REWARD LEARNING IN A COMMUNITY CANNABIS USE SAMPLE

REWARD LEARNING CAPACITY IN A COMMUNITY SAMPLE OF INDIVIDUALS WHO USE CANNABIS

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Lay Abstract

Cannabis use has been related to impairments in reward processing. An important element of reward processing is *reward learning*, which means to form an association between a behaviour and a positive outcome. This study evaluated if individuals who use cannabis recreationally can learn reward associations unrelated to the substance, and if reward learning is affected by greater cannabis use. In this study, 38 participants who use cannabis and 34 control comparisons completed a reward learning task, and cannabis participants completed questionnaires about their use. The results showed that cannabis and control groups performed equally well on the task, but longer duration of cannabis use and higher potency was related to poorer performance. This suggests that individuals who use cannabis can learn non-drug reward associations, however, reward learning impairments may arise with greater severity of use. The findings are important in improving our understanding of the potential consequences of cannabis use.

Abstract

Rationale: Cannabis use has been related to poor psychosocial and socioeconomic outcomes, which may be due, in part, to impairments in forming non-drug reward associations. However, few studies have objectively evaluated reward learning in cannabis use populations.

Purpose: To investigate reward learning capacity in a community sample of individuals who use recreational cannabis, using the Probabilistic Reward Task (PRT), and to evaluate performance in relation to cannabis use characteristics.

Methods: Thirty-eight individuals who use cannabis and 34 control participants completed the PRT, in which reward learning was evidenced by the development of a response bias toward the more frequently rewarded stimulus. Relationships between response bias and cannabis use characteristics were explored (e.g., frequency, chronicity, potency) along with comorbid psychiatric symptoms (i.e., depression).

Results: Both cannabis and control groups developed a response bias across 3 blocks of the PRT. No group differences in response bias emerged, however, in the cannabis group, there was a trend for lower response bias in relation to greater chronicity and self-reported potency.

Conclusion: The results suggest that a community sample characterized by a range of cannabis use patterns, are not impaired in the ability to form non-drug related reward associations, although deficits may emerge with greater severity of use. These findings are important in supporting therapeutic approaches where forming reward associations outside of cannabis use are imperative, as well as informing public awareness and policy around cannabis use patterns.

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List of Figures and Tables

List of Abbreviations and Symbols

PRT:	Probabilistic Reward Task
IN-MAC:	Integrated Neuroscience of Motivation and Change
CUD:	Cannabis use disorder
VTA:	Ventral tegmental area
L-DOPA:	Levodopa
NAc:	Nucleus accumbens
d-amphetamine:	Dextroamphetamine
EEfRT:	Effort Expenditure for Rewards Task
CB1R:	Cannabinoid type 1 receptor
GABA:	γ-aminobutyric acid
THC:	Δ^9-tetrahydrocannabinol
D2/D3:	Dopamine receptors
RDoC:	Research Domain Criteria Initiative
MDD:	Major depressive disorder
rMDD:	Remitted major depressive disorder
BDI:	Beck Depression Inventory
n:	Number of participants in group
N:	Total number of participants in sample
M.I.N.I.	Mini-International Neuropsychiatric Interview
HiREB:	Hamilton Integrated Research Ethics Board
CUDIT-R:	Cannabis Use Disorder Identification Test – Revised
BDI-II	Beck Depression Inventory – Second Edition
AUDIT:	Alcohol Use Disorder Identification Test
IBM:	International Business Machines Corporation
SPSS:	Statistical Package for Social Sciences
ANOVA:	Analysis of variance
ΔRB:	Delta response bias (change from block 1 to block 3)
t:	T-test statistic
F/M/O:	Female, Male, Other
g:	Grams

F:	F-test statistic
RT:	Reaction time
χ^2:	Chi-squared test statistic
r:	Pearson correlation test statistic
r_{pb}:	Point biserial correlation test statistic
CMCR:	Michael G. DeGroote Centre for Medicinal Cannabis Research
ADHD:	Attention deficit hyperactivity disorder
PMS:	Premenstrual syndrome

Declaration of Academic Achievement

Dr. Balodis and myself developed the research questions for the current project. Dr. Balodis was responsible for the design of the project and obtaining approval from the Hamilton Integrated Research Ethics Board. Students and research assistants of the IN-MAC lab at the Peter Boris Centre for Addictions Research were responsible for collecting experimental data. I was responsible for analyzing and interpreting all data, and writing the manuscript.

Chapter 1: General Introduction

Overview

The cannabis landscape in Canada reflects high rates of recreational use in the general population, particularly since the legalization of non-medical cannabis by the federal government in 2018 (Rotermann, 2021). Nearly 20% of Canadians over the age of 16 report having used cannabis in a recent three month period (Health Canada, 2021b), with 7.9% of this group indicating daily or near-daily use (Rotermann, 2021). Cannabis is now perceived as the most socially acceptable substance, after alcohol, whereby the majority of Canadians believe that occasional use has little to no risk involved (Health Canada, 2021b). However, evidence suggests several harms and potential negative outcomes associated with frequent and heavy cannabis use, including: lower educational attainment (Fergusson et al., 2015); higher rates of depression and psychosis (Gobbi et al., 2019); increased risk of illicit substance use (Hall, 2014); and developing cannabis use disorder (CUD; Silins et al., 2014).

Substance use, mainly problematic use, is increasingly conceptualized in the context of deficient reward learning (Lewis, 2018) – a form of reinforcement learning where behaviour is modified after associating a stimulus with a positive outcome (National Institute of Mental Health, 2009). Reward learning can be considered under the broad construct of *reward processing*, which also encompasses: the motivation to pursue reward; the anticipation of; and response to, reward (Berridge & Robinson, 2003). Evidence suggests that individuals who use cannabis show lower educational attainment and occupational status (Schaefer et al., 2021), along with greater absence and discharge rates from their jobs (Airagnes et al., 2019; Zwerling et al., 1990). These negative psychosocial and socioeconomic outcomes may be due, in part, to impairments in the ability to form reward associations outside of cannabis use (i.e., reward learning); with increased consumption, cannabis becomes overvalued at the expense of other

reward. Additionally, most treatments for CUD require learning novel positive reinforcers (e.g., contingency management), therefore therapeutic goals may be negatively affected if individuals are deficient in forming these associations. Thus, understanding reward learning capacity in cannabis use populations is imperative.

The first chapter of this thesis outlines 1) an overview of reinforcement learning theory; 2) reward learning and its corresponding neurocircuitry; 3) the relationship between reward learning, motivation and the 'amotivational syndrome' in the context of cannabis; 4) psychosocial outcomes and mechanisms of cannabis; 5) an overview of a performance-based measure to objectively evaluate reward learning: the Probabilistic Reward Task; and concludes with an introduction to the current study. Chapter two contains an original manuscript in preparation for submission to *Neuropsychopharmacology*, titled 'Reward learning capacity in a community sample of individuals who use cannabis'. Chapter 3 concludes with a general discussion, integrating findings from the current study with the extant literature.

Fundamentals of Reinforcement Learning Theory

In order to effectively adapt and survive in its environment, an animal must learn ways in which to maximize reward and reduce punishment (Sutton & Barto, 1998). 'Reward' is conceptualized as the positive value held by an object, behavioural act or internal physical state (Schultz et al., 1997). One model of learning, termed 'reinforcement learning', suggests that a positive reinforcer (i.e., reward) serves to increase the likelihood of a behaviour (Rescorla & Wagner, 1972). In this way, repeatedly assessing the outcome of an action reveals the expected likelihood of reward, and through the receipt of reward, the action that led to the outcome is strengthened (Sutton & Barto, 1998; Thorndike, 1898). Similarly, negative reinforcement leads to the avoidance of an aversive outcome (O'Doherty et al., 2017; Schultz, 2007). An element that

is crucial to efficient reinforcement learning, is prediction error; specifically, reward prediction error is the difference between the expected – or predicted – reward and the magnitude and timing of the actual reward received (Schultz et al., 1997). This fine-grained understanding of a key subconstruct of learning, has allowed for testable neural models of reward learning.

Neurocircuitry Involved in Reward Learning

The neural basis of reward has been extensively studied, in particular, the primary role played by the neurotransmitter dopamine (Baik, 2013). Early work by Olds and Milner (1954) revealed that rats would repeatedly press a lever in exchange for electrical stimulation via electrodes implanted in the brain (Olds & Milner, 1954). They discovered that electrodes placed in areas densely populated with dopamine neurons, mainly regions associated with the medial forebrain bundle, produced the highest reinforcement rates (i.e., lever pressing; Corbett & Wise, 1980; Gardner, 2011; Mora & Myers, 1977; Wise, 1978). Similarly, rodents treated with dopamine receptor blockers were impaired in their ability to learn to bar press to receive a rewarding food pellet (Beninger, 1989). Using electrical recording of midbrain dopamine neurons, monkeys learning a behavioural task to receive food reward, saw an increase in phasic dopamine when reward was received (Schultz et al., 1993). In a similar paradigm, monkeys were trained on a behavioural task to receive food, and additionally, were randomly delivered food reward. Not only was dopamine significantly increased during learning of the stimulus that predicted reward, but also in response to the delivery of free, unpredicted reward (Mirenowicz & Schultz, 1994, 1996). This is in line with learning theory that highlights the importance of unpredicted reward, namely, reward prediction error (Dickinson, 2012). Therefore, dopamine is not simply signaling the receipt of reward itself, but codes for the discrepancy between the prediction of expected reward and the actual reward received (Schultz et al., 1997). When reward

is greater than predicted (i.e., positive prediction error) midbrain dopamine levels increase, in contrast, when reward is less than predicted (i.e., negative prediction error), dopamine is decreased from baseline (Schultz, 2016). This prediction error allows for the modification of behaviour, until the outcome is reliably predicted, resulting in learning of behaviour that leads to positive (i.e., rewarding) or negative (i.e., aversive) outcomes (Schultz & Dickinson, 2000). Once the reinforcer is established and reward consistently occurs as predicted, behaviour is no longer adapted and dopamine release remains at baseline (Schultz, 2016; Schultz & Dickinson, 2000).

Beyond midbrain dopamine activity, the neurocircuitry involved in reward learning encompasses widespread neural networks that form what is known as the mesolimbic dopamine system, which projects dopamine mainly from the ventral tegmental area (VTA), to areas of the limbic system and striatum (Baik, 2013; Haber & Knutson, 2010; Koob, 1992; Wise, 1998). Importantly, areas of the striatum have emerged as playing a central role in the process of reward learning (O'Doherty et al., 2004). In human neuroimaging studies, increased activation is seen in the striatum, primarily during the period of reward prediction error, where participants learn to respond for food (Berns et al., 2001; McClure et al., 2003; O'Doherty et al., 2003; Pagnoni et al., 2002), or monetary reward (Haruno, 2004; Yacubian, 2006). When participants are administered L-DOPA or haloperidol, dopamine levels are enhanced or reduced, respectively. Compared to haloperidol-treated participants, the increase in striatal dopamine via L-DOPA resulted in greater propensity for choice behaviour that led to larger monetary outcomes on a behavioural task (Pessiglione et al., 2006). Additionally, the processing of social reward activates overlapping neural circuitry involved in monetary reward (Izuma et al., 2008; Lin et al., 2012). Collectively,

the evidence highlights the central role of the mesolimbic dopamine pathway in reward, and in the learning process of a variety of reward types.

Reward Learning, Motivation and the 'Amotivational Syndrome'

An important element of general reward processing, is the motivation to direct internal and external resources toward the pursuit of reward in the first place (Berke, 2018). Broadly, motivation is defined as the "cognitions, emotions and behaviours involved in the activation, execution and persistence of goal-directed behaviour" (Kleinginna & Kleinginna, 1981). In a continual cycle, motivation uses predictions of anticipated reward to stimulate behaviour, and learning takes into account the outcome of a past behaviour to evaluate its utility (Berke, 2018). The initial stage of motivation, in which engaging in a behaviour increases the likelihood of a desired outcome, is referred to as "appetitive" or "seeking" (Salamone & Correa, 2012). An area of the striatum, the nucleus accumbens (NAc), has long been understood to play a central role in reward-seeking behaviour of both natural reward (i.e., food, sex) and substance-based reward (i.e., drugs with dependence potential; Salamone et al., 2003). Specifically, dopamine in the NAc acts as a modulator of various functions of motivated behaviour, including the exertion of effort (Salamone et al., 2003, 2005). Rats injected with haloperidol directly into the NAc, showed a substantial decrease in lever-pressing to receive food reward, and chose to consume the less-preferred option of freely available chow (Cousins et al., 1993; Cousins & Salamone, 1994; Salamone et al., 1991). In human control participants, administration of dopamine agonist *d*-amphetamine, increases effort exertion for monetary reward, on the validated Effort Expenditure for Rewards Task (EEfRT; Treadway et al., 2009), particularly on trials of lower reward probability (Wardle et al., 2011). Similarly, greater effort expenditure was found to be positively correlated with dopamine function in striatal regions (Treadway et al., 2012). This evidence

highlights the behavioural and neural overlap between reward learning and functions of motivation.

Early evaluations of individuals who use cannabis, associated frequent use with a general lack of motivation. This 'amotivational syndrome' coined by McGlothin and West (1968), classified cannabis use populations as passive and non-productive, and ultimately impaired in their capacity for goal-directed behaviour (McGlothin & West, 1968). A recent literature review on cannabis use and motivation, reveals notable heterogeneity in findings (Pacheco-Colón, Limia, et al., 2018). There is evidence for self-reported reductions in motivation in a daily use sample, compared to those who use infrequently (Kouri et al., 1995), as well as in individuals meeting dependence criteria versus a non-dependent group (Looby & Earleywine, 2007). Further characterization of cannabis use reveals an association between reduced motivation and increased cannabis quantity, CUD symptoms and problematic use, while other relationships between cannabis patterns and specific subconstructs of motivation were lost when controlling for depression and other substance use (Petrucci et al., 2020). Neuroimaging evidence also supports the association between impaired motivation and cannabis use; reduced striatal dopamine synthesis capacity in a regular cannabis use group, was associated with reduced motivation on a self-report scale (Bloomfield et al., 2014). Conversely, other studies using a variety of subjective assessments have not found a relationship between motivation and regular cannabis use (Barnwell et al., 2006; Pacheco-Colón, Coxe, et al., 2018). The discrepant results may be explained by how the respective cannabis groups were differentially characterized (i.e., inclusion criteria based on frequency of use, or dependence criteria), and the variation in which studies accounted for potential confounds (e.g., depression symptomatology, other substance use).

Considering that self-report measures are inherently prone to bias, performance-based tasks assessing motivation provide a more objective approach to evaluating this construct in cannabis use populations, although this literature is sparse. A study that used a behavioural motivation task, found that an adolescent regular cannabis use sample, switched sooner than controls from a progressive ratio reinforcement schedule based on effortful responses, in exchange for receipt of monetary reward, to a "nonwork" reinforcement schedule (Lane et al., 2005). In contrast, investigation using the EEfRT revealed that a light-using cannabis group chose high effort trials more often than controls (Taylor & Filbey, 2021), translating to *increased* motivation for monetary reward; this relationship was strengthened among those who report greater cannabis use (Acuff et al., 2022). However, participants under acute cannabis intoxication show significantly decreased effort exertion for reward, compared to placebo (Lawn et al., 2016), in a dose-dependent manner (Wardle et al., 2022). Although evidence for a relationship between reduced motivation and cannabis use is mixed, the literature suggests a potential role for frequency and severity of use (i.e., dependence) as well as confounds (e.g., depression symptoms) that warrant further investigation.

Psychosocial Outcomes and Mechanisms of Cannabis

The association between cannabis use and negative psychosocial and socioeconomic outcomes is often exacerbated with increased use and earlier initiation, however, those that use cannabis report lower perceived risk associated with the drug, compared to those who do not use (Health Canada, 2021b). Younger age of cannabis use onset is associated with lower academic achievement (Hooper et al., 2014; Maggs et al., 2015; Melchior et al., 2017); adolescents who use cannabis are less likely to participate in extra-curricular activities (Darling, 2005), exercise and sport (Henchoz et al., 2014), and report lower feelings of connectedness to their school

community (Dever et al., 2012). Moreover, frequent cannabis use is related to decreased likelihood of obtaining a bachelor's degree (Maggs et al., 2015), lower self-reported productivity, and higher absence rates from school or work (Buckner et al., 2010), although causality is difficult to establish. However, a longitudinal study provides strong evidence for a dose-dependent relationship between greater frequency of use during adolescence, and poorer life outcomes in adulthood, even after controlling for several potential confounds (Silins et al., 2014). It is possible that with increased use, cannabis attains greater value at the expense of other reward. With continued use of the substance, a shift in hedonic homeostasis may occur as a result of dysregulation in brain reward systems, thereby leading to further cannabis use (Koob & Le Moal, 1997). Cannabis primarily exerts its reinforcing effects by indirectly increasing midbrain dopamine via the endocannabinoid system (Bossong et al., 2009). Normally, endogenous cannabinoids (i.e., 2-arachidonoylglycerol and anandamide) bind to cannabinoid type 1 receptors (CB1Rs) on GABAergic and glutamatergic nerve terminals (Pertwee, 2008). Activation of CB1Rs leads to retrograde suppression of excitation and inhibition, at the glutamatergic and GABAergic nerve terminals, respectively (Lecca et al., 2012; Marinelli et al., 2007), which synapse onto midbrain dopamine neurons to modulate transmission (Bloomfield, Ashok, et al., 2016). With acute cannabis administration, THC – the main psychoactive component – binds to CB1Rs on GABAergic terminals in the VTA, which disinhibits dopamine transmission, and therefore increases dopamine release in midbrain projection sites (Pierce & Kumaresan, 2006). However, chronic THC exposure has been associated with dopamine hypoactivity (Volkow et al., 2014), due in part, to the sensitization of midbrain dopamine D2/D3 autoreceptors, resulting in decreased dopamine release (Ginovart et al., 2012). This is in line with the 'reward deficiency hypothesis' which posits that functional deficits in areas of the reward pathway, result in lower

gratification from natural reward, and thus increase the pursuit of drugs (e.g., cannabis) as a means to supplement this diminished reward response (Blum et al., 2000). This impaired capacity to form natural reward associations may partly explain the negative psychosocial and socioeconomic consequences seen in those who frequently use cannabis.

A Performance-based Measure of Reward Leaning: The Probabilistic Reward Task

The Research Domain Criteria Initiative (RDoC) framework, parses reward into 3 constructs of the positive valence system, comprising: (i) reward responsiveness; (ii) reward learning and; (iii) reward valuation (National Institute of Mental Health, 2009). A subconstruct of reward learning under this framework is 'probabilistic and reinforcement learning' which can be measured via the Probabilistic Reward Task (PRT; Pizzagalli et al., 2005). The PRT was adapted from a signal detection task (Tripp & Alsop, 1999) by Pizzagalli and colleagues (2005), as a means to objectively measure hedonic capacity (i.e., the ability to derive pleasure from typically-rewarding stimuli; Audrain-McGovern et al., 2012). In signal-detection tasks, participants are asked to choose which of two different stimuli are presented by making the appropriate response, and positive feedback – in this case, monetary reward – is provided for correct responses in a pseudorandom order (i.e., not all correct responses are rewarded; Pizzagalli et al., 2005). The primary outcome of interest on the PRT is *response bias*: the general tendency to make one response over the other, regardless of which stimulus was presented (Pizzagalli et al., 2005; Tripp & Alsop, 1999). Importantly, correct responding of one stimulus is rewarded at a rate three times greater than the other; this asymmetrical reinforcement schedule is crucial for inducing a preference for the response paired with the more frequent reward (Johnstone & Alsop, 2000; McCarthy, 1991; McCarthy & Davison, 1979). Thus, the degree of response bias toward the more frequently rewarded stimulus, allows for the evaluation of how

behaviour is changed as a function of prior reinforcement (Pizzagalli et al., 2005). Response bias development on the PRT has been related to dopaminergic transmission, whereby administration of pramipexole (found to decrease striatal dopamine at low doses), impairs response bias development in human control participants, compared to placebo (Pizzagalli, Evins, et al., 2008). Evaluation using a rat analog of the PRT, mirrored the effect of pramipexole in humans, and showed that *d*-amphetamine (0.5mg/kg) facilitated response bias development, compared to saline-treated rats (Der-Avakian et al., 2013). In contrast, *d*-amphetamine administration (10/20mg) in human control participants, had no significant effect on response bias (Soder et al., 2021), highlighting the need for future studies to delineate the mechanism of dopaminergic involvement in PRT reward learning.

The PRT has been widely applied in populations with depression and symptoms of anhedonia. Anhedonia is a key feature of depression, defined as a loss of interest or pleasure from typically pleasurable stimuli (APA, 2013), thought to result in part, from impairments in motivation and/or reward learning (Treadway, 2011). The PRT literature suggests that compared to controls, individuals with elevated depressive symptoms (Pizzagalli et al., 2005), subclinical depression (Liu et al., 2011), and diagnoses of major depressive disorder (MDD; Liu et al., 2011; Pizzagalli, Iosifescu, et al., 2008; Vrieze et al., 2013) show impaired reward learning, as evidenced by a reduction or absence of response bias development. This impairment has been consistently correlated with self-reported anhedonic symptoms (Bogdan & Pizzagalli, 2006; Liu et al., 2011; Pizzagalli et al., 2005; Pizzagalli, Goetz, et al., 2008; Pizzagalli, Iosifescu, et al., 2008; Vrieze et al., 2013), and has been shown to predict persistent MDD diagnoses post-treatment (Vrieze et al., 2013); individuals with remitted MDD (rMDD) also show reduced response bias compared to controls (Pechtel et al., 2013; Whitton et al., 2016). Deficits in

integrating reinforcement history, particularly among those who may be impaired in experiencing reward (i.e., anhedonia), may in turn affect the ability to initiate goal-directed behaviour (Pizzagalli, Iosifescu, et al., 2008). It is important to distinguish anhedonia from apathy here: apathy is defined as a reduction or loss of motivation, particularly in seeking reward (Robert et al., 2009; Skumlien et al., 2021) and was outlined as a core feature of the cannabis 'amotivational syndrome' (McGlothin & West, 1968). Both apathy and anhedonia are aspects of deficient reward processing (Skumlien et al., 2021), however anhedonia is better understood in the context of reward *learning* specifically.

Research evaluating reward learning using the PRT among substance-use populations is sparse. While nicotine has been shown to enhance reward learning on this task (Barr et al., 2008; Janes et al., 2015; Liverant et al., 2014), only one study has previously assessed reward learning using the PRT in a cannabis use sample (Lawn et al., 2016). A study by Lawn and colleagues (2016) found that a cannabis group showed significantly lower response bias, compared to controls, and in fact, did not develop a response bias across blocks. It is important to note that all individuals in the experimental group met dependence criteria for cannabis, and used high potency cannabis on at least half of the occasions in which they consumed the substance. However, less is known about reward learning capacity among individuals characterized by a wider range of use patterns.

Introduction to the Current Study

Impaired ability to form new reward associations may result in negative psychosocial and socioeconomic consequences, and affect treatment adherence in cannabis use populations. Therefore, understanding reward learning capacity in individuals who use cannabis is crucial. To date, no study has assessed reward learning using the PRT in a community sample characterized

by a range of recreational cannabis use patterns (e.g., frequency, chronicity, potency). The current study had two main objectives:

1. Evaluate reward learning capacity in a community sample of individuals who use cannabis ≥2 times/month, compared to controls, using the PRT. It is hypothesized that the cannabis group will show impaired reward learning (i.e., lower response bias) compared to the control group.
2. In the cannabis group, evaluate the relationship between reward learning capacity and cannabis use characteristics (i.e., frequency, weekly quantity, self-reported potency, age of initiation, years of use, dependence). It is hypothesized that indications of more severe cannabis use (i.e., higher frequency, quantity, potency, earlier age of initiation, greater years of use, and dependence) will be associated with greater impairments in reward learning.

Chapter 2: Manuscript

REWARD LEARNING CAPACITY IN A COMMUNITY SAMPLE OF INDIVIDUALS WHO USE CANNABIS

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Abstract

Cannabis use has been linked to deficient reward processing, however, little is known about its relation to the specific construct of reward learning, in which behaviour is modified through associating a novel stimuli with a positive outcome. The Probabilistic Reward Task, based on signal detection theory, was used to objectively evaluate reward learning in 38 individuals who use recreational cannabis and 34 control comparison participants from the community. Reward learning was evidenced by the development of a response bias, which indicates the propensity to modulate behaviour as a function of prior reinforcement. Both cannabis and control groups demonstrated reward learning, with no group differences in response bias development. Among cannabis participants, trending significant relationships between greater chronicity, self-reported potency and poorer reward learning were found. The ability to form non-cannabis reward associations is promising for the success of therapeutic interventions for problematic cannabis use, however, indications of severity of use in relation to poorer reward learning suggests a need for a better pharmacological and pharmacokinetic understanding of cannabis.

Introduction

Cannabis persists as the most widely used illicit drug worldwide, whereby an estimated 4% of the global population aged 15-64 consumed cannabis in 2020; rates of use have steadily increased in the last decade [1]. Despite the popular belief that cannabis use poses little to no risk [2,3], several lines of evidence reveal potential negative psychosocial and mental health consequences associated with frequent use, including: lower academic achievement [4]; higher rates of depression and psychosis [5]; increased risk of developing cannabis use disorder (CUD, [6]); and engaging in other substance use [7]. With more countries moving toward cannabis legalization, understanding the mechanisms through which cannabis use is linked with adverse outcomes is imperative.

Emerging longitudinal studies suggest a dose-dependent relationship between greater cannabis use and poorer psychosocial and socioeconomic outcomes [6,8–11]. This may be due, in part, to impairments in forming positive associations outside of cannabis use; with increased consumption, cannabis becomes overvalued at the expense of other rewards. Therefore, substance use disorders are increasingly conceptualized in the context of altered reward learning [12]. Reward learning is a form of reinforcement learning in which behaviour is modified after associating novel stimuli with a positive outcome [13]. Areas of the striatum play a central role in reward learning [14], whereby phasic dopamine release facilitates forming an association between behaviour and outcome [15]. With acute cannabis use, the primary psychoactive component, Δ^9-tetrahydrocannabinol (THC), binds to cannabinoid type 1 receptors (CB1Rs) to indirectly increase dopamine transmission in areas of the mesolimbic dopamine system [16]. However, chronic use is often associated with hypodopaminergic transmission in these areas [17–19], potentially leading to lower gratification from natural reward, and the subsequent

pursuit of cannabis as a means to compensate for a diminished reward response (i.e., reward deficiency hypothesis [20]).

Behavioural reward learning studies in humans evaluate how stimuli acquire rewarding properties and facilitate preference formation, with notable heterogeneity in findings in cannabis populations. While some studies find similar task performance between cannabis and control participants [21–24], others show that cannabis use is related to significantly reduced reward learning [25–27]. Findings are limited by methodological variability, and inconsistency in cannabis use parameters (e.g., frequency, chronicity, potency, abstinence), which often vary widely or are not reported. Nevertheless, there is some evidence for greater impairment with chronic use [28,29], increased frequency [30,31], higher THC potency [32] and dependence [33]. With careful consideration of a range of cannabis use characteristics, the present study aims to evaluate reward learning in a recreational cannabis use sample.

A validated behavioural paradigm was used to objectively evaluate reward learning in a community sample of individuals who use cannabis recreationally (≥2 uses/month). The Probabilistic Reward Task (PRT), based on original signal detection theory, evaluates the propensity to modulate behaviour as a function of prior reinforcement [34]. Using a modified version of the PRT, a previous study found that cannabis-dependent participants who frequently use high potency cannabis, showed no reward learning compared to controls [35]. However, task performance has not been evaluated in a community sample characterized by a range of recreational cannabis use patterns. Based on prior findings [35], we hypothesized that compared to non-using controls, participants in the cannabis group would show reduced capacity to learn non-drug related reward, as evidenced by an impaired ability to form a response bias on the PRT. Moreover, we reasoned that greater cannabis severity (e.g., increased frequency, chronicity,

potency and dependence), would be related to further reward learning impairment. While causality is difficult to establish through a cross-sectional evaluation, these findings would support the notion that deficits in forming novel associations outside of cannabis result in greater use, to supplement for a diminished reward response.

Methods

Participants

A total of 106 individuals participated in the study. The population was separated into two groups, including individuals who use cannabis recreationally (n = 55) and control participants (n = 51), recruited from the Hamilton community via flyers and online advertisements. Eligibility criteria were: (1) nineteen years of age or older; (2) no current organic psychosis; (3) no substance dependence in the control group; (4) in the cannabis group, participants were included if they used cannabis ≥2 times/month at the time of assessment. One participant in the control group was removed for meeting alcohol dependence criteria (n =1). After applying quality control measures on the PRT (see PRT Calculations and Quality Control section below), the final sample reported was N = 72 (cannabis group, n = 38; control group, n = 34). A breathalyzer confirmed no alcohol use prior to the session (n = 64). Individuals in the cannabis group completed a urine toxicology screen on the day of assessment and tested positive for: THC (n = 31), amphetamine (n = 1), benzodiazepines (n = 3), oxycodone (n = 1); n = 4 showed a negative screen for all substances, but met inclusion criteria for self-reported cannabis use; n = 3 had missing urine screens. Participants were assessed with the Mini-International Neuropsychiatric Interview (M.I.N.I. [36]), to determine Axis 1 psychiatric and substance use diagnoses; n = 17 in the cannabis group met criteria for substance dependence [37], with cannabis being the most frequently used substance. Participants met criteria for: generalized anxiety disorder (n = 5 cannabis, n = 1 control); current major depressive episode (n = 4 cannabis, n = 1 control); past major depressive episode (n = 19 cannabis, n = 3 control). Participants provided informed consent and were reimbursed with gift cards for study

completion. The study was approved by the Hamilton Integrated Research Ethics Board (HiREB) and was conducted in accordance of the Declaration of Helsinki.

Physiological Measures

Breathalyzer

Blood alcohol concentrations were evaluated through Breath Alcohol Level using a handheld Alco-Sensor® Breathalyzer (Intoximeters, Inc, St. Louis, MO, USA).

Urine screen

Participants provided a urine sample on the day of assessment that was tested to qualitatively assess substances in the sample (Rapid TOX Cup® II, American Bio Medica Corporation, Kinderhook, NY, USA).

Self-report/Clinical Measures

Marijuana History Questionnaire

Evaluates use patterns including weekly quantity and relative THC content of typically-consumed cannabis.

Marijuana Smoking History Questionnaire [38]

Collects information regarding: frequency of cannabis use; age of initiation; years of use.

Cannabis Use Disorder Identification Test – Revised (CUDIT-R, [39])

A brief 8-item valid measure used to identify problematic cannabis use.

Beck Depression Inventory-II (BDI-II, [40,41])

A validated 21-item self-report scale that evaluates symptoms of depression.

Reward Learning Behavioural Task

Probabilistic Reward Task [34]

The task followed the protocol established by Pizzagalli et al., (2005). In brief, participants were presented simple cartoon faces with two different mouth lengths that were difficult to differentiate and were asked to quickly identify if they saw the short or long mouth (Figure 1). Participants could win money based on correct identification of the stimulus, and were not informed that one of the stimuli ('rich' stimulus) was reinforced three times more frequently than the other ('lean' stimulus). An alternate version of the task presented different nose lengths on the cartoon faces; participants were randomized to the mouth/nose version, as well as the version in which the short or long mouth/nose was the more frequently rewarded stimulus. The task contained 3 blocks of 100 trials, each block lasted approximately 8 minutes. Participants were informed that only a portion of correct responses would receive reward feedback and were instructed to try their best on the task. Participants were compensated a set amount for study completion, but not specifically for task earnings.

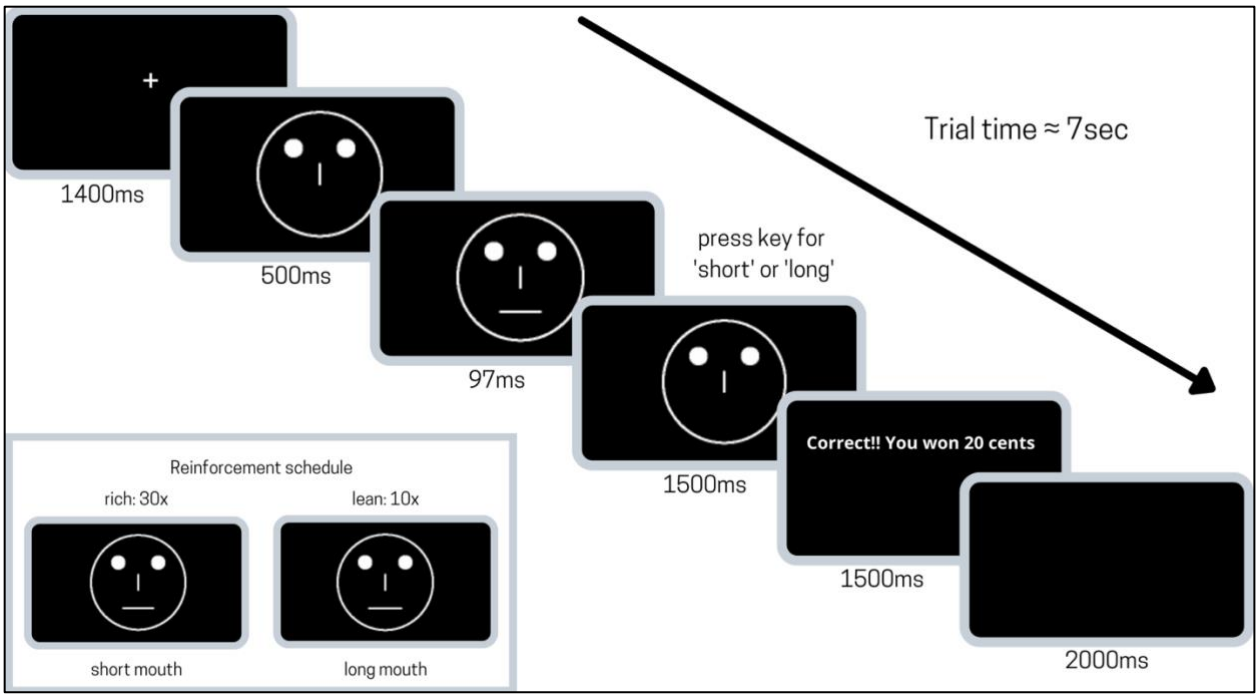

Figure 1. Diagrammatic representation of the Probabilistic Reward Task (PRT). Each trial begins with a fixation cross on the screen, followed by a mouthless face. A face with a short or long mouth appears, then a mouthless face for 1500ms or until the participant responds with the appropriate 'e' or 'i' key to indicate which mouth was presented. Feedback is presented on 40 correct trials in each block ("Correct! You won 20 cents"). A blank screen is shown following reward feedback, whereafter the next trial begins. Each trial lasts approximately 7 seconds; participants complete 3 blocks of 100 trials each for a total of 300 trials.

PRT Calculations and Quality Control

Trials where reaction time was <150 ms or >2500 ms, and remaining trials with reaction time outside the range of ±3SD from the mean, were excluded. Participants with <80 % valid trials, and a reward ratio of <2 in any block were removed (33; Diego Pizzagalli personal communication, June 2022). After application of these criteria, n = 17 in the cannabis group and n = 16 in the control group were excluded. Individuals who did not meet quality control criteria, did not differ from participants included in the final sample in age, gender, or cannabis use

characteristics, with the exception of a larger range of weekly quantity among participants included in the final sample ($p < .05$). The main task outcome is response bias, with other important outcomes including discriminability, accuracy and reaction time. Response bias and discriminability are calculated as:

$$Response\ bias: logb = \frac{1}{2}\log\frac{rich_{correct} * lean_{incorrect}}{rich_{incorrect} * lean_{correct}}$$

$$Discriminability: logd = \frac{1}{2}\log\frac{rich_{correct} * lean_{correct}}{rich_{incorrect} * lean_{incorrect}}$$

Statistical Analyses

All analyses were carried out using IBM Statistical Package for Social Sciences (IBM SPSS version 28). Data was assessed for normality, homoscedasticity and outliers. When data violated the aforementioned assumptions, appropriate non-parametric tests were used (e.g., Greenhouse-Geisser correction). T-tests and chi-square tests were used to determine differences in demographic characteristics between groups. To evaluate PRT performance, a 2 group (cannabis, control) X 3 Block (1, 2, 3) repeated-measures ANOVA was conducted, with response bias and discriminability as dependent variables. An additional within-subjects factor of stimulus (rich, lean) was used for accuracy and reaction time. Change in response bias (ΔRB; change between blocks 3 and 1) was correlated with cannabis use characteristics and BDI-II scores (as previously applied in Lawn et al., (2016)).

Results

Demographics (Table 1)

The groups did not differ in age, gender, education, or yearly household income, however, the cannabis group scored significantly higher on depression severity (BDI-II), $t(67) = 3.44$, $p = .05$, compared to controls.

Table 1. Demographics and cannabis use characteristics.

	Cannabis (*n* = 38)	Control (*n* = 34)
Age (years)	42.2±13.4	36.6±14.9
Gender (F/M/O)	24/14/0	23/10/1
Education		
College, university or graduate school/High school/Trade school	24/12/2	28/5/1
Yearly household income		
<$15,000	18.4%	14.7%
$15-75,000	47.3%	44.1%
$75-120,000	23.7%	14.6%
>$120,000	5.3%	5.9%
Ethnicity		
European/Native North American/Asian/Other	24/2/3/9	25/2/3/4
Cigarette use	*n* = 13	*n* = 2
BDI-II score*	12.9±13.6	4.4±5.4
Alcohol use		
Never	34.2%	29.4%
2-3 times weekly	10.5%	8.8%
≥4 times weekly	10.5%	0%
Monthly or less	21.1%	38.2%
2-4 times monthly	13.2%	17.6%

Cannabis use frequency			
	≥once daily	62.2%	
	1-6 times weekly	24.3%	
	2-3 times monthly	13.5%	
Potency (% THC)			
	20-30	40%	
	"I do not know"	37%	
	10-19	17.2%	
	5-9	2.9%	
	0-4	2.9%	
Age of cannabis use initiation		19.3±9.7	
Years of cannabis use		17.9±14.7	
Weekly quantity (g)		9.0±9.6	
CUDIT-R score		10.2±6.5	

Probabilistic Reward Task (PRT)

Response bias (Figure 2). A 2 x 3 repeated measures ANOVA revealed a main effect of block ($F(2,140) = 4.63$, $p < .05$), showing a significant increase in response bias over time; pairwise comparisons showed a significant increase from block 1 (0.09±0.17) to block 2 (0.16±0.19, $p < .05$), from block 1 to block 3 (0.16±0.24, $p < .05$), but not between block 2 and block 3 ($p > .05$). There was no significant group difference ($F(1,70) = 0.12$, $p > .05$) or group x block interaction ($F(2,140) = 0.66$, $p > .05$), nor was there a significant group difference for ΔRB ($F(1,70) = 0.02$, $p > .05$). Response bias findings using alternative PRT quality control criteria are presented in the Supplementary Material.

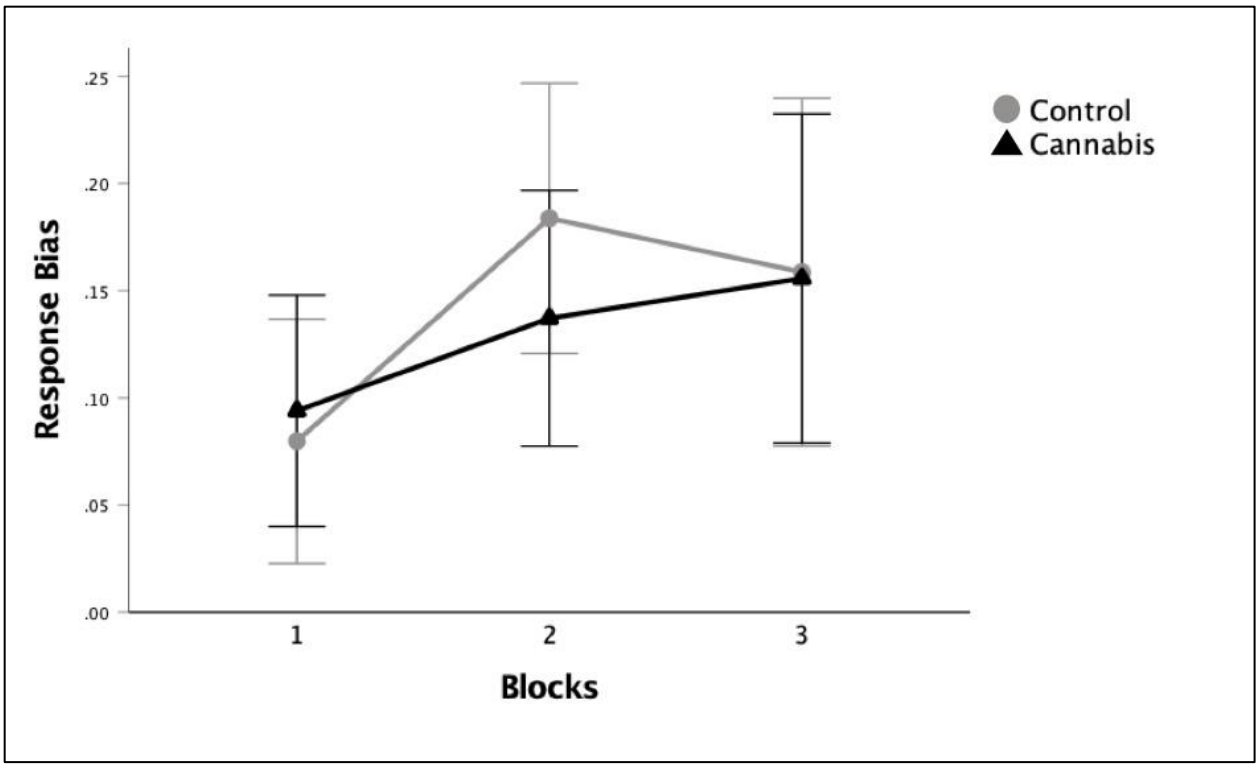

Figure 2. Mean response bias in cannabis and control groups across 3 blocks on the PRT. Both cannabis and control groups developed a response bias toward the more frequently rewarded (rich) stimulus. A significant increase between block 1 and block 2, and from block 1 to block 3 emerged. No significant group difference or interaction effects were found.

Discriminability (Figure 3). A 2 X 3 repeated measures ANOVA revealed a main effect of block ($F(2,140) = 3.30$, $p < .05$), showing higher discriminability scores across blocks (block 1: 0.34 ± 0.17, block 2: 0.38 ± 0.21, block 3: 0.39 ± 0.21). Pairwise comparisons did not reveal any significant differences between blocks (all $p > .05$). There was no difference between groups overall ($F(1,70) = 1.70$, $p > .05$). There was a significant block x group interaction effect ($F(2,140) = 4.49$, $p < .05$), where the cannabis group had significantly lower discriminability scores than the control group on block 3 (0.33 ± 0.18 vs. 0.45 ± 0.22, $p < .05$).

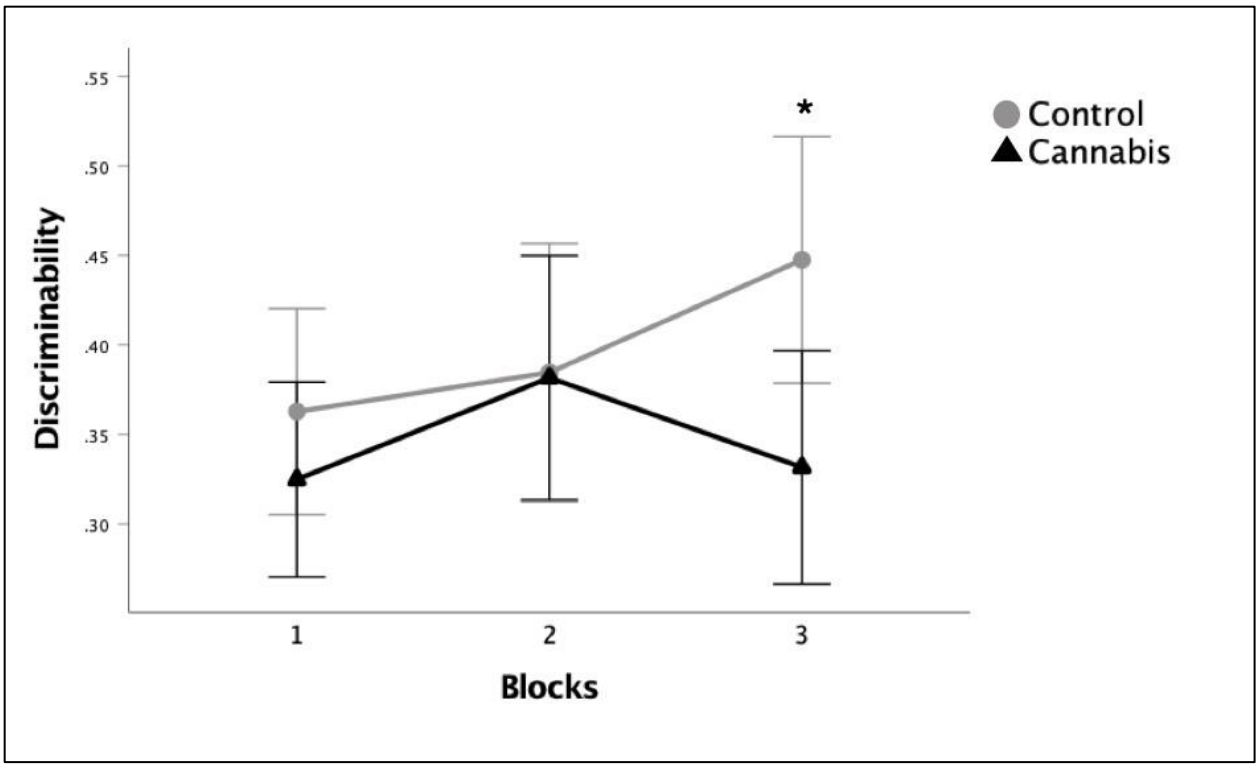

Figure 3. Mean discriminability in cannabis and control groups across 3 blocks on the PRT. Discriminability scores increased across blocks, with no significant differences between blocks. Groups did not differ across blocks, however, an interaction effect showed that cannabis participants had significantly lower scores on block 3 only.

Accuracy (Figure 4A). A 2 X 3 repeated measures ANOVA with block and stimulus (rich, lean) as factors, revealed a main effect of stimulus ($F(1,70) = 66.28$, $p < .05$), with greater accuracy for the rich stimulus in all three blocks (rich, 0.75 ± 0.09 vs. lean, 0.62 ± 0.11, $p < .001$). There was a significant block x group interaction ($F(1.81,126.65) = 3.45$, $p < .05$; pairwise comparisons did not reveal any significant results). There was a significant block x stimulus interaction ($F(2,140) = 4.43$, $p < .05$) where rich accuracy in block 2, and block 3 were higher than block 1 (both $p < .05$). No other effects or interactions were significant.

Reaction time (RT; Figure 4B). A 2 X 3 repeated measures ANOVA revealed a main effect of block ($F(1.55,108.58) = 4.83$, $p < .05$), showing a decrease in RT over blocks. There was also a main effect of stimulus ($F(1,70) = 17.60$, $p < .05$), with shorter RT for the rich stimulus compared to the lean stimulus in all three blocks (rich, 468±109 vs. lean, 481±111, $p < .05$). No other effects or interactions were significant.

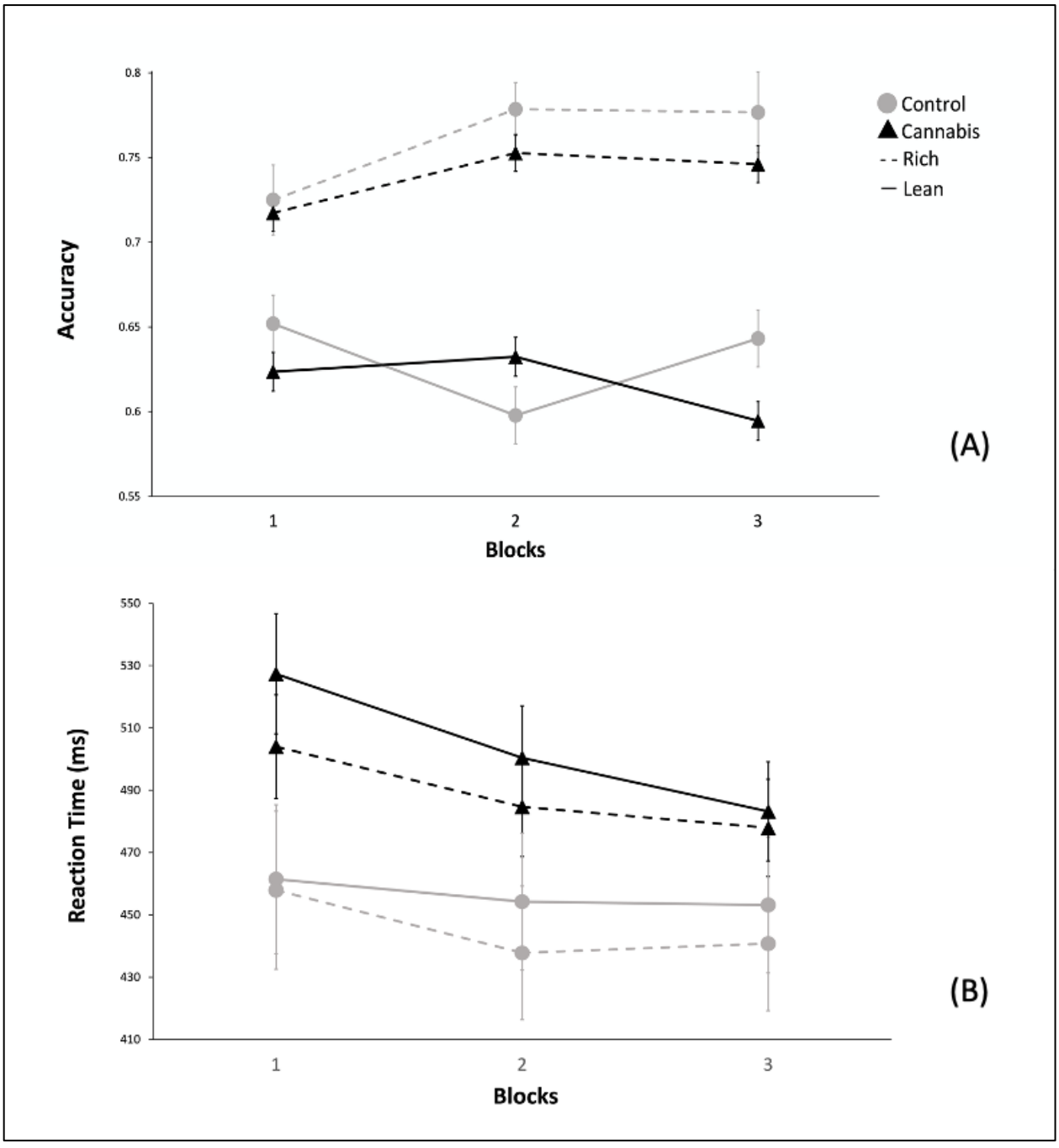

Figure 4. Accuracy and reaction time (RT) in cannabis and control groups across 3 blocks on the PRT. Panel A: Both groups showed greater accuracy for the rich compared to the lean stimulus in each block. No group differences in accuracy emerged. A block x stimulus interaction revealed greater accuracy for the rich stimulus in blocks 2 and 3 compared to block 1. Panel B: Both groups showed decreased RT across blocks, and faster RT for the rich compared to the lean stimulus in each block. No group differences in RT or interaction effects emerged.

Control Analyses

As in prior studies [34] and due to the importance of the reinforcement ratio in producing a response bias, we ran control analyses to ensure that groups did not differ in the amount of feedback received during the task. T-tests revealed that cannabis and control groups did not differ in the number of rewarded trials received (cannabis rich: 28.61±2.22 vs. control rich: 28.58±1.70, $t(70) = 0.08$, $p > .05$ cannabis lean: 9.68±.56 vs. control lean: 9.67±.36, $t(70) = 0.08$, $p > .05$; rich/lean ratio: cannabis: 2.96±.18 vs. control: 2.98±.21, $t(70) = -0.19$, $p > .50$). In addition, groups did not differ in the number of participants allocated (randomized) to the mouth or nose version of the task, $\lambda^2(1)= 0.076$, $p > .05$, nor did they differ in number of participants assigned (randomized) to the version in which the short or long mouth/nose was the more frequently rewarded stimulus, $\lambda^2(1)= 1.79$, $p > .05$.

Correlations with Cannabis Use Characteristics

A Pearson correlation found no significant relationship between ΔRB and cannabis use characteristics: frequency, age of initiation, weekly quantity, or CUDIT-R scores (all $p > .05$). However, a trend for years of use, $r(36) = -.30$, $p = .077$ and potency, $r(19) = -.33$, $p = .052$ emerged. To explore differences in 'high' THC (20-30%, $n = 14$) versus 'low' (0-20%, $n = 8$), a

point biserial correlation was conducted, and revealed a significant negative correlation, $r_{pb}(19) = -.61$, $p = .003$.

The correlation between ΔRB and BDI-II score was non-significant, $r(33) = .28$, $p > .05$. As in Pizzagalli et al,. (2005), the cannabis group was dichotomized into 'low' BDI (score <16) and 'high' BDI-II (score ≥16), as this has been shown to be an accurate cutoff of depression severity [42]. The point biserial correlation between ΔRB and low/high BDI-II was also non-significant, $r_{pb}(33) = .20$, $p > .05$. Given the absence of a significant correlation with BDI-II and no group differences in response bias, BDI-II was not entered as a covariate, to maximize statistical power.

Discussion

The goal of the present study was to investigate reward learning capacity in a community sample of individuals who use cannabis recreationally. We recruited participants who reported ≥2 uses/month, in order to capture a range of use patterns, however, the majority (62.2%) of our sample reported (at least) daily use. The proportionally higher rates of daily or near daily use are in line with both Canadian [43] and U.S. trends [44]. Using an objective behavioural measure, we found that both cannabis and control participants demonstrated reward learning over time; specifically, both groups developed a response bias toward the more frequently rewarded stimulus. In contrast to our main hypothesis, the cannabis group did not show significant impairment relative to controls, in the ability to modulate behaviour as a function of prior reinforcement. However, the cannabis group did not exceed the control group in mean response bias on any block. Both groups showed higher accuracy and faster reaction time for the rich compared to the lean stimulus, confirming that the reinforcement schedule was effective in producing a general preference for the more frequently rewarded stimulus; this is consistent with prior PRT studies [35,45–47]. Discriminability also did not differ between groups overall, indicating that cannabis and control participants found the task equally difficult. However, on the final block, the cannabis group displayed lower discriminability than controls, perhaps suggesting a state of fatigue by the end of the task, or differences in sustained attention. Finally, contrary to our secondary hypothesis, we did not find that response bias in the cannabis group was correlated with parameters of cannabis use, with the exception of trending significant relationships with chronicity and potency.

The response bias findings emerging from the present study, stand in contrast to the only previous evaluation of a cannabis sample using the PRT [35]. In that study, the cannabis group

had a significantly lower response bias compared to controls, and in fact, did not develop a response bias across blocks [35]. Notably, all participants in their sample met dependence criteria, and reported consumption of high-potency cannabis (i.e., 'skunk') on ≥50% of cannabis-using occasions, although the cannabinoid content that constituted 'high-potency', was not defined. Moreover, the current sample varied widely in self-reported potency, and when this variable was explored by dichotomizing into 'low' versus 'high' (relative to the potency range of our sample), a significant relationship emerged with respect to ΔRB: higher reported THC was related to more impaired response bias. Other behavioural tasks that tap into elements of reward learning have mixed findings in showing reward learning deficits in cannabis use populations. However, those that demonstrate impaired learning, often find greater deficits in relation to greater chronicity [28,29] frequency [30,31], higher THC potency [32] and dependence [33]. Similarly, animal studies show that cannabis administration, particularly high THC doses, results in failure to develop reward associations in a conditioned place preference paradigm, or even led to place aversion [48–50] and attenuates electrical self-stimulation [51,52]. Together, the evidence suggests a potential dose-dependent relationship, where greater reward learning impairment is associated with indications of more severe cannabis use. This is also supported by molecular imaging studies where cannabis-dependent participants show a reduction in amphetamine and methylphenidate-induced striatal dopamine release, which was inversely related to frequency [19] and dependence severity [53]. However, functional neuroimaging evidence is inconsistent. A chronic use sample showed reduced striatal activity during a reward processing task, and importantly, a longitudinal evaluation revealed that increasing cannabis use was associated with subsequent blunted striatal responses [54]. In contrast, there is evidence for increased striatal activity during reward processing, which positively correlated with chronicity

[24], while others report no difference between cannabis and control participants [55,56]. Future imaging studies are needed to assess the neural substrates, particularly in striatal networks, during reward learning.

Interestingly, we did not find a relationship between response bias and depressive symptoms (BDI-II score) in the cannabis group. This finding contrasts previous literature showing significantly impaired response bias in populations with depressive (mainly anhedonic) symptoms [34,57] and clinical diagnoses of MDD [47,58]. The average BDI-II score for this group (12.9) suggests mild mood disturbance, not indicative of clinical depression, which may explain the lack of relationship between depression and reward learning in our sample. Moreover, given the heterogeneity in depressive symptomatology, symptoms experienced by individuals in our cannabis group may not reflect an anhedonic symptom profile.

Overall, the main findings from the current study suggest that individuals who use recreational cannabis are able to form reward associations outside of cannabis use. Therefore, the negative psychosocial and socioeconomic outcomes reported with frequent cannabis use, may be influenced to a greater degree, by impaired motivation to initiate goal-directed behaviour [59,60], as opposed to the specific aspect of learning. Future studies should attempt to delineate the role of motivated reward seeking versus associative reward learning in cannabis use populations.

The use of an objective behavioural measure of reward learning is a strength of the current study, as most previous studies in cannabis populations have used tasks that indirectly evaluate facets of reward learning, with alternative primary outcomes (e.g., Iowa Gambling Task – decision-making; Monetary incentive Delay Task – reward anticipation). While the heterogeneity of a community sample allows for greater generalizability, it also results in a large

range of cannabis use characteristics, limiting a clear understanding of the role of specific metrics. Moreover, we did not assess quantitative indices of cannabinoid metabolites, which would provide a more refined understanding of residual intoxication or withdrawal, and the effect of THC potency. The latter is particularly relevant considering reports of a steady increase in THC content in cannabis preparations over the past twenty years [61]. A recent recommendation to standardize the quantification of cannabis use metrics across research and clinical settings, outlines a framework that includes the evaluation of cannabinoids in urine or saliva to determine THC potency and recency of use [62]. Another limitation is that our sample consisted predominately of Caucasian individuals, limiting representation and applicability of the findings to other racial and ethnic groups. The majority of participants also identified with the female gender, although no gender differences emerged in our analyses. A limitation in the PRT literature is the inconsistent quality control criteria applied to the task. However, when applying a variety of criteria to our dataset (see Supplementary Material), including criteria used in Lawn et al., (2016), no group differences in response bias emerged. Importantly regardless of which set of criteria were applied, participant exclusion did not bias one group over the other (cannabis vs controls).

Given the commonly reported link between cannabis use and an 'amotivational syndrome' empirical evidence to characterize reward processing facets in this population is necessary. The present study adds to the limited extant literature on cannabis use and reward learning – a subconstruct of reward processing – and suggests that individuals who use cannabis recreationally, maintain the ability to learn non-drug reward associations. Nevertheless, the evidence indicates a potential role for greater cannabis use severity (i.e., chronicity, potency) and poorer reward learning, which warrants further investigation.

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Supplementary Material

Methods and Results

We applied alternate quality control criteria to our dataset and evaluated response bias on the PRT. These criteria include the approach used in Lawn et al., 2016, more liberal criteria than that used in the present study, as well as the omission of any quality control criteria.

PRT quality control applications matching Lawn et al., 2016 criteria

A 2 X 3 repeated measures ANOVA with group as a between-subject factor (cannabis vs controls) and block as the within-subject factor (block 1, block 2, block 3) was conducted, with response bias as the dependent variable. Based on criteria applied in Lawn et al., (2016), trials were excluded where reaction time was <100 ms or >1500 ms, and participants with <80 % valid trials, and received reinforcement on <25 rich or <6 lean stimuli, had <55% accuracy for the rich stimulus and/or <55% accuracy overall, were removed from analyses. Application of these criteria reduced the original sample size to N = 48 (cannabis, n = 24, control, n = 24). No significant group differences emerged ($F(1,46) = 0.22$, $p > .05$; Figure S1).

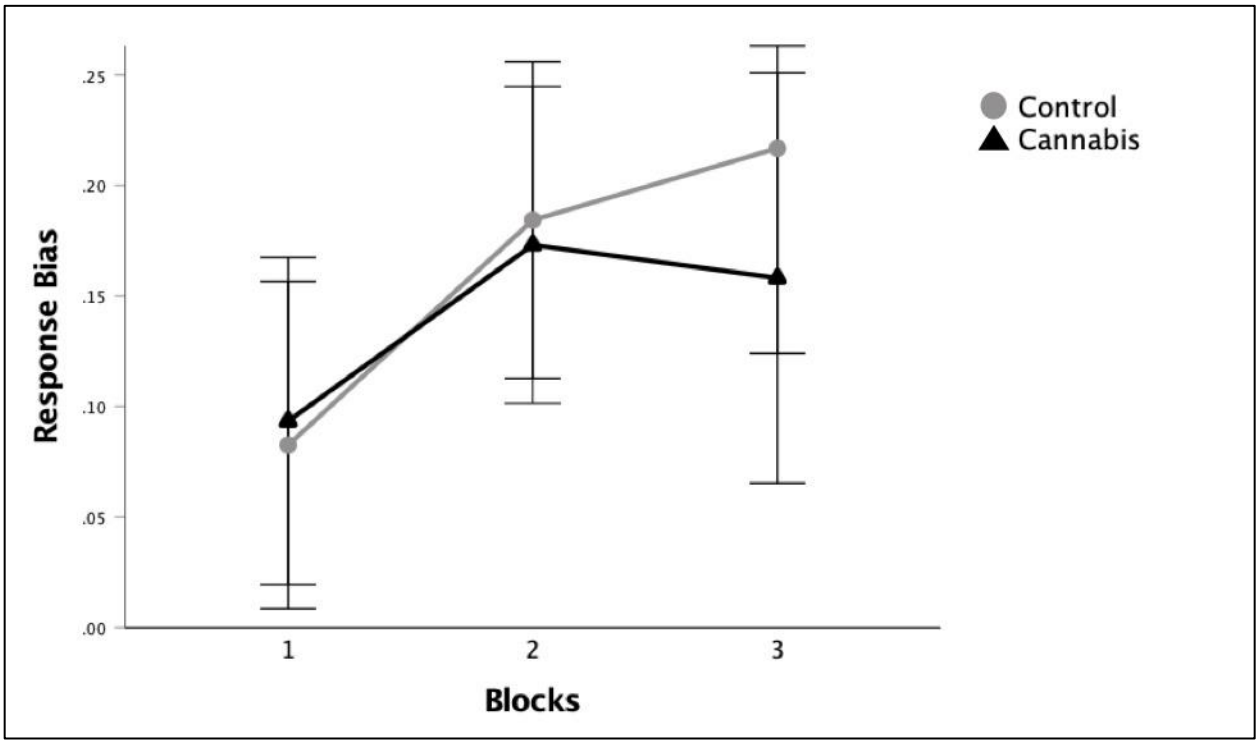
Alternate versions of PRT quality control criteria (Figure S2).

Version 1: Cutoffs used in the current study (N = 72, 38 cannabis, 34 control). No significant group differences ($F(1,70) = 0.12$, $p > .05$).

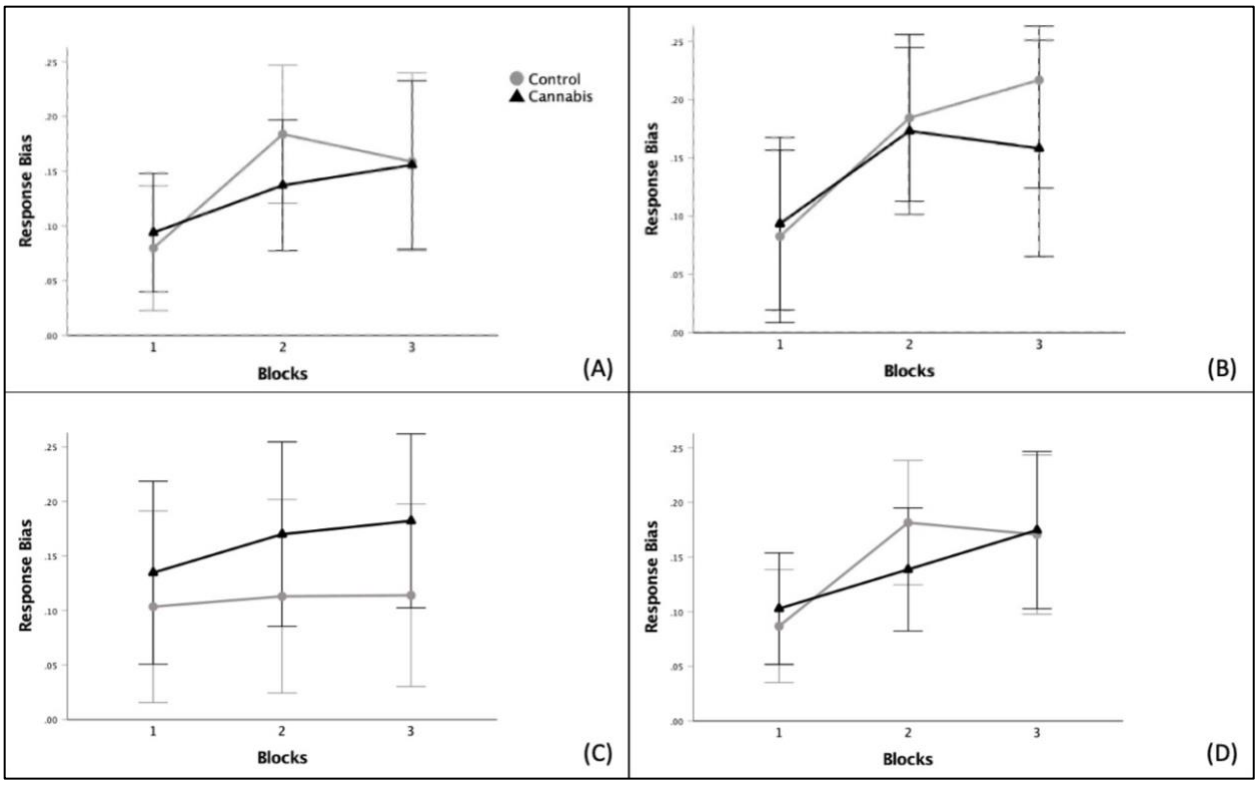
Version 2: Cutoffs from Lawn et al., 2016 (N = 48, 24 cannabis, 24 control). No significant group differences ($F(1,46) = 0.22$, $p > .05$).

Version 3: No cutoffs applied to original dataset. Consists of all participants who met inclusion criteria for the current study (N = 105, 55 cannabis, 50 control). No significant group differences ($F(1,103) = 1.31$, $p > .05$).

Version 4: Trials were excluded where reaction time was <150ms or >2500ms and participants were removed if they had <50 % valid trials or a rich/lean reward ratio <2 in any block (N = 81, 41 cannabis, 40 control). No significant group differences emerged ($F(1,79) = 0.06$, $p > .05$).



Supplementary Figure 1. Mean response bias in cannabis and control groups across 3 blocks on the PRT using quality control criteria from Lawn et al., (2016). No group differences in response bias emerged.



Supplementary Figure 2. Response bias by group across blocks using varied PRT quality control criteria. Panel A = Version 1 (current study); Panel B = Version 2 (Lawn et al., 2016); Panel C = Version 3 (no criteria); Panel D = Version 4 (more liberal criteria for number of valid trials per block). In all versions outlined above, no significant group differences in response bias emerged.

Chapter 3: General Discussion

Summary

The primary aim of the present study was to investigate reward learning capacity in a community sample of individuals who use cannabis recreationally. We recruited participants who reported ≥2 uses/month, in order to capture a range of use patterns, however, the majority of our sample (62.2%) reported daily use. High rates of daily use are reflective of a national cannabis sample, whereby recent estimates indicate that among those who report past month use, 35% consume cannabis daily or almost daily (Health Canada, 2021a). Although the sample in the current study is over-representative of those who use daily, this may suggest a recruitment bias; individuals who use more frequently may be more likely to volunteer for cannabis-related research. Using an objective measure of reward learning, we found that cannabis and control groups both showed significant reward learning over time. Specifically, the cannabis group did not show significant impairment in the development of a response bias toward the more frequently rewarded stimulus, which is in contrast to our main hypothesis. Although group differences were not significant, the cannabis group did not exceed the control group in response bias on any block. Finally, contrary to our secondary hypothesis, we did not find that response bias in the cannabis group was correlated with parameters of cannabis use (i.e., frequency, weekly quantity, age of initiation, CUDIT-R score), with the exception of a trending significant relationship with chronicity and potency.

PRT Secondary Variable Outcomes

Outcomes related to secondary variables on the PRT, revealed that both groups showed greater accuracy and faster reaction time for the rich compared to the lean stimulus in each block, indicating that the reinforcement schedule was effective in producing a general preference

for the more frequently rewarded stimulus. This is in line with previous PRT studies, where the experimental group (e.g., depression, nicotine use) and control group, perform similarly on secondary measures of accuracy and reaction time, with better performance for the rich stimulus (AhnAllen et al., 2012; Bogdan & Pizzagalli, 2006; Lawn et al., 2016; Liverant et al., 2014; Pechtel et al., 2013; Pizzagalli et al., 2005; Pizzagalli, Iosifescu, et al., 2008). In addition, discriminability improved across blocks, but did not differ between groups, indicating that both cannabis and control participants found the task equally difficult, and improved in differentiating between stimuli as the task progressed, consistent with a prior PRT study in a cannabis sample (Lawn et al., 2016). Other studies show mixed results with respect to discriminability; some show improvement across blocks for both experimental and control groups (Bogdan & Pizzagalli, 2006; Lawn et al., 2016; Liverant et al., 2014) and others find that groups maintain discriminability scores over time (AhnAllen et al., 2012; Barr et al., 2008; Janes et al., 2015; Liu et al., 2011; Morris & Rottenberg, 2015; Pizzagalli et al., 2005, 2007; Pizzagalli, Goetz, et al., 2008; Pizzagalli, Iosifescu, et al., 2008; Vrieze et al., 2013). In addition, past studies reveal no group differences in discriminability (AhnAllen et al., 2012; Bogdan & Pizzagalli, 2006; Hou et al., 2020; Lawn et al., 2016; Liu et al., 2011; Liverant et al., 2014; Morris & Rottenberg, 2015; Pizzagalli et al., 2005, 2007; Pizzagalli, Goetz, et al., 2008; Pizzagalli, Iosifescu, et al., 2008; Vrieze et al., 2013), while a select few found that controls had higher discriminability scores (Janes et al., 2015; Pechtel et al., 2013; Wilkinson et al., 2021). Surprisingly, a group by block interaction showed that the cannabis group had significantly lower discriminability than controls on block 3 only, suggesting a potential influence of response fatigue in the last block, or group differences in sustained attention. Given the high comorbidity between cannabis use and attention deficit hyperactivity disorder (ADHD), and evidence for acausal link between ADHD

and lifetime cannabis use (Soler Artigas et al., 2020), future studies should consider attentional impairments and ADHD symptomatology when administering reward learning tasks.

Relationship Between Reward Learning and Cannabis Use Characteristics

The response bias findings emerging from the present study, contrast a previous PRT evaluation, where cannabis participants did not develop a response bias across blocks, compared to controls (Lawn et al., 2016). This study used only 2 blocks of the PRT, thus limiting our understanding as to whether the cannabis group may have developed a response bias by block 3. Another important consideration is the characterization of their cannabis sample compared to the current study. In Lawn et al., (2016), all participants in the cannabis group met dependence criteria (measured by the Severity of Dependence Scale, Gossop et al., 1995) and reported consumption of 'high-potency' cannabis on at least 50% of the occasions in which they used cannabis, although the authors did not define what constituted 'high-potency'. In contrast, our sample was community-based, and varied in meeting dependence criteria (assessed by the M.I.N.I., n = 17 met dependence criteria) and self-reported THC potency. In fact, 37% were not aware of the THC content of the cannabis they typically consume. While a significant portion of the general Canadian population do not know the relative potency of their cannabis (20%), this rate has decreased in recent years (Health Canada, 2021b), suggesting a greater awareness of cannabinoid content. When we dichotomized self-reported potency into 'lower' (0-20%) versus 'higher' (20-30%) THC (respective to the potency range of our sample), a significant relationship emerged with the change in response bias between the first and final block (ΔRB); higher THC potency was related to lower ΔRB. There has been a significant increase in THC potency in the past several decades; global estimates of 3-4% THC content in the early 1990s (Cascini et al., 2012) have increased two-to-four-fold in some countries (United Nations Office

on Drugs and Crime, 2021). Recent Canadian estimates suggest an average THC concentration of 16.1% in the legal market and 20.5% in the illegal market (Mahamad et al., 2020). While potency continues to increase, the definition of what constitutes 'high-potency' cannabis remains inconsistent. Some suggest ≥10% (Di Forti et al., 2019; Freeman et al., 2014), while others consider >20% THC to be high-potency (Freeman et al., 2019; Mahamad et al., 2020). Emerging evidence suggests a strong relationship between frequent use of high-potency cannabis (14-16% THC) and psychosis onset (Di Forti et al., 2014, 2015), emphasizing the importance of delineating the role of potency in adverse outcomes. While the exploratory potency analysis in the current study is in a small subgroup, it nevertheless supports the role of potency in reward learning.

In addition to a relationship with potency, we found a trend between lower ΔRB and increasing years of cannabis use. Similarly, other studies assessing elements of reward learning have shown more impaired performance with higher chronicity (Delibaş et al., 2017; Hermann et al., 2009) frequency (Bolla et al., 2005; Verdejo-Garcia et al., 2007), THC potency (Shannon et al., 2010) and dependence (Gonzalez et al., 2012). However, others have found no relationship with reward learning and severity of cannabis use parameters, mainly chronicity (Alameda-Bailén et al., 2018; Tamm et al., 2013; Verdejo-García et al., 2013). Studies in animal models have shown that THC, particularly in high doses, results in failure to develop reward associations in conditioned place preference paradigms, or even led to place aversion (Han et al., 2017; Sañudo-Peña et al., 1997; Vann et al., 2008), and attenuated electrical self-stimulation (Katsidoni et al., 2013; Wiebelhaus et al., 2015). This potential dose-dependent relationship between indications of more severe cannabis use and impaired reward learning, is also supported by molecular imaging studies; cannabis-dependent participants show reduced amphetamine and

methylphenidate-induced dopamine release in the striatum, which is negatively correlated with frequency (Volkow et al., 2014) and severity of dependence (van de Giessen et al., 2017). However, functional neuroimaging evidence is less consistent. A chronic use sample showed reduced striatal activity during a reward processing task (Monetary Incentive Delay Task, Knutson et al., 2000), and a longitudinal evaluation showed that increased cannabis use was associated with blunted striatal activity at later time points (Martz et al., 2016). In contrast, there is evidence for an increased striatal response, which positively correlated with chronicity (Nestor et al., 2010), while others have found no difference between cannabis and control participants (Enzi et al., 2015; Karoly et al., 2015). This highlights the need for future imaging studies to evaluate neural activity, particularly in striatal nodes and networks, during reward learning tasks, with careful surveillance of cannabis use characteristics, including frequency, potency and chronicity.

Lack of significant associations between response bias development and cannabis use characteristics in the current study, could also be attributed to a number of methodological factors, including the large variability in cannabis use characteristics reported by our sample, therefore subgroup analyses of specific metrics are likely underpowered. In addition, cannabis use characteristics were collected via self-report, which are prone to subjective bias, and may lead to invalid or inconsistent responding as a result of fatigue or periods of inattention. This highlights the need for consistency checks during data collection, to improve validity and reliability of the data (Schell et al., 2022). Moreover, some measures were answered on a Likert scale as opposed to a continuous scale, resulting in the potential loss of specificity on some measures.

PRT Quality Control Criteria

Another important consideration when comparing the current study to a previous cannabis PRT study (Lawn et al., 2016), is the use of quality control checks applied to the PRT. Generally, studies using the PRT are vastly inconsistent in the use of quality control criteria. These criteria can include: the removal of trials where response time was faster than 150 ms and slower than 1,500 ms (Bogdan & Pizzagalli, 2006; Pechtel et al., 2013; Whitton et al., 2016) or 2,500 ms (AhnAllen et al., 2012; Dillon et al., 2022; Pizzagalli et al., 2005), and additional outliers outside the range of $\pm$3SD from the mean. Participants may be removed from analyses if they had more than 20 outlier trials per block based on reaction time (AhnAllen et al., 2012; Dillon et al., 2022; Liverant et al., 2014); others set this cutoff as 10 per block (Kaiser et al., 2018; Patel et al., 2020; Whitton et al., 2018, 2021). Some studies specified the requirement of receiving at least 25 rich rewarded stimuli per block (AhnAllen et al., 2012; Liverant et al., 2014), no fewer than 6 lean rewarded stimuli (Dillon et al., 2022) and/or a rich/lean reward ratio of no less than 2 (Dillon et al., 2022; Kaiser et al., 2018). Others also removed participants with accuracy scores below 55% (Janes et al., 2015; Kaiser et al., 2018; Whitton et al., 2018, 2021) or 60% (AhnAllen et al., 2012; Liverant et al., 2014), and some studies did not indicate the application of any quality control checks (Hou et al., 2020; Liu et al., 2011). Lawn et al., (2016) used several of the aforementioned criteria, that when applied to our dataset, did not change the non-significant group differences in response bias across blocks (see Manuscript Supplementary Material). Applying a variety of other cutoff criteria to our dataset, as well as omitting any quality control measures, all resulted in no significant group differences in response bias (see Manuscript Figure S2). Importantly, regardless of which set of criteria were applied, participant exclusion was not biased toward one group compared to the other (cannabis vs controls). While

the quality control criteria selected in the current study led to a substantial 32% loss of our original sample, this is consistent with data reduction rates in previous PRT studies (AhnAllen et al., 2012; Lawn et al., 2016; Liverant et al., 2014); the vast majority of studies do not explicitly state the reduction in sample size after the application of quality control checks, or the methodological reason(s) behind selection of specific criteria. The use of quality control criteria is necessary, in order to retain participants who were engaged and sufficiently attended to the task, performed the task correctly and experienced the asymmetric reinforcement ratio intended to induce a response bias. There is a need for consistency and transparency in the field when applying quality control measures to the PRT, in order to ensure reliable data reduction and to allow for consistent comparison across studies. Moreover, given increasing use of the PRT across a range of psychopathology and substance use populations, proper justification for the use of these criteria will have large implications for study findings.

Another methodological difference between the current study and previous PRT studies is that while the majority provided additional compensation based on task earnings, we did not compensate participants in addition to the standard amount received for study completion. However, there is evidence to suggest that performance on lab-based behavioural tasks, as measured by response speed and accuracy, does not differ when reward is delivered in the form of monetary compensation, course credit (Walsh et al., 2021), or via a hypothetical point system (Shen & Chun, 2011). This indicates that motivation to attend to and engage with the task is not dependent on performance-contingent financial reward, and that the absence of receiving task earnings on the PRT in the current study, did not likely negatively affect motivation and subsequent performance.

Common Comorbidities with Cannabis Use and Reward Learning Outcomes

Interestingly, we did not find a significant relationship between response bias and depressive symptoms. This was unexpected, given the high comorbidity rate between cannabis and depression (Rogers et al., 2021) and strong evidence suggesting significantly impaired response bias in populations with depressive (mainly anhedonic) symptoms (Liu et al., 2011; Pizzagalli et al., 2005) and clinical diagnoses of MDD (Pizzagalli, Iosifescu, et al., 2008; Vrieze et al., 2013). Not surprisingly, BDI-II scores were significantly higher for cannabis participants than controls in the current study. However, the average score in the cannabis group (12.9) is not indicative of clinical depression (16; Sprinkle et al., 2002), which may explain the lack of relationship between depression and response bias. Moreover, given that depression is a highly heterogenous condition, symptoms experienced by those in our cannabis group may not reflect an anhedonic symptom profile, commonly seen in individuals with clinical depression. A PRT assessment of individuals with remitted major depressive disorder (rMDD) showed that cigarette smoking status affected reward learning; rMDD participants who smoke had higher response bias scores than the rMDD non-smoking group, and showed comparable performance to a smoking group without a history of depression (Janes et al., 2015). Moreover, nicotine withdrawal-induced deficits in response bias are more pronounced in those with rMDD (Pergadia et al., 2014). The enhancing effect of nicotine on reward learning (Barr et al., 2008) may supplement the deficits experienced by those with past (Janes et al., 2015) or current depression (Liverant et al., 2014). Nicotine-induced heightened reward sensitivity is thought to occur via activation of nicotinic acetylcholine receptors, thereby increasing phasic dopamine in the mesolimbic dopamine system (Kenny & Markou, 2006). Although cannabis and cigarette use frequently co-occur (Hindocha et al., 2015), the subset of cannabis participants reporting current

cigarette use in the present study (n = 13) was too low to detect any significant effects on PRT performance. In Lawn et al., (2016), response bias did not correlate with depression severity (measured by the Beck Depression Inventory, BDI), cigarette use, or cannabis dependence severity. However, when BDI score and cigarette use (i.e., cigarettes per day) were included as covariates, the significant group difference in response bias was lost, suggesting a role for confounding psychiatric comorbidities and co-use of other substances in evaluating cannabis use and reward learning.

Consideration of Intoxication, Withdrawal, and Abstinence

Overall, the main findings from the present study suggest that individuals who use recreational cannabis are able to form reward associations outside of the substance. Studies evaluating aspects of reward learning in a cannabis use sample (e.g., Iowa Gambling Task, Salience Attribution Test), are mixed in showing deficient (Becker et al., 2014; Casey & Cservenka, 2020; Moreno et al., 2012; O'Donnell et al., 2021; Tamm et al., 2013; Verdejo-Garcia et al., 2007; Verdejo-García et al., 2013; Whitlow et al., 2004), or similar reward learning capacity compared to control participants (Alameda-Bailén et al., 2018; Becker et al., 2018; Bishara et al., 2009; Bloomfield, Mouchlianitis, et al., 2016; Costa Porfirio et al., 2020; Delibaş et al., 2017; Dougherty et al., 2013; Fridberg et al., 2010; Gonzalez et al., 2012; Hermann et al., 2009; Lamers et al., 2006; Quednow et al., 2004). An important consideration when evaluating any substance-use population, is the state of the individual at the time of assessment (i.e., acutely intoxicated, in active withdrawal, or abstinent). Acute intoxication studies have shown no reward learning deficits while under cannabis influence, compared to placebo (Ramaekers et al., 2006; Vadhan et al., 2007), however potency and time delay of task performance after administration, should be considered when interpreting these results. In the vast majority of studies, an

abstinence period of 24 – 48 hours is recommended to participants, prior to assessment, however, without objective evaluation (e.g., saliva, plasma or urine screen), it is possible that individuals may be under the influence of residual cannabis, or experiencing withdrawal. Studies that intentionally evaluated participants during a period of abstinence, found lower task performance compared to controls during short term (25 day) abstinence, versus no impairment during a long term (7 month) abstinence period. It is important to consider that the aforementioned studies use behavioural tasks that contain an element of associative learning, however they have separate primary outcomes (e.g., decision-making). There is a need for future studies that use objective measures of reward learning (i.e., PRT) to delineate the effects of acute intoxication, versus objectively verified abstinence.

The intact ability to form novel reward associations outside of cannabis use is promising for the success of treatment and intervention strategies for problematic cannabis use, where learning non-drug related associations is crucial (e.g., contingency management). However, if reward learning deficits emerge with greater severity of use, these types of strategies may be less effective for populations with more problematic use patterns. Given the absence of reward learning deficits in the current cannabis use sample, the negative psychosocial and socioeconomic consequences often described in cannabis use populations, may be considered in the context of impaired motivation to initiate goal-directed behaviour (Pacheco-Colón, Limia, et al., 2018; Skumlien et al., 2021), as opposed to the specific capacity to form reward associations. If cannabis use does not in fact, impair reward leaning, individuals may be less motivated to pursue potential reward, which supports the central role of apathy in the cannabis ‘amotivational syndrome’ (McGlothin & West, 1968). Nevertheless, individuals in the current study showed sufficient motivation to initiate participation in the study, indicating at least some capacity for

pursuing goal-directed behaviour. Future studies should attempt to elucidate the role of motivated reward seeking versus associative reward learning in cannabis use populations, through the use of objective measures of reward learning (e.g., PRT) and motivation (e.g,. EEfRT). Additionally, longitudinal studies are necessary (e.g., using data from the Adolescent Brain Cognitive Development study), in order to determine if potential reward processing deficits precede, or are a consequence of, cannabis use.

Strengths, Limitations & Future Directions

The current study has important strengths, including the use of the PRT as an objective behavioural measure of reward learning. While previous studies in cannabis populations have used behavioural tasks that indirectly evaluate facets of associative learning, the PRT is unique in objectively and systematically assessing reward learning through a reinforcement schedule intended to induce preference toward a frequently rewarded, non-drug stimulus. There has been only one prior study to use this task in a cannabis sample. Although quality control measures applied to our sample resulted in significant data loss (32% reduction from the original sample), these criteria are necessary in order to control for participants who did not adequately attend to, or correctly perform the task, ensuring reliable response bias outcomes. Moreover, we collected a variety of different cannabis use characteristics (e.g., frequency, chronicity, quantity, potency, dependence), allowing for a holistic evaluation of the influence of cannabis use behaviours. The recruitment of participants with a range of use patterns created a highly heterogenous sample, which allows for generalizability to the general population, however, it also limits a clear understanding of the specific role of certain metrics. For example, since the sample varied widely in frequency, subgroup analyses were underpowered to detect any significant effects on response bias. Additionally, our sample consisted primarily of Caucasian individuals, limiting

representation and generalizability of the findings to other racial or ethnic groups. The majority (65%) of participants also identified with the female gender; while males are over-representative of individuals who use cannabis in the general population (Health Canada, 2021a), the current study adds to the cannabis literature which has predominately recruited those identifying with the male gender, including Lawn et al., (2016). Nevertheless, no gender differences emerged in our analyses. A previous PRT study compared participants with and without pre-menstrual syndrome (PMS), during different phases of their menstrual cycle, and showed lower response bias among individuals with PMS compared to no PMS, during the luteal phase, but not the follicular phase (Hou et al., 2020). This highlights the importance of considering menstrual phase in reward learning studies. Exploratory analysis in the current sample indicated that those in the luteal phase had slightly lower response bias scores compared to those in the follicular phase, however subgroups were underpowered to detect significant differences. Future evaluations should carefully consider the influence of sex, gender, and menstrual phase on reward learning in cannabis participants. Importantly, we did not evaluate quantitative indices of cannabinoid metabolites, which would allow for a more refined understanding of residual intoxication or withdrawal, and the influence of potency on reward learning. A recent recommendation by Lorenzetti and colleagues (2021) outlines a framework to standardize the quantification of cannabis use parameters across research and clinical settings, which includes the evaluation of cannabinoids in urine or saliva, to quantify THC and determine recency of use (Lorenzetti et al., 2021).

Conclusions

Given the popular rhetoric around an ‘amotivational syndrome’ associated with frequent cannabis use, empirical evidence is necessary in characterizing reward processing among

individuals who use cannabis. The present study adds to the limited extant literature on reward learning – a specific subconstruct of reward processing – in cannabis use populations. The findings do not support the existence of reward learning deficits in a community-based, recreational cannabis use sample, and suggest that these individuals are able to integrate reinforcement history to learn non-drug reward. Further research is needed to elucidate the role of learning and motivation in reward processing, with consideration of a potential dose-dependent effect of cannabis use severity.

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