Université de Montréal

Investigation of the Relation Between Substance Use and Cognitive Performance and its Mediating Effect on Psychopathology Symptoms

Par

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Projet de thèse

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Résumé

      Le projet de thèse porte sur la consommation de substances psychoactives chez les adolescents et le lien séquentiel entre la consommation de drogues, la performance cognitive, et la santé mentale des jeunes. Les objectifs de la thèse sont : 1) de tester la relation entre la prise de cannabis, ou d'alcool, et la performance cognitive, et d'en observer la séquence, 2) de vérifier si la relation entre la consommation et la performance cognitive permet, en partie, de comprendre l'apparition de symptômes de psychopathologie chez les jeunes, et 3) de définir les pratiques les mieux fondées empiriquement pour prévenir la consommation de substances chez les adolescents.

      Le premier chapitre de la thèse évalue la relation et la séquence entre les habitudes de consommation d'environ 4000 jeunes de la région métropolitaine de Montréal (Qc, Canada) et la trajectoire de leur développement cognitif sur une période de quatre ans. Dans un deuxième chapitre, la thèse évalue comment la relation entre la consommation et la performance cognitive de ces mêmes jeunes peut expliquer, sur une période de cinq ans, une partie de la relation observée entre la consommation et l'apparition de symptômes de psychopathologie. Dans un dernier chapitre, la thèse fait la revue des données portant sur trois types d'interventions préventives afin d'identifier comment la recherche empirique peut bonifier les efforts de prévention de la toxicomanie chez les adolescents.

      Les données ont été extraites d'une cohorte d'adolescents issus de la population générale, suivis longitudinalement, dans le cadre de l'étude Co-Venture (n = 3826, âgés de 12 ans à l'admission dans l'étude, suivis annuellement pendant 5 ans).

Les résultats ont démontré que, bien que certains facteurs semblent prédisposer un sous-groupe de jeunes à une consommation hâtive ainsi que des difficultés neuropsychologiques, la consommation de drogues, notamment de cannabis, semble liée, de façon à la fois ponctuelle et durable, à un délai du développement cognitif, plus particulièrement des fonctions exécutives. Cette association avec le cannabis semble, en faible partie, jouer un rôle médiateur dans la relation qui unit cette consommation et l'émergence de symptômes de psychopathologie chez les adolescents. Toutefois, des facteurs prédisposants semblent contribuer à l'association entre ces trois variables. Bien que la recherche identifie que plusieurs programmes de prévention peuvent être efficaces, la majorité d'entre eux présentent des effets modestes et ponctuels. Les programmes les plus probants semblent s'inscrire dans le registre des approches de prévention ciblées.

Pour bonifier nos méthodes de prévention de la toxicomanie chez les adolescents, nous pourrions tenir compte de certains facteurs prédisposants et les utiliser comme cible d'intervention; par exemple, le fonctionnement cognitif basal pourrait constituer une piste intéressante. De plus, le tempérament ou la personnalité semblent mieux établis pour prévenir la consommation de façon durable et pour aborder les enjeux cognitifs et psychologiques associés à la consommation abusive de substances.

Mots-clés : Alcool, cannabis, adolescence, fonctions cognitives, symptômes de psychopathologie, devis longitudinaux, médiation, prévention

Abstract

This thesis project addresses adolescents' substance misuse and the sequential link between drug use, cognitive performance, and mental health outcomes in youth. The objectives of this thesis are: 1) to test the relation and sequence between cannabis or alcohol use and cognitive outcomes, 2) to verify if the relation between substance use and cognitive outcomes could help understand, in part, why young substance users report psychopathology symptoms, and 3) to review evidence-based interventions to prevent adolescent substance misuse and to assess what contribution could stem from the collected empirical data.

The first chapter of this thesis assesses the relation and sequence between substance use behaviour of nearly 4000 youth from the Montreal metropolitan area (QC, Canada) and their cognitive development over four years. In a second chapter, this thesis analyzes how the association between substance use and cognitive outcomes could partially explain, over five years, the link observed between substance use and the appearance of psychopathology symptoms. In a final chapter, this thesis reviews data surrounding three types of preventative interventions to identify how empirical research could improve addiction prevention strategies.

The data was extracted from a group of adolescents issued from the general population followed longitudinally in the scope of the Co-Venture study (n = 3826, from 12 years of age upon admission to the study, followed up annually for a period of five years).

The results demonstrated that, although certain factors seem to predispose a sub-group of young people to early consumption and neuropsychological difficulties, drug

consumption, especially cannabis consumption, seem to reliably predict a delay in the development of cognitive faculties, particularly the executive functions of the brain. This association with cannabis appears, to a small extent, to partially mediate the link already observed between said consumption and the emergence of psychopathology symptoms in adolescents. Still, predisposing factors seem to contribute to the association between these three variables. Although research would appear to show that several prevention strategies could be effective, most of them present modest and punctual results. The best-substantiated programs appeared to be those that adhered to a targeted prevention approach.

To improve our methods of substance use prevention, one could take predisposing factors into account and use them to inform specialized intervention. Baseline cognitive functioning could constitute a particularly promising avenue. All the same, certain predisposing factors such as temperament or personality seem better equipped to prevent early-onset substance misuse and to address the psychological and cognitive issues associated with adolescent substance intake.

To improve addiction prevention methods in adolescents, one could factor into account predisposing factors and use them to inform specialized intervention; for example, baseline cognitive functioning could constitute a promising avenue. In addition, temperament or personality traits seem better established to prevent early-onset substance use and to address the psychological and cognitive issues associated with adolescents' substance misuse.

Key words: Alcohol, cannabis, adolescence, cognitive functions, psychopathology symptoms, longitudinal data, mediation, prevention

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Abbreviations

ADHD: Attention deficit hyperactivity disorder
AUD: Alcohol use disorder
BSI: Brief symptoms inventory
CMS: Child memory scale
CUD: Cannabis use disorder
DEP-ADO: Detection of alcohol and drug problems in adolescents' questionnaire
DV: Dependent variable
FIML: Full information maximum likelihood
IMP: Impulsivité
IQ: Intellectual quotient
IV: Independent variable
MLM: Multi-level model
PALP: Passive avoidance learning paradigm
PN: Désespoir/pensées négatives
RCT: Randomised controlled trials
RE-CLPM: Random effect - cross-lagged panel model
SA: Sensibilité à l'anxiété
SDQ: Strengths and difficulties questionnaire
SES: Socioeconomic status
SF: Recherche de sensations fortes
SUD: Substance use disorder
SURPS: Substance use risk profile scale
SWM: Spatial working memory
THC: Tetrahydrocannabinol

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Review

par

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1. Introduction

1.1 Terminology and Epidemiology of Substance Use

The Diagnostic and Statistical Manual of Mental Disorders 5th version (American Psychiatric Association, 2013) defines Substance Use Disorders (SUD) as "a cluster of cognitive, behavioural and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems". The framework presented in the Diagnostic and Statistical Manual of Mental Disorders 5th version marks a departure from previous taxonomies showcased in the now outdated Diagnostic and Statistical Manual of Mental Disorders 4th version. The new SUD label refers to what used to be different diagnoses, namely: 1) substance abuse disorder, which indicated problematic substance use behaviour that was marked by recurrent, but not consistent binge use episodes, and 2) substance dependence disorder, which described problematic, daily, and sustained substance use. These clinical distinctions remain in some previously published works in the field but are, in practice, subsumed by the new SUD label. SUD's now consist of 11 criteria, each belonging to one of four clusters: impaired control (inability to decrease or stop use), social impairment (inability to fulfill social roles or maintain social relations due to substance use), risky use (consuming in hazardous situations or maintaining use despite harm) and pharmacological symptoms (tolerance and withdrawal). Among the most prevalent SUD's are Alcohol Use Disorder (AUD)[1] and Cannabis Use Disorder (CUD).

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[1] Though it is common to refer to individuals who exhibit or report problematic alcohol use behaviours as "alcoholics", that label does not carry any specific clinical or empirical meaning. It is somewhat understood in the field to refer to AUD and will be interpreted as such in this dissertation unless otherwise specified.

Results from the National Epidemiologic Survey on Alcohol and Related Conditions suggest that about 17.8 % of the United States population will suffer because of their alcohol consumption at some point in their lifetime (Hasin et al., 2007). The 12-month prevalence of AUD in the US is also very high: estimated at 4.6% in youth (12-17 years of age) and 8.5% in adults, with greater prevalence among males compared to females (12.4% and 4.9% respectively) (American Psychiatric Association, 2013). Rates of AUD also vary within different communities: Native Americans and whites tend to show a higher prevalence of alcohol use disorders (Wu, 2011) and socioeconomic status was inversely related to alcohol use disorder (Charitonidi et al., 2016). In Quebec's youth, alcohol use typically begins in high school[2] (Institut de la statistique du Québec, 2014). According to these data, alcohol use is already frequent among 1st-year high school students (prevalence of 23.4%) and slowly builds up over time. By the end of high school, alcohol use has become the norm for most students (prevalence of 83.1%). Furthermore, the same data suggests that binge drinking, defined as consuming five or more standard units of alcohol on a single occasion, is very frequent among Quebec's youth. For students in grade 7, 31.1% of alcohol-using students report at least one episode of binge drinking in the last year, while 76.5% of 11th graders report at least one episode of binge drinking in the last year (Institut de la statistique du Québec, 2014).

Cannabis Use Disorder (CUD) displays a similar clinical presentation to AUD. The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders now recognizes

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[2] Given the heterogeneity between school systems in Quebec, Canada and the United-States, an equivalence table was provided in Annex 1 to facilitate understanding in between jurisdictions.

the existence of cannabis tolerance and withdrawal symptoms. Tolerance is said to disappear within months of ceasing cannabis use, while withdrawal from cannabis use mostly consists of irritability, anxious/depressed mood, restlessness, sleep difficulty and appetite/weight loss. Though mainly diagnosed on its own, CUD can also be diagnosed simultaneously with other SUD's. In the United States, CUD's 12-month prevalence has been evaluated at 3.4% in youth, while declining at 1.5% in adults. Sex seems to be inconsistently associated with the 12-month prevalence of CUD: while US teens show only a slight difference in prevalence rates (3.8% males, 3.0% females), adult males are more likely to suffer from the disorder than adult females (2.2% and 0.8% respectively). As was found for AUD, CUD's prevalence seems to differ between communities: Native Americans and whites tend to show a higher prevalence of cannabis use disorders (Wu, 2011) and socioeconomic status was inversely related to cannabis use disorder (Charitonidi et al., 2016). In Canada and Quebec, the prevalence of cannabis consumption seems to be particularly high amongst high school students (Adlaf, 2004). Approximately 15% of 15-year-old Quebecers reported a regular (monthly) consumption of cannabis over the last 6 months, and 40% of the same age group reported using cannabis within the last year. Trends suggest an increase in cannabis consumption among youth: within the 1990s, its use tripled among 8th graders (6% to 18%) and doubled for 10th (15% to 35%) and 12th graders (22% to 39%) (Johnston, O'Malley, Bachman & Schulenberg, 2006). Reports indicate that cannabis consumption within Quebec's youth is among the highest in western countries (Dubé, Bordeleau, Cazale, Fournier, Traoré, Plante, Courtemanche, & Camirand, 2008).

1.1.1 Harmful effects of Alcohol and Cannabis

Given the frequency of alcohol and cannabis consumption amongst both adults and adolescents, it is urgent to assess how these substances are affecting their health. When abused, they are harmful substances that are associated with deleterious effects on individuals' physical health, mental health and, on a wider scale, on society.

In its 2014 Global status report on alcohol and health, the World Health Organization reported that 3.3 million deaths (5.9% of deaths worldwide) were caused by harmful alcohol use and that 5.1% of the burden of disease is the result of alcohol. Some of these afflictions include harm to the gastrointestinal, cardiovascular, and nervous systems (American Psychiatric Association, 2013). Those harmful effects include namely cardiomyopathy, cardio-arrhythmias, steatosis/cirrhosis of the liver, pancreatitis, Wernicke encephalopathy, and Korsakoff's syndrome (Nationa Institute on Alcohol Abuse and Alcoholism, 2020). Korsakoff's syndrome, although rare, marks one of the most severe instances of the harm of alcohol on the human body. It is defined as a severe condition characterized by anterograde and retrograde amnesia, executive dysfunction, and confabulation (Arts et al., 2017). This demonstrates that alcohol, when misused, can result in compromised physical well-being.

Cannabis misuse can also lead to physical problems, but the evidence is less conclusive than for alcohol. In a review conducted by Gordon, Conley, and Gordon (2013), cannabis use was related to higher susceptibility to infectious and sexually transmitted diseases, cancers of the head, neck and lungs, oral cavity diseases, chronic bronchitis, arterial diseases, and urological problems. Despite these findings being replicated in other reviews (Hall, 2014; Volkow, Baler, Compton & Weiss, 2014), other studies failed to detect the same effects. For

example, in a review conducted by Hill and Weiss (2016) chronic cannabis use was found to relate to periodontal diseases, but not to cardiovascular or pulmonary conditions. The uncertainty surrounding the body's way of metabolizing cannabis further complicates our understanding of cannabis's association with biological disorders. Confounding variables, such as other substance use, also make it more difficult to quantify the specific contribution of cannabis to these conditions. Further research is necessary to establish with certainty the risks of cannabis on physical health. However, most authors advise minimal cannabis intake.

Beyond physical ailments, alcohol use disorder (AUD) and cannabis use disorder (CUD) have also been linked to a variety of other mental conditions. Common psychiatric diagnoses comorbid with AUD and CUD include major depressive disorder, generalized anxiety disorder, conduct disorder, antisocial personality disorder, schizophrenia and bipolar disorder (American Psychiatric Association, 2013; Gobbi et al., 2019; Kessler et al., 1996; Volkow, Baler, Compton & Weiss, 2014). The presence of comorbidity usually indicates poor prognosis and treatment response (Aharonovich et al., 2006). It is still unknown whether alcohol or cannabis, though their effects on physical health, namely brain health, are responsible for the appearance of these conditions.

In addition to its impact on physical and mental health, alcohol misuse results in significant economic and social harm (Goetzel et al., 2003; Sanderson & Andrews, 2002), which is likely to increase with world population growth. For instance, emerging reports show that cases of cirrhosis of the liver, a medical complication that arises in severe cases of alcohol misuse, are on the rise (Wong & Huang, 2018). These findings indicate social trends

linked to an increase in public expenses for the healthcare sector, heightened stress on certain communities, and more frequent instances of disability amongst active members of society.

With regards to cannabis use, early and sustained consumption is also linked to sociological problems. Regular or heavy use of cannabis amongst adolescents and young adults has been linked to a variety of consequences, including increased likelihood of consuming illicit drugs, greater risk of motor vehicle accidents, and increased involvement in criminal activities (Fergusson, Horwood & Swain-Campbell, 2002; Hill and Weiss, 2016). Further research on the association between cannabis misuse and criminality suggests that much of the association is due to drug-related offences (Pedersen and Skadhamar, 2009). This association remained significant while controlling for other substance use, socioeconomic status, level of education and past offences. This specific observation can be hypothesized as either a specific effect of the illicit substance use on behaviour or as a secondary effect related to drug policy and societal management of illicit drug-using behaviours. The latter hypothesis is an important part of the argument in favour of policy reforms surrounding illicit drugs (Department of Justice of Canada, 2019). This shows that cannabis misuse is a problem that radiates to society at large through its association with criminal behaviour, motor vehicle safety, and the burden of addiction on the healthcare system.

Alcohol and cannabis misuse thus contribute to a variety of adverse effects: medical conditions, mental disorders, and wider societal costs. Addictive behaviours, due to their negative impact on judgment and self-control, perpetuate not only alcohol and cannabis use but also the myriad problems they contribute to. Due to this self-perpetuating cycle, to better

address the issue of alcohol and cannabis addiction, it is essential to assess their impact on cognitive abilities.

1.2 Alcohol and Cognition

The deleterious effects of heavy alcohol use on the brain are indisputable. Some neurological conditions, like Korsakoff's syndrome and Wernicke's encephalopathy (Krabbendam et al., 2000; Saxton et al., 2000) are clear examples of the neurotoxic effect of alcohol. Some researchers (Parsons, 1998) have argued that there exists a continuum of impairment within the alcohol using population, with severe impairment appearing in individuals who most severely abuse alcohol and subtle impairment appearing in individuals with less severe, but regular and heavy alcohol intake.

This spectrum is visible in adult alcohol misusers. In a review conducted by Seigneurie et al. (2013), adult alcohol misusers showed anatomical and physiological differences when compared to their non-addicted counterparts. Differences include a reduction of white and grey matter in the frontal and medial temporal cortex, thalamus, caudate nucleus, and cerebellum. The authors also reported a dose-response effect that is compatible with the model presented by Parson (1998). Higher alcohol exposure was related to a higher reduction in brain volume, even when controlling for age, sex, education, physical height, and body weight.

As is the case for adults, data from adolescent studies show that adolescent brains are negatively impacted by exposure to alcohol. For example, a decrease in the prefrontal cortex and left hippocampal volumes (Squeglia et al., 2009; Tapert et al., 2002) has been observed amongst adolescent alcohol users when compared to adolescents who do not use alcohol.

These findings correspond to some degree to results reported by Seigneurie et al. (2013). Despite parallels between adolescent and adult alcohol users, a dose-response effect remains difficult to establish because adolescent studies tend to compare acute users to non-users rather than measuring alcool intake as a continuous variable across their samples.

However, there is some ground to hypothesize a dose-response effect in adolescents as well. For instance, findings from animal studies (Crews et al., 2000) do indicate that adolescent rats show a reduction in brain volume that corresponds to their alcohol exposure. This combined with evidence of a continuum of effects in human adults does suggest a similar continuum in human adolescents. Furthermore, the same animal study suggests that adolescent alcohol exposure could carry a specific risk for the developing brain. Despite lower doses of alcohol administered to adolescent rats than adult rats, the younger rats showed a greater reduction in brain volume when compared to their adult counterparts (Crews et al., 2000). This could mean that adolescence represents a critical window in brain development more susceptible to the harmful effects of alcohol.

Beyond effects on neuroanatomy and neurophysiology, alcohol also seems related to cognitive performance. In cognitive tasks designed to measure different aspects of brain functioning, heavy alcohol users tend to underperform compared to sober individuals. In a meta-analysis of 62 studies, totalling 5032 subjects, Stavro et al. (2012) reviewed the persistence of cognitive deficits in 12 cognitive domains following short (less than 1 month), medium (between 1 and 12 months) or long-term (more than 12 months) self-reported abstinence. Results suggest that the verbal ability, speed of processing, working memory, attention, problem-solving, inhibition and visuospatial domains were diminished by alcohol

abuse at all three time points, with moderate effect sizes at short and medium-term, and small effect sizes after 1 year of abstinence. These results echo similar findings in the adolescent population (Hanson et al., 2011; Lisdahl et al., 2013; Nguyen-Louie et al., 2015). This could indicate a potential direct effect of alcohol on the brain and its behaviour, as measured by cognitive tasks.

Other research teams have investigated the association between brain and alcohol but approached the question from a different direction. Research has demonstrated that children of alcoholics, before any alcohol use, are a group at significant risk for experiencing alcohol problems during their lifetime (Schuckit, 1984). Evidence suggests that part of their vulnerability to the addictive properties of alcohol might be the result of premorbid neurophysiological anomalies. Reduced capacity for inhibitory control (Tarter et al., 1989; López-Caneda et al., 2014), described as the capacity to withhold a response that is no longer in line with one's goals, seems particularly related to future alcohol problems within this group. Studies looking at children of alcoholics' response to stop-signal tasks, a gold standard for measuring inhibitory control in humans, show an impaired ability to inhibit behaviour when compared to a control group (Nigg et al., 2004). These findings were also replicated in a study of Spanish children of alcoholics age 6 to 12 (Díaz et al., 2007). In their study, children of alcoholics had significantly worse performance on cognitive tests used (e.g.: WISC-R Similarities, Block Design and Digit Symbol subtests, the Toulouse-Piéron test and the Stroop test). As documented in different reviews (Park & Schepp, 2014; Castellanos-Ryan and Conrod, 2020), similar deficits have been documented in this population, namely domains of task shifting, IQ, verbal abilities, and event potential surrounding decision-

making (e.g.: P300). Systematic reviews of the literature tend to indicate that there could be shared premorbid characteristics, such as impulsive temperament or different neuropsychological phenotype, responsible for the association between cognitive performance and addictive behaviour (Nigg et al., 2006; Park & Schepp, 2014; Castellanos-Ryan and Conrod, 2020). Since associations between alcohol and cognitive performance go in both directions, it becomes difficult to establish the distinct contribution of early alcohol use to later cognitive outcomes.

1.3 Cannabis and Cognition

Cannabis use also has an impact on human cognitive abilities. Researchers have observed that while intoxicated with cannabis, individuals were more likely to exhibit notable deficits in attention, executive functioning, working memory and episodic memory (Crean, Crane & Mason, 2011; Crane, Schuster, Fusar-Poli & Gonzalez, 2013; Jacobus et al., 2013; Lisdahl et al., 2013; Pope et al., 2001; Grant et al., 2003; Tapert et al. 2007). These effects were observable in all subjects (regular, occasional, or non-consumer) and seemed to persist over the short term after intoxication had resolved (Crean, Crane & Mason, 2011; Crane, Schuster, Fusar-Poli & Gonzalez, 2013; Pope et al., 2001; Grant et al., 2003). In adults, the cognitive deficits that accompany cannabis consumption were understood to fade away after a few weeks of abstinence (Pope et al. 2001), although there is mounting evidence of chronic effects of cannabis use in adults. As reviewed by Broyd et al (2016), memory, attention, psychomotor function, and executive function show signs of persistent effects of cannabis use. The age of onset of cannabis use seems to be relevant when predicting an individual's future performance on a cognitive task. Adolescent-onset cannabis use has been positively

correlated to lower cognitive performance in several studies (Hanson et al., 2011; Lisdahl et al., 2013; Nguyen-Louie et al., 2015). In a cohort study of 1037 participants tested at age 13 and 38, acute cannabis consumption before age 18 was associated with lower performance on an IQ test (Meier, et al., 2012). However, this association only held for a very small portion of the population, given the rarity of acute consumption of cannabis before age 18, and that no relation was detected for individuals who regularly consumed cannabis after age 18 (Meier, et al., 2012). This finding was in part replicated in another study that associated adolescent cannabis use initiated before the age of 16 with longer-lasting trial and error learning and reward processing difficulties in early adulthood (Castellanos-Ryan et al., 2016).

Just like alcohol, the association between cannabis and cognition is not unidirectional. For instance, beyond establishing cannabis use as a potential predictor of cognitive performance, Castellanos-Ryan et al. (2016) also reported that cognitive performance before cannabis use initiation could predict earlier cannabis engagement. Poor short-term memory, low working memory performance and higher verbal IQ scores were associated with earlier onset of cannabis use in adolescent males. Rioux et al. (2018) also reported that high verbal IQ in early adolescence predicted early-onset cannabis use in adolescence. Additionally, other findings showed that poor executive functioning was predictive of later substance use on a broad spectrum of substances. Despite these findings, more evidence is required in this field of addiction research (Lorenzetti et al., 2016; Smith et al., 2014). As reviewed by Squeglia and Gray (2016), common predictors for both early-onset cannabis use and early onset alcohol use involve poor inhibitions, working memory deficits, abnormal activation of

the brain during inhibition tasks, lower frontal and parietal lobe activation during visual working memory tasks, and higher superior frontal regions activity during a reward processing task.

1.4 An Alternative Hypothesis to Understand Substance Misuse and Cognition

As shown above, the evidence for substance misuse's effect on cognition remains difficult to interpret. Cognition could be 1) potentially influenced by substance misuse, 2) potentially contributing to substance misuse, or 3) be explained, along with substance misuse, by other pre-existing variables. Cognitive profiles, temperamental disposition, genetical factors and sociodemographic characteristics could increase the risk for early-onset alcohol and/or cannabis use (Argyriou, Um, Carron & Cyders, 2018; Crews & Boettiger, 2009; Gillespie, Neale & Kendler, 2009; Sherva et al., 2016; Verdejo-García, Lawrence & Clark, 2008). For example, a longitudinal twin study conducted by Cousijn et al. (2013) reported that premorbid differences in activation levels of the decision making and reward processing systems were predictive of future cannabis involvement in adolescence and adulthood, suggesting premorbid cognitive processes to be involved in future cannabis use. Pagliaccio et al. (2015) went further, reporting that common vulnerability factors (e.g.: genetic predispositions, inherited traits, temperamental disposition, etc.) were quantitatively more important to brain development than substance misuse use. The causal chain is therefore difficult to establish and points towards potential common vulnerability factors that predispose to both cognitive difficulties and early-onset substance use. This conflicting evidence call for a reappraisal of the way we study the association between substance use and cognitive performance. In other words, new empirical studies should quantitatively

account for a shared vulnerability to better estimate the specific contribution of substance use behaviour on cognitive performance.

1.5 Adolescent Brain Development and Basis for Developmental Sensitivity

The research reviewed above invites us to reevaluate our understanding of addiction and cognition. This reevaluation invites us to incorporate a developmental perspective into our approach. A dominant model of adolescent neurological development focuses on the apparent maturational gap between limbic regions and prefrontal cortex development (Galvan et al., 2006; Hare et al., 2008; Ernst et al., 2005; Geier et al., 2009; Van Leijenhorst et al., 2010). As reviewed by Casey and Jones (2010), available data suggests that certain brain regions, namely the nucleus accumbens, amygdala and striatum develop at a nonlinear rate when compared to other regions, such as the prefrontal cortex, which develops linearly across maturation from childhood to adulthood. One such region, the striatum, seems functionally involved in detecting and learning about novel stimuli (Delgado, 2007). Motivation and interpretation of cues in decision-making contexts also seem to involve this region (Galvan et al., 2006). This system's rapid development in adolescence accounts for the increase in adolescent risk-taking behaviour when compared to children (who both present underdeveloped limbic and prefrontal systems). This also specifically accounts for adolescents' increase sensitivity to rewards when compared to adults (Casey & Jones, 2010). In other words: adolescents enter a period where their brain is more capable of reason but is still very susceptible to emotional bias. These neurological data also help understand how adolescence is typically associated with the emergence of risky behaviours, like substance misuse (Van Leijenhorst et al., 2010). This normal

developmental course of increased emotional influence and risk-taking leaves the

adolescent brain vulnerable to addiction. Robinson and Berridge (2008), in their review of

the incentive sensitization theory of addiction, have posited that substance use in

adolescents can metaphorically "hijack" the ventral striatum with stimulation, thus

downregulating top-down prefrontal control regions, which can further entrench addictive

behaviours in adolescents.

The adolescent brain is still plastic, but transitioning towards adulthood, a more static

state (Spear, 2013). The adolescent brain remains plastic to experience-dependant change.

This plasticity, although essential, could, unfortunately, lead to severe and lifelong

trajectories of addiction. As reviewed in Carpenter-Hyland and Chandler (2007),

histological findings indicate that nervous cells adapt at a cellular level to alcohol intake,

over-developing N-methyl-D-aspartate receptors, a type of glutamate receptor on neurons,

and enlarging dendritic spines in cultured hippocampal cells. These adaptive responses to a

more alcohol-rich environment seem to reinforce pathways stimulated when consuming

drugs such as alcohol. Whether these changes can be repaired remains unknown, but certain

variations could account for different trajectories in adolescent substance users. This does

suggest that adolescent brains could respond differently to substance exposure depending

on the age of exposure: if exposed at a young age, the brain could either tolerate the injury

as it is reorganizing or conversely show a more drastic response when exposed at a

vulnerable transitive stage. This will be referred to as the developmental sensitivity

hypothesis in this dissertation.

1.6 Theoretical Models

Though both alcohol and cannabis use seem to be related to impaired cognitive functioning, there can be no certainty that these substances caused the observed deficits (Peeters et al., 2013). An alternative explanation is that these deficits predate consumption. That is, mild cognitive deficit precedes early-onset substance use, giving the illusion of neurotoxicity, while, constituting a premorbid condition that becomes more problematic for the individual at a later period of development. In other words, maybe the observed deficits indicate that poor cognitive abilities are a risk factor for future substance problems. As mentioned previously in the context of alcohol use, temperamental dispositions, such as impulsivity, given its association with both lower cognitive performance and substance misuse (Daruna & Barnes, 1993; Robbins et al., 2012), could account yet again for the common variance between substance use behaviour and cognitive performance in adolescence. Impulsive youth might face difficulty coping with increased autonomy accompanying adolescence, which would strain cognitive capabilities and result in maladaptive substance-based coping (Argyriou, Um, Carron & Cyders, 2018).

Another roadblock in understanding the harmful effects of substances on the developing brain is the unclear pattern of lasting and transient effects of substance use on cognitive processes. As documented by Stavro et al. (2014), and Crean et al. (2011), different functions seem to recover, although at different rates, while other functions, as documented by Meiers et al. (2012) and Castellanos-Ryan et al. (2016), show effects that might persist even after a year. It remains uncertain to what extent the age of onset informs susceptibility to cognitive difficulties. Depending on the state of neurodevelopment, neurotoxicity or

recovery might be influenced: could younger brains be more resilient or vulnerable due to plasticity? The question persists.

When trying to infer causality between substance use and cognition, three theoretical models can account for the observed association. The first model stipulates that psychotropic substances, such as alcohol and cannabis, directly cause the observed impairment in performance. This hypothesis will be referred to as the neurotoxicity model. Empirically, this model would be confirmed if consumption of these substances were to negatively predict future performance on cognitive tasks in the absence of concurrent substance use, controlling for initial performance on said task. This model is represented in Figure 1. This model would dictate that prevention of cognitive decline would be achieved by reducing substance use, and that cognitive impairment is a by-product of substance misuse.

Figure 1. Neurotoxicity Model
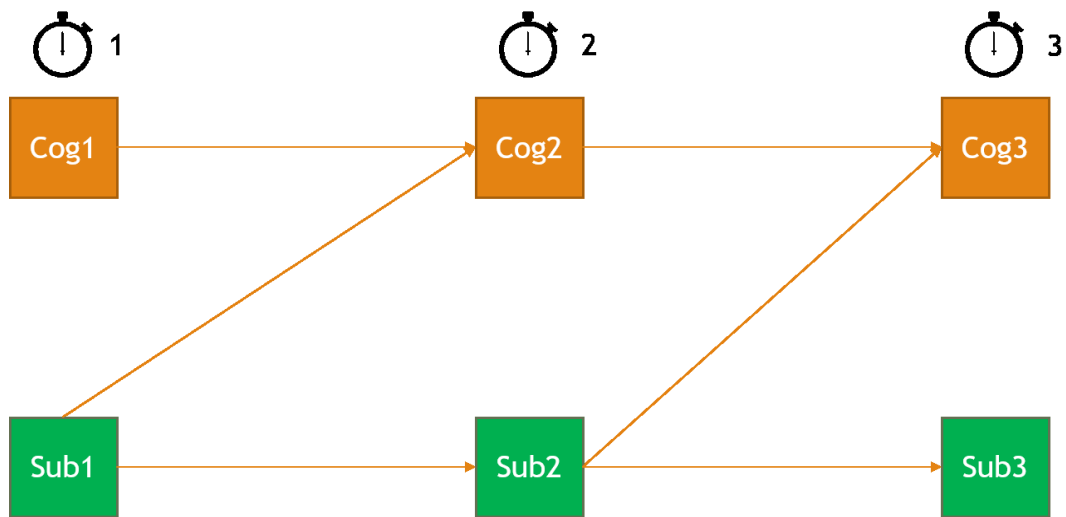
Note: Schema representing cognitive performance (Cog) and substance use (Sub) measured at three-time points. Neurotoxic effect represented as diagonal arrows.

Another theoretical model which could account for the relation between cognitive performance and substance use might take into consideration discrepant findings. A different model could inverse the association, stating that premorbid traits, such as poor cognitive performance at onset, a certain genetic phenotype, a base temperamental disposition, etc., would predict future substance misuse, as poor planning and poor learning would predict a predisposition towards engaging in substance use, and preventing disengagement from problematic consumption habits. This will be referred to as the common vulnerability factor model. Empirically, this hypothesis would be validated if we observe a general tendency for early substance misusers to also be presenting cognitive deficits. A visual representation of the model is presented in Figure 2.

Figure 2. Common Vulnerability Factor Model
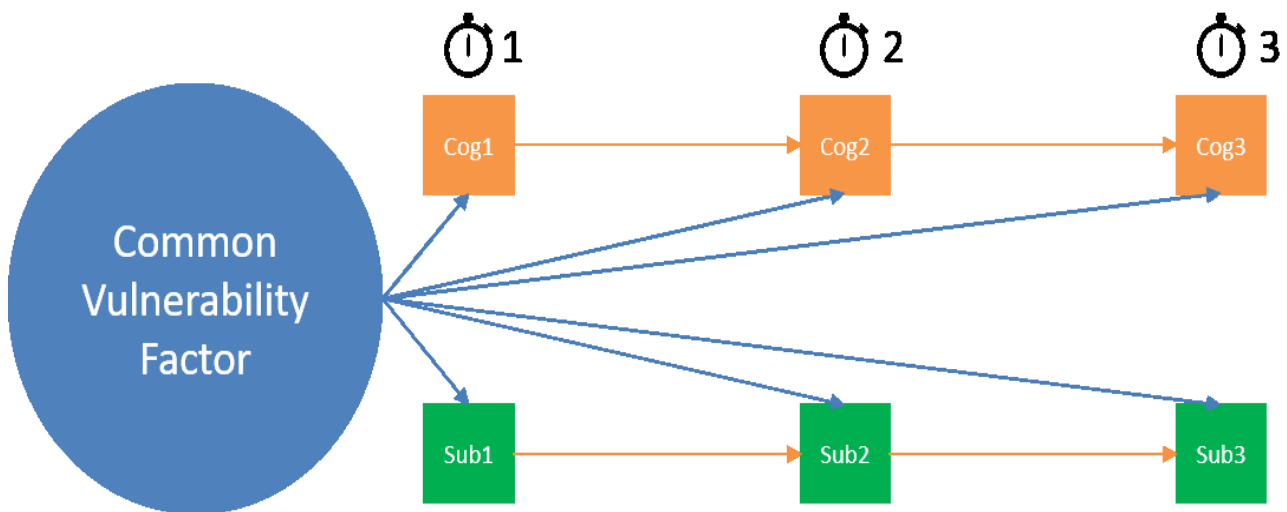
Note: Schema representing cognitive performance (Cog) and substance use (Sub) measured at three-time points. Common vulnerability factor (blue) represented as a general predictor of cognitive performance and substance use throughout time.

There exists one last model which could explain the relationship between substance use and cognitive performance. This model describes this association from a fluid perspective. Rather than speculating that one variable will systematically predict the other over the long term, this model suggests that consumption is associated with impaired cognitive performance only in the short term. Through mechanisms of neurotoxicity and neuroplasticity, a subsequent reduction/cessation of substance use would attenuate cognitive impairment observed previously, potentially related to neuroplasticity, which might be age-dependent. By contrast, persistent or increasing consumption behaviours would accentuate or increase cognitive impairment. This will be referred to as the neuroplastic model, considering that change in consumption behaviours would modulate the brain's capacity to compensate for the neurotoxic effects of psychotropic substances. Evidence confirming this hypothesis would reveal systematic correlations between consumption and cognition across various time points, without long-term predicting effects of one variable over the other. This model is represented in Figure 3. This model is supported by the results of Stavro et al.'s (2012) study which suggests the possibility of some level of recovery from the cognitive deficits associated with alcohol if individuals remain abstinent over a short period.

Figure 3. Neuroplastic Model
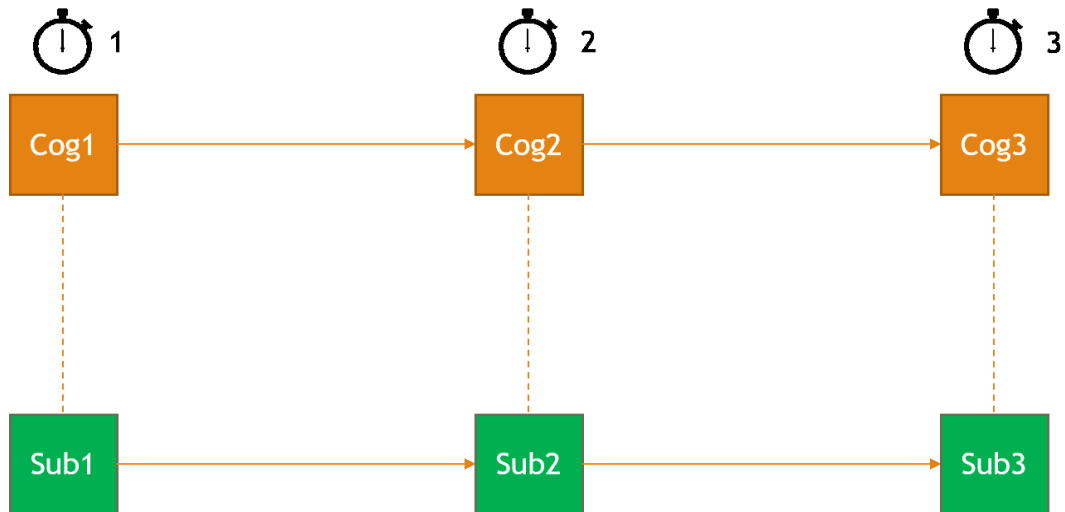
Note: Schema representing cognitive performance (Cog) and substance use (Sub) measured at three-time points. Pathoplastic effect represented as dotted lines.

Finally, as discussed in a previous section, there could exist moments in development that either relate to increased sensitivity or resilience to the effect of substance use. For instance, if cannabis use is initiated before age 16, it might lead to longer-lasting impairment on certain domains of cognition as opposed to similar subjects initiating substance use at age 18 (Castellanos-Ryan et al., 2016; Meier et al., 2012). Beyond direct neurotoxicity the timing of exposure becomes relevant. This effect will be referred to as a developmental sensitivity effect in this dissertation.

1.7 The association with Psychopathology Symptoms

1.7.1 Substance Use and Psychopathology

The association between substance use and cognitive development is highly consequential to clinical care with addicted patients or problematic users. According to some research, psychopathology can be understood as a spectrum of difficulties affecting either predominantly emotional or predominantly behavioural responses (Achenbach, 1966). On one end of the spectrum are internalizing disorders, which captures mental disorders whose locus of suffering is mostly internal, like depressive disorders and anxiety disorders (e.g.: depressed or anxious mood). On the other end are externalizing disorders, which capture mental disorders whose locus of suffering is reflected in externally visible behavioural problems, such as conduct disorders or attention deficiency hyper-activity disorders (e.g.: aggressive behaviours or behavioural disinhibition). This model of mental disorders has been confirmed empirically using factor analysis (Achenbach, 1966). As reported in the literature, substance misuse and mental disorder are highly comorbid, both on the internalizing and externalizing continuum (Rush et al., 2008). The rate of cooccurrence between all SUD's and any other mental health problem is estimated to be as high as 60% identifying comorbidity between these conditions as a norm rather than an exception. Substance misuse, such as alcohol or cannabis misuse, has been related to the full continuum of psychopathology (Richardson, 2010; Tomlinson et al., 2004).

Evidence also leads to believe that this association is mutually reinforcing. According to a study conducted by Farmer et al. (2016), which investigated the longitudinal association between cannabis use disorder and mental health problems, individuals presenting a cannabis

use disorder at age 16 were more likely to present mental health problems, both internalizing and externalizing, at later follow-ups. The emergence of these disorders seemed to further predict a sustained cannabis use disorder until follow-up at age 30. Beyond its association with internalizing and externalizing psychopathology, adolescent-onset cannabis use has been linked to the emergence of psychotic problems in adulthood (Large et al., 2011). Furthermore, a study conducted by Bourque et al. (2017) found that increase in adolescent consumption of cannabis could predict higher levels of self-reported psychotic-like experiences, which are also related to an increased risk of psychosis. This suggests that adolescent cannabis use is related to symptom apparition throughout development, just as shown for mood and conduct-related problems.

1.7.2 Cognition and Psychopathology

Another emerging body of literature relates to cognitive performance in certain domains and its association with psychopathology. Executive functioning, a cluster of cognitive processes related to information processing and behaviour regulation (e.g.: behavioural inhibition), has been significantly linked to externalizing problems. A meta-analysis conducted by Schomaker et al. (2013) identified a small to moderate association between lower executive functions and externalizing problems ($d = 0.22$). Poor executive functioning has also been shown to predict adolescent substance misuse, specifically alcohol use, tobacco use and cocaine use (Smith et al., 2014).

Though externalizing problems and cognitive performance seem to have benefited from a wide array of empirical investigation, the same cannot be said about our understanding of cognition and internalizing problems. Though attempts have been made to understand the

link between cognition and internalizing disorders, evidence remains unclear. Just as for externalizing problems, executive functions could be related to major depressive disorder (Gohier et al., 2009; Hammar & Ardal, 2009), more evidence is necessary to fully establish it. Beyond executive functions, memory problems (e.g.: recall memory) also could be implicated with major depression (Hammar & Ardal, 2009). At a broader level, attribution biases could be related to the full cluster of internalizing problems (Viana & Gratz, 2012).

1.7.3 Potential for a Mediating pathway

Cognitive impairment has been documented as a common clinical complication in the context of treatment with clients suffering from substance use disorder and comorbid psychopathologies (Aharonovich et al., 2006). Though research exists on the association between certain substance use patterns, such as cannabis use, and psychopathology symptoms, as well as on cognitive performance and psychopathology symptoms, few studies have investigated the combined contribution of substance use behaviour and cognitive performance on mental health symptoms presentation. There is no evidence, to our knowledge, that either confirmed or rejected the possibility for the association between substance use, such as cannabis, and psychopathology symptoms to be accounted for by the neuropsychological consequences of substance misuse. Considering the existing literature, this potential mediating pathway is to be explored. This mediating pathway could take the form presented in Figure 4. Though some evidence goes against the suggested mediating pathway (Argyriou, Um, Carron & Cyders, 2018; Crews & Boettiger, 2009; Gillespie, Neale & Kendler, 2009; Sherva et al., 2016; Verdejo-García, Lawrence & Clark, 2008), this does not exclude the potential for psychoactive substances, namely cannabis, to contribute, through cognitive impairment, to the increase or exacerbation of psychopathology symptoms.

In other words, bidirectionality does not exclude the potential for significant partial mediation, which would fit both empirical and clinical data. Robust longitudinal designs can provide the necessary power and control to explore these hypotheses.

Figure 4. Mediation Model of the Association between Substance Use, Cognitive performance, and Psychopathology Symptoms
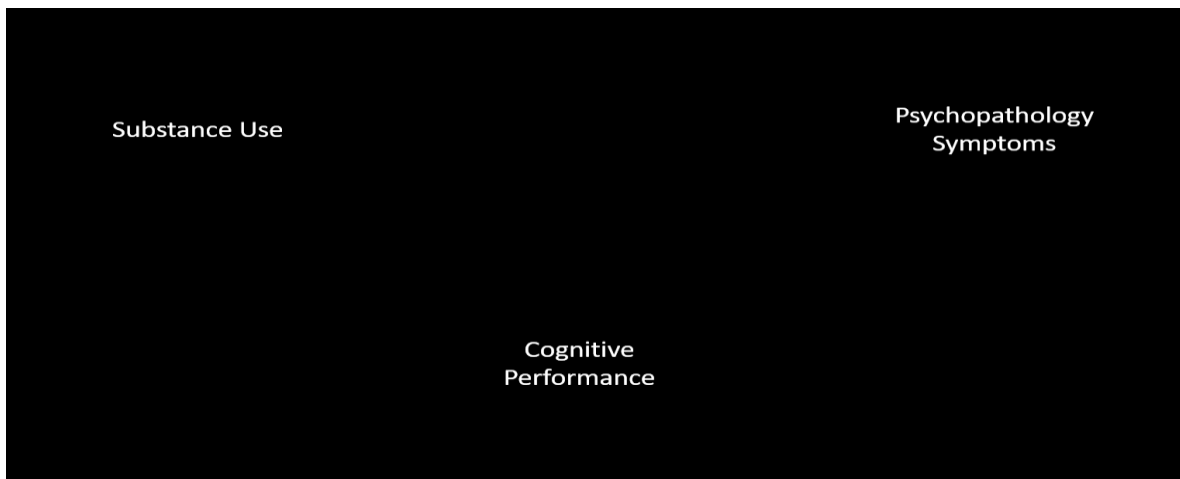
Note: Substance use measured at time 1, Cognitive performance measured at time 2, and psychopathology symptoms measured at time 3. The schema represents how substance use might partially relate to psychopathology symptoms through its indirect effect on cognitive performance (mediating pathway).

1.8 Implications for Prevention

So far, this review has addressed the topic of substance use, its complex relation to cognitive development, and its ramifications for comorbidity. Though already providing insight into the fundamental mechanisms of addiction, this dissertation also strives to further prevention science.

Theoretical and clinical research can be understood as opposite ends of a shared continuum. However, one does not preclude the other and both theoretical and clinical research can inform one another. Empirical findings from theoretical research can be used to refine existing clinical research and answer pressing questions on the ground. In the context of addiction research, here are some questions that could unite theoretical concerns described previously and relevant clinical concerns:

What prevention tools are used in Canadian and American schools to limit substance engagement in youth? How effective are they at reducing substance use? Do they provide the means to address co-occurring problems associated with substance misuse in adolescents, such as cognitive problems and psychiatric comorbidity? Are they deployed at the right time to produce the desired preventive effects? These questions remain for the most part unanswered.

Meta-analyses by Faggiano et al. (2014) and Carney et al. (2016) provide effect sizes measuring the impact of certain interventions on adolescent substance use behaviour. They allow evaluation of the state of prevention science at different thresholds of prevention, namely universal prevention and indicated interventions. Their findings are discussed to a greater extent in the third chapter of this dissertation. First, the chapter briefly summarises key risks associated with early adolescent substance misuse. Then, the chapter tries to familiarise the reader with a classification of different levels of preventive approaches, ranging from universal prevention programs to targetted prevention programs, and indicated programs. Once the different levels of prevention are clear, a review of evidence and conclusions drawn by Faggiano et al (2014) are presented to inform the reader of the

effectiveness and gaps in universal prevention programs. This presentation is followed by a similar review of findings focusing on indicated programs, as reported by Carney et al. (2016). These meta-analyses are quite critical of prevention research and command new models and strategies to face the specific challenge of adolescent substance misuse.

Once the gaps in current prevention efforts are made clear, a closer look into a specific model of prevention named Preventure is presented (Conrod et al., 2000; Morin, Harris & Conrod, 2017). This review strives to demonstrate how differently conceptualized prevention practices could better address the broader issues surrounding adolescent substance misuse, namely comorbidity and developmental sensitivity of the brain when substance use is initiated early in adolescence. The Preventure model is presented at greater length in the final chapter.

Once fully presented, this review serves as a basis for a full discussion into ways to integrate empirical findings (provided in chapters 1 and 2) and clinical work. Should certain cognitive domains be assessed and used as a basis for prevention efforts? Are cognitive training programs of relevance in preventing adolescent substance use? What should be targeted in preventive programs? How could certain targets lead to lower substance use, preserved cognitive function and better mental health? These questions constitute the basis of this discussion.

1.9 Objectives

As reviewed above, alcohol and cannabis misuse seem to relate to a wide variety of issues. Among said issues are the ambiguous association with cognitive problems, the yet unclear mechanisms underlying the overlap between early substance misuse and psychiatric

comorbidity, and the difficulty in identifying effective and adequate prevention programs capable of addressing the challenges brought forward by adolescent substance misuse.

In light of this information, the objectives of this dissertation are threefold: 1) to investigate the nature of the relation between cognitive performances and alcohol/cannabis consumption considering three theoretical models (common vulnerability, neurotoxic and neuroplastic), 2) to investigate the potential for cognitive performance to play a mediating role in the association between cannabis use and psychopathology symptoms, and 3) to review the evidence for current cannabis use prevention programs and investigate, using the example of the Preventure model of intervention, new avenues to further improve our preventive strategies.

The specific objective of the first chapter is to adequately test for the different temporal relationships that could unite adolescent substance use and cognitive outcomes in a large population-based sample of adolescents from Montreal, Canada, over 4 years. To achieve this, this first chapter aims to simultaneously test for the relevance of the common vulnerability factor effect, the neurotoxic effect of cannabis, and the dose-dependent pathoplastic effect. Unlike other studies that aim to either test for short-term ($\leq$ 1 year) or long-term ($\geq$ 4 years) effects, this study is designed to test proximal and distal effects of substance use on the developing brain. This should provide better insight into the sequence of effects and shed light on developmental-sensitivity effects, such as critical periods of brain maturation more susceptible to alcohol or cannabis use.

The specific objective of the second chapter is to integrate into a single model cannabis use, cognitive performance and psychopathology symptoms while testing for potential

mediation. Given the more ambitious nature of the model, this analysis strictly investigates the effects as they relate to cannabis use. This should result in a more manageable amount of models to prepare and interpret. In addition, results from the first chapter of the thesis provide a strong theoretical basis for cannabis' neurotoxicity model, but only a weak theoretical basis for alcohol's neurotoxicity model, which leads to the exclusion of alcohol as a main variable. The same population-based sample of adolescents from Montreal, Canada is employed, this time with data-points spanning 5 years, due to the pace of data collection by the time this chapter is written. The specific aim of this chapter is to quantify the association between all three main variables using the same common vulnerability factor model, neurotoxic model, and pathoplastic model.

The specific objective of the final chapter of this dissertation is to offer a selective narrative review of the state of preventive care research for cannabis use in adolescents. This review aims to determine what are the evidence-based preventive programs to limit cannabis use in adolescent youth, highlight gaps in existing universal and indicated interventions programs currently offered in Canada and the United States, and show how targetted prevention can provide key advantages for prevention, as demonstrated by research conducted on the Preventure program. A more thoughtful analysis of how to integrate cognitive findings to prevention efforts such as Peventure is part of a longer discussion in the concluding portion of the dissertation.

1.10 Hypotheses

For our first investigation, we anticipate all theoretical models to be significant in representing the relation between substance use and cognitive outcomes. Considering the effect of premorbid executive functions on early-onset substance use (Nigg et al., 2004), we hypothesize that response inhibition and working memory (two subcomponents of executive functions) will be associated with earlier onset of alcohol use and generally heavier alcohol use across assessments. With regards to alcohol, previous research has identified an association between adolescent binge drinking and cognitive functions (Lisdahl et al., 2013). Therefore, we anticipate that further increases in alcohol consumption will predict lower scores on working memory, inhibitory control, and recall memory abilities, above and beyond common vulnerability effects. In the case of recall memory, previous research has suggested that the effects of alcohol use on memory are transient (Stavro et al., 2013), leading us to hypothesize common vulnerability and neuroplastic associations in that domain.

Still in our first empirical study, with regards to cannabis use, we expect to find support for the common vulnerability model, especially with regards to inhibitory control (Castellanos-Ryan et al., 2016). Additionally, previous research indicates the existence of neurotoxic effects resulting from cannabis use in the domains of recall memory and IQ (Lisdahl et al., 2013; Meier et al., 2012). Animal studies have shown that chronic exposure to THC causes dose-dependent neurotoxic effects, and that hippocampus, amygdala, septum, and cortex are rich in cannabinoid receptors (Solowij et al., 2012). Knowing that abnormalities in temporal and hippocampal regions seem linked to human cannabis use (Rocchetti et al., 2013) we hypothesize additional recall memory deficits will be linked to

cannabis use. As literature remains inconclusive about the transient or lasting nature of these impairments, both neurotoxic and neuroplastic effects are hypothesized. Given the existing literature positing that adolescence might constitute a critical period of sensitivity to drug effects, we expect our effects to be time-dependant, meaning that early substance use should be more impairing on cognitive performance than substance use occurring later in adolescence, documenting the presence of a developmental sensitivity effect.

For our second investigation, we hypothesize that, above and beyond other associations, we should detect a mediation of cognitive performance on the association between cannabis use and psychopathology symptoms, both on the externalizing and internalizing spectrum. Specifically, we expect substance use to relate to lower inhibitory control capabilities, which should mediate the association between cannabis use and both externalizing and internalizing psychopathology. Given the existing link between memory functioning and depressive symptomatology (Hammar & Ardal, 2009), we expect substance use's relation with delayed recall memory to be a mediator of the association between substance engagement and internalizing symptoms specifically.

Investigation of the Relation Between Substance Use and Cognitive Performance and

its Mediating Effect on Psychopathology Symptoms

DESCRIPTION OF RESEARCH AND METHODOLOGY

par

Jean-François G. Morin

2. Description of research and methodology

2.1 Participants

This study is part of a larger project called Co-Venture, which is a longitudinal, population-wide, randomized-controlled trial assessing the 5-year efficacy of a preventive workshop developed to reduce adolescent substance misuse. The trial used schools as the randomization unit. In other words, schools were recruited and randomized to either the intervention condition (receive the program within the 1st year after enrollment), or to the control condition (a waitlist control where the program was given within the later portion of the trial). Out of a potential 3971 students, A total of 3826 participants (47% female) were recruited from 31 schools (17 French; 14 English) in the region of Montreal and were asked to complete a battery of digital questionnaires and cognitive tasks[3]. The questionnaires were administered using a secure web platform the students could access from their computer laboratory at their school. The participants are asked to provide data once a year over 5 years. The Co-Venture trial began in 2012 and formally concluded in 2019. Recruitment was conducted at the school level, meaning that schools were approached and invited to participate in the study. Schools were selected taking into consideration the socioeconomic, cultural, and linguistic diversity within the Montreal region. Participating schools agreed to organize assessment periods during class time. Schools invited their 2012 cohort of students to respond to a series of questionnaires. Fifty percent of participating schools received training and support in the implementation of the Preventure workshops as part of the

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[3] For more information about attrition in the sample and polysubstance use, refer to Appendix 2.

experimental group. Schools in the control group were offered to receive the Preventure training during their 4th year of participation and were instructed to offer the program starting with their 2016 cohort, where students were not part of the study's sample. Participants were all students in grade 7 (between ages 12-13) at initial recruitment. Parental consent was gathered before testing and intervention. Additionally, child assent was verified right before the beginning of the testing session and right before starting the Preventure workshop. Testing usually took place at the schools and lasted between 40 and 90 minutes. Between 20 and 40 students were present during each testing period. Preventure workshops were given throughout the 1st year of the investigation. Each of the two sessions lasted 90 minutes and was given once a week over two weeks. In the context of chapter 1, participant data up to year 4 will be used for our analyses, while data up to year 5 will be used for chapter 2.

The scope of the study was remarkable for its size and diversity. This sample was designed to be representative of Montreal's youth population and presented a unique opportunity to explore questions relating to developmental psychopathology. It is however true that certain schools were treated differently to others because of random assignment to either experimental or control conditions. Given that the experimental condition entailed a preventive intervention to delay and limit substance misuse in adolescents, one could expect a certain impact on reported results when investigating the association between substance use, cognitive and mental health outcomes. For instance, reduced substance engagement could reflect positively on cognitive and mental health variables in certain schools, therefore biasing results reported. Although these concerns are valid, the broad scope of the sample

and adequate analytical strategy mitigate potential biases. Nevertheless, these concerns are going to be mentioned in the discussions throughout the dissertation.

2.2 Main variables

2.2.1 Substance use

Alcohol consumption and cannabis consumption is assessed yearly using the Detection of Alcohol and Drug Problems in Adolescents' Questionnaire (DEP-ADO; Germain, Landry, Tremblay, Brunelle & Bergeron, 2005). This questionnaire consists of 51 items that ask participants to rate the frequency of their consumption for each substance on a 6-point scale. The scale ranges from 0 "Never used" to 5 "Use every day". The DEP-ADO has previously demonstrated good construct validity, internal consistency, test-retest, and intermodal execution reliability in Quebec youth (Landry et al., 2004). Some may raise concern over the self-report nature of the instrument. In the assessment of adolescent substance-related behaviours and substance-related problems, self-report measures have been found to maintain good discriminant and predictive validity (Clark & Winters, 2002; White & Labouvie, 1989). For this investigation, three variables were extracted: 1) alcohol use frequency, 2) typical alcohol intake quantity, and 3) cannabis use frequency. Alcohol consumption frequency and the typical quantity of alcohol consumed were merged by creating an interaction factor (e.g.: multiplying the reported quantity value to the frequency value reported) to create a single variable. This new variable is sensitive to differences in both alcohol dose and frequency of consumption, thereby distinguishing frequent light drinkers from frequent heavy drinkers (Sobell & Sobell, 2003). Given the absence of an item evaluating the quantity of cannabis use, the cannabis frequency item was the only cannabis

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item retained for our analyses. Substance use variables are used as both dependent and independent variables in our investigation.

2.2.2 Cognitive measures

To assess cognitive traits, participants complete a series of computerized cognitive tasks measuring spatial working memory (SWM), delayed memory recall, response inhibition, and perceptual reasoning. Cognitive data is collected yearly. All variables derived from these cognitive tasks are used as both dependent and independent variables in our analyses.

Spatial Working Memory (SWM): Our measure of SWM is similar to an instrument used in the Cambridge Neuropsychological Test Automated Battery (CANTAB; Owens, Downes, Sahakian, Polkey & Robbins, 1990). This task has sound psychometric properties and has been validated with both adults and children (Cambridge Cognition, 2016). This version of the test, called "Find the Phone" asks participants to "search for the ringing phone" in a display. After finding the ringing phone, participants must remember and avoid selecting the phone that has already rung as they work through the remaining phones. SWM deficit is operationalized as the total number of errors (picking up a phone that has already rung) during the task.

Delayed Recall Memory: To measure memory recall, participants are asked to complete the "Dot location task" taken from the Children Memory Scale (Cohen, 1997). The task consists of a single display of dots arranged in a pattern that participants need to memorize on 3 trials of 5 seconds each. After approximately 35 minutes following the learning phase, participants are asked to reproduce the pattern they learned previously. Each

correctly placed dot awards points. The total number of points scored was used as our delayed recall memory variable. The task has been validated for children ages 5 to 16 and presents acceptable internal consistency and test-retest reliability (Cohen, 2001).

Perceptual Reasoning: To assess perceptual reasoning in our sample, participants are asked to complete a short matrix reasoning task similar to Raven's "Standard Progressive Matrices Test". The display consists of a 3x3 matrix filled with 8 symbols and an empty slot. To complete the task, the participant must "solve the puzzle" by selecting the correct pictogram from a list of symbols that complies with the implicit rule of the matrix. Each new puzzle increases in difficulty. For each correct selection, the participant accumulates points towards a final score. This final score is used in our analyses as a measure of perceptual reasoning. Research has demonstrated that administration of a parsimonious number of items (9 matrices) maintained the psychometric properties of the original 60 item version of the task, and scores obtained using the 9 item version correlated very highly with the 60-item version (Bilker, Hansen, Brensinger, Richard, Gur & Gur, 2012).

Inhibitory Control: Inhibitory Control is measured using the Passive Avoidance Learning Paradigm (PALP) (Castellanos-Ryan, Rubia, & Conrod, 2011; Newman & Wallace, 1993), which is a test that follows a "go/no-go" paradigm. The test presents the participant with a display consisting of a white screen with a score box. At each trial, the participant is presented with a number cue (e.g.: the number 12). At each presentation of the number cue, the participant has the choice to either press or refrain from pressing the space bar within a limited time frame. Following the participant's response, the participant is told if his or her response was correct or incorrect. A reward (0.10 points) or punishment (-0.10

points) is then attributed, updating the number displayed in the score box. The test is divided into two conditions: the Reward/Reward (RR) condition and the Reward/Punish (RP) condition. In the first condition (RR), the participant is rewarded for each correct response, be it correct presses (pressing the space bar for good numbers) or correct omission (not pressing the space bar for bad numbers). Wrong answers, like omission errors (failing to press the space bar for good numbers) and commission errors (pressing the bar for bad numbers), are not punished in this condition. In the RP condition, however, correct hits are rewarded, but commission errors are punished. Correct omissions and omission errors do not influence the score. Inhibitory control is operationalized as the number of commission errors committed across both conditions, with a higher error count indicating poorer inhibitory control. This strategy has been used in the past and is correlated with other methods of measuring inhibition (LeMarquand et al., 1998).

2.2.3 Psychopathology symptoms

Psychopathology symptoms were measured yearly using a combination of two scales. Internalizing symptoms were measured using the Brief Symptoms Inventory (BSI; Derogatis, 1993) which measures levels of anxiety and depression-related symptoms. The questionnaire consists of 53 self-reported items using a 5-point Likert scale. Administration usually takes four minutes. The instrument has shown acceptable internal reliability as well as acceptable to excellent test-retest reliability ($\alpha > 0.7$; $r = 0.7$-0.9; Aroian & Patsdaughter, 1989; Derogatis, 1993). "Anxiety" and "Depression" subscale scores of the BSI were used in the models.

Externalizing symptoms were measured using the "ADHD/Conduct symptoms" subscale of the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997). The questionnaire consists of a 25-item questionnaire that samples ten domains of competency, fourteen domains of difficulties, and a single "neutral" item. The test is available in a self-reported, parent-rated, or teacher-rated version. The items can be rated on a three-point Likert scale ("not true", "somewhat true", "very true"). The questionnaire has shown validity, as indicated by a high correlation with other instruments measuring behavioural problems in youth ($r = 0.9$). The measure also demonstrated good specificity/sensitivity properties, as measured by ROC analyses (area under the curve = 0.9, 95% C.I.). SDQ's ADHD/Conduct subscale scores were used as outcome variables in our models.

2.2.4 Control Variables

Analyses are controlled for potential covariates. Identified covariates include: 1) sex, 2) age at baseline, 3) ethnic background, 4) socioeconomic status and 5) use of another psychoactive substance. Sex and age are measured using demographic information provided on the questionnaire. This research uses sex as a variable that distinguishes between biological characteristics that differ between individuals[4]. In the absence of a specific question evaluating ethnic affiliation, ethnicity is estimated using participant-reported parent's country of birth and participant's own country of birth. The latter variables are compounded in a single variable, which is dichotomized as "Caucasian" or "non-Caucasian". This coding method has been used in previous research (Conrod et al., 2006; O'Leary-Barrett

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[4] However, one can note that our questionnaires did ask for participant's "gender" by inviting them to select if they were "a boy or a girl", despite trying to assess biological sex.

et al., 2016; Stewart & Devine, 2000) The socioeconomic status is estimated using the Family Affluence Scale, a 10-item questionnaire that evaluates the level of affluence by the material goods reported as being owned by the participant. A total score over 10 is produced, with a score of 10 indicating a high level of affluence. In its validation study (Boyce, Torsheim, Currie & Zambon; 2006), the Family Affluence Scale showed good construct validity and criterion validity. This score is used in our analyses. This research is interested in comparing both the common and the specific contributions of alcohol consumption and cannabis consumption. Therefore models must alternatively evaluate cannabis consumption and alcohol separately and then control for one another in a separate model. As a result, each model was conducted twice: once by assessing the contribution of each substance individually (what could be called a "general model"), and the other will let both predictors compete for variance (what could be called a "specific model").

2.3 Analytical Strategy Used in Chapter 1

One of the main objectives of this dissertation is to investigate the directionality of the relation between cognition and substance use. As previously stated, well-controlled longitudinal strategies are necessary to fully examine this data. A statistical model capable of testing for neurotoxic, neuroplastic and common vulnerability effects within a single analysis should be employed. Without eliminating it, this strategy can partially mitigate the potential for type I error associated with multiple testing. This constitutes a more conservative analysis than other research methodologies.

Therefore, a multilevel modelling approach, namely a random intercepts and slopes multilevel linear model, is used. It permits users to observe the effect of time on all variables

while simultaneously testing inter- and intra-individual changes through time. The model can be used hierarchically to first establish, using growth modelling, that the variables are indeed fluctuating with time. Next, these models can be used to decompose the effect of each predictor or independent variable (IV) at all four time points into two separate parameters. The first parameter, named the "between subject" effect, represents the association between the average inter-individual differences on an IV throughout all time points of the survey. This between-subject effect is obtained by regressing the variance of a subject's data over all time points into an intercept latent variable. In other words, it can provide an average effect of a given IV on a given outcome over the full duration of the study. This is used in our models to assess the common vulnerability factor model. The second parameter, called the "within-subject" effect, represents intra-individual changes on the IV across each year on an outcome over time. This within-subject effect is extracted by transforming the variance between data points into a slope variable. This slope represents the average change in reports from one time-point to the next and is used to assess pathoplasticity in our model. This slope variable can be adjusted, by excluding time 4 data, to test for the neurotoxic model by estimating its lagged effect on the DV.

2.3.1 Models Computed in Chapter 1

The following analyses are conducted using the software "R". Given the progress of the Co-Venture data collection when writing this chapter, four time points are used in the analyses. This chapter estimates three multilevel linear models assessing the association of cannabis and alcohol use with four domains of cognition (spatial working memory, delayed recall memory, perceptual reasoning, and inhibitory control). This means that a total of 12

models are computed in total, three for each cognitive domain studied. The models are calculated as followed: one assessing the effect of cannabis, the other one assessing the effect of alcohol, the other assessing both cannabis and alcohol use simultaneously. Models follow three iterative steps. First, a model estimates the intercept and slope parameter for the cognitive variables (DV) without substance use (growth model). A second model estimates the effect of substance use (IV) by adding in the IV (between-subject effect, within-subject effect, and lagged within-subject effect) into the growth model (main effect model). A final model estimates the potential developmental sensitivity effect by adding a moderation effect (substance use by time effect) in a model estimating the quadratic effect of time. Effects at the between-individual level are interpreted as indicative of common vulnerability, within-individual effects will be interpreted as pathoplastic effects, while within-individual lagged effects are interpreted as neurotoxic effects. The effects and their associated interpretation are illustrated in Figure 5.

Finally, effect sizes of substance use variables on cognitive domains are computed using Cohen's f^2. Using Cohen's (1988) guidelines, an f^2 value of 0.35 or more is interpreted as a large effect size, an f^2 value of 0.15 or more is interpreted as a medium effect size, an f^2 value of 0.02 or more is interpreted as a small effect size, and anything bellow 0.02 is interpreted as a very small effect. Missing data on the main variables were handled through Full Information Maximum Likelihood (FIML). School was included as a cluster-level variable.

Figure   5.   Effects   and   Corresponding   Interpretations   Used   in   Chapter   1
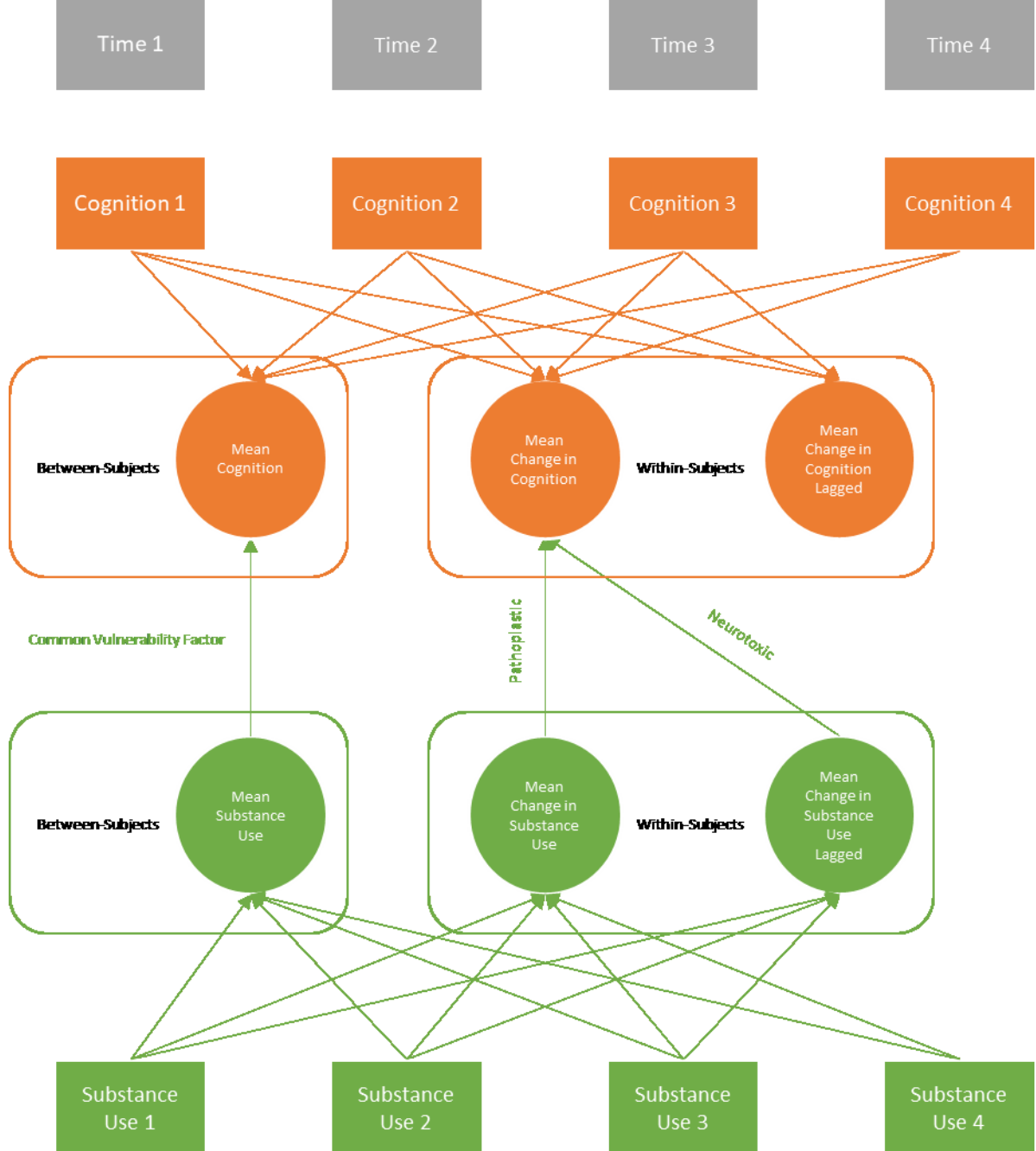
Note: This multilevel computational method tests between-subject differences at one level and then various within-subject processes at a second level, allowing for the investigation of concurrent and time-lagged relationships between sets of variables. Cognitive performance (orange) and substance use (green) were measured at four time points (time 1 represents assessment in the 7th grade, time 2 in 8th grade, and so on).

The first model proposes an underlying vulnerability factor that might contribute to early-onset substance use and the likelihood of continued and heavy use over time (center left arrow). Two within-subject effects (right boxes) reflect processes that are consequential to substance use and cognition. The neurotoxicity model (center right arrow) suggests that past substance use predicts future impairment in cognitive function that remains over a significant period, regardless of whether the substance use continues. The pathoplastic model (central arrow) suggests that consumption is associated with impaired cognitive performance, but only in the short term, and that through mechanisms of neuroplasticity, abstinence, or reduction in consumption, the cognitive impairment subsides. Finally, the developmental sensitivity effect would suggest that substance use at a critical period in development will lead to neurotoxicity, depending on the neuromaturational state of the brain region (with larger neurotoxicity or neuroplasticity effects at earlier times than at later times).

2.4 Analytical Strategy Used in Chapter 2

This framework used to assess between, within and lagged effects can be further used to model mediational effects. Using an adapted form of the Random Effect - Cross-Lagged Panel Model (RE – CLPM), we can, again, break down variables into their latent component (between- and within-effects) and create indirect effect terms that allow testing for mediating pathways. As presented by Wu, Carroll and Chen (2018), this type of modelling typically estimates indirect effects from year to year. In this case, we opted to adapt the model to regress between, within and lagged effects as variables rather than observed scores from year to year.

As for our previous analyses, the effect of each predictor or independent variable (IV) at all five time-points is regressed into three separate parameters, namely between-subjects, within-subject and within-subject lagged. The "between subject" effects represent the association between the average inter-individual differences on an IV throughout the survey. This between-subjects effect is obtained by regressing the variance of a subject's data over

all time points into an intercept latent variable. In other words, it can provide an average effect of a given IV (e.g.: cannabis use frequency) on a DV (e.g.: externalizing symptoms) over the full duration of the survey. This is used in our models to assess the common vulnerability factor model. The "within-subject" effects represent intra-individual changes on the IV across each year on an outcome over time. This within-subject effect is extracted by transforming the variance between data points into a slope variable. This slope, again, represents the average change in reports from one time-point to the next and is used to assess pathoplasticity. This slope variable can also be adjusted to test for the neurotoxic model by estimating its lagged effect on the DV. The mediator variables are subject to the same treatment as to also extract these between-subjects, within-subjects, and lagged parameters.

Once the between-subjects, within-subjects, and lagged parameters of the IV and mediators are obtained, direct effects of each parameter on the DV, direct effects of the mediator on the DV and indirect effects of the IV through each of the mediators on the DV are estimated.

2.4.1 Models Computed in Chapter 2

The following analyses were conducted using the software Mplus. In chapter 2, multilevel path analysis is employed. Cannabis use frequency (IV) is the only substance under investigation. This reflects the relative importance of cannabis, as reported in chapter 1, and also serves to focus the analysis and generate a more manageable quantity of models to interpret. A separate model is conducted for each permutation mediator variable (four domains of cognition) and dependant variables (two domains of psychopathology symptoms). In other words, a total of eight models is conducted assessing the mediation of

four domains of cognition (mediators: spatial working memory, delayed recall memory, perceptual reasoning, and inhibitory control) on two domains of psychopathology symptoms (DVs: externalizing symptoms and internalizing symptoms).

First, the direct association of frequency of cannabis use (IV) with the cognitive variable (mediator) is estimated at a between-subject, within-subject, and within-subject lagged level.

Next, the model estimates the direct association of the cognitive variable (mediator) with the domain of psychopathology symptom (DV) again assessing the between-subject effect, within-subject effect, and within-subject lagged effect of the mediating variable.

Finally, the indirect association of cannabis, as mediated by cognitive performance, with psychopathology symptoms is estimated at three levels: between-subject, within-subject, and within-subject lagged. This time, five time-points are included in the model. Figure 6 illustrates the mediational model used and the different paths assessed.

Though direct effects are reported, indirect effects constitute the core of reported results. If significant effects of mediation for between-subject effects are significant, this is interpreted as validation that the common vulnerability factor model is relevant to the association between cannabis use, cognition, and psychopathology symptoms. If a significant effect of mediation is found at a within-subject level, over and above between-subjects effect, this is interpreted to indicate the pathoplasticity model to adequately represent the association between cannabis use, cognition, and psychopathology symptoms. Finally, if a significant effect of mediation is found at a within-subject lagged level, over

and above between-subjects and within-subject, this is interpreted to indicate neurotoxicity model relevance when associating between cannabis use, cognition, and psychopathology symptoms.

Finally, the effect sizes of the relation between substance use variables with cognitive domains and psychopathology symptoms will be computed using Cohen's f^2. The same will be provided for the association of cognitive domains with psychopathology symptoms. Using Cohen's (1988) guidelines, an f^2 value of 0.35 or more is interpreted as a large effect size, an f^2 value of 0.15 or more is interpreted as a medium effect size, an f^2 value of 0.02 or more is interpreted as a small effect size, and anything bellow 0.02 is interpreted as a very small effect.

Figure 6. Multilevel Path Analysis Model of Mediation Used in Chapter 2
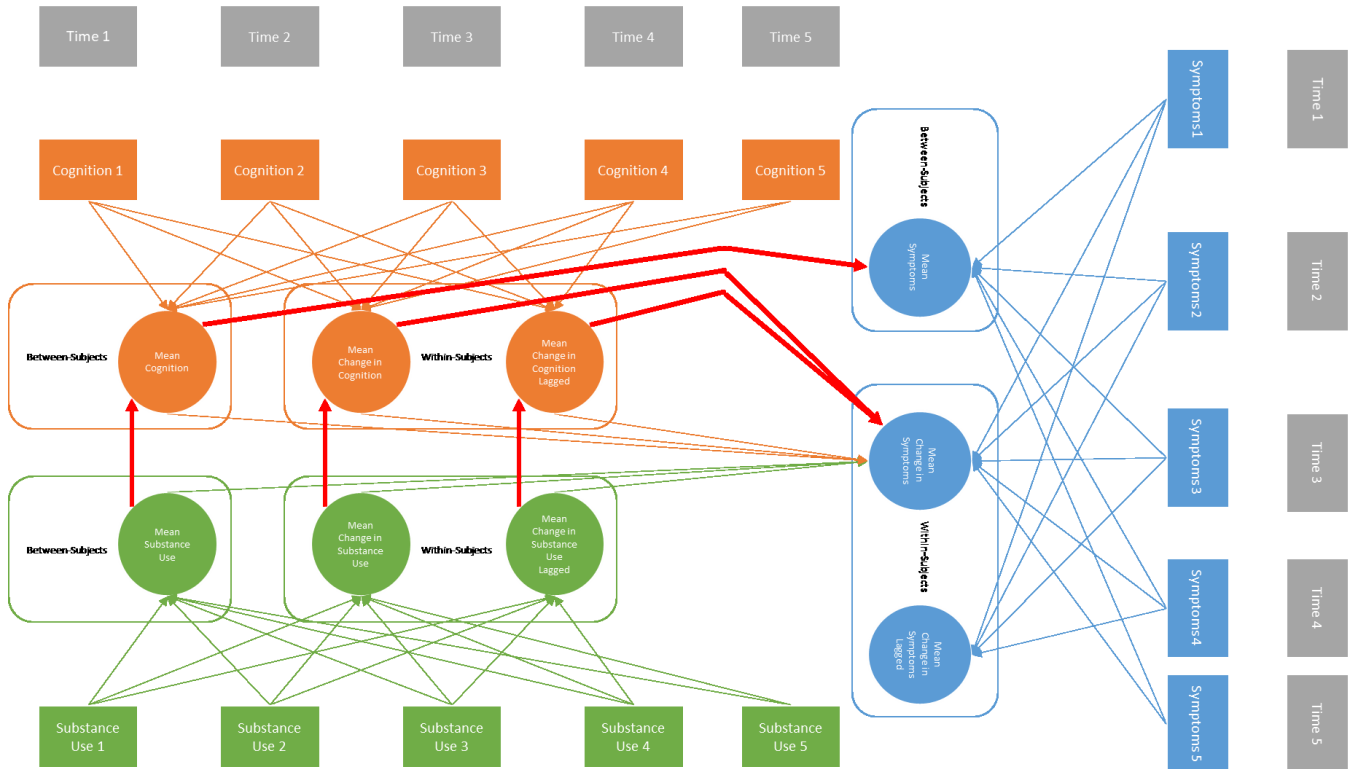
Note: This adapted form of the Random Effect - Cross-Lagged Panel Model (RE – CLPM) tests between-subject differences at one level and then various within-subject processes at a second level, allowing for the investigation of concurrent and time-lagged relationships between sets of variables. Cognitive performance (orange), substance use (green), and psychopathology symptoms (blue) were measured at five time-points (time 1 represents assessment in the 7th grade, time 2 in 8th grade, and so on). The first model proposes an underlying vulnerability factor that might contribute to average substance use and cognitive performance. This underlying vulnerability factor is stable over time (Between-Subject, lefthand-side boxes). Two within-subject effects (righthand-side box) reflect the average level of change from year to year for substance use and cognitive development. The level of change observed at a given year is captured by the within-subject effect, while the level of change observed in the previous year is captured by the within-subject lagged effect. The neurotoxicity model uses lagged effects to estimate how previous substance use, through its relation with cognitive impairment, relates to longer-term psychopathology symptoms. The pathoplastic model uses within-subject effects to estimate how substance use change in a given year, through its link with cognitive performance, relates to longer-term psychopathology symptoms. Pathoplastic models short-term effects. Indeed mechanisms of neuroplasticity, abstinence, or reduction in consumption are shown to allow cognitive performance to recover and psychopathology symptoms subside.

Investigation of the Relation Between Substance Use and Cognitive Performance and

its Mediating Effect on Psychopathology Symptoms

Chapter 1. A population-based analysis of the relationship between substance use and

adolescent cognitive development

par

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Title: **A population-based analysis of the relationship between substance use and adolescent cognitive development.**

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JFGM, MHA, and PC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract: 249 words

Background: Alcohol and cannabis misuse are related to impaired cognition. When inferring causality, four non-exclusive theoretical models can account for this association: 1) a common underlying vulnerability model, 2) a neuroplastic model in which impairment is concurrent with changes in substance use, including abstinence due to neuroplastic processes; 3) a neurotoxic model of long-term impairment consequential to substance use and 4) a developmental-sensitivity hypothesis of age-specific effects. Using a developmentally sensitive design, this study investigates relationships between year-to-year changes in substance use and cognitive development.

Methods: An population-based sample of 3826 7th Grade students from 31 schools consisting of 5% of all students entering high school from 2102-2013 in the Greater Montreal region were assessed on alcohol and cannabis use, recall memory, perceptual reasoning, inhibition, and working memory yearly for four years using school-based computerised assessment. Multilevel regression models performed separately for each substance simultaneously tested vulnerability (between-person), concurrent and lagged within-person effects on each cognitive domain.

Outcomes: Common vulnerability effects were detected for cannabis and alcohol on all domains. Cannabis use, but not alcohol consumption, showed lagged (neurotoxic) effects on inhibitory control, working memory and concurrent effects on delayed memory recall and perceptual reasoning (with some evidence of developmental sensitivity). Cannabis effects were independent of any alcohol effects.

Interpretation: Beyond the role of cognition in vulnerability to substance use, the concurrent and lasting effects of adolescent cannabis use can be observed on important

cognitive functions and appear to be more pronounced than those observed for alcohol.

Introduction:

Beyond their acute effects, alcohol and cannabis misuse have been associated with abnormal learning, decision making and cognitive functioning, as well as lower academic performance.[1] Meta-analyses link cannabis to poor cognition in a number of domains, namely learning, memory, attention and working memory,[2] regular and heavy alcohol use to poor verbal fluency, speed of processing, episodic and working memory, attention, executive functions, inhibition/impulsivity, and visuospatial abilities.[3] These effects have been shown in adults and adolescents.[2-8] Studies also suggest that some of these impairments persist (e.g., IQ, working memory, inhibition, etc.),[3,4] while others recover as consumption changes (e.g., processing speed, recall memory, attention, etc.).[3,5] Imaging studies with adolescent substance users also indicate smaller structural volumes[9] in brain regions responsible for these cognitive functions, such as the prefrontal cortex and left hippocampus. What has yet to be established in the literature is the extent to which such cognitive impairments represent underlying vulnerability to misuse substances or direct consequence of substance use or misuse.

The literature investigating the relationship between adolescent substance use and brain functions is mixed[3-8,12,13] and might depend on how childhood cognitive deficits that exist before the onset of substance use are accounted for in such analyses.[14,15] Few studies have investigated the relationship between cognitive functions and substance use repeatedly over time, and instead simply test pre-post differences in cognition at a given follow-up period. Even fewer studies have considered the continuum of substance use behaviour and tend to compare non-users to occasional or problematic users. It is important that new large-scale studies incorporate developmentally-sensitive designs that

model the impact of year-to-year changes in substance use on age-related changes in cognition.

In the absence of experimental designs, large-scale, longitudinal designs with multiple repeated assessments provide an opportunity to explore inferences about causality between two variables by examining how changes in one domain are related to changes in another repeatedly overtime. As depicted in Figure 7, computational models can test the extent to which changes in one behaviour lead to concurrent or lasting changes on the other (e.g., after increases in the substance use subside), but require large, prospective datasets. To our knowledge, very few such datasets have been available to dissociate the antecedent cognitive risk factors from the consequences of substance misuse on adolescent cognitive development from this perspective.

Insert Figure 7 here

Using this multi-variate, multi-level framework, the association between substance use and cognition can be investigated with respect to four theoretical hypotheses, also shown in Figure 7. Recognising that cognitive factors are also implicated in risk for early onset substance use,[16] we hypothesised that working memory and response inhibition (two executive functions of the frontal lobes) would be associated with overall risk for early onset and heavier substance use generally (vulnerability hypothesis). Consistent with previous research suggesting a relationship between adolescent binge drinking and cognitive functions,[7] we hypothesised that, further increases in alcohol consumption would predict impaired spatial working memory, recall memory, perceptual reasoning, and inhibition, above and beyond common vulnerability. The literature also suggests that effects of heavy alcohol consumption on memory recover over time,[3] suggesting common

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vulnerability and neuroplasticity hypotheses will be support for alcohol and memory functions.

The effects of cannabis use should also conform to a vulnerability hypothesis, particularly with respect to inhibitory function,[1] but additional cognitive consequences of adolescent cannabis use are hypothesised on measures memory function and general IQ, such as perceptual reasoning.[7,10] Considering results from animal studies showing that chronic administration of THC causes dose-dependent neurotoxic changes in brain regions that are rich in cannabinoid receptors, such as hippocampus, amygdala, septum and cortex,[16] and that abnormalities in hippocampal and temporal structures seem particularly linked to human cannabis use,[17] we hypothesised that additional visual-spatial memory deficits will be consequential to cannabis use in adolescence, where both neuroplastic and neurotoxic models are considered, as the literature relating to the degree to which these effects last beyond the consumption period in humans remains inconclusive . A fourth model will also be tested, the developmental sensitivity model, informed by current neurodevelopmental theories,[18] suggesting cognitive functions linked to prefrontal cortex (executive cognitive functions, such as working memory, response inhibition and perceptual reasoning) should show age-dependent effects, with earlier onset use being linked to greater impairment.

Using data from a large, longitudinal study of adolescents assessed repeatedly on substance use and cognitive functions through the critical developmental period when substance use onset and brain maturation overlap, the current study represents a unique opportunity to study the effects of cannabis and alcohol on various cognitive domains with enough power to model the complex nature of these relationships. Results from this

highly conservative analysis might help guide drug policy around the need for investment into evidence-based preventive interventions, which currently represents the smallest of all costs attributed to substance use in Western society.[19]

Methods

Participants

This study utilises data from the Co-Venture Trial,[20] a longitudinal, population-based, randomised-controlled trial assessing the five-year efficacy of a personality-targeted drug and alcohol prevention programme, named Preventure. A total of 3826 grade seven participants (47% female, mean age = 12.7 [SD = 0.5] years, 58% of European origin) were recruited from 31 schools in the Montreal area. This school sample of adolescents studied annually from grade 7 until grade 11 is epidemiologically representative of each of its respective school districts with respect to average size and socioeconomic index. The sample of participating schools represents 15% of all schools across all school districts of the greater Montreal area. The study sampled on average 76% of all grade 7 students across schools, suggesting that the cohort included 6.0%-11.4% of the entire population of 7th grade students of the Greater Montreal Area in 2012 and 2013. Only two school-level exclusion criteria were specified: 1) the school must agree to study protocol, including randomisation and 5-year school-based follow-up, and 2) the school could not have more than 50% of year 7 students having official educational codes that indicate special learning needs. Participating schools were randomly assigned to 1) deliver the Preventure programme to grade seven high-risk adolescents, or 2) deliver the programme to subsequent grade seven cohorts 3 years later. There were no exclusion criteria specified for students, other than being able to provide informed assent and

parental consent. All participating grade seven students in September 2012 or 2013 completed a confidential annual web-based survey during class time (from grade seven to grade ten) to assess cognition and substance use. Confidentiality was assured by emphasizing parents and teachers would not have access to survey results and by automatically anonymizing assessments. Ethical approval was obtained from Sainte-Justine's Hospital Ethics Committee in Montreal. Depending on the school, either passive or active parental consent was obtained.

Quality and reliability of the data were evaluated using automated algorithms assessing valid response ranges on cognitive tasks and a sham drug item on substance use self-reports. All participants who consented to the study were included in the analysis if 75% of their data across all items and assessment points was considered complete and reliable. Among the 3826 adolescents who consented to participate, 3659 (95.6%) passed the data quality control requirements while also providing the required minimal demographic information (sex and socioeconomic status [SES]). Attrition was not predicted by any covariates (sex, $p=0.431$; SES, $p=0.876$). While the intervention delivered in this trial is expected to impact substance use behaviour, there is no reason to expect that the intervention will impact how substance use behaviour will subsequently affect cognitive functions, so all participants, regardless of intervention exposure were included in the analysis.

Predictors
Alcohol and cannabis use were assessed using the 'Detection of alcohol and drug problems in adolescents' questionnaire (DEP-ADO).[21] Once a year, for four consecutive years, participants rated their consumption frequency for each named substance on a six-

point scale (0=Never, 5=Every day) and, for alcohol specifically, provided the typical number of drinks consumed when they take alcohol. No quantity measure was gathered for cannabis, as cannabis quantity assessment remains a challenge in the field.[22] Three variables were extracted at each time point: 1) alcohol use frequency, 2) typical alcohol intake quantity in a typical drinking occasion, and 3) cannabis use frequency. Alcohol consumption frequency and quantity were multiplied at each time point to create a Quantity/Frequency variable for each four years of measure. This variable is sensitive to differences in dose and frequency of consumption, thereby distinguishing frequent light drinkers from frequent heavy drinkers.[23] When self-report measures are used in a context that guarantees confidentiality, they are considered more accurate than collateral reports or biologic measures of adolescent substance use because they are better at capturing the episodic and illicit nature of adolescent substance use.[24,25] All participants in this study agreed that parents and school staff would not have access to self-report information unless such information indicated imminent risk of harm. Consumption distributions are represented in Table 1.

Insert Table 1 here

Outcomes
All tasks are described in more detail in the study protocol.[20] Spatial Working Memory (SWM) was measured with the 'Find the Phone' task, based on the Self-Order Pointing Task[26] and the SWM subtest in the Cambridge Neuropsychological Test Automated Battery (CANTAB). Delayed Recall Memory was assessed with a computerised task based on the Dot Location test of the Child Memory Scales (CMS).[27] Participants are asked to reproduce a previously learned pattern of stimuli 30 minutes later. Perceptual

Reasoning was assessed using a selection of items from the Cattell's Culture-Fair Test. Participants completed a sequence of puzzles progressively increasing in difficulty. This 9-item task correlates highly with the 60-item Raven's Perceptual Reasoning Matrices.[28]

Inhibitory Control was measured using the Passive Avoidance Learning Paradigm (PALP).[29,30] Participants learn, by trial and error, to respond to "good" numbers and to withhold responses to "bad" numbers by experiencing rewards to correct press/omissions and punishments to incorrect presses/omissions. This strategy has been used in the past and is correlated with other measures of inhibition, and with prefrontal cortical activation during other go-no-go tasks.[31]

Covariates
Baseline SES was controlled using the Family Affluence Scale for Adolescents.[32] Analyses also controlled for self-reported gender. Additional confounding variables were investigated in sensitivity analyses, including ethnicity (assessed based on country of origin of the child and parents), and family intactness (living with both biologic parents (69% of the sample), or not).

Analyses
Multilevel Linear Modelling (MLM) assessed the influence of cannabis (frequency) and alcohol (quantity × frequency) consumption on four domains of cognition. Three MLM were conducted: one for cannabis, one for alcohol and a combined model. Time parameter was coded as wave. Predictors were person-mean centered. Normality and homoscedasticity of residuals were examined for each step of the models. For all MLM's, the first model, estimated the Intercept and Time parameter and evaluated the contribution of three predictors: average use over four years (between-subject differences in consumption), change in use this year compared to person's mean (within-subject

difference in consumption), and substance use the year before compared to person's mean (lagged within-subject difference in consumption). A final model, employed for the substance specific models, added interaction parameters: interaction of time by average use over four years, interaction of time by change in use this year compared to person's mean, and interaction of time by substance use the year before compared to person's mean. Effects of between-person differences were interpreted as a common vulnerability between consumption and poor neurocognitive performance. Within-person effects (increased consumption that year) were interpreted as pathoplastic effects, while time-lagged within-person effects (consumption last year) were interpreted as neurotoxic effects. The most parsimonious of three iterative steps for each analysis was identified using likelihood ratio test. Only effects revealed to be significant in the most parsimonious model were interpreted.

Missing data on the main variables were handled through Full Information Maximum Likelihood (FIML). School was included as a cluster-level variable. As a sensitivity analysis, and to ensure the robustness of our results, all models were re-estimated excluding users at the first year to focus only on those who started using later.

The *ICC* function from *psych* package in R statistical environment was used to estimate the within person stability of cognitive data over time. and revealed ICCs of 0.74 for working memory, 0.80 for perceptual reasoning, 0.58 for delayed memory recall, and 0.68 for response inhibition.

Results

Cannabis: Table 2 presents cannabis results. The first model indicated that average frequency of cannabis use over four years (between-subject differences) predicted lower performance on working memory (β=0.51, S.E.=0.25, p=0.04), perceptual reasoning (β=-.25, S.E.=0.08, p=0.001), and inhibition (β=1.19, S.E.=0.48, p<0.01) over that same time period. Over and above the significant between-person effects, a significant within-person effect showed that any further increase in cannabis use frequency was associated with impairment in delayed recall memory in that same year (β=-0.14, S.E.=0.05, p<0.01). A significant within-person lagged effect revealed that any further increases in cannabis use frequency predicted further impairment on the inhibition task one year later (β=1.05, S.E.=0.41, p=0.01). Similar, yet marginal, cannabis lagged effects were revealed for working memory (β=0.36, S.E.=0.19, p=0.06).

Including interactions with time only improved model fit for the perceptual reasoning model, and revealed a time by between-person interaction, suggesting stronger within-person, or concurrent, differences (β=-0.66, S.E.=0.22, p=0.003) in early adolescence than late adolescence (β=0.16, S.E.=0.07, p=0.01). Sensitivity analysis focusing on drug and alcohol naïve participants at Time 1 showed the same pattern of results.

Insert Tables 2-4 here

Alcohol: Table 3 presents alcohol results. The first model indicated average frequency × quantity of alcohol consumption over four years was related to lower spatial working memory performance (β=0.09, S.E.=0.05, p<0.05), lower perceptual reasoning scores (β=-0.06, S.E.=0.02, p<0.01) and more errors on inhibitory control task (β=0.27, S.E.=0.09, p<0.01) over the same time period, which is consistent with a common vulnerability hypothesis between these cognitive domains and alcohol use. No within-

subject alcohol effects reached significance for any of the cognitive domains studied. As the model including time interactions did not significantly improve model fit, no interaction terms are interpreted.

Combined Alcohol-Cannabis Model: Table 4 presents an integrated model accounting for the effect of alcohol and cannabis simultaneously. Specific between-group effects were revealed for alcohol and perceptual reasoning (β=-0.04, S.E.=0.02, *p*=0.03). No within-person effects of alcohol were detected in the combined model. Specific between-group effects were also revealed for cannabis and inhibitory control (β=1.48, S.E.=0.57, *p*<0.01). Lagged within-person effects showed that cannabis use frequency in a given year further predicted lower performance on the inhibitory control task a year later (β=1.18, S.E.=0.44, *p*<0.01) and marginally predicted working memory performance a year later (β=0.36, S.E.=0.21, *p*<0.09), over and above changes in alcohol consumption. Increases in cannabis use frequency in a given year were also related to lower score on the delayed recall memory task in that same year (β=-0.13, S.E.=0.05, *p*=0.01).

Discussion

Vulnerability model
Cannabis and alcohol models yielded evidence in favour of common vulnerability: individuals more likely to use cannabis showed lower working memory, perceptual reasoning, and inhibitory control and individuals prone to heavier alcohol consumption showed working memory, perceptual reasoning, and inhibitory control impairments. These findings are in line with previous research.[1,3,15,29] In the combined model, our results suggest that the common vulnerability between working memory and cannabis was not significant above and beyond alcohol use and vice versa, suggesting that poor

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working memory could constitute a non-specific common vulnerability to substance misuse in adolescence.[3,15] Novel findings were those suggesting a common vulnerability process that is specific to low perceptual reasoning and alcohol consumption, and a common vulnerability that is specific to cannabis and poor inhibitory control.

Neuroplasticity Hypothesis
Our results suggest neuroplastic (concurrent) effects of cannabis and, contrary to hypotheses, did not reveal such effects for alcohol. Over and above the effect of being a user of cannabis across adolescence, when increases in cannabis use frequency were observed in a given year, reductions in delayed recall memory and perceptual reasoning were observed in that same year, and these effects were independent of any changes in alcohol quantity/frequency. The transient effects of cannabis on episodic memory have been reported in animal and human studies[33] investigating long-term cognitive outcomes of cannabis exposed subjects who later achieved abstinence.[4] The ability to encode and retrieve memories are regulated by the circuitry of the medial-temporal lobe, including the hippocampus, and which is rich in endocannabinoid receptors.[16]

Neurotoxicity Hypothesis
Findings were also consistent with a lasting or neurotoxic effect of cannabis on two domains of cognition: inhibitory control and working memory. This study showed that cannabis use in a given year was associated with impaired inhibitory control and working memory one year later, over and above any common vulernability. As reviewed by Volkow et al.,[2] two meta-analyses summarising case-control studies comparing users, non-users, and former users, suggest small but broad effects of cannabis on cognitive functioning. Moreover, a longitudinal analysis of adolescent cannabis users reported longterm effects of early onset and persistent cannabis use on measures of executive

functioning, verbal IQ, and decision-making.[10] Functional imaging studies have also shown that adolescent cannabis users show abnormal prefrontal cortex activation during a working memory task and altered patterns of functional connectivity in frontotemporal networks.[7] Working memory and response inhibition critically involve a network linking the prefrontal cortext to the posterior parietal cortex and the striatum and animals studies indicate that the acute effects of cannabis on working memory are mediated through CB1 receptors in the prefrontal cortex and hippocampus.[34] Considering that at least one experimental study with animals failed to demonstrate lasting working memory impairments following adolescent exposure to cannabis[33] and the fact that our analyses revealed marginal lagged effects for working memory, it will be important to further explore the nature of the long-term relationship between cannabis and working memory. One possiblity worth exploring with available human data is whether these mild effects on working memory might be secondary to the effects of cannabis on other cognitive processes.

In the current study, relationships between adolescent cannabis use and response inhibition were robust and consistent with both common vulnerability and neurotoxicity hypotheses. Youth and adults with heavy substance use patterns have been shown to differ from their age and sex-matched controls on cognitive, behavioural and neural measures of disinhibition.[14,15] Longitudinal studies also confirm that some differences exist prior to onset of substance use.[29] Our results suggest that poor response inhibition is both implicated in vulnerability to early-onset cannabis use specifically (between-person effects) and consequential to increases in cannabis use. The novel findings resulting from this study are that changes in response inhibition following onset of cannabis use appear

to be specific to cannabis and long-lasting. These lasting neurotoxic effects could explain why early-onset substance use is so critically involved in future risk for addiction, as poor response inhibition and it's neural correlates have been consistently identified as key risk factors for substance use initiation and maintenance.[31,35]

Developmental Sensitivity

To investigate whether exposure to substances at earlier ages was associated with more severe impairment, we examined the interaction between each of these potential effects and the quadratic effect of time and did not find evidence of developmental sensitivity on three of the four cognitive domains. By contrast, as illustrated in Figure 8, the between and concurrent relationships between cannabis and perceptional reasoning were more pronounced at earlier stages of adolescent development, indicating that early onset users are more impaired on perceptual reasoning and the additional effect of their cannabis use in a given year is particularly harmful to their perceptual reasoning abilities during the early adolescent period.

Relevance

The results of this highly conservative and sensitive analysis demonstrate that cannabis is associated with more concurrent and long term consequences on cognitive functions than alcohol, even when accounting for the effects of both substances within a single model and any potential underlying common vulnerability to all sets of problems. While previous twin studies [40] examined effects of cannabis on general IQ and only found evidence in favour of a common vulnerability hypothesis, our study was uniquely designed and powered to test year-by-year changes in cognition and substance use, and

was likely more sensitive to within-person processes. Levels of cannabis use in this sample were low and infrequent (although 76 daily cannabis users were detected at time 4), but analyses nevertheless detected cognitive changes that were consequential to small increases in cannabis use. No such effects were detected for alcohol. It will be important to conduct similar analyses with this cohort or similar cohorts as they transition to young adulthood when alcohol and cannabis use become more severe. This might be particularly relevant for alcohol effects: while the acute effects of alcohol on response inhibition, working memory and episodic memory are clearly established, the neurotoxic effects on working memory might only be observable following binge drinking,[36] in female drinkers,[37] or in older drinking populations.[38]

Limitations

Quantity or dose of cannabis exposure could not be assessed in this study, which is not unique to the current sample.[22] It is expected that as legal and regulated cannabis markets emerge in North America, youth will eventually be able to refer to their consumption in terms of standard units in the way that alcohol quantity was assessed in the current study. Furthermore, while all assessments of cognitive function took place in school classroom setting under close supervision by research staff, which speaks to the ecological validity of the cognitive data collected, it would be important to link these results to standardised high school leaving exam scores and other meaningful academic outcomes as this cohort transitions to young adulthood.

In summary, this study uniquely contributes to an emerging literature on neurocognitive consequences of alcohol and cannabis by investigating this question in a population-based sample, and while accounting for multi-level effects. In a context where policies

and attitudes regarding substance use are being reconsidered, this research might

contribute by highlighting the importance of protecting youth from adverse effects of

consumption, particularly those substances that appear to have effects consistent with the

neurotoxic hypothesis.[39]

Figure 7. Neurotoxicity and Neuroplastic Models
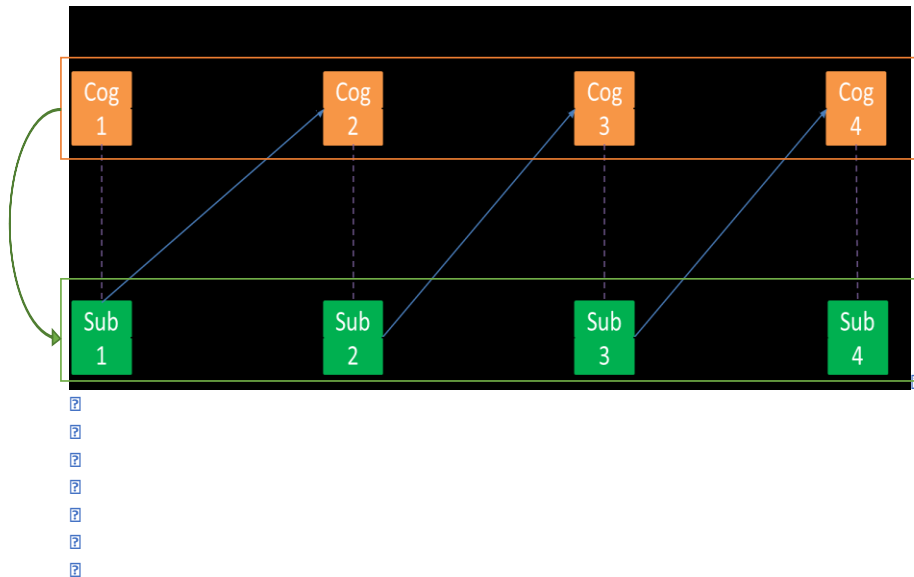
Multi-level modeling of causality: This multi-level computational method tests between-person differences at one level and then various within-person processes at a second level, allowing for the investigation of concurrent and time-lagged relationships between sets of variables. Cognitive performance (Cog) and substance use (Sub) measured at four time points. The first hypothesis proposes an underlying cognitive *vulnerability* that might contribute to early onset substance use and the likelihood of continued and heavy use over time (green arrow).[21,22] Three within-person effects reflect processes that are consequential to substance use: the *neurotoxicity* hypothesis stipulates that past substance use causes impairment in cognitive function in some lasting way, regardless of whether the substance use continue (blue arrow); [17] the *neuroplasticity* hypothesis suggests that consumption is associated with impaired cognitive performance, but only in the short term and that through mechanisms of neuroplasticity, abstinence, or reduction in consumption the cognitive impairment subsides (hashed lines); and finally, *developmental sensitivity* hypothesis, where substance use at a critical period in development will lead to neurotoxicity, depending on neuro-maturational state of the particular brain region (larger neurotoxicity or neuroplasticity effects at earlier times than later times).

Table 1**. Frequency Distribution for Substance Use Variables**

Frequency	Never	Occasionally	Once a Month	Once or Twice a Week	Three Times or More Per Week	Every Day
Cannabis Use Frequency on Year 1	95.41%	2.76%	0.71%	0.45%	0.32%	0.37%
Cannabis Use Frequency on Year 2	90.20%	6.27%	1.50%	1.12%	0.53%	0.38%
Cannabis Use Frequency on Year 3	80.09%	12.29%	2.20%	2.95%	1.17%	1.30%
Cannabis Use Frequency on Year 4	71.19%	17.91%	3.62%	3.47%	1.81%	2.00%
Alcohol Use Frequency on Year 1	63.56%	31.77%	2.97%	1.39%	0.18%	0.13%
Alcohol Use Frequency on Year 2	48.66%	41.62%	7.18%	2.21%	0.24%	0.10%
Alcohol Use Frequency on Year 3	35.86%	46.04%	11.67%	6.06%	0.23%	0.13%
Alcohol Use Frequency on Year 4	23.87%	44.61%	18.89%	11.73%	0.60%	0.30%
Number of Drinks on Drinking Occasion	**0**	**1 to 2**	**3 to 5**	**5 to 8**	**More than 8**	
Alcohol Use Quantity on Year 1	85.37%	11.58%	1.81%	0.81%	0.44%	
Alcohol Use Quantity on Year 2	74.97%	18.67%	3.55%	2.15%	0.66%	
Alcohol Use Quantity on Year 3	65.44%	21.51%	7.22%	4.33%	1.49%	
Alcohol Use Quantity on Year 4	59.33%	19.75%	10.51%	8.68%	1.74%	

Note: Alcohol use quantity variables were categorised for presentation purposes. Alcohol use quantity was used as a continuous variable in the analyses.

Table 2. Estimated Parameters for all Cannabis Models.

	Predictors	Working Memory			Perceptual Reasoning			Delayed Recall Memory			Inhibitory Control		
		Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)
Model 1	Intercept	22.210	1.411	0.000	14.814	0.396	0.000	17.516	0.376	0.000	38.422	2.940	0.000
	Time	-6.745	0.947	0.000	1.196	0.263	0.000	-9.440	0.261	0.000	-8.972	1.995	0.000
	$I(Time^2)$	0.802	0.159	0.000	-0.089	0.044	0.042	1.976	0.044	0.000	0.862	0.333	0.010
	Socio-Economic Status	0.124	0.079	0.118	-0.041	0.025	0.097	-0.017	0.016	0.277	0.286	0.151	0.058
	Gender	1.843	0.266	0.000	0.311	0.084	0.000	0.051	0.054	0.341	0.440	0.509	0.387
	Cannabis Between-Subjects	**0.505**	**0.246**	**0.040**	-0.251	0.077	0.001	-0.044	0.057	0.443	**1.912**	**0.482**	**0.000**
	Cannabis Within-Subjects	0.022	0.166	0.894	-0.084	0.045	0.064	**-0.140**	**0.048**	**0.004**	0.420	0.352	0.232
	Cannabis Within-Subjects (Lagged)	**0.361**	**0.192**	**0.061**	0.076	0.053	0.151	0.004	0.057	0.948	**1.045**	**0.411**	**0.011**
Model 2	Intercept	22.104	1.494	0.000	14.729	0.420	0.000	17.485	0.399	0.000	39.075	3.104	0.000
	Time	-6.706	1.010	0.000	1.276	0.281	0.000	-9.415	0.278	0.000	-9.517	2.119	0.000
	$I(Time^2)$	0.802	0.169	0.000	-0.107	0.047	0.023	1.971	0.047	0.000	0.969	0.354	0.006
	Socio-Economic Status	0.122	0.079	0.124	-0.040	0.025	0.109	-0.017	0.016	0.290	0.281	0.151	0.063
	Gender	1.863	0.267	0.000	0.297	0.084	0.000	0.048	0.054	0.372	0.499	0.510	0.328
	Cannabis Between-Subjects	1.426	0.854	0.095	**-0.789**	**0.231**	**0.001**	-0.027	0.225	0.906	3.904	1.727	0.024
	Cannabis Within-Subjects	0.576	0.785	0.463	**-0.661**	**0.221**	**0.003**	-0.323	0.194	0.096	3.660	1.665	0.028
	Cannabis Within-Subjects (Lagged)	0.191	0.950	0.841	0.084	0.266	0.754	0.107	0.234	0.648	0.712	2.082	0.732
	Time*Cannabis Between-Subjects	-0.315	0.265	0.235	**0.177**	**0.072**	**0.014**	-0.006	0.084	0.944	-0.639	0.543	0.240
	Time*Cannabis Within-Subjects	-0.126	0.249	0.612	**0.159**	**0.071**	**0.025**	0.061	0.067	0.360	-0.927	0.529	0.080
	Time*Cannabis Within-Subjects (Lagged)	0.124	0.298	0.676	-0.046	0.084	0.584	-0.038	0.080	0.632	0.265	0.647	0.682

Note: Significant effects are marked in **bold** character. Performance on Working Memory and Inhibitory Control task was measured by counting number of errors; a lower score indicates a better performance.

Table 3. Estimated Parameters for all Alcohol Models.

	Predictors	Working Memory			Perceptual Reasoning			Delayed Recall Memory			Inhibitory Control		
		Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)
Model 1	Intercept	22.214	1.414	0.000	14.905	0.396	0.000	17.585	0.376	0.000	38.303	2.945	0.000
	Time	-6.797	0.952	0.000	1.104	0.264	0.000	-9.477	0.261	0.000	-8.905	2.003	0.000
	$I(Time^2)$	0.814	0.160	0.000	-0.071	0.044	0.108	1.980	0.044	0.000	0.871	0.335	0.009
	Socio-Economic Status	0.124	0.080	0.121	-0.035	0.025	0.162	-0.019	0.016	0.245	0.243	0.153	0.113
	Gender	1.834	0.267	0.000	0.313	0.084	0.000	0.058	0.054	0.280	0.400	0.511	0.434
	Alcohol Between-Subjects	**0.094**	**0.047**	**0.048**	**-0.057**	**0.015**	**0.000**	-0.010	0.011	0.352	**0.273**	**0.093**	**0.003**
	Alcohol Within-Subjects	-0.002	0.026	0.936	-0.010	0.007	0.143	0.000	0.008	0.985	0.063	0.056	0.265
	Alcohol Within-Subjects (Lagged)	0.031	0.035	0.375	-0.005	0.010	0.568	-0.013	0.010	0.188	-0.019	0.071	0.789
Model 2	Intercept	22.359	1.553	0.000	14.878	0.436	0.000	17.547	0.415	0.000	38.329	3.227	0.000
	Time	-6.914	1.052	0.000	1.146	0.293	0.000	-9.438	0.289	0.000	-8.989	2.208	0.000
	$I(Time^2)$	0.836	0.176	0.000	-0.082	0.049	0.094	1.971	0.049	0.000	0.893	0.369	0.015
	Socio-Economic Status	0.124	0.080	0.121	-0.035	0.025	0.162	-0.018	0.016	0.253	0.251	0.153	0.102
	Gender	1.840	0.267	0.000	0.308	0.084	0.000	0.053	0.054	0.326	0.435	0.511	0.395
	Alcohol Between-Subjects	0.123	0.164	0.453	-0.148	0.046	0.001	-0.019	0.042	0.649	0.101	0.339	0.767
	Alcohol Within-Subjects	0.067	0.130	0.607	-0.060	0.037	0.103	-0.062	0.032	0.051	0.532	0.286	0.062
	Alcohol Within-Subjects (Lagged)	0.024	0.172	0.890	-0.028	0.049	0.563	0.035	0.040	0.385	-0.703	0.374	0.060
	Time* Alcoho Between-Subjects	-0.008	0.051	0.872	0.029	0.014	0.039	0.004	0.016	0.820	0.035	0.106	0.738
	Time*Alcohol Within-Subjects	-0.020	0.040	0.619	0.012	0.011	0.297	0.019	0.011	0.073	-0.129	0.088	0.141
	Time*Alcohol Within-Subjects (Lagged)	0.004	0.052	0.937	0.002	0.015	0.898	-0.018	0.013	0.183	0.212	0.113	0.061

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Note: Significant effects are marked in **bold** character. Performance on Working Memory and Inhibitory Control task was measured by counting number of errors; a lower score indicates a better performance.

Table 4. Estimated Parameters for Combined Models.

Predictors	Working Memory			Perceptual Reasoning			Delayed Recall Memory			Inhibitory Control		
	Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)
Intercept	22.201	1.418	0.000	14.892	0.397	0.000	17.532	0.377	0.000	38.509	2.843	0.000
Time	-6.792	0.953	0.000	1.131	0.264	0.000	-9.449	0.262	0.000	-8.931	1.913	0.000
I(Time^2)	0.809	0.160	0.000	-0.076	0.044	0.087	1.977	0.044	0.000	0.847	0.320	0.008
Socio-Economic Status	0.128	0.080	0.111	-0.037	0.025	0.146	-0.018	0.016	0.270	0.241	0.153	0.115
Gender	1.840	0.267	0.000	0.314	0.084	0.000	0.053	0.054	0.328	0.458	0.509	0.368
Alcohol Between-Subjects	0.051	0.056	0.355	**-0.039**	**0.017**	**0.026**	-0.008	0.013	0.551	0.126	0.109	0.246
Alcohol Within-Subjects	-0.008	0.027	0.760	-0.008	0.008	0.277	0.006	0.008	0.469	0.017	0.060	0.773
Alcohol Within-Subjects (Lagged)	0.006	0.037	0.862	-0.008	0.010	0.457	-0.010	0.011	0.364	-0.098	0.077	0.200
Cannabis Between-Subjects	0.451	0.294	0.125	-0.153	0.092	0.094	-0.012	0.067	0.863	**1.482**	**0.567**	**0.009**
Cannabis Within-Subjects	0.044	0.180	0.805	-0.081	0.049	0.099	**-0.132**	**0.052**	**0.010**	0.527	0.380	0.165
Cannabis Within-Subjects (Lagged)	**0.357**	**0.207**	**0.085**	0.098	0.057	0.085	0.001	0.060	0.986	**1.181**	**0.443**	**0.008**

Note: Significant effects are marked in **bold** character. Performance on Working Memory and Inhibitory Control task was measured by counting number of errors; a lower score indicates a better performance. In the context of sensitivity analysis, Models were re-estimated with ethnicity and family intactness as covariates. Results did not indicate any changes in the pattern of significant associations (presented in supplemental materials).

Table 5. Supplementary Sensitivity Analysis including Family Intactness and Ethnicity as Covariates.

	WM			IQ			DLR			INH		
	Estimate	Std. Error	Pr(>|t|)	Estimate	Std. Error	Pr(>|t|)	Estimate	Std. Error	Pr(>|t|)	Estimate	Std. Error	Pr(>|t|)
$I(TIME^2)$	0.807	0.160	0.000	-0.075	0.044	0.090	1.975	0.044	0.000	0.840	0.320	0.009
Socio-Economic Status	0.175	0.081	0.031	-0.046	0.025	0.072	-0.033	0.016	0.040	0.339	0.154	0.028
Gender	1.872	0.267	0.000	0.302	0.084	0.000	0.050	0.054	0.354	0.469	0.508	0.355
Non-European	1.304	0.298	0.000	-0.303	0.094	0.001	-0.398	0.060	0.000	2.290	0.569	0.000
Family Intactness	-0.435	0.299	0.146	0.272	0.094	0.004	-0.003	0.060	0.962	0.407	0.574	0.478
Alcohol Between-Subjects	0.082	0.056	0.142	**-0.045**	**0.017**	**0.010**	-0.016	0.013	0.204	0.184	0.110	0.094
Alcohol Within-Subjects	-0.008	0.027	0.771	-0.008	0.008	0.277	0.007	0.008	0.373	0.021	0.060	0.722
Alcohol Within-Subjects (Lagged)	0.004	0.037	0.921	-0.007	0.010	0.489	-0.007	0.011	0.488	-0.107	0.077	0.164
Cannabis Between-Subjects	0.418	0.296	0.157	-0.126	0.092	0.173	-0.021	0.067	0.748	**1.593**	**0.571**	**0.005**
Cannabis Within-Subjects	0.050	0.180	0.779	-0.082	0.049	0.095	**-0.136**	**0.052**	**0.008**	0.534	0.379	0.159
Cannabis Within-Subjects (Lagged)	0.358	0.207	0.085	0.099	0.057	0.083	0.000	0.060	0.995	**1.182**	**0.443**	**0.008**

Figure 8. Between-Subject and Within-Subject (Concurrent and Lagged) Relationships Between Cannabis Use Frequency and Working Memory Errors, Perceptual Reasoning Performance, Delayed Memory Recall Performance, and Inhibitory Control Errors
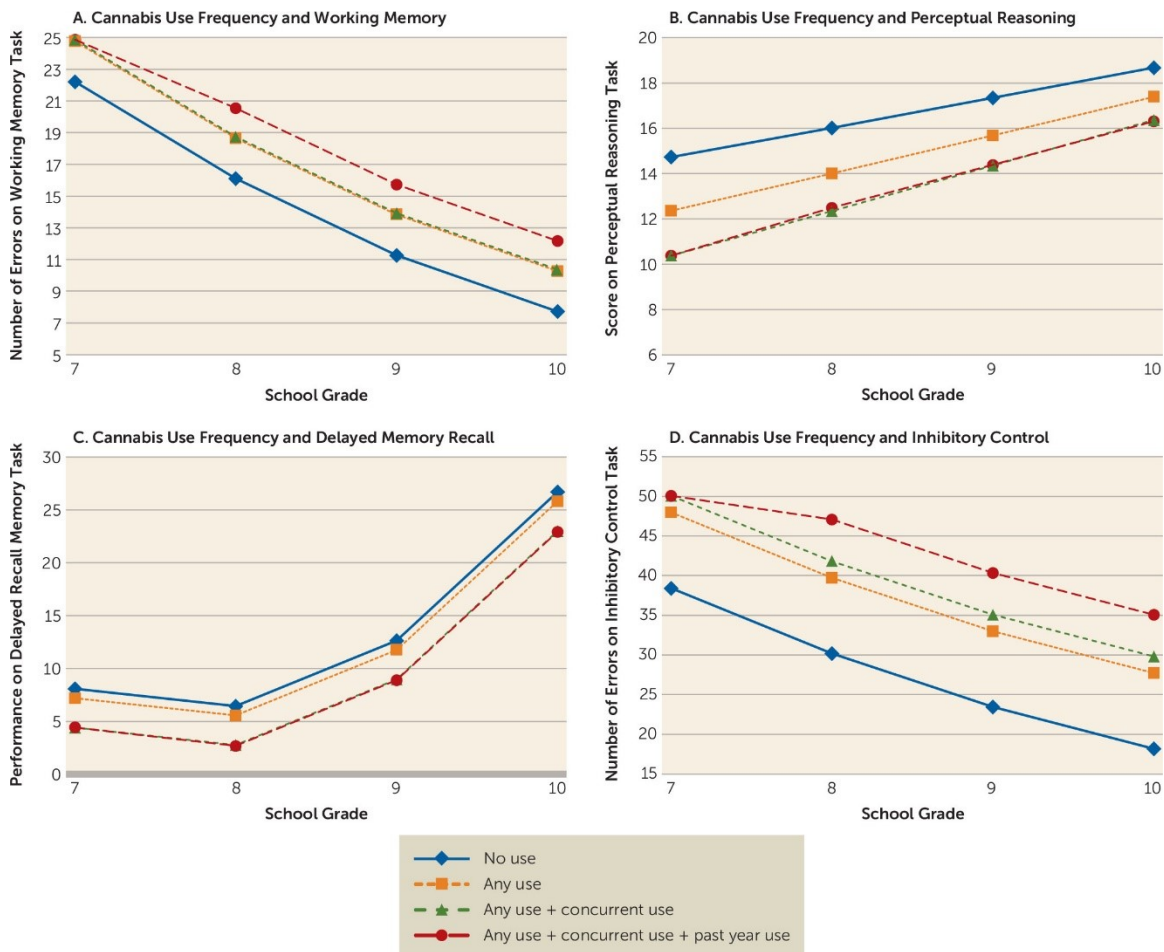
Note: Lagged effects were calculated starting in 8th grade. For working memory, performance was measured by counting the number of times a previously chosen stimulus was selected on a given trial (i.e., spatial working memory errors); lower scores indicate better performance. For perceptual reasoning and delayed memory recall, performance was calculated as a score, with higher scores indicating better performance. For inhibitory control, performance was measured by counting the number of commission errors across both conditions of the task; lower scores indicate better performance.

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Investigation of the Relation Between Substance Use and Cognitive Performance and its

Mediating Effect on Psychopathology Symptoms

Commentary on Chapter 1

par

Jean-François G. Morin

3.1. Commentary on Chapter 1

Due to space limitations imposed in published reviews, some information had to be left out of the original manuscript presented in chapter 1. As a complement to readers, we would like to bring clarifications about the sample under investigation, the analytical strategy employed, effect sizes of reported results and the specificity of the cannabis results.

Related to the sample used in chapter 1, ethnicity was estimated using parents' country of origin. European origins reflect caucasian ethnicity in this study. Also, though this research refers to gender, the variable truly measured is biological sex, which is more consequential to the neurobiological and cognitive processes we are investigating.

In the analyses section of chapter 1, we presented an abbreviated form of the analytical strategy and the figures shown reflected the theoretical model rather than the actual complexity of the analyses performed. For more information on this chapter's analytical strategy, the full methodology section provides detailed figures and explanations.

The study mostly reports on the significance of the effects It is true that this large sample allowed us to detect small effects of substance use as it relates to the developing brain, which indicates that cognitive performance and substance use are already associated. Complementary data presented in appendix 3 also show that the effect sizes of the results are well below the threshold for small effects, which indicates that such effects are not being readily noticeable without proper tools. Noticing those very small effects could prove relevant if one is to understand and avoid greater impairments that one can observe in the adult clinical population (Stavro, Pelletier & Potvin, 2012). On the topic of Cohen's f^2,

despite providing information on the association of substance use with cognitive domains, the specific quantity of effects at each level is not captured by Cohen's f^2. This methodological choice was in part driven by the absence of consensus for reporting effect sizes in multi-level models, namely, to quantify how important a between or a within-level effect is (Lorah, 2018). This also makes it difficult to calculate the between-subject level of variance explained in the models, which makes it difficult to estimate the size of the common vulnerability factor that seems significant when looking at the data. We hope this estimation provides some light to the importance of the effects presented.

Though this study reports on specific effects of cannabis, it is important to note that adolescents who report cannabis use overwhelmingly report using alcohol as well[5]. Though cannabis' role in this association is significant, combined effects of alcohol and cannabis are to consider.

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[5] For added information on the overlap between cannabis use and alcohol use in the sample, refer to Appendix 2.

Investigation of the Relation Between Substance Use and Cognitive Performance and

its Mediating Effect on Psychopathology Symptoms

Chapter 2. Cognitive Performace Mediates the Relationship Between Cannabis Use and

Psychopathology Symptoms in Adolescents: A Longitudinal, Multi-Level Analysis.

par

Jean-François G. Morin

This previous publication shows that cannabis use, over and above alcohol use, can be linked to adolescents' brain development, most notably in the domain of inhibitory control. This association gives further credit to the hypothesis that long-term cognitive impairment resulting from substance misuse, such as cannabis, could play a role in the onset of comorbid psychopathology.

A lot of emerging research is associating child and adolescent psychopathology to lower cognitive performance, as measured on a variety of psychometric tasks, and as observed behaviourally through academic performance and educational perseverance. The question remains: does cannabis, through its association with the developing brain, is further linked to the apparition of psychopathology symptoms?

This next chapter of the present dissertation offers a unique opportunity to explore this relation. In fact, under the current standards of empirical research, to infer causality within this context, one would have to conduct a randomized-controlled experimental design, which would put vulnerable minors in jeopardy. To avoid those ethical perils while still contributing to time sequence inference, a natural experimental design can permit us to observe distinctions within a sample of youth naturally using or abstaining to use cannabis.

This kind of investigation not only contributes to further our understanding of the effect of substance use on the developing brain but also contributes to our understanding of psychopathology at large and can help better inform clinical care and prevention efforts for youth.

4. Chapter 2. Cognitive Performace Mediates the Relationship Between Cannabis Use and Psychopathology Symptoms in Adolescents: A Longitudinal, Multi-Level Analysis.

This manuscript is to be submitted.

Authors:

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Abstract:

Background: The relationship between cannabis and cognition has been well established, both in adults and adolescents. The link between early cannabis use and psychopathology has also been well documented. What is lacking is the investigation of a potential path between substance use and psychopathology mediated by cognitive impairment.

Methods: 5-year data from 3826 adolescents starting the 7th grade in 2012 or 2013 and who agreed to take part in a randomized controlled trial for substance abuse prevention were used to determine levels of cannabis use, psychopathology symptoms, and cognitive performance. Using multi-level path analysis, we estimated the between and within-person effects of cannabis use and its relation to psychopathology through inhibitory-control, delayed-recall memory, spatial working memory, and perceptual reasoning.

Results: Results indicated that impairments in perceptual reasoning, linked to higher cannabis use, were associated with internalizing symptoms (anxiety/depression) of a lesser magnitude at a between-person level (trait-level; B=-0.07, p=0.001). For the externalizing symptoms (ADHD/conduct), between-person (trait-level) mediating path through inhibitory-control, perceptual reasoning, and spatial working memory were significant (B=0.05, p=0.002; B=0.06, p<0.001; B=0.03, p=0.007 respectively). The significant mediating pathway from cannabis use, through its association with perceptual reasoning, was linked to higher reported internalizing symptoms at the within-subject level (B=0.01, p=0.021). Significant mediation also showed that impairments in delayed-recall memory and perceptual reasoning, related to cannabis use, was associated with an increased

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magnitude of externalizing symptoms (ADHD/conduct) at a within-person level (B=0.002, p=0.036; B=0.004, p=0.021).

Summary: The transient neuropsychological effects of cannabis on perceptual reasoning seem to mediate the relationship between cannabis use and internalizing problems as adolescents modulate their consumption. Cannabis-related neuropsychological effects on externalizing symptoms, and to some degree internalizing symptoms, seem also influenced by differences between individuals, complicating the establishment of time-sequence of effects.

Impact: This study suggests cannabis could induce a cognitive state linked to increased internalizing and externalizing symptoms, while also keeping into account the common vulnerability reflected in the association between adolescent cannabis use, cognition, and internalizing/externalizing symptoms. Preventive interventions deployed to at-risk youth should be identified, disseminated, and implemented to limit cannabis harm to youth.

Introduction:

The United Nations Office on Drugs and Crime's report on drugs mentions cannabis as the

most widely used drug on the global scale (United Nations Office on Drugs and Crime,

2019), although cannabis has become licit in many jurisdictions. Many actors, including the

task force at the National Institutes of Health (NIH), have provided statements highlighting

the risks associated with early-onset use of cannabis on youth's cognitive and affective

development (National Institute on Drug Abuse, 2017). In a global context where many

jurisdictions, including the US and Canada, are contemplating or proceeding with the

legalization of cannabis, these results are concerning, especially considering how

adolescents, representing a large proportion of actual cannabis users, might be more

vulnerable to these effects. It is now necessary to further our scientific understanding of the

effects of cannabis on the developing brain and its potential repercussions on later mental

health outcomes for vulnerable youth. One such question relates to the mediational role of

cognitive performance on the association between cannabis and psychopathology

symptoms.

Many studies have investigated the association between cannabis use and cognitive

functioning. Most studies employed cross-sectional designs investigating the effects of

cannabis on adults' brains, usually comparing non-using adults to adults suffering from a

cannabis use disorder. Few studies investigated its effects on adolescent users, and fewer

still have looked at adolescent cannabis users from onset of use to later adolescence using a

longitudinal design. Such longitudinal studies (Lisdahl et al., 2013; Nguyen-Louie et al.,

2015; Squeglia et al., 2009; Meier et al., 2012; Castellanos-Ryan et al., 2016) found that

cannabis use triggers neuropsychological consequences, in other words, impairment on cognitive performance persistent over a long-term period (over a year). These effects seem to be related to THC's toxicity to neurons (Rocchetti et al., 2013; Sarne, Asaf, Fishbein, Gafni & Keren, 2011; Scallet, 1991). In a set of two studies conducted on mice, Tselnicker, Keren, Hefetz, Pick & Sarne (2007) and Senn, Keren, Hefetz & Sarne (2008) found that a small dose of THC (0.001 mg/kg) injected directly into the brain triggered neurotoxic changes and lowered the animal's performance in the Morris water maze task and water T-maze task respectively. Specific domains of cognitive functioning seem affected in human subjects. As reviewed by Volkow et al. (2016), attention, speed processing, recall memory, inhibitory control and working memory have been associated with cannabis misuse. Using data provided by the Coventure Trial (O'Leary-Barrett et al., 2017; Morin et al, 2019), a sample of 3826 high school students from the Montreal Metropolitan Area were longitudinally followed up on their substance use habits and cognitive development. Special attention was given to parse out common vulnerability factors, concurrent and neurotoxic effects of substance use on cognition. Effects of cannabis on inhibitory control and delayed recall memory were detected and shown to persist above and beyond the effect of alcohol use. These effects, albeit small, were shown to be additive. This suggests that cannabis can be harmful to adolescents' cognitive performance. Whether these effects translate to functional outcomes (e.g.: academic achievement, academic perseverance, etc.) remains to be clarified.

Beyond its effects on cognition, as reviewed by Richardson (2010), cannabis use has been associated with the full continuum of psychopathology. In a study conducted by Farmer et

al. (2016), individuals were assessed on four occasions between age 16 and 30 for cannabis use disorder and mental health problems. Results indicated that individuals suffering from a cannabis use disorder in earlier assessments presented high rates of later emerging internalizing or externalizing disorders. The emergence of these disorders seemed to further predict the maintenance of cannabis use disorder. Furthermore, cannabis misuse, especially adolescent-onset cannabis use, has been linked to the emergence of psychotic disorders (Large et al., 2011). Additionally, Bourque et al. (2017) found that an increase in adolescent consumption of cannabis predicted higher self-reported levels of psychotic-like experiences, which are also related to increased risk for psychosis. Although cannabis use seems associated with to onset of psychopathology, a potential common vulnerability factor that accounts for both cannabis use and psychopathology could be at play. As reviewed by Basu and Ghosh (2015), the endocannabinoid system is involved in both cannabis use and a variety of psychiatric problems, suggesting a neurological basis for comorbidity between cannabis misuse and psychiatric problems. Unfortunately, these common causal factors are rarely controlled for in longitudinal designs. There is no evidence, to our knowledge, that either confirmed or rejected the possibility for these associations to be accounted for by the neuropsychological consequences of cannabis use.

Another emerging body of literature relates to the association between cognitive profiles and psychopathology. Data suggests that executive functions, more precisely behavioural inhibition, are significantly linked to externalizing problems. A meta-analysis conducted by Schomaker et al. (2013) identified a medium correlation between executive functions and the risk of developing an externalizing problem (effect size of 0.22). Premorbid cognitive

functioning also seems to consistently predict adolescent-onset substance misuse, especially alcohol, tobacco, and cocaine use (Smith et al., 2014). Though some attempts have been made to associate premorbid cognitive functioning to the emergence of internalizing disorders, evidence remains unclear. Though executive functioning (Gohier et al., 2009; Hammar & Ardal, 2009), memory problems (Hammar & Ardal, 2009) and attribution biases (Viana & Gratz, 2012) seems relevant to internalizing problems, more evidence is needed to establish that a causal relationship exists.

Considering the existing relations between cannabis use, cognitive functioning, and psychopathology symptoms apparition, the possibility for a mediating pathway is to be considered. Furthermore, data from the Coventure Trial (O'Leary-Barrett et al., 2017) provide an opportunity to investigate whether there are mental health consequences to the cognitive consequences of cannabis. The model in Figure 9 seems plausible considering the previous literature, though never tested in its entirety using a developmentally sensitive design. Robust longitudinal designs can provide the necessary power and control to explore these hypotheses.

Figure 9. Mediation Model of the Association between Cannabis Use, Cognitive performance, and Psychopathology Symptoms
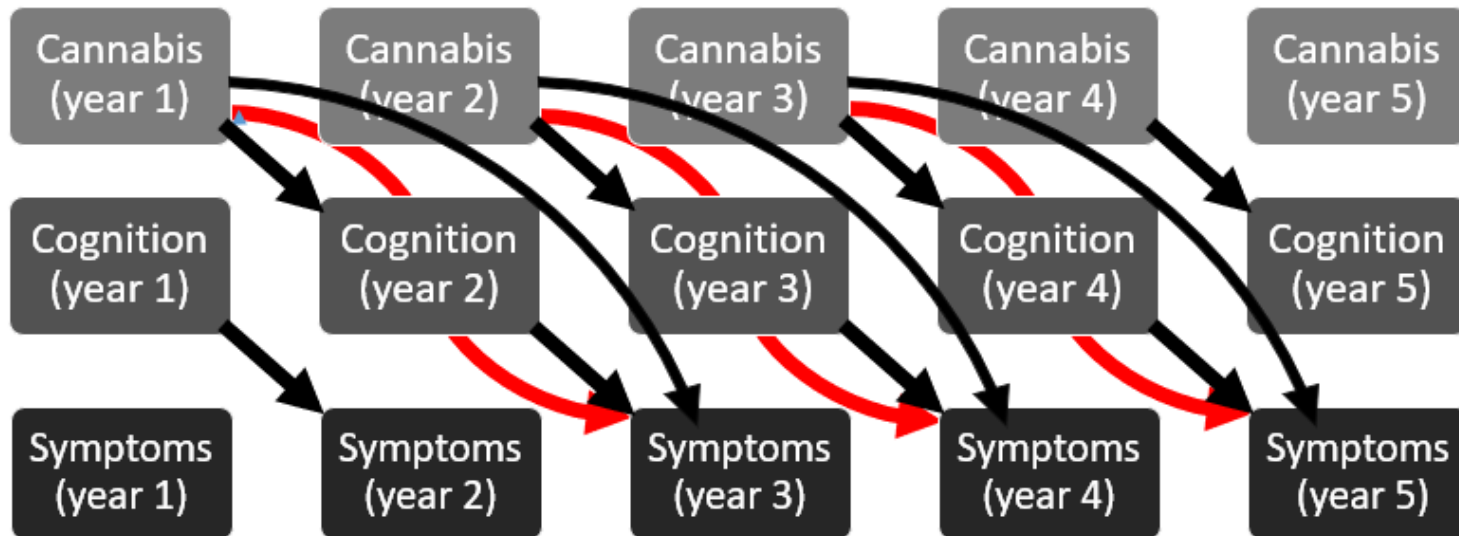
These research questions call for rigorous methodology. When investigating the relationship between cannabis use, cognitive performance, and psychopathology symptoms, one must pay careful attention to shared underlying variables that contribute to the emergence of all three outcomes. Genetic, temperamental, socio-demographic, and environmental factors can set individuals at higher risk for substance-related problems, psychopathology and lagged cognitive development. For example, Verdejo-García et al. (2019), in their review, identified an association between early-onset cannabis use, lagged cognitive development and pre-existing vulnerability factors, such as epigenetic endophenotypes and temperamental impulsivity. These same variables were also involved in contextualizing early-onset psychopathology (Basu & Ghosh, 2015). Multi-level longitudinal designs provide an effective framework to numerically distinguish the impact of a specific behaviour (e.g.: cannabis use) from that of the subjects' background (e.g.: genetic makeup, temperament, socio-demographic realities, environmental factors, etc.). As shown in a previous study (Morin et al., 2019), multi-level longitudinal modelling can capture how changes in cannabis intake (within-subject effect) can relate to cognition independently from a subject's characteristics (between-subject effect). This allows to better assess the effect of cannabis without inflating it.

This study aimed to test the mediation effect of cognitive performance on the association between cannabis use and changes in later psychopathology symptoms above and beyond other competing associations that support a common vulnerability hypothesis. To achieve those aims, a multi-level longitudinal analytical strategy was employed. According to a neurotoxicity hypothesis, we hypothesize that, above and beyond other associations, a

mediating effect of cognition on the association between adolescents' cannabis use and psychopathology symptoms should be observed. Specifically, we expect cannabis-related impairments in inhibitory control (as demonstrated previously using this dataset) to mediate the association between cannabis use and both externalizing and internalizing psychopathology (yet to be investigated in this dataset). Given the existing link between memory functioning, perceptual reasoning and depressive symptomatology (Hammar & Ardal, 2009; Afzali, Oleary-Barrett, Séguin & Conrod, 2018), we expect cannabis-related effects on delayed recall memory to be a mediator of the association between cannabis and internalizing symptoms.

Methods:

Participants

Data from the Co-Venture study (O'Leary et al., 2017) was gathered for this longitudinal population-wide study. Co-Venture is a randomized controlled trial assessing the efficacy of a personality-based substance use prevention program over a 5-year period. A sample of 3826 out of a potential 3971 students (96% enrollment, 47% female, mean age at time 1 = 12.7 [SD = 0.5]) was generated by recruiting 31 schools from the Montreal area. Attention was paid to schools' socioeconomic, cultural, and linguistic diversity. Schools were randomly assigned to either: deliver the Preventure program to high-risk 7th graders enrolled in the study, or to deliver the program to future 7th graders who were never part of the study 3 years later. September 2012/2013 grade seven students were followed annually until grade eleven through confidential web-based surveys conducted during class hours.

The assessment provided information on students' cognitive abilities, substance use habits

and psychopathology symptoms. Data were quality-controlled using sham items to detect

false self-reports and below chance level criterion for performance on cognitive tasks.

Failure to pass quality control resulted in the removal of that data from our analyses.

To maintain the confidentiality of youths' reports, parents and teachers agreed to not access

participants' survey results and assessments were automatically anonymized after

completion. Ethical approval was obtained from Sainte-Justine's Hospital Ethics

Committee in Montreal. Consent was handled differently amongst schools, either using

passive or active consent. Students' active assent was systematically obtained before

testing.

Most students passed quality control and provided minimal demographic information (sex

and socioeconomic status [SES]) to be included in the analyses (3612 out of 3826 students:

95.6%). Neither sex nor SES predicted attrition in the sample (p=0.431; p=0.876

respectively).

Variables

Substance use (IV): Cannabis use was assessed with a modified and validated version of the

'Detection of alcohol and drug problems in adolescents' questionnaire (DEP-ADO; Landry

et al., 2004). The DEP-ADO demonstrated good psychometric properties (Landry et al.,

2004). Once a year, for five consecutive years, participants rated their consumption

frequency on a six-point scale (0=Never, 5=Every day). Though quantity or dose measure

would have been relevant, cannabis quantity and dose assessments remain a challenge in

the field (Piontek, Kraus & Klempova, 2008). Average cannabis use over a 5-year period was used as a between-subject predictor of cognitive performance and psychopathology symptoms, while the variation of cannabis use from one year to another was used as a within-subject predictor of cognitive performance and psychopathology symptoms.

Psychopathology (DV): Psychopathology symptoms were measured yearly for 5 consecutive years using a combination of two scales. Internalizing symptoms were measured using the Brief Symptoms Inventory (BSI) which measures levels of anxiety and depression-related symptoms. The instrument has shown acceptable internal reliability as well as acceptable to excellent test-retest reliability ($\alpha > 0.7$; $r = 0.7$-0.9; Aroian & Patsdaughter, 1989; Derogatis, 1993). "Anxiety" and "Depression" subscale scores of the BSI were used in the models as outcome variables. Externalizing symptoms were measured using the Strengths and Difficulties Questionnaire (SDQ). The questionnaire has shown validity, as indicated by a high correlation with other instruments measuring behavioural problems in youth ($r = 0.9$; Goodman, 1997). The measure also demonstrated good specificity/sensitivity properties, as measured by ROC analyses (area under the curve = 0.9, 95% C.I.; Goodman, 1997). SDQ's ADHD/Conduct subscale scores were used as outcome variables in our models.

Cognition (Mediator): All tasks are described in more detail in the study protocol (O'Leary et al., 2017). Spatial Working Memory (SWM) was measured with the 'Find the Phone' task, based on the Self-Order Pointing Task (Cragg & Nation, 2007) and the SWM subtest in the Cambridge Neuropsychological Test Automated Battery (CANTAB). This task has sound psychometric properties and has been validated with both adults and children

(Cambridge Cognition, 2016). Delayed Recall Memory was assessed with a computerized task based on the Dot Location test of the Child Memory Scales (CMS; Cohen, 2001). The task has been validated for children ages 5 to 16 and presents acceptable internal consistency and test-retest reliability (Cohen, 2001). Participants are asked to reproduce a previously learned pattern of stimuli 30 minutes later. Perceptual Reasoning was assessed using a selection of items from Cattell's Culture-Fair Test. Participants completed a sequence of puzzles progressively increasing in difficulty. This 9-item task correlates highly with the 60-item Raven's Perceptual Reasoning Matrices (Bilker et al., 2012). Inhibitory Control was measured using the Passive Avoidance Learning Paradigm (PALP; Castellanos-Ryan et al., 2011; Newman & Kosson, 1986). Participants learn, by trial and error, to respond to "good" numbers and to withhold responses to "bad" numbers by experiencing rewards to correct press/omissions and punishments to incorrect presses/omissions. This strategy has been used in the past and is correlated with other measures of inhibition, and with prefrontal cortical activation during other go-no-go tasks (Whelan et al., 2012).

Covariates

Baseline SES was controlled using the Family Affluence Scale for Adolescents (Boyce et al., 2006). Analyses also controlled for sex, ethnicity, and overall alcohol use across the five time points.

Analytical Strategy

Using an adapted Random Effect - Cross-Lagged Panel Model (RE – CLPM; Wu, Carroll, Chen, 2018), we can, break down variables into their latent component (between- and within-effects) and create indirect effect terms that allow testing for mediating pathways. This strategy will be used to test our hypotheses.

The effect of each predictor or independent variable (IV) at all five time points will be regressed into three separate parameters, namely between-subjects, within-subject and within-subject lagged. The "between subject" effects represent the association between the average inter-individual differences on an IV throughout the survey. This between-subjects effect is obtained by regressing the variance of a subject's data over all time points into an intercept latent variable. In other words, it can provide an average effect of a given IV (e.g.: cannabis use frequency) on a DV (e.g.: externalizing symptoms) over the full duration of the survey. This is used in our models to assess the common vulnerability factor model. The "within-subject" effects represent intra-individual changes on the IV across each year on an outcome over time. This within-subject effect is extracted by transforming the variance between data points into a slope variable. This slope represents the average change in reports from one time-point to the next and is used to assess pathoplasticity. This slope variable can also be adjusted to test for the neurotoxic model by estimating its lagged effect on the DV. The mediator variables will be subject to the same treatment as to also extract these between-subjects, within-subjects, and lagged parameters.

Once the between-subjects, within-subjects, and lagged parameters of the IV and mediators will be obtained, direct effects of each parameter on the DV, direct effects of the mediator

on the DV and indirect effects of the IV through each of the mediators on the DV will be estimated.

Models

The following analyses were conducted using the software Mplus. Multilevel path analysis will be employed. Cannabis use frequency (IV) will be the only substance under investigation to focus the analysis and generate a more manageable quantity of models to interpret. A separate model will be conducted for each permutation mediator variable (four domains of cognition) and dependant variables (two domains of psychopathology symptoms). In other words, a total of eight models will be conducted assessing the mediational effect of four domains of cognition (mediators: spatial working memory, delayed recall memory, perceptual reasoning, and inhibitory control) on two domains of psychopathology symptoms (DVs: externalizing symptoms and internalizing symptoms).

First, the direct effect of frequency of cannabis use (IV) as it relates to the cognitive variable (mediator) will be estimated at a between-subject, within-subject, and within-subject lagged level.

Next, the model will estimate the direct effect of the cognitive variable (mediator) as it relates to the domain of psychopathology symptom (DV) again assessing the between-subject effect, within-subject effect, and within-subject lagged effect of the mediating variable.

Finally, the indirect effect of cannabis, as mediated by cognitive performance, in relation to psychopathology symptoms will be estimated at three levels: between-subject, within-subject, and within-subject lagged. To estimate these effects, the product of two

coefficients (cannabis and cognitive performance; cognitive performance and psychopathology symptoms) will be used. This time, five time-points will be included in the model. A visual representation of the paths assessed in this model[6] is represented in Figure 10.

Though direct effects will be reported, indirect effects will constitute the core of reported results. If significant effects of mediation for between-subject effects are significant, this will be interpreted as validation that the common vulnerability factor model is relevant to the association between cannabis use, cognition, and psychopathology symptoms. If a significant effect of mediation is found at a within-subject level, over and above between-subjects effect, this will be interpreted to indicate the pathoplasticity model to adequately represent the association between cannabis use, cognition, and psychopathology symptoms. Finally, if a significant effect of mediation is found at a within-subject lagged level, over and above between-subjects and within-subject, this will be interpreted to indicate neurotoxicity model relevance when associating between cannabis use, cognition, and psychopathology symptoms.

Missing data on the main variables were handled through Full Information Maximum Likelihood (FIML). School was included as a cluster-level variable.

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[6] A detailed version of the figure is presented in the methodology section of this dissertation under "Model Computed in Chapter 2".

Finally, effect sizes of substance use variables on cognitive domains and psychopathology symptoms will be computed using Cohen's f^2. The same will be provided for the effect of cognitive domains on psychopathology symptoms.

Figure 10. Cross-Lagged Panel Model Path Analysis of Mediation Used
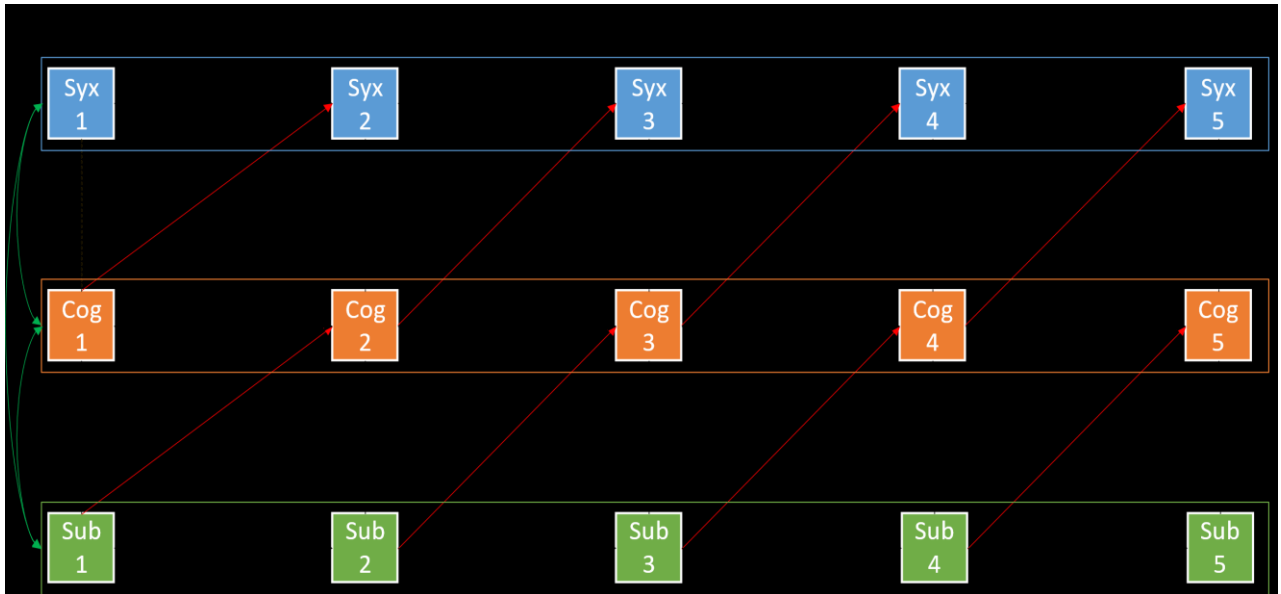
Note: An adapted Random Effect - Cross-Lagged Panel Model (RE – CLPM) tests between-subject differences (green lines) at one level and then various within-subject processes (hashed and red lines) at a second level, allowing for the investigation of concurrent and time-lagged relationships between sets of variables. One of four domains of cognitive performance (Cog; orange), cannabis use (Sub; green), and one of two domains of psychopathology symptoms (Syx; blue) are measured at five time-points (time 1 represents assessment in the 7th grade, time 2 in 8th grade, and so on). The between-subject effects refer to the mean level of use over the 5 time points, while the within-subject and lagged effects reported involve an average of each effect over the 4 (lagged) or 5 (concurrent) associations, as time was not considered as a moderator in this analysis given there were no time-specific hypotheses in this study.

Results:

Descriptive Statistics: Table 6 presents the descriptive statistics for all variables included in the model.

Table 6. Descriptive Statistics of Variables Used in Analyses

Variable Name	Minimum value	Maximum value	Mean	Standard Deviation

Family Affluence Scale Score	0.00	10.00	5.39	1.7
Sex	0.00	1.00		
Alcohol Use Quantityxfrequency	0.00	100.00	2.41	5.3
Cannabis Use Frequency	0.00	5.00	0.34	0.8
Inhibitory Control Errors	0.00	80.95	22.54	17.2
Delayed Recall Memory Score	1.00	16.00	8.39	3.7
Spatial Working Memory Errors	0.00	62.00	12.17	9.6
Perceptal Reasoning Score	0.00	23.00	17.15	3.0
Externalizing Symptoms Reported	0.00	20.00	6.14	3.3
Internalizing Symptoms Reported	0.00	48.00	7.78	8.9

Model results of the effects of cannabis in relation to externalizing symptoms and internalizing symptoms, and of cannabis effect in relation to cognition: Table 7 presents the results of mediational analyses. The model indicated that cannabis use, across all 5 years (between subjects) and within each year (within-subjects), was associated with higher levels of externalizing symptoms (B= 1.92, $p<0.001$; B= 0.25, $p<0.001$ respectively). and internalizing symptoms (B= 2.15, $p<0.001$; B= 0.55, $p<0.001$, respectively). A significant lagged-effect of cannabis use associated with externalizing and internalizing symptoms was also detected (B= -0.28, $p<0.001$; B= -0.46, $p<0.001$, respectively).

Cannabis during a 5-year period (between-subject effect) was also significantly associated with impairment on all four domains of cognition, namely delayed recall memory (B= -0.25, $p<0.001$), inhibitory control (B= 1.72, $p<0.001$), perceptual reasoning (B= -0.39, $p<0.001$), and working memory (B= 0.68, $p<0.001$). A significant within-person effect showed that any further increase in cannabis use frequency during a given year was associated with impairment in delayed recall memory (B=-0.14, $p<0.001$), more inhibitory control errors (B=0.63, $p=0.001$), and impairments in perceptual reasoning performance

(B=-0.06, *p*=0.021) in that same year. Significant lagged-effects also showed that above

mean use and current use, higher levels of cannabis use the year before was associated with

more inhibitory control errors (B=1.06, *p*=0.001), and more spatial working memory errors

(B=0.40, *p*=0.004).

Table 7. Direct Effects of Cannabis, Cognitive Performance and Indirect Effect of Cognitive Performance on Cognitive Development and Internalizing/Externalizing Symptoms

	Predictors	Internalizing Symptoms			Externalizing Symptoms		
		Estimate	Std. Er	Pr(>|t|)	Estimate	Std. Er	Pr(>|t|)
Delayed Recall Memory	Time	0.465	0.056	0.000	0.080	0.021	0.000
	Socio-Economic Status	-0.214	0.066	0.002	0.003	0.026	0.461
	Sex	5.008	0.227	0.000	-0.048	0.089	0.297
	Cannabis Between-Subjects	**2.155**	**0.249**	**0.000**	**1.922**	**0.111**	**0.000**
	Cannabis Within-Subjects	**0.551**	**0.088**	**0.000**	**0.251**	**0.031**	**0.000**
	Cannabis Within-Subjects (Lagged)	**-0.460**	**0.125**	**0.000**	**-0.275**	**0.045**	**0.000**
	Cannabis/Cognition Between-Subjects	**-0.256**	**0.072**	**0.000**	**-0.251**	**0.072**	**0.000**
	Cannabis/Cognition Within-Subjects	**-0.133**	**0.037**	**0.000**	**-0.139**	**0.038**	**0.000**
	Cannabis/Cognition Within-Subjects (Lagged)	-0.010	0.042	0.410	-0.002	0.044	0.487
	Cognition Between-Subjects	0.137	0.118	0.126	-0.070	0.047	0.072
	Cognition Within-Subjects	-0.011	0.023	0.317	**-0.015**	**0.008**	**0.036**
	Cognition Within-Subjects (Lagged)	0.007	0.026	0.400	**-0.275**	**0.045**	**0.000**
	Indirect Between-Subjects	-0.033	0.034	0.126	0.016	0.013	0.072
	Indirect Within-Subjects	0.001	0.003	0.317	**0.002**	**0.001**	**0.036**
	Indirect Within-Subjects (Lagged)	0.002	0.008	0.400	-0.006	0.003	0.110
Inhibitory Control	Time	0.434	0.051	0.000	0.050	0.018	0.004
	Socio-Economic Status	-0.216	0.063	0.000	-0.004	0.027	0.437
	Sex	4.976	0.226	0.000	-0.016	0.088	0.428
	Cannabis Between-Subjects	**2.144**	**0.263**	**0.000**	**1.899**	**0.106**	**0.000**
	Cannabis Within-Subjects	**0.557**	**0.094**	**0.000**	**0.246**	**0.031**	**0.000**
	Cannabis Within-Subjects (Lagged)	**-0.466**	**0.130**	**0.000**	**-0.300**	**0.046**	**0.000**
	Cannabis/Cognition Between-Subjects	**1.685**	**0.522**	**0.001**	**1.719**	**0.523**	**0.002**
	Cannabis/Cognition Within-Subjects	**0.648**	**0.208**	**0.001**	**0.632**	**0.216**	**0.001**
	Cannabis/Cognition Within-Subjects (Lagged)	**1.054**	**0.305**	**0.000**	**1.062**	**0.314**	**0.001**
	Cognition Between-Subjects	-0.009	0.013	0.250	**0.028**	**0.005**	**0.000**
	Cognition Within-Subjects	-0.001	0.006	0.416	0.003	0.002	0.085
	Cognition Within-Subjects (Lagged)	-0.006	0.006	0.179	-0.001	0.002	0.357
	Indirect Between-Subjects	-0.014	0.025	0.250	**0.048**	**0.017**	**0.002**
	Indirect Within-Subjects	-0.001	0.004	0.416	0.001	0.001	0.085
	Indirect Within-Subjects (Lagged)	-0.006	0.007	0.179	-0.001	0.002	0.358
Perceptual Reasoning	Time	0.573	0.046	0.000	0.098	0.017	0.000
	Socio-Economic Status	-0.211	0.061	0.000	-0.010	0.027	0.362
	Sex	5.007	0.218	0.000	-0.052	0.088	0.267
	Cannabis Between-Subjects	**2.189**	**0.253**	**0.000**	**1.873**	**0.111**	**0.000**
	Cannabis Within-Subjects	**0.570**	**0.089**	**0.000**	**0.250**	**0.030**	**0.000**

	Cannabis Within-Subjects (Lagged)	**-0.443**	**0.127**	**0.001**	**-0.287**	**0.044**	**0.000**
	Cannabis/Cognition Between-Subjects	**-0.390**	**0.092**	**0.000**	**-0.392**	**0.091**	**0.000**
	Cannabis/Cognition Within-Subjects	**-0.060**	**0.030**	**0.021**	**-0.058**	**0.029**	**0.021**
	Cannabis/Cognition Within-Subjects (Lagged)	-0.010	0.042	0.410	-0.002	0.044	0.487
	Cognition Between-Subjects	**0.191**	**0.058**	**0.001**	**-0.151**	**0.024**	**0.000**
	Cognition Within-Subjects	**-0.159**	**0.031**	**0.000**	**-0.067**	**0.011**	**0.000**
	Cognition Within-Subjects (Lagged)	**-0.082**	**0.034**	**0.006**	**-0.033**	**0.012**	**0.003**
	Indirect Between-Subjects	**-0.072**	**0.030**	**0.001**	**0.059**	**0.016**	**0.000**
	Indirect Within-Subjects	**0.009**	**0.005**	**0.021**	**0.004**	**0.002**	**0.021**
	Indirect Within-Subjects (Lagged)	0.001	0.004	0.412	0.000	0.002	0.485
Spatial Working Memory	Time	0.445	0.044	0.000	0.065	0.015	0.000
	Socio-Economic Status	-0.220	0.064	0.001	-0.005	0.027	0.412
	Sex	4.909	0.224	0.000	0.052	0.092	0.291
	Cannabis Between-Subjects	**2.129**	**0.265**	**0.000**	**1.908**	**0.107**	**0.000**
	Cannabis Within-Subjects	**0.564**	**0.092**	**0.000**	**0.248**	**0.031**	**0.000**
	Cannabis Within-Subjects (Lagged)	**-0.442**	**0.126**	**0.000**	**-0.293**	**0.043**	**0.000**
	Cannabis/Cognition Between-Subjects	**0.686**	**0.273**	**0.004**	**0.682**	**0.277**	**0.007**
	Cannabis/Cognition Within-Subjects	-0.043	0.104	0.330	-0.048	0.102	0.317
	Cannabis/Cognition Within-Subjects (Lagged)	**0.382**	**0.151**	**0.005**	**0.395**	**0.147**	**0.004**
	Cognition Between-Subjects	-0.025	0.022	0.119	**0.045**	**0.009**	**0.000**
	Cognition Within-Subjects	-0.004	0.009	0.336	**0.010**	**0.003**	**0.000**
	Cognition Within-Subjects (Lagged)	0.004	0.010	0.350	**0.006**	**0.003**	**0.042**
	Indirect Between-Subjects	-0.015	0.018	0.122	**0.030**	**0.013**	**0.007**
	Indirect Within-Subjects	0.000	0.001	0.443	0.000	0.001	0.317
	Indirect Within-Subjects (Lagged)	0.001	0.004	0.354	0.002	0.002	0.050

Note: Significant effects are marked in bold character. Performance on Working Memory and Inhibitory Control task was measured by counting the number of errors; a lower score indicates a better performance. For each cognitive domain, covariates are presented with a white background, the direct effects of cannabis parameters (IVs) on psychopathology symptoms (DVs) are reported in the following grey background. The next white background reports the direct effect of cannabis parameters (IVs) on the cognitive domain (mediator). The second grey background reports the direct effect of the cognitive domain parameters (mediators) on psychopathology symptoms (DVs). Finally, the last white background section reports the indirect effects of each parameter on psychopathology symptoms (IVs → Mediators → DVs)

Effects of cognition in relation to externalizing symptoms and internalizing symptoms:

Delayed Recall Memory: Figure 11 shows the direct and indirect effects of cannabis and delayed recall memory as it relates to externalizing symptoms. Average performance on delayed recall memory task across 5 years does not seem associated with either externalizing or internalizing symptoms during those 5 years, therefore there was no evidence of common vulnerability between delay memory recall and psychopathology. However, a dip in delayed recall memory score within one year was associated with higher externalizing symptoms within that same year (B=-0.02, *p*=0.04). Furthermore, this within-subject effect partially mediated the association between cannabis and externalizing symptoms: increase in cannabis use within a given year, through a reduction in performance on a delayed recall memory task in that same year, was linked to higher reported externalizing symptoms in that given year (B=0.01, *p*=0.04). There was no significant signal for such mediation when looking at internalizing symptoms. Despite the presence of a lagged effect associating poor delayed recall memory score to higher externalizing symptoms the next year (B=-0.28, *p*<0.001), criteria for lagged mediation were not met because no significant effect of past year change in cannabis use related to delayed recall memory. No such signal was detected for internalizing symptoms.

Figure 11. Visual Representation of the Mediating Effect of Cannabis Use on Externalizing Symptoms Through Delayed Recall Memory at the Within-Subject Level.
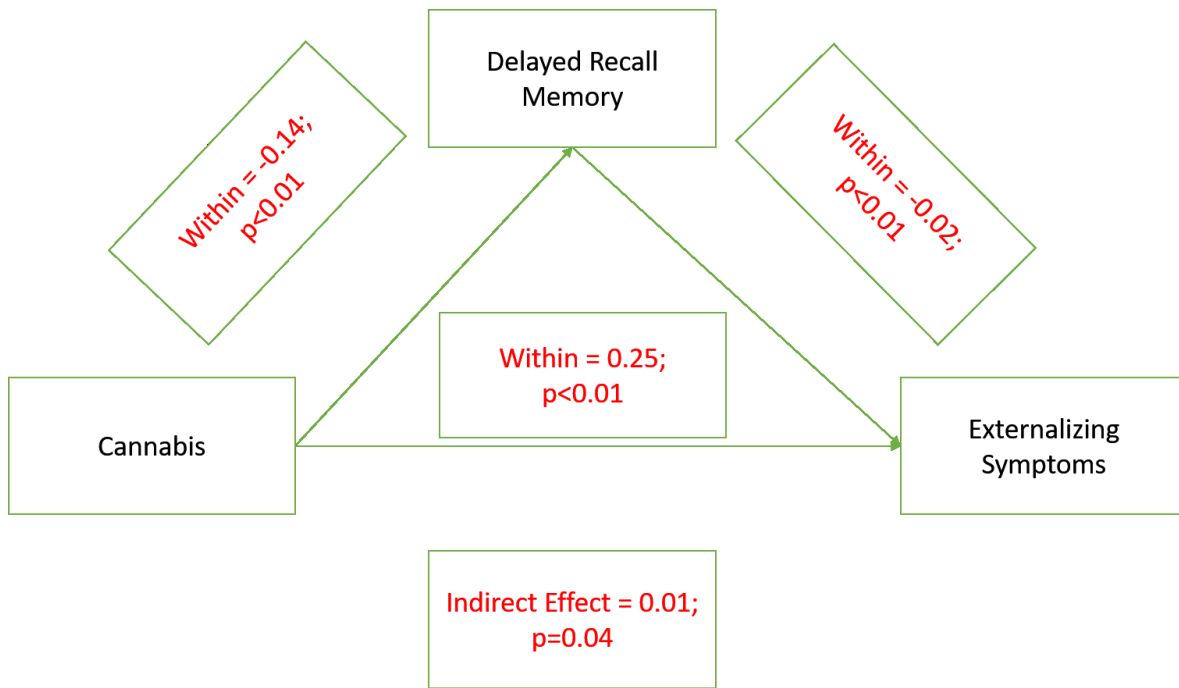
Note: Cannabis = Cannabis use Frequency; Estimates of direct effects are provided above their corresponding arrow; Indirect effect measures the significance of the mediating pathway.

Inhibitory Control: Figure 12 shows the direct and indirect effects of cannabis and inhibitory control as it relates to externalizing symptoms at a between-subjects level. A higher number of errors on the inhibitory control task across 5 years seems to be linked to higher externalizing symptoms reported on average during those 5 years ($B=0.03$, $p<0.01$). No such effects were observed for internalizing symptoms. Furthermore, this between-subject effect seems to partially mediate the association between cannabis and externalizing symptoms: higher levels of cannabis use over 5 years, through a higher number of errors on an inhibitory control task in that period, is linked to higher reported externalizing symptoms across that same 5 year period ($B=0.05$, $p<0.01$). There was no indirect between-

subject for internalizing symptoms. No within-subject or lagged effects were detected for

inhibitory control measures.

Figure 12. Visual Representation of the Mediating Effect of Cannabis Use on Externalizing Symptoms Through Inhibitory Control Errors at the Between-Subjects Level.
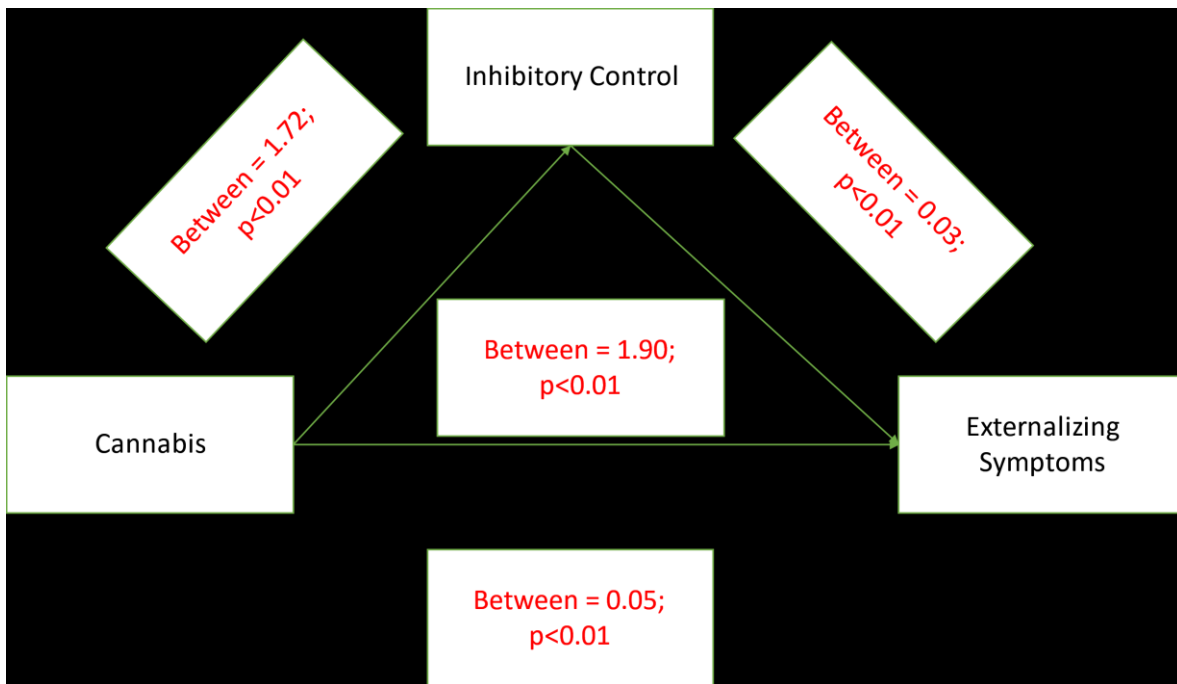
Note: Cannabis = Cannabis use Frequency; Estimates of direct effects are provided above their corresponding

arrow; Indirect effect measures the significance of the mediating pathway.

Perceptual Reasoning: Lower average performance on a perceptual reasoning task across 5

years was associated with higher externalizing symptoms and lower internalizing symptoms

reported during those 5 years (B=-0.15, *p*<0.001; B= 0.19, *p*=0.01 respectively). A relative

reduction in perceptual reasoning score within 1 year was associated with higher

externalizing or internalizing symptoms within that same year (B=-0.07, *p*<0.001; B=-0.16,

p<0.001 respectively). Significant lagged effects also associated lower perceptual reasoning

score in the previous year to higher self-reported externalizing and internalizing symptoms the following year (B=-0.03, *p*=0.003; B=-0.08, *p*=0.006 respectively). Furthermore, a between-subject effect partially mediated the association between cannabis and both externalizing and internalizing symptoms: Higher overall levels of cannabis use across 5 years were related to high risk for externalizing symptoms through lower general performance on perceptual reasoning tasks over the 5 years, (B=0.06, *p*<0.001). The same can be observed for internalizing symptoms (B=-0.07, *p*=0.001). At the within-subject level, cannabis use in a given year was also related to higher risk for externalizing and internalizing symptoms in that same year through lower performance on perceptual reasoning in that same year (B=0.004, *p*=0.021; B=0.009, *p*=0.021 respectively). No lagged mediation effects were reported.

Working Memory: At the between-person level, the tendency to make more working memory errors across all 5 years was associated with greater risk for externalizing symptoms, but not internalizing symptoms, during those 5 years (B=0.05, *p*<0.01). In addition, at the within-person level, a rise in the number of errors committed on a working memory task within 1 year was associated with higher externalizing symptoms, but not internalizing symptoms, within that same year (B=0.01, *p*<0.01). Lagged effects also showed that a higher number of errors on working memory last year was linked to more reported externalizing symptoms the next year (B=0.006, *p*=0.04) The model investigating mediation at the between-subject level showed that the association between cannabis and externalizing symptoms was partially mediated by working memory errors (B=0.03, *p*=0.01). This was not the case for internalizing symptoms. No significant mediation was

observed at the within-subject or lagged level for either externalizing or internalizing symptoms.

Effect sizes of substance use variables and cognitive variables are provided in Table 8.

Table 8. Effect sizes of cannabis and cognitive domains on psychopathology symptoms

	Externalizing symptoms (f^2 value)	Internalizing symptoms (f^2 value)
cannabis Use	0.049	0.011
Delayed Recall Memory	N.S.	N.S.
Perceptual Reasoning	0.002	0.001
Spatial Working Memory	0.001	N.S.
Inhibitory Control	0.001	N.S.

Note: N.S.: Non-significant finings as reported in the main analysis. According to Cohen (1988), f^2 values below 0.02 are considered small effect sizes.

Discussion:

The study aimed to investigate the mediational role of cognitive deficits resulting from cannabis use and its relation to the already existent association between cannabis use and psychopathology symptoms (internalizing and externalizing symptoms). Our study benefitted from a large, population-based, cohort of adolescents, assessed longitudinally using a multi-level model. The sample, which mostly consisted of non-users at baseline, allowed us to capture the onset of use and its associated effects through high school. This unique design and dataset allow for a novel investigation of the effects of cannabis use and its relation with mental health outcomes while controlling for potential common vulnerability, and the extent to which the relation between cannabis and mental health are mediated by cannabis-associated cognitive deficits.

Summary of results:

Between effects: Evidence of between-subject mediation between cannabis use and externalizing symptoms was supported through three domains of cognition, namely inhibitory control, perceptual reasoning, and spatial working memory. Delayed recall memory did not get this support. This means that individuals with higher levels of cannabis use frequency compared to the cohort's mean frequency of use tended to show lower scores and a higher number of errors on perceptual reasoning, inhibition and working memory tasks which were linked to generally higher reported externalizing symptoms over that period. This pattern of results can suggest a common vulnerability factor (e.g.: genes, temperament, environmental factor, etc.) could account for the broad tendency of certain individuals to engage in cannabis use, develop poor perceptual reasoning, inhibition and working memory, and also experience more externalizing symptoms throughout their adolescence. This pattern of results is in accordance with previous reports indicating that the link between externalizing problems and cannabis use can be attributable in some regards to a common vulnerability, such as impulsivity (Rioux et al., 2016). Between-subject mediation between cannabis and internalizing symptoms was only supported through perceptual reasoning. Delayed recall memory, inhibitory control and working memory did not reach significance. This suggests that higher levels of cannabis use frequency compared to the cohort's mean frequency of use tended to show lower scores on perceptual reasoning which was linked to generally higher reported internalizing symptoms over that period. This also suggests a common vulnerability factor (e.g.: genes, temperament, environmental factor, etc.) could account for the broad tendency of certain

individuals to engage in cannabis use, develop poor perceptual reasoning, and also experience more internalizing symptoms throughout their adolescence.

Within effects: Evidence of within-subject mediation between cannabis use and externalizing symptoms was supported through two domains of cognition, namely delayed recall memory, and perceptual reasoning. Inhibitory control and spatial working memory did not get this support. This means that individuals who, in a given year, show higher levels of cannabis use frequency compared to their mean frequency of use tended to show lower scores on delayed recall memory and perceptual reasoning, which was linked to generally higher reported externalizing symptoms on that year. This pattern of results can suggest a transient effect of cannabis on reported externalizing symptoms through delayed recall memory and perceptual reasoning, but that those effects can be compensated through mechanisms of neuroplasticity. This pattern of association seems to reflect the sensitive nature of memory function as an indicator of proximal substance use change or psychopathology symptoms variations (Trivedi, 2006). Evidence of within-subject mediation between cannabis use and internalizing symptoms was supported through perceptual reasoning. Delayed recall memory, inhibitory control and spatial working memory did not get this support. This means that individuals who, in a given year, show higher levels of cannabis use frequency compared to their mean frequency of use tended to show lower scores on perceptual reasoning that same year, which was linked to generally higher reported internalizing symptoms on that year. This pattern of results can suggest a transient effect of cannabis on reported internalizing symptoms through perceptual reasoning, but that this effect can be compensated through mechanisms of neuroplasticity.

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Relevance:

The results of this study demonstrate the presence of a dissociating path from the increasing frequency of cannabis use to cognitive impairment and clinical symptoms. Common vulnerability and time-sensitive effects of cannabis linked to perceptual reasoning seem connected to internalizing symptoms. Certain subtypes of depression could share a common vulnerability with poor higher-order cognitive functioning. In a longitudinal study conducted by Zammit et al. (2004), 50 087 Swedish men age 18-20 years were conscripted and cognitively assessed in the context of compulsory military training. Data on clinical diagnosis of schizophrenia, bipolar disorder and major depression was added. Using this data, they found that premorbid levels of IQ were associated with a higher risk of schizophrenia and major depression, but not bipolar disorder. This again provides some indication that between-subjects common vulnerability factors could account for the association between higher-order cognitive functions and internalizing symptoms. The absence of significant mediational lagged association between cannabis use, neuropsychological functioning and psychopathology could contrast some arguments advanced by Gobbi et al. (2019). In their review of the literature linking cannabis and depression, Gobbi et al (2019) conclude that the small, but significant, ORs linking adolescent cannabis use with depressive symptoms and suicidal behaviour suggests a causal path through changes in brain anatomy and physiology. This did not validate the sort of mediating pathway suggested and rather emphasizes the existence of common underlying factors capable of accounting for both cannabis use, the risk for depression and impaired cognitive abilities. Our data does reflect that the degree of variance explaining

psychopathology symptoms, as reported in Mplus R-Squared output, was much bigger when looking at our between-subject effects ($R^2 > 0.40$) when compared to our within-subject effects ($R^2 < 0.01$).

With regards to concurrent pathoplastic effects, Radenhausen and Anker (1988), while assessing the effect of depressed mood induction on reasoning abilities in a non-depressed college student sample, found that induced depressed mood did interfere with reasoning capabilities as measured by a verbal reasoning task. Scult et al. (2016), in their systematic review of the literature, reported that cognitive performance as measured using IQ was lowered in the context of clinical depression. Cannabis use is associated with both time-sensitive perceptual reasoning difficulties (Morin et al., 2019) and depressive symptomatology (Thomas, 1993), which could account for the pathoplastic effects reported in this study. Imaging studies have also supported cannabis' neurological effects to account for such effects (Renard et al., 2018).

Another key finding is the appearance of dissociation between internalizing and externalizing symptoms. Our findings suggest that, contrary to internalizing symptoms, the path from cannabis use to externalizing symptoms is attributable to broader between individual differences in cognitive performance. This pattern of association has been reported in the past, suggesting a certain consistency of our results with regards to substance misuse and externalizing symptoms trajectories (Holmes et al., 2016). These results can be interpreted as a form of continuity with the common vulnerability hypothesis, meaning that pre-existing dispositions would be responsible for the initiation of cannabis use and its link to broader cognitive difficulties and externalizing symptoms. This common

vulnerability could be temperamental dispositions, namely trait impulsivity (Rioux et al., 2016), which correlates highly with all three variables.

At a within-subject level, cannabis misuse, poor delayed working memory and perceptual reasoning functions were also associated with higher levels of self-reported externalizing behaviours. These time-sensitive effects suggest that an increase in cannabis use over a year usually relates to reasoning problems and memory problems in the same year, which in turn relate to inattentive/oppositional behaviours in the short term. This could be interpreted as reflective of the effects of cannabis intoxication on the adolescent brain. Cannabis has been shown to negatively affect memory function and reasoning abilities in the short term (Crean et al., 2011) as well as inattentive and delinquent behaviours in adolescence (Tims et al., 2002).

Strengths and limitations

Though some might reject mediation on the basis that all these relations are to some degree bi-directional (Cousijn et al., 2013; King, Iacono & McGue, 2004; Snyder, 2013), this does not preclude the potential of cannabis-related neuropsychological impairment to contribute, above and beyond bi-directional links, as a mediator to the observed association between cannabis use and psychopathology symptoms. This study's contribution relies on its ability, through its analytical strategy, to account for some of the bi-directionality by parsing out common vulnerability factors from within-subjects variations. Although it can be said that a cross-lagged pannel analysis would have been better suited to the question of bi-directionality, the addition of random effects made this analysis worthwhile.

Another strength of the current study lies in its very large sample of youth assessed annually on cannabis use, cognitive performance, and psychopathology symptoms from early to late adolescence. Due to the exceptionally large sample size and repeated, our analyses tested independent and mediated effects of cannabis and cognitive performance on adolescents' symptomatology. This allowed for the detection of very small effects, but significant nonetheless. The school-based, computerized battery allowed for a convenient, standardized, and ecologically valid assessment of cognitive function throughout the study, without significant attrition or burden to the participants and schools.

Reliance on self-report measures for substance use and psychopathology symptoms could constitute a limitation. However, such measures have been found to possess good reliability/validity when assessed under conditions in which confidentiality is assured and there are no consequences to reporting substance use or psychopathology symptoms (Clark & Winters, 2002; White & Labouvie, 1989). All participants in this study agreed that parents and school staff would not have access to self-report information unless such information indicated an imminent risk of harm. The assessment included a sham drug item to catch false reporting and quality control protocol filtered out unreliable self-reports or cognitive data by identifying unrealistic or inconsistent responses, further supporting the validity of data. Despite these precautions, the self-reported nature of the data should be kept into consideration.

The level of cannabis exposure could not be properly assessed in this study. Quantifying the dose of cannabis consumed is an ongoing discussion in the field of addiction research (Piontek et al., 2008). With legal and regulated cannabis markets emerging in North

America, we can expect future studies to allow youth to rate their consumption with standard units, as is the case for alcohol and tobacco.

In summary, this study provides new insight into the neurodevelopmental aspects of early-onset cannabis use and psychopathology symptoms. In a context cannabis use becomes more tolerated and legalized, this research indicates the importance of protecting youth from adverse effects of consumption and clarifies how psychopathology symptoms relate to substance engagement and cognitive development.

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Investigation of the Relation Between Substance Use and Cognitive Performance and

its Mediating Effect on Psychopathology Symptoms

Chapter 3. Approche ciblant la personnalité pour prévenir les troubles liés au cannabis.

par

Jean-François G. Morin

We can conclude from the previous chapters of this thesis that, despite significant associations between cannabis use and psychopathology symptoms concurrent to associations between cognitive performance and psychopathology symptoms, psychopathology symptoms do not seem to be fully mediated by cognitive impairment resulting from increased substance use. The effects we do observe seem to suggest a between-subject effect hypothesized as a common vulnerability effect, that could account for the association.

This suggests that individuals likely to consume and present mental health disorders could be identified and assisted using pre-existing characteristics, may they be cognitive, genetic, or temperamental, as a screen. To prevent early substance misuse and address mental health risk before the emergence of symptoms, available data suggests that one needs to accurately identify adolescents at higher risk and provide efficacious interventions.

This next chapter aims to offer an up-to-date review of the existing trends and approaches in cannabis use prevention research. This next chapter takes the form of a selective narrative review. Based on two meta-analyses specifically addressing the efficacy of preventive programs at the universal and indicated level, the authors aimed to give readers a broad and rigorous portrait of prevention science for adolescent cannabis use.

This review also highlighted the benefits of targeted prevention, which seem to pair well with findings highlighted in chapters 1 and 2. Both the previous and next chapters clearly express the importance of identifying and assisting the most vulnerable youth.

Integration of empirical findings and clinical evidence will make the object of a full

discussion in the final section of the dissertation.

5. Chapter 3. Approche ciblant la personnalité pour prévenir les troubles liés au cannabis.

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Considérations

de l'interprétation des données, de la préparation, de la révision ou de l'approbation du manuscrit, ni de la décision de le soumettre à des fins de publications.

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Résumé :

Plusieurs adolescents expérimentent avec le cannabis au cours de leur parcours secondaire. Bien qu'il existe de nombreux programmes de préventions de l'utilisation du cannabis, peu de recherche s'intéresse à l'impact réel de ces stratégies sur la consommation des adolescents. Les données les plus récentes issues des meilleures méta-analyses suggèrent que les programmes de prévention universels et les programmes de prévention indiqués sont marginalement efficaces à réduire la consommation et sont limités dans la durée de leurs effets au long terme. Ce constat est alarmant, puisque de nombreuses données de recherche illustrent que cette consommation précoce peut entraîner des conséquences importantes au plan du développement du cerveau et de la psychopathologie. Une option encore sous-utilisée demeure la prévention sélective, nommément le modèle de prévention ciblant la personnalité. Ce modèle, nommé Préventure, fut rigoureusement testé empiriquement. Il cible les jeunes les plus à risque d'une cohorte sur la base de leurs traits de personnalité et propose deux ateliers de 90 minutes ciblant les difficultés liées à ces traits. Les résultats sont durables dans le temps et entraînent des bénéfices tant sur le plan de la consommation que sur le plan de la psychopathologie. À la lumière de ce bilan et à des fins de protection des jeunes vulnérables, il est recommandé de considérer une dissémination plus large des programmes de prévention sélectifs à l'échelle du territoire.

Introduction

De nombreuses écoles au Québec et ailleurs au Canada offrent des programmes de prévention visant à réduire l'expérimentation et la consommation de drogues des adolescents. Parmi les substances les plus utilisées chez les jeunes, et par conséquent les plus ciblées dans ces programmes, figure l'alcool, le tabac et le cannabis. Ces programmes, hautement variables, proposent différents modes d'interventions afin de prévenir les problèmes de drogues chez les jeunes. Jusqu'à tout récemment, peu d'écrits se sont penchés sur l'évaluation rigoureuse de ces programmes, surtout quant à leur efficacité à réduire la prévalence et la fréquence de consommation de cannabis chez les adolescents. Un nombre suffisant de documentations a maintenant été colligé, rendant possible la production de méta-analyses explorant l'efficacité de ces programmes face au problème de la consommation de cannabis à l'adolescence. Toutefois, les résultats de ces analyses révèlent des effets limités de ces programmes. Le constat est d'autant plus décevant qu'une littérature émergente associe la consommation de cannabis à l'apparition de difficultés cognitives, de symptômes de psychopathologie et même à un risque accru de passage vers un trouble psychotique. Il existe pourtant d'autres modèles de prévention encore sous-utilisés. Cette revue se penchera sur un de ces modèles, soit le modèle Préventure. Dans un premier temps, un court bilan des risques de la consommation adolescente de cannabis sera exposé. Par la suite, une revue des stratégies de prévention et les résultats des méta-analyses les plus récentes seront présentés. Pour conclure, une présentation d'un modèle de prévention sélectif ciblant la personnalité sera discutée afin de montrer la voie vers une prévention plus efficace à l'échelle de la population adolescente.

Conséquences d'une consommation précoce de cannabis à l'adolescence

Dans le contexte de la recherche sur le cannabis, il devient clair que l'utilisation de cette substance en bas âge peut avoir des effets délétères importants sur le développement cognitif et affectif de l'adolescent. En effet, de nombreuses études établissent un lien entre la consommation de cannabis et des difficultés importantes sur le plan cognitif (Lisdahl et al., 2013; Nguyen-Louie et al., 2015; Squeglia et al., 2009) et sur le plan de la psychopathologie (Farmer et al., 2016; Richardson, 2010). Des devis transversaux conduits auprès d'adultes et d'adolescents marquent une association à la baisse entre les ressources d'attention, de vitesse de traitement et de mémoire de rappel chez les personnes aux prises avec des problèmes d'usage du cannabis (Volkow et al., 2016). Ces difficultés semblent dans certains cas s'estomper avec une durée d'abstinence d'au moins 30 jours, mais certaines études laissent entendre que les déficits cognitifs liés au cannabis pourraient perdurer jusqu'à plus d'une vingtaine d'années après la consommation, surtout si cette dernière avait commencé à l'adolescence (Meier et al., 2012; Castellanos-Ryan et al., 2016).

Outre les effets sur la performance cognitive, l'utilisation du cannabis en bas âge semble aussi liée à un sérieux problème au niveau de la psychopathologie, nommément l'apparition d'un trouble psychotique dans la jeune vingtaine (Large et al., 2011; Moore et al., 2007). On constate aussi une association positive entre la consommation de cannabis et les difficultés comportementales (Farmer et al., 2016; Richardson, 2010). Ces impacts au niveau de la santé mentale rendent doublement importante la prévention de la consommation du cannabis chez les adolescents et soulève le besoin urgent d'utiliser des

programmes de prévention capables d'adresser le problème de la comorbidité entre la consommation de cannabis et les difficultés sur le plan de la santé mentale.

Revue des approches en prévention

Le domaine de la recherche empirique sur les stratégies de prévention de la toxicomanie classe les approches en quatre paliers différents. Cette division est basée sur le type d'intervention, mais aussi sur la proportion d'individus ciblés par ces interventions. Cette taxonomie est représentée sous forme de pyramide à la Figure 13.

Figure 13. Paliers de prévention en fonction du nombre de personnes ciblées par l'intervention.
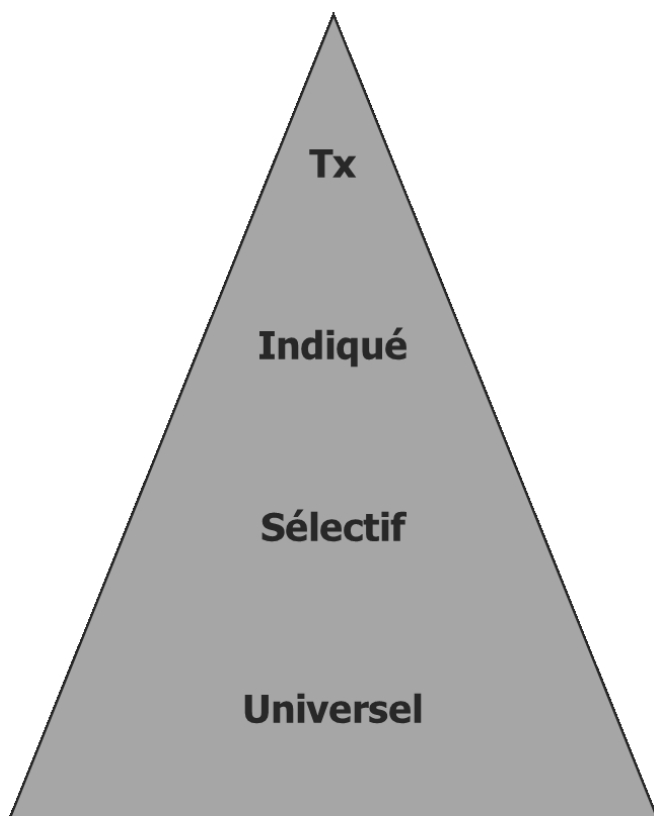
Programmes universels

À la base de la pyramide figurent les interventions dites « universelles », qui constituent la première ligne d'intervention à caractère préventif. Ce palier de prévention vise à offrir, à l'échelle de toute la population, une intervention d'intensité faible à modérée, présumant que tous les individus de la population présentent un certain risque de développer le problème ciblé, soit la consommation précoce de cannabis dans le contexte de ce chapitre. Ces interventions, par leur nature, se doivent d'être assez générales dans leurs visées et leurs propos, puisqu'elles doivent demeurer pertinentes tant pour les jeunes qui n'auraient jamais consommé, que pour ceux qui consomment déjà le cannabis.

Programmes sélectifs

Le deuxième palier représenté porte sur les interventions dites « sélectives ». Ces programmes, souvent plus courts que les programmes universels, se démarquent par leur tentative d'offrir des interventions plus directement pertinentes aux jeunes selon un trait ou une caractéristique spécifique (ex. : une personnalité impulsive) constituant un facteur de risque pour le développement d'un problème donné (ex. : la consommation précoce de cannabis). Cette présélection en fonction d'un facteur de risque conduit les programmes de cette nature à offrir des services à un nombre plus restreint d'individus au sein d'une population. Ce type d'intervention relativement récent a émergé dans le domaine de la prévention des comportements agressifs chez les enfants. Les progrès réalisés dans le domaine de la recherche sur l'étiologie des problèmes de comportements chez les adultes ont conduit les chercheurs à s'intéresser aux premiers marqueurs de l'agression chez les enfants de niveau préscolaire ou primaire. Les recherches ont révélé que les jeunes enfants les plus réactifs/agressifs de tempérament que leurs pairs étaient beaucoup plus à risque de

développer des problèmes de comportements persistants tout au long de leur vie (Tremblay et al, 2004). Ce marqueur de tempérament a ensuite été utilisé pour cibler les jeunes enfants à risque. Une fois identifiés, des interventions préventives ciblant précisément leur réactivité et agressivité ont considérablement réduit leur risque de développer un trouble de comportement (Bryant et al., 1999). Ces interventions, bien qu'efficaces dans le domaine de l'agression, demeurent encore peu nombreuses dans le domaine de la prévention des toxicomanies, malgré un progrès important dans notre compréhension des déterminants tempéramentaux de la toxicomanie.

Programmes indiqués

Plus haut, figure le palier dit « indiqué », qui vise à endiguer plutôt qu'à prévenir les premiers signes d'apparition d'un problème de consommation. Ces interventions s'inspirent souvent de la tradition des interventions motivationnelles brèves, dont la plus populaire est celle de l'entretien motivationnel (Miller & Rollnick, 1991). Les programmes indiqués sont offerts aux consommateurs problématiques qui ne remplissent pas encore les critères de sévérité nécessaire à l'attribution d'un diagnostic. Ces programmes sont souvent donnés en formats brefs, s'échelonnant sur moins de cinq rencontres. Lors des rencontres, l'adolescent, en compagnie d'un intervenant, explore les avantages et désavantages de sa consommation dans l'espoir de susciter un changement d'attitudes et de comportements. Comme le programme s'adresse aux jeunes consommateurs, le nombre d'individus ciblés par ces programmes est considérablement restreint par rapport aux niveaux précédents.

Traitement

En fin, au sommet de la pyramide, on retrouve le traitement. Ce dernier niveau n'est plus du ressort de la prévention. Le traitement, plus intensif, vise donc un suivi en pédopsychiatrie ou en équipe multidisciplinaire. Ce type d'intervention, par son intensité et son coût, est réservé à un petit nombre d'individus présentant les besoins les plus élevés. Ces programmes sont discutés dans un autre chapitre de cet ouvrage.

Revue des approches universelles

À notre connaissance, seuls les approches de préventions universelles et les traitements indiqués ont récemment fait l'objet de méta-analyses. La revue systématique des écrits la plus récente portant sur les programmes universels, produite par Faggiano et collègues (2014), inclut un ensemble de 51 études qui évaluaient différents programmes de prévention visant à réduire la consommation de cannabis et/ou de drogues chez un total de 127 146 étudiants de niveau secondaire. Cette revue tentait de distinguer l'efficacité relative et combinée de trois archétypes de stratégies d'intervention différente : l'entraînement aux habiletés sociales, le recadrage des normes sociales et les programmes d'éducation aux drogues.

La première approche identifiée, aussi la plus répandue, était celle portant sur l'entraînement aux habiletés sociales. Ce type de stratégie d'intervention se base sur les travaux de recherche de Bandura (1977) et sa théorie de l'apprentissage social, stipulant que les jeunes apprennent, par observation, imitation et renforcement, à utiliser des drogues. En d'autres termes, on apprend à utiliser, et parfois à abuser, du cannabis. Pour contrer ce processus d'apprentissage, les programmes basés sur l'entraînement aux

habiletés sociales offrent un cursus informé des techniques de la thérapie cognitive comportementale, comme l'enseignement d'habilités interpersonnelles, la formulation de buts personnels à long terme, la résolution de problèmes, la prise de décisions équilibrées, les stratégies de coping, les habilités d'assertion comportementale et les habilités de refus. Une fois transmises, ces compétences permettraient aux jeunes de ne pas développer une consommation problématique : les jeunes peuvent prendre de meilleures décisions, utiliser des stratégies de coping plus adaptées que la consommation de cannabis, résister à la pression de leurs pairs et mieux affirmer leur refus de consommer. Parmi les interventions appartenant à cette approche figure le « Life Skills Training Program » (LSTP ; Seal, 2006), le programme SMART (Hansen, 1988), le programme « Adolescent Decision-Making » (ADM ; Snow, 1992), le programme GATEHOUSE (Bond, 2004), le programme KEPT LEFT (Resnicow, 2008) et le programme « Drug Abuse Resistance Education » (DARE; Clayton, 1996).

La deuxième approche identifiée était celle visant le recadrage des normes sociales. En effet, les jeunes sont nombreux à surestimer la consommation de drogues et d'alcool des adultes près d'eux et la consommation de leurs pairs (McGuire et al., 1968 ; Evans et al., 1976). Les jeunes sont aussi exposés, au-delà de leur environnement social à un environnement médiatique faisant, consciemment ou inconsciemment, la promotion de l'usage de substances, comme le cannabis. Les programmes ciblant les normes sociales visent donc à recadrer ces normes biaisées véhiculées par les proches des adolescents et les médias. Ces programmes tentent de développer chez les jeunes : la capacité d'accueillir avec critique les messages qu'ils reçoivent de leur entourage quant aux drogues et la

capacité de résister à la pression de consommer. Ces programmes prennent la forme d'ateliers informatifs, souvent des activités « Mythe ou Réalité ? » dans lesquels du matériel éducatif est présenté. Ces cursus passent en revue les mythes entourant la fréquence typique de consommation, les motifs d'utilisation, et la sécurité des substances psychoactive, comme le cannabis. Parmi les programmes figurants dans cette catégorie, on retrouve le programme ALERT (Ellickson, 2003 ; St Pierr, 2005 ; Ringwalt, 2009), le programme Alcool/Tabac/Drogues (ATD; Copeland, 2010), le programme The No Drug Program (TND; Sun, 2006) et le programme informatisé CLIMATE (Newton, 2009).

La dernière approche identifiée porte sur les campagnes d'information et d'éducation relatives aux drogues. Ces programmes présument qu'une meilleure connaissance des effets néfastes des drogues serait suffisante pour entraîner une réduction de la consommation chez les adolescents. Ces programmes prennent souvent la forme de cours magistraux, incluant présentation multimédia, témoignages, démonstration devant le groupe, etc. Ces programmes demandent, en général, moins d'implication de la part des jeunes assistant à la présentation, considérant qu'ils ne visent pas l'enseignement d'attitudes ou de comportements différents que l'adolescent doit mettre en pratique, mais plutôt l'acquisition de nouvelles connaissances. Au rang de ces programmes figurent le modèle d'intervention de Sexter et collègues (1984), et le programme de Sigelman et collègues (2003).

Au bilan, les programmes offrant les meilleurs résultats étaient ceux appartenant à la fois à la classe des programmes visant l'entraînement aux habiletés sociales et à la classe des programmes visant le recadrage des normes sociales. Parmi ces programmes figure l'intervention Take Charge of Your Life (TCYL; Sloboda, 2009), le programme TND (Sun,

2006) et l'intervention UNPLUGGED (Faggiano, 2010 ; Gabrhelik, 2012). En d'autres termes, l'union d'un cursus visant à la fois l'acquisition d'habiletés et le recadrage de normes sociales en un seul et même programme serait ce qu'il y a de plus efficace, pouvant réduire le risque de développer une consommation de cannabis d'environ 21 % à court terme, et réduisant le risque de développer une consommation de cannabis d'environ 17 % à plus long terme (Faggiano, 2014). La comparaison entre approches uniques n'a pas révélé la supériorité claire d'une approche en prévention, mais laisse entendre que les programmes basés sur les habiletés sociales tendent à être supérieurs aux programmes d'autres approches. En effet, ceux-ci tendent à démontrer des réductions de la consommation de cannabis à hauteur de 10 % à court terme, et 14 % à plus long terme. Il est toutefois à noter que ces programmes étaient plus nombreux dans l'étude, jusqu'à deux fois plus nombreux que les programmes visant les normes sociales, ce qui aurait pu jouer en la faveur des programmes ciblant l'acquisition d'habiletés sociales.

Au-delà des résultats rapportés, certaines critiques peuvent être formulées à l'égard du degré d'avancement du domaine de la recherche empirique sur les programmes de prévention universels de la toxicomanie chez les jeunes. D'une part, on déplore l'absence de nouvelles études comparant les programmes, limitant la capacité d'établir une hiérarchie des approches. De plus, peu d'écrits évaluent la valeur relative des modules proposés dans un même programme, ce qui limite la capacité de créer de nouveaux programmes plus courts n'incluant que les meilleurs modules. Comme la recherche tarde à identifier ce qui est à l'origine de l'effet préventif dans chaque atelier, il est tristement normal de constater que certains programmes nouvellement développés causent des effets iatrogènes que des

programmes développés auparavant ont eux aussi engendrés. Finalement, les auteurs regrettent le manque de raffinement théorique des programmes étudiés, soulignant que peu de programmes universels émergent d'une compréhension riche des facteurs responsables du développement et du maintien des problèmes de consommation. Certains programmes ne possèdent même pas les bases d'une formulation théorique et le peu de programmes en possédant gravite autour des deux mêmes théories de la dépendance, soit la théorie de l'apprentissage social de Bandura (1977), ou la théorie du comportement planifié (« theory of planned behaviour ») de Ajzen (1985). Considérant les progrès remarquables de la recherche en étiologie de la toxicomanie (Conrod & Nicolau, 2016), il est surprenant que les programmes de prévention tardent à intégrer ces trouvailles dans leur conceptualisation du problème et leurs cibles cliniques.

Revue des approches indiquées

Une seconde méta-analyse (Carney et al., 2016), cette fois étudiant les programmes de prévention indiqués courts, offerts en milieu scolaire, génère des résultats comparables. Cette étude, regroupant un nombre plus limité d'études (six) totalisant 1176 étudiants, montre que les ateliers courts de prévention pourraient contribuer à réduire la quantité de consommation, la fréquence d'utilisation, le nombre de symptômes d'abus et de dépendance au cannabis lorsque comparés à un protocole d'évaluation de la consommation sans intervention quelconque ($d = 0,26 – 0,97$). La plupart de ces programmes courts (environ cinq rencontres) sont inspirés des techniques de l'entretien motivationnel et des thérapies motivationnelles brèves (Miller 1985 ; 1986 ; 1987 ; Miller & Rollnick, 1991). Certaines craintes ont été formulées quant à la qualité des devis évaluant l'efficacité de ces

programmes. Les résultats de la méta-analyse semblent confirmer les soupçons soulevés par des revues antérieures. Les effets, bien que positifs et significatifs, tendent à faiblir au fil du temps. Bien que les jeunes adolescents recevant ces programmes rapportent une diminution de la fréquence et de la quantité de cannabis qu'ils consomment, ces effets fléchissent une fois franchi le cap des quatre mois. Ces programmes sont aussi peu nombreux à générer quelques effets durables dans une période de plus de 24 mois, ce qui limite l'utilité de ces programmes dans la lutte contre l'expérimentation et la consommation de cannabis chez les adolescents. Ces programmes sont aussi peu efficaces à décourager des adolescents n'ayant jamais consommé de cannabis à poursuivre sur la voie de l'abstinence. Comme les techniques d'entretien motivationnel visent à soutenir la réflexion sur les avantages et inconvénients de la consommation dans le but de soutenir le processus normal de changement, ces discussions sont rarement productives pour les jeunes adolescents n'ayant aucun avantage à rapporter quant à l'utilisation du cannabis, à défaut d'en avoir fait l'expérience au préalable. En somme, les programmes d'interventions brèves, bien qu'une excellente façon d'offrir des soins aux adolescents dont l'utilisation du cannabis devienne problématique, demeurent peu efficaces à entraîner un retard de l'âge de la première consommation, retombée primordiale pour tout programme visant un effet de prévention.

Innovation : une prévention sélective basée sur la personnalité[7]

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[7] Le contenu présenté dans cette section constitue un texte vulgarisé destiné à un public moins habitué à la recherche clinique. Pour une revue empirique davantage rigoureuse, nous avons ajouté, à l'Annexe 3. Information Complement to Chapter 3, un extrait de chapitre publié faisant la revue systématique des essais cliniques évaluant l'efficacité du programme Preventure.

Les résultats provenant des techniques de prévention universelles et sélectives sont décevants. D'une part, les programmes universels, bien qu'efficaces pour certains, sont généralement limités dans leur impact, puisqu'ils focalisent sur des thèmes peu spécifiques aux jeunes à risque plus élevé de consommer. D'autre part, les programmes indiqués, bien qu'utiles pour freiner le passage vers un trouble lié au cannabis, n'offrent aucun avantage pour repousser l'âge du début de la consommation. À la lumière de ces trouvailles, il serait avantageux de bonifier notre arsenal d'interventions préventives en investissant davantage dans le palier d'interventions sélectives, palier encore sous-utilisé. Notre attention se portera plus particulièrement sur le programme de prévention Préventure, un programme de prévention sélectif qui cible les traits de personnalité.

Un premier avantage que présente Préventure est sa capacité à aborder le problème épineux de la comorbidité chez les consommateurs problématiques de cannabis. En effet, un des problèmes difficiles à adresser dans les autres paliers de prévention, et même dans le contexte de certains traitements bien établis, porte sur la cooccurrence de difficultés sur le plan de la consommation et de la santé mentale (ex. : une personne abusant du cannabis et présentant des comportements délinquants). Tel que propose Conrod et collègues (2000), il est possible de bonifier notre prévention des problèmes de toxicomanie en tenant compte d'une vaste littérature portant sur les facteurs de risque associé au passage vers un trouble de consommation et/ou un trouble psychiatrique plus tard dans le développement.

Ces facteurs de risque se déclineraient selon cinq axes représentant des facteurs de personnalités distincts, associés à des profils cognitifs et motivationnels sous-jacents (Castellanos-Ryan et al., 2011 ; Rioux, C. et al., 2016). Ces cinq profils de personnalité sont

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les suivants : Sensibilité à l'Anxiété (SA), Impulsivité (IMP), recherche de Sensations

Fortes (SF), désespoir/Pensées Négatives (PN) et le profil vulnérable à la psychose. Ces

cinq profils sont capables de prédire l'acquisition future de problèmes de toxicomanie, les

motivations conduisant à l'utilisation des substances, la préférence pour certaines

substances plus que d'autres ainsi que des tendances cognitives et comportementales plus

générales (ex. : tendances antisociales, anxieuses ou dépressives ; Conrod & Niklaou,

2016). Par exemple, les individus sensibles à l'anxiété rapportent utiliser les substances

pour réguler leur anxiété et leurs émotions négatives, alors que les personnes portées à la

recherche de sensations fortes sont plus nombreuses à rapporter utiliser des substances pour

altérer et augmenter certains aspects de leur expérience (Woicik et al, 2009). Plus qu'un

facteur de risque, ces traits de personnalité peuvent aussi devenir un facteur de maintien

chez les personnes qui développent un problème de consommation, rendant ces facteurs

pertinents tant au niveau de la prévention qu'au niveau du traitement. À l'appui, les

personnes présentant un haut niveau de sensibilité à l'anxiété, souvent très intolérantes aux

symptômes de retraits liés à l'arrêt d'une consommation, ont plus de chances de rechute

quand ils tentent d'arrêter de fumer (Zvolensky et al., 2008).

Outre son innovation sur le plan théorique et clinique, un autre avantage de Préventure

porte sur sa forme. En effets, le programme Préventure propose d'offrir une prévention plus

intensive, tout en restant très brève, à une proportion réduite des adolescents d'une cohorte.

Cette prévention est offerte avant qu'ils ne développent de problèmes sur le plan de la

consommation ou de la santé mentale. Pour ce faire, le programme Préventure propose

d'identifier les personnes les plus à risque de développer des problèmes de santé mentale et

de consommation sur la base d'un dépistage proposé à l'ensemble d'une population étudiante. Ce dépistage s'opère à l'aide d'un court questionnaire, le Substance Use Risk Profile Scale (SURPS), une échelle de 24 items. Sur la base du questionnaire, entre 40 et 50 % des jeunes répondants sont identifiés comme présentant un risque élevé, soit le fait de montrer un niveau élevé d'un des quatre traits de personnalité identifié par la recherche (SA, IMP, PN ou SS). Les jeunes identifiés sont ensuite, sur la base des résultats du questionnaire répartis en petits groupes. Les jeunes présentant un même profil sont regroupés à fin d'offrir à ces jeunes une intervention répondant spécifiquement aux enjeux rattachés à leur profil de personnalité. À titre d'exemple, les jeunes chercheurs de sensations fortes sont regroupés pour parler des difficultés reliées à la prise de risque non calculée, alors que les jeunes sensibles à l'anxiété sont regroupés pour discuter de leur tendance à surestimer le degré de risque auquel une situation les expose.

Comme la plupart des programmes de prévention étudiés en recherche s'échelonnent sur cinq à quinze rencontres, certains pourraient se montrer sceptiques quant à la possibilité d'aider les jeunes en un nombre plus limité de rencontres. Toutefois, le modèle Préventure est capable de générer des retombées positives en l'espace de seulement deux rencontres de 90 minutes pour un total de trois heures de contact avec les jeunes. Cette économie de temps remarquable en comparaison aux programmes universels s'échelonnant parfois sur plus d'une quinzaine de rencontres est entre autres attribuable à la nature plus ciblée des interventions. En effet, l'impact des techniques enseignées en ateliers augmente lorsque les discussions portent sur des enjeux spécifiques à chaque profil de personnalité.

Les ateliers eux-mêmes, bien que différents dans leur contenu, suivent une formule semblable. Les ateliers visent d'abord à centrer les jeunes autour de leurs objectifs personnels à long terme. Une fois identifiés, les jeunes cernent certains aspects de leur profil de personnalité comme un frein à l'atteinte de leurs buts. Ils identifient ensuite leurs pensées comme une cible concrète pour prendre contrôle des situations difficiles. Ils identifient donc leurs erreurs de pensées dictées par leur profil de personnalité, les confrontent et génèrent des pensées alternatives plus aidantes dans l'atteinte de leurs buts. Pour faire avancer cet agenda, le programme Préventure s'inspire des meilleures pratiques issues de la recherche en psychologie clinique : segments psychoéducatifs, techniques d'entretien motivationnel, analyse fonctionnelle cognitive comportementale et méthodes de confrontation empathique. Toutes ces techniques convergent vers le même objectif : que le jeune développe une meilleure compréhension de lui-même, développe les outils nécessaires à une meilleure gestion de sa personnalité et poursuit avec plus d'assurance ses buts personnels à long terme.

Un troisième avantage de la méthode Préventure est la rigueur de la recherche derrière son développement et le soutien empirique dont est doté le programme. En effet, comme recensé précédemment, le programme entraîne en moyenne une réduction de taille modérée à élevée de la consommation de drogues chez les adolescents (Conrod & Nikolaou, 2016 ; Morin, Harris & Conrod, 2017). Parmi les études soutenant le programme, plusieurs essais randomisés contrôlés soutiennent que le programme peut être implanté avec succès et efficacité dans un milieu scolaire. Ce milieu d'implantation permet d'offrir des services nécessaires dans un milieu que les jeunes fréquentent déjà. Cette possibilité d'utiliser

l'école comme port d'attache permet de contourner le problème de la référence et de l'accès aux services en communauté pour les adolescents. L'avantage d'offrir Préventure dans les écoles s'accompagne du bénéfice que le programme peut être offert avec fidélité par des intervenants de la communauté ayant suivi une formation offerte par l'équipe de recherche. Cela implique que les écoles désirant offrir Préventure peuvent le faire de façon autonome, une fois que les intervenants de l'école ont été formés. Des données en provenance de la recherche révèlent que les ateliers offerts par des intervenants formés accotent l'efficacité des ateliers offerts par des membres de l'équipe de recherche quant à leur capacité à réduire le risque de développer une consommation chez les jeunes.

Bien que le programme Préventure ait davantage fait ses preuves quant à sa capacité de différer l'âge de la première consommation d'alcool, certains résultats de recherche démontrent l'efficacité du programme à identifier les jeunes les plus à risque d'utiliser le cannabis et à différer l'âge de la première consommation de cannabis. Selon une récente étude (Mahu et al., 2015), les jeunes les plus à risque de développer une consommation de cannabis serait les chercheurs de sensations fortes, qui seraient en partie motivés à utiliser le cannabis afin d'altérer leur expérience du monde. De plus, une étude de survie a fait la démonstration que les jeunes ayant reçu l'intervention Préventure ont près de 17 % plus de chances de ne pas développer de consommation de cannabis et ce même deux ans après la réception de l'atelier. Ces données préliminaires soutiennent que le modèle d'intervention ciblé préconisé par Préventure constitue une stratégie prometteuse pour protéger les jeunes des méfaits du cannabis.

Conclusion

Le cannabis, étant une substance nocive pour le développement cognitif et affectif des adolescents, il est primordial d'utiliser des stratégies de prévention informées des récentes découvertes au plan neurodéveloppemental. Malheureusement, les meilleures méta-analyses sur les stratégies de préventions universelles et indiquées indiquent que peu d'interventions sont en mesure de différer l'âge de la première consommation et entraîner une réduction à long terme de la consommation de cannabis chez les adolescents. Toutefois, les données frappantes des interventions sélectives, comme le modèle d'intervention Préventure, constituent une avenue prometteuse pour une prévention capable de protéger les adolescents plus vulnérables aux effets d'une consommation précoce de cannabis. En somme, il est urgent pour nos dirigeants, en voie de légaliser la vente et la consommation récréative du cannabis, de prendre connaissance des interventions les plus efficaces et ainsi mettre en applications les mesures les plus à même de protéger les jeunes.

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Investigation of the Relation Between Substance Use and Cognitive Performance and

its Mediating Effect on Psychopathology Symptoms

General Discussion and Conclusion

par

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6. General discussion

6.1 Review of Key Findings from Empirical Studies

In summary, this research aimed to: 1) get a clearer understanding of the relationship between substance use and cognitive functioning by testing three different models of association (e.g.: common vulnerability factor, pathoplastic and neurotoxic) using multi-level models, 2) investigate how these cognitive correlates could mediate the association between substance use, namely cannabis use, and mental health problems along externalizing and internalizing continuum, and 3) to review the different kind of prevention models and their efficacy in reducing substance misuse in adolescence and discuss how empirical findings of the two previous chapters might inform clinical efforts in substance misuse prevention.

In chapter 1 of this dissertation, the investigation sought to examine what kind of harms, both short and long term, could befall early-onset substance users, looking at very light and heavy users. Furthermore, the investigation also sought to contrast these effects from potential common vulnerability factors (e.g.: pre-existing genetic, temperamental, or cognitive traits) that would account for differences between individuals. Analyses presented in this empirical study documented small neurotoxic effects of substance use as they relate to cognitive performance: adolescent cannabis use in a given year was shown to be negatively associated with inhibitory control on the next year over and above adolescent alcohol use. A similar trend, though not significant, was reported between past year's cannabis use and next year's working memory function. Other documented effects consisted of equally small concurrent effects of cannabis in relation to the domain of delayed recall memory. These observations not only show how substance use behaviour is acquired during adolescence but

also highlight how early substance use behaviour, like cannabis use, can already share a link to their developing cognitive functions. Despite these effects being small, evidence from adult substance misusers shows how impactful these effects can become with sustained misuse (Stavro et al., 2012). Common vulnerability factor was also detected, suggesting that certain individuals seem more likely to pick up early substance use habits and exhibit lower performance on cognitive tasks. Namely, individuals who exhibited cannabis use and/or alcohol use tended to underperform when compared to their peers on working memory, perceptual reasoning, and inhibitory control. This reinforces the notion that other factors are to be considered to fully understand how adolescents' substance use and cognition relate to one another. This information is relevant when considering prevention strategies: early indicators of use and cognitive lapses in expected development should be clarified to provide rapid care.

Knowing that substance misuse, especially cannabis use, can interfere with adolescents' cognitive development, the question of psychiatric comorbidity remained unanswered. The objective of the second empirical study, presented in chapter 2, was to clarify if there were any relationship between cannabis use, its negative association to cognitive performance, and the emergence of psychopathology symptoms. Results indicated that the association between cannabis use and psychopathology symptoms was partially related to cognitive performance at a mostly between-subject level. In other words, using cannabis, along with its negative relation with domains of cognition (e.g.: inhibitory control, working memory, delayed recall memory, perceptual reasoning), is associated with higher levels of psychopathology symptoms reported (e.g.: internalizing and externalizing), but

underlying premorbid mechanisms could account for this pattern of association. To a lesser degree, students who increase their cannabis intake from one year to the next tend to also experience increases in their symptoms through the negative relation between cannabis use and cognitive performance. These results partially substantiate empirical (Gobbi et al., 2019; Richardson, 2010; Renard, Rushlow & Laviolette, 2018) and clinical observations: early substance misusers tend to show worst mental health trajectories and develop more comorbid psychopathologies. It is important to note that, despite significant mediational effects, the mediation was not total. Furthermore, the mediations were time-limited, which further prevents establishing directionality. This further emphasizes that other factors, such as common vulnerability effects, are to be considered, as they represent important portions of the effect reported. Additionally, these results dampen the enthusiasm surrounding cognitive remediation. Adolescents' cognitive performance, as reported in chapter 2, does not seem to have the hypothesized link to psychopathology symptoms' trajectory.

6.2 How Empirical Findings Can Assess and Improve Prevention Efforts

Data from chapter 1 and chapter 2 show that adolescent substance use, more specifically cannabis use, is related to cognitive problems and psychopathology symptoms. Furthermore, these associations, while partly related to the neurochemical properties of cannabis (as indicated by within-subjects effects), appear also to be driven by pre-existing differences between individuals (between-subjects effects). These findings highlight key components that should be integrated into our prevention strategies. First, they need to delay substance use initiation and encourage reduced substance intake to avoid cognitive and mental health problems linked to cannabis use. Next, prevention needs to better isolate and

target common vulnerability factors that could drive early substance intake, cognitive trajectories, and psychopathology susceptibilities.

Chapter 3 begins this reflection by establishing the nature of prevention efforts currently deployed in Canada and the United States. The bulk of prevention approaches fit in two broader categories, namely universal prevention programs and indicated interventions. To a lesser extent, targeted prevention programs are also administered.

The review then proceeded to establish the effectiveness of said prevention approaches. Despite state mandate to provide prevention resources in schools, few of the programs delivered in Canada or the United States have been empirically validated (Fazel, Patel, Thomas & Tol, 2014). These observations were fleshed out in detail in a narrative selective review of the literature presented in chapter 3 of this dissertation. In a nutshell, prevention approaches aiming to limit adolescent cannabis use, mostly universal or indicated, struggle in delaying the onset of use and reducing levels of use beyond a short-term period (Morin & Conrod, 2019; Faggiano et al., 2014; Carney et al., 2016; Porath-Waller et al., 2010). Only the most intensive universal prevention programs seem to generate moderate effects on substance use. Universal programs are held back by two factors: 1) they need to be generic enough to stay relevant to all students but fail to be specialized enough to youth most at risk for early use, and 2) they only focus on substance use while ignoring other cooccurring problems. Indicated prevention, despite providing significant improvement to students struggling with substance use, does not provide lasting benefits to patients who enroll in them.

Targeted prevention, on the other hand, seems to circumvent these shortcomings. This prevention strategy focuses on the early identification of pupils most at risk of substance misuse and uses common traits amongst youth to coordinate interventions. The result is a workshop that stays relevant for youth and can address substance use behaviours and other associated problem behaviours. Targeted prevention has been shown effective in addressing aggressive behaviours in young children (Tremblay et al., 2004), delaying and reducing alcohol use in adolescents (Conrod et al., 2011; Morin, Harris & Conrod, 2017), and reducing cannabis engagement in adolescents (Mahu et al., 2015). With data presented in this dissertation, targeted preventions benefit from stronger empirical support.

As reported in chapters 1 and 2, even in an adolescent sample, over the full continuum of users, substance use is linked to cognitive ability and psychopathology symptoms. Considering information shared in chapter 3, universal programs, for the most part, do not provide the means to address cooccurring problems associated with adolescents' substance use. In a review conducted by Ogilvy (1994), despite recognizing skills training as an appropriate tool to bring about real-life change, this intervention alone might not prove sufficient. Contextual factors (Ogilvy, 1994), if not considered, might go unanswered, undermining skills effectiveness or reliability. For instance, teaching drug refusal skills to an adolescent with low premorbid behavioural inhibition ability and high externalizing symptoms, such as inattention and impulsivity, will prove significantly more challenging and might be very fragile if not rehearsed regularly in immediately relevant contexts.

Indicated and targeted prevention programs, on the other hand, seem more appropriate in addressing cooccurring problems. Indicated prevention is usually delivered

individually and follows a motivational-based model of intervention. This results in a personalized plan, tailored to patients' goals, context, specific strengths, and unique challenges. This allows patients and service providers to consider cognitive and psychopathology elements while delivering indicated treatment. Targeted prevention programs, through their reliance on risk profile evaluation, can prospectively prepare for cognitive and psychiatric problems associated with the behaviour targeted. For instance, the Preventure program, through its use of personality risk profiling (Castellanos-Ryan et al., 2013), can provide interventions that both address substance use, but also provide contextually relevant interventions on behavioural and emotional problems associated with a given profile (e.g.: Anxiety Sensitivity workshop targeting both substance misuse and behavioural avoidance).

As reported in chapter 1 of this dissertation and by other research groups (Castellanos-Ryan et al., 2016; Meier et al., 2012), cannabis use initiation in early adolescence (e.g.: before age 16 or 18) seems associated with more impairment on measures of cognition. Clinical findings also show earlier substance use to correlate with higher rates of psychiatric comorbidity (Costello, Erkanli, Federman & Angold, 1999). This indicates that prevention, to achieve maximal benefits for adolescents, needs to be delivered in a certain developmental window where substance use can be delayed, therefore reducing related harms and the likelihood of severe trajectories. On this criterion, indicated programs struggle. By design, these prevention strategies rely on the apparition of mild to moderate symptoms before being offered. Although necessary in the global hierarchy of care, indicated programs' failure to delay the onset of use might account for why treatment effects are harder to maintain. Failing

to avert negative consequences associated with early substance use might trigger subtle changes in cognitive and mental state that could result in increased sensitivity to relapse. This hypothesis could be tested in another research beyond this dissertation.

Timely delivery of interventions is better achieved with universal or targeted prevention. Universal programs are usually easier to deploy to students early in their adolescence before the majority engages with substances such as cannabis. This can lead, in some cases (Faggiano et al., 2014), to delayed onset of cannabis use, although usually not maintained over time. Targeted prevention models usually operate similarly to universal programs by offering services before the onset of use to kids previously assessed as high-risk for early substance misuse. These programs tend to demonstrate lasting effects over time, and some have demonstrated effects suggesting a delay in substance use after following the program (Conrod, Castellanos & Mackie, 2008; O'Leary-Barrett et al., 2010; Morin, Harris & Conrod, 2017).

To increase the effectiveness of early substance use prevention programs, better effectiveness data, dissemination of evidence-based prevention approaches, flexibility in addressing cooccurring problems with substance use, and timely delivery to avoid time-sensitive harms of early use should be integrated. As demonstrated by efficacy data reported on targeted programs, screening for vulnerability to substance misuse is key. In this optic, knowing that pre-morbid cognitive functioning does predict risk for substance engagement, does this factor constitute an adequate screening tool? Based on the results of the empirical studies presented in chapter 1, chapter 2 and other research (Castellanos-Ryan et al., 2016; Nigg et al., 2004), cognitive domains related to executive functioning appear to be good

candidates for such a screen. Chapter 1 and 2 of this dissertation identify mainly inhibitory control, and to a lesser extent spatial working memory, to signal differences between individuals also presenting early onset use of alcohol or cannabis. These findings do echo similar reports by Nigg et al. (2006). Although promising, the practicality of such a screen is debatable. Cognitive assessment usually requires time, material resources and appropriately trained labour to accurately administer and interpret said screening.

Though executive function screens might help us detect adolescents at risk for early substance misuse, their potential as targets for early intervention is yet to be established. It is still unclear whether changes in cognitive abilities trigger later change in substance use. These associations were not modelled in our analyses but might constitute an interesting step in furthering research in this field. Cognitive remediation treatments, which aim to improve cognitive functions on a given domain using cognitive tasks, have received some attention over the past decade. In a review by (Kim et al., 2018), evidence for positive effects of cognitive remediation for adults diagnosed with substance use disorder was reported when assessing recovery of their executive functions. Substance use outcomes also showed that patients who received cognitive remediation tended to remain stable in their substance use, rather than seeing their consumption increase like the control group. The number of days of abstinence was not influenced by cognitive remediation. In a review by Rochat & Khazaal, (2019), they concluded that cognitive remediation benefitted from selecting key domains that readily translate to functional problems to be more effective as treatment options. Considering the low threshold of cognitive difficulties reported in the sample used for this dissertation, cognitive remediation might not constitute a good choice of early intervention

for addressing the emergence of psychopathology in teens. Results reported in study 2 signal suggest that cognition only partially reflects on psychopathology, may it be externalizing or internalizing, making cognitive remediation less indicated to target both substance use and comorbid psychopathology.

Though cognitive screening and remediation remain to be thoroughly assessed, other variables could already constitute adequate factors for early targeted prevention. Temperamental dispositions or personality dimensions have already been linked to early substance use, cognitive performance, and psychiatric symptoms. Traits such as impulsivity (Kozak et al., 2018) and emotional dysregulation (Moffitt et al., 2011) have been extensively associated with early-onset use. These traits can serve as excellent screens and targets for intervention given the wide clinical knowledge on assessment and treatment of these traits (e.g.: Dialectical Behavioural Therapy; Linehan, 2014). Delivering interventions targeting these traits could lead to better self-control and subjective well-being, lowering interest or reliance on substance use for self-regulation, might augment meta-cognitive and executive functioning abilities, and limit subjective distress driving psychopathology symptoms.

By combining information gathered from all three chapters from this dissertation, one can identify that there exist effective preventive intervention programs, with targeted programs affording a wide array of advantages when trying to delay the onset of use. Programs of choice should address cooccurring problems with substance use be delivered early to avoid time-sensitive harms of early use. Though cognitive risk profiles and cognitive remediation might afford novel ways to assess and prevent early substance misuse, further research is required to establish its utility. Beyond cognitive targets, temperamental

disposition and personality traits afford an excellent framework to identify and prevent early onset-substance misuse.

6.3 Contributions and Limitations of Research

We believe this dissertation constitutes a modest, yet valuable contribution to the existing body of knowledge in the field of addiction research and clinical practice. First, this line of research provides a clear perspective on the current portrait of preventive interventions addressed to adolescents in Canada and the United States. The review presented in chapter 3 presents data from rigorous meta-analyses. These provide adequate ground to explore current gaps in prevention, which serves as the main motive of this project. The gaps identified are that certain models of intervention fail to delay the early use of cannabis while others fail to account for and address cooccurring problems. In fact, despite substantial research efforts in addiction medicine, preventing substance misuse remains an important challenge. Early lower-threshold and flexible interventions targeting youth before the onset of addictive behaviours present themselves to be a cost-efficient (Bukoski & Evans, 1998) strategy to limit substance misuse in society. Youth-targeted programs, such as the Life Skills Training Program (LSTP ; Seal, 2006) and the CLIMATE program (Newton, 2009) constitute interesting avenues for a coordinated prevention strategy in communities. There exist intervention models that combine comorbidity and developmentally sensitive strategies. These are usually selective in nature, offering a screen and tailored interventions to adolescents corresponding to specific profiles. One such program that has been abundantly referenced in this dissertation is the Preventure program. The author believes that such programs constitute a promising avenue for addiction medicine because they can assess and alter behaviours or predispositions that pose a risk for severe trajectories before they

materialize into life-threatening conditions. These types of programs address current gaps in services and their clinical relevance merits dissemination.

Beyond clinical relevance, this dissertation also contributes empirically to our understanding of addiction. This novel approach to modelling substance use in youth would not be possible without a substantial amount of data and observations. It is therefore important to recognize the quality of the sample used to conduct the research. The Co-Venture Trial (O'Leary-Barrett et al., 2017) was designed to be representative and capture a wide portion of high school students of all ethnicities, linguistic communities, and social standing. This recruitment effort strived to represent the adolescents of the Greater Montreal area at a near populational level. This strategy also provided statistical power and longitudinal perspective on relevant data, which lends itself to novel multi-level longitudinal modelling, an important new tool in empirical research. The breadth of the yearly assessment conducted also provided a substantial array of data. Sociodemographic measures, substance use behaviour measures, mental health screenings and cognitive performance testing were all integrated into a single database, making it a great tool for longitudinal modelling. Moreover, the populational strategy applied to construct this sample also made it possible to investigate how substance use behaviours were affecting the whole continuum of substance users, not just comparing high users to abstinent teens, which is a usual sacrifice to make in lower sample studies (Hanson et al., 2011; Lisdahl et al., 2013; Nguyen-Louie et al., 2015). This thoughtful design was the spearhead of research. Now, other projects, such as the ABCD project ("ABCD Study", 2020) funded by the NIH, are designed in similar ways, which speaks to the quality of the sample selected.

Another methodological strength of this dissertation is that it lends itself to time sequence inference. It has been argued that causal inference in experimental research is not strictly contingent on a single "gold standard" method but is rather can be attempted with different experimental designs and degrees of caution (Dunning, 2008). Some research questions, either for practical reasons or ethical motives, cannot comply with the gold standards of causal inference, namely Randomised Controlled Trials (RCT; Kabisch, Ruckes, Seibert-Grafe & Blettner, 2011). RCT are rigorous research endeavours where participants are randomly assigned to groups and exposed to carefully introduced variables in a double-blinded fashion. This, of course, does not lend itself to all research questions, especially ones focusing on dangerous behaviours or vulnerable populations (e.g.: drug and alcohol use for minors). In absence of practical and morally sanctionable ways to fulfill the gold standard of RCTs, other designs must be employed. Quasi-experimental designs or naturalistic studies (Dunning, 2008) can provide different avenues to tackle such questions. A naturalistic study posits that we can observe, compare, and interpret the evolution groups differently exposed to naturally occurring risky behaviours. This allows one to observe if a certain behaviour (e.g.: substance misuse) is associated with certain consequences (e.g.: impaired cognitive development, or the emergence of psychopathology symptoms). Of course, for the interpretation to be valid, certain conditions must be met: 1) a causal sequence must be met (the predictor must temporally precede the predicted variable), 2) there must be theoretical rationale to substantiate the causal inference (animal model, histology, case reports, etc.), and 3) other potentially confounding third variables must be anticipated and accounted for in the model (e.g.: age, sex, socioeconomic status, etc.). The Co-Venture Trial, because of its longitudinal design and the extent of its assessment battery provided a solid foundation for

such analyses. Pupils were assessed yearly, which allowed for sequences to be established. Cannabis consumption did relate to cognitive performance a year later, which did link to psychopathology symptoms the subsequent year. Both sets of analyses and models also integrated confounding variables, such as sex and socioeconomic status, which affords more confidence in the hypothesized causal chain. There is also a rationale for this mediating pathway, as shown in animal models. In a study conducted by Tselnicker, Keren, Hefetz, Pick and Sarne (2007) and Senn, Keren, Hefetz and Sarne (2008), THC exposure in rats was positively associated with reduced brain volumes and atypical behaviours. This specific design along with the employed analytical strategy and previous findings gave a better insight into the potential sequential chain of adolescent substance use, cognitive performance, and psychopathology symptoms. We now know that cannabis use in adolescents could partially influence delays in natural cognitive development, which in return could jointly contribute to the emergence of psychopathology symptoms. In the absence of more controlled designs, this strategy constitutes our best attempt at peering into probable sequential chain inference.

To better contextualize the findings reported, the results of this dissertation need to be interpreted critically. One important caveat of the presented research is its inability to firmly establish causation. The presented sequential associations are to be interpreted as tentative. The reason for this lies in the absence of a random assignment of participants. As mentioned before, the ethical responsibility of the research team precluded the assignment of adolescents into groups of abstinent, low, moderate, or high substance users. Members of a vulnerable population should not be deliberately exposed to serious harm for research gain. Therefore, other methods must be employed. These necessary alternatives, by sacrificing

random assignment of participants, carry with them the possibility to falsely interpret the relation between variables under scrutiny. The purpose of random assignment in empirical psychology is to mitigate the effects of unmeasured or unaccounted factors between subjects by integrating an additional degree of randomness. For example, if we suspected that certain unmeasured traits (e.g.: genetic disposition, pre-natal exposure to substances, etc.) may bias the results, randomly assigning participants between levels of substance exposure would or could make groups comparable on these traits if the sample size is large enough. This would limit the ability of a given trait to bias the results. Of course, the present investigation cannot afford to randomly assign participants, which opens itself to falsely inferring a causal chain where a potential third variable might be at play. Certain research has successfully established that family history of substance misuse trigger differential biological responses to alcohol exposure. In a study conducted by Ingjaldsson, Laberg and Thayer (2003), participants with a positive history of alcoholism were shown to be more aroused than their negative counterparts when invited to ingest alcohol, which suggests a form of hereditary sensitivity to substances. That innate sensitivity might also relate to cognitive performance, as proposed by Pihl and Peterson. (1995). Prenatal exposure to substances, such as alcohol and cannabis, has been associated with both earlier onset of substance use and cognitive performance issues (Sithisarn, Granger & Bada, 2012). In its updated report on maternal cannabis use, the Canadian Centre on Substance Use and Addiction (Porath et al., 2018) reports that children of mothers using cannabis before and surrounding birth tend to show deficits in certain domains of cognition (e.g.: executive functioning, response inhibition, visuospatial working memory, etc.) as well as early-onset and higher levels of substance use. This is not to say that the reported results are invalid. In the absence of more encompassing

longitudinal models, this constitutes relevant information that has clinical value. The principle of precaution (Goldstein, 2001) would dictate that in the presence of data that points to potential harm, one should adopt protective measures. This is exactly the case with the results reported in this dissertation: if results could suggest cognitive and mental health difficulties resulting from cannabis use, they need to circulate and inform public health measures. Again, the results do clarify some aspects of directionality and temporality of associations, but caution claims are not in good taste in this context.

Related to study design, both chapters, though able to control for some models of association, were unable to account for the full array of different paths that could link substance use, cognitive and psychopathology data. The studies do not report on the specific effect of cognitive change on later substance use, which deserves to be investigated further. Despite this limitation, the results presented do constitute an adequate attempt to control for the many associative paths uniting substance use, cognitive functioning and mental health.

Effect sizes are also worth pointing out as a limitation to our interpretation of the results. Both in chapter 1 and chapter 2, the effects reported are all below the small effect threshold. This does signify that if it were not for the dimensions of our sample, it is very likely these effects would have gone undetected. Despite that, these effects do seem to indicate how sustained problematic use can likely cumulate into the clinical impairments we observe in adults. It is also worth mentioning that, of the effect size reported, the portion of variance explained (R^2) generated in chapter 2 revealed that between-level models explain more variance than within-level models, further emphasizing conclusions drawn with regards to common vulnerability and prevention.

Another limitation of both empirical studies is attributable to the scientific design of the Co-Venture trial, namely that it is a randomized control trial assessing the effects of a short intervention aiming to delay the onset of substance misuse. This raises the concern that differences between subjects in the sample, resulting from assignment to short intervention delivery, might have biased the results reported on substance use and its subsequent link to cognitive performance and psychopathology symptoms. This limitation needs to be considered when interpreting the results but does not necessarily invalidate the totality of the findings reported. In all likely hood, intervention might have delayed onset of use, therefore lowering occasions of early substance use across part of the sample. Despite potentially lower cannabis use in parts of the sample, the full study did detect a link between cannabis use, cognitive performance and psychiatric symptoms. Though it remains to be tested, concerns that intervention might affect the association between substance use and cognition are difficult to justify theoretically. It would be surprising for a brief intervention to affect adolescents developing brains to the point that their brain responds, at a metabolic level, differently to substance use (e.g.: cannabis). Nevertheless, future designs could attempt to replicate these findings in similar samples without the additional clinical component and verify the validity of the results.

Another point to address is the limited array of cognitive measures. Cognition is an umbrella term that captures the implicit and explicit processes on which our thinking and behaviour rely. Naturally, it was expected that in the context of Co-Venture, cognitive testing had to sample a limited number of domains. Despite that expectation, recent research has highlighted key domains of cognition that have remained unassessed in the context of Co-

Venture, namely attention and verbal processing. Attention seems to be a sensitive domain to substance misuse (Volkow et al., 2016; Crean et al., 2011; Crane et al., 2013), namely alcohol and cannabis misuse. These results hold for adult subjects and adolescent subjects. Furthermore, lower performance on verbal processing tasks has also been linked to substance misuse. This more crystallized domain of cognition could have given another opportunity to understand how substance misuse influences different levels of cognitive performance. Of course, those measures, though beneficial, would constitute a significant cost to the studies. Adolescents were already submitted to a long testing battery and could not afford additional performance tasks which require time and concentration. Furthermore, verbal processing tasks would have posed a difficult challenge, as it would have been difficult to compare data from a task that some completed in the French language, while other participants would have completed the task in English. Nevertheless, Co-Venture did contribute to the scope of addiction research by providing cognitive performance measures on a wide scale of developing teens.

Another limitation of this study relates to questions about the representativeness of the sample and the findings extracted. Though sex was used as a covariate in the analyses of this dissertation, potential differences between sexes were not reported quantitatively. This limits our understanding of the role of sex differences in the observed pattern of relation between substance misuse, cognitive performance, and psychopathology symptoms. Relatedly, despite the sample of the Co-Venture trial affording substantial statistical power to data analysis, whether it is truly representative of the full population of Montreal adolescents remains to be verified. It is important to recognize that ethnicity was estimated

rather than measured explicitly. Despite ethnic differences not being the focus of the presented analyses, a systematic and well-established method to measure racial diversity of the sample would have been desirable. Such methods have been described at length by research communities (Ross, Hart-Johnson, Santen & Zaidi, 2020) and the United States Census Bureau ("2020 Census Frequently Asked Questions About Race and Ethnicity", 2021). Nevertheless, recruitment of schools was conducted purposefully to account for different ethnicities, social stratus, linguistic differences, and geographical differences within the region. This does reflect somewhat positively on the representability of findings, but firm quantitative evidence remains critical to verify the accuracy of these findings.

6.4 Paths for Further Inquiry

As stipulated above, the present research breaks new ground for further investigation in the field of addiction. A first step to expand this line of inquiry would be to address some of the limitations discussed. The integration of more cognitive domains, namely attention and verbal processing, would constitute an excellent first step. Attention has shown itself in recent years to be of importance in understanding the effects of substance misuse and its link to cognitive functioning (Amir & Bahri, 1999). The different tasks selected in the Co-Venture trial (O'Leary-Barrett et al., 2017) were chosen to capture functions with limited overlap: delayed recall memory is conceptually different from perceptual reasoning (a more crystallized form of cognitive function), which in turn is different from executive functioning skills such as inhibitory control and working memory. Our results have suggested that executive functioning (notably inhibitory control) seems more responsive to the long-term effects of early-onset cannabis use. Attention could prove itself equally sensitive to the harms of substance misuse. Despite its technical challenges when looking at a bilingual population

(e.g.: students from the Greater Montreal area), verbal processing would be equally interesting to integrate into future research. In a set of studies conducted by Petersen et al. (2013) and Kavish, Helton, Vaughn and Boutwell (2020), verbal ability in early childhood seemed to partially predict the later emergence of externalizing and internalizing symptoms in elementary school children. This could further benefit the proposed model of a mediating pathway between substance misuse, cognitive performance, and psychopathology symptoms emergence.

Another way to improve on the research conducted would be to reassess the data using cross-lagged pannel analysis with the specific aim of better understanding the time-sequencing of effects. The analytical strategy used in the dissertation prioritized broad-scale change, which allowed an overall outlook on the associations studied but made it difficult to establish moment-to-moment associations between substance use at a specific year and later outcomes. This revision could allow to further exploit the longitudinal richness of the data.

Beyond the addition of more measures and redesigning analyses, broadening the conceptual framework of the presented model could benefit the field. It was mentioned throughout this dissertation that temperamental disposition, such as impulsivity, might account for part of the effect documented, maybe as a moderator. In the context of this project, temperament has been used as a term referring to a mostly innate, probably biological to some degree, propensity to experience certain emotions and proneness to react in particular ways. This broad conceptualization of temperament was most notably established in Kagan's research (1997). It is equally documented that children with more impulsive temperaments are more likely to present atypical or impaired cognitive developments and to also engage in

substance use at an earlier age (Verdejo-García, Lawrence & Clark, 2008). The Co-Venture Trial (O'Leary-Barrett et al, 2017), which provided the data used in both chapters 1 and 2 of this dissertation, was developed to test out the effectiveness of an intervention, the Preventure model (Conrod et al., 2000), targeting certain traits. These traits can be understood to have some basis in temperament (Kagan, 1997). Impulsivity, sensation seeking, anxiety sensitivity and hopelessness could provide some context to understand how the biological interface and early experiences in development could orient substance engagement and brain sensitivity to the effects of psychoactive substances.

Finally, the line of research presented in this dissertation could carry on investigating young adults. The strength of the Co-Venture project was its ability to follow up adolescents throughout their development and establish how certain behaviours, namely substance misuse, could influence their trajectories. It is to be expected that young adults will increase their substance intake in their late teens to mid-twenties (Romine & Reynolds, 2005), which leads one to wonder what impact do those behaviour pose on cognitive development, which is still in progress well after adolescence. Young adulthood also marks the onset of certain mental disorders and substance use disorders (Copeland, Shanahan, Costello & Angold, 2011). These questions deserve to be investigated with rigorous empirical designs, such as Co-Venture, and keeping track of these participants might better inform how substance use engagement in young adulthood shapes cognitive profiles, psychopathology, and substance use problems.

7. Conclusion

In conclusion, this dissertation constitutes a modest yet significant step forward in addiction research. Based on these findings, there is ground to advocate for better dissemination of early targeted interventions designed to delay and limit substance misuse in adolescents. These efforts should not only help limit substance use behaviours in adolescents, but also protect their cognitive development, limit the likelihood of developing comorbid mental health problems, and diverge certain pupils from developing personally and socially harmful addiction problems. These results also contribute to an ongoing political debate surrounding the legalization and accessibility of cannabis in Canada and strive to contribute facts to this debate. Dissemination of this research is, in the author's humble opinion, relevant to informed and sound policy making, but that assessment is the prerogative of decision-makers.

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Appendix 1. Equivalency Table of School Grade across Quebec, Other Canadian Provinces, and United-States Education Systems

Table 9. Equivalency of School Grade across Quebec, Other Canadian Provinces, and United-States Education Systems

Territory/Age of Pupils		12-13 years	13-14 years	14-15 years	15-16 years
Quebec	Name of establishment frequented	High School (École secondaire)			
	Name of school grade	Secondary 1 (Secondaire 1)	Secondary 2 (Secondaire 2)	Secondary 3 (Secondaire 3)	Secondary 4 (Secondaire 4)
Other Canadian Provinces	Name of establishment frequented	High School			
	Name of school grade	Grade 7	Grade 8	Grade 9	Grade 10
United-States	Name of establishment frequented	Middle School		High S	
	Name of school grade	Grade 7	Grade 8	Grade 9	Grade 10

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Appendix 2. Supplemental Information about the Co-Venture Sample

Table 10. Missing Data and Attrition in the Sample

	Year 1	Year 2	Year 3	Year 4	Year 5
Valid	3826	3362	3045	2855	1999
Missing	145	609	926	1116	1972

Note: The first row indicated the number of participants who logged in to the data collection platform at each year of the study, while the second row indicates the number of students who did not connect to the platform and provided any data. Chi-square analyses revealed no difference between responders and non-responders based on sex, ethnicity or substance use behaviours.

Table 11. Rates of Substance Use Across Years in the Study

	Alcohol	Cannabis	Cocaine	Opiates
Year 1	36.70%	4.60%	0.60%	0.30%
Year 2	52.00%	9.90%	0.60%	1.20%
Year 3	65.10%	20.00%	0.90%	1.80%
Year 4	76.50%	28.80%	1.80%	3.20%
Year 5	81.50%	36.60%	1.80%	2.90%

Note: Percentage of participating students for each year who report using either one of the following substances.

Table 12. Rates of Cannabis Users also Using Alcohol

Year 1	84.50%
Year 2	91.20%
Year 3	95.40%
Year 4	97.80%
Year 5	98.20%

Note: Percentage of participating students for each year who report a cannabis consumption that also reports using alcohol.

Appendix 3. Supplementary Material for Chapter 1

Table 13. Sensitivity Analysis including Family Intactness and Ethnicity as Covariates.

	Spatial Working Memory			Perceptual Reasoning			Delayed Recall Memory			Inhibitory Control		
	Estimate	Std. Error	Pr(>|t|)	Estimate	Std. Error	Pr(>|t|)	Estimate	Std. Error	Pr(>|t|)	Estimate	Std. Error	Pr(>|t|)
I(TIME^2)	0.807	0.160	0.000	-0.075	0.044	0.090	1.975	0.044	0.000	0.840	0.320	0.009
Socio-Economic Status	0.175	0.081	0.031	-0.046	0.025	0.072	-0.033	0.016	0.040	0.339	0.154	0.028
Sex	1.872	0.267	0.000	0.302	0.084	0.000	0.050	0.054	0.354	0.469	0.508	0.355
Non-European	1.304	0.298	0.000	-0.303	0.094	0.001	-0.398	0.060	0.000	2.290	0.569	0.000
Family Intactness	-0.435	0.299	0.146	0.272	0.094	0.004	-0.003	0.060	0.962	0.407	0.574	0.478
Alcohol Between-Subjects	0.082	0.056	0.142	**-0.045**	**0.017**	**0.010**	-0.016	0.013	0.204	0.184	0.110	0.094
Alcohol Within-Subjects	-0.008	0.027	0.771	-0.008	0.008	0.277	0.007	0.008	0.373	0.021	0.060	0.722
Alcohol Within-Subjects (Lagged)	0.004	0.037	0.921	-0.007	0.010	0.489	-0.007	0.011	0.488	-0.107	0.077	0.164
Cannabis Between-Subjects	0.418	0.296	0.157	-0.126	0.092	0.173	-0.021	0.067	0.748	**1.593**	**0.571**	**0.005**
Cannabis Within-Subjects	0.050	0.180	0.779	-0.082	0.049	0.095	**-0.136**	**0.052**	**0.008**	0.534	0.379	0.159
Cannabis Within-Subjects (Lagged)	0.358	0.207	0.085	0.099	0.057	0.083	0.000	0.060	0.995	**1.182**	**0.443**	**0.008**

Note: Std. Er : Standard error; Pr(>\|t\|) : *P*-value; Significant effects are marked in **bold** character. Performance on Working Memory and Inhibitory

Control task was measured by counting the number of errors; a lower score indicates a better performance. In the context of sensitivity analysis, Models

were re-estimated with ethnicity and family intactness as covariates. Results did not indicate any changes in the pattern of significant associations (presented in supplemental materials).

Table 14. Effect Sizes of Cannabis and Alcohol Use On Cognitive Domains

	Alcohol (f^2 value)	Cannabis (f^2 value)
Delayed Recall Memory	N.S. findings	0.001
Perceptual Reasoning	0.003	0.004
Spatial Working Memory	0.001	0.001
Inhibitory Control	0.002	0.003

Note: N.S.: Non-significant finings as reported in the main analysis. According to Cohen (1988), f^2 values below 0.02 are considered small effect sizes.

Appendix 4. Information Complement to Chapter 3

A systematic review of the evidence supporting the Preventure model of prevention

Chapter published in *Oxford Handbooks Online*, published in 2017, under the direction of

Oxford Handbooks.

Reference: Morin, J-F. G., Harris, M., Conrod, P.J. (2017). A Review of CBT Treatments for Substance Use Disorders. In Oxford Handbooks (Eds.), *Oxford Handbooks Online*(pp. 30-37). Oxford: Oxford Handbooks.

Auteurs :

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Personality-Targeted Brief Interventions for Substance Misuse and Comorbid Psychopathology: A New Treatment Approach

Substance use disorders have a high rate of co-occurrence with other psychiatric conditions, and as highlighted above, comorbid psychopathology has been identified as a moderator of treatment response, even for traditional CBT interventions. Conrod and Stewart (2000) proposed an adaptation to the relapse prevention model for substance use disorders to incorporate findings from a large literature on common and specific risk factors across substance use and other psychiatric symptoms.

This literature indicates that risk for substance use disorders and concurrent psychiatric problems exist along several continua, often based on personality traits and underlying cognitive/motivational profiles (Castellanos-Ryan et al., 2014; Rioux, C. et al., 2016). These profiles can explain risk for future substance misuse, reasons for substance use/misuse, types of substances that are likely to be abused, and other important cognitive and behavioural tendencies, such as proneness towards disinhibited and antisocial behaviour, depressive symptoms, or panic/anxiety (Conrod & Nikolaou, 2016). As illustrated in Figure 14, the risk for psychopathology and SUD can be represented along five trait dimensions, each with their specific cognitive, motivational profile and pattern of substance misuse and comorbid psychiatric problems. These risk trajectories are associated with very different reasons for substance use. For example, an anxiety sensitivity profile is consistently associated with substance use motives for anxiety and emotion regulation, whereas a sensation-seeking profile tends to be associated with substance use for enhancement reasons (e.g., Woicik et al., 2009). Beyond simple risk factors, these personality dimensions can also contribute to the maintenance of substance-related problems once they occur, making the personality

profiles relevant as a target for treatment. For example, anxiety sensitivity is associated with intolerance of nicotine withdrawal symptoms and risk for early relapse during a smoking cessation attempt (Zvolensky et al., 2008).

Figure 15 demonstrates how the relapse prevention model can be modified to differentially address these underlying risk trajectories to address vulnerability to substance misuse and psychiatric symptoms in a more personalized manner.

Figure 14. Personality Risk Factors for SUD's and Other Mental Health Problems
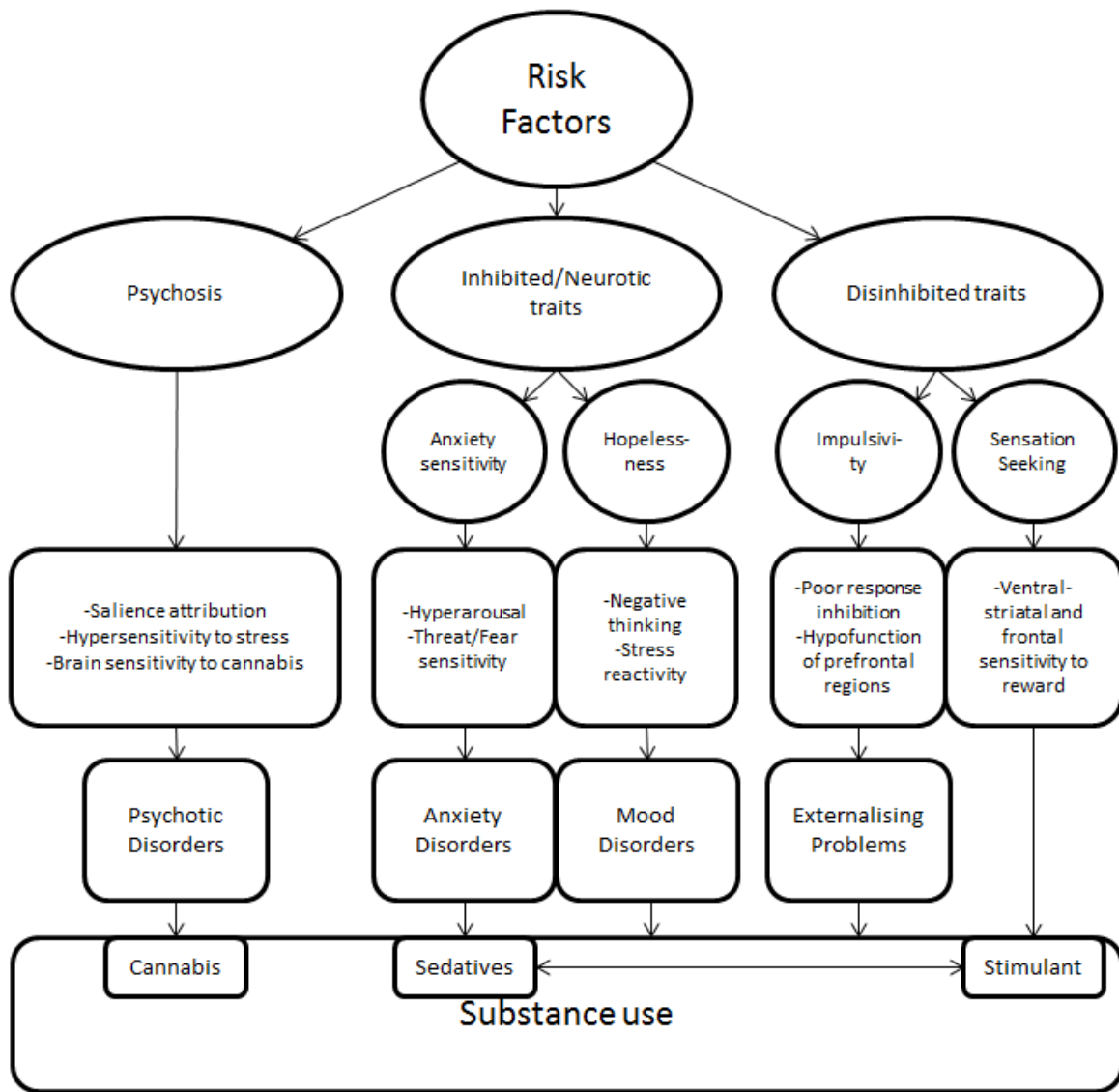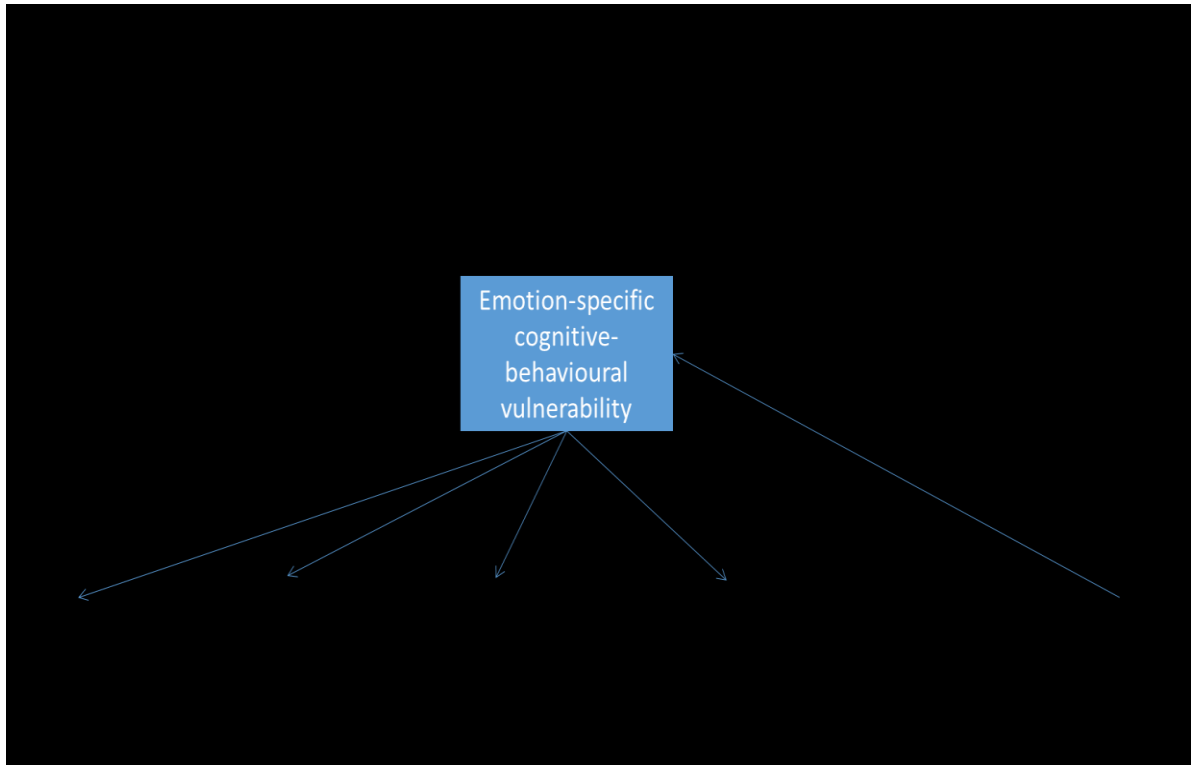
Figure 15. Integrating Personality Risk Factors in the Relapse Prevention Model

Procedure:

Personality-targeted interventions can be offered in group or individual-based interventions, which tend to be brief (1-4 sessions), due to the targeted nature of the intervention. As interventions target risk factors rather than problem symptoms, they can be offered as brief interventions for substance misuse or as a selective preventative intervention. In either format, four different intervention manuals have been developed to specifically target four personality risks: Anxiety Sensitivity, Hopelessness, Impulsivity and Sensation Seeking. These traits are reliably measured using the Substance Use Risk Profile Scale (SURPS), a 23-item scale measuring these four traits (Woicik, et al., 2009). This scale has been translated into several different languages and evaluated for use with individuals 12 years old and older. When used as a screening tool, it is recommended to use the procedure

described and validated by Castellanos-Ryan et al., (2011), by which individuals are identified as high risk based on a standard deviation from the population from which they were screened. In other settings, this is not possible, so it is recommended to either use deviation from published standard norms, or the highest mean score of all four scales when deciding which personality-targeted intervention is most appropriate for an individual. In both scenarios, when an individual scores high (screens positive) on more than one personality risk factor, it is recommended to start intervening on the most deviant personality trait. Individuals with similar personality profiles are guided through the intervention when administered in a group format.

The school-based intervention program is a very brief treatment offered over 2-3 sessions of 90 minutes over a 2-3 week period, for a total of 3 hours of therapy. The targeted nature of this intervention is conducive to brief therapy, given that the discussion topics and exercises are tailored to the needs of each specific personality profile. The treatment follows a structured format, using manuals to guide discussions and present exercises for each session. Manuals also feature vignettes to facilitate exchanges, normalize experiences related to the targeted trait, and encourage participant disclosure. The intervention manuals have been tailored to youth as young as 12 years of age (Preventure; Conrod et al., 2008; 2010) and for college students (Watt et al., 2006).

The first session aims to build a positive and engaging group dynamic while building a common understanding of the problem. Clients start by setting long-term personal goals for themselves. After a brief discussion about obstacles to goal pursuit, the group is introduced to the personality trait, a frequent obstacle when pursuing personal goals. This component sets the personality trait as the center of therapy and begins to focus attention on

tackling obstacles and diminishing the consequences associated with the trait. To assist clients in managing their personality traits, the therapist presents a decision-making exercise that the group applies to a vignette. Clients then learn to deconstruct their experiences in sensation, thoughts, and behaviours, and to identify automatic thoughts as the catalyst for problematic behaviours and ineffective coping strategies. As homework, clients are asked to describe and deconstruct a situation in which they had difficulty managing their personality traits.

In the second session, clients learn to identify their cognitive distortions and challenge them. Cognitive distortions most relevant to each personality profile (e.g., jumping to conclusions for Impulsivity, catastrophizing for Anxiety Sensitivity, or internalization for Hopelessness) are presented, and members of the group share opinions about the distortions. The group moves on to identifying and confronting the distortion illustrated in a vignette. As a final exercise, clients retrospectively identify and challenge their cognitive distortions. The treatment ends with a review of the material covered across the two workshops and a discussion about the importance of a healthy lifestyle and social relations in the pursuit of personal goals.

Personality-targeted interventions have also been evaluated when delivered in an individual format to adults living in the community who suffer from SUDs (Conrod et al., 2000) or Anxiety Disorders (Olthuis, et al., 2015). The adult, individual format is very similar to the group-based format described above and can even be distance-delivered through telephone or email coaching (Olthuis, et al., 2015).

Evidence:

A recent review of personality-based model of intervention for substance misuse has been conducted by Conrod (2016). The following Table 15 is a reformatted version of the table presented in Conrod (2016). A description of individual studies follows.

Table 15: Overview of Sources Reviewed

Authors	Sample	Experimental conditions	Outcome	Effect size
Conrod et al. (2000)	123 Alcohol and/or prescription drug-dependent women	Personality-targeted interventions vs Control (informational video)	Alcohol use Alcohol Quantity x Frequency Dependence Symptoms Remission Prescription Drug Use	$d = 0.47$ N.S. $d = 0.47$ $d = 0.46$ $d = 0.58$
Conrod et al. (2006)	297 High risk high school drinkers	Personality-targeted interventions vs Control	Alcohol Use (4mo) Binge Drinking (4mo) Drinking Problems (4mo)	N.S. $d = 0.37$ $d = 0.32$
Watt et al., (2008)	107 college students	Personality-targeted interventions vs Control	Drinking Frequency Drinking Problems	N.S. $d = 0.37$
Conrod et al., (2008; 2010; 2011)	347 high risk high school students	Personality-targeted interventions vs Control	Alcohol Use (6mo) Binge Drinking (6mo) Drinking Problems (6mo) Drinking Problems (2yr) Drug Use Frequency (2 yr) Cannabis Use (2 yr) Cocaine Use (2yr)	$d = 0.22$ $d = 0.21$ $d = 0.35$ $d = 0.33$ $d = 0.25$ $d = 0.16$ $d = 0.80$
Lammers et al. (2015)	699 high risk high school drinkers	Personality-targeted interventions vs Control	Alcohol Use (12mo) Binge Drinking (12mo) Drinking Problems (12mo)	N.S. $d = 0.33$ N.S.
Conrod et al. (2014); Mahu et al. (2015)	995 high risk high school students	Personality-targeted interventions vs Control	Alcohol Use (2yr) Drinking Q (2yr) Binge Drinking (2yr) Binge Drinking-freq (2yr) Binge Drinking-growth (2yr) Drinking Problems (2yr) Cannabis Use (2 yr)	$d = 0.68$ $d = 0.36$ $d = 0.88$ $d = 0.38$ $d = 2.07$ $d = 1.02$ N.S.
Newton et al. (2016)	493 high risk high school students	Personality-targeted interventions vs Control	Alcohol Use (3yr) Binge Drinking (3yr) Drinking Problems (3yr)	$d = 0.47$ $d = 0.65$ $d = 0.54$
Olthuis et al. (2015)	80 Anxiety Sensitive adults from the community	CBT intervention over the phone vs Control (waitlist)	Alcohol Use Binge Drinking Drinking Problems (physiological) Drinking Problems (interpersonal)	Not reported Not reported $d = 0.64$ $d = 0.48$

Note: Cohen's *d* values retrieved from Conrod (2016).

The personality-targeted CBT approach has been evaluated in several recent randomized trials. One trial used a treatment matching design in which substance misusing participants were randomized to participate in brief personality-targeted interventions or identical brief CBT interventions that did not target their primary personality profile, and

both interventions were compared to a brief supportive counselling session (Conrod et al., 2000). This trial showed that substance-using women reporting a range of substance use behaviours and problems, responded more favourably to a brief intervention if that intervention targeted their most prominent personality trait. These findings were subsequently replicated in samples of early-onset adolescent drinkers (Conrod et al., 2006) and anxiety-sensitive college students (Watt et al., 2006). Since the personality-targeted approach mainly addresses the management of personality risk, rather than specifically managing substance misuse, many of these trials also showed that concurrent mental health symptoms were reduced by the intervention, in addition to problematic substance use behaviours (Castellanos-Ryan et al., 2006; O'Leary-Barrett, et al., 2013; Olthuis, et al., 2015; Watt et al., 2006). Furthermore, as these traits are highly predictive of adolescent-onset substance use, misuse and problems (see Castellanos-Ryan et al., 2013), the personality-targeted approach has also been shown to be a highly effective strategy for preventing substance misuse and concurrent emotional and behavioural problems among high-risk youth (Conrod, et al., 2008; 2010; 2011; 2013; Mahu et al., 2015; O'Leary-Barrett et al., 2010; 2013). This approach has proven to be effective when delivered in different cultural and educational contexts, as well (e.g., Lammers et al., 2011 and Newton et al., 2016).

Conclusion:

This novel treatment model shows great promise as both an effective model for detection and prevention of substance-related problems in youth, as well as an effective model to personalize interventions while maintaining their brevity for active substance misusers. The interventions also have the advantage of addressing concurrent mental health and personality factors that are known to maintain many substance use problems and

complicate their treatment. Furthermore, because the intervention approach does not directly target substance use behaviours, but rather risk factors for such behaviours, the approach adapts well to the context of early intervention or prevention, as well as the relapse prevention stage and can address all forms of substance misuse associated with a particular personality trait rather than have to focus on one target behaviour.