to reach groups such as PWUDs (Batista et al., 2016).

### 5.3 Limitations

There are several limitations with the study's cannabis administration methodology. In order to meet with researchers virtually, participants needed to possess a moderate understanding of computers and web-conference software such as Zoom. This may limit the generalizability of the NCAP to other groups with less technological literacy. However, a recent study demonstrated the use Zoom for cognitive assessments of acute cannabis use in a community sample (Cuttler et al., 2021).

In contrast to lab-based studies, we were not able to directly verify the quantity of cannabis consumed and relied on self-report. This study instructed participants to "get as high as they would normally get" and relied on self-report of acute cannabis effects. It is possible that some participants chose to not use as much cannabis as they typically would and therefore did not experience the same degree of acute cannabis effects which they typically might have. Balancing ecological validity with standardization is imperative, as such, this protocol may be best suited to a within-subjects design unless additional parameters are put in place to ensure consistency across participant level of acute cannabis effects. In the future, research staff could visually confirm the quantity of cannabis consumed by each participant.

A limitation of using a repeated-measures design is the phenomenon of practice effects which are improvements in cognitive test performance due to repeated exposure to the test. In the present study, practice effects were mitigated by scheduling appointments a minimum of 30 days apart. The CLVT-3 has a standard and an alternative protocol which were used for this study and

allowed us to present a different list of words in each of the two appointments. Despite attempts to mitigate practice effects with a month-long retest interval, and use of available alternate forms, the appointments were also counterbalanced such that some participants used cannabis in their first appointment while some used it during their second appointment. There was no evidence of an association between the order of appointments and outcomes of interest.

The study assessed select cognitive domains that are often examined in studies on cannabis. However, this study only assessed five cognitive domains and it is possible that we did not assess other domains in which cannabis is impairing. Additionally, there may be more sensitive and comprehensive measures to assess for differences in cognition. However, these objectives need to be considered in terms of participant time and energy. Finally, this study made efforts to reduce extrapharmacological factors such as stigma, stereotype threat, and expectancies. Our findings would have been strengthened with the inclusion of validated measures to capture these factors. Without such measures, we can only conjecture about whether we achieved our goal of reducing these factors with the NCAP.

### 5.4 Future Directions

There are a number of important considerations for future research. A key question remains as to whether cognitive effects differ between a lab-based setting when compared to those assessed with the NCAP. Future research should extend the current findings by comparing acute cannabis effects on cognition at-home and in the laboratory. Findings would also help to better characterize the preference of research setting rather than relying on participants to predict their comfort about a setting they were not assessed in. Given that the effect size of cannabis on cognition appears to be small among frequent users, future research should also strive to recruit more participants in order to have increased power to find effects.

Previous studies on the cognitive effects of cannabis use should be replicated with the NCAP to determine the generalizability of this novel approach. Examining the feasibility of the NCAP in other age groups may identify a need for additional protocol steps, such as familiarizing participants with the videoconferencing platform before the study. Adopting the NCAP procedure stands to reduce barriers for both researchers and participants and develop our research capabilities to fit the landscape of cannabis use today. Future research should be aware of the impact of contextual factors (e.g., setting, presence of authority figure, task instructions) and individual differences (e.g., tolerance) and exercise caution against over-interpreting neurocognitive findings. It is recommended that studies examining cannabis and cognition employ a within-subjects design to help account for individual differences and reduce the risk of misattributing differences in cognition to ACU.

Future studies should characterize the relationship between tolerance, ACU and cognition. If tolerance to cognitive effects of ACU develops as has been postulated in this present study, it will be important to know how many cannabis doses it takes to achieve this tolerance and how quickly it diminishes. These findings will have important implications for medical patients and workplaces.

### 5.5 Conclusion

The present body of work found that ACU did not affect cognitive performance among individuals who used cannabis near daily. From a methodological perspective, the findings highlight the importance of characterizing acute cannabis effects in discrete groups rather than across all types of users (naive vs. frequent). This more nuanced approach to research will generate more accurate data and in turn, improve the accuracy of public health messaging and medication counselling for those using CTP.

The failure to identify any cognitive impairment is especially salient for patients who may be concerned about side-effects from daily cannabinoid therapy. Patients are rightly concerned about the impairing effects of medication. It is well-known that at least 25 classes of commonly used medications impact cognition and pose a safety risk for activities such as driving (Hetland & Carr, 2014). While driving simulation studies have demonstrated an increased risk of unsafe driving following ACU, these effects are less pronounced among CTP users. Further, previous studies have shown that cannabis users tend to overestimate their level of impairment (Perkins et al., 2021) - a finding that was also demonstrated in the present study. Taken together, these findings suggest that cannabis is an appealing treatment option for individuals concerned about unwanted cognitive side-effects of medication.

In addition to high rates of medication use, older adults report higher rates of cognitive issues due to the natural aging process and development of diseases. Cannabinoid therapies may be particularly well-suited for this demographic. Indeed, older adults are the fastest growing demographic of new cannabis users in North America (Han & Palamar, 2020).

Canada is well-positioned to be a leader in cannabis science. The NCAP will contribute to creating a research landscape that can better characterize the true effects of cannabis use. By moving towards a more accurate assessment of acute cannabis effects, research will help to reduce misconceptions and stigma in meaningful ways. This will ultimately lead to safer and more informed cannabis use in a region with some of the highest rates in the world.

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# APPENDIX

## Roles and Responsibilities

### *Study Coordinator*

A study coordinator is recommended to facilitate appointment scheduling, coordinate and assign participants to research assistants, and facilitate recruitment, communication, and payment. The study coordinator may also act as a research assistant or maintain a separate role, depending on the scope of the study.

### *Research Assistants*

Research assistants should be at the graduate student level or higher with clinical research experience and a strong ability to establish rapport. To reduce the white-coat effect and stigma activation, research assistants should be demographically similar to participants, i.e. in a study of undergraduate psychology students, research assistants were peer-appearing graduate students in Clinical Psychology. Further, the title Research Assistant is used in communication with participants rather than a more formal title. As session times correspond with the time of day when participants typically use cannabis, the research assistants will typically need to provide availability in the evenings. The number of research assistants required depends on the scope of the study and pace of data collection.

## Study Sites

Participants and research assistants join the video conference from their home environment in a distraction-free (e.g., phone on silent) and private space (e.g., no one in the room, closed door). Participants require a reliable, high-speed internet connection and a computer or other device

with a large screen to connect via video conference. If research assistants need to join from a research lab, steps should be taken to de-medicalize the visible environment and create a homey atmosphere.

## Recruitment

Participants are invited to participate via email (Appendix II). A study description along with the eligibility criteria and a copy of the consent form are included in the email. If participants express interest in participating, their first appointment is booked with a research assistant.

### *Retention*

In the pilot study, the participants attended two appointments one month apart. To reduce attrition and absenteeism, email confirmation is sent at the time of booking and email reminders are sent the day before each session. In addition, the following options may increase participant retention when feasible:

- Collecting phone numbers for reminders and contacting absentees at scheduled appointment time
- Shorter intervals between appointments
- Paying participants at the end of the second appointment
- The session is scheduled during the time of day (i.e., morning, afternoon, evening) when the participant "usually consumes cannabis."

The participant is emailed the day before their session and reminded to refrain from using cannabis during the day (i.e., from waking up) prior to their appointment time. They are provided

the consent form prior to their appointment so that they can provide verbal consent during the video session. Log-on information is provided in the email.

A step-by-step description of the session is also provided and included the following instructions:

- Prepare your cannabis (e.g., joint rolled, pipe packed) prior to the session.
- Join the call from your home environment in a distraction-free (e.g., phone on silent) and private space (e.g., no one in the room, closed door).
- The quantity of cannabis consumed during the study should be the same as a typical use session as defined by you, in other words "get as high as you would normally get."

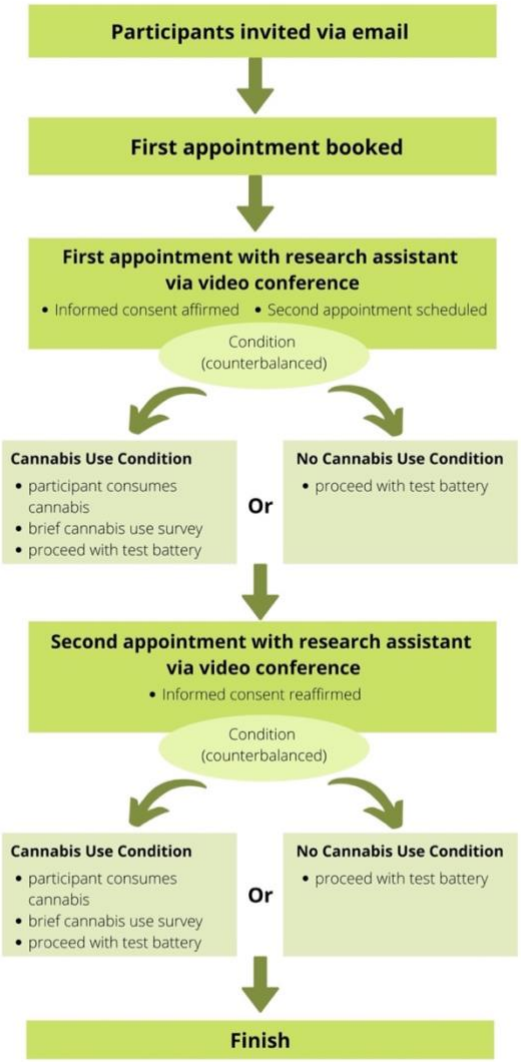
The study is described, and verbal consent is obtained prior to the consumption of cannabis. If it is the participant's first session, their second appointment is scheduled prior to beginning the study to ensure they are able to return for a second time point. The web cameras are turned off during cannabis self-administration via inhalation and a 5-minute timer is shared onscreen. Once the time has elapsed, web cameras are turned back on and a brief cannabis use interview is conducted (Appendix II). Participants are asked about their current subjective level of intoxication (i.e., "How high are you compared to when you usually get high?"). A brief survey is administered to record data on the quantity of cannabis consumed, inhalation method used (e.g., vaporizer, bong, joint), chemovar familiarity and access, and whether they know the common name of the chemovar (e.g., purple kush). The research assistant proceeds with the research condition (e.g., administers the test battery) approximately 5 minutes following cannabis use.

A within-subjects design is recommended to help control for individual differences. The appointments should be counterbalanced (cannabis use during first session vs. cannabis use

during second session). If using cognitive tests, an alternative form should be utilized for the second time point as appropriate. Both appointments, should be scheduled for the same time of day to account for diurnal effects (i.e., morning, afternoon, or evening).

**Figure 1**

*Naturalistic Cannabis Use Assessment Protocol Study Flow*



**Recruitment Email Templates**

*Email 1*

Hello,

While completing the METRIC-L Online study, you gave your consent to be contacted for follow-up studies being conducted by Dr. Zach Walsh, a Professor in the Department of Psychology at the University of British Columbia Okanagan.

The purpose of this study is to validate an at-home cannabis administration procedure and to assess changes in cognition due to cannabis intoxication.

If you choose to participate in the study, you will be asked to complete an assessment conducted via a secure video conference platform.

You will be asked to inhale (e.g., smoke, vaporize, dab) your own cannabis while at home.

Upon completion of both assessments, you will be paid $20 CAD via e-transfer.

If you are interested in participating, please respond to this email to set up an appointment. A consent form is attached to this email so that you may review it before deciding to schedule an appointment.

Thank you,

Co-Investigator

Michelle St. Pierre

*Email 2*

Hello,

Thank you so much for your interest in the study! I have a couple questions before we schedule our first session. 1) On average, how many days of the week do you smoke/vape cannabis? 2) Is there a timeframe in which you normally use (e.g., only evenings 7-10pm, or wake and bake) – we will schedule both of your appointments during this time.

Thank you,

Co-Investigator

Michelle St. Pierre

**Post-Cannabis-Use Survey**
The following questions are verbally administered and recorded by the research assistant.

1. Did you:
   - Smoke
   - Vaporize
   - Dab
   - Other:_____

2. How high are you compared to when you usually get high?
   - Higher than usual
   - About as high as usual
   - Less high than usual

3. How much cannabis did you consume?
____(#)
   - Puffs
   - Tokes
   - Bowls
   - Other _____

4. How familiar are you with the cannabis you used?
   - Very familiar
   - Somewhat familiar
   - Somewhat unfamiliar
   - Unfamiliar

5. Where did you get it from?
   - Dispensary
   - Non-government source
   - Someone gave it to me
   - I grew it myself

6. Do you know what strain you used? YES/NO
If yes, _____ (name it here)