CHRONIC USE EFFECTS, OR JUST THE EFFECTS OF USING CHRONIC?

CHRONIC USE EFFECTS, OR JUST THE EFFECTS OF USING CHRONIC? EXAMINING THE ROLES OF LIFETIME AND CURRENT SEVERITY OF CANNABIS USE IN NEUROCOGNITIVE PERFORMANCE AND ADHD SYMPTOMS.

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TITLE: Chronic use effects, or just the effects of using chronic? Examining the roles of lifetime and current severity of cannabis use in neurocognitive performance and ADHD symptoms.

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Lay Abstract

It is unclear to what extent cannabis use effects mental functions such as memory, attention, and intelligence. The goal of this research was to investigate how recent and early-life cannabis use is related to these cognitive functions and real-life problems with attention and impulse control as seen in ADHD. Two studies were performed to investigate these relationships, and together found recent cannabis use rather than lifetime use to be predictive of performance on select cognitive abilities and ADHD symptoms. Age of first cannabis use and lifetime use were not associated with differences in cognition, suggesting that cannabis use in adolescence may not necessarily cause lasting detrimental changes. Rather, people who have symptoms of ADHD may be more likely to use cannabis earlier and in more problematic ways.

Abstract

Cannabis use is becoming increasingly prevalent in Canada and the United States, where legality and public perception have recently shifted to be more permissive of recreational use. Despite established negative health consequences associated with persistent use, there remains considerable debate in the scientific community surrounding the potentially harmful effects of cannabis use on human cognition. Evidence exists that heavy cannabis use predicts diminished performance within several neurocognitive domains and also predicts greater risk of having ADHD. Further evidence suggests that earlier age of first cannabis use strengthens these associations, however the findings in these literatures are mixed and in need of further delineation. This thesis sought to examine continuous associations among current cannabis use severity, age of first use, neuropsychological performance, and ADHD symptomatology. Two studies using large samples of community adults were conducted. Study 1 analyzed data from the Human Connectome Project, and examined performance on a battery of neuropsychological measures among young adults, and found recent use to be the strongest predictor of differences in episodic memory and processing speed, and CUD predicted lower fluid intelligence. Lifetime exposure to cannabis was not associated with any outcome measures. Study 2 examined similar associations in a sample of adults representative of the Hamilton community, and also included self-reported symptoms of ADHD. Study 2 found current cannabis use severity to be predictive of more impulsive reward preferences, and also of both hyperactive-impulsive and inattentive symptoms of ADHD. Both studies found a lack of support for the role of age of first cannabis use in differential cognitive performance, and

also failed to find associations between cannabis involvement and several cognitive domains such as working memory, behavioural inhibition, executive function, and psychomotor dexterity. These findings challenge some of the current literature, and highlight the necessity of further investigation to better understand interrelationships among cannabis use, cognition, and ADHD.

Key Words: cannabis, cannabis use disorder, age of first use, cognition, neuropsychology, ADHD.

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List of Abbreviations and Symbols

α: Type I error rate alpha

ADHD: Attention Deficit/Hyperactivity Disorder

AFU: Age of first use

ASRS: Adult self-report scale

AUC: Area under the curve

AUDIT: Alcohol Use Disorders Identification Test

β: Standardized regression coefficient Beta

CUD: Cannabis Use Disorder

CUDIT-R: Cannabis Use Disorders Identification Test – Revised

DSM-5: Diagnostic and Statistical Manual of Mental Disorders: 5th edition

FTND: Fagerstrom Test of Nicotine Dependence

h: Probability discounting rate

HCP: Human Connectome Project

k: Delay discounting rate

MCQ: Monetary Choice Questionnaire

NIH: National Institute of Health

PATH: Population Assessment for Tomorrow's Health

PCA: Principal Components Analysis

PCQ: Probabilistic Choice Questionnaire

SPCPT: Short Penn Continuous Performance Test

SSAGA: Semi-Structured Assessment for the Genetics of Alcoholism

THC: Δ^9-tetrahydrocannabinol

UDS: Urine drug screen

WHO: World Health Organization

Declaration of Academic Achievement

This thesis consists of two primary research articles designed to investigate dimensional associations among current and lifetime cannabis use characteristics, task-based neuropsychological measures, and self-reported ADHD symptoms. I, Tashia Petker, am the author of this thesis and am also the first author of the two studies comprising this work. The data for Study 1 was collected as part of the Human Connectome Project at Washington University, Missouri, and the analytic strategy was developed in collaboration with my supervisor, James MacKillop, Michael Amlung, and contributing authors from the University of Georgia: Max Owens, Assaf Oshri, and Lawrence Sweet. Study 1 has been submitted for publication in the journal *Neuropsychopharmacology* and is currently awaiting peer-review. The data for Study 2 was collected as part of the Population Assessment for Tomorrow's Health (PATH) research registry at the Peter Boris Centre for Addictions Research, and the analytic plan for the present study was developed in collaboration with James MacKillop. In addition to my supervisor and co-authors listed, the members of my committee (Louis Schmidt and Geoff Hall) also contributed their constructive criticisms and guidance to the design of studies described in this thesis.

Chapter 1: Introduction

Cannabis is the most widely used illegal substance worldwide, with rates of use increasing at a more rapid rate than any other illicit drug (World Health Organization, 2010). This phenomenon is most apparent in North America, which represents the highest prevalence of use worldwide (United Nations Office on Drugs and Crime, 2014) where legality and public opinion surrounding medicinal and recreational cannabis use have become more tolerant. For instance, Canada and the United States have experienced increased rates of use while overall perception of cannabis as harmful has decreased in recent years. Several regions in the United States and Canada federally have recently committed to legalization of recreational cannabis use, and this could potentially cause further decreases in perceived risks and an increase of cannabis use in the general population. Given these current trends, the scientific investigation of potential physical and mental health risks of cannabis use is of great priority for public health interests.

Despite ongoing scientific debate, there are some health risks associated with regular, prolonged cannabis use that are well supported by the literature to date. Lung illnesses from smoked cannabis, motor vehicle injuries due to intoxicated driving, and an increased risk for psychotic disorders are all established health consequences associated with cannabis use (Imtiaz et al., 2016; Volkow, Baler, Compton, & Weiss, 2014). Most importantly, heavy cannabis use confers substantial risk for developing a cannabis use disorder (CUD), which is characterized by loss of control over use, tolerance and withdrawal effects, and significant psychosocial impairments. The current prevalence of

CUDs in the Canadian population is 0.3-0.8%, and CUD is the greatest contributor to cannabis-related burden of disease (Imtiaz et al., 2016). Additionally, the adverse effects of cannabis use on cognitive performance in adaptive functioning abilities such as memory, intelligence, and attention have gained considerable research interest in recent years, however the findings of these studies remain mixed and in need of resolution. For instance the acute effects of administering the psychoactive component of cannabis Δ^9-tetrahydrocannabinol (THC) has been consistently shown to diminish performance on a range of neurocognitive tasks (Broyd, Van Hell, Beale, Yücel, & Solowij, 2016), however the more distal effects of THC exposure after periods of abstinence remain unclear. Due to high heterogeneity in study methods, participant characteristics of cannabis use histories, and differential controlling for potential confounds, much of the evidence for the adverse effect of cannabis on cognitive ability remains conflicting (Broyd et al., 2016; Ganzer, Bröning, Kraft, Sack, & Thomasius, 2016). Furthermore much of the evidence comes from small-sample studies, highlighting a need for large, well-controlled investigations to further delineate these relationships.

The negative association between cannabis use and cognitive performance may directly relate to psychopathology, specifically to issues with memory, concentration and impulse control. Attention deficit/hyperactivity disorder (ADHD) is a condition that is characterized by these impairments, and those with a lifetime diagnosis of ADHD are more likely to use cannabis than other drugs (Molina et al., 2013). There is also a very high comorbidity rate between ADHD and problematic cannabis use, with estimates of

34-36% of those in treatment for CUD also meeting criteria for ADHD (Notzon et al., 2016; Van de Glind et al., 2013), indicating the presence of a complex relationship between functional impairments due to CUD and ADHD. It remains unclear however whether the observed relationship is limited to individuals with clinical diagnoses, or whether it can also be observed on a continuum among people with subclinical levels of cannabis use and/or ADHD symptoms. Much of the evidence comes from studies using small, case-control designs between diagnostic groups, and there is a relative paucity of large-scale studies examining ADHD symptoms dimensionally.

Another major question that remains unanswered in the literature is whether using cannabis during development confers greater risk for cannabis-related harms to adult cognitive functioning. The highest rates of overall and increasing use are observed in adolescents and emerging adults (Rotermann & Macdonald, 2018), and there has been a pronounced scientific interest in the potentially damaging effects of cannabis use during this developmental period. Cross-sectional studies have repeatedly found that younger age of first cannabis use is associated with more severe cannabis use and worse cognitive performance in adulthood (Gruber, Sagar, Dahlgren, Racine, & Lukas, 2012; Pope et al., 2003; Solowij et al., 2011). There are several longitudinal studies examining cognitive changes after cannabis initiation, however the findings of this body of work remain mixed (Meier et al., 2018; Mokrysz et al., 2016; Scott et al., 2018). The causal relationship between age of first cannabis use and adult ADHD symptomology is also still unclear. Adults with a childhood ADHD generally have a younger age of cannabis (and other

substance use) initiation (e.g., Lee, Humphreys, Flory, Liu, & Glass, 2011), which suggests ADHD may be a risk factor for later problematic substance use. Taken together, the state of the current literature on the interrelationships between ADHD, cannabis use, and cognitive functioning is still in its infancy and in need of more studies to parse the causal relationships.

The works presented in this thesis were aimed to address several aforementioned gaps in the literature. Primarily, both studies sought to describe associations between cognitive task performance, severity of current cannabis use, and age of first use in large, representative samples of adults with varying degrees of cannabis involvement. Study 1, "*Cannabis involvement and neuropsychological performance: findings from the Human Connectome Project"* examined these relationships in a sample of 1211 young adults (ages 22-36), including a measure of recent cannabis use as indicated by THC presence in urine drug screening. Study 1 also included an extensive battery of neuropsychological tasks examining episodic memory, fluid intelligence, attention, working memory, executive function, impulsivity, processing speed, and psychomotor dexterity. Study 2, *"Cannabis use, cognitive performance, and attention deficit/hyperactivity disorder in a large sample of community adults"* investigated associations of interest among a sample of 958 young to older adults (age 18-65) who completed tasks assessing verbal short-term memory, working memory, behavioural inhibition, risky decision-making, impulsivity, and verbal intelligence. Study 2 had the unique aim of examining dimensional hyperactive-impulsive and inattentive ADHD symptom profiles in relation to cannabis

use, and utilized self-reported experiences of ADHD symptoms as a measure of real-world cognitive function problems. Both studies examined continuous relationships among cannabis use variables and neuropsychological measures while controlling for potential confounds sometimes ignored in previous studies, such as age, sex, income, alcohol and tobacco use. The following discussion describes the current works in detail and provides critical commentary on their findings.

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Chapter 2: Cannabis involvement and neuropsychological performance: Findings from the Human Connectome Project

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Abstract

Background and Aims: There is evidence that heavy cannabis use is associated with decreases in cognitive domains such as memory and attention, but findings are mixed and studies often are limited by small sample sizes and narrow adjustment for potential confounding variables. The current study examined associations between recent, lifetime, and problematic cannabis use with performance on a variety of neuropsychological tasks.

Design: Data were obtained from the young adult cohort of the Human Connectome Project. Associations between cannabis involvement and task performance were evaluated using a dimensional (continuous) design.

Setting: Data were collected at Washington University in St. Louis, MO, USA as part of the Human Connectome Project. Data analysis was conducted at McMaster University in Hamilton, ON, Canada.

Participants/Cases: 1211 young adults (54% female) with no history of severe psychiatric, neurological, or neurodevelopmental disorders.

Measurements: Cannabis involvement comprised recent cannabis use (presence of THC in urine), total number of lifetime uses, cannabis use disorder (CUD), and age of first use. The neuropsychological battery comprised performance in episodic memory, fluid intelligence, attention, working memory, executive function, impulsivity, processing speed, and psychomotor dexterity. Covariates were age, sex, income, alcohol use, and tobacco use.

Findings: Urinary THC status was associated with worse performance on episodic memory and processing speed tasks, and CUD+ status was associated with lower fluid intelligence. Effect sizes were small. No other significant associations were present.

Conclusions: Recent cannabis use is associated with deficits in memory and psychomotor performance, and CUD is associated with lower overall cognitive functioning, but other deficits in neurocognitive functioning were not present and differential influence of earlier initiation was not evident. Apparent residual effects of recent use, although small in magnitude, may have important relevance for occupational settings. **Abstract word count =** 285

Introduction

Cannabis is the most commonly used illicit drug in the world, with an estimated 2.5% of the world's population reporting any last-year cannabis use, and consumption increasing at a faster rate than other commonly used drugs such as opioids and cocaine (1). Increases in use are particularly apparent among adolescents and young adults (2), and may escalate further with legalization of recreational use in several states in the U.S. and federally in Canada. Regular cannabis use has been associated with a number of adverse health consequences; for example, motor vehicle injuries, cannabis use disorder (CUD), increased risk of psychotic disorders, and chronic bronchitis are all established forms of harm (3,4).

In addition to negative health consequences, there is considerable concern and interest in the adverse effects of cannabis use on cognitive abilities, such as memory, attention, and learning. Of the many chemical constituents found within cannabis, the most well-studied is the psychoactive component, Δ^9-tetrahydrocannabinol (THC). Acute administration of THC has been repeatedly shown to decrease performance on a variety of neuropsychological tasks (5). In addition, many studies have reported associations between long-term cannabis use and impaired cognition both during and after acute intoxication, although the evidence to date is mixed in terms of consistent findings and methodological rigor. A recent systematic review by Broyd et al. (5) sought to synthesize the literature examining the acute and residual effects of cannabis use on performance during task-based neuropsychological measures. Based on findings from 105 studies, they

found evidence for the detrimental effect of both acute and chronic cannabis use on verbal learning and memory, attention, and psychomotor performance. However, it was determined that the evidence for impacts on other cognitive domains (i.e., working memory, executive functions, and decision making) were weak and/or conflicting. Another systematic review by Ganzer et al. (6) focused on the neurocognitive impacts of chronic cannabis use during an extended period of abstinence, finding evidence for persistent memory deficits during abstinence and mixed findings for other cognitive domains. Lastly, although few studies have investigated the effects of cannabis use on motor learning, a recent synthesis of the existing literature identified evidence for persistent motor deficits and emphasized the need for further investigation (7). Across the existing literature, however, it is acknowledged there are substantial inconsistencies and mixed findings in the links between cannabis and cognition (cite aformentioned reviews). In turn, the observed inconsistency in findings has been interpreted as potentially resulting from the heterogeneity in study methods, such as different or low resolution measures and the potential impact of other substance use or other confounders that are not addressed. A further issue is statistical power, as most studies have had relatively small sample sizes.

There is also concern regarding the extent to which age of first cannabis use impacts cognitive performance, as people who begin using cannabis during critical periods of brain development may be vulnerable to lasting neuropsychological changes. Previous studies suggest that younger age of initiation is associated with heavier cannabis use and

more severe and enduring deficits (8–10). The evidence for this association, however, comes largely from cross-sectional data, and therefore cannot speak to causality of early use with cognitive changes. To date, there are only a handful of prospective longitudinal studies of the association between adolescent cannabis use and neuropsychological impairment, the methods and findings of which are largely mixed (e.g., 11,12). Thus, it is still an open question whether differences in cognitive functioning are antecedent to adolescent cannabis use, or if cannabis use during the developmental period contributes to cognitive decline.

Given the conflicting and inconsistent findings within the literature discussed above, the current study sought to use data from the Human Connectome Project to understand the links between cannabis use and cognitive functioning. Specifically, this study leveraged a relatively large sample of young adults and extensive neuropsychological battery to examine the associations between cannabis involvement and performance in a variety of neurocognitive domains. Cannabis involvement was defined using multiple indicators, including recent use (urine THC+), total lifetime use, cannabis use disorder and age of first cannabis use. The primary aim was to examine the effects of cannabis involvement in relation to neurocognitive performance.

Methods

Participants

Participants comprised the full sample from the WU-Minn Human Connectome Project (HCP) young adult cohort. Exclusion criteria included having severe neurodevelopmental

disorders, pre-existing psychiatric or neuropsychiatric disorders, and other illnesses that may confound neuroimaging data (i.e., high blood pressure, diabetes), and having a premature birth. See Van Essen et al. (13) for detailed description of recruitment and screening procedures. Descriptive statistics for participants with complete data are in Table 1 (*N*=1121); missing data patterns are described below in Data Analysis.

Assessments

Substance use: Substance use involvement was evaluated using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; 13). The cannabis module included the following measures: ever used cannabis (yes/no), age of first use (grouped by age bins <14, 15-17, 18-20, 20+; coded such that earlier age reflected greater severity), number of times ever used cannabis (1-5, 6-10, 11-100, 101-999, 1000+). Problematic cannabis use was assessed using the SSAGA module for DSM-IV-TR Marijuana Abuse and/or Dependence; participants meeting criteria for abuse or dependence were coded as CUD+. The alcohol module of the SSAGA assessed quantity, frequency and severity of alcohol use. The present analyses included a measure of frequency of drinking in the last year. Similarly, tobacco use was assessed using the SSAGA self-report items, and the number of days in the past 7 days participants reported any tobacco use was included as a measure of recent smoking status. On the same day as neurocognitive task assessments, participants were asked to provide breath and urine samples to detect recent use of alcohol, cannabis, and other drugs. Recent use of cannabis was determined by positive result for THC in the urine drug screen.

Neurocognitive Tasks

Picture Sequence Task: Episodic memory was assessed using the NIH-Toolbox's Picture Sequence Memory Test (15). Within a trial, illustrated objects and actions are presented one at a time and arranged into a demonstrated order, then back to a random order, and the participant must move the pictures into the order demonstrated. Scores are determined based on their total number of correctly positioned adjacent pairs of pictures over three learning trials, and converted to an age-adjusted scale score. Sequence lengths vary from 6-18 pictures depending on age; participants in the HCP dataset were presented with 15-picture sequences.

Penn Progressive Matrices: Fluid intelligence was measured using an abbreviated version of Raven's Progressive Matrices (16), which has 24 items and 3 bonus items, arranged in increasing order of difficulty. The participant is presented with arrangements of squares (i.e., 2x2, 3x3, or 1x5) forming a pattern, with one square missing. The participant must pick one the missing square on the pattern from five response choices, and the task is discontinued after the participant makes 5 consecutive incorrect answers. Scoring is based on the number of correct responses.

Short Penn Continuous Performance Task: Sustained attention was assessed using the Short Penn Continuous Performance Test (SPCPT; 16). Subjects are presented with vertical and horizontal lines flashed on the computer screen for 300ms, in two blocks of 90 stimuli. In one block, they are asked to respond when the lines form a number. In the other block, they are asked to respond when the lines form a letter. Some trials present a

distractor, where the lines form a shape that is neither letter nor number. The total score is based on number of correct responses and reaction time.

Card Sort Task: The set-shifting component of executive function was assessed using the NIH Toolbox's Dimensional Change Card Sort task (15). In each trial, participants must match a visual target stimulus to one of two stimuli based on either shape or colour. The dimension being matched is sometimes switched, therefore requiring cognitive flexibility to change sorting rules to match the correct stimulus. Scoring is based on a combination of accuracy and reaction time.

Flanker Task: The ability to inhibit attention to irrelevant stimuli (i.e., component of executive function) was measured using the NIH-Toolbox's Flanker Inhibitory Control and Attention Test (15). In each trial, the participant must indicate the direction that the target arrow is pointing, while ignoring the direction of the distractor arrows (flankers). The flanker arrows face the same direction as the target arrow during congruent trials, and opposite direction as the target arrow on incongruent trials. Scores are determined based on accuracy and reaction time, and converted to an age-adjusted scale score.

Pattern Completion Task: Processing speed was assessed using the NIH-Toolbox's Pattern Completion task, which requires participants to indicate whether two adjacent pictures are the same or different (15). Scoring is based on number of items correct within a 90-second time limit, and this raw score is converted to an age-adjusted scale score.

Delay Discounting Task: Immediate reward preference – or devaluing of delayed rewards – was assessed using an adjusting-amount monetary choice task. In this paradigm, each trial asks subjects to indicate whether they would rather receive a smaller

immediate reward (e.g., $100 today) or a larger delayed reward (e.g., $200 in 3 months). Delay in time to receipt of later reward was kept fixed, and the reward amounts were titrated based on participant's choices until points of indifference were determined. The variable used to measure how steeply participants discounted delayed rewards was area-under-the-curve (AUC), a valid and reliable index of immediate reward preference (18). Given the strong correlation between the two magnitudes (r=.676 p= 1.34E-160), the AUC variables for smaller (i.e., $200) and larger (i.e., $40,000) delayed reward conditions were averaged into a single composite variable.

Penn Word Memory Test: Verbal episodic memory was measured using the Penn Word Memory Test, a forced-choice recognition task (19). In the encoding phase, subjects are shown a series of 20 target words and asked to remember them. The delayed recognition trials require participants to identify from a list of 40 words (20 of which are distractor items) the words that were in the original list. They can respond by choosing from "definitely no", "probably no", "probably yes", and "definitely yes". Performance measures are number of correctly identified target words and reaction time for true positive responses.

List Sorting Task: Working memory was assessed using the NIH-Toolbox's List Sorting Task (15), in which participants are presented with a series of visual (pictures) and oral (spoken names) of various foods and animals. In the 1-List condition, participants presented with and asked to order either animals or foods from smallest to largest. In the 2-List condition, participants are presented with both animal and food lists and are asked to order each list by increasing size. The number of list items increases with subsequent

trials, and the task is discontinued after 2 subsequent incorrect trials. Raw scores are the sum of total correct items, which is converted to an age-adjusted scale score.

9-hole Pegboard: Psychomotor dexterity was measured using the NIH Toolbox's 9-hole Pegboard Dexterity Test (20). Participants are required to accurately place and remove 9 plastic pegs into a pegboard as quickly as possible. This procedure is performed for 1 practice and 1 timed trial for each hand, and raw scores are time to completion recorded separately for each hand.

Data Analysis

First, the data were examined for missingness, finding <1.0% missing for all variables of interest. Only participants with complete data were subsequently analyzed. Next, outlying values (Z-scores > 3.29) for dependent variables were winsorized to one unit greater than the closest non-outlying value (21). There were a total of 26 cases with outlying variables requiring winsorizing: 0.26% of Word Memory cases, 0.53% of Card Sort cases, 0.26% of Flanker task cases, and 1.25% of SPCPT cases. Distribution normality was examined and scores on the Penn Word Memory Test, Flanker task, and Delay Discounting AUC were all normalized using square-root transformations; performance on the SPCPT, and Penn Progressive Matrices were normalized using logarithmic transformations. Correlations were used to identify appropriate covariates from demographic and other substance use variables (i.e., age, sex, income, years of education, tobacco use, and alcohol use). The primary analyses comprised hierarchical linear regression models to examine cannabis variables (and covariates) in relation to

neurocognitive task performance. Specifically, to reduce the likelihood of type I errors, covariates were entered in a first step and the cannabis involvement variables were then entered collectively in a second step (effectively acting as an omnibus test) and then examined further if they significantly improved the overall model (ΔR^2). Collinearity among independent variables was evaluated using a variance inflation factor of >2.50 and a tolerance of <0.20 as criteria for detecting multicollinearity. Of the cannabis involvement variables, only THC+ status, lifetime cannabis exposure, and CUD diagnosis were included in the primary model because age of first use and lifetime cannabis use were collinear (see below). Recognizing the relatively large number of tests being conducted, a Type I error threshold (α) of .005 was used to reduce the likelihood of false positive findings (22). All analyses were conducted in IBM SPSS Statistics, v.25.

Results

Preliminary Analyses

Age, sex, income, years of education, tobacco use, and alcohol use were all significantly correlated with cannabis use variables (Table 2). They were therefore subsequently included as covariates in the first block of hierarchical regressions for each dependent variable. Of note, lifetime cannabis use and age of first use were strongly correlated (r=.80, $p<10^{-267}$) and subsequently were not examined in joint models to avoid collinearity. Zero-order correlations among the cannabis variables and neurocognitive measures are reported in Table 3, revealing numerous significant associations in the absence of adjustment for potential confounders.

Regression Models

In the hierarchical regressions, after controlling for covariates, cannabis involvement explained significantly more variance within performance on the Progressive Matrices, Picture Sequence, and Pattern Completion tasks (Table 4). Individual coefficients are presented in Table 5. Closer inspection of the coefficient matrices reveal that the significant omnibus models were largely driven by significant associations between THC+ status and task performance. Specifically, positive THC drug screen was associated with significantly fewer correct responses for the Picture Sequence task, and lower age-adjusted scaled scores for the Pattern Completion task. In addition, having met diagnostic criteria for CUD was associated with significantly fewer correct responses on the Progressive Matrices.

Hierarchical regressions replacing lifetime cannabis exposure with cannabis age of first use in the cannabis involvement block (to avoid collinearity) did not substantively change any models (significant and nonsignificant model changes all remained the same), and age of first use was not a significant predictor in the examination of individual coefficients. These results are presented in Supplemental Materials Table 1 and Table 2.

Discussion

The primary aim of this study was to examine associations between cannabis involvement and neurocognitive task performance, and the secondary aim was to determine whether age of initiation of cannabis use moderates the effect of cannabis use on cognition. Overall, it was determined that recent use of cannabis as indicated by the presence of

THC was the strongest determinant of neurocognitive task performance. THC presence in urine was inversely related to performance on Picture Sequence Task and Pattern Completion, such that individuals who screened positive for THC tended to exhibit worse episodic memory and slower processing speed than those who screened negative. Interestingly, the only neurocognitive domain significantly predicted by CUD status was fluid intelligence, as measured by Penn Progressive Matrices.

The finding that THC presence predicts poorer performance on an episodic memory task is in line with previous studies finding a similar association between acute THC administration or recent cannabis use and episodic memory (23–25). Diminished processing speed as a function of recent THC exposure is also consistent with the literature: several studies have found that, compared to placebo controls, subjects administered THC required more time to make decisions (26,27), and performed slower on direct measures of processing speed (28). A recently-published meta-analysis of 69 studies examining impact of cannabis use in young adults found no difference in effect size based either on age of first use or mean age of sample (29). However, the authors found that 72 hours of abstinence substantially reduced the observed cognitive deficits associated with cannabis use, and this is consistent with the present findings of recent use having stronger associations with cognitive performance than age of onset, lifetime use, and severity of use.

With regard to the Penn Progressive Matrices finding, fluid intelligence being lower for those who have met criteria for CUD is also compatible with the literature examining IQ differences between levels of severity of cannabis use. A longitudinal co-twin study by Meier et al. (11) tested the IQ of twins at ages 5, 12 and 18, and found that adolescents meeting criteria for CUD had lower IQ in childhood than adolescents without cannabis dependence, but that these differences predated the age of first cannabis use. Furthermore, they found no association between CUD status and changes in IQ over the developmental period, which supports the idea that differences in IQ as a function of problematic cannabis use predates the onset of use itself. Taken together, these findings emphasize recent THC exposure, rather than the cumulative effect of total lifetime exposure or having cannabis-related problems, as being the prepotent factor for observable differences in episodic memory and processing speed. Differences in intelligence as a function of CUD status within our sample may also have predated cannabis involvement, however without repeated measures of IQ over the developmental period this is necessarily speculation.

Interestingly, cannabis involvement failed to predict performance on measures of cognitive control and impulsivity, processes that have generally been associated with addictive behavior and other conditions associated with deficits in self-regulation (30–33). However, for cannabis, the literature is inconsistent for whether inhibition is worsened in cannabis users (6) and, likewise, this is consistent with other studies not detecting associations between a monetary discounting task and cannabis use. In other

words, these findings are compatible with a broader literature indicating cannabis involvement may systematically be different from other substance involvement in these domains. Other previous studies did find that cannabis rewards were discounted more steeply than monetary rewards (24,34,35) among individuals with CUD and it may be that pattern would have been evident in the HCP cohort, but the delay discounting task employed in the neurocognitive battery was exclusive to monetary rewards so that it is necessarily speculation.

Two other nuances bear on these findings. First, it is important to note that although the associations observed were statistically significant, they were small in magnitude in terms of effect sizes. Given the large sample size, it was possible to use an extensive list of covariates and detect subtle differences in neuropsychological performance, and modest differences were indeed what was detected. Second, a common theme was that the neuropsychological tasks that were significantly predicted by cannabis involvement were nonverbal, falling within the visuospatial domain of cognition. The measures involving simple visuospatial processing (i.e., Pattern Completion and Card Sorting Task) in particular were the outcomes significantly predicted by presence of THC. This provides more evidence of visuospatial consequences to a literature that is somewhat conflicting (6), but it is also worth noting that these effects may be less readily detectable experientially (as opposed to deficits in declarative episodic memory), obscuring them from the individual. Considered together, although the effects were small, certain occupational settings (e.g., pilot, air traffic controller, crane operator, school bus driver)

have very high stakes when it comes to visuospatial cognition and even small deficits may add significant risk, especially if the individual is unaware of subtle changes in performance.

These results should be interpreted with due consideration of a number of limitations. The data do not provide fine-grained measures of quantity and frequency of cannabis use, peak level of use (and recency of peak use), type of cannabis, or method of administration, all of which could have provided greater understanding of the links between cannabis and cognition. Similarly, CUD diagnosis reflects lifetime status, not current status, which would substantially add resolution. However, the HCP study was principally designed to understand human brain connectomics, not consequences of cannabis use per se, so the relatively coarse measurement of cannabis involvement is not surprising. A related consideration is that the age range was restricted to adults age 22-36, again to optimize the overall HCP design, and thus may not capture the neurotoxic effects of prolonged heavy use over many years. On the other hand, a major strength of the present study is its large sample and extensive battery of neuropsychological assessments. As such, analyses were well-powered to detect even small differences and diverse aspects of cognitive performance were tapped. Less a limitation than a consideration, the HCP cohort represents a relatively healthy population when it comes to cannabis use, with greater representation of lower level use than very heavy use. However, a critical question when it comes to cannabis and cognition is whether effects pertain to low-level use that

reflects common recreational patterns and this study addresses this question, suggesting no effects in most domains.

To conclude, the present findings provide evidence for significant links between recent cannabis use on select neurocognitive abilities, and an association between CUD and fluid intelligence, but not in other areas and do not suggest a differential influence of early age of first use. Although the effect sizes were of small magnitude and most domains were unaffected, this study nonetheless documents potential risks of cannabis use to individuals in professions that rely on optimum cognitive performance.

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Table 1. Sample characteristics (N=1121)

	N(%)/Mean(SD)
Age	28.8 (3.7)
Sex	54.4% Female
Income	$40k - $49k/year
Years Education	14.9 (1.8)
Smokers	237 (21.1%)
Alcohol Freq	1-3 days/month
Lifetime Cannabis Use	
Never used	482 (43.0%)
1-10 times used	317 (28.3%)
11-100 times used	139 (12.4%)
101-999 times used	76 (6.8%)
1000+ times used	107 (9.5%)
CUD+	109 (9.7%)
UDS THC+	135 (12.0%)
Cannabis AFU	
>21 years old	124 (11.1%)
18-20 years old	203 (18.1%)
15-17 years old	233 (20.8%)
<14 years old	79 (7.0%)

Notes: CUD= Cannabis Use Disorder; UDS = urine drug screen; THC = tetrahydrocannabinol; AFU = age of first use.

Table 2. Zero-order correlation matrix between potential covariates and cannabis involvement variables.

	1	2	3	4	5	6	7	8	9	10
1. Sex	—									
2. Age	.214**	—								
3. Income	.004	.268**	—							
4. Education	.041	.091**	.390**	—						
5. Tobacco Use	-.145**	.007	-.187**	-.326**	—					
6. Alcohol Use	.205**	.054	-.075	-.118**	-.064*	—				
7. UDS THC+	-.141**	-.085**	-.248**	-.288**	.325**	-.100**	—			
8. CUD+	-.182**	-.022	-.089*	-.112**	.228**	-.128**	.271**	—		
9. Cannabis AFU	-.127**	-.001	-.099**	-.145**	.298**	-.215**	.329**	.409**	—	
10. Lifetime Cannabis Use	-.194**	-.012	-.156**	-.169**	.353**	-.269**	.502**	.556**	.800**	—

Notes: UDS = Urine Drug Screen; THC = tetrahydrocannabinol; CUD = Cannabis Use Disorder; AFU = age of first use; SPCPT = Short Penn Continuous Performance Task.

* Correlation is significant at the .005 level (2-tailed)

** Correlation is significant at the .001 level (2-tailed)

Table 3. Zero-order correlation matrix between cannabis involvement variables and neuropsychological task performance

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. UDS THC+	—													
2. CUD+	.271**	—												
3. Cannabis AFU	.329**	.409**	—											
4. Lifetime Cannabis Use	.502**	.556**	.800**	—										
5. Word Memory Test	-.123**	-.040	-.061*	-.063	—									
6. Flanker Task	.111**	.006	.037	.058	-.079	—								
7. Card Sorting Task	-.087**	.018	.005	.017	.150**	-.512**	—							
8. SPCPT	-.069	.035	-.009	.014	.111**	-.119**	.152**	—						
9. Progressive Matrices	.145**	-.041	.074	.050	-.218**	.137**	-.195**	-.188**	—					
10. Delay Discounting	-.137**	-.016	-.056	-.056	.114**	-.056	.058	.064	-.215**	—				
11. Picture Sequence Task	-.165**	-.028	-.026	-.061	.242**	-.150**	.214**	.160**	-.293**	.081*	—			
12. Pattern Completion	-.144**	.010	-.043	-.041	.143**	-.379**	.425**	.123**	-.157**	.047	.204**	—		
13. List Sorting Task	-.140**	-.014	-.038	-.043	.158**	-.138**	.209**	.145**	-.341**	.125**	.345**	.182**	—	
14. 9-hole pegboard	-.174**	-.073	-.071	-.127**	.107**	-.139**	.165**	.057	-.154**	.119**	.194**	.192**	.108**	—

Notes: UDS = Urine Drug Screen;THC = tetrahydrocannabinol; CUD = Cannabis Use Disorder; AFU = age of first use; SPCPT = Short Penn Continuous Performance Test * Correlation is significant at the .005 level (2-tailed)
** Correlation is significant at the .001 level (2-tailed)

Table 4. Hierarchical regressions comprising covariate model (Sex, Age, Income, Education, Tobacco Use, Alcohol Use) and cannabis involvement variables (UDS THC, Lifetime Cannabis Use, CUD) in relation to neuropsychological performance.

Neuropsychological Variable	Covariate Model R^2	*p*	Cannabis Involvement ΔR^2	*p*
Word Memory Test	.051	<.001*	.003	.353
Flanker Task	.026	<.001*	.008	.021
Card Sorting Task	.033	<.001*	.003	.345
SPCPT	.049	<.001*	.008	.029
Progressive Matrices	.142	<.001*	.010	.004*
Delay Discounting	.066	<.001*	.003	.327
Picture Sequence Task	.069	<.001*	.011	.004*
Pattern Completion	.022	<.001*	.014	.001*
List Sorting Task	.071	<.001*	.005	.102
9-hole Pegboard	.105	<.001*	.005	.083

Notes: UDS = Urine Drug Screen; THC = tetrahydrocannabinol; AFU = Age of first use; CUD = Cannabis Use Disorder; SPCPT = Short Penn Continuous Performance Task * Significant at the $p < .005$ level.

Table 5. Individual hierarchical regressions of covariates and cannabis involvement variables in relation to neuropsychological performance for models significant at the p<.005 level.

Model	**Variables**	**Progressive Matrices**		**Picture Sequence**		**Processing Speed**	
		β	***p***	β	***p***	β	***p***
	Gender	.145	<.001*	.152	<.001*	.026	.411
	Age	.084	.005*	-.035	.255	-.038	.231
Covariate	Income	-.066	.035	.069	.035	.060	.070
Model	Education	-.258	<.001*	.172	<.001*	.077	.022
	Tobacco	.096	.002*	.021	.515	.000	.993
	Alcohol	.036	.230	-.017	.583	-.050	.111
Cannabis	UDS THC+	.057	.089	-.121	<.001*	-.132	<.001*
Involvement	Lifetime Uses	.046	.233	.028	.486	-.007	.873
	CUD+	-.104	.002*	.033	.342	.055	.119

Note: UDS = Urine Drug Screen; THC = tetrahydrocannabinol; CUD = Cannabis Use Disorder

*Significant at the $p < .005$ level.

Supplemental Materials 1. Hierarchical regressions comprising covariate model (Sex, Age, Income, Education, Tobacco Use, Alcohol Use) and cannabis involvement variables (UDS THC, CUD and cannabis AFU).

Neuropsychological Variable	**Covariate Model R^2**	***p***	**Cannabis Involvement ΔR^2**	***p***
Word Memory Test	.051	<.001*	.003	.351
Flanker Task	.026	<.001*	.008	.020
Card Sorting Task	.033	<.001*	.002	.434
SPCPT	.054	<.001*	.005	.114
Progressive Matrices	.143	<.001*	.011	.002*
Delay Discounting	.066	<.001*	.002	.410
Picture Sequence Task	.070	<.001*	.011	.003*
Pattern Completion	.021	<.001*	.016	<.001*
List Sorting Task	.067	<.001*	.006	.066
9-hole Pegboard	.105	<.001*	.005	.087

Note: UDS = Urine Drug Screen; THC = tetrahydrocannabinol; CUD = Cannabis Use Disorder; AFU = age of first use

* Significant at the $p < .005$ level.

Supplemental Materials 2. Individual hierarchical regressions of covariates and cannabis involvement variables in relation to neuropsychological performance for regression models significant at the p<.005 level.

Model	Variables	Progressive Matrices		Picture Sequence		Processing Speed	
		β	*p*	β	*p*	β	*p*
Covariate Model	Gender	.144	<.001*	.152	<.001*	.026	.404
	Age	.084	.004*	-.035	.258	-.036	.247
	Income	-.067	.032	.068	.037	.060	.073
	Education	-.256	<.001*	.173	<.001*	.076	.025
	Tobacco	.094	.002*	.020	.532	.005	.873
	Alcohol	.036	.213	-.017	.576	-.056	.074
Cannabis Involvement	UDS THC+	.062	.047	-.117	<.001*	-.127	<.001*
	Cannabis AFU	.057	.073	.031	..347	-.042	.222
	CUD+	-.103	.001*	.035	.278	.065	.047

Notes: UDS = Urine Drug Screen; THC = tetrahydrocannabinol; AFU = age of first use; CUD = Cannabis Use Disorder

*Significant at the $p < .005$ level.

Chapter 3: Cannabis Use, Cognitive Performance, and Attention Deficit/Hyperactivity Disorder in a Large Sample of Community Adults

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Abstract

Background/Aims: There is evidence that heavy cannabis use predicts both lower cognitive performance and increased incidence of Attention-Deficit Hyperactivity Disorder (ADHD), however, the literature is still mixed and in need of dimensional analyses among large samples. The current study examined associations among cannabis use severity and age of first use in relation to neurocognitive performance and ADHD symptoms.

Design: Participants were community adults aged 18-65 (N=958) who attended a single-session assessment including computerized neuropsychological tasks, self-report questionnaires assessing substance use, psychopathology and related factors. Dimensional relationships were investigated using multiple hierarchical regressions to examine associations between cannabis involvement, neurocognitive task performance, and self-reported ADHD symptoms.

Findings: After controlling for age, income, sex, alcohol and tobacco use, cannabis use severity predicted greater endorsement of both hyperactive-impulsive and inattentive ADHD symptoms, as well as more impulsive decision making preferences (delay discounting), but not general verbal intelligence, short-term verbal memory, working memory, behavioral inhibition, or risky decision making (probability discounting). Age of first cannabis use was not significantly associated with any neurocognitive variables or ADHD symptomatology.

Conclusions: The current findings provide support for the link between current severity of cannabis use, but not age of first use, and problems with hyperactivity, inattention, and

impulsivity, but not other cognitive domains. Earlier cannabis use was not associated with any cognitive indicators.

Introduction

Cannabis is one of the most widely used substances, with an estimated 2.5% of the world's population reporting any past-year use (World Health Organization 2010). These estimates are higher in regions with changing political climates surrounding the legalization of cannabis use, such as in the United States with 9.5% (Hasin et al. 2015) and Canada with 12.3% (Rotermann & Macdonald 2018). Although many people only try cannabis or use it infrequently, those who engage in regular use of cannabis are at an increased risk of experiencing negative health consequences such as cannabis use disorder (CUD), psychotic disorders such as schizophrenia, chronic bronchitis, and injuries or death due to cannabis impairment in motor vehicle accidents (Volkow et al. 2014; Imtiaz et al. 2016).

Among the adverse health consequences associated with cannabis, there is also considerable interest in the effects of cannabis use on cognitive functioning. The most well studied component of the cannabis plant is Δ^9-tetrahydrocannabinol (THC), the psychoactive chemical constituent. Recent syntheses of the literature in this area provide consistent evidence for the acute and persisting impacts of THC exposure on neurocognitive performance in a variety of domains, particularly verbal learning, memory, attention, and psychomotor speed (Broyd et al. 2016; Ganzer et al. 2016). However these reviews also report a great deal of inconsistency present in the literature regarding the effect of cannabis use on other domains, such as working memory, inhibitory control and decision-making, and the need for further investigation in these

areas. Common issues noted in studies examining cannabis use and cognition include low statistical power due to small sample sizes, failure to control for the impact of alcohol and tobacco use, and the use of low-resolution measures to assess degree of cannabis involvement.

The impact of cannabis use on cognition has direct implications for an individual's ability to function well in their daily life. For example, cognitive functions such as attention, working memory, and executive control are critically important for life skills such as planning, sustaining attention and effort, organizing, and controlling one's own behaviour and emotions. Deficiency in these skills is also present in those with Attention Deficit Hyperactivity Disorder (ADHD), a common neurodevelopmental disorder characterized by difficulties with planning, sustained attention, behavioural inhibition, working memory and more immediate reward preferences (Hervey et al. 2004; Lijffijt et al. 2005; Willcutt et al. 2005; Jackson & MacKillop 2016). In DSM-5, a diagnosis of ADHD can be given to both children and adults, and is specified by the individual's symptom profile as being predominantly hyperactive-impulsive, inattentive, or combined type (American Psychiatric Association 2013). However, these symptoms can also be evaluated dimensionally among subclinical populations using validated screening measures (e.g., Adult ADHD Self-Report Scale; Kessler et al. 2005). Problematic cannabis use in particular is a common comorbidity with ADHD diagnosis; cannabis is the most commonly used illicit drug among those with a lifetime diagnosis of ADHD (Molina et al. 2013) and the prevalence of ADHD among adults seeking treatment for CUD has been

estimated at 34-46% (Notzon et al. 2016; Van de Glind et al. 2013). Among a large community sample of cannabis users, it was found that daily users were more likely to meet criteria for the hyperactive-impulsive subtype than the inattentive subtype of ADHD, an association that was not found in nondaily users (Loflin et al. 2014). Taken together, these studies indicate a seemingly maladaptive relationship between ADHD symptomatology and cannabis use severity: individuals with ADHD are more likely to use cannabis, which may further exacerbate preexisting cognitive weaknesses associated with their symptoms.

An additional consideration of increasing interest in the aforementioned literature is the age of first cannabis use, specifically, whether earlier age of initiation strengthens associations between current cannabis use severity and neuropsychological deficits, and also in relation to ADHD diagnosis. For instance, substantial evidence from cross-sectional studies suggests that earlier age of cannabis initiation is associated with heavier cannabis use and more prolonged neurocognitive deficits (Pope et al. 2003; Gruber et al. 2012; Solowij et al. 2011). Similarly, individuals diagnosed with ADHD tend to initiate substance use and specifically cannabis use earlier than those without the disorder (Charach et al. 2011; Lee et al. 2011; Molina et al. 2013; Pingault et al. 2012). Several questions about these associations still remain unanswered in the literature, such as whether age of first use per se is actually causal of neuropsychological deficits and/or ADHD symptom persistence, or whether it simply reflects a risk factor for more severe overall involvement. A major limitation of these studies are the small sample, case-

control comparisons of adolescents and young adults with and without and ADHD diagnosis, and may not be applicable to people who experience subclinical levels of ADHD experiences (e.g., easily distracted, difficulty waiting in line, forgetting important deadlines) but do not meet full criteria for diagnosis. These findings are also largely limited to adolescence and emerging adulthood, a period of development where dramatic changes and instability in cannabis use are typical, and may not be applicable to adults in general who have stable patterns of cannabis use.

The current study seeks to address some of the aforementioned gaps in the literature by examining these questions within a relatively large sample of community adults. Using a dimensional design, the first aim was to examine associations between cannabis involvement and neuropsychological task performance for general verbal intelligence and the specific cognitive domains of behavioural inhibition, short-term verbal memory working memory, risky decision-making and delay discounting. The second aim was to examine associations between cannabis involvement and both hyperactive-impulsive and inattentive symptoms of ADHD. Last, the present study sought to parse differential contributions between severity of current cannabis use and age of first cannabis use.

Methods

Participants

Participants comprised a subsample of the Population Assessment for Tomorrow's Health (PATH) Research Registry at the Peter Boris Centre for Addictions Research. This is a

registry of community adults in the Hamilton, ON, area who completed a single cross-sectional assessment to join the registry and be eligible for future research projects. Participants were recruited using flyers, print, social media, and bus advertising, and word of mouth. Eligibility criteria comprised: 1) age 18-65 years old; 2) willingness to be contacted for future studies on mental health and addiction; 3) at least a 9th grade education (for sufficient literacy); 4) at least weekly use of a computer or smartphone (to ensure ability to complete online assessments); 5) no medical condition that would prevent future participation in studies; 6) willingness to provide informed consent to participate. Eligibility did not include any minimum substance use requirement. Only participants who reported any lifetime use of cannabis were included in this report to ensure all participants had a valid age of first use. The participants (N=958) are described in Table 1, generally reflecting a group of middle-aged adults, slightly more female than male, who report moderate levels of alcohol and cannabis use, but limited tobacco use.

Procedure

Eligible participants were invited to the Peter Boris Centre for Addictions Research for a single in-person assessment visit lasting approximately 3 hours. During the study session, participants were asked to complete a computerized battery of questionnaires assessing demographics, family history of addictive disorders, mental health symptoms for a range of psychopathology, current substance use and addictive behaviours. Participants also completed behavioural tasks on the computer measuring inhibitory control, short-term verbal memory, working memory, risky decision-making, immediate reward preference,

and verbal intelligence (described below) and non-invasive biometric data were also gathered (not reported here), although a urine drug screen was not collected Participants received up $40 CAD for their time. All procedures were approved by the Hamilton Integrated Research Ethics Board (Project #2017-1074, Title: "*Population Assessment for Tomorrow's Health"*).

Self-Report Assessments

Cannabis Involvement

Cannabis use was assessed using the Cannabis Use Disorders Identification Test – Revised (CUDIT-R; Adamson et al. 2010), which measures the number of symptoms of DSM-5 Cannabis Use Disorder (CUD), which considers the frequency of cannabis use as well as the severity of cannabis-related problems endorsed by the individual. Higher scores indicate greater severity of cannabis use and related problems, and a score of 8 or higher is considered a viable cutoff to positively screen for CUD (Adamson et al. 2010). The age of first cannabis use was determined by a single item asking participants, "*How old were you when you first used cannabis?*". Since the current study's primary aim was to identify differences in cognitive performance in relation to degrees of cannabis involvement, only participants who endorsed having ever used cannabis in their lifetime were included in analyses. The internal reliability of CUDIT-R items was determined to be α=0.814.

Other Substance Use Involvement

Alcohol use was assessed using the Alcohol Use Disorders Identification Test (AUDIT; Saunders et al. 1993), which measures the number of symptoms of DSM-5 Alcohol Use Disorder. The AUDIT takes into account frequency of drinking as well as the severity of alcohol-related problems experienced by the individual. Internal reliability of AUDIT items was determined to be $\alpha = 0.799$. Tobacco use was assessed using the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al. 1991), which assesses the frequency and severity of tobacco use, such that higher scores indicate greater severity of nicotine dependence. The internal reliability of the FTND in this sample was determined to be $\alpha = 0.312$.

ADHD Symptoms

Symptoms of Attention Deficit Hyperactivity Disorder were assessed using the World Health Organization (WHO) Adult ADHD Self-Report Scale (ASRS; Kessler et al., 2005). This measure is a screening tool used to assess the degree to which subjects endorse experiencing symptoms of inattention and hyperactivity/impulsivity associated with ADHD. For the purpose of the present analyses, subscale scores were generated symptom subtypes, with internal reliability coefficient $\alpha = 0.829$ and $\alpha = 0.862$ for hyperactive-impulsive and inattentive symptoms, respectively.

Cognitive Assessments

Go/No-Go Task: Response inhibition and behavioural impulsivity was assessed using a computerized Go/No-Go task (Kiehl et al. 2001). Participants were required to response as quickly as possible to a target (Go) stimulus, and to refrain from responding to a distractor (No-Go) stimulus. Outcome variables include number of Commission Errors (responded on a "No-Go" trial), number of Omission Errors (failure to respond on a "go" trial), and mean reaction time for "Go" trials. To screen for valid effort, inclusion criteria of <20% omission errors and <10% commission errors were used, excluding 3.5 (%) participants.

Shipley Verbal Scale: This subtest of the Shipley Institute of Living Scale – Second Edition (Shipley-2; Shipley 2009) is a short measure of crystallized intelligence, and was administered to participants in the PATH study using a computerized version of the test. The Shipley Verbal Scale requires participants to choose the correct synonyms of English words which progress in difficulty over 40 trials. Raw scores were calculated by summing the number of correct responses, and standardized verbal IQ scores were generated using age norms.

Digit Span Task: Short-term verbal memory and working memory were assessed using a computerized Digit Span task (Schroeder et al. 2012). This task is broken up into two components: Digits Forward, measuring short-term verbal memory, and Digits Backward, measuring working memory. In both conditions, participants are presented with a string of numbers read aloud by a recorded voice via headphones, and are required to input the numbers heard verbatim immediately after. The procedure for Digits

Backward is the same, except participants must input the string of numbers in the reverse order as they heard them presented. Outcome measures used in the present analyses were Digit Spans for both forwards and backwards conditions. To exclude individuals who misunderstood the task instructions or exhibited low effort, individuals who had spans ≤ 2 for the forwards condition, <2 for the backwards condition, or a total of ≤ 5 between the two conditions (reliable digit span = 6), were excluded from analyses (2.2% excluded).

Probability Discounting: Risky decision making, defined as preference for smaller, certain rewards over larger but uncertain rewards was assessed using a 30-item Probabilistic Choice Questionnaire (PCQ; Madden et al. 2009). In this task, participants were asked to choose between a small amount of money with 100% probability of receipt, and a larger amount of money with varying degrees of certainty of receipt (e.g., "Would you rather have $20 for sure (100% chance) or a 1-in-10 chance of winning $80 (10% chance)?"). The degree to which an individual discounts uncertain rewards was quantified by systematically increasing the probability of receiving the larger reward until the participant changed their preference from certain to uncertain rewards. Each participant was assigned a probability discounting rate (*h* value) based on their choices of uncertain rewards across trials for small, medium, and large uncertain rewards. Given very high correlations among the different magnitudes (rs = .605-.856, ps$<10^{-96}$), *h* values were combined using principle components analysis (PCA; oblique rotation, direct oblimin, $\delta=0$) into a single composite probability discounting rate across reward sizes (VanderBroek et al. 2016; Amlung & MacKillop 2014).

Delay Discounting: Preference for smaller immediate rewards over larger delayed rewards (a behavioural economic measure of impulsivity) was assessed using an augmented version of the 27-item Monetary Choice Questionnaire (MCQ; Kirby, Petry, & Bickel, 1999). The MCQ asks participants to choose between a smaller amount of money available immediately and a larger amount of money available after some delay in time (e.g., "Would you rather have $40 today or $52 in 62 days?"). The present study's discounting task consisted of 36 items (Towe et al. 2015), which included the original 27-item MCQ, plus six items sensitive to highly impulsive discounting and three control items to detect low-effort or misunderstanding of the task (e.g., "Would you rather have $20 today or $60 today?). Individuals who chose the smaller immediately available reward for two or more control items were not retained for further analyses (0.4% excluded). Each participant was assigned a discounting rate (*k* value) based on their choices of immediate rewards across trials for small, medium, and large-sized delayed rewards. Given very high correlations among the magnitudes (rs = .695-.807, ps$<10^{-138}$), *k* values for the three reward sizes were combined using principal components analysis (PCA; oblique rotation, direct oblimin, δ=0) into a single composite measure of discounting rate across reward magnitudes (VanderBroek et al. 2016; Amlung & MacKillop 2014).

Data Analysis

First, all data were screened for patterns of missing data and low-effort responses within the variables of interest, and only participants with complete and valid data were included

in final analyses (*N*=958). Next, distribution normality was examined and scores for AUDIT, FTND, cannabis age of first use, Shipley Verbal, Go/No-Go Commission & Omission Errors. Go/No-Go mean reaction time for "Go" trials were normalized using square-root transformations; *h*-values for Probability Discounting and *k*-values for Delay Discounting were normalized using lg10 transformations prior to undergoing PCA analysis. Correlations were used to identify appropriate covariates from demographic and other substance use variables (i.e., sex, age, income, tobacco use, and alcohol use). For primary analyses, hierarchical linear regression models were used to examine covariates and cannabis involvement in relation to neuropsychological task performance. In each model, the first step comprised of covariates, and the second step comprised the cannabis involvement measures (i.e., cannabis age of first use, CUDIT-R total score), which were examined to see if they significantly improved the model based on change in R^2.. Collinearity among independent variables was evaluated using a variance inflation factor of >2.50 and a tolerance statistic of <0.20 as criteria for detecting multicollinearity. A Type I error (α) threshold of .05 was used to detect significant findings. All analyses were conducted in IBM SPSS Statistics, Version 25.

Results

Preliminary Analyses

Age, sex, income, AUDIT and FTND scores were all significantly correlated with cannabis use variables (Table 2). Specifically, CUDIT-R scores were positively associated with alcohol and tobacco use, and negatively associated with age and income.

Younger age of first cannabis use was also associated with higher alcohol and tobacco use. Therefore, they were subsequently included as covariates in the first model of the hierarchical linear regressions for each of the cognitive measure.

Zero-order correlations between cannabis use variables, neurocognitive task performance, and self-reported ADHD symptoms are reported in Table 3. Many significant associations were revealed prior to incorporating covariates reflecting potential confounds. For example, more severe cannabis use as indicated by higher CUDIT-R scores significantly predicted steeper discounting of delayed rewards, a higher number of commission errors and faster reaction time on the Go/No-Go task, and greater endorsement of both hyperactive-impulsive and inattentive ADHD symptoms. Earlier age of first cannabis use was associated with higher CUDIT-R scores, and more inattentive ADHD symptoms, but was not associated with performance on any objective neuropsychological measures. Having more hyperactive-impulsive ADHD symptoms predicted steeper delay discounting, a greater number of commission errors and faster reaction time on Go/No-Go task, whereas more inattentive ADHD symptoms predicted higher Shipley Verbal scaled scores, less risky probability discounting, greater commission errors and faster reaction time on Go/No-Go task.

Regression Models

The regression models are presented in Table 4 and, after controlling for covariates, the cannabis involvement model significantly increased the variance in three domains.

Specifically, cannabis was significantly associated with greater hyperactive-impulsive and inattentive ADHD symptoms. Examination of the individual coefficients revealed that the largest and most significant associations were between CUDIT-R total scores and self-reported ADHD symptoms (with virtually identical β coefficients). Age of first cannabis use was not significantly associated with hyperactive or inattentive ADHD symptoms.

The cannabis involvement model also had a near-significant change in R-square for Delay Discounting (p = .052). Individual coefficients revealed that this was entirely attributable to level of cannabis severity (CUDIT-R), not age of first use (Table 5). Consistent with previous studies, greater cannabis use was associated with more impulsive discounting of future rewards.

Cannabis involvement was not associated with significant explanatory value for Shipley Verbal Scaled Score, Probability Discounting, Go/No-Go performance measures, or Digit Span performance.

Discussion

The primary aims of this study were to examine associations between cannabis use and both objective measures of neurocognitive performance and ADHD symptomatology, and to parse the degree to which cannabis-related problems and age of first use are differentially associated with performance. After controlling for covariates, the cannabis use model significantly predicted ADHD symptom endorsement and had near-significant

association with delay discounting, but was not associated with any other neuropsychological performance measures. Overall, it was found that severity of cannabis-related problems was the specific factor for observable differences in both inattentive and hyperactive ADHD symptoms, as well as impulsive delay discounting. Age of first cannabis use was not significantly associated with any outcome variables.

The finding that higher cannabis use severity predicted more hyperactive and inattentive ADHD symptoms is consistent with the larger literature. For instance, large epidemiological studies have found evidence for the link between a greater number of both inattentive and hyperactive-impulsive symptoms and increased risk for substance use disorders, such as alcohol, nicotine, cannabis, cocaine and other illicit drugs (Capusan et al. 2016; Estévez et al. 2016; Gudjonsson et al. 2012). What is less clear from cross-sectional designs is whether cognitive challenges captured by ADHD symptoms are consequences of heavy cannabis use, or whether people who experience difficulties with impulse control and/or distractibility are more likely to engage in problematic cannabis use. However, a meta-analysis of longitudinal studies found evidence for the increased risk of developing a substance use disorder associated with a childhood diagnosis of ADHD (Lee et al. 2011), supporting a causal path from ADHD to cannabis use. Despite being cross-sectional, the present study did not find earlier age of first use to be predictive of current ADHD symptoms, which obliquely provides support for the idea that ADHD predates cannabis effects on cognition (evidence of a link between earlier onset and ADHD would support the opposite direction) and represents a self-selection bias.

The meta-analytic evidence comes from study designs that dichotomized participants into either ADHD positive or ADHD negative (Lee et al. 2011), rather than examine continuous associations between number of inattentive, and hyperactive-impulsive symptoms with cannabis use outcomes. However, endorsement of subclinical levels of ADHD symptoms is far more common than meeting full criteria for ADHD diagnosis and the use of dimensional versus categorical analyses comes from genetic evidence for a large overlap between subtypes (McLoughlin et al. 2007; Bidwell et al. 2017). Some studies have examined the association between cannabis use and ADHD symptoms dimensionally, and have found differential relationships by symptom subtype. A large prospective twin study examining similar outcomes found that only hyperactive-inattentive symptoms predicted later substance related problems (Elkins et al. 2007), although a more recent longitudinal study examined differential associations between childhood and current ADHD symptom subtypes and cannabis use outcomes in adulthood, finding a pronounced effect of persistent inattentive symptoms on severity of cannabis-related problems (Bidwell et al. 2014). In contrast, the current study's findings were that cannabis use severity was predictive of both types of ADHD symptoms at virtually identical levels of association, and did not replicate the differential effects reported in the above studies. Importantly, despite having the largest effect size for cannabis involvement of all dependent variables, the absolute magnitudes of effects would still be considered small in magnitude

Cannabis use severity significantly predicted delay discounting outcomes, such that a higher number of cannabis-related problems was associated with greater preference for immediately-available rewards. This finding is congruent with the literature concerning addictive behaviours broadly, as a growing body of literature has established strong evidence for the association between immediate reward preference and addictive behaviours and disorders characterized by impulsivity and poor self-regulation (Amlung et al. 2016; MacKillop, Amlung, Few, Ray, et al. 2011; Jackson & Mackillop 2016; Amlung et al. 2017). A recent meta-analysis synthesized the findings of 12 studies and 2654 individuals examining delay discounting in relation to cannabis use, determining a small overall effect size (r=0.10, p=.04) with trend-level significance (Amlung et al. 2017). The current findings in regards to cannabis use and delay discounting are therefore congruent with the literature to date. In uncorrected correlations, a significant positive association was present between delay discounting and hyperactive-impulsive symptoms (r=.079, p = .014), but not for inattentive symptoms. This is also in line with previous evidence for steeper delay discounting in those with predominantly hyperactive-impulsive ADHD symptoms than predominantly inattentive (Scheres et al. 2010; Noreika et al. 2013; Solanto et al. 2001), and further emphasizes the utility of dimensional examination of ADHD symptom by subtype to better understand the relationship between self-reported and objective measures of impulsivity.

Interestingly, age of first cannabis use was not significantly predictive of any neurocognitive performance measures or self-reported ADHD symptoms. Despite the

growing interest in age of first cannabis use and a wealth of studies examining its associations with neurocognitive task performance, the evidence for the impact of earlier age of onset on later cognitive ability is still mixed. A recent review synthesizing this work concluded that although the evidence for deleterious effects of recent cannabis use on cognitive performance is well-established, the mixed evidence for a compounding effect of earlier age of first use is likely due to heterogeneity in study methods, including cognitive assessments used and granularity of cannabis use assessments (Broyd et al. 2016). These conclusions were mirrored in a recent meta-analysis of cross-sectional studies concluding a lack of evidence for the moderating role of age of first use on the effect of heavy cannabis use on cognitive functioning (Scott et al. 2018). Similarly, a recent large prospective twin study found that differences in intelligence predate the onset of cannabis use in adolescence, and that earlier age of first use was not predictive of subsequent neuropsychological decline (Meier et al. 2018). In terms of ADHD symptomatology, evidence exists suggesting that greater severity of ADHD symptoms among those with a childhood diagnosis is associated with an earlier initiation of cannabis use (e.g., Lisdahl et al. 2016; Lee et al. 2011; Pingault et al. 2012; Bidwell et al. 2014). However, after controlling for covariates, the present analyses failed to replicate findings of a positive association between age of first cannabis use and self-reported symptoms of either hyperactive-impulsive or inattentive symptoms. This discrepancy may be due to differences in methods; the evidence for this association comes from studies recruiting small samples of individuals with a diagnosis of ADHD, and the relationship is likely specific to clinical populations rather than relatively healthy individuals with subclinical

levels of ADHD symptoms. It is also possible that age of first cannabis use is more determinative among young adults who are closer in age to their first exposure than older adults who may not have used consistently, or even recently, in their adult life. Future studies interested in determining the causal nature of this relationship should consider using fine-grained measures of cannabis use history, methods of use, and patterns of recent use. However, in addition to no associations with age of first use, another general pattern of findings was that cannabis involvement was largely unrelated to cognitive performance in most domains. In this way, these findings converge with the conclusion of the recent National Academies of Sciences review (Board on Population Health and Public Health Practice et al. 2017) that notable effects on cognition tend to be present only in samples with very high levels of use.

The results presented here should be interpreted with several considerations. Limitations include that the assessment battery did not include any measures of history of conduct disorder. These are potential confounding variables that can meaningfully influence the relationship between cannabis and other domains (see Ganzer et al. 2016 for a review). It is possible that after controlling for behavioural problems in adolescence, associations between cannabis use severity and ADHD symptomatology would be reduced. Another limitation of this study was the lack of an objective measure of recent cannabis exposure, such as a urine drug screen for THC. The acute impact and potential chronic effects of THC consumption on neurocognitive performance have been well-documented in the literature (See Broyd et al. 2016 for a review), and having a biometric marker of THC

exposure as a predictor variable would have strengthened analyses, and may also have revealed significant associations that are associated with recent use rather than history of cannabis use or related problems.

On the other hand, a strength of the current study is the large sample size, which is well-powered to detect even small magnitude associations between variables of interest. Additionally, much of the literature to date has based inclusion on dichotomized diagnostic groups for cannabis use and/or ADHD populations, the findings of which cannot be generalized to describe trends in the general population. Additionally, the present sample was considerably older and captures a wider age span across adulthood than many previous studies examining cannabis use and cognition. Previously, the emphasis has been the potential effect of cannabis among adolescents and emerging adults, but less on individuals who are many years past their age of cannabis initiation. The present analyses were subsequently able to examine a wider range of age of initiation of cannabis use (ages 8-64 reported) than samples limited to young adulthood, providing rare insight to the role of age of first use on cognition among adults. Importantly, no age of first use associations were detected despite a large proportion of participants reporting an early age of first use (35.3% before age 15) and a moderate number exceeding the cut-off for current cannabis misuse (*N*=133). The present study therefore serves to fill part of a noted gap in the literature, dimensional relationships between cannabis involvement and diverse aspects of cognition across the lifespan in a general population sample of community adults.

In conclusion, in a comparatively large sample of community adults, the present study provides further evidence for the relationship between problematic cannabis use and the experience of hyperactive-impulsive and inattentive ADHD symptoms, as well as further evidence of a parallel association with impulsive delay discounting. Given the cross-sectional design, these findings cannot directly speak to the causality of the observed relationships, and highlights the need for more prospective investigation across the lifespan. Beyond these findings, with sufficient power to detect small effect size associations, the study revealed no significant links between cannabis use and overall verbal intelligence, short-term verbal memory, working memory, risk propensity, or behavioral inhibition, and no evidence linking younger age of first use to poorer cognitive performance. As such, these findings illustrate the need for further mapping of the variable links (and lack thereof) between cannabis use and cognition across levels of use and the lifespan.

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Table 1. Sample characteristics (***N*=958**)

	N(%)/Mean(SD)/ Median
Age	39.51 (13.71)
Sex	56.5% Female
Income	$75k - $90k/year
AUDIT Total	4.83 (4.39)
FTND Total	0.62 (1.67)
Cannabis AFU	17.73 (5.78)
CUDIT-R Total	3.10 (5.39)

Notes: AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test of Nicotine Dependence; CUDIT-R = Cannabis Use Disorders Identification Test - Revised; AFU = Age of First Use.

Table 2. Zero-order correlation matrix between potential covariates and cannabis involvement variables.

	1	2	3	4	5	6	7
1. Age	—						
2. Sex	.127**	—					
3. Income	.188*	-.038	—				
4. AUDIT total	-.176**	-.214**	.029	—			
5. FTND total	.000	-.093**	-.209**	.050	—		
6. CUDIT total	-.229**	-.136**	-.272**	.124**	.201**	—	
7. Cannabis AFU	.158**	-.006	.053	-.114**	-.101**	-.107**	—

Notes: AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test of Nicotine Dependence; CUDIT = Cannabis Use Disorders Identification Test; AFU = Age of first use.

* Significant at the $p<.05$ level (2-tailed).

** Significant at the $p<.01$ level (2-tailed).

Table 3. Zero-order correlation matrix between cannabis involvement variables, neuropsychological task performance, and ADHD symptoms.

	1	2	3	4	5	6	7	8	9	10	11	12
1. CUDIT-R total	—											
2. Cannabis AFU	-.107**	—										
3. Shipley Verbal	-.015	.039	—									
4. Probability Discounting	-.044	.056	-.084**	—								
5. Delay Discounting	.112**	-.019	-.176**	.050	—							
6. GNG Commission Errors	.099**	-.021	.002	.025	.021	—						
7. GNG Omission Errors	.012	-.017	-.184**	.061	.108**	.083*	—					
8. GNG Go Mean RT	-.124**	.057	-.135**	.003	.026	-.640**	.188**	—				
9. Digit Span Forwards	-.021	-.008	.196**	-.060	-.105**	.014	-.123**	-.165**	—			
10. Digit Span Backwards	-.015	.006	.194**	-.013	-.140**	-.016	-.187**	-.144**	.468**	—		
11. ADHD Hyperactive	.216**	-.046	.007	-.027	.079*	.112**	.004	-.105**	.018	.053	—	
12. ADHD Inattentive	.207**	-.072*	.100**	-.108**	.057	.109**	.008	-.089**	.002	.009	.625**	—

Notes: CUDIT-R = Cannabis Use Disorders Identification Test - Revised; AFU = Age of first use; GNG = Go/No-Go; RT = Reaction Time; ADHD = Attention Deficit Hyperactive Disorder.
*Significant at the $p<.05$ level (2-tailed).
** Significant at the $p<.01$ level. (2-tailed).

Table 4. Hierarchical regressions comprising covariate model (Age, Sex, Income, AUDIT total, FTND total), and cannabis involvement model (Cannabis AFU, CUDIT-R total) in relation to neuropsychological task performance and ADHD symptoms (N=958).

Neuropsychological Variable	Covariate Model R^2	*p*	Cannabis Involvement ΔR^2	*p*
Shipley Verbal	.056	<.001	.001	.486
Probability Discounting	.014	.003	.005	.072
Delay Discounting	.059	<.001	.006	.052
GNG Commission Errors	.089	<.001	.001	.564
GNG Omission Errors	.051	<.001	.001	.602
GNG Go Mean RT	.237	<.001	.000	.773
Digit Span Forwards	.042	<.001	.001	.490
Digit Span Backwards	.042	<.001	.000	.817
ADHD Hyperactive	.032	<.001	.028	<.001
ADHD Inattentive	.019	<.001	.028	<.001

Notes: AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test of Nicotine Dependence; AFU = Age of first use; CUDIT-R = Cannabis Use Disorders Identification Test - Revised; ADHD = Attention Deficit Hyperactivity Disorder.
*Significant at $p<.05$ level.

Table 5. Individual hierarchical regressions of covariates and cannabis involvement variables in relation to neuropsychological task performance and ADHD symptoms (N=958).

Model	**Variables**	**Delay Discounting**		**ADHD Hyperactive**		**ADHD Inattentive**	
		β	***p***	β	***p***	β	***p***
Covariate Model	Age	.085	.011	-.095	.005	-.061	.072
	Sex	-.013	.698	.071	.030	-.004	.892
	Income	-.065	.052	-.031	.358	-.027	.434
	AUDIT total	-.071	.031	.043	.191	.023	.478
	FTND total	.192	<.001	.053	.110	.025	.456
Cannabis Involvement	Cannabis AFU	-.010	.756	.000	.991	-.037	.254
	CUDIT-R total	.081	.017	.180	<.001	.174	<.001

Notes: AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test of Nicotine Dependence; AFU = age of first use; CUDIT-R = Cannabis Use Disorders Identification Test – Revised.

Chapter 4: Discussion

The aims of the two studies undertaken for this thesis were threefold: 1) to describe associations between cognitive task performance and cannabis involvement in representative samples of adults; 2) to investigate the relationships between cannabis use with dimensional experiences of ADHD symptoms; 3) to determine whether earlier age of first cannabis use contributes to differences in neurocognitive performance and/or ADHD symptom endorsement. Both Study 1 and Study 2 addressed the first and third goals, and Study 2 uniquely addressed associations between cannabis involvement and ADHD symptomatology.

Study 1 found evidence for recent cannabis use as indicated by the biometric presence of THC to be predictive of neuropsychological task performance among young adults. Specifically, THC presence was determinant of poorer performance on tasks assessing episodic memory and processing speed. A positive diagnosis of CUD predicted worse performance on a measure of fluid intelligence, but no other tasks in the neurocognitive battery. Study 2 revealed cannabis use severity as measured by the CUDIT-R screener to be the strongest determinant of ADHD symptoms, with similar predictive power for both hyperactive-impulsive and inattentive subtypes. In this sample of adults, higher cannabis use severity was also predictive of more immediate reward preference in the delay discounting task. Interestingly, age of first cannabis use was not a significant predictor of any neuropsychological task measures in both samples examined. It also was

unassociated with either hyperactive-impulsive or inattentive ADHD symptoms in Study 2.

The findings presented here are partially in agreement with the literature to date, however it is important to restate that the literature itself remains mixed in terms of findings and methodologies. The finding that recent THC exposure predicts worse episodic performance and slower processing speed is congruent with the body of work examining acute effects of cannabis use (Broyd, Van Hell, Beale, Yücel, & Solowij, 2016), and provides further support for the utility of biometric measures when assessing recent cannabis use. This finding highlights a considerable weakness of Study 2's design: there was no objective measure of recent use or lingering THC presence. It is possible that at least part of the value of CUDIT-R scores in predicting cognitive functioning could be due to recent cannabis use that would have been captured in a urine screen for THC, however without such a measure this is necessarily speculation. Future studies interested in following up on this line of inquiry may wish to include a drug screen as an adjunct to self-report measures to parse effects of recent use from more distal use (e.g., patterns of use over the last year). The finding from Study 1 that those who met criteria for CUD diagnosis tended to have lower fluid intelligence scores was also in line with a previous study examining IQ differences between dichotomized CUD groups, however it was also determined that IQ differences predated the age of first cannabis use (Meier et al., 2018). These findings are in line with a pattern of findings in recent longitudinal studies examining IQ and cannabis use in adolescence (Castellanos-Ryan et al., 2017; Fried,

Watkinson, James, & Gray, 2002; Jackson et al., 2016; Mokrysz et al., 2016), which collectively indicate a lack of causality of associations reported in cross-sectional studies. Although the present analyses were cross-sectional and cannot directly speak to the issue of causality, both Study 1 and Study 2 found a lack of support for the association between age of first cannabis use and neurocognitive measures. Instead, it appears that recent use and recent severity of use are more determinative of current cognitive functioning than adolescent use or lifetime history of CUD. Furthermore these findings suggest that if differences in cognitive performance exist, they may not be observable in low-severity samples. This is consistent with a new National Academies of Sciences review (Board on Population Health and Public Health Practice, Health and Medicine Division, & National Academies of Sciences Engineering and Medicine, 2017) which concluded that only samples with high levels of cannabis use show considerable impacts on cognition.

In interpretation of the current findings, it is important to consider the similarities and differences between the two studies discussed. In terms of similarities, both studies used large nonclinical samples recruited from their communities. This allows for some generalizability of the findings to people more broadly, which is not possible in studies comparing clinical groups (e.g., ADHD versus healthy controls). Furthermore both studies collected age of first cannabis use data and examined cannabis-related problems consistent with the diagnostic criteria for CUD. A similar battery of neuropsychological tasks were used in both study designs and notably included a measure of delay discounting, which is a relatively new measure that is not often included in cognitive

assessments. Both studies also share a common limitation: they did not include a measure of conduct disorder or antisocial personality features, variables that were found to be a common covariate in the cannabis and ADHD literature. They also differed in several ways that contributed uniquely to the overall findings of this work. Although both samples were large, they represent two distinct age groups; Study 1 sampled young adults ages 22-36 and Study 2 represented adults across the lifespan ages 18-65. Thus, the findings of Study 1 are relevant to and challenge the larger literature supporting a negative impact of early cannabis use among young adults. Study 2 therefore contributes to a gap of the literature examining the effects of early cannabis use on older adults who are many years past their first exposure to cannabis, and suggests that earlier age of first use is not associated with cognitive decreases among older adults. An important difference is also present in the unique contribution of Study 2 to the sparse literature on dimensional associations between ADHD symptoms and cannabis use, and highlights the need for more prospective studies to determine the causal nature of these relationships.

In conclusion, the works completed and discussed in this thesis provide considerable evidence for the role of recent cannabis use, rather than adolescent or lifetime use, in observed differences in cognitive task performance. The use of large community samples provided the present analyses with statistical power to detect subtle differences in performance on a variety of neurocognitive measures, and was able to characterize significant dimensional associations among ADHD symptoms, impulsivity, intelligence, episodic memory and processing speed as they relate to recent cannabis use and related

problems. In consideration of recent longitudinal studies published reporting a non-causal relationship between adolescent cannabis use and differences in cognitive functioning, the findings in this thesis also indicate that cannabis use in adolescence is likely not the cause of observable cognitive differences after controlling for current use and other covariates. Instead, preexisting differences in intelligence, cognitive profiles, and ADHD-related vulnerabilities are likely risk factors for earlier initiation of cannabis use and later problematic use. This emerging pattern in the literature has important implications for public health policy, as there is an ongoing debate about what would be an appropriate minimum age of purchase of recreational cannabis once legalization legislation is implemented. Perhaps more concern should be directed towards which adolescents and young adults are at risk of developing cannabis-related problems once use is initiated; individuals with a diagnosis of ADHD, lower IQ, or who may be at risk for other related issues such as psychotic disorders and other problematic substance use, may be more likely to experience negative cognitive impacts of cannabis use than those without these issues. This line of research is still in need of further investigation before sound recommendations could be made to guide legislation, however it serves to challenge some preconceived ideas about cannabis use during development and the magnitude of cognitive impact current use actually confers. Future studies and synthetic reviews are still needed before these findings can be translated to public education on risky cannabis use.

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