THE EFFECT OF FREQUENT CANNABIS USE ON THE MAIN COMPONENTS OF EXECUTIVE FUNCTIONING

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Abstract

The legalization of recreational cannabis use in Canada has raised many questions regarding its immediate and sustained effect on the performance of various critical daily tasks (e.g., driving). To investigate the sustained effect, we created an online battery of tasks that assess the main components of executive functioning that are involved in all aspects of our daily activities. The performance of healthy, young (age= 17-64; *M*= 21.7, *SD*=6.0) frequent cannabis users (at least once a week; $n > 93$), infrequent users (at least once in last 3 months; $n > 58$), and non-users (never used cannabis before; $n > 253$) is compared. Here, selective visual attention (using a serial visual search task), response inhibition (using a Go/No-Go task), visuospatial working memory (using a visuospatial N-back task), and cognitive flexibility and set shifting ability (using Trails B of the Trail Making Test) was analyzed. No significant differences in performance were found on any of the measures of executive functioning components between frequent users, infrequent users, and non-users. Except for greater accuracy on the visual search task in both frequent and infrequent users compared to non-users (small effect size- approximately 3% more accurate). Additionally, secondary analyses were carried out to assess the effect of sex, last occasion of cannabis use, age of cannabis-use onset, length of cannabis use (in years), and reason for cannabis use (medical, or recreational) on executive functioning performance in frequent cannabis users. No significant effects were found on most measures of executive function with the exception of the following findings: (a) frequent cannabis users who were under the influence of cannabis during the study performed worse on the Trail Making Test than those who were not under the influence at the time of the study (medium effect size- approximately 20 seconds slower), (b) frequent-user females were significantly faster in their responses than frequent-user males on the visual search task (small effect size- approximately .4 seconds faster), and (c) frequent users with an early-onset of cannabis

use (before age 16) were significantly less accurate on the Go/No-Go task than their late-onset counterparts (after age 16; small effect size- less accurate by approximately .25 dprime units). Overall, the findings suggest that sustained, frequent cannabis use did not impair the main components of executive functioning. However, this study found some evidence of an impairment in frequent users associated with acute cannabis use on cognitive flexibility and set shifting ability, a slight sex difference favouring frequent-user females on selective visual attention compared to frequent-user males, and an impairment in early-onset cannabis users on response inhibition compared to late-onset users.

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Table of Contents

List of Figures

List of Tables

Chapter 1: Introduction and Literature Review

Many countries and states around the world have begun to legalize the recreational use of cannabis (also known as marijuana, weed, pot, etc.), with Canada lifting the ban in 2018 (Stats Canada, 2018). The legalization of recreational cannabis use has enhanced public awareness and introduced an increasing number of questions with regards to its effect on daily activities at home, at work, and while driving or operating machinery (Burggren et al., 2019; Rotermann, 2021). These daily activities all rely on several aspects of executive functioning processes such as the modulation of attention, impulse inhibition, working memory, and cognitive flexibility which engage several brain regions that are affected by cannabis use (Porfirio et al., 2020; Nicholls et al., 2015; Burggren et al., 2019). Cannabis exerts its effects on these brain regions through the binding of THC (the main psychoactive ingredient found in cannabis) to CB1 receptors that are distributed in high densities all over the cerebral cortex. Specifically, CB1 receptors are widely present in the prefrontal cortex, anterior cingulate cortex, hippocampus, basal ganglia, and the cerebellum (Nicholls et al., 2015). As these regions are integral to several aspects of executive functioning, it becomes crucial to investigate how cannabis use affects these processes.

Certainly, there are other capacities in the brain that may be affected with frequent cannabis use, and it is next to impossible to investigate all relevant processes in any one study. However, it is crucial to select complimenting processes that are involved in most, if not all, of our daily tasks and activities, and this is what I attempted to do here. I have investigated the effect of frequent cannabis use on the main components of executive functioning that are involved in most of our daily activities, which involve the input of visual sensory information, the cognitive processing of that information, and the execution of an appropriate motor response. I have also assessed set

shifting and cognitive flexibility using a task that engaged and overlapped all the aforementioned processes and that acted as an overarching measure of performance on all tasks.

Overall, the existing research on the effect of cannabis use on the main components of executive functioning has been limited and inconclusive due to several limitations and confounding factors. This is partly due to the uncertain nature of cannabis and how different strains, doses, and potencies may lead to different types of effects that may not always be the same for every individual. However, there are other significant limitations that pertain to specific study designs and procedures such as the use of uncommon measures to assess functioning, small sample sizes, and bias sample compositions. Accordingly, this study has determined the effect of frequent cannabis use on the main components of executive functioning in a large sample of frequent users, infrequent users, and non-users of cannabis, while also resolving some limitations from previous investigations.

Limitations of Existing Research

Without a doubt, it is difficult to control for the unpredictable effects of cannabis, especially when attempting to investigate frequent/long-term effects of use. However, there are other limitations that include (but not limited to) small sample sizes and biased sample compositions, which are mainly caused by the fact that cannabis is illegal in most countries and states around the world. In turn, this difficultly in recruiting participants drives researchers to recruit participants who may be heavy users and undergoing treatment for a cannabis-use disorder, or to recruit participants from other existing studies that are not particularity investigating cannabis, but have reported cannabis use (e.g., Rangel-Pacheco et al., 2021). For the same reason, researchers often do not exclude participants who may use other illicit substances which can impact the validity of their findings. Additionally, there is a lack of consensus among studies when

it comes to defining a regular or frequent user in terms of how often they use cannabis. For example, some studies define a regular user as one who uses at least once a month (e.g., Tamm et al., 2013), while others define it as a someone who uses cannabis at least once a week (e.g., Grant et al., 2019). This lack of consensus can lead to conflicting findings where a cannabis-user group in one study may be made up of both moderate to heavy users, while another study may only contain light users. Finally, most studies usually test only a few cognitive processes that might be relevant for daily life. Here, I attempted to tackle these limitations in the research using a large sample of frequent users, infrequent users, and non-users of cannabis.

Additionally, previous research on how cannabis use affects the main components of executive functioning has been inconclusive where most studies that report impairments mostly investigate acute or immediate effects (e.g., Bogaty et al., 2018; Gonzalez et al., 2017). Other studies that have investigated long-term or frequent-use effects have made contrasting conclusions with some finding impairments in users (e.g., Solowij & Battisti, 2008), while others have not (e.g., Tait et al., 2011). An understanding of how cannabis exerts its effects on the central nervous system is necessary to be able to form more accurate conclusions about its true effect.

Cannabinoids

Cannabis is a psychoactive substance that is produced by the dried leaves, stems, and flowering buds of the cannabis plant. The most commonly used species of cannabis are Sativa and Indica, which are available in different breeds (also known as strains) such as Blue Dream, Purple Kush, OG Kush, and many more (Spindle et al., 2019). Mainly, these breeds and strains of cannabis differ in the amount of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) that they contain, creating chemotypes that are either THC-dominant, CBD-dominant, or hybrid (mix of both).

THC and CBD are the main chemical ingredients found in cannabis products out of more than 100 other cannabinoids. While THC is known for inducing the psychoactive effects that accompany cannabis use, CBD is known for providing therapeutic benefits (Spindle et al., 2019; CCSA, 2019). The psychoactive effect of THC in cannabis is produced through its interaction with the endocannabinoid system in the brain. The endocannabinoid system is mainly composed of CB1 (Cannabinoid type 1) and CB2 (Cannabinoid type 2) receptors which mediate the effect of endogenous cannabinoids. With the ingestion or inhalation of cannabis, THC binds to CB1 receptors where it exerts its agnostic effects and in turn prompts functional changes in cognitive and motor processes (Böcker et al., 2020; Nicholls et al., 2015; CCSA, 2019; Lu & Mackie, 2016). On the other hand, some of the therapeutic benefits of CBD include the alleviation of stress, anxiety, and chronic and acute pain (Spindle et al., 2019; Grotenhermen, 2003).

Several studies have investigated the effect of cannabis use on brain regions rich in CB1 receptors that are associated with executive functioning processes. These regions include the prefrontal cortex, anterior cingulate cortex, hippocampus, basal ganglia, and the cerebellum (Lorenzetti et al., 2016; Chang & Chronicle, 2007; Ogunbiyi et al., 2019). Several studies have reported neuroanatomical alterations in these regions in cannabis users compared to control subjects (Lorenzetti et al., 2016; Chye et al., 2020; Martin-Santos et al., 2010). Specifically, sustained cannabis use has been associated with volumetric reductions in most of these regions that may be caused by a THC-induced neurotoxicity caused by the accumulation of THC in neurons (Solowij et al., 2011: Lorenzetti et al., 2016). Other studies have found evidence that cortical CB1 receptors in these critical regions undergo signalling changes and downregulation with persistent cannabis use, which may lead to the development of cognitive deficits (Mizrahi et al., 2017; Ogunbiyi et al., 2019). Reduced cerebral blood flow has also been found in regular

cannabis users, specifically in the prefrontal cortex which may also contribute to impairments in several components of executive functioning such as working memory, attention, decision making, and cognitive flexibility (Martin-Santos et al., 2010). Furthermore, it is important to note that the psychoactive component, THC, has been shown to be associated with the brain region alterations reported in several studies. While CBD has been shown to offer protective factors against the negative effects of THC on the brain (Lorenzetti et al., 2016; Sagar et al., 2020). With the legalization of recreational cannabis use, cannabis products have become more potent in THC while also decreasing in concentrations of CBD. This indicates that the effect of recreational cannabis use on the brain may be increasing in magnitude over the coming years (Owens et al., 2020; Lorenzetti et al., 2016). Overall, these findings further point to the importance of thoroughly investigating whether these structural and functional alternations associated with regular cannabis use, translate to behavioural and cognitive impairments in frequent cannabis users.

Additionally, there are objective effects that accompany acute cannabis use, such as increased heart rate, body tremors, and impairments in memory, attention, and motor performance (CCSA, 2019). While subjective effects of acute cannabis use include feelings of relaxation, euphoria, and distortions of perception, which in turn reinforce its use and make it an appealing substance (CCSA, 2019; Böcker et al., 2020). Another reinforcing factor to cannabis use is the widespread belief that it is non-addictive in nature because it was (and still is) widely used for medical and healing purposes. Accordingly, cannabis is the most widely used psychoactive substance for recreational and medical purposes in the world (GDS, 2016; Böcker et al., 2010) which further demonstrates the importance of investigating its effect on executive functioning. Hence, some of the previous findings on the effect of cannabis use on the main components of executive functioning is reviewed below.

Selective Visual Attention

Selective visual attention is the processing of several sources of visual stimuli while maintaining focus or attending to a relevant stimulus in the presence of distractors (Johnston & Dark, 1986). It is modulated by an interaction of several brain regions including (but not limited to) the inferior parietal areas, the anterior cingulate system, and the dorsolateral prefrontal cortex (Nicholls et al., 2015). This attentional process which relies on top-down processing is crucial in almost all aspects of our daily activities such as searching our environment for a particular item or looking for a friend in a crowd of people. The effect of cannabis use on selective visual attention has not been significantly investigated in previous research. Mostly, studies have utilized varying and uncommon tasks that are also often not pure measures of selective visual attention.

For example, in a study by Nusbaum and colleagues (2017), 39 cannabis users who were abstinent on the day of testing (87% usually used cannabis daily or more) and 40 non-users (had less than 10 lifetime occasions of cannabis use) completed the flexible attentional control task (FACT) which assesses forms of attentional control. In this task, participants were cued with either the word ‘friend’ or ‘foe’ before they were shown either a smiling or a frowning emoticon on the screen. They were instructed to make a left mouse click when a smiling emoticon appears, and a right mouse click when a frowning emoticon appears. They found that compared to non-users, cannabis users did not exhibit overall impairments in task performance, however, they presented a reduced reliance on top-down attentional control when cues were valid and instead made use of other strategies to complete the task.

Similarly, Rangel-Pacheco and colleagues (2020), administered an arrow-based Eriksen flanker task to assess selective visual attention to 24 cannabis users who were abstinent on the day of testing (usual use of cannabis was at least once weekly) and 24 non-users (had no prior cannabis

use) while undergoing magnetoencephalography (MEG) recordings. Participants were presented a set of five arrows that were pointing either to the left, or to the right and were instructed to make a left or right button response depending on the direction of the middle arrow. The results of the study indicated no difference between cannabis users and non-users in both accuracy and average reaction times on the task. However, they found that cannabis users presented weaker theta activity and altered fronto-occipital connectivity in the incongruent task condition compared to non-users. They interpreted that these findings may demonstrate compensatory processes that cannabis users adopt in order to maintain performance on the task.

Response Inhibition

Response inhibition (also known as impulse inhibition) is the ability to supress a speeded motor action or response when required to by environmental contingencies (Miller & Cohen, 2001). This mechanism involves the activation of several brain regions where CB1 receptors are widely present including the inferior, dorsolateral, and medial frontal cortex, the anterior cingulate cortex, the basal ganglia, and the cerebellum (Borgwardt et al., 2008). Response inhibition is extremely important in activities such as driving or operating machinery where it may be necessary to supress an action in our everchanging environments. The effect of cannabis use on response inhibition processes has been extensively investigated but nevertheless most studies tend to have multiple limitations.

For example, Grant and colleagues (2019) recruited 16 cannabis users (who used at least once a week) and 214 non-users (had no use over the last 12 months) to complete a battery of tasks to assess cognitive functions. Cannabis users were not required to abstain from cannabis use prior to the study as the researchers were interested in capturing the effect of cannabis use under naturalistic circumstances. All participants completed a Stop-Signal task to assess response

inhibition. This task requires participants to make a left or right button press that is congruent to the direction of an arrow presented on the screen, but to refrain from making a response when an auditory tone is presented (stop signal). They found no difference between cannabis users and non-users on both accuracy and reaction times. However, it is important to point out that the group sizes of this study were significantly unmatched, and because the cannabis group sample size was small, the study was likely underpowered.

Comparatively, in another study, cannabis users who were abstinent on the day of the study (n=20, usually used at least monthly) did not differ from non-users (n=21, had used less than four times in the previous year) in their performance on a response inhibition task (Go/No-Go Task) (Tamm et al., 2013). In a Go/No-Go task, participants are instructed to make a response when presented with stimuli that indicate a 'Go' trial and to refrain from making any responses to a specific stimulus that indicates a 'No-Go' trial.

Notably, Borgwardt and colleagues (2018), found no difference in response inhibition performance on a Go/No-Go task in 15 participants (had fewer than 15 occasions of lifetime use, with no use in the past month) who completed the task subsequently after receiving a dose of either THC, CBD, or a placebo in a placebo-controlled, repeated-measures study. However, these participants also underwent functional magnetic resonance imaging (fMRI) while completing the task which revealed that following THC consumption, participants had reduced and weakened activation in the right inferior frontal gyrus and the anterior cingulate cortex. This finding indicates that THC may influence other modalities that involve the activation of these regions such as performance monitoring, or selective attention, and not necessarily on response inhibition (Borgwardt et al., 2008).

Although the studies mentioned utilized similar tasks that are also pure measures of response inhibition processes, they all lacked a sufficient sample size, which may indicate the absence of appropriate statistical power to detect differences between groups. In addition, all studies were carried out in states and countries where recreational cannabis use is illegal, which poses challenges related to participants' honesty about their regular patterns of cannabis use, and other illegal substance use (Ponto, 2016).

Visuospatial Working Memory

Visuospatial working memory is the temporary storage, processing, and manipulating of visual and spatial stimuli (Rizzo & Vecera, 2002). The dorsolateral and ventrolateral prefrontal cortex, hippocampus, Parahippocampal gyrus, and posterior parietal cortex (and others) where CB1 receptors are abundantly found, are all involved in visuospatial working memory processes (Smith et al., 2010; Ren et al., 2019). This aspect of working memory is directly utilized at home and the workplace when having to carry out any task that requires the temporary storage of information about the physical characteristics and locations of items in our environment.

Research on the effect of cannabis use on working memory has mainly investigated its effect on verbal working memory (e.g., using a digit span task) with a limited focus on the visuospatial aspect of working memory. Notwithstanding, most studies that do in fact investigate the effect of cannabis on visuospatial working memory tend to rely on uncommon and less reliable measures and often utilize very small sample sizes.

For example, the same study described in the above section by Grant and colleagues (2019) had participants (16 cannabis users and 214 non-users) complete a spatial working memory task where participants were required to search for a yellow token inside several boxes using an elimination strategy. As the number of boxes increased, the task became more difficult and

participants were likely to make more errors (e.g., revisiting empty boxes). The results showed no difference between cannabis users and non-users in their performance on the task, both in terms of the number of errors they made and the strategies they utilized.

However, in a repeated-measures placebo-controlled study, 10 cannabis users (who used cannabis from once a month to once a week) received either a placebo or a cannabis containing cigarette (on day 1 vs. day 2) before completing a visuospatial working memory task (N-Back). This task required participants to remember the location of a dot that was presented in one of six possible locations on the screen either 1 or 2 trials back. The findings indicated that cannabis use induced some impairments in performance, specifically, a reduction in accuracy was observed in the high load condition of the task (2-Back vs. 1-Back), along with an increase in reaction times for both load conditions, in comparison to placebo (Ilan et al., 2004). Yet, it should be noted that the small sample size utilized in this study, and the fact that effective blinding in cannabis trials including regular users tends to be challenging and unreliable, are considerable limitations to these findings (National Academies of Sciences, Engineering, and Medicine, 2017; Wright et al., 2021).

On the same note, Smith and colleagues (2019) administered a similar Visuospatial 2-Back Task to 10 cannabis users (use at least once a week) and 14 non-users while undergoing fMRI. However, here, cannabis users were not asked to abstain from cannabis prior to completing the study. No difference was found between cannabis users and non-users on all measure of task performance (accuracy and reaction times). fMRI results indicated that cannabis users exhibited significantly greater activations in the right inferior frontal gyrus, left middle frontal gyrus, and the right superior temporal gyrus when performance on the control condition of the task was subtracted from performance on the working memory condition of the task. Interpretation of this finding indicates that the brain of cannabis users is required to work harder (increased effort that

is evident through greater activations of task-relevant regions) to maintain performance on visuospatial working memory tasks (Smith et al., 2019). It is important to point out again that the small sample size utilized in this study is a limitation to generalizability of these findings.

Cognitive Flexibility (Set Shifting)

Cognitive flexibility is the central component of executive functioning, and it includes the mental ability to effectively switch between activities and adjusting attention and working memory processes with the goal of producing appropriate actions and responses (Dajani & Uddin, 2015; Deák & Wiseheart, 2015). It involves CB1-receptor-dense brain regions that include the ventrolateral and dorsolateral prefrontal cortex, anterior cingulate cortex, inferior and superior parietal cortices, inferior temporal cortex, occipital cortex, the caudate, and the thalamus (Dajani & Uddin, 2015). This component of executive functioning is involved with all aspects of our actions as it enables us to effectively make decisions when presented with the simplest of challenges. For example, a challenge can be as simple as pushing to open a door that fails to open by pulling (Canas et al., 2006).

Several studies have investigated how cannabis users differ from non-users on cognitive flexibility; most have administered the Trail Making Test to assesses performance. The Trail Making Test (TMT) is widely used and established as an overarching task to assess several aspects of executive functioning. The test includes two trails, whereas Trails A involves the consecutive connection of circles that solely contain numbers (e.g., 1-2-3-4), Trails B requires participants to consecutively connect circles and alternate between letters and numbers (e.g., 1-A-2-B-3-C) as fast as possible (Reitan & Wolfson, 1985 as cited in Tombaugh, 2003).

To investigate the effect of cannabis on cognitive flexibility, Porfirio and colleagues (2020) administered Trail B of the TMT to 30 cannabis users who abstained for 24 hours prior to the study

(had used on an average of 12.86 times in the last month) and 30 non-users. They found no difference between cannabis users and non-users in their performance on the task (Porfirio et al., 2020). Besides examining how cannabis use affects response inhibition (described earlier), Tamm and colleagues (2013) also administered a TMT Trail B to 20 cannabis users (usually use at least monthly) and 21 non-users (have not used in the last year) to assess cognitive flexibility. Similarly, they did not find a difference on task performance between the two groups.

Furthermore, a study on the acute effect of cannabis on cognitive flexibility administered the TMT- Trail B to 70 cannabis users (had used at least once and up to 10 times a month) where half of the participants received a cannabis containing cigarette (N=35), while the second half (N=35) received a placebo. The results of the study demonstrated that those who received an active cannabis cigarette did not differ in their performance on the Trail Making test (Anderson et al., 2010). However, as mentioned previously, effective blinding in cannabis trials is difficult to establish especially in regular cannabis users, as they tend to be more sensitive in determining the difference between a placebo and a cannabis containing cigarette, which poses as a limitation to these findings (National Academies of Sciences, Engineering, and Medicine, 2017; Wright et al., 2021).

Evidently, the studies mentioned here all utilized reasonable sample sizes and have all reported analogous findings which speaks to the validity and reliability of the Trail Making Test as a measure of set shifting and cognitive flexibility. This goes to demonstrate that it a compelling test to use as an overarching measure of the main components of executive functioning that will be investigated in this study.

Aim of Current Study

The current study compared the performance of a large sample of frequent cannabis users, infrequent users, and nonusers on the main components of executive functioning with the purpose of determining the effect of frequent cannabis use on the proposed measures. This study also aimed to fill some of the current gaps in cannabis research by addressing and resolving a few of the most common limitations found in the research. To do this, frequent users were defined as those who use cannabis at least once a week, or more, as this is the definition that most previous studies have adopted. Infrequent users were defined as those who used cannabis at least once in the last three months prior to the study up to using a few times a month.

One advantage to this study was the legalization of recreational cannabis use in Canada, which enabled me to recruit a less biased sample of users as the legality eliminates challenges that are related to honesty about patterns of use, and increases the likelihood that users are obtaining cannabis products from legal sources which must adhere to regulations aimed at creating safer products (Rotermann, 2020; Ponto, 2006). Furthermore, all participants who reported recreational use of opiates or other illicit substances besides cannabis were excluded from the study. Participants were assessed on measures of selective visual attention (using a Serial Visual Search task), response inhibition (using a Go/no-Go task), visuospatial working memory (using a visuospatial N-Back task), and set shifting/cognitive flexibility (using a Trail Making Test-Trail B). These established measures were chosen for assessment as they are involved in almost all daily activities that encompass sensory input, cognitive integration, and motor output.

Furthermore, secondary analyses were performed to determine whether there is a difference in how frequent cannabis use affects males, versus females. Some studies have found sex differences in cannabis users on cognitive and motor task performance (e.g., Anderson et al.,

2010; Makela et al., 2006), which may be due to the storage of THC in fatty tissues which is found in larger amounts in females (Anderson et al., 2010). Additionally, the age of cannabis use onset and length of cannabis use was examined as there is evidence that suggests early, versus late cannabis use, leads to greater cognitive impairments due to use during critical developmental stages (Burggren et al., 2019). Finally, this study also aimed to determine whether a difference exists in how cannabis affects performance in those who use for medical versus recreational reasons. Medical users have previously demonstrated improved performance which may be due to the alleviation of physical and mental symptoms (e.g., if used for pain or anxiety; Burggren et al., 2019).

Study Goals and Hypotheses

The goals of the current study were to: (a) determine whether the frequent use of cannabis has an effect on the main components of executive functioning, in comparison to controls, (b) determine whether there is a difference in how frequent cannabis use affects the main components of executive functioning in males versus females, and (c) determine whether those that use cannabis frequently for medical versus recreational purposes perform differently on tasks that assesses the main components of executive functioning. My hypotheses for the current study were: (a) frequent cannabis use will not have a detrimental effect on various aspects of executive functioning, given the results of similar research studies, (b) if frequent cannabis use is found to have a significant and meaningful effect on executive functioning performance, males who are frequent users of cannabis will perform better than female frequent users on executive functioning tasks, given that females tend to have a higher storage of THC in fatty tissues, and (c) those who use cannabis frequently for medical purposes will perform better than those who use for

recreational purposes, given the possible alleviation of medical symptoms which in turn contributes to better overall performance.

Chapter 2: Method

Participants

Participants were recruited from the Undergraduate Research Participants Pool (URPP) at York University and received course credit as compensation for their participation. As this study was part of a larger-scale investigation that included the assessment of several demographic and lifestyle factors besides cannabis use, approximately 47% of cannabis users (frequent and infrequent) included here enrolled in other studies that were not labelled for assessing the effect of cannabis use. All participants provided electronic informed consent prior to participating. The study was approved by the Human Participants Review Committee at York University. Eighty participants were excluded for not completing part one of the study, and 65 participants were excluded for not completing part two. Two-hundred and ninety-nine participants completed only part one to satisfy their course credit requirement, which terminated data collection for tasks included in part two of the study. Twelve participants were excluded for suffering from a neurological condition: epilepsy (two), stroke (one), idiopathic intracranial hypertension (one), multiple sclerosis (one), and prefer not to say (seven). Fifty-seven participants were excluded for using opiates or other substances recreationally besides cannabis. Twenty participants were excluded for not wearing their vision corrective devices and not being able to see the screen well enough to participate. Seven participants were excluded for using a phone or a tablet to complete the study instead of a laptop or desktop computer.

As the data for this study was collected over four academic sessions, some changes were made to the N-Back task and the Visual Search task at different timepoints which restricted the

use its data. For the N-Back task, data included here was collected over the fall of 2020 and winter of 2021. Data for the Visual Search task was collected over the fall of 2020, and winter and summer of 2021. As for the Go/No-Go task and the Trail Making Test, data was collected over the fall of 2020, and the winter, summer, and fall of 2021. This, in addition to the screening criteria for each task and incomplete task attempts, resulted in different sample sizes for each task. An a priori repeated measures ANOVA power analysis was conducted using the software 'G*Power' (Faul et al., 2007) to calculate the sample size required to achieve a small effect size (f =.10), with a power of .80, using alpha of .05. The results suggested that at least 46 participants are required in each group to detect a small effect size and achieve a power of .80. A small effect size is theoretically meaningful as most previous studies that find an effect associated with cannabis use tend to report small effect sizes. The number of participants included in this analysis markedly surpasses the required number of participants indicated by the power analysis.

With regards to cannabis use, participants who indicated on the questionnaire that they have never used cannabis before were placed in the 'nonusers' group. While participants who indicated they have used cannabis either once or twice in the past three months, around once a month, or a few times a month were placed in the 'infrequent users' group. Participants who indicated they use cannabis either once a week, a few times a week, or daily were placed in the 'frequent users' group. One-hundred and thirty-four participants were excluded for indicating that they have used cannabis before but had not used in the past three months. Sample sizes for each task and group and demographics: age, sex, ADHD (attention deficit hyperactivity disorder) diagnosis, and playing video games), are reported in Table 1.

Several statistical tests were carried out for each task to determine whether there were any known demographic differences between the groups. As the sample sizes differed for each task,

any tests for demographic differences will only be reported from the task with the highest sample size (Go/No-Go task, n=723) as it would be most representative of the overall sample. The age of all participants ranged from 17 to 64 (M= 21.7, SD= 6.0). One-way ANOVAS were carried out for each task that determined there was no significant difference in age between the three groups, $F(2, 720) = .785$, $p = .457$, $\eta^2 = .002$. This finding was confirmed with a follow-up Bayesian one-way ANOVA that determined there was strong evidence for the absence of an effect of age on the frequency of cannabis use (BF_{10}=.041). Overall, there was a significantly higher proportion of participants who identified as females (73.7%) than males (26.3%) in our sample. However, those who identified as females were not significantly more likely to be users of cannabis (both frequent and infrequent) than those who identified as males (35.8% versus. 33.2%), as confirmed using a two-sided exact binomial test, p =.198, 95% CI [.318, .401]. Further, participants with a diagnosis of ADHD were significantly more likely to be users of cannabis (both frequent and infrequent) than non-users (9.8% versus 3.6%). This was confirmed using a two-sided exact binomial test, p < .00, 95% CI [.065, .142]. Video game players were also significantly more likely to be cannabis users (both frequent and infrequent) than non-users (49.6% versus 42.6%) which was confirmed using a two-sided exact binomial test, p =.026, 95% CI [.433, .559].

Table 1.

Demographics/Descriptive Statistics for All Participants per Task

Task	Frequent users	Infrequent users	Non-users
Go/No-Go Task	***n*=143**	***n*=111**	***n*=469**
Sex (males):	*n*=36	*n*=27	*n*=127
Age (*M*, *SD*):	22.2 (4.7)	21.3 (4.3)	21.6 (6.6)
Video games players:	*n*=78	*n*=48	*n*=200
ADHD diagnosis:	*n*=15	*n*=10	*n*=17
Visual Search Task	***n*=143**	***n*=98**	***n*=420**
Sex (males):	*n*=37	*n*=24	*n*=120
Age (*M*, *SD*):	22.2 (4.8)	21.2 (4.2)	21.1 (7.1)
Video games players:	*n*=78	*n*=42	*n*=171
ADHD diagnosis:	*n*=14	*n*=10	*n*=13
N-Back Task	***n*=93**	***n*=58**	***n*=253**
Sex (males):	*n*=23	*n*=14	*n*=71
Age (*M*, *SD*):	22.1 (4.7)	21.3 (4.3)	21.5 (6.5)
Video games players:	*n*=52	*n*=25	*n*=110
ADHD diagnosis:	*n*=7	*n*=7	*n*=8
Trail Making Test	***n*=111**	***n*=81**	***n*=351**
Sex (males):	*n*=27	*n*=20	*n*=96
Age (*M*, *SD*):	22.4 (5.0)	21.3 (4.3)	22.0 (7.2)
Video games players:	*n*=59	*n*=34	*n*=155
ADHD diagnosis:	*n*=8	*n*=9	*n*=12

Cannabis users:

Aside from the general group demographics reported in Table 1., both frequent and infrequent cannabis users answered questions with regards to their patterns of cannabis use. These are reported in Table 2A. for frequent users, and Table 2B. for infrequent users. Generally, most

frequent users reported using cannabis either daily (approximately 45%), or a few times a week (approximately 44%), while a smaller proportion reported using once a week (approximately 11%). On the other hand, the majority of infrequent users reported using once or twice in the past three months (approximately 45%), or a few times a month (approximately 35%), with a smaller percentage who reported using around once a month (approximately 18%).

Furthermore, participants were asked to specify whether they use cannabis for recreational or medical reasons, or both. Recreational use also included using cannabis socially (e.g., sharing with friends), or spiritually for religious practices. Medical use included using cannabis to help with sleep disturbances, to relieve anxiety, to relieve pain, or as an appetite stimulant. Generally, the majority of cannabis users (regardless of frequency) reported using for either recreational reasons, or for both recreational and medical reasons. While a minority of all cannabis users reported using solely for medical reasons. For frequent users, a higher proportion of participants reported both recreational and medical use (approximately 64%). While most infrequent users reported using solely for recreational reasons (approximately 66%).

Participants also reported the last time they had used cannabis which was then filtered to identify whether they had used during the time of the study, within the last 24 hours of the study, or if they had not used within the last 24 hours of the study. Most frequent users reported using cannabis within the last 24 hours (approximately 67%), while a minority of participants (approximately 8%) indicated being under the influence during the time of the study. On the other hand, no infrequent users indicated being under the influence of cannabis during the study, with the majority (approximately 86%) specifying that they had not used in the last 24 hours prior to the study. However, a minority of infrequent users (approximately 9%) did indicate that they used cannabis within the last 24 hours.

As for the age of cannabis-use onset, on average, both frequent and infrequent cannabis users reported using cannabis since the age of 16-17. The age of cannabis-use onset ranged from the age of 12 to the age of 43 for frequent users, and from the age of 13 to 26 for infrequent users. The length of cannabis use, in years, was also assessed and was computed by subtracting participants' age of cannabis-use onset, from their current reported age. On average, frequent users used cannabis for approximately 5.5 years. While infrequent users used cannabis for approximately 3.8 years, on average.

Participants reported the method of cannabis ingestion which varied from inhalation (bong, blunts, joints, hand pipe, vaporizers, hookah), oral (edibles, oils), or both. On average, approximately 56% of frequent users reported using cannabis only through inhalation, approximately 4% reported using orally, and approximately 40% reported using both inhalation and oral methods. On the other hand, approximately 44% of infrequent users reported only using methods of inhalation, approximately 18% reported using orally, and approximately 37% reported using both methods of ingestion.

Finally, cannabis users were also asked to indicate how often they combined cannabis and alcohol, on average. This was done using a 5-point Likert scale that ranged from never (1), to every single time (5). The majority (approximately 81%) of both frequent, and infrequent cannabis users indicated that they never (32.9% versus 41.4%), or almost never (49.7% versus 39.6%) combine cannabis and alcohol.

Table 2A.

Cannabis Patterns of Use for Frequent Users Per Task

Use Patterns	Go/No-Go Task (*n*=143)	Visual Search Task (*n*=143)	N-Back Task (*n*=93)	Trail Making Test (*n*=111)
Frequency of use				
Once a week:	*n*=18 (12.6%)	*n*=17 (11.9%)	*n*=9 (9.7%)	*n*=13 (11.7%)
A few times a week:	*n*=61 (42.7%)	*n*=62 (43.4%)	*n*=42 (45.2%)	*n*=48 (43.2%)
Daily:	*n*=64 (44.8%)	*n*=64 (44.8%)	*n*=42 (45.2%)	*n*=50 (45.0%)
Reason for use				
Recreational:	*n*=36 (25.2%)	*n*=39 (27.3%)	*n*=21 (22.6%)	*n*=25 (22.5%)
Medical:	*n*=19 (13.3%)	*n*=20 (14.1%)	*n*=7 (7.5%)	*n*=13 (11.7%)
Both:	*n*=88 (61.5%)	*n*=84 (58.7%)	*n*=65 (69.9%)	*n*=73 (65.8%)
Last used				
During study:	*n*=9 (6.3%)	*n*=11 (7.7%)	*n*=11 (11.8%)	*n*=8 (7.2%)
Last 24 hours:	*n*=96 (67%)	*n*=96 (67.1%)	*n*=61 (65.6%)	*n*=76 (68.5%)
Not in last 24 hours:	*n*=35 (24.5%)	*n*=33 (23.1%)	*n*=19 (20.4%)	*n*=24 (21.6%)
Age of use onset				
Mean (*SD*):	16.9 (3.1)	16.9 (3.1)	16.6 (1.9)	16.4 (3.3)
Range:	12-43	12-43	13-21	7-43
Length of use (years)				
Mean (*SD*):	5.3 (4.7)	5.3 (4.9)	5.5 (5.5)	6.0 (5.3)
Range:	0-29	0-29	0-29	0-29

Table 2B.

Cannabis Patterns of Use for Infrequent Users Per Task

Use Patterns	Go/No-Go Task (*n*=111)	Visual Search Task (*n*=98)	N-Back Task (*n*=58)	Trail Making Test (*n*=81)
Frequency of use				
Once-twice in past 3 months:	*n*=50 (45.0%)	*n*=47 (48.1%)	*n*=25 (43.1%)	*n*=36 (44.4%)
Around once a month:	*n*=21 (18.9%)	*n*=18 (18.4%)	*n*=10 (17.2%)	*n*=13 (16.0%)
A few times a month:	*n*=40 (36.0%)	*n*=33 (23.1%)	*n*=23 (39.7%)	*n*=32 (39.5%)
Reason for use				
Recreational:	*n*=71 (64.1)	*n*=64 (68.4%)	*n*=38 (65.6%)	*n*=53 (65.4%)
Medical:	*n*=8 (7.2%)	*n*=8 (8.2%)	*n*=6 (10.3%)	*n*=6 (7.4%)
Both:	*n*=31 (28.1%)	*n*=25 (25.5%)	*n*=13 (22.4%)	*n*=21 (25.9%)
Last used				
During study:	*n*=0	*n*=0	*n*=0	*n*=0
Last 24 hours:	*n*=10 (9.0%)	*n*=8 (8.2%)	*n*=6 (10.3%)	*n*=7 (8.6%)
Not in last 24 hours:	*n*=96 (86.5%)	*n*=84 (85.7%)	*n*=50 (86.2%)	*n*=69 (85.2%)
Age of use onset				
Mean (SD):	16.9 (3.1)	17.5 (2.4)	17.3 (1.8)	17.6 (2.5)
Range:	12-43	13-26	13-21	14-26
Length of use (years)				
Mean (SD):	5.3 (4.7)	3.7 (3.8)	4.0 (4.3)	3.7 (3.5)
Range:	0-29	0-22	0-22	0-20

Experimental Set-up

Apparatus

This was an online browser study that was completed on participants' personal computers or laptops. Participants accessed the study using individualized anonymous links on the URPP SONA system. Questionnaires were conducted on Qualtrics, an online survey software, with

embedded links to tasks. The study's tasks were programmed using PsychoPy, an open-source software, and were run on Pavlovia, the accompanying experiment server.

Questionnaire

Participants answered the following demographics questions: age, sex, handedness, whether they suffer from a neurological condition, whether they play video games, and whether they were wearing vision correction devices (if needed). Additionally, participants also completed a cannabis-use questionnaire that included the following questions: whether they have used cannabis before and if so, the frequency of cannabis use in the last three months (7-point Likert scale), primary method of intake (e.g., bong, joint, oil, etc.), reason for use (e.g., recreational, medical), age of cannabis-use onset, last time they used cannabis, description of their usual dose (e.g., mg of THC, number of hits, etc.), whether they combine cannabis and alcohol (if so, how often), and whether they use opiates or other recreational drugs or substances (besides cannabis). All participants also completed an additional set of questions as part of the questionnaire (e.g., history of concussion, family history of dementia, the Pittsburgh Sleep Quality Index, etc.) that are unrelated to cannabis use and will not be addressed here.

Tasks

Participants performed eight tasks in this study. However, only four of these tasks were used in this project and are described below. The other four tasks that were not used in this project include a motor acuity task (Tunneling), two visuomotor adaptation tasks (Mirror Reversal and Horizonal Mirror Reversal), and task switching. All eight tasks can be found and accessed at this URL: https://thartbm.github.io/SMCL-online/

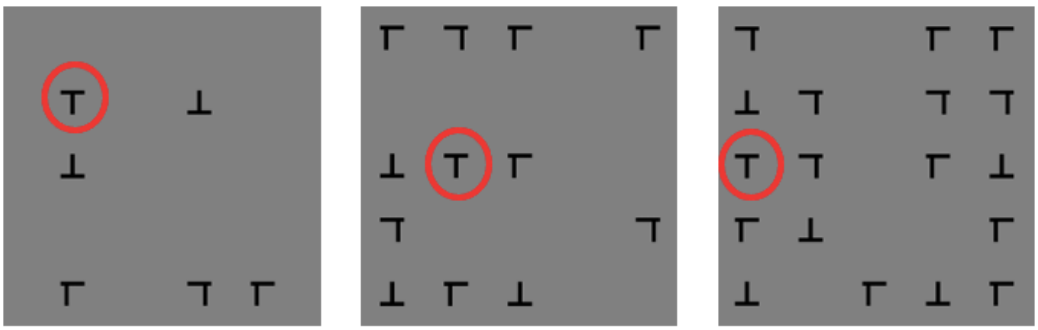
Visual Attention- Serial Visual Search Task

The Visual Search task (shown in Figure 1, adapted from Treisman & Gelade, 1980; Stoet, 2010, 2017) required participants to search for a target among several shapes presented on the screen. Here, participants were instructed to search for an upright letter "T", among distractors that resemble the letter. The location of the target and distractors was randomized among 25 different locations on the screen for each trial. Participants were required to respond by pressing "x" on their keyboard when the target was present, and "m" when the target was absent. No timeout for trials was set, meaning that a response was required in order to proceed to the next trial. Also, participants did not receive feedback about their performance on the task.

Furthermore, the task consisted of three blocks of 54 trials each (total of 162 trials). An instruction screen was presented between the blocks where participants also had the opportunity to rest. Once ready to proceed to the next block, participants pressed the "enter" key on their keyboard. A target was present among the distractors for half of the trials of a block (27/54 trials) and the number of shapes on the screen (set size) was either 6, 12 or 18. Within each block of 54 trials, each of the six combinations of set size and whether the target was present or absent, occurred 9 times, in fully randomized order. The dependent measures for this task included the reaction time (RT) and accuracy both when the target was present and absent.

Figure 1

Visual Search Task- participants were required to search for an upright "T" through an array of irregularly shaped "T"s. The three array set sizes are shown (6,12,18).



Response Inhibition- Speeded Go/No-Go Task

During this task (adapted from Stoet, 2010, 2017), participants were presented with either a blue circle containing the word “GO”, or an orange circle containing the words "NO GO", on each trial. Participants were instructed to make a response on “GO” trials by pressing the “space” key on their keyboard, and to inhibit a response on “NO-GO” trials. The task consisted of 300 trials that were divided into three blocks of 100 trials. Before each block, participants were reminded of the instructions and also given the opportunity to rest. Within each block, trials were pseudorandomized with 1 in every 5 trials being a “NO-GO” (resulting in 20% of total trials being “NO-GO”). Each trial had a timeout of two seconds where the next trial appeared if a response was not made. The dependent measures for this task included the reaction time (RT) on hit and false alarm trials, and accuracy.

Figure 2

Go/No-Go Task. Participants were asked to respond when presented a "GO" stimulus and to inhibit a response when a "NO-GO" stimulus is presented.

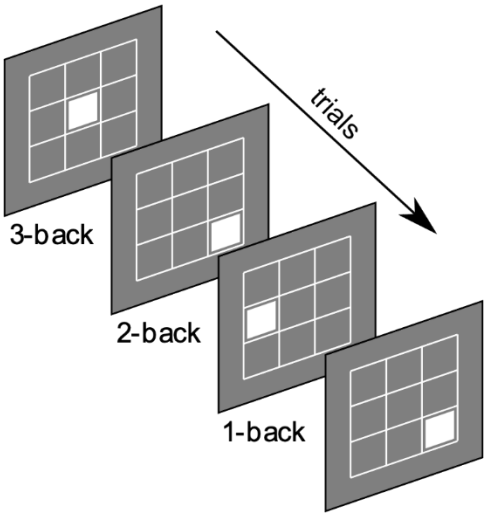
Visuospatial Working Memory- Visuospatial N-Back Task

Participants were presented a 3x3 square grid where a white square was presented in one of the nine grid locations, each trial. The task (adapted from Dores et al., 2017) consisted of three blocks where each block corresponded to the following conditions: 1-Back, 2-Back, and 3-Back, respectively, indicating that the position of the square on that many trials back had to be compared to the current position of the square. For example, in the 3-Back condition, participants were required to compare the location of the square in the current trial, to the location of the square that was presented three trials back. If the square appeared in the same location as n-trials back, they were instructed to press the “space” key on their keyboard. And if the square on the current trial did not appear in the same location as n-trials back, they were to refrain from making a response. Each trial took two seconds. The colour of the grid changed to green when a correct response was made, and to red when an incorrect response was made. This feedback is only provided on trials where participants made a response by pressing the “space” key. Furthermore, each block was made up of 60 trials with the following ratio of randomized response to non-response trials: 1-Back = 17:43, 2-Back = 14:46, and 3-Back = 15:45. This ratio was intended to be 15:45 for all three blocks, however, due to a programming error, this was not true. After each block, participants were presented instructions for the next condition and also given the opportunity to rest. The

dependent measures for this task included the reaction time (RT) on hit and false alarm trials and accuracy.

Figure 3

Visuospatial N-Back Task. Participants were required to remember the location of the white square that was presented n-trials back. The three load sizes are shown in this figure (1-Back, 2-Back, and 3-Back).



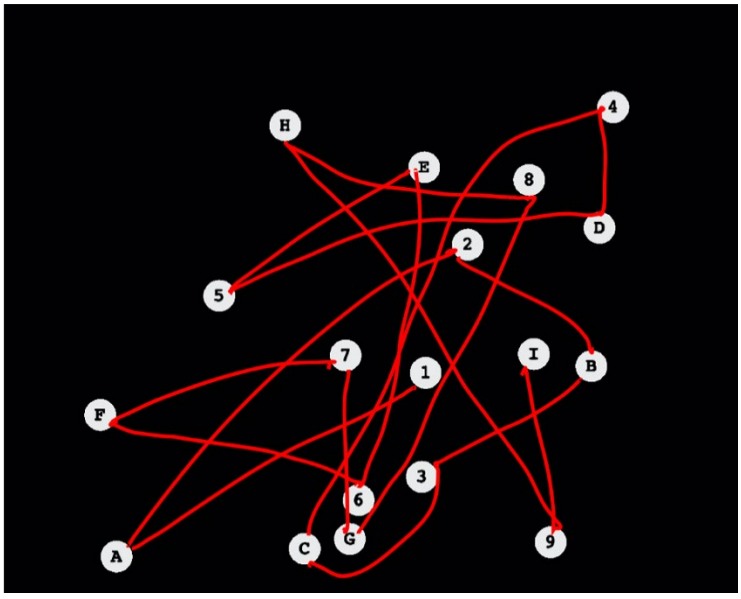
Cognitive Flexibility (Set Shifting)- Trail Making Test (Trail B)

Participants were presented a set of 18 circles that were randomly scattered on the screen. Nine out of the 18 circles contained the numbers 1-9, while the rest of the circles contained the letters A-I. Participants were instructed to use their mouse or cursor to connect the circles while alternating between letters and numbers (i.e., 1-A-2-B-3-C, etc.) as fast as possible (adapted from Reitan & Wolfson, 1985 as cited in Tombaugh, 2003). A straight line was drawn from the previous to the current circle, only when the current circle contained the correct next symbol, so that participants had to correct any errors before they continued. The task consisted of five trials where the circles were scattered differently on each trial. Also, at the end of each trial, the total completion

time (s) was displayed on the screen. The dependent measure for this task was the total completion time (ms) for each trial which is the difference between the time at movement of onset and time at movement offset.

Figure 4

Trail Making Test, Trail B. Participants were required to connect the circles while alternating between letters and numbers as fast as possible. Numbers include 1-9, letters include A-I.



Procedure

After accessing the study using their individualized links, participants provided electronic informed consent, then completed the questionnaire which was then followed by the completion of the executive functioning tasks. As this study consisted of eight tasks (four of which are used in this project) and a relatively large questionnaire, the study was split into two equal-length sessions to prevent fatigue. The order of the tasks was randomized for each participant to ensure that task order was not a confounding variable. Task instructions and a chance to rest and reduce fatigue was provided to participants prior to starting each task. After completing all tasks,

participants were redirected to the SONA system where they were automatically credited for their participation.

Data Screening

Since this was an online browser study, it was impossible to ensure that participants followed the instructions and completed the tasks accurately. Several screening criteria were implemented for each task to assess whether participants performed the tasks adequately. All incomplete attempts for each task were excluded from analysis. For the Go/No-Go task, N-back task, and Visual Search task, trials with reaction times below 0.1 seconds were excluded from all analyses as these trials indicated reflexive responses. In addition, other screening criteria were implemented that were specific to fit the framework of each task. For the Go/No-Go task, participants who failed to respond to at least 95% of the 'go' trials were excluded. This is to rule out participants who were distracted and missed a substantial number of trials due to the set trial timeout of 2 seconds. For the Visual Search task, all trials with response times above 30 seconds were excluded to rule out trials where participants may have gotten distracted in their environment. Additionally, participants whose error rate exceeded 33.33% for any of the set sizes (6, 12, or 18) were excluded from analysis. For the N-Back task, participants were excluded if they did not make a correct response for at least 50% of the trials that required a response in 1-Back, 25% in 2-Back, and 1% in 3-Back. Task-specific screening criteria resulted in the removal of 5.4% of participants who attempted the Go/No-Go task, 4.1% of participants who attempted the Visual Search task, and 18.7% of participants who attempted the N-Back task. The high percentage of participants who were removed from the N-Back task given the liberality of the screening criteria can be explained by the difficult nature of the task. As for the Trail Making Test, no specific screening criteria was set other than ensuring participants completed the task fully. This is because the task

required participants to correct any connection errors before being able to proceed and it was also designed to prevent participants from skipping any connections.

Data Analysis

The aim of this study was to investigate whether frequent cannabis users, infrequent users and non-users differ in their performance on four tasks assessing each main component of executive functioning under naturalistic circumstances. I also investigated whether there are any sex differences in performance on the tasks by testing for the presence of an any interactions between sex and group. Specifically, I was also interested in determining whether there is a difference in how frequent cannabis use affects males and females. Additionally, I conducted secondary analyses to determine whether the length of cannabis use (in years), the age of cannabis-use onset (before age 16, or after age 16), the last occasion of cannabis use (during study, within last 24 hours, or not within the last 24 hours), and whether cannabis was used for medical or recreational purposes influence performance on the tasks. The alpha level for all statistical tests was set to .05 and all data processing and analyses were carried out in RStudio (R version 4.0.4). Linear mixed effects models were carried out using the lmerTest package in R (Kuznetsova et al., 2017). Bayesian analyses were carried out for non-significant main effect findings with regards to the frequency of use, and the effect of age of cannabis-use onset to differentiate between null and indeterminant results. This was done using the BayesFactor package in R (Morey & Rouder, 2021). For all analyses, multiple comparisons were only carried out where a main effect was statistically significant with the aim of further specifying differences between groups. However, if a statistically significant main effect was determined along with a statistically significant interaction, multiple comparisons were only carried out on the interactions. Details on how each task was analyzed is discussed below.

Visual Search Task

Performance on this task was be determined by comparing the average reaction times (RTs) and the proportion of correct trials on target present versus target absent trials for each array set size. To compare RTs on the task, in A linear mixed effects model (LME) was carried out which included the target (absent, or present), array set size (6, 12, or 18), Target x Set Size interaction, group (frequent users, infrequent users, or non-users), sex (female, or male), and a Group x Sex interaction for fixed effects. Participant IDs were included as a random effect to account for within-subject effects. The dependent variable was average reaction times (RT) in seconds. An analysis of variance (ANOVA) output was extracted using Satterthwaite approximation of degrees of freedom on the LME to evaluate the effect of each predictor. Partial eta squared was used to provide estimates of effect sizes. Estimated marginal means (*EMM*) along with standard error (*SE*) are reported as descriptive statistics for post hoc tests. The analysis of the comparison of proportion of correct trials on the task was identical to the RT analysis except for the dependent variable being the proportion of correct trials instead of RT.

To test for the effect of length of cannabis use, age of cannabis-use onset, reason for cannabis use, and the last occasion of cannabis use, a linear mixed effects model (LME) was carried out which included the target (absent, or present), array set size (6, 12, or 18), Target x Set Size interaction, sex (female, or male), use reason (recreational, medical, or both), last use (not within last 24 hours, within last 24 hours, or during study), age of cannabis-use onset (early, or late-onset), and length of use (in years) for fixed effects. Participant IDs were included as a random effect to account for within-subject effects. Average RTs, in seconds, or the proportion of correct trials (a separate LME analysis) was set as the dependent variable. An analysis of variance (ANOVA) output was extracted using Satterthwaite approximation of degrees of freedom on the

LME to evaluate the effect of each predictor. Partial eta squared was used to provide estimates of effect sizes. Estimated marginal means (*EMM*) along with standard error (*SE*) are reported as descriptive statistics for post hoc tests.

Go/No-Go Task

Task performance was be measured by comparing the average reaction times for "GO" and "NO-GO" trials. Reaction times of responses on "NO-GO" (failure to inhibit a response) trials are expected to be shorter than reaction times on "GO" trials. A d-prime (d') sensitivity index was also computed as a measure of performance on the task. D-prime (d') was calculated by computing the standardized difference between the hit rate (proportion of trials making a response when presented a "GO" stimulus) and the false alarm rate (proportion of trials making a response when presented a "NO-GO" stimulus). A higher d-prime (d') indicates higher sensitivity on the task where participants were more accurately discriminate between the "GO" and "NO-GO" stimuli which would result in a higher hit rate and a lower false alarm rate. This would in turn indicate that participants with a higher d-prime (d') are performing above chance and thus are more accurate on the task than those with a lower d-prime (d').

To compare RTs on the task, a linear mixed effects model (LME) was constructed to include trial type (hit, or false alarm), group, sex, and a Group x Sex interaction. Participant IDs were included as a random effect to account for within-subject effects. The dependent variable was the average RT, in seconds. An analysis of variance (ANOVA) output was extracted using Satterthwaite approximation of degrees of freedom on the LME to evaluate the effect of each predictor. Partial eta squared was used to provide estimates of effect sizes. Estimated marginal means (*EMM*) along with standard error (*SE*) are reported as descriptive statistics for post hoc

tests. The effect of sex and cannabis-use patterns (reason for use, last occasion of use, age of cannabis-use onset, and length of use) on RTs in frequent users was analyzed similarly.

D-prime (d') was analyzed by fitting a multiple linear regression (MLR) to include the effect of group, sex, and an interaction between group and sex on d-prime. An analysis of variance (ANOVA) output was extracted to evaluate the effect of each predictor. Partial eta squared was used to provide estimates of effect sizes. Estimated marginal means (*EMM*) along with standard error (*SE*) are reported as descriptive statistics for post hoc tests. The effect of sex and cannabis-use patterns (reason for use, last occasion of use, age of cannabis-use onset, and length of use) on d-prime in frequent users was analyzed similarly.

N-Back Task

Performance on this task was measured by examining the average reaction times on hit and false alarm trials for each load size (1-Back, 2-Back, 3-Back). Hit trials are those where a response is made when the location of the square matches the location of the square n-trials back, and false alarm trials are those where a response is made when the location of the square does not match the location n-trials back. As with the Go/No-Go task, d-prime (d') was be calculated by taking the standardized difference between the hit and false alarm rate on the task. A higher d-prime (d') would indicate more sensitivity and accuracy in discriminating and deciding whether the white square appeared in the same location n-trials back. Lower d-prime scores are expected as the load size increases (from 1-Back to 2-Back to 3-Back) as the task will become more difficult.

To test for differences in RT, a linear mixed effects model (LME) was constructed to include load size (1-Back, 2-Back, 3-Back), group, sex, and a Group x Sex interaction. Participant IDs were included in the model as a random effect to account for within-subject effects. The dependent variable was average reaction time on hit trials (or false alarm trials where a separate

model was fitted), in seconds. An analysis of variance (ANOVA) output was extracted using Satterthwaite approximation of degrees of freedom on the LME to evaluate the effect of each predictor. Partial eta squared was used to provide estimates of effect sizes. Estimated marginal means (*EMM*) along with standard error (*SE*) are reported as descriptive statistics for post hoc tests. The effect of sex and cannabis-use patterns (reason for use, last occasion of use, age of cannabis-use onset, and length of use) on hit and false alarm RTs in frequent users was analyzed similarly.

Differences in d-prime was tested using a linear mixed effects model (LME) that included d-prime (d') as the dependant variable, and load size, group, sex, and a Group x Sex interaction as fixed effects. Participant IDs were included as a random effect to account for within-subject effects. An analysis of variance (ANOVA) output was extracted using Satterthwaite approximation of degrees of freedom on the LME to evaluate the effect of each predictor. Partial eta squared was used to provide estimates of effect sizes. Estimated marginal means (*EMM*) along with standard error (*SE*) are reported as descriptive statistics for post hoc tests. The effect of sex and cannabis-use patterns (reason for use, last occasion of use, age of cannabis-use onset, and length of use) on d-prime in frequent users was analyzed similarly.

Trail Making Test (Trail B)

Performance on this task was determined by measuring the time (in milliseconds) it takes participants to make all the connections on a given trial (completion time). Completion time (CT) on trial one was analyzed using a multiple linear regression (MLR) that included group, sex, and a Group x Sex interaction as the explanatory variables of the model. Completion time for trial one, in seconds, was included as the dependent variable of the model. An analysis of variance (ANOVA) output was extracted to evaluate the effect of each predictor. Partial eta squared was

used to provide estimates of effect sizes. Estimated marginal means (*EMM*) along with standard error (*SE*) are reported as descriptive statistics for post hoc tests. The effect of sex and cannabis-use patterns (reason for use, last occasion of use, age of cannabis-use onset, and length of use) on CT in frequent users was analyzed similarly. Additionally, the average of the completion times for trials two-five were tested similarly. Generally, participants are expected to become faster (lower completion time) with increased practice as the trials progress. Therefore, the goal of this analysis was to determine whether frequent cannabis users, infrequent users, and non-users differ in terms of how much their completion time declines with increased practice.

Chapter 3: Results

Effect of cannabis use on the main components of executive functioning:

Selective Visual Attention- Serial Visual Search Task

Reaction Time Across Groups. The main effect of target was statistically significant and large, $F(1) = 2160$, $p < .001$; $\eta p^2 = .40$, 95% CI [.37, .42]. The main effect of set size was also statistically significant and large, $F(2) = 3426$, $p < .001$; $\eta p^2 = .67$, 95% CI [.66, .69]. Similarly, the interaction between target and set size was statistically significant with a medium effect size, $F(2) = 149.15$, $p < .001$; $\eta p^2 = .08$, 95% CI [0.07, 0.10]. A post hoc Tukey test showed that RTs on target absent trials (*EMM*=3.4, *SE*=.05) were significantly higher than RTs on target present trials (*EMM*=2.5, *SE*=.05) for all three set sizes ($p < .001$). RTs for the 6-array set size condition (target absent: *EMM*=2.2, *SE*=.05; target present: *EMM*=1.7, *SE*=.05) were significantly lower than RTs on the 12-array set size condition (target absent: *EMM*=3.5, *SE*=.05; target present: *EMM*=2.5, *SE*=.05; $p < .001$), and RTs for the 12-array set size condition were also significantly lower than the RTs on the 18-array set size condition (target absent: *EMM*=4.6, *SE*=.05; target present: *EMM*=3.3, *SE*=.05; $p < .001$). Therefore, as expected, RTs increased as a function of array set size. As the

number of items presented increases, so does the search time which leads to higher RTs, shown in Figure 10.

The main effect of group on RT, shown in Figure 10, was not statistically significant, $F(2) = 2.76$, $p = .064$; $\eta p^2 = .008$, 95% CI [0, .03]. A Bayesian repeated measures ANOVA indicated strong evidence in favour of an absence of the effect of frequency on RTs ($BF_{10}=.046$). Also, the main effect of sex on RT (shown in Figure 11) was not statistically significant, $F(1) = .92$, $p = .337$; $\eta p^2 = .001$, 95% CI [0, .01]. However, the interaction between group and sex was statistically significant, but very small, $F(2) = 3.13$, $p = .044$; $\eta p^2 = .009$, 95% CI [0, .03]. A post hoc Tukey test showed that for frequent users, females (*EMM*=2.8, *SE*=.09) had significantly lower RTs than males (*EMM*=3.2, *SE*=.15; $p < .05$). However, the difference between females (*EMM*=3.0, *SE*=.10) and males (*EMM*=3.1, *SE*=.18) was not significant for infrequent users ($p = .787$), and non-users (females: *EMM*=2.9, *SE*=.05; males: *EMM*=2.8, *SE*=.08; $p = .166$).

Reaction Time in Frequent Users. Like the effects reported above for the general task patterns, the main effect of target was statistically significant and large, $F(1) = 537.9$, $p < .001$; $\eta p^2 = .44$, 95% CI [.39, .48]. The main effect of set size on RT was also significant and large, $F(2) = 781.1$, $p < .001$; $\eta p^2 = .69$, 95% CI [.60, .72]. The interaction between target and set size was significant and this effect size was medium, $F(2) = 38.43$, $p < .001$; $\eta p^2 = .10$, 95% CI [.06, .14].

The main effect of sex in frequent users was statistically significant and small, $F(1) = 4.27$, $p = .041$; $\eta p^2 = .04$, 95% CI [0, .13]. Like the previous analysis, females (*EMM*=2.8, *SE*=.12) had significantly lower RTs than males (*EMM*=3.2, *SE*=.16). The effect of cannabis-use reason was not statistically significant, $F(2) = .31$, $p = .735$; $\eta p^2 = .005$, 95% CI [0, .05]. Last occasion of cannabis use, shown in Figure 7, was also not statistically significant, $F(2) = .22$, $p = .802$; $\eta p^2 =$

.004, 95% CI [0, .04]. The main effect of length of cannabis use (shown in Figure 8) on RT was also not statistically significant, $F(1) = .81$, $p = .692$; $\eta p^2 = .13$, 95% CI [0, .11]. The age of cannabis-use onset on RT was not statistically significant, $F(1) = .002$, $p = .968$; $\eta p^2 = .00001$, 95% CI [0, .004]. A follow-up Bayesian repeated measures ANOVA on the effect of age of cannabis-use onset on RT indicated moderate evidence for the absence of an effect ($BF_{10}=.319$).

In sum, the typical observable pattern of increases in RTs as the number of distractors increase (Treisman & Gelade, 1980; Wolfe 2001) was found. RTs on target absent trials were found to be significantly higher than RTs on target present trials for all three set sizes. As for the frequency of cannabis use, there was no significant difference between frequent users, infrequent users, and non-users on RTs on the task. There was also no significant difference in RTs between males and females on the task. However, there was a significant interaction between the cannabis-use frequency group and sex, where frequent-user females were found to be significantly faster than frequent-user males. Further analysis of cannabis-use patterns in frequent users indicated that the last occasion of cannabis use, the reason for cannabis use, the length of cannabis use, and age of cannabis-use onset had no significant effect on RTs on the task.

Figure 5

Reaction Time for Target Absent and Target Present Trials Across Groups. Error Bars Represent 95% Confidence Interval.

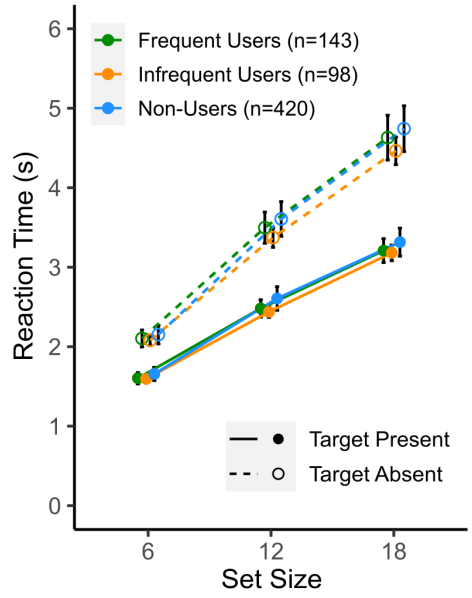


Figure 6

Reaction Time for Target Absent and Target Present Trials Across Groups for Males and Females. Error Bars Represent 95% Confidence Interval.

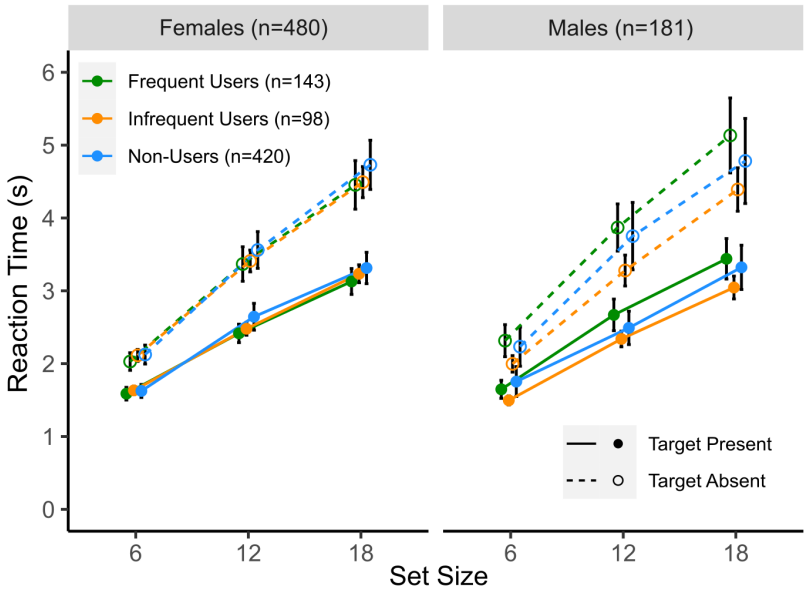


Figure 7

Effect of Last Occasion of Cannabis Use on Reaction Times When Target is Absent and Present in Frequent Users. Error Bars Represent 95% Confidence Interval.

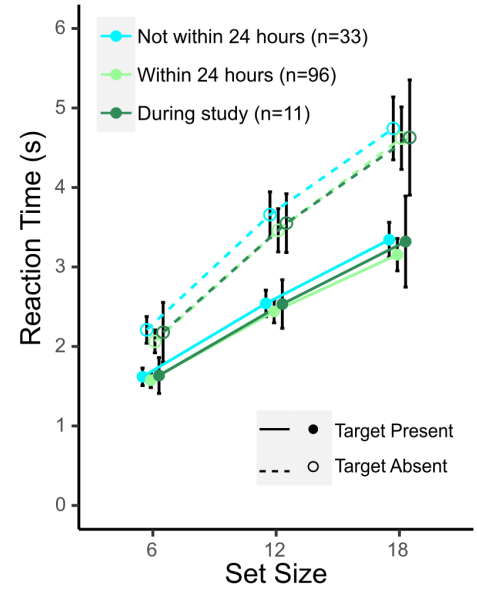
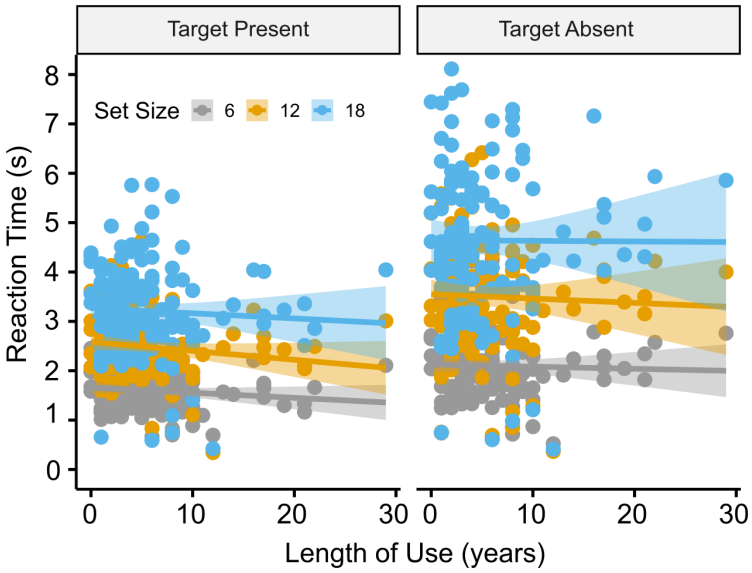


Figure 8

Effect of Length of Cannabis Use on Reaction Time in Target Absent and Target Present Trials in Frequent Users.



Proportion Correct (Accuracy) Across Groups. As shown in Figure 9, the main effect of target on proportion of correct trials was statistically significant and large, $F(1) = 4313$, $p < .001$; $\eta_p^2 = .57$, 95% CI [.55, .58]. The main effect of set size was small but statistically significant, $F(2) = 97.02$, $p < .001$; $\eta_p^2 = .06$, 95% CI [.04, .07]. Also, the interaction between target and set size was statistically significant but small, $F(2) = 87.57$, $p < .001$; $\eta_p^2 = .05$, 95% CI [.04, .07]. Proportion of correct trials on target absent trials (*EMM*=.97, *SE*=.006) was significantly higher than the proportion of correct on target present trials (*EMM*=.72, *SE*=.006). A post hoc Tukey test indicated that there was a significant difference between the three set sizes on the proportion of correct trials but only for the target present trials. Accuracy on target present trials decreased as the array set size increased. The proportion of correct target present trials on the 6-array set size condition (*EMM*=.79, *SE*=.007) was significantly higher than the proportion of correct trials on the 12-array set size condition (*EMM*=.71, *SE*=.007; $p < .001$), and the proportion of correct trials on the 12-array set size condition was significantly higher than the 18-array set size condition (*EMM*=.67, *SE*=.007; $p < .001$). Accuracy on target absent trials did not significantly differ between the three array set sizes: 6 versus 12 ($p = .993$), 6 versus 18 ($p = .868$), and 12 versus 18 ($p = .917$).

The main effect of group (shown in Figure 9) on the proportion of correct trials was statistically significant but small, $F(2) = 7.61$, $p < .001$; $\eta_p^2 = .02$, 95% CI [.004, .05]. A Tukey post hoc test showed that frequent users (*EMM*=.85, *SE*=.01) were significantly more accurate than non-users (*EMM*=.82, *SE*=.006; $p < .05$) and infrequent users (*EMM*=.85, *SE*=.01) were also significantly more accurate than non-users ($p < .05$). However, the difference between frequent users and infrequent users was not statistically significant ($p = .999$). Furthermore, the effect of sex (shown in Figure 5) on the proportion of correct trials was small but statistically significant, $F(1) = 5.60$, $p < .05$; $\eta_p^2 = .009$, 95% CI [.0002, .03], where males (*EMM*=.85, *SE*=.01) were

slightly, but significantly, more accurate than females (*EMM*=.83, *SE*=.006; $p < .05$). The interaction effect (shown in Figure 5) between group and sex was statistically not significant, $F(2) = .51$, $p = .601$; $\eta_p^2 = .002$, 95% CI [0, .01].

Figure 9

Proportion of Correct Trials for Target Absent and Target Present Trials Across Groups. Error Bars Represent 95% Confidence Interval.

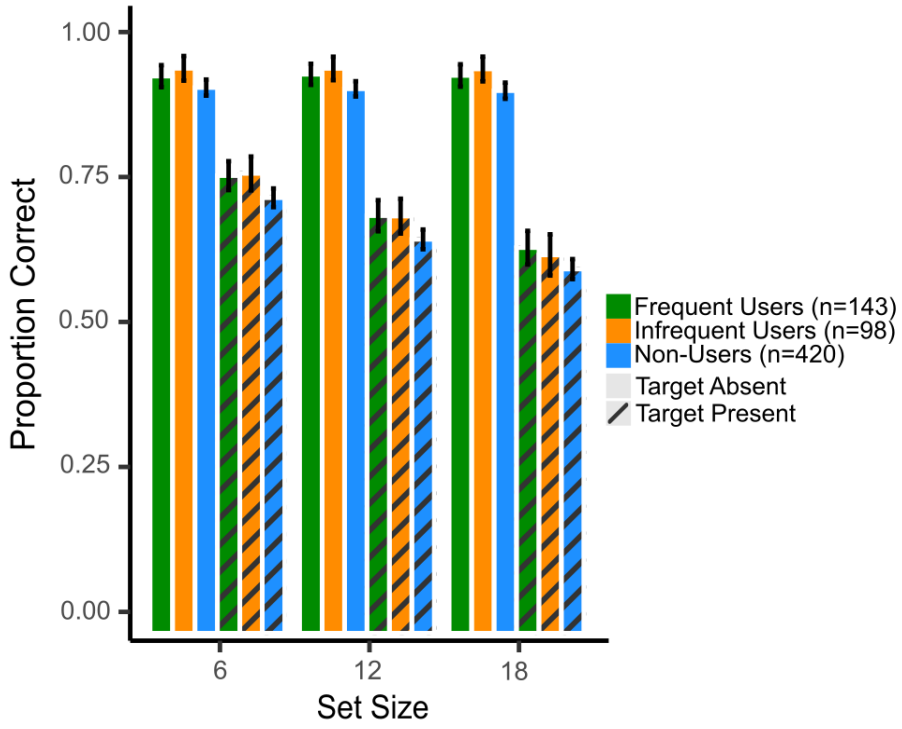
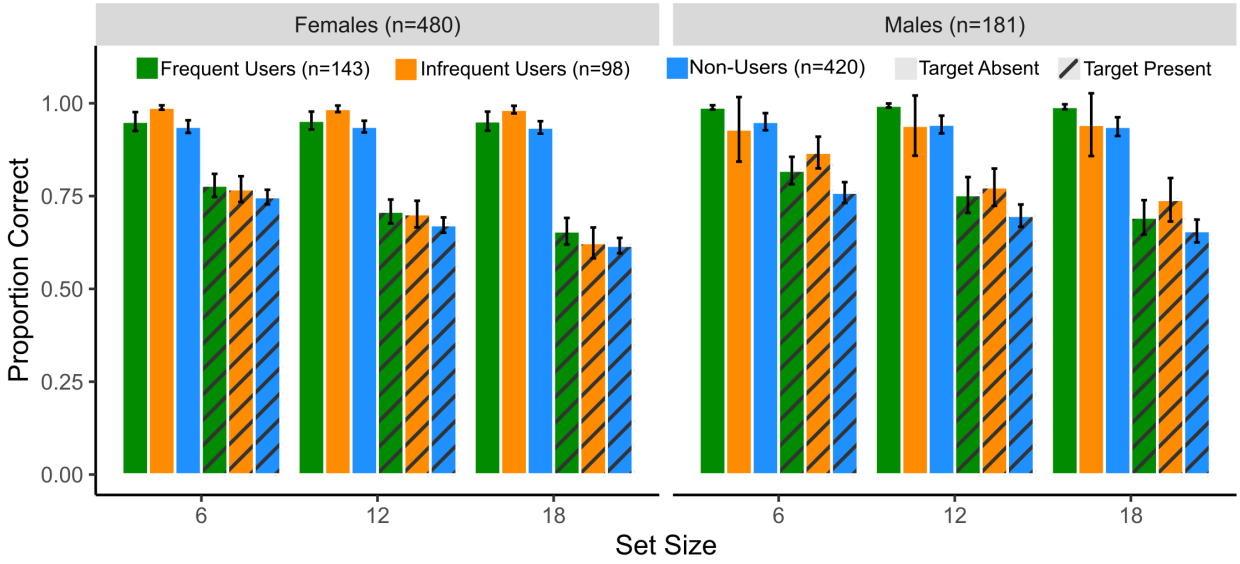


Figure 10

Proportion of Correct Trials When Target is Absent and Present Across Groups for Females and Males. Error Bars Represent 95% Confidence Interval.



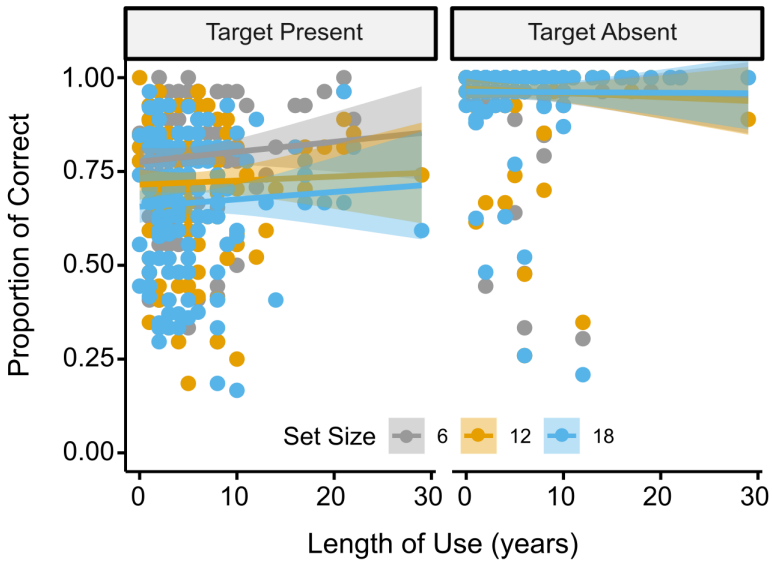
Proportion Correct (Accuracy) in Frequent Users. Like the previous analysis, the main effect of target was statistically significant and large, $F(1) = 1083$, $p < .001$; $\eta p^2 = .61$, 95% CI [.57, .64]. The main effect of set size was also statistically significant with a medium effect size, $F(2) = 25.16$, $p < .001$; $\eta p^2 = .07$, 95% CI [.03, .10]. Likewise, the interaction between target and set size was significant and the effect size was medium, $F(2) = 25.35$, $p < .001$; $\eta p^2 = .07$, 95% CI [.04, .11]. Accuracy on target absent trials (*EMM*=.98, *SE*=.01) was significantly higher than accuracy on target present trials (*EMM*=.75, *SE*=.01; $p < .001$). A Tukey post hoc test also indicated that for target present trials only, accuracy decreased as the array set size increased. Accuracy on the 6-array set size condition (*EMM*=.81, *SE*=.02) was significantly higher than the 12-array set size (*EMM*=.74, *SE*=.02), which was higher than the accuracy on the 18-array set size condition (*EMM*=.69, *SE*=.02; $p < .001$).

The main effect of sex on proportion of correct trials in frequent users was not statistically significant, $F(1) = 2.73$, $p = .101$; $\eta p^2 = .02$, 95% CI [0, .09]. Similarly, the main effect of use reason, $F(2) = .33$, $p = .720$; $\eta p^2 = .005$, 95% CI [0, .04], last occasion of cannabis use, $F(2) = .40$, $p = .671$; $\eta p^2 = .006$, 95% CI [0, .05], length of use (shown in Figure 11), $F(1) = .060$, $p = .438$; $\eta p^2 = .005$, 95% CI [0, .05], and the age of cannabis-use onset, $F(1) = 1.19$, $p = .276$; $\eta p^2 = .009$, 95% CI [0, .07] were not statistically significant. A follow-up Bayesian repeated measures ANOVA on the effect of age of cannabis-use onset use on the proportion of correct indicated moderate evidence for absence of the effect ($BF_{10}=.310$).

In sum, the proportion of correct trials on target absent trials was significantly higher than the proportion of correct on target present trials. However, for target present trials only, there was a significant decrease in accuracy as the number of distractors increased. Although the effect size was small, frequent cannabis users and infrequent cannabis users were found to be significantly more accurate than non-users on the task, with no significant difference in accuracy between frequent users and infrequent users. Overall, males were found to be significantly more accurate than females on the task regardless of cannabis-use frequency, with a small effect size. However, there was no significant difference between frequent user females and frequent user males, suggesting that frequency of use did not affect the accuracy of males and females differently. Finally, there was also no significant effect of last occasion of cannabis use, length of cannabis use, cannabis use reason, and age of cannabis-use onset in frequent users on their accuracy on the task.

Figure 11

Effect of Length of Cannabis Use on Proportion of Correct Trials in Frequent Users on the Visual Search Task.



Response Inhibition- Speeded Go/No-Go Task

Reaction Time Across Groups. The results indicated that the main effect of trial type (shown in Figure 12A) was statistically significant and large, $F(1) = 708.7$, $p < .001$; $\eta p^2 = .51$, 95% CI [.46, .55]. Reaction times on hit trials (*EMM*=.37, *SD*=.06) were significantly higher than reaction times on false alarm trials (*EMM*=.29, *SD*=.08). The main effect of group (shown in Figure 12A) was not statistically significant, $F(2) = 1.63$, $p = .197$; $\eta p^2 = .005$, 95% CI [0, .02]. A follow-up Bayesian repeated measures ANOVA on the effect of cannabis use frequency on RT indicated moderate evidence for absence of the effect (BF_{10}=.294). On the other hand, the main effect of sex (shown in Figure 13A and 13B) on reaction times was statistically significant but very small, $F(1) = 5.05$, $p < .05$; $\eta p^2 = .007$, 95% CI [0, .02]. Results indicated that females (*EMM*=.33, *SD*=.07) had significantly higher RTs than males (*EMM*=.32, *SD*=.08). The

interaction between group and sex (shown in Figure 13A and 13B) was not statistically significant, $F(2) = 2.21$, $p = .111$; $\eta p^2 = .006$, 95% CI [0, .02].

Reaction Time in Frequent Users. As reported in the previous analysis, the effect of trial type was statistically significant and large, $F(1) = 116.29$, $p < .001$; $\eta p^2 = .46$, 95% CI [.34, .56]. Reaction times on hit trials (*EMM*=.36, *SD*=.05) were significantly higher than reaction times on false alarm trials (*EMM*=.29, *SD*=.08). Also, like the main effect of sex across groups, the effect of sex in frequent users was statistically significant but small, $F(1) = 5.61$, $p < .05$; $\eta p^2 = .04$, 95% CI [.0007, .13]. Specifically, females (*EMM*=.33, *SD*=.08) had significantly higher reaction times than males (*EMM*=.31, *SD*=.06).

The main effect of cannabis-use reason was not statistically significant, $F(2) = 1.60$, $p = .206$; $\eta p^2 = .02$, 95% CI [0, .09]. Similarly, last occasion of cannabis use (shown in Figure 14) did not have a significant effect on reaction time, $F(2) = .91$, $p = .407$; $\eta p^2 = .01$, 95% CI [0, .07]. The length of cannabis use (shown in Figure 15A) also did not have a statistically significant effect on reaction time, $F(1) = .04$, $p = .840$; $\eta p^2 = .0003$, 95% CI [0, .03]. Similarly, the age of cannabis-use onset did not have a statistically significant effect on reaction time, $F(1) = 1.50$, $p = .223$; $\eta p^2 = .01$, 95% CI [0, .07]. A follow-up Bayesian repeated measures ANOVA on the effect of age of cannabis-use onset on RT indicated moderate evidence for absence of an effect of length of use (BF_{10}=.215).

Overall, RTs on hit trials on this task were significantly higher than RTs on false alarm trials. As for the effect of cannabis-use frequency, there was no significant difference between frequent users, infrequent users, and non-users. In general, females were found to be significantly slower than males on RTs on this task, with a very small effect size. The interaction between

cannabis-use frequency and sex was not significant. When analysing RT performance of frequent users, the effect of sex remained significant but also very small. However, as females were also found to be slower than males regardless of cannabis-use frequency, and because the interaction was between group and sex was not significant, the difference observed between female and male frequent users does not suggest a differential effect of cannabis use on sex. Finally, last occasion of cannabis use, length of cannabis use, age of cannabis-use onset, and cannabis-use reason did not affect RTs on this task.

Figure 12

Boxplots of Reaction Times (Panel A) and Accuracy (d-prime; Panel B) on the Go/No-Go Task Across Groups. Boxplots show the interquartile range of the data with the median represented by the black horizontal line in each box. Whiskers indicate the upper and lower data extremes.

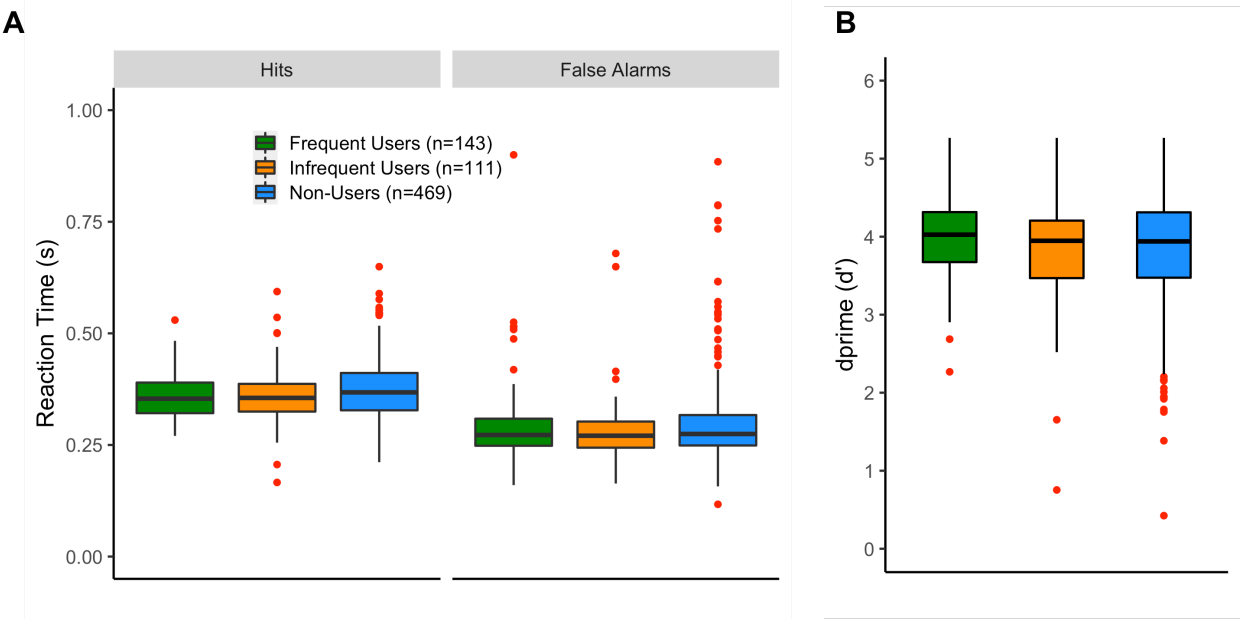


Figure 13

Boxplots of Reaction Times for Hit (Panel A) and False Alarm (Panel B) Trials on the Go/No-Go Task Across Sex and Groups. Boxplots show the interquartile range of the data with the median represented by the black horizontal line in each box. Whiskers indicate the upper and lower data extremes.

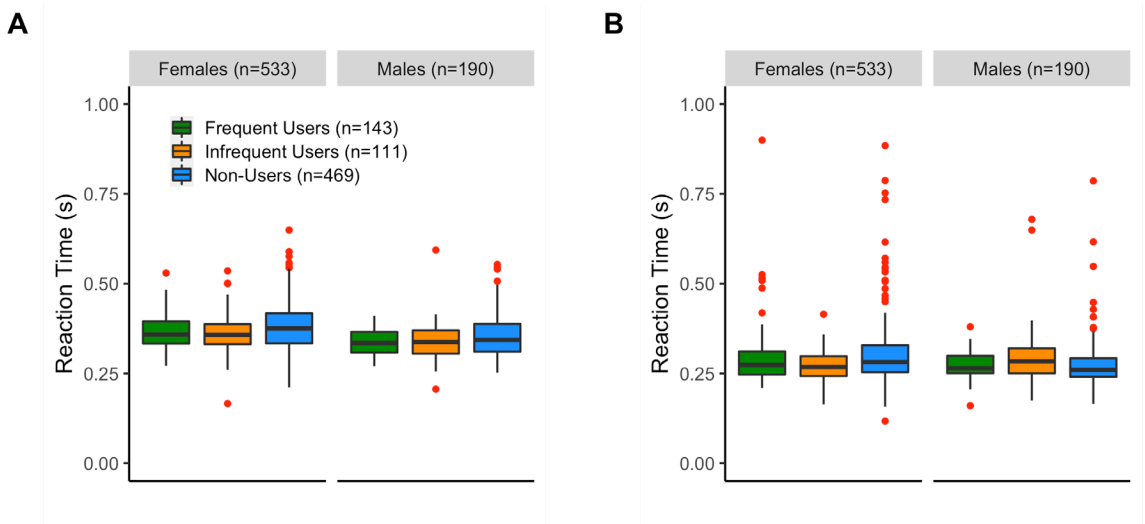


Figure 14

Effect of Last Occasion of Cannabis use on Reaction Times in Frequent Users on the Go/No-Go Task. Boxplots show the interquartile range of the data with the median represented by the black horizontal line in each box. Whiskers indicate the upper and lower data extremes.

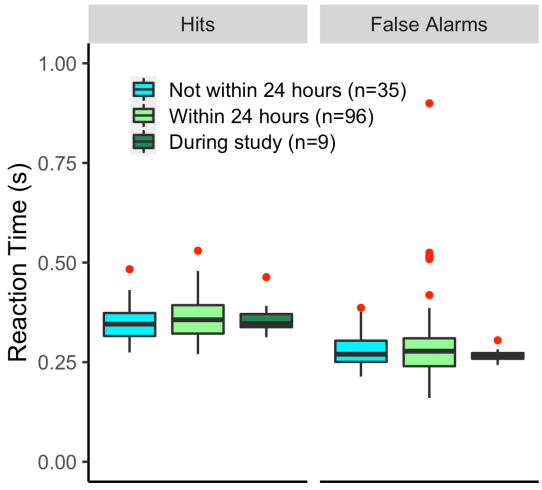
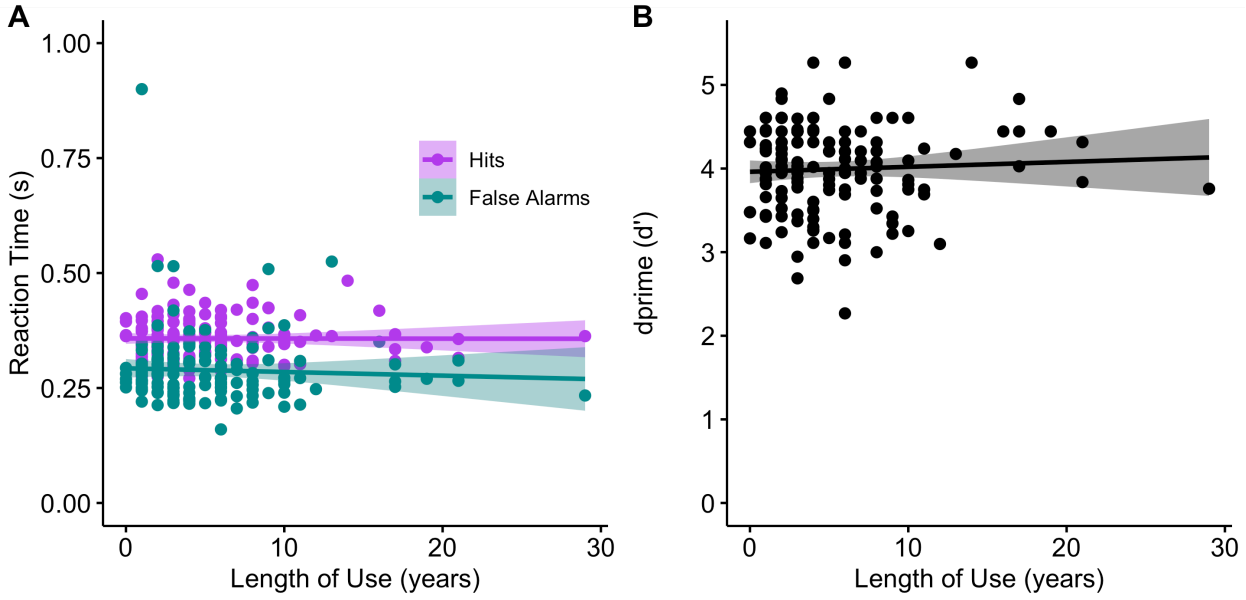


Figure 15

The effect of Length of Cannabis Use on Reaction Times of Hits and False Alarm Trials (Panel A) and on Accuracy (dprime; Panel B) on the Go/No-Go Task



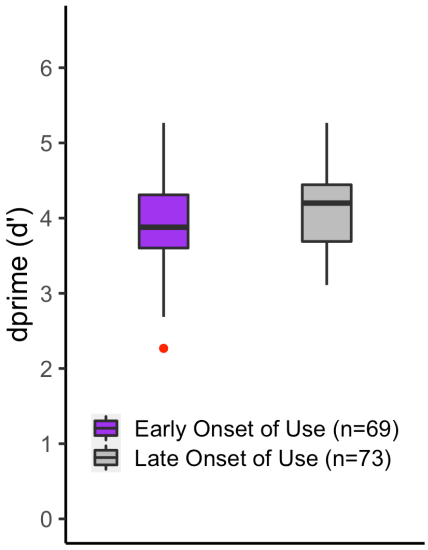
Accuracy (d-prime) Across Groups. The main effect of group (shown in Figure 12B) on d-prime was not statistically significant, $F(2, 708) = .70$, $p = .498$; $\eta p^2 = .00001$, 95% CI [0, .003]. A follow-up Bayesian ANOVA on the effect of cannabis use frequency on d-prime indicated moderate evidence for absence of the effect (BF_{10}=.136). Also, the main effect of sex on accuracy on the task was not statistically significant, $F(1, 708) = .009$, $p = .923$; $\eta p^2 = .002$, 95% CI [0, .01]. Likewise, the interaction between group and sex was not statistically significant, $F(2, 708) = .87$, $p = .420$; $\eta p^2 = .002$, 95% CI [0, .01].

Accuracy (d-prime) in Frequent Users. The main effect of sex on d-prime in frequent users was not statistically significant, $F(1, 132) = 3.17$, $p = .077$; $\eta p^2 = .02$, 95% CI [0, .10]. Similarly, the effect of cannabis-use reason was not statistically significant, $F(2, 133) = .89$, $p = .413$; $\eta p^2 = .01$, 95% CI [0, .07]. The main effect of last occasion of cannabis use was also not statistically

significant, $F(2, 132) = 2.81$, $p = .064$; $\eta p^2 = .04$, 95% CI [0, .12]. Furthermore, the length of cannabis use (shown in Figure 15B) did not have a statistically significant effect on d-prime, $F(1, 132) = 2.92$, $p = .090$; $\eta p^2 = .02$, 95% CI [0, .09]. However, the age of cannabis-use onset (shown in Figure 16) had a significant, but small effect on d-prime, $F(1, 132) = 5.91$, $p < .05$; $\eta p^2 = .04$, 95% CI [.001, .13]. Specifically, early-onset users (*EMM*=3.79, *SD*=.11) were significantly less accurate than late-onset users (*EMM*=4.04, *SD*=.08).

Figure 16

Effect of Age of Cannabis-Use Onset on Accuracy (d-prime) in Frequent Users on the Go/No-Go Task. Boxplots show the interquartile range of the data with the median represented by the black horizontal line in each box. Whiskers indicate the upper and lower data extremes.



Overall, accuracy on the task did not significantly differ between frequent cannabis users, infrequent users, and non-users. There was also no significant difference between males and females on task accuracy. This effect was also not significant between female and male frequent users. Further, there was no significant interaction between cannabis-use frequency and sex on accuracy on the task. Analyses on patterns of cannabis use in frequent users indicated that

cannabis-use reason, the length of cannabis use, and last occasion of cannabis use did not have a significant effect on task accuracy. However, early-onset cannabis users were significantly less accurate on the task than late-onset users.

Visuospatial Working Memory- Visuospatial N-Back Task

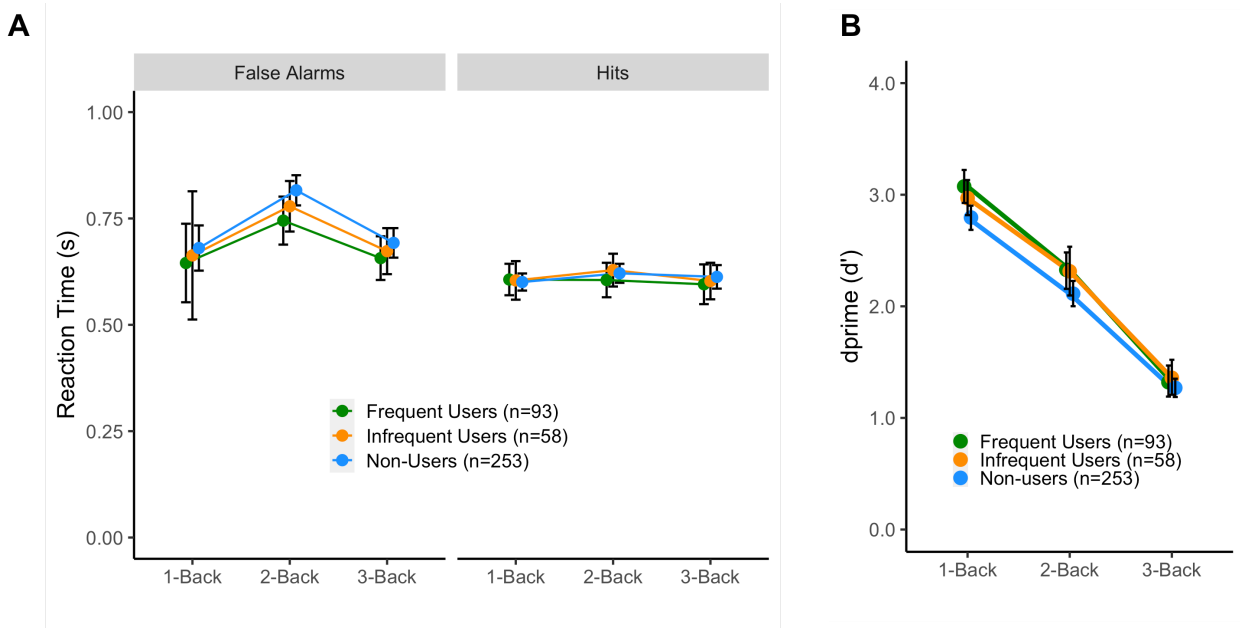
Hit Trials Reaction Time Across Groups. The results indicated that the main effect of load size on hit trial reaction time (shown in Figure 17A) was not statistically significant, $F(2) = 1.52$, $p = .220$; $\eta p^2 = .004$, 95% CI [0, .01]). This indicated that reaction time on hit trials was consistent across the three load sizes. The main effect of group (shown in Figure 17A) was also not statistically significant, $F(2) = .05$, $p = .954$; $\eta p^2 = .0002$, 95% CI [0, .003]. A follow-up Bayesian repeated measures ANOVA on the effect of cannabis-use frequency on hit RTs indicated extreme evidence for an absence of the effect on RTs ($BF_{10} < 10^{-5}$). Similarly, effect of sex on hit reaction times was also not statistically significant, $F(1) = .62$, $p = .434$; $\eta p^2 = .007$, 95% CI [0, .08]. The interaction between group and sex was also not statistically significant, $F(2) = .87$, $p = .421$; $\eta p^2 = .004$, 95% CI [0, .02].

False Alarm Trials Reaction Time Across Groups. The main effect of load size on false alarm reaction times (shown in Figure 17A) was statistically significant and the effect size was medium, $F(2) = 23.79$, $p < .001$; $\eta p^2 = .07$, 95% CI [.03, .11]. A post hoc Tukey test revealed that false alarm trial reaction times on the 1-Back (*EMM*=.65, *SE*=.02) condition were significantly lower than false alarm trial reaction times on the 2-Back (*EMM*=.78, *SE*=.02) condition ($p < .001$). False alarm reaction times on the 2-Back condition were also significantly higher than reaction times on the 3-Back condition (*EMM*=.67, *SE*=.02; $p < .001$). However, there was no statistically significant difference in false alarm reaction times between the 1-Back and the 3-Back condition ($p = .612$).

On the other hand, the main effect of group on false alarm reaction time (shown in Figure 17A) was not statistically significant, $F(2) = .14$, $p = .865$; $\eta p^2 = .0007$, 95% CI [0, .009]. A follow-up Bayesian repeated measures ANOVA on the effect of cannabis-use frequency on false alarm RTs indicated moderate evidence for an absence of the effect on RTs (BF_{10}=.192). The main effect of sex was also not statistically significant, $F(1) = .008$, $p = .930$; $\eta p^2 = .00002$, 95% CI [0, .005]. However, the interaction between group and sex was statistically significant but small, $F(2) = 3.59$, $p = .028$; $\eta p^2 = .02$, 95% CI [0, .05]. A Tukey post hoc test on the interaction indicated that frequent user females (*EMM*=.66, *SE*=.02) were significantly faster on false alarm reaction times (had lower RTs) than non-user females (*EMM*=.75, *SE*=.02; $p < .05$). However, there was no statistical difference between frequent and infrequent user females (*EMM*=.70, *SE*=.03; $p = .505$), or between infrequent user and non-user females ($p = .432$). There was no significant difference between frequent user (*EMM*=.74, *SE*=.04) and non-user males (*EMM*=.67, *SE*=.02; $p = .417$), frequent and infrequent user males (*EMM*=.69, *SE*=.05; $p = .824$), or infrequent user and non-user males ($p = .937$).

Figure 17

Average Reaction Times (Left Panel) and Accuracy (d-prime; Right Panel) on the N-Back Task Across Groups. Error Bars Represent 95% Confidence Interval.



Hit Trials Reaction Time in Frequent Users. Like the main task analysis, the effect of load size on hit trial reaction times in frequent users was not statistically significant, $F(2) = .22$, $p = .803$; $\eta p^2 = .002$, 95% CI [0, .02]. The main effect of sex was also not statistically significant, $F(1) = 1.84$, $p = .179$; $\eta p^2 = .02$, 95% CI [0, .12]. Cannabis-use reason also did not have a significant effect on hit trial reaction times, $F(2) = 1.37$, $p = .259$; $\eta p^2 = .03$, 95% CI [0, .12]. Similarly, the last occasion of cannabis use, $F(2) = .48$, $p = .618$; $\eta p^2 = .01$, 95% CI [0, .08], the length of cannabis use (shown in Figure 18A), $F(1) = .30$, $p = .588$; $\eta p^2 = .004$, 95% CI [0, .07], and the age of cannabis-use onset, $F(1) = .04$, $p = .834$; $\eta p^2 = .0005$, 95% CI [0, .04] did not have a significant effect on hit trial reaction times. A follow-up Bayesian repeated measures ANOVA on the effect of age of cannabis-use onset on hit RTs indicated extreme evidence for an absence of the effect on RTs (BF_{10}=.002).

False Alarm Trials Reaction Time in Frequent Users. Like the main group findings, the effect of load size on false alarm trial reaction times was statistically significant but it was small, $F(2) = 3.74$, $p < .05$; $\eta p^2 = .05$, 95% CI [0, .13]. A post hoc Tukey test indicated that the difference in false alarm reaction time between the 1-Back (*EMM*=.67, *SE*=.05) and 2-Back (*EMM*=.76, *SE*=.04) condition, and between the 1-Back and 3-Back (*EMM*=.68, *SE*=.04) condition was not statistically significant ($p = .073$ and $p = .965$, respectively). However, the difference between the 2-Back and 3-Back condition was statistically significant, with RTs on the 2-Back condition being significantly higher, ($p < .05$).

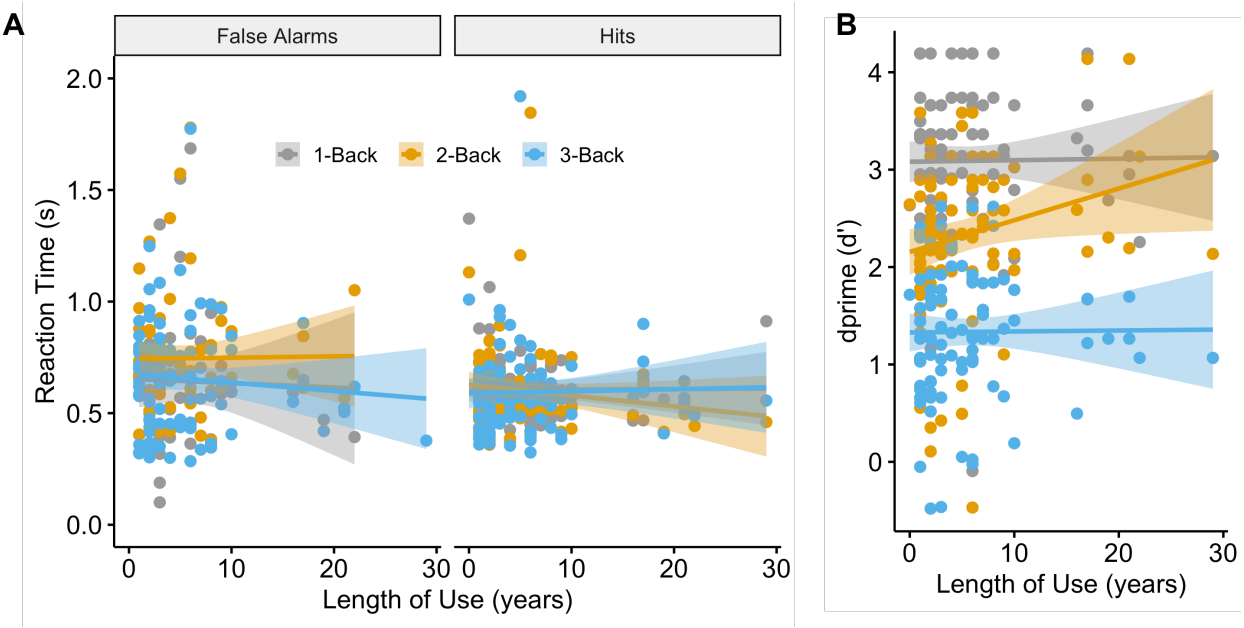
The main effect of sex on false alarm reaction times in frequent users was not statistically significant, $F(1) = 2.62$, $p = .109$; $\eta p^2 = .03$, 95% CI [0, .13]. Similarly, the main effects of cannabis-use reason, last occasion of cannabis use, length of cannabis use (shown in Figure 18A), and age of cannabis-use onset were not statistically significant, $F(2) = 1.23$, $p = .298$; $\eta p^2 = .03$, 95% CI [0, .11], $F(2) = 2.27$, $p = .109$; $\eta p^2 = .05$, 95% CI [0, .15], $F(1) = .72$, $p = .400$; $\eta p^2 = .008$, 95% CI [0, .08], and $F(1) = .08$, $p = .783$; $\eta p^2 = .0009$, 95% CI [0, .05], respectively. A follow-up Bayesian repeated measures ANOVA on the effect of age of cannabis-use onset on false alarm RTs indicated strong evidence for an absence of the effect on RTs (BF_{10}=.062).

In sum, analyses of hit and false alarm RTs on the N-Back task indicated that as the load size increased from 1-Back, 2-Back, to 3-Back, only RTs on the false alarm trials significantly changed. Specifically, RTs on the 2-Back condition were significantly higher than RTs on the 1-Back and 3-Back conditions, with no significant difference between RTs on 1-Back and 3-Back. Further there was no significant difference between frequent users, infrequent users, and non-users in RTs on both hit and false alarm trials. Similarly, the effect of sex regardless of group membership did not affect hit or false alarm RTs. However, there was a small significant

interaction between cannabis-use frequency and sex, where female frequent users were found to have significantly lower RTs than female non-users. In frequent users, sex, last occasion of cannabis use, length of cannabis use, cannabis-use reason, and age of cannabis-use onset did not have a significant influence on RTs for both hit and false alarm trials.

Figure 18

Effect of Length of Cannabis Use on False Alarm and Hit Trial Reaction Times (Panel A) and Accuracy (dprime; Panel B) in Frequent Users on the N-Back Task.

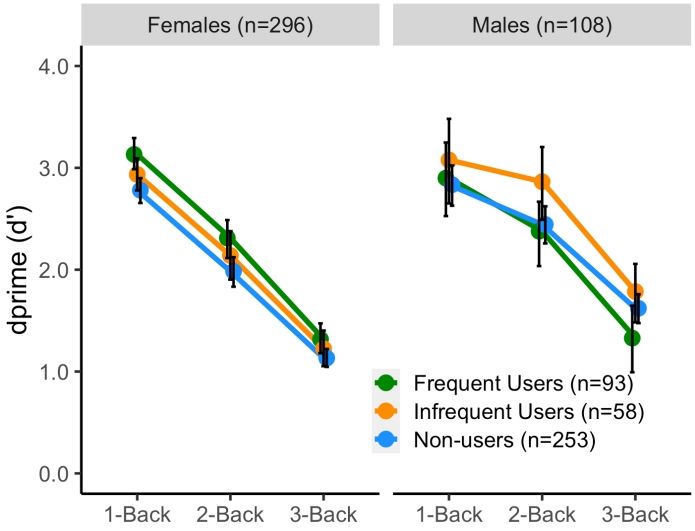


Accuracy (d-prime) Across Groups. The main effect of load size on d-prime (shown in Figure 17B) was statistically significant and large, $F(2) = 699.4$, $p < .001$; $\eta p^2 = .63$, 95% CI [.53, .67]. A Tukey post hoc test showed that d-prime on the 2-Back (*EMM*=2.3, *SE*=.05) condition was significantly lower than d-prime on the 1-Back condition (*EMM*=3.0, *SE*=.05; $p < .001$). It was also significantly lower on the 3-Back (*EMM*=1.4, *SE*=.05) condition than on the 1-Back condition ($p < .001$), and on the 2-Back condition ($p < .001$). This indicates that as the load size increased, d-prime (accuracy) significantly decreased.

Furthermore, the effect of group (shown in Figure 17) on d-prime was not statistically significant, $F(2) = 2.32$, $p = .099$; $\eta p^2 = .01$, 95% CI [0, .04]. A follow-up Bayesian ANOVA on the effect of cannabis-use frequency on d-prime indicated anecdotal evidence for an absence of the effect on d-prime (BF_{10}=.397). The effect of sex on d-prime (shown in Figure 19) was statistically significant but small, $F(1) = 9.23$, $p = .003$; $\eta p^2 = .02$, 95% CI [.003, .06]. The interaction between group and sex was also statistically significant but small, $F(2) = 3.37$, $p = .035$; $\eta p^2 = .02$, 95% CI [0, .05]. A Tukey post hoc test revealed that frequent user females (*EMM*=2.3, *SE*=.07) were significantly more accurate (had a higher d-prime) than non-user females (*EMM*=1.9, *SE*=.05; $p < .05$). However, female frequent users were not significantly different from female infrequent users (*EMM*=2.1, *SE*=.09; $p = .386$), who were also not significantly different from female non-users ($p = .365$). D-prime for male frequent users (*EMM*=2.2, *SE*=.13), infrequent users (*EMM*=2.6, *SE*=.16), and non-users (*EMM*=2.3, *SE*=.07) did not significantly differ ($p = .779$, $p = .166$, $p = .268$, respectively).

Figure 19

Accuracy (d-prime) on the N-Back Task for Females and Males Across Groups. Error Bars Represent 95% Confidence Interval.



Accuracy (d-prime) in Frequent Users. The main effect of load size on d-prime was statistically significant and large, $F(2) = 225.25$, $p < .001$; $\eta p^2 = .71$, 95% CI [.65, .76]. Identical to the main group analysis, a Tukey post hoc test showed that d-prime on the 2-Back condition (*EMM*=2.2, *SE*=.12) was significantly lower than d-prime on the 1-Back condition (*EMM*=3.0, *SE*=.12; $p <$ .001). It was also significantly lower on the 3-Back condition (*EMM*=1.2, *SE*=.12) than on the 1-Back condition ($p < .001$), and on the 2-Back condition ($p < .001$). This indicated that as the load size increased, d-prime (accuracy) significantly decreased.

The main effect of sex on d-prime in frequent users was not statistically significant, $F(1) = .73$, $p = .395$; $\eta p^2 = .009$, 95% CI [0, .09]. Cannabis-use reason also did not have a significant effect on d-prime in frequent users, $F(2) = .61$, $p = .547$; $\eta p^2 = .01$, 95% CI [0, .08]. The last occasion of cannabis use did not have a significant effect on accuracy on the task, $F(2) = .03$, $p =$

.974; ηp^2 = .0006, 95% CI [0.00, 0.001]. Similarly, the length of cannabis use (shown in Figure 18B), $F(1) = .24$, $p = .623$; ηp^2 = .003, 95% CI [0, .07] and the age of cannabis-use onset, $F(1) = 3.48$, $p = .066$; ηp^2 = .04, 95% CI [0, .15] did not have a significant effect on d-prime in frequent users. A follow-up Bayesian repeated measures ANOVA on the effect of age of cannabis-use onset on d-prime indicated anecdotal evidence for the absent of the effect on d-prime (BF_{10}=.933).

Altogether, accuracy on the task (as measured using d-prime), significantly declined as the working memory load increased. There was no significant difference in accuracy between frequent users, infrequent users, and non-users. The effect of sex, and the interaction between sex and cannabis-use frequency were significant where frequent user females were significantly more accurate than non-user females. In frequent users, sex, last occasion of cannabis use, length of cannabis use, age of cannabis-use onset, and cannabis-use reason did not have a significant effect on accuracy on the task.

Cognitive Flexibility (Set Shifting)- Trail Making Test (Trail B)

As this task consisted of five trials (Shown in Figure 20) which is different from the traditional way that the Trail Making Test is carried out, the total completion times (CTs) for trial one, and the average completion times for trials two-five were analyzed separately. A repeated measures ANOVA was carried out to test for the difference in completion time between each trial. The main effect of trial was statistically significant and large, $F(4, 2164) = 241.5$, $p < .001$; ηp^2 = .31, 95% CI [.23, .34]. A Tukey post hoc test showed that completion time for trial one (*EMM*=51.5, *SD*=26.1) was significantly higher ($p < .001$) than the completion times for trials two (*EMM*=35.4, *SD*=15.1), three (*EMM*=33.8, *SD*=14.8), four (*EMM*=32.7, *SD*=15.6), and five (*EMM*=30.8, *SD*=11.3). Completion times continued to decrease as the trials progressed, with a

significant decrease after every other trial: CT for trial two was significantly higher than CT for trial four ($p < .05$), and CT for trial three was significantly higher than CT for trial five ($p < .001$).

Completion Time for Trial One Across Groups. The main effect of group on completion time for trial one (Shown in Figure 21) was statistically not significant, $F(2, 537) = 2.42$, $p = .090$; $\eta p^2 = .01$, 95% CI [.0008, .04]. A follow-up Bayesian ANOVA on the effect of cannabis-use frequency on CT indicated anecdotal evidence for an absence of the effect on CT (BF_{10}=.484). On the other hand, the main effect of sex (shown in Figure 22) on completion time for trial one was statistically significant but very small, $F(1, 537) = 6.83$, $p = .009$; $\eta p^2 = .003$, 95% CI [0, .02]. Specifically, females (*EMM*=51.9, *SE*=1.5) were significantly slower (had a higher completion time) than males (*EMM*=43.8, *SE*=2.7; $p < .05$). The interaction between group and sex was not statistically significant, $F(2, 537) = .88$, $p = .417$; $\eta p^2 = .01$, 95% CI [0, .03].

Figure 20

Completion Time for Trials One to Five Across Groups on the Trail Making Test. Error Bars Represent 95% Confidence Interval.

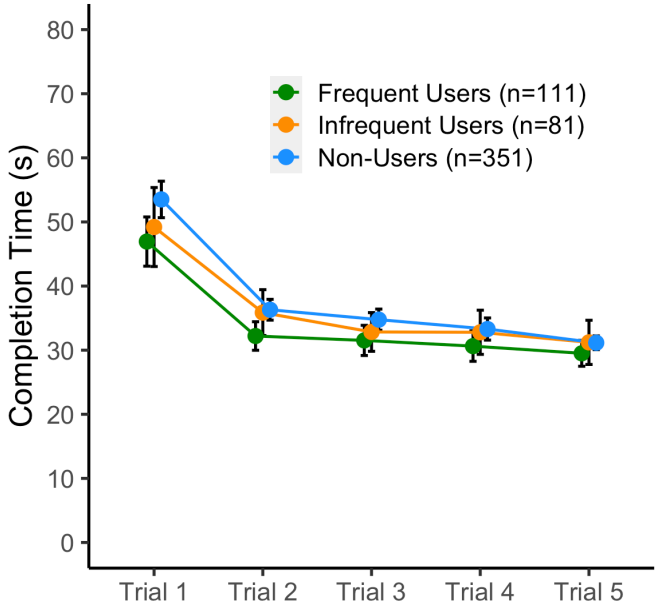


Figure 21

Boxplots of Completion Time One Across Groups on the Trail Making Test. Boxplots show the interquartile range of the data with the median represented by the black line in each box. Whiskers indicate the upper and lower data extremes.

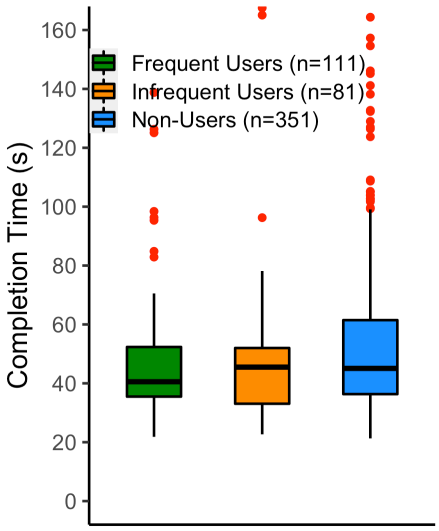
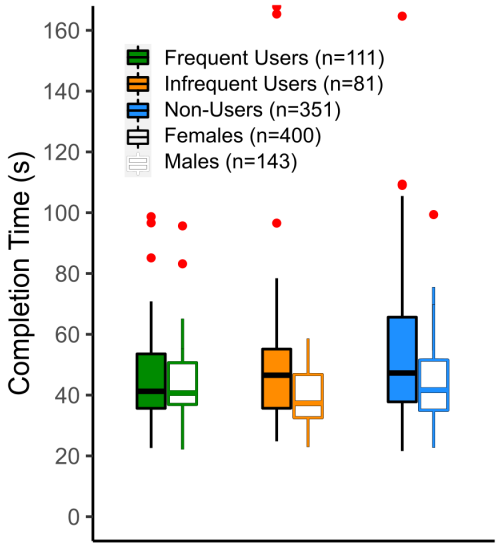


Figure 22

Boxplots of Completion Time One for Females and Males Across Groups on the Trail Making Test. Boxplots show the interquartile range of the data with the median represented by the black horizontal line in each box. Whiskers indicate the upper and lower data extremes.



Completion Time for Trial One in Frequent Users. The main effect of sex on completion time for trial one was not statistically significant, $F(1, 90) = 1.11$, $p = .294$; $\eta p^2 = .01$, 95% CI [0, .09]. Cannabis-use reason also did not have a significant effect on completion time, $F(2, 90) = .68$, $p = .510$; $\eta p^2 = .01$, 95% CI [0, .08]. However, the last occasion of cannabis use (shown in Figure 23) had a significant, medium sized effect on completion time for trial one, $F(2, 90) = 6.47$, $p < .01$; $\eta p^2 = .13$, 95% CI [.02, .25]. A post hoc Tukey test showed that frequent users who did not use cannabis in the last 24 hours (*EMM*=39.1, *SE*=3.4) were not significantly different from those who used in the last 24 hours (*EMM*=45.6, *SE*=2.9; $p = .224$). However, frequent users who did not use cannabis in the last 24 hours were significantly faster (lower completion time) than those who used while doing the study (*EMM*=62.3, *SE*=5.7; $p < .001$). Frequent users who used cannabis in the last 24 hours were also significantly faster than those who used cannabis during the study ($p < .05$). This indicates that frequent users who were under the influence of cannabis while doing the study had significantly higher completion times. On the other hand, the length of cannabis use (shown in Figure 24), $F(1, 90) = .14$, $p = .707$; $\eta p^2 = .002$, 95% CI [0, .05] did not have a significant effect on completion time for trial one. Similarly, the age of cannabis-use onset also did not have a significant effect on completion time for trial one, $F(1, 90) = .48$, $p = .488$; $\eta p^2 = .005$, 95% CI [0, .07]. A follow-up Bayesian independent samples t-test on the effect of age of cannabis-use onset on CT indicated moderate evidence for an absence of the effect on CT (BF_{10}=.212).

Figure 23

Effect of Last Occasion of Cannabis Use on Completion Time One in Frequent Users on the Trail Making Test. Boxplots show the interquartile range of the data with the median represented by the black horizontal line in each box. Whiskers indicate the upper and lower data extremes.

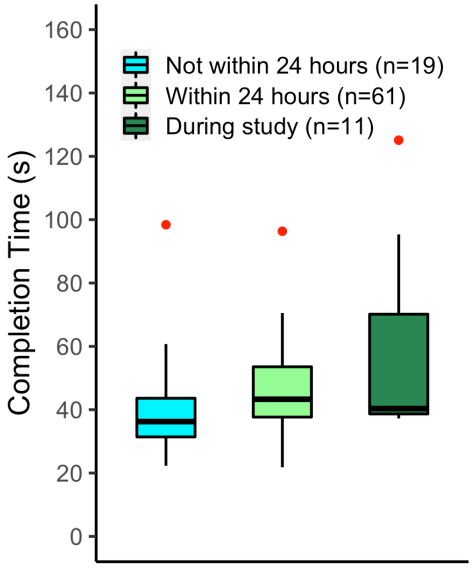
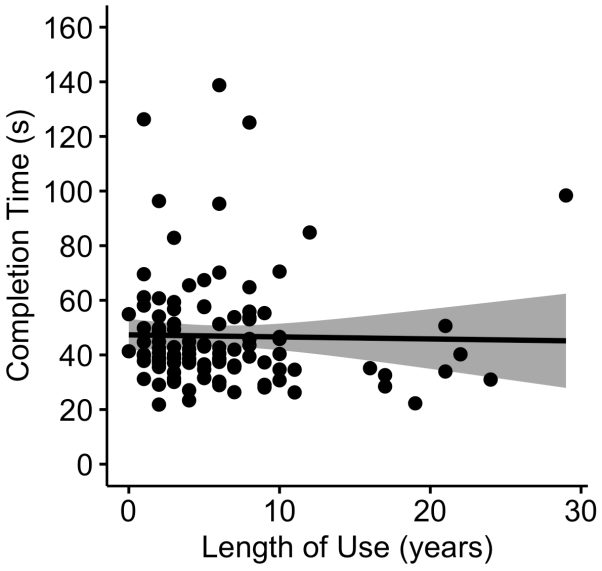


Figure 24

Effect of Length of Cannabis Use on Completion Time One in Frequent Users on the Trail Making Test.



In sum, analysis of completion times (CTs) on trials one to five indicated that CTs significantly decreased with increased practice, specifically after every other trial. CTs on trial one did not significantly differ in frequent users, infrequent users, and non-users. Meanwhile, females were found to be significantly slower than males regardless of their group membership. However, there was no significant difference in CTs between female and male frequent users, suggesting no differential effect of sex on CT. The length of cannabis use and the reason for cannabis use did not have a significant effect on CT in frequent users. However, the last occasion of cannabis use had a significant medium-sized effect on CT. Specifically, frequent users who did not use cannabis in the last 24 hours, and frequent users who used cannabis in the last 24 hours were both significantly faster than those who used while doing the study. This suggests an impairment associated with an acute effect of cannabis use.

Average Completion Time for Trials Two to Five Across Groups. The main effect of group on average completion time for trials two to five was not statistically significant, $F(2, 537) = 1.46$, $p = .233$; $\eta p^2 = .03$, 95% CI [.007, .06]. A follow-up Bayesian ANOVA on the effect of cannabis-use frequency on CT indicated moderate evidence for an absence of the effect on CT (BF_{10}=.323). However, the main effect of sex was statistically significant but very small, $F(1, 537) = 15.06$, $p < .001$; $\eta p^2 = .006$, 95% CI [0, .02], where females were significantly slower (*EMM*=34.0, *SE*=.68; had higher completion times) than males (*EMM*=28.8, *SE*=1.2). On the other hand, the interaction between group and sex was not statistically significant, $F(2, 537) = 1.66$, $p = .191$; $\eta p^2 = .005$, 95% CI [0, .02].

Average Completion Time for Trials Two to Five in Frequent Users. The main effect of sex did not have a statistically significant effect on average completion time for trials two to five, $F(1, 90) = .34$, $p = .562$; $\eta p^2 = .004$, 95% CI [0, .07]. Similarly, the main effect of cannabis-use reason

did not have a statistically significant effect, $F(2, 90) = .43$, $p = .649$; $\eta_p^2 = .01$, 95% CI [0, .07]. Also, the last occasion of cannabis use (shown in Figure 25), $F(2, 90) = 1.88$, $p = .158$; $\eta_p^2 = .04$, 95% CI [0, .13], the length of cannabis use (shown in Figure 26), $F(1, 90) = .68$, $p = .411$; $\eta_p^2 = .008$, 95% CI [0, .08], and the age of cannabis-use onset, $F(1, 90) = .49$, $p = .486$; $\eta_p^2 = .005$, 95% CI [0, .07] did not have a statistically significant effect on average completion time for trials two to five. A follow-up Bayesian independent samples t-test on the effect of age of cannabis-use onset on CT indicated anecdotal evidence for an absence of the effect on CT (BF_{10}=.486).

Overall, analysis of the average CT on trials two to five indicated that there was no significant effect of cannabis-use frequency on CTs. However, like the analysis of trial one, females were significantly slower than males, but this effect size was very small. Additionally, the interaction between cannabis-use frequency and sex on CT was not significant. Finally, in frequent users, the effect of sex, last occasion of cannabis use, the length of cannabis use, cannabis-use reason, and age of cannabis-use onset was not significant.

Figure 25

Effect of Last Occasion of Cannabis Use on Average Completion Time for Trials Two to Five in Frequent Users on the Trail Making Test. Boxplots show the interquartile range of the data with the median represented by the black horizontal line in each box. Whiskers indicate the upper and lower data extremes.

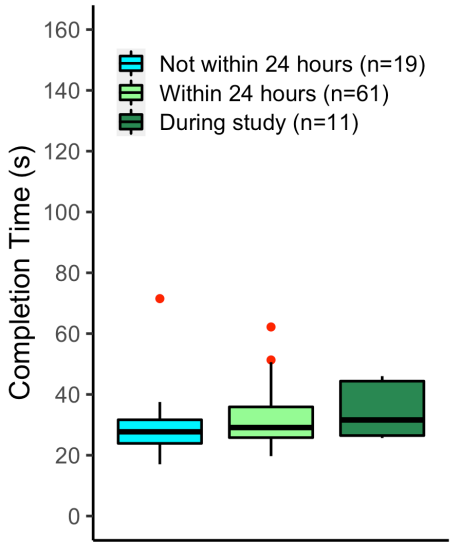
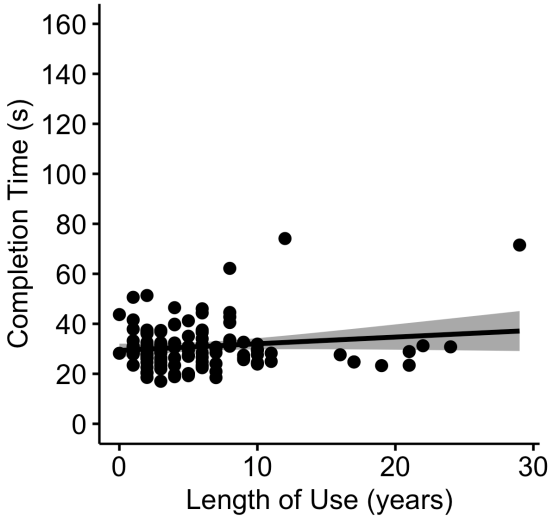


Figure 26

Effect of Length of Cannabis Use on Average Completion Time for Trials Two to Five in Frequent Users on the Trail Making Test



Discussion

Summary of Findings

The main purpose of this study was to determine whether the frequency of cannabis use affects executive functioning performance in a large sample of participants tested under naturalistic circumstances. The performance of frequent cannabis users, infrequent users, and non-users was compared on measures of selective visual attention, response inhibition, visuospatial working memory, and set shifting (cognitive flexibility). The hypothesis of this study was confirmed as findings indicated that cannabis-use frequency did not have a meaningful effect on performance on any of the tasks, except for the Visual Search task where both frequent users and infrequent users were significantly more accurate than non-users.

Further, it was of interest to determine whether the frequency of cannabis use had a differential effect on executive functioning in males and females. The findings indicated that the frequency of cannabis use did not differentially affect the performance of males and females on measures of response inhibition, visuospatial working memory, and set shifting abilities. However, although the effect size was small, female frequent users were found to be significantly faster in their responses than male frequent users on the Visual Search task. This was not attributable to a general sex difference in performance on the task. Additionally, female frequent users were found to be significantly more accurate than female non-users on the visuospatial N-Back task, yet they were also significantly faster (lower RT) when making errors on the task.

In frequent users, the reason for cannabis use (recreational, medical, or both) did not have a significant effect on any of the measures. Similarly, the length of cannabis use (in years) also did not have a significant impact on the performance of any of the tasks. The effect of the last occasion of cannabis use (during study, within the last 24 hours of the study, or not within the last 24 hours

of the study) on the executive functioning measures was also explored. The findings indicated that the effect of the last occasion of cannabis use did not significantly affect performance on the Visual Search task, the Go/No-Go task, and the visuospatial N-back task. However, on the Trail Making Test, frequent users who were under the influence of cannabis while doing the study were significantly slower than those who used cannabis within the last 24 hours of the study, and also significantly slower than those who did not use cannabis within the last 24 hours of the study. On the other hand, the age of cannabis-use onset was associated with a difference in performance on the Go/No-Go task where frequent users who initiated cannabis use before the age of 16 were significantly less accurate on the task than those who initiated use after the age of 16.

Discussion of Findings

With regards to the frequency of cannabis use, the findings of this study are consistent with previous studies that utilized similar measures to investigate the nonacute effects on executive functioning in regular cannabis users. The aim of these studies was to determine whether there are any lasting effects of cannabis on cognition that remain past the acute effects stage. For example, as discussed earlier, Grant and colleagues (2019) found no difference between cannabis users and non-users on tasks of response inhibition and visuospatial working memory. Likewise, Tamm et al. (2013), and Borgwardt et al. (2018) also found no significant difference in response inhibition and visuospatial working memory performance in cannabis users. Similarly, Rangel-Pacheco and colleagues (2020) and Nusbaum and colleagues (2017) found no difference between cannabis users and non-users on selective visual attention measures. Notably, although the effect size was small, we found that frequent and infrequent users were more accurate than non-users on our measure of visual attention. This finding is still important even after noting the small effect size as it indicates that cannabis users are not performing worse than nonusers on the task. As for cognitive

flexibility and set shifting abilities, several studies that administered the Trail Making Test like this study, found no significant difference in the performance of cannabis users in comparison to non-users (Porfirio et al., 2020; Tamm et al., 2013). Similarly, Scholes and Martin-Iverson (2010) also found no significant difference in the performance of cannabis users on the Wisconsin Card Sorting Task which is known to be a reliable measure of executive functioning.

Conversely, some studies also investigating nonacute effects of cannabis have found some impairments in cannabis users. For example, Lisdahl and Price (2012), found that cannabis users who had current, frequent cannabis use demonstrated deficits in sequencing ability, psychomotor speed, and cognitive inhibition compared to demographically matched controls. However, it is important to note that in this study, cannabis users were not excluded for having other illicit drug use as long as the number of these occasions was below 100 in their lifetime and below ten in the past year. Also, subjects in the control group were included even if they were infrequent cannabis users and had previous episodes of illicit drug use. Further, it was reported that the cannabis group had significantly greater lifetime and past year alcohol use than the control group (Lisdahl & Price, 2012). Accordingly, the reported deficits may not necessarily be the cause of the frequent cannabis use as there are several confounds in the study that may account for these findings.

Additionally, Thames et al. (2014) compared the performance of recent and past (last use more than 28 days before study) cannabis users to non-users on several measures including executive functioning (using the Trail Making Test and Color-Word Test). They found that recent users performed significantly worse than past users and non-users on all neurocognitive measures including executive functioning. Additionally, they also reported that past users performed significantly worse than non-users solely on executive functioning measures. Although recent, frequent users demonstrated several neurocognitive deficits, it is possible that the observed effect

was the result of an acute influence of cannabis which has previously been shown to be impairing in some studies (Anderson et al., 2010; Hunault et al., 2009; Ilan et al., 2004). This is plausible as recent use was confirmed through toxicology screening. Further, although an executive functioning deficit was observed in past users, it is important to note that the effect was small in magnitude and may lack practical significance (Thames et al., 2014).

While the current study's findings are analogous to most previous findings on the nonacute effect of cannabis, it contributes to the literature in several ways. First, this study is one of the first to utilize a large sample of both frequent and infrequent cannabis users with 254 participants completing at least one of the tasks (143 frequent users). Second, the study was carried out in a legalized-cannabis jurisdiction which may promote greater honesty on self-reported patterns of cannabis use. Third, participants with prior illicit drug or substance use were excluded from the study to ensure a purer measure of the effect of cannabis on executive functioning. Fourth, this study utilized well established tasks and aimed to include several measures of performance with the purpose of tapping into a considerable number of executive functioning components. Lastly, the sample of cannabis users assessed in this study was made up of approximately 75% female which is uncommonly found in previous literature where males make up the majority of samples (Francis et al., 2022).

Furthermore, this study also investigated whether sex differences exist in the effect of cannabis use on executive functions and whether more frequent use affected the sexes differently. The findings of this study did not replicate previous findings that showed a performance deficit in female cannabis users as compared to male cannabis users. For example, Hirst et al. (2020) investigated chronic effects and showed that in a sample of cannabis users, males outperformed females on Trails B of the Trail Making Test. However, in that study females and males

demonstrated similar performance levels on tasks of visual learning and memory. Similarly, Savulich et al. (2021) found that female cannabis users were outperformed by male cannabis users on measures of attention and executive functioning that included a spatial working memory component. However, females performed better than males on a measure of visual recognition memory (Savulich et al., 2021). This finding is somewhat consistent with our results where female frequent users demonstrated lower RTs on the Visual Search task. This may indicate that female frequent users may have a better memory for already searched distractors and may therefore employ a better search strategy than male cannabis users. On the other hand, similar to our findings, Pope et al. (1997) did not report any sex differences in heavy and light cannabis users (44% female) on measures of visuospatial working memory, response inhibition, and attention. However, in this study, female heavy cannabis users with daily use performed significantly worse than female light users. Although this comparison was made between heavy and light cannabis users, it is inconsistent with our finding of female frequent users being more accurate than female nonusers on the visuospatial N-Back task. Notably, the sample size of females in Pope et al.'s (1997) study was very small (nine heavy users and 15 light users) compared to our study.

It is important to note that most studies that have investigated sex differences in the effect of cannabis use tend to examine acute cannabis effects more so than chronic effects. Most of these studies tend to report that male and female cannabis users perform similarly on neurocognitive tasks while under the influence of cannabis (Crane et al., 2013). These studies also report greater subjective effects in females following cannabis administration than males which has led to the exploration of whether these subjective effects transfer to differential cognitive and behavioural performance (e.g., Sholler et al., 2020). Otherwise, the current research on sex differences in regular and frequent cannabis use under nonacute conditions on executive functioning is limited

and uncommon. Therefore, these findings contribute significantly to the literature as this is the first known study to examine sex differences in a large sample of cannabis users on tasks assessing the main components of executive functioning. Ultimately, this study does not find any substantial sex differences in the effect of cannabis-use frequency on executive functioning.

Previous studies have suggested that medical cannabis use may improve cognitive performance as it is followed by the alleviation of symptoms such as anxiety and pain (Burggren et al., 2019; Eadie et al., 2021). This is partly because medical use is often initiated at an older age and may place a lesser impact on the brain than cannabis use that is initiated at a young age during critical development periods of the brain (Gruber et al., 2018). Sagar et al. (2020) found that medical cannabis patients undergoing a 12-month medical cannabis treatment significantly improved (assessed at baseline, three months, six months, and 12 months) on measures of executive functioning (assessed using TMT, WCST, and a Stroop test) compared to baseline performance. Patients in that study reported using cannabis of greater concentrations of CBD relative to THC which was associated with the improved performance as CBD is thought to mitigate the negative effects of THC on the brain (Sagar et al., 2020). The current study did not find differences in the performance of frequent cannabis users who used solely for recreational purposes, medical purposes, or both. This is possibly because the current study may be underpowered in this regard with a small number of participants reporting cannabis use solely for medical purposes (approximately 7%). Certainly, this is expected as the sample assessed in this study predominantly consisted of healthy, young adults who may not have the need to use cannabis particularly for medical purposes. Bayesian analyses were carried out to determine whether this finding was in fact indeterminate due to the small sample of medical users. The results indicated anecdotal to strong evidence for the absence of an effect of use reason on all measures utilized in

this study. This may indicate that the reason for cannabis use (recreational, medical purposes, or both) may not be associated with differences in executive functioning performance and that this finding is not necessarily due to the small sample of medical users utilized here.

Several studies have reported that cannabis use that is initiated during vulnerable neurodevelopmental periods leads to significant decrements in several neurocognitive domains, specifically, executive functioning (Gruber et al., 2012; Dahlgren et al., 2015). This is because executive functions heavily rely on the prefrontal cortex which has been shown to mature slower than other brain regions. Indeed, it has been shown that between the ages of 12-16 and 23-30, the dorsal, medial, and lateral regions of the frontal lobes undergo greater neuromaturational changes than other regions (Sowell et al., 1999). These neuromaturational changes are known to rely greatly on the endocannabinoid system which is why cannabis use that is initiated during vulnerable developmental periods are thought to affect these processes (Viveros et al., 2012).

Previous studies have compared cannabis users who initiated use before the age of 16 to those who initiated use after the age of 16 to determine whether the age of cannabis-use onset is associated with differences in influences performance on executive functioning. Using the same criteria, this study compared early-onset to late-onset frequent cannabis users on executive functioning performance. The findings of the current study indicated that initiation of cannabis use at an early age did not affect performance on selective visual attention, visuospatial working memory, and cognitive flexibility and set shifting abilities. However, frequent users with an early age of cannabis-use onset were significantly less accurate on the measure of response inhibition. The findings of this study (excluding response inhibition) did not replicate previous findings that showed that early-onset cannabis users demonstrated deficits in some executive functioning components compared to late-onset users under nonacute conditions (Gruber et al., 2012; Dalhgren

et al., 2015; Fontes et al., 2011). However, Gruber et al. (2012) reported similar findings to the current study where no significant differences in performance were demonstrated on the Trail Making Test between early and late-onset cannabis users. Further, like the findings of the current study, Fontes et al. (2011) administered the Go/No-Go task as part of a battery to early and late-onset cannabis users and found that participants who initiated cannabis use at an early age performed worse on the task.

Additionally, unlike most behavioural studies where this has been neglected, the length of cannabis use (in years) was also explored as grouping cannabis users based on the age of cannabis-use initiation does not account for this. Over all measures used in this study to assess the main components of executive functioning, the length of cannabis use was not found to affect performance levels in frequent cannabis users. This finding is consistent with previous findings that have suggested that durations of cannabis use below 10 years do not significantly executive functioning performance (Lovell et al., 2019; Schreiner & Dunn, 2012).

Surely, there appears to be some effect of early versus late initiation of cannabis use on particular executive functioning components. However, the length of cannabis use does not appear to affect performance on these measures given the moderate length of use reported in this study. Essentially, these findings greatly contribute to the limited and inconsistent research that currently exists on the effect of length of cannabis use and age of cannabis-use onset on executive functioning components.

As the current study attempted to assess cannabis users under naturalistic circumstances (like Grant et al., 2019) and did not require cannabis users to abstain from cannabis before participating the study, the last occasion of cannabis use was evaluated to distinguish acute from residual effects of cannabis. In frequent users, the majority of participants reported using cannabis

within the last 24 hours of the study (approximately 67%). While a very small portion reported using during the time of the study (approximately 7%). The findings indicated that the last occasion of cannabis use did not influence selective visual attention, visuospatial working memory, and response inhibition performance. However, cognitive flexibility and set shifting performance was significantly worse in frequent users who were under the influence of cannabis during the study compared to those who used within the last 24 hours and those who did not. This effect (although small in magnitude) replicated findings from a previous study investigating the acute effect of cannabis on cognitive flexibility and set shifting performance (assessed using the TMT; Anderson et al., 2010). Nonetheless, the current sample consisted of a small number of participants who reported being under the influence of cannabis during the study which may indicate that it is underpowered when it comes to detecting an acute effect on executive functioning performance. However, previous studies also reported no significant effect of acute cannabis use on measures of response inhibition (Hart et al., 2001; Ramaekers et al., 2006). Notably, studies investigating acute effects of cannabis use on selective visual attention and visuospatial working memory are scarce, except for two studies that found slowed responses after acute administration of THC on selective visual attention and visuospatial working memory (Hunault et al., 2009; Ilan et al., 2004). Additionally, the current study did not find any significant residual impairments within the 24-hour period following acute administration of cannabis. Ultimately, findings from both the current study and previous studies on the acute and short-term residual effects of cannabis on executive functioning are inconsistent and require substantial further investigations.

Conclusion

Overall, the current study has demonstrated that the main components of executive functioning are not affected by the frequency of cannabis use in a large sample of young, healthy university students. Of particular importance, frequent cannabis users who used cannabis at least once a week to daily were not impaired in comparison to both infrequent users and nonusers. Secondary analyses in frequent cannabis users on sex differences, reason for cannabis use, age of cannabis-use onset, length of use, and last occasion of use did not yield substantial significant effects on most measures utilized here to assess the main components of executive functioning.

Limitations and Future Research

This study has potential limitations. First, the sample utilized in this study was composed of young, healthy, and high functioning university students with no known neurological conditions and no history of illicit substance use. Although this is necessary to be able to distinguish the pure effect of cannabis use, the findings may not generalize to the broader population of cannabis users. Future studies should recruit a more diverse sample of cannabis users of varying ages and socioeconomic statuses. Second, cannabis users in this study were not required to abstain from cannabis use prior to their participation, as the aim was to assess users under naturalistic circumstances. Although the last occasion of cannabis use was included in the analyses, it may be argued that the study did not thoroughly assess nonacute effects of cannabis. However, as this was a fully online browser study, it would have been difficult to ensure that participants did in fact abstain. This minimal control can be argued as a caveat of online studies as abstinence of cannabis is normally confirmed using urine drug screening in other studies. Third, the sample utilized here was composed of a greater proportion of females (approximately 74%) than males. Although this can be argued as a limitation of the current study, previous studies have consistently reported using

samples that were mainly composed of males. Therefore, this study partly contributes to the limited literature on the effect of cannabis use in females. Finally, as participants self-enrolled in this study, it can be argued that there was a self-selection bias where high-functioning cannabis users opted to participate in the research. However, as this study was part of a larger-scale investigation that included the assessment of several demographic and lifestyle factors besides cannabis use, approximately 47% of cannabis users (frequent and infrequent) enrolled in other studies that were not labelled for assessing the effect of cannabis use.

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