Psychosis and Cannabis: An Investigation of Individual and Combined Effects on Cognition and White Matter

by

Lezlee Mckenzie

Submitted in partial fulfilment of the requirements
for the degree of Master of Science

at

Dalhousie University
Halifax, Nova Scotia
July 2020

DEDICATION PAGE

This thesis is dedicated to my father. In every accomplishment of mine, is you.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Reduced cognitive functioning has been observed in individuals with early phase psychosis (EPP) and is similar to reductions in cognitive functioning in non-psychiatric populations who use cannabis. Less clear, however, is the combined effect of EPP and cannabis use on cognition. Furthermore, it is believed that reduced white matter integrity occurs in the brains of individuals with EPP and cannabis users and may underlie the noted dysfunctions. To clarify the impact of cannabis use and EPP individually, as well as the combined effect, two studies were executed. Study 1 utilized a clinical database of EPP patients with low/no or moderate/severe cannabis use and found those with moderate/severe use had better psychomotor speed and working memory. Prospective data was collected for Study 2 which included a healthy control comparison group as well as structural white matter neuroimaging techniques to investigate the individual and combined effects of EPP and cannabis use on cognition and white matter integrity. Controls outperformed EPP patients on tasks of working memory, executive functioning, and psychomotor speed. Cannabis use negatively impacted working memory, executive functioning, and verbal learning and memory. The integrity of white matter in the left prefrontal region was reduced for those with EPP compared to controls. Cannabis use did not affect white matter. High rates of cannabis use in those with EPP warrant further investigation into the relationship between EPP and cannabis use to assess the individual and combined impacts of each on cognitive functioning and white matter.

LIST OF ABBREVIATIONS USED

ANOVA	Analysis of Variance
CBD	Cannabidiol
CUD	Cannabis Use Disorder
CVLT-III	California Verbal Learning Task (Version III)
DESPOT1	Driven Equilibrium Single Pulse Observation of T1
DESPOT1-HIFI	Driven Equilibrium Single Pulse Observation of T1 with Incorporation of B1 Field Inhomogeneities
DESPOT1-no	Driven Equilibrium Single Pulse Observation of T1 with no Incorporation of B1 Field Inhomogeneities
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (Version 5)
DTI	Diffusion Tensor Imaging
EPP	Early Phase Psychosis
EPP-	Early Phase Psychosis, no CUD
EPP+	Early Phase Psychosis, with CUD
FLIRT	Linear Image Registration Tool
HC	Healthy Control
HC-	Healthy Control, no CUD
HC-	Healthy Control, with CUD
ISL	International Shopping List Task
MANOVA	Multivariate Analysis of Variance
MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MP3RAGE	Magnetization-prepared Rapid Acquisition Gradient Echo
MRI	Magnetic Resonance Imaging
NART	National Adult Reading Test
NSEPP	Nova Scotia Early Psychosis Program
O-DSST	Oral Digit Symbol Substitution Task
ONB	One Back Task
ROI	Region of Interest

SCID	Structured Clinical Interview for Substance Use Disorders for the DSM-5
T1	Longitudinal Relaxation Time
THC	Delta-9-tetrahydrocannabinol
TMT-A	Trail Marking Task Part A
TMT-B	Trail Marking Task Part B
WHO-ASSIST	The World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation to my supervisor, Dr. Philip Tibbo, for being an exemplar scientist and clinician. His investment in improving the well-being of those with early phase psychosis has been incredibly inspiring. His faculties as a researcher have served to improve my own, and it has been with his ongoing teaching and guidance that this project was possible.

I also must thank my committee members, Dr. Candice Crocker, Dr. Kimberley Good, and Dr. Alissa Pencer. The guidance I have been provided by the committee has been invaluable. All members modelled an excitement in discovery to me, and for that I am grateful. Their insights were indispensable and encouraged my development as a researcher throughout the program.

This research would not have been feasible if not for the help of Amira Hmidan. Whether recruiting, coordinating or conducting participant data collection, or fulfilling other duties, her dedication to the project made it possible. I am further indebted to the research team at the Nova Scotia Early Psychosis Program more broadly. Their individual expertise and guidance has been integral.

Finally, I am incredibly grateful for my family and friends, who I cannot thank enough for their ongoing support throughout this endeavor. They all had a part in encouraging me throughout graduate studies, and have been a source of strength, love, and determination. At times, it is possible they believed in me more than I believed in myself and always made sure to express it. To Atlas, who was at my side throughout every part of the program on all fours, thank you for being the absolute best companion throughout this journey.

Chapter 1 Introduction

1.1 Psychosis

Primary psychotic disorders principally refer to psychotic symptomatology that is not the result of substance use, an underlying medical condition, or a primary mood disorder with psychotic symptoms (American Psychiatric Association, 2013). Psychotic symptoms include positive symptoms such as hallucinations, and delusions (e.g. paranoia), among others, and are characterized as additions to ones' feelings, thoughts, or broader experience that are not present in the general population (Garety et al., 2001). Negative symptoms differ in that they are a reduction in the usual experiences of an individual, such as emotional withdrawal or difficulty with the demands of abstract thinking (Correll & Schooler, 2020). Additionally, individuals experiencing psychosis can have difficulties in cognitive domains, as well as general symptoms of being psychologically unwell, such as experiencing tension (Reininghaus, Priebe, & Bentall, 2013).

Schizophrenia spectrum disorders share psychotic symptoms as a defining feature. Schizophrenia impacts approximately 1% of the population and accounts for approximately 2% of healthcare expenditures in Canada (Goeree et al., 2005). While schizophrenia is extremely heterogeneous, it involves a combination of hallucinations, delusions, negative symptoms, disorganized thinking, and abnormal motor behaviour. Furthermore, symptoms must be persistent over time (i.e., at least six months), influence daily life significantly, and such symptoms are used to determine the severity of the illness. Schizophreniform disorder is

diagnosed with similar criteria to schizophrenia, but involves a shorter duration of illness (i.e., symptoms have persisted for less than six months, but for longer than one month), and has a lifetime prevalence rate of 0.11% (Goldner et al., 2002). Schizoaffective disorder also involves hallucinations, delusions, negative symptoms, disorganized thinking, and abnormal motor behaviour, but individuals with schizoaffective disorder also experience a concurrent mood episode (e.g., a depressive episode) for the majority of illness duration (American Psychiatric Association, 2013). Schizoaffective disorder is separate from a mood disorder resulting in psychosis (e.g., bipolar 1), as individuals must experience at least two weeks of the aforementioned symptoms in the absence of a major mood episode. Affective psychoses are a separate phenomenon, where the psychotic symptoms are secondary to a primary mood disorder such as a major depressive disorder or a bipolar mood disorder. Furthermore, disorders that are generally considered primary psychotic disorders, such as schizophrenia spectrum disorders (e.g., schizophrenia, schizophreniform, and schizoaffective disorders) are, in practice, considered as separate from substance/medication-induced psychosis, though the DSM-5 does not make this differentiation.

1.1.1 First-episode/Early Phase Psychosis

Early psychosis, or first-episode psychosis, describes the first time that an individual experiences clinically significant psychotic symptoms. This first episode generally occurs in late adolescence or young adulthood and can result in a significant disruption in daily life (Jablensky, 1997). The first episode typically occurs between the ages of 18 and 35 (Jones, 2003), with males generally

presenting with symptoms earlier than females (Benes et al., 2004; Eranti et al., 2003). The onset of the illness, therefore, occurs within a critical period of neurobiological and psychosocial development (Peters, 2002). Brain maturation continues throughout late adolescence and early adulthood, as individuals are often obtaining an education or entering the workforce (Bava et al., 2006; Gould et al., 2005). As a result, the disruption that psychosis can present during this period is robust.

Fortunately, the first episode, or earliest phase of psychosis has been studied at length, and recovery is most likely when it is treated at this early stage (McGorry, 2015). Early intervention services provide targeted treatment for individuals with early phase psychosis (i.e., within the first five years of illness-onset; Bertelsen et al., 2008; Nolin et al., 2014; Petersen et al., 2005). Successful early intervention programs typically offer a wide variety of easily accessible services (e.g., an individual biopsychosocial treatment approach, comorbid substance use disorder treatment, individual and group-based psychosocial treatments, ongoing evaluations of the program's services, etc.). When early intervention services are implemented, significant symptom reductions can be observed in both the short- and long-term, as well as enhanced patient satisfaction and social outcomes (Petersen et al., 2005). Furthermore, early intervention services can reduce the socioeconomic burden of psychosis by a reduction in the use of emergency room and inpatient services (Liffick et al., 2017).

1.1.2 Psychosis and Cognition

Cognitive deficits that are known to occur in early phase psychosis (EPP) have been traditionally less studied than clinical symptoms of psychotic disorders (Addington, Brooks, & Addington, 2003). Cognitive functioning, however, is an important aspect of early psychosis, with some studies providing evidence that cognition can predict long-term functional outcomes (Allott et al., 2011; Lystad et al., 2016). Impaired cognitive functioning is relatively homogenous between psychotic disorders, is pronounced even in EPP (Addington & Addington, 2002; Addington et al., 2003; Bora & Murray 2014), and furthermore, these deficits are not fully explained by premorbid intellectual functioning (Rossi et al., 2016).

Deficits in particular cognitive domains arise from the literature and most frequently reported are difficulties with learning and memory, psychomotor speed, processing speed, attention, and executive functioning overall (Green, 1998; McCleery et al., 2014; Rossi et al., 2016; Townsend, Malla, & Norman, 2001). Processing speed describes how quickly one can take in target information, process that information, and adequately respond (e.g., recognizing and responding to a visual pattern; Whitman, 2010). Executive functioning encompasses a number of cognitive skills but broadly refers to an individual's capacity to manage their cognitive resources to complete a function (Whitman, 2010). For example, an individual must allocate their attention and planning capacities, and access their memory to plan out a grocery list. Executive functioning allows the monitoring and deployment of these individual capacities. Within learning and memory deficits in psychosis, Zabala and colleagues (2010) and Addington et al. (2003) have provided evidence that individuals with

psychosis overall perform worse than healthy controls with no psychiatric diagnosis. Similarly, difficulties with attention, reduced executive functioning, and difficulties with processing speed have been consistently observed relative to healthy controls (Mathias et al., 2017; McCleery et al., 2014; Rossi et al., 2016; Zabala et al., 2010).

In a meta-analysis by Fioravanti et al. (2012), 240 studies were identified that discussed cognitive functioning and schizophrenia with the inclusion of a healthy control group. Results showed that while there is heterogeneity in how strong the effect of having schizophrenia is in each domain, all domains assessed (i.e., attention, executive functioning, memory, and language) were significantly impacted by the presence of schizophrenia. Moreover, the researchers used transformed effect sizes which allowed for the calculation of the likelihood that an individual with schizophrenia would perform worse than a control participant. The domain of memory had the strongest effect of patient status, as participants with schizophrenia had the greatest likelihood of showing reduced functioning in the memory domain compared to controls. Participants with schizophrenia had an 81% probability of having reduced performance on measures of memory compared to control participants (i.e., only 19% of patients performed similarly to controls). However, the researchers noted that many studies failed to match sample sizes of comparison groups, and the researchers found that large effect sizes were overrepresented in small samples using correlations, which were consistent with results from a previous meta-analysis (Fioravanti et al., 2005). Furthermore, as outlined in the aforementioned meta-analysis, there were

incongruencies in how stringently matched the controls were to patients (e.g., in age, intelligence, and sex), in conjunction with the variance within the patient population (e.g., age of onset of illness and treatment exposure).

Furthermore, Fatouros-Bergman and colleagues (2014) also performed a meta-analysis and found that verbal memory, working memory, and processing speed were the most impacted domains. In their study, medication-naive patient samples from the literature were compared to healthy controls to assess the influence of psychosis in the absence of antipsychotics (i.e., a more pure effect). While verbal memory, working memory, visual memory, attention, processing speed, and executive functioning were all significantly worse in the patient samples than in healthy controls, the largest standardized mean differences between patients and healthy controls were in verbal memory, working memory, and processing speed.

There is evidence of second generation antipsychotic medications improving the reductions in cognitive functioning present in psychosis, particularly for executive functioning (Hill et al., 2010; Meltzer & McGurk, 1999). However, Hill et al. (2010) caution that while evidence shows that improvements in cognitive functioning are statistically significant for those using second generation antipsychotics, these improvements are small. Furthermore, a debate has occurred around practice effects, and whether the noted improvements are genuine improvements and not improvements from performing the tasks on multiple occasions (Cuesta et al., 2001; Goldberg et al., 2007). It can also be postulated that reductions in cognitive deficits are the result of symptom

reduction (such as that in successful antipsychotic intervention), as illness severity is associated with worse cognitive outcomes (Barder et al., 2013; Fitzgerald et al., 2004).

1.1.3 Psychosis and Cannabis Use

The relationship between psychosis and cannabis is complex and well-researched. Green, Young, and Kavanaugh (2005) estimate approximately 23% of individuals who have a diagnosis of psychosis have lifetime misuse of cannabis. While between 34% and 44% of first-episode patients have a substance dependency, cannabis is consistently reported as one of the most used substances (Abdel-Baki et al., 2017; Myles et al., 2016; Van Mastrigt et al., 2004). Lifetime prevalence rates of cannabis use disorder (CUD) are markedly high in EPP, with the rate of lifetime dependence nearing half of the population (Koskinen et al., 2010). Past-year prevalence of a CUD in the EPP population is substantially larger than in the general population, with 14% of patients meeting criteria for a CUD, while past-year CUD rates in the general population in Canada are 1-2% (Anthony, 2006; Hall & Pacula, 2003; Leos-Toro et al., 2017; Ouellet-Plamondon et al., 2017; Van Mastrigt et al., 2004). Recently, Di Forti and colleagues (2019) found lifetime prevalence rates of cannabis use in individuals with a psychotic disorder to be approximately 65%, while lifetime use was significantly less in controls at 46%. Lifetime prevalence rates of up to 86% in those with psychosis have been reported (Sembhi & Lee, 1999).

Cannabis use can contribute to developing psychosis (Di Forti et al., 2015; Di Forti et al., 2019; Marconi et al., 2016; Tucker, 2009), and its use may also

succeed the onset of symptoms (Bizzarri et al., 2009). Cannabis use is also a significant predictor of treatment outcomes within EPP, as the use of cannabis typically exacerbates symptoms and results in a poorer prognosis (Foglia et al., 2017; Setién-Suero et al., 2019). Concerning clinical symptoms of psychosis, discontinued cannabis use in individuals who used the drug at the onset of treatment results in outcomes similar to patients who did not use the substance when treatment began, and symptoms for these two groups are reduced compared to patients who continued to use (or began using) cannabis (Setién-Suero et al., 2019). Additionally, the rates of relapse are significantly higher in individuals who use cannabis (Schoeler et al., 2016; Zammit et al., 2008), resulting in more disruption to individuals' lives.

In the context of early psychosis, the age of onset of cannabis use has been shown to be associated with the development of the first episode of psychosis, where the initiation of regular use at a younger age results in a greater likelihood of subsequently presenting with a psychotic disorder (Arseneault et al., 2002). Similarly, the use of cannabis with high delta-9-tetrahydrocannabinol (THC) potency has also been consistently shown to be linked with the eventual development of a psychotic disorder, as well as the overall amount of cannabis an individual uses (Di Forti et al., 2014). These factors result in an earlier onset of symptoms compared to individuals who are not using and eventually develop psychosis. A meta-analysis by Large et al. (2011) showed the age of onset of psychosis to be approximately three years earlier in cannabis users. Di Forti et al. (2014) tested the association between age of onset of psychosis and the age of

onset of cannabis use and found that the age participants first used cannabis did not significantly affect the age of psychosis onset when factors such as how often individuals used cannabis, the THC potency, and gender were controlled for. Therefore, it is likely a combination of cannabis use parameters, as well as individual differences that moderates the relationship between cannabis use and an earlier onset of psychosis.

There have been theories proposed to help explain the increased use of cannabis in this population, despite the problematic effects of the drug on clinical outcomes. Degenhardt et al. (2003) tested these theories by using data from eight birth cohorts. The first theory explored by the authors, that cannabis use causes psychotic disorders to develop, was not supported fully by the data. While some data did show cannabis use resulted in subsequent psychosis, the researchers suggested that cannabis use had occurred in individuals who would eventually develop psychosis regardless of cannabis exposure. The second theory, that cannabis use causes psychosis to develop in individuals predisposed to psychotic disorders, was supported with evidence of a reduction in the age of onset of a psychotic disorder in cannabis-using individuals, as predicted by modelling of the hypothesis. The third theory, that the prognosis and severity of psychosis are worsened by cannabis use was supported in part, though the chronicity of schizophrenia was not worse for cannabis users compared to non-users. Lastly, the researchers tested the hypothesis that individuals who are diagnosed with psychosis are more likely to become regular cannabis users. Evidence agreed with the fourth hypothesis that individuals with psychosis are more likely to regularly

use cannabis. It must be noted that evidence for all four theories exists beyond the modelling and the assessed fit of the model for each hypothesis using cohort data and that all four hypotheses likely contribute in some way to increased rates of cannabis use in this population. Recently, literature reviews by Hamilton and Monaghan (2019) and Ksir and Hart (2016) have suggested that evidence points to a shared vulnerability between the two (i.e., that there is a predisposition for early and heavy cannabis use in those who will eventually develop a psychotic disorder). However, Hamilton and Monaghan (2019) in particular note that research is skewed toward finding biological explanations for the theories of cannabis use in individuals with psychosis, and sociocultural factors should also be looked to for consideration as well.

1.2 Cannabis Use and Cognition

As with psychosis and cognition, the use of cannabis has been studied in relation to cognition in the general population. It has been postulated that the deficits cannabis causes in cognition in healthy individuals mimic the reduced cognitive abilities seen in individuals with a psychotic disorder (Solowij, & Michie, 2007). In a brief overview of the literature, Curran and colleagues (2016) described that overall, some evidence exists that describes a decrease in overall intellectual functioning in individuals who developed a CUD, though studies with less frequent use show no difference in overall functioning. More specifically, long term use of cannabis influences executive functions such as decision making and encoding novel memories. The authors also note that known acute effects of the drug, such as decreased attention and deficits in working memory are reported

in chronic users in various studies, but there is no consensus that these occur consistently in long term use.

In a systematic review, Broyd et al. (2016) sought to differentiate acute and chronic effects of cannabis on cognition. Several consistencies appeared for acute and chronic effects, including impaired attention, memory, and executive functioning. Within the domain of memory, reduced verbal learning and memory abilities are a feature of acute intoxication as well as chronic exposure. Working memory is similarly impacted in both acute and chronic use, although the extent seems to vary more than it does with verbal learning and memory. Attention is widely accepted as being impacted by acute exposure but is less consistently reported as reduced in regular users. However, in chronic users who are abstinent for several weeks, reduced attention can still be observed compared to non-users. Concerning executive functioning, acute intoxication mirrors chronic use in heavy users, such that cannabis hinders performance.

Scott et al. (2018) performed a meta-analysis assessing various domains of cognitive functioning in cannabis users and non-users from adolescence and early adulthood. Learning, executive functioning, processing speed, and attention were significantly impacted in the cannabis-using group, such that non-users had significantly greater performances on tasks in the domains overall. Additional explanatory variables were included in the model other than cannabis use alone, including the age of onset of cannabis use and how long each study required cannabis users to be abstinent prior to cognitive testing. While age at first use did not predict cognitive outcomes in this sample, the mean duration of abstinence in

users did significantly influence cognitive performance, with a three-day abstinence period reducing the impact of cannabis to approximately zero.

In a sample of healthy individuals within their meta-analysis, Schoeler et al. (2016) compared memory abilities of non-users (i.e., had never met criteria for dependence and/or had no lifetime history of regular use and/or did not use at the time of data collection) to cannabis users. Eighty-eight studies in total were included. Global memory was found to be significantly impaired in healthy individuals who were cannabis users compared to non-users. Particular domains of memory were more affected by cannabis use, namely, prospective memory, working memory, verbal immediate and delayed recall, verbal recognition, verbal learning, and visual recognition. Of course, the grouping in the original studies included in the meta-analysis varies, and as such there was likely significant heterogeneity in cannabis use in the users and non-users.

1.3 Psychosis, Cannabis Use, and Cognition

With evidence accumulating that both cannabis and psychosis have similar impacts on cognition and that cannabis use is heightened in the EPP population compared to healthy individuals (Green, Young, & Kavanagh, 2005; Van Mastrigt, Addington, & Addington, 2004), researchers have begun to explore the impact of cannabis use on cognition within individuals with psychosis. Research assessing the effect of cannabis on cognition, and the effect of psychosis on cognition has been relatively homogenous (i.e., both cannabis and psychosis independently are typically reported to negatively influence similar cognitive domains), such is not the case when assessing the impact of cannabis on cognition

within psychosis populations. Some evidence indicates that when EPP patients use cannabis, outcomes on cognitive tasks are worse than for EPP patients who are non-users (Bogaty et al., 2018), while other studies cite no difference (Bogaty et al., 2018; Yucel et al. 2012). Some research even suggests that patients using cannabis actually have increased cognitive performance compared to those with EPP who do not use (Bogaty et al., 2018; Potvin et al., 2008; Rabin et al., 2011; Schoeler et al., 2016; Yucel et al., 2012). All effect sizes from the meta-analyses, regardless of the direction of the effect and the specific domain, describe differences of less than one standard deviation between users and non-users, generally indicating that significant effects are modest when present.

A meta-analysis by Potvin et al. (2008) found that substance use as a whole impacts the cognition of individuals with schizophrenia in different ways, and differs based on which substance(s) an individual is using. The researchers found that individuals with a substance use disorder performed significantly better on tasks assessing psychomotor speed. Concerning cannabis specifically, reasoning and visual memory were enhanced in the individuals with a cannabis use disorder, an effect that did not occur for other substances in the various domains assessed. The researchers also found age was a significant predictor of the size of the effect that substance use had on overall cognitive functioning, working memory, and speed of information processing, such that increased age was associated with smaller effect sizes in the domains. This work highlighted the importance of considering age when assessing the literature, as the effect of substance use differs over time.

Rabin et al. (2011) performed a meta-analysis of eight studies on cognition in schizophrenia specifically for individuals with and without a CUD. In all domains assessed, cognitive performance was increased in individuals with a cannabis use disorder, including improved memory, visuospatial skills, executive functioning, and language skills. Importantly, Rabin and colleagues (2011) did not include any studies in the meta-analysis which did not exclude participants based on comorbid substance use, in an attempt to specifically assess the impact of cannabis on cognition in schizophrenia.

Yucel et al. (2012) first performed a systematic review and meta-analysis to assess cognition in individuals with psychosis who were and were not using cannabis, followed by a novel study within their report. Results from the meta-analysis showed that those with psychosis who had lifetime cannabis use had greater scores of global cognition, working memory, visual memory, executive functioning, and processing speed, and that this effect was not found in studies that only measured recent use. Next, the researchers collected cognitive data in first-episode psychosis patients specifically as well as healthy controls. Users were defined as having used more than two grams of cannabis per week for a minimum of two years (i.e., regular use). Results demonstrated that as a whole, first-episode participants performed worse than healthy controls on all tasks. Better cognitive performance on tasks measuring executive functioning, verbal and non-verbal memory, and working memory was observed in the first-episode participants who were cannabis users relative to those who did not use.

Schoeler et al. (2016) similarly investigated psychosis patients with and without cannabis use to compare memory functioning specifically between the two as well as to healthy controls by way of a meta-analysis of 88 studies. The researchers found that cannabis-using psychosis patients performed significantly better than their non-using counterparts, particularly for visual recall and recognition, and verbal recognition. Contrary to the results of Potvin et al. (2008), the adverse effects of cannabis use on memory (observed in the healthy control sample) increased with age, though Schoeler et al. (2016) focused on cannabis specifically and not substance use broadly.

Bogaty and colleagues (2018) performed a meta-analysis on 14 existing studies that reported cognitive measures in young psychosis patients who either regularly used cannabis (at least once per week for the last six months) or did not use cannabis. No significant differences between users and non-users were found for processing speed and overall verbal memory. Verbal working memory, however, was significantly reduced in the cannabis-using patients, with the largest effect size of all cognitive measures (Hedge's g = -.76). Worse performance on measures of sustained attention was also observed for cannabis-using patients compared to non-using patients. Better performance was observed for executive functioning and verbal learning in patients that were cannabis users compared to the patients that were not users. These results suggest that domain-specific specific impairments/enhancements – and the absence of either – can occur as a result of regular cannabis use in individuals under the age of 25.

Overall, there is inconsistent evidence that cannabis impacts cognition in psychosis patients. While there is evidence of a potential "protective" effect of cannabis on cognition in this population, there are also indications that cannabis does not have an impact. Furthermore, because there are relatively well-described deficits associated with chronic and acute exposure to cannabis in healthy populations, it raises the question of how cannabis could seem to enhance performance on neuropsychological tasks in individuals with EPP. The present state of the literature does not provide an obvious answer, which likely reflects methodological differences between studies. Potential confounds, such as accounting for premorbid functioning and polysubstance use are inconsistently controlled for in the literature. Furthermore, measures of cannabis use are extremely heterogeneous. Terms like "regular", "chronic", and "lifetime" use may be well defined within studies, but are seldomly readily comparable between studies. Whereas studies using CUD status have results that are easier to evaluate in the context of one another, the stringency means these studies encompass only a portion of the cannabis-using EPP patients. The metrics for evaluating cognitive functioning are similarly unstandardized within the literature. While reliable neuropsychological tools with good construct validity should reproduce similar results within cognitive domains (even if the exact task differs), the inconsistency in measures of cannabis use combined with the heterogeneity of the tasks between studies may further obscure the impacts of cannabis on cognition. Some research has looked at biological variables, such as brain structure and function, to help elucidate how cannabis and EPP influence cognition.

1.4 White Matter Imaging

White matter describes brain tissue comprised of axons which typically have a fatty coating (i.e., myelin). Axons carry neural signals throughout the brain, and the myelin coating serves to facilitate the transmission of electrical signals. The myelin layer, which is crucial to effective signal transmission, is created by oligodendrocytes, a type of neuroglia in the central nervous system (Baumann & Pham-Dinh, 2001; Fields, 2010). The maturation of white matter involves the brain's endogenous cannabinoid system, and this process coincides with the crucial developmental period that is adolescence and early adulthood, with the myelination process dropping off significantly in young adults (Bava et al., 2006). The brain's endocannabinoid system is intractably involved in this period, with a significantly higher density of cannabinoid receptors found on the neuroglia responsible for white matter development in the adolescent brain (Chadwick et al., 2013).

1.4.1 Psychosis and White Matter Imaging

Brain white matter is implicated in both EPP as well as in chronic psychotic disorders, with structural abnormalities in white matter evident even prior to the onset of an individual's first episode of psychosis (Carletti et al., 2012; Roalf et al., 2019). One theory that has been postulated regarding the white matter differences seen between psychosis patients and controls is the dysconnectivity hypothesis (Friston & Frith, 1995). This hypothesis posits that the presentation of psychotic disorders arises from aberrant neurophysiology. In particular, the difficulties incurred are the result of atypical interaction between

regions in the brain, and the atypical interaction is the result of widespread anatomical dysconnectivity due to compromised white matter tracts. As a result, researchers have made substantial efforts to describe white matter abnormalities in individuals with psychosis. In vivo neuroimaging techniques have been used since the dysconnectivity hypothesis first was described more than two decades ago to test the hypothesis.

Magnetic resonance imaging (MRI) offers a number of techniques that inform researchers on macro and microstructural white matter differences, such as volumetric differences, and differences in the organization and integrity of white matter. Structural MR techniques, such as T1 and T2 maps, can yield measures of the relaxation time of tissues and can be used to look at white matter differences regionally. Structural methods such as driven equilibrium single pulse observation of T1 with the incorporation of B_1 field inhomogeneities (DESPOT1-HIFI) can provide longitudinal relaxation times (i.e., the time it takes the net magnetization vector to achieve full recovery after a radiofrequency pulse is applied) in white matter which are indicative of myelin quantity in far less time than traditionally required (Deoni, 2007). Other methods, such as diffusion tensor imaging (DTI) are employed to assess microstructural differences in white matter in particular in vivo with a level of precision once only possible posthumously. DTI measures the movement of water molecules within the brain, which is a strong indicator of the integrity of white matter. Because axons are not water-soluble, the diffusion of water within and around an axon can describe the quality of the axonal bundles.

Pérez-Iglesias et al. (2010) assessed individuals with EPP as well as controls to examine what abnormalities are present specifically within the early phase of psychosis. The researchers used DTI to measure white matter integrity in age, sex, education, and handedness-matched EPP patients and healthy controls. In particular, fractional anisotropy values were used to estimate areas with the greatest abnormalities (i.e., the lowest values of anisotropy). Several main areas with the greatest abnormalities between the EPP patients and healthy controls were found, including the corpus callosum and internal capsule broadly, the longitudinal fasciculi (superior and inferior), forceps major, and the thalamic radiation (superior and anterior). Again, this dysconnectivity of major neural pathways is believed to underlie – at least in part – symptom expression. More recently, Rae et al. (2017) performed DTI between healthy controls and EPP patients to assess neurite density. Participants with EPP were shown to have decreased neurite density in areas that had also shown reduced fractional anisotropy relative to controls. Abnormalities in neurite density in EPP patients are likely reflective of reduced myelination, density, and axonal count in interhemispheric, corticospinal, and association tracts.

1.4.2 Cannabis Use and White Matter Imaging

Utilizing data from healthy individuals enrolled in the Human Connectome Project Consortium, Orr et al. (2016) compared the structural integrity of white matter in cannabis users and non-users. First, the team assessed whether recreational cannabis use has an impact on white matter. The researchers found that fractional anisotropy values were reduced in individuals with an earlier

age of onset of cannabis use particularly in the longitudinal fasciculi (inferior and superior), forceps major and minor, similar to the results from Zorlu et al. (2016) when synthetic cannabinoids were used regularly. These areas also had increased radial diffusivity, a second indicator of reduced structural integrity of white matter. Increased radial diffusivity and decreased fractional anisotropy were more pronounced in the right hemisphere of the brain. Conversely, a meta-analysis of 17 studies by Lorenzetti et al. (2019) did not find differences in global white matter between healthy controls who did use cannabis and those who did not. Three studies were identified which focused on cannabis use and white matter by Crocker et al. (2017) which excluded any studies with polysubstance use (Gruber et al., 2014; Epstein et al., 2014; Zalesky et al., 2012). DTI results from the three studies indicated that decreases in fractional anisotropy were not regionally specific, indicating white matter networks are affected globally. Furthermore, the results from Clark et al. (2012) did show that in individuals with a CUD, fractional anisotropy was significantly reduced in prefrontal and parietal regions.

1.4.3 Psychosis, Cannabis Use, and White Matter Imaging

The combined effects of cannabis and EPP on the structural integrity of white matter have also been studied. Three comparison groups of recent-onset schizophrenia patients were studied by Dekker et al. (2010). Cannabis-naive patients, early-onset cannabis users (less than 15 years old at the onset of regular use), and late-onset cannabis users were compared. No differences were found between early- and late-onset cannabis users. Fractional anisotropy was found to be reduced in the cannabis-naïve patients compared to individuals with early-

onset use, particularly in the posterior corpus callosum. The density of white matter in the left temporal lobe and right occipital lobe was also found to be reduced in cannabis-naïve patients compared to early-onset users. In other words, it appears white matter was affected in the corpus callosum, temporal lobe, and occipital lobe in individuals in the early stages of psychosis who do not use cannabis compared to cannabis users.

Tract-based-spatial-statistics were used by Haller et al. (2014) to analyze the combined effect of cannabis use and first-episode psychosis on white matter tracts, with analyses within the cannabis-using group to compare heavy users with more light users, as well as having a non-user group as a control. Fractional anisotropy values revealed no difference between users and non-users in white matter tracts. Furthermore, when split by heavy versus light use, no differences were found based on tract-based-spatial-statistics using fractional anisotropy values. Axial, radial, and mean diffusion parameters of white matter which measure water diffusion parallel to a tract, perpendicular to a tract, and overall diffusivity, respectively, also did not differ between any of the three groups.

A systematic review of in vivo structural imaging and post mortem studies in individuals with psychosis (with and without cannabis use) was conducted by Rapp et al. (2012). In-vivo results for patients with established schizophrenia showed a significant difference in white matter abnormalities between cannabis users versus non-users, but only in frontal regions. Cookey, Bernier, and Tibbo (2014) similarly reviewed the imaging literature to compare how cannabis influences white matter integrity within individuals with EPP, as well as in

healthy controls. One study, James et al. (2011), was identified which compared white matter using DTI between EPP patients who used cannabis versus those who did not. Results showed that projection tracts, association tracts, and callosal tracts all had significantly reduced fractional anisotropy values in the cannabis-using EPP sample compared to non-using EPP patients.

It has been well described, therefore, that both cannabis use and EPP can impact white matter integrity (as well as evidence of the effects of the two combined). Furthermore, the dysconnectivity hypothesis theorizes that the symptoms of psychotic disorders are the result of compromised white matter tracts (Friston & Frith, 1995). White matter integrity may therefore provide some explanation for the differences in cognitive functioning noted in EPP and cannabis use individually, and for the discrepant findings in individuals with EPP who use cannabis compared to those who abstain.

1.4.4 White Matter Imaging and Cognition

In a recent literature review, Lazar (2017) describes the role of white matter in working memory from the existing evidence. It has been well documented that the various cortices are involved in working memory (particularly the frontal, parietal, and temporal cortices), and white matter is integral to the communication between the cortices. In particular, in healthy individuals, the integrity of the superior and inferior longitudinal fasciculi, the cingulum bundle, the corpus callosum, the uncinate fasciculus, and the fronto-occipital fasciculi were correlated with working memory performance. Corresponding findings exist from a longitudinal study by Krogsrud et al. (2018),

which provide evidence of an association between decreased microstructural integrity (measured with mean, radial, and axial diffusion, as well as fractional anisotropy) and worse working memory performance in the tracts highlighted by Lazar (2017).

Executive functioning has been associated with the degree of white matter hyperintensities (i.e., white matter lesions), which disrupt the signal pathways between the cortices, as indicated by a meta-analysis by Kloppenborg and colleagues (2014) as well as Debette and Markus (2010). However, executive functioning has been more widely researched in relation to gray matter, and much less work has assessed the role of white matter in executive functioning in healthy young adults. Concerning healthy aging, however, it has been demonstrated that the integrity of white matter fiber tracts is related to executive functioning (Ystad et al., 2011). Fractional anisotropy in particular fiber bundles connecting the inferior putamen to the anterior default mode network, the thalamus to the anterior default mode network, and the inferior putamen to the sensory cortices were correlated significantly with executive functioning. Furthermore, the white matter maturation in the adolescent brain has been associated with executive functioning (Asato et al., 2010). Projection and association tracts, in particular, were implicated. Additionally, as the quality of interhemispheric connections increased through adolescence, executive functioning capacity increased.

Prefrontal regions of the brain have been well documented for their role in "higher-order" cognitive faculties, denoted broadly as executive functions, which include capacities such as attention, inhibition, and working memory among

others (Alvarez & Emory, 2006; Aron, 2007). Prefrontal activation has been associated with tasks measuring executive functioning (Shibuya-Tayoshi et al., 2007; Stuss et al., 2001). Furthermore, individuals with reduced activation in prefrontal regions show worse performance on these tasks (Fujiki et al., 2013). Executive functioning performance is at its peak in early adulthood, following the critical neurodevelopmental period involving white matter maturation that is adolescence (Anderson et al., 2010; Bava et al., 2006). Prefrontal regions are closely associated with more specific functions such as working memory and verbal learning abilities (Cohen et al., 1994; Savage et al., 2001) Therefore, prefrontal white matter is integral to tasks requiring higher-order cognitive functions.

White matter has also been associated with verbal learning and memory scores (Takeuchi et al., 2011). The researchers found similarities in regions associated with working memory and verbal learning and memory. The volume of prefrontal and temporal white matter was significantly correlated with verbal learning and memory scores. Fractional anisotropy values in the superior parietal region were positively correlated with performance. In Krogsrud et al.'s (2018) longitudinal study, however, no evidence of an association between mean, radial, and axial diffusion, as well as fractional anisotropy and verbal memory ability was found. Lesions in the cingulum bundle, the fronto-occipital fasciculus, and in the left temporal and thalamic regions have been correlated with reduced verbal learning and memory abilities in individuals with neurodegenerative disease (Sepulcre et al., 2008). Furthermore, Savage et al. (2001) showed evidence of

prefrontal activation during a verbal encoding paradigm. Activation in the left inferior prefrontal region predicted which individuals utilized effective verbal learning strategies, indicating that activation is enhanced in individuals with better strategies, and therefore better verbal learning and memory.

The pars triangularis is a triangular-shaped portion of the inferior frontal gyrus known to be involved in semantic processing and cognitive control of memory (Demb et al., 1995; Gabrieli et al., 1998). That is, this region is activated during tasks that require semantic encoding and retrieval. For instance, if presented with 10 words from two categories, the encoding process automatically recognizes meaning and will categorize the words even if the categories are not explicit in the presentation of the words (Petrides & Pandya, 2012; Small et al., 1995). This encoding has been associated with activation of the pars triangularis (Demb et al., 1995; Dolan, & Fletcher, 1997). Semantic working memory has also been associated with activations of this area (Gabrieli et al., 1998). Therefore, this region is integral to cognitive tests involving both verbal learning and memory as well as working memory due to its activation during tasks that involve encoding and retrieval.

1.5 Goals and Hypotheses

While inconsistencies arise in both the cognitive and neuroimaging domains around what exactly is affected by cannabis use, psychosis, and the two combined, little research has distinctly focused on this issue. Structural abnormalities in white matter underlie the cognitive domains most influenced by cannabis use in healthy individuals (i.e., verbal learning and memory, working

memory, executive functioning, and attention; Epstein et al., 2014; Kloppenborg et al., 2014; Petker 2019). Similar domains of cognition are implicated in psychosis overall including verbal learning and memory, working memory, psychomotor speed, and executive functions, with psychosis reducing performance (Green, 1998; McCleery et al., 2014; Rossi et al., 2016; Townsend, Malla, & Norman, 2001). Indeed, it is known that the white matter integrity of areas responsible for these functions is implicated in individuals with psychosis (Pérez-Iglesias et al., 2010). More inconsistent is the impact of cannabis on cognition in individuals with EPP. However, no known studies to date assess cannabis use in an EPP and healthy sample concerning cognitive functioning and white matter imaging specifically, nor do any attempt to tie together white matter abnormalities and differences (or lack thereof) in cognitive performance.

To resolve discrepancies in the existing literature, as well as to provide novel evidence, two studies were conducted. These studies specifically sampled EPP patients within the first six months after the onset of clinically significant symptoms of primary psychotic disorders. Much of the existing research samples more broadly in both duration of illness and diagnoses, which may occlude certain effects specific to early stages versus more chronic illness as well as primary versus secondary psychoses. Any resulting findings of the two present studies would be descriptive of a subset of EPP patients with relatively short duration of a primary psychotic illness. The samples offered a unique view of the individual and combined effects of EPP and cannabis use on cognition and white matter.

The first study had a retrospective approach, using pre-existing data on cognitive tests as well as substance use data from a clinic specialized in early intervention services for EPP. This retrospective approach allowed for a preliminary probe into the effects of cannabis on verbal learning and memory, working memory, psychomotor speed, and executive functioning. The second study employed four experimental groups: healthy controls with no CUD (HC-), healthy controls with a CUD (HC+), EPP participants with no CUD (EPP-), and EPP participants with a CUD (EPP+) and aimed to provide clarity and additional evidence for the results of Study 1 with the use of neuroimaging techniques as well as a measure of premorbid cognitive functioning. Four cognitive domains consistently impacted by cannabis, psychosis, and (in some but not all studies) the combination of the two were assessed, and include verbal learning and memory, working memory, executive functioning, and psychomotor speed. In addition to a more controlled approach, the second study allowed for the intentional selection of cognitive tasks. Additional data were garnered for Study 2, and in particular, white matter imaging was conducted to compare the four groups on the longitudinal relaxation time of white matter tissue in areas found to be common amongst the groups as well as being implicated in cognition (i.e., the pars triangularis and prefrontal white matter).

Previous research lends itself to several directional hypotheses to be resolved by the aforementioned studies, including:

1. HC overall (i.e., regardless of CUD status) will outperform EPP patients overall on cognitive tasks.

2. Individuals with no CUD overall (i.e., regardless of HC or EPP status) will outperform individuals with a CUD overall on cognitive tasks.
3. Within the HC sample, HC- will outperform HC+ on cognitive tasks.
4. HC overall will have reduced longitudinal relaxation times in the pars triangularis and prefrontal white matter than EPP patients overall (i.e., greater white matter integrity).
5. Within the HC sample, HC- will have reduced longitudinal relaxation times (i.e., greater white matter integrity) in the pars triangularis and prefrontal white matter compared to HC+.

Two non-directional research questions arise from the state of the literature, (i.e., that there exists evidence indicating no difference, while most indicate cannabis acts as a protective factor within EPP samples on cognition, and others still indicating worse cognitive outcomes and white matter integrity):

1. Will EPP- and EPP+ differ in cognitive performance?
2. Will longitudinal relaxation times (i.e., white matter integrity) differ in the pars triangularis and prefrontal region between EPP- and EPP+?

Finally, one overall research question exists:

3. Will a significant difference in both cognitive performance and longitudinal relaxation times (i.e., white matter integrity) occur between the four groups? If so, will differences in white matter

integrity help explain the presence or lack of differences found in cognition?

Chapter 2 Study 1:
The Impact of Cannabis Use on Cognition in Early Phase Psychosis

2.1 Introduction

As previously noted, the combined impact of cannabis use and EPP is unclear, with some studies indicating worse cognitive outcomes (Bogaty et al., 2018), some indicating enhanced cognitive outcomes (Potvin et al., 2008; Rabin, Zakzanis, & George, 2011; Schoeler et al., 2016; Yucel et al., 2012), and others citing no difference (Bogaty et al., 2018; Yucel et al. 2012). The most consistently cited cognitive domains are executive functioning, working memory, and verbal learning and memory. The mixed state of the literature on how cannabis influences cognition in individuals with EPP lent itself to one specific research question: will individuals with EPP differ in cognitive performance (on tasks of executive functioning, working memory, and verbal learning and memory) based on cannabis use? Study 1 approached this research question using a retrospective database analysis from the Nova Scotia Early Psychosis Program (NSEPP) with the goal of disentangling whether cannabis use influences cognition in EPP patients, and if so, whether this influence was positive or negative.

2.2 Method

2.2.1 Participants

Data available for research purposes was obtained from the NSEPP outcomes database in Halifax, Nova Scotia. The retrospective analysis included patients admitted to the NSEPP from 2009 to 2017. All patients had a DSM-

4/DSM-5 diagnosis of a primary psychotic disorder made by an attending psychiatrist within the clinic (American Psychiatric Association, 2000; American Psychiatric Association, 2013). Patients with all relevant cognitive tests (i.e., the One Back Task, Trail Making Tasks, and International Shopping List Task) and substance use information at clinic entry were included (i.e., all data were collected within the first three months of entry to the program). Individuals with problematic substance use (i.e., a suspected substance use disorder) for substances other than cannabis, alcohol, and tobacco (e.g., stimulants) were excluded. In total, 121 individuals in the database met inclusion criteria with no comorbid substance use disorder (excluding cannabis, alcohol, and/or tobacco). Of those 121 patients, 77.70% were male (n = 94), and 22.30% were female (n = 27). The mean patient age was 23.60 (SD = 3.83).

2.2.2 Materials

To measure substance use, the World Health Organization's Alcohol, Smoking, and Substance Involvement Screening Test (WHO-ASSIST) was used (World Health Organization, 2002). The WHO-ASSIST is a clinical tool to assess the use of psychoactive substances to better inform care. It includes eight questions, of which six are assigned a score. First, patients are asked about what substances they have used, and then various questions about the parameters of use (e.g., frequency of use in the last three months, attempts to control/cease use, high-risk behaviours pertaining to use, problems associated with use, etc.) are scored. The lowest an individual can score on a question is zero, with four questions having a maximum score of six, one of seven, and one of eight. The

questions are repeated for all substances a patient has used, and a sum of scores for each substance is obtained. This measure allowed participants to be binned into either the low/no cannabis use category or moderate/severe cannabis use. The WHO-ASSIST has been demonstrated to be a valid tool for measuring substance use in the general population with good discriminative properties (Humeniuk et al., 2008). Furthermore, the tool has been validated for substance use in the EPP population (Hides et al, 2009). Evidence shows that cut-off scores used to successfully identify substance use disorders in EPP populations are more conservative (Cookey et al., 2020; Hides et al, 2009), and therefore lower cut-off scores were used for these analyses. This approach was successfully employed for a recent publication derived out of this same NSEPP database that examined cannabis and alcohol use and symptoms, but not cognitive indices (Cookey et al., 2020). These cut-off scores were four or less for all drugs of abuse, excluding cannabis, where a cut-off score of two was used.

Several cognitive measures were available to compare working memory, executive functioning, and verbal learning and memory between groups. A measure of psychomotor speed was also included. Results from the International Shopping List Task (ISL) were used as a measure of verbal learning and memory. The One Back Task (ONB) was used to measure working memory. Lastly, the Trail Making Task parts A and B (TMT-A/B) were used to assess psychomotor speed and executive functioning, respectively. The ONB and ISL tasks were administered through the CogState computerized cognitive battery for schizophrenia (Westerman et al., 2001). The CogState battery for schizophrenia

includes up to eight neuropsychological tasks in the domains associated with compromised cognitive performance in individuals with schizophrenia. The battery has been validated against other established cognitive batteries designed for schizophrenia such as the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) battery, as well having good validity when compared to non-specific batteries testing the same functions (Pietrzak et al., 2009; Yoshida et al., 2011).

The ONB task is a constrained n-back task where the participants are required to selectively respond to stimuli on the current trial based on whether the stimuli are the same as the stimuli of the previous trial. The participant must, therefore, hold the knowledge of what stimuli occurred on the previous trial while making a decision on the current trial, and update this information in order to be successful on the subsequent trial. Performance on the ONB, therefore, measures working memory, as the information is held long enough to perform an operation, and must be then immediately updated following an action based on new information (Jaeggi et al., 2010; Meule 2017). Scores on the ONB task in Cogstate are the mean of transformed response times on trials where a participant had correct responses using a log 10 (milliseconds; ms) transformation. The ISL measures verbal learning and memory by requiring the free recall of 12 words presented verbally on three trials in the form of a culturally-sensitive shopping list (Lim et al., 2009). The ISL is a reliable memory task with good sensitivity and validity (Pietrzak et al., 2009; Thompson et al., 2011). This task measures immediate verbal learning and memory, as the participants recall words

immediately after each trial, and correct responses for each trial are summed to create a total number of correctly recalled words.

The TMT-A and TMT-B were administered using paper and pencil as a measure of psychomotor speed as well as executive functioning, respectively. Part A instructs participants to connect numbers, in chronological order (i.e., 1 – 2 – 3), that are randomly organized on a page as quickly as possible and without removing the pencil from the paper. Part A was included as reduced psychomotor speed is a potential extrapyramidal symptom of antipsychotic treatment, as well as a deficit in the disorder itself – though it is less cited in the literature of combined effects of EPP and cannabis. Part A, therefore, was included to check for between-group differences which would more likely be a consequence of extrapyramidal symptoms such as slowed motor response. Part B has a similar format to part A and includes randomly organized letters in addition to randomly organized numbers. Participants are required to connect numbers and letters in both chronological and alphabetical order. For example, starting at one, the task would require a participant to do the following: 1 – A – 2 – B – 3 – C. Both the TMT-A and TMT-B are timed, and the time a participant takes to complete each part in seconds is the participant's score for that portion. The TMT-A and TMT-B have been used widely for their reliability (Fals-Stewart, 1992) and validity (Sánchez-Cubillo et al., 2009).

2.2.3 Procedure

Cognitive data were first harvested from the CogState online repository for the NSEPP clinic using anonymized participant codes. All participants who

had completed the CogState battery at the clinic had given consent to have their data accessed for research purposes. Date of birth and sex were also collected for sample demographics. ONB and ISL scores were individually harvested for participants who had completed both tasks at clinic entry. Anonymized participant codes from the CogState repository for participants with both ONB and ISL scores were matched with the corresponding secondary anonymous clinical identification code for the individual. Using the clinical identifier, a clinical research database was accessed in which patient records are available for individuals who have consented to their clinical data being used for research purposes. From the clinical research database, TMT-A and TMT-B scores, as well as substance use data, were obtained for individuals who had data available at clinic entry and had no additional drug use (excluding alcohol and tobacco) above cannabis use.

WHO-ASSIST substance use scores led to the exclusion of 65 participants with cognitive data due to probable substance use disorders with drugs other than cannabis, leaving 121 participants with relevant data. Individuals with cannabis use scores who also had comorbid alcohol or tobacco use were retained for statistical power, as the prevalence of the use of both substances in the EPP population is extremely high (Tsuang et al., 1998). To be binned in the low/no use category, individuals had cannabis scores below two, and all other substance use scores below four, including alcohol, to have a homogenous low/no use comparison group. The moderate/severe group encompassed any individual with a cannabis use score of two or more, with all other substance use scores below

four, with the exclusion of alcohol and tobacco, again to retain statistical power. Therefore, the moderate/severe group included both patients with only cannabis use disorders, as well as patients meeting criteria for both alcohol and cannabis use disorders.

With respect to statistical analyses, sample demographics were first calculated. Cognitive scores for the two groups (i.e., low/no cannabis use and moderate/severe cannabis use) were submitted to a multivariate analysis of variance (MANOVA), with the independent variable of group and four dependent variables (i.e., ONB, TMT-A, TMT-B, and ISL scores). Tests of between-subjects effects were used to determine between-group differences on each of the four cognitive tasks to assess whether the domain tested was affected by group. Estimated marginal means for the four tasks were consulted for tasks with between-group differences to determine the directionality of the effect.

2.3 Results

2.3.1 Statistical Assumptions

To assess whether cannabis use influenced scores on the ONB, TMT-A, TMT-B, and ISL, data were submitted to a one-way MANOVA. To ensure this test was appropriate for the data, a variety of assumptions about the data were checked. The study design ensured several assumptions were met, including the use of at least one categorical independent variable with two or more groups and two or more dependent variables measured on a continuous scale. Second, independence of observations could be assumed based on the nature of the study.

A MANOVA also requires multivariate normality, so standardized residuals were submitted to a histogram and P–P plot for visual assessment. The P–P plot and histogram indicated this assumption was met. Next, a check for univariate outliers was conducted using boxplots. Two outliers (i.e., a value greater than three standard deviations from the mean) were observed, one for the TMT-A and one for the TMT-B. These values were both winsorized to retain the extremity of the scores while ensuring the outliers did not affect the analyses. Mahalanobis distance was then used to check for multivariate outliers. Mahalanobis distance was calculated for each participant's scores. A critical value of 18.47 was determined based on the number of dependent variables (i.e., 4). Three values exceeded this threshold by five or less. The multivariate outliers were retained to again include the extremity of the scores, rather than omit the participants.

Next, the data were checked to ensure there was no multicollinearity of dependent variables. Pearson's correlation coefficients were calculated for the four dependent variables. The four dependent variables had significant small to moderate bivariate correlations. Since all correlations were significant and no correlations exceeded .90, no multicollinearity of dependent variables was assumed. The linearity of dependent variables in each usage group was then checked using two scatterplot matrices. All four tasks had linear relationships in both usage groups.

Finally, homogeneity of variance was tested for using Levene's test of equality of variances. Levene's test was non-significant for all four dependent

variables, therefore homogeneity of variance was assumed. Box's M was then used to test for homogeneity of variance-covariance matrices. Box's M was non-significant ($F(10, 8636.62) = 1.93$, $p = .036$).

2.3.2 Cognitive Results

The average WHO-ASSIST cannabis score was zero ($SD = 0$) for the low/no group ($n = 25$), and 13.75 ($SD = 9.90$) for the moderate/severe group ($n = 96$). The mean age for the low/no use group was 23.36 ($SD = 3.03$). The sex distribution of the low/no use group was 60% males and 40% females. The moderate/severe use group had a mean age of 23.68 ($SD = 3.99$), with 83% of this group being male and 17% female.

The omnibus MANOVA revealed a significant effect of usage group on cognitive performance (Pillai's Trace = .10, $F(4, 116) = 3.38$, $p = .012$, partial $\eta^2 = .10$). To determine if this effect held for each dependent variable, tests of between-subjects effects were consulted. Results from the tests of between-subjects effects can be found in Table 1. The effect of usage on cognitive performance was significant for only the ONB task and the TMT-A. Estimated marginal means were used to determine the directionality of the difference between groups. In both tasks, the moderate/severe usage group performed significantly better than the low/no usage group. This effect suffered from extremely small effect sizes for both the ONB task and the TMT-A (partial $\eta^2 = .08$ and .05, respectively). Figure 1 shows mean scores on the four tasks between the two groups with error bars showing the 95% confidence interval around the mean.

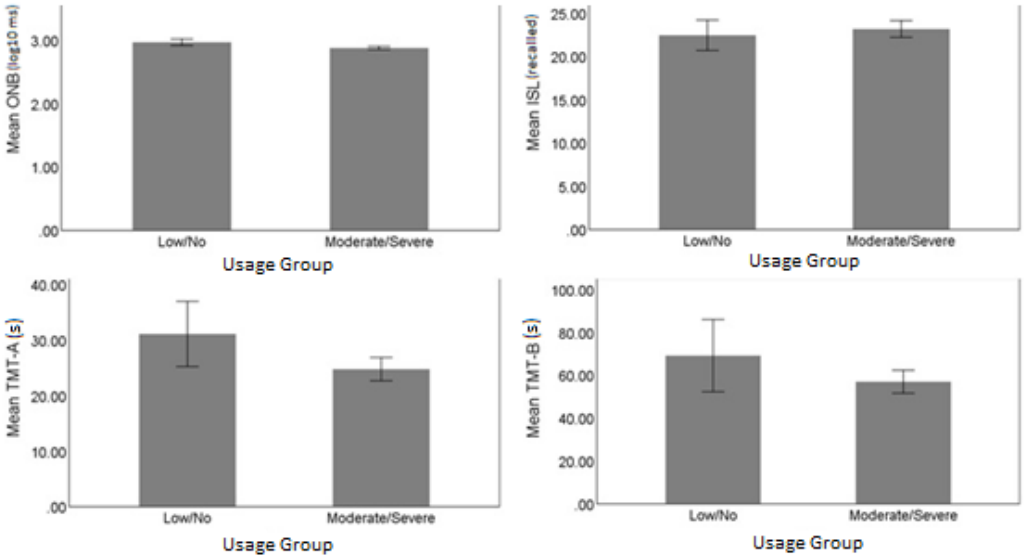
Table 1

ANOVA Table for Tests of Between-Subjects Effects for each Dependent Across Usage Group in Study 1.

Variable	Group	*n*	*df*	*df* error	*F*	*p*	partial η^2
ONB			1	119	10.11	.002**	.08
	Low/no	25					
	Moderate/severe	96					
TMT-A			1	119	6.05	.015*	.05
	Low/no	25					
	Moderate/severe	96					
TMT-B			1	119	3.11	.080	.03
	Low/no	25					
	Moderate/severe	96					
ISL			1	119	.46	.492	.00
	Low/no	25					
	Moderate/severe	96					

Note. Sample size and tests of between-subjects effects for the One Back Task (ONB), Trail Making Task part A (TMT-A), Trail Making Task part B (TMT-B), and International Shopping List Task (ISL) across the two usage groups.
$^{*}p < .05$ $^{**}p < .01$ $^{***}p < .001$

Figure 1.
Mean scores on the One Back Task (ONB), International Shopping List Task (ISL), Trail Making Task part A (TMT-A), and Trail Making Task part B (TMT-B) in EPP patients with low/no cannabis use or moderate/severe cannabis use. Error bars represent a 95% confidence interval around the mean.



2.4 Preliminary Discussion

Study 1 was employed to answer research question one (i.e., whether cognition in EPP groups would differ based on cannabis use). The results suggest that cannabis use does impact cognition in individuals with EPP, but only for the ONB and TMT-A tasks. Small effect sizes between groups indicated that less than 10% of the variance in performances was accounted for by cannabis use. The direction of this effect was that the EPP group with moderate/severe cannabis use performed better on these tasks than those with low/no cannabis use. For the remainder of the tasks (i.e., the TMT-B and ISL), no effect of cannabis use was observed. Therefore, Study 1 suggests that working memory and psychomotor speed are less intact in individuals with EPP who have low/no use of cannabis

compared to those with moderate/severe cannabis use, while executive functioning and verbal learning and memory are similar regardless of use. To contextualize these findings within the literature, the results of Study 1 are in part in accordance with those of Rabin et al. (2011), and Yucel et al. (2012). Rabin et al. (2011) found memory and executive functioning were influenced by cannabis use in individuals with schizophrenia, though Study 1 did not find executive functioning to be impacted by use. Yucel and colleagues (2012) similarly found working memory scores were greater in individuals with psychosis who were regular cannabis users, but again, other effects observed such as improved verbal learning and memory and executive functioning were not observed in Study 1.

The significant differences in psychomotor speed (i.e., TMT-A performance) between groups may be some indication of extrapyramidal symptoms in the low/no use group, rather than an effect of cannabis as inferential statistics suggested. Since the moderate/severe group had significantly better psychomotor speed, this may mean they had less extrapyramidal symptoms such as slowed motor speed compared to the low/no use group. Furthermore, in the evaluation of these results, it must be noted that while univariate outliers were winsorized, three multivariate outliers were included in the analysis, and therefore results should be assessed with regard to this violation.

One additional and concerning limitation to Study 1 was the inability to assess whether the two groups (i.e., low/no and moderate/severe cannabis use) differed in premorbid functioning. When comparing the cognitive functioning between groups, it is important to consider whether the groups had any additional

variables which may have confounded results. Indeed, one important factor to consider is whether the enhanced cognitive functioning was the result of a better general intellectual functioning in one group compared to the other. The results of Study 1 cannot confidently determine that the effects on performance were due to cannabis without knowing whether these groups were inherently different in cognitive functioning overall. Furthermore, while Study 1 provided some evidence of the effect of cannabis on cognition in EPP, it did not provide the ability to assess the overall impact of cannabis and EPP individually, and therefore only provided information pertaining to one of the research questions which arose from the literature. Study 2 sought to answer the remainder of the hypotheses and research questions born out of the literature, as well as incorporating a measure of premorbid intelligence to ensure that the comparison of cognition across groups was reasonable.

Chapter 3 Study 2: The Individual and Combined Impact of Cannabis Use and Early Phase Psychosis on Cognition and White Matter

3.1 Introduction

Results from Study 1 indicated that for those with EPP, cannabis use did significantly impact cognitive performance. Particularly, those with EPP with moderate/severe cannabis use had significantly better scores for tasks of working memory and psychomotor speed than those with EPP with low/no cannabis use, albeit with extremely small effect sizes. Study 1 found no significant differences in executive functioning or verbal learning and memory between the moderate/severe and low/no cannabis use groups. Study 2 aimed to further disentangle the effects of both EPP and cannabis use on cognition using a prospective design. The prospective design allowed for the inclusion of healthy controls in addition to EPP participants in order to assess more pure effects (or lack thereof) of EPP and cannabis on the cognitive domains assessed in Study 1 (i.e., individual effects as outlined in hypotheses one, two, and three). Furthermore, the combined effect of cannabis use and EPP could be further probed with tools that were not pre-selected, which was the scope of research questions one and three. Finally, additional information could be obtained about the effects of EPP and cannabis use on white matter integrity, and importantly, the combined effect, as outlined in research questions two and three. A neuroimaging measure was employed to see whether white matter integrity could help in explaining the individual and combined effects of EPP and cannabis use on cognition.

3.2 Method

3.2.1 Participants

To further explore the research questions and test the hypotheses, 21 participants with EPP were recruited through the NSEPP program of the Nova Scotia Health Authority. Clinicians were informed of the research project and were asked to discuss involvement in research with their patients. If a patient indicated interest and consented to being contacted for research, the patient was approached for participation. Ten additional participants were recruited through the Prevention and Early Intervention Program for Psychosis in London, Ontario. Demographic data for participants can be found in Table 2. Participants had a DSM-5 diagnosis of a primary psychotic disorder by an attending psychiatrist within the clinics (American Psychiatric Association, 2013). In particular, 48% of the sample had a diagnosis of an unspecified schizophrenia spectrum and other psychotic disorder, 38% had a diagnosis of schizophrenia, 10% had a schizoaffective disorder diagnosis, and 5% had a diagnosis of substance-induced psychosis. These disorders have been shown to have similar profiles of cognitive deficits (Bora et al., 2009) though some evidence suggests smaller deficits in those with schizoaffective disorder (Goldstein et al., 2005; Torniainen et al., 2012). Testing occurred within the first six months of entry to the clinics. Of the 31 total EPP participants, 22 were male and 9 were female. The average age for the EPP group was 24.65 (*SD* = 4.82). All prescribed antipsychotic medications were second generation antipsychotics, with 29.03% of patients receiving long-acting injectable antipsychotic treatment.

Forty-six healthy controls were recruited at the Halifax site from local universities and community colleges, from online advertising, and word of mouth. One additional healthy control was tested at the Early Intervention Program for Psychosis in London, Ontario. Healthy controls were defined as having no active psychiatric diagnosis, no use of psychopharmaceuticals, and no first-degree relatives with known schizophrenia or bipolar disorder. A 1:1 ratio of males to females was obtained. The average age of healthy controls was 23.96 (*SD* = 3.98). Sociodemographic data that were collected for all participants included: age, sex, and diagnosis (if in the EPP group). This information can be found in Table 2.

Table 2

Demographics of the Sample of Study 2.

	Group			
	HC-	HC+	EPP-	EPP+
n	25	18	5	18
Sex (%)				
Male	40%	67%	40%	72%
Female	60%	33%	60%	28%
Age				
M(SD)	24.19(3.95)	23.63(4.10)	24.60(5.36)	24.67(4.68)
Diagnosis (%)				
Schizophrenia	N/A	N/A	0%	50%
Schizoaffective Disorder	N/A	N/A	0%	12.50%
Substance-Induced Psychosis	N/A	N/A	0%	12.50%
Unspecified Schizophrenia Spectrum and Other Psychotic Disorder	N/A	N/A	100%	25%

Note. Sample demographics for Study 2, including sample size (*N*), sex (percentage; %), mean age (*M*) and standard deviation (*SD*) for healthy controls with no cannabis use disorder (HC-), healthy controls with a cannabis use disorder (HC+), early phase psychosis participants with no cannabis use disorder (EPP-), and early phase psychosis participants with a cannabis use disorder (EPP+). Clinical diagnosis is described in percentages for the EPP groups.

To participate, all participants were required to speak and read English at a grade eight level at least, be between 18 and 35 years of age, and were required to meet MRI safety criteria (see Appendix). Participants with a previous traumatic brain injury, active or past history of seizures, or known progressive brain disease (e.g., multiple sclerosis, Parkinson's disease, Alzheimer's disease) were excluded. A structured clinical interview for substance use disorders was used to screen if participants had any additional substance use outside of the use of cannabis and/or alcohol (American Psychiatric Association, 2013). Participants were excluded if

they met criteria for a substance use disorder for any substance except alcohol and cannabis. Alcohol use disorders were not an exclusion criterion, as comorbid alcohol use is highly prevalent in the EPP population and would have dramatically reduced sample size (Van Mastrigt et al., 2004). Additionally, participants were excluded if there was ongoing or historical (past-year) regular stimulant use (e.g., regular cocaine use, use of prescription amphetamines).

3.2.2 Materials

To group participants by cannabis use as well as to screen for additional substance use, the Structured Clinical Interview for Substance Use Disorders (SCID) for the Diagnostic Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013) was used. The SCID module for substance use disorders was selected due to its nearly universal use in the field; allowing results to be easily understood in the context of the current literature. The wide use of the SCID to diagnose substance use disorders is likely a result of the tool's well-established reliability and validity (Kranzler, Kadden, Babor, Tennen, & Rounsaville, 1996). The measure contains 13 alcohol-specific questions and 22 questions that can serve for any additional substances a participant reports using in the past 12 months, eight of which list classes of drugs and require participants to discuss the use of all drugs they have taken in the past year. The SCID also provides leading questions for each item, and pathways for inquiry based on participants' answers to optimize data collection. Pertaining to alcohol use disorders, a threshold of two to three positive items indicates a mild alcohol use disorder, four to five positive items indicate a moderate alcohol use disorder, and

more than five positive items indicate severe alcoholism. To meet the criteria for a CUD, the thresholds are equivalent to those from alcohol use disorders (i.e., mild, two to three items; moderate, four to five items; severe, six or more items). In the current study, participants meeting criteria for a CUD were binned into one group (i.e., CUD positive), regardless of the level of CUD, for the sake of statistical power. Four groups were identified for the purpose of this research (i.e., HC-, HC+, EPP-, and EPP+).

The National Adult Reading Test (NART; Nelson & Willison 1991) was used to obtain an estimate of premorbid IQ for both EPP participants as well as healthy controls. NART scores were used to determine whether the experimental groups differed in IQ to be sure the groups could be reasonably comparable in cognitive functioning. This task requires participants to read a list of words, pronouncing each to the best of their ability. Correct/incorrect pronunciations are recorded on a scoring sheet and are used to calculate premorbid IQ. The NART was selected due to its validity and reliability at estimating premorbid functioning (Crawford et al., 2001). The NART has also been successfully used in individuals with schizophrenia (Crawford et al., 1992). Furthermore, the tool can be administered in considerably less time than other measures of premorbid intelligence (e.g., the Weschler Abbreviated Intelligence Scale; Weschler, 1999).

The oral and written Digit Symbol Substitution Tasks (O-DSST, W-DSST; Wechsler, 2008) were used to measure participants' working memory. The O-DSST provides participants with a legend containing nine symbols with corresponding single-digit numbers for each symbol. Participants must orally

recite the number corresponding to each randomly ordered symbol listed, in consecutive order. The W-DSST requires participants to fill in blank spaces below randomly ordered symbols with the corresponding number in consecutive order. Both portions of the DSST allow participants 90 seconds to match the symbols to their corresponding numbers with the goal of correctly completing as many matches as possible. The DSST is a widely used neuropsychological tool for screening for cognitive impairment/dysfunction in healthy individuals as it has robust reliability and validity (González-Blanch et al., 2011). Additionally, the DSST has been regularly used in schizophrenia populations as it reliably measures a central deficit in the disorder (Dickinson et al., 2007) and it has been shown to validly measure working memory dysfunction in EPP patients specifically (Leeson et al., 2010). Furthermore, the DSST was part of a broader research project that participants were enrolled in at the respective clinics.

To assess psychomotor speed and executive functioning, the Trail Making Task parts A and B (TMT-A; TMT-B; Reitan, 1958) were used (see Study 1). Time-to-complete (in seconds) was used for each portion of the task. The tests were selected due to their validity in individuals with schizophrenia (Cuesta et al., 2007), as well as in EPP patients (Galderisi et al., 2009). Furthermore, these tasks have been used to assess the impact of cannabis on psychomotor speed and executive functioning (Preedy, 2016; Thames et al., 2014), and are completed in less than five minutes.

Verbal learning and memory were measured using the California Verbal Learning Task version 3 (CVLT-III; Delis et al., 2017) alternate form. The

CVLT-III has been widely adopted to measure verbal learning and memory due to its precision, reliability, and validity (Woods et al., 2006). The CVLT-III was collected as part of a broader research project and was selected as it is used on a large scale in neurocognitive research in schizophrenia (Rannikko et al., 2012; Rannikko et al., 2015) as well as being validated for use in EPP (Friis et al., 2002). Furthermore, this task was selected due to its use in healthy controls who use cannabis (Hirst et al., 2017; Schuster et al., 2016; Solowij, & Battisti, 2008). Trials one through five of the task consist of reading 16 nouns aloud from four distinct categories and having participants recall as many words as they can, in any order, each time the list is read. Next, a new list of 16 words (i.e., list B) is introduced and read aloud a single time. Participants must recall only words from list B for this trial. Following list B, the next trial is a free recall trial of all words from the first list (i.e., short delay free recall). Participants are then asked to recall all words from the first list from each category with a category cue (i.e., short delay cued recall). Following a 20-minute delay, participants are required again to freely recall all words from the first list (i.e., long delay free recall), and are once again prompted to recall all words from each category with a cue (i.e., long delay cued recall). A particular strength of the CVLT is its scaled scoring. Raw recall scores are converted to age-adjusted scaled scores ($M = 10$, $SD = 3$) based on a participant's age, which is an important factor to consider when assessing cognitive abilities (Husa et al., 2014; Paolo et al., 1997). To assess verbal learning and memory as a whole, rather than components (e.g., short term verbal memory), core scaled recall scores from trials 1-5, list B free recall, short delay free recall,

short delay cued recall, long delay free recall, and long delay cued recall were summed to provide a global verbal learning and memory score for each participant (Delis et al., 2017). Global verbal learning encompasses various components of verbal learning and memory (e.g., encoding, short and longer-term retrieval, cued retrieval, etc.) and therefore provides a comprehensive indication of learning and memory functioning on the whole.

At both study sites, an MR750 three-Tesla scanner with 32-channel phased-arrayed head coil (GE Medical Systems, Waukesha, Wisconsin) was used to obtain T1 relaxation times of brain white matter. T1 maps were obtained to measure the rate of longitudinal relaxation after a full inversion pulse was applied (i.e., the rate at which the net magnetization vector of tissues returns to alignment with B_0 following a radiofrequency pulse in the transverse plane, B_1). Similar to the prevalent T1 maps in the literature, white matter integrity was assumed based on longitudinal relaxation times. Three total T1 relaxation times were obtained for two regions (bilaterally): MP3RAGE (magnetization-prepared rapid acquisition gradient echo), DESPOT1-no (driven equilibrium single pulse observation of T1 with no correction for B_1 field inhomogeneities), and DESPOT1-HIFI (driven equilibrium single pulse observation of T1 with correction for B_1 field inhomogeneities). The use of these methods to measure white matter is preferable to standard T1 maps because DESPOT1-HIFI and MP3RAGE are robust to radiofrequency field inhomogeneities and are not dependent on proton densities, and therefore provide a clearer contrast between grey and white matter, allowing for a robust analysis of white matter (Deoni, 2007; Lutti et al., 2014). Neither the

DESPOT1-HIFI and MP3RAGE techniques have been used in the context of cannabis use and/or EPP, therefore the current study was a preliminary probe into their use in the field. Furthermore, the MP3RAGE technique is not yet validated as an approach. The current study included the DESPOT1-HIFI and MP3RAGE techniques to get an initial trial of the methods in the population.

3.2.3 Procedure

All participants were first screened via the telephone for the following criteria: MRI safety criteria, no ongoing or historical regular stimulant use, no history of seizures or previous traumatic brain injury, no known progressive brain disease, and were between the ages of 18-35. Furthermore, the healthy controls were also screened for active psychiatric diagnoses, use of psychopharmaceuticals, and were asked if they had first degree relatives with known schizophrenia or bipolar disorder. Once participants were confirmed eligible, they were asked for an in-person meeting at the NSEPP Clinic in Halifax, Nova Scotia, or the Early Intervention Program for Psychosis in London, Ontario for collection of demographic data and study measures. At the start of the in-person visit, the study was reviewed in detail and informed consent was obtained. The sociodemographic data was first collected and then prior to beginning the cognitive tasks, the SCID substance use module was administered to later assign participants to group (i.e., CUD positive/+ or CUD negative/-). The CVLT-III trials 1-5, list B free recall, short delay free recall, and short delay cued recall were then administered which allowed a 20-minute delay before the long delay recall trials. During the delay, participants completed the O-DSST, W-

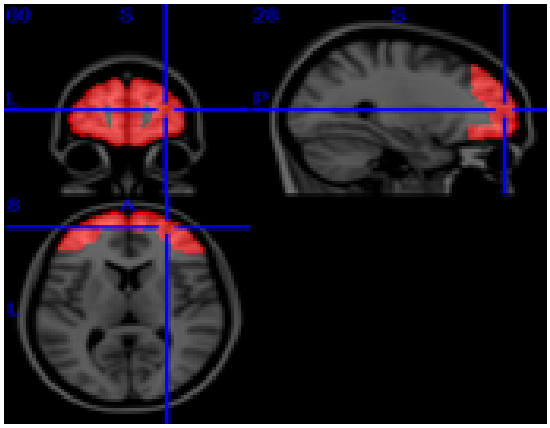
DSST, TMT-A, TMT-B, and NART. Upon completion of the cognitive tasks, participants were compensated for their time and scheduled for an MRI within two weeks of the initial visit. All participants were compensated $10 an hour for every hour they participated in study-related activities.

On the date of the MRI, participants entered the neuroimaging suite for each respective clinic. Participants were required to fill out another comprehensive MRI screening form, remove any metal from their body (e.g., piercings), and change into a hospital gown if their clothes did not meet safety criteria. Once in the scanner, the imaging sequence began, and whole-brain voxel-wise T1 images were obtained in the sagittal plane using a 22 cm^2 frame of view. A time-to-echo of 1.7 ms and a repetition time of 6.8 ms were used with a 13.9 kHz bandwidth. Multi-flip angle spoiled gradient echo images were obtained; a spoiled gradient echo scan was obtained at both four and 18 degrees. An inversion recovery spoiled gradient echo scan at five degrees was obtained using an inversion time of 450 ms. Once the scans were completed, participants were provided their belongings as well as compensation.

A transformation matrix was created for the T1-weighted image and map by registering individual T1 maps to T1 images using automated linear registration (FLIRT). This matrix was then applied to a gray matter mask which was produced in the processing of the T1-weighed anatomical image using FLIRT, resulting in a mask that lined up with the T1 map. Gray matter masking was used because it provided optimal differentiation of brain regions despite the white matter focus of the study. The mask was subsequently applied to the T1

map using FSL Maths. Registration using FLIRT was performed with the individual T1 map to the MNI152 standard brain (Fonov et al., 2009; Fonov et al., 2011), resulting in a transformation matrix, which was then applied to the T1 map. The pars triangularis and prefrontal white matter were selected as regions of interest (ROI) bilaterally. Next, the transformation matrix from the T1 maps and MNI152 standard brain were applied to the ROIs using FLIRT. A threshold of .05 was used to mask the transformed ROIs, which was applied to the gray matter masked T1 map. Mean relaxation times were then calculated for each ROI for the MP3RAGE, DESPOT1-HIFI, and DESPOT1-no measures respectively. The inclusion of all three T1-weighted relaxation times was because while all three methods are optimal for white matter imaging (Deoni, 2007; Hung et al., 2013), it was unclear which would be most sensitive to between-group differences if such differences existed. Furthermore, prefrontal white matter refers approximately to the frontal pole (see Figure 2), but will be discussed conservatively as the prefrontal white matter.

Figure 2.
The left and right frontal pole from the MNI152 standard brain using MNI152_T1_2mm.nii.gz. The frontal pole (bilaterally) was determined using the standard brain, but results were described as prefrontal white matter. Copyright (C) 1993–2009 Louis Collins, McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University.



Demographic information was calculated, followed by descriptive statistics for the groups. Results from the NART were analyzed using a two-way ANOVA to assess whether the participants differed in IQ based on group (i.e., EPP versus HC) or CUD status (i.e., + or -). Scores for each neuropsychological task were submitted to a two-way multivariate analysis of variance (MANOVA), with the independent variables of group (i.e., HC and EPP) and CUD (i.e., + and -) and five dependent variables: O-DSST scores, W-DSST scores, TMT-A scores, TMT-B scores, and CVLT-III scores. Tests of between-subjects effects were consulted to assess which cognitive scores differed, and estimated marginal means indicated the direction of that difference.

Longitudinal relaxation times (T1) from the MP3RAGE and DESPOT1-no and DESPOT1-HIFI measures were submitted to three separate two-way MANOVA procedures, with the independent variables of group and use, and

dependent variables of T1 in the regions of interest (i.e., the pars triangularis and prefrontal region, bilaterally).

3.3 Results

3.3.1 Statistical Assumptions

A variety of assumptions must be met to compare the effect of group (i.e., HC versus EPP) and CUD status (i.e., + or -) using a two-way MANOVA. The study design ensured that there were two or more continuous dependent variables and two categorical independent variables (with independence of observations within the independent variables). Histograms and P–P plots indicated that the assumption of multivariate normality was met.

To determine whether any univariate outliers existed in the data, boxplots were created for the five dependent variables (i.e., the O-DSST, W-DSST, TMT-A, TMT-B, and CVLT scores) for each combination of group and CUD status. One outlier was detected in the data for the TMT-A. The score was winsorized to retain the extremity of the participant's performance while ensuring the outlier did not affect the analyses. To determine whether multivariate outliers occurred, a threshold for the critical Mahalanobis distance was found to be 20.52. No values equalled or exceeded this threshold.

Bivariate Pearson correlation coefficients were calculated between the five dependent variables for each combination of group and CUD status to ensure no multicollinearity of dependent variables. All variables had small to moderate correlations, with the exception of the W-DSST and TMT-A in the HC- group (r = .07, p = .758), for the W-DSST and TMT-A and for the CVLT-III and the

TMT-B in the HC+ group *(r* = -.07, *p* = .775, and *r* = .02, *p* = .954, respectively). Of the significant correlations, no multicollinearity occurred. Next, the assumption of linearity was checked using a scatterplot matrix for each combination of group and CUD status and each of the five tasks. Linear relationships existed for all five cognitive tasks amongst the levels of group and CUD status.

Box's M was non-significant ($F(30, 8997.22) = 1.38$, $p = .080$), indicating that there was homogeneity of variance-covariance matrices. Finally, Levene's test of equality of variances was non-significant for all tasks excluding the TMT-A ($p = .030$) and the O-DSST ($p = .031$). Therefore, equality of variances was assumed for three of the five tasks, with analyses proceeding with recognition of this violation.

3.3.2 Cognitive Results

NART scores were submitted to a two-way analysis of variance (ANOVA) to test whether premorbid intelligence differed between groups (i.e., a main effect of HC versus EPP) or based on CUD status (i.e., a main effect of + or - status). The mean NART scores for HC- and HC+ were 117.38 ($SD = 5.41$) and 115.42 ($SD = 7.06$), respectively. The EPP- group had a mean NART score of 111.51 ($SD = 4.42$), and EPP+ had a mean NART score of 111.46 ($SD = 4.51$). The omnibus ANOVA revealed no significant interaction between group and CUD status ($F(1, 69) = 0.46$, $p = .501$, partial $\eta^2 = .01$). No main effect was found for CUD status ($F(1, 69) = 0.41$, $p = .522$, partial $\eta^2 = .01$). A main effect of group (i.e., HC versus EPP) was found ($F(1, 69) = 11.04$, $p = .001$, partial $\eta^2 =$

.14). Estimated marginal means were consulted to determine the direction of the difference between EPP and HC, and HC was found to have a higher average NART score with a mean difference of 4.91 (95% CI [1.96, 7.86]). It should be noted that while a statistically significant difference existed between NART scores, overlap in the confidence intervals around the means for all combinations of group and CUD status was found. Therefore, analyses proceeded.

In total, 11 participants had missing data for one or more dependent variables. Pillai's Trace was used to examine the inferential statistics as it is robust to unequal sample size in groups. The two-way MANOVA revealed no significant interaction between group and CUD status (Pillai's Trace = .04, $F(5, 58) = .43$, $p = .824$, partial $\eta^2 = .04$). A significant main effect of group (i.e., HC versus EPP) was found (Pillai's Trace = .25, $F(5, 58) = 3.80$, $p = .005$, partial $\eta^2 = .25$). Tests of between-subjects effects (Table 3) revealed the main effect of group held for each dependent variable except the CVLT-III. Estimated marginal means indicated reduced performance in the EPP group relative to the HC group. A significant main effect of CUD status (i.e., + or -) was also found (Pillai's Trace = .23, $F(5, 58) = 3.55$, $p = .007$, partial $\eta^2 = .23$). Tests of between-subjects effects revealed the main effect of CUD held for each dependent variable except the W-DSST and TMT-A. Estimated marginal means indicated reduced performance in individuals with a CUD.

Table 3

Means, Standard Deviations, and ANOVA Table for Tests of Between-Subjects Effects for Each Dependent Variable in Study 2.

Variable	Predictor	*n*	*M*	*SD*	*df*	*df* error	*F*	*p*	partial η^2
W-DSST	Group				1	62	12.08	.001**	.30
	HC	43	62.98	11.87					
	EPP	23	48.83	11.39					
	CUD status				1	62	3.32	.073	.05
	-	30	62.60	7.80					
	+	36	58.11	11.82					
O-DSST	Group				1	62	12.94	.001**	.17
	HC	43	60.72	9.82					
	EPP	23	48.52	8.34					
	CUD status				1	62	4.94	.030*	.07
	-	30	61.23	8.70					
	+	36	52.50	11.17					
TMT-A	Group				1	62	8.08	.006**	.12
	HC	43	21.49	6.70					
	EPP	23	27.57	9.09					
	CUD status				1	62	0.19	.668	.00
	-	30	22.90	8.84					
	+	36	24.19	7.49					
TMT-B	Group				1	62	5.31	.025*	.08
	HC	43	48.84	20.59					
	EPP	23	72.65	31.15					
	CUD status				1	62	5.06	.028*	.08
	-	30	46.67	17.73					
	+	36	65.86	30.48					
CVLT-III	Group				1	62	3.49	.067	.05
	HC	43	103.19	23.28					
	EPP	23	80.04	28.84					
	CUD status				1	62	13.93	.000***	.18
	-	30	110.40	24.30					
	+	36	82.39	23.37					

Note. Means, standard deviations, and between-subjects effects for the Oral Digit Symbol Substitution Task (O-DSST), Written Digit Symbol Substitution Task (W-DSST), Trail Making Task part A (TMT-A), Trail Making Task part B (TMT-B), and California Verbal Learning Test version three (CVLT-III). Means are split by group and CUD status (i.e., healthy (HC), early phase psychosis participants (EPP), and no CUD (-), or having a CUD (+).
*$p < .05$ **$p < .01$ ***$p < .001$

3.3.3 Neuroimaging Results

Statistical assumptions were checked for each two-way MANOVA carried out (i.e., for each measure). The study design ensured that two or more continuous dependent variables were used, with two categorical independent variables (in which independence of observations is met for each). Multivariate normality was assumed from histograms and P–P plots of standardized residuals for each measure.

From the MP3RAGE values, two outliers were found for the HC- group. One participant had scores greater than three standard deviations from the mean for all four ROIs (i.e., left and right prefrontal region and left and right pars triangularis), the second for only the left prefrontal region. One outlier was found from the HC+ group. No outliers were found for EPP- or EPP+. From DESPOT1-no values, one outlier was identified for the HC- group in the right pars triangularis. No outliers were found for HC+. Two outliers were found for EPP- (both in the left frontal region). One outlier occurred in EPP+ for the right pars triangularis. From DESPOT1-HIFI values, no outliers were found for HC- or EPP-. The HC+ group had one outlier in the left prefrontal region. One outlier occurred in the EPP+ ground for the left pars triangularis. While in the conventional sense values which fall outside of three standard deviations of the mean are deemed outliers, these imaging techniques have not been used within the context of cannabis use and EPP, and therefore, no range of normal is known. This, and the necessity to retain extremities, was the rationale to not exclude nor winsorize the values. From the MP3RAGE and DESPOT1-no values, no

participants were found to equal or exceed the critical Mahalanobis distance value, indicating no multivariate outliers for these techniques. From the DESPOT1-HIFI values, one participant exceeded the threshold. Again, this participant was deemed acceptable to keep, so as to retain their extremity.

The relaxation time for all four ROIs was significantly correlated for the MP3RAGE, DESPOT1-no, and DESPOT1-HIFI values. Evidence of multicollinearity (i.e., $r > .90$) was detected for every region but the left and right pars triangularis for MP3RAGE values for HC-, for all regions for HC+, for the left and right prefrontal white matter for EPP-, and for no regions for EPP+. No evidence of multicollinearity was found between ROIs from the DESPOT1-no values. Lastly, no multicollinearity was detected for DESPOT1-HIFI values.

Linearity of dependent variables for each combination of group and CUD status was assessed using scatterplots for the ROIs for the individual sets of imaging values (i.e., for each two-way MANOVA to be used). Linearity was observed for all matrices for the three imaging methods.

Box's M was non-significant for the MP3RAGE, DESPOT1-no, and DESPOT1-HIFI values, therefore equality of covariance matrices was assumed. Levene's test was not significant for any region for MP3RAGE values or either of the DESPOT1 techniques, therefore error variance was assumed to be equal across all groups in each of the three measures.

Pillai's Trace was used to analyze the results of the two-way MANOVAs due to unequal group size for all three imaging measures. The MP3RAGE values revealed there was no interaction between group and CUD (Pillai's Trace = .03,

$F(4, 51) = 0.44$, $p = .782$, partial $\eta^2 = .03$). There was no significant main effect of group (Pillai's Trace = .03, $F(4, 51) = 0.41$, $p = .801$, partial $\eta^2 = .03$) and no significant main effect of CUD status (Pillai's Trace = .05, $F(4, 51) = 0.67$, $p = .620$, partial $\eta^2 = .05$).

The DESPOT1-no values revealed no evidence of an interaction between group and CUD status (Pillai's Trace = .05, $F(4, 45) = 0.62$, $p = .652$, partial $\eta^2 = .05$). A main effect of group was observed (Pillai's Trace = .24, $F(4, 45) = 3.53$, $p = .014$, partial $\eta^2 = .24$). Tests of between-subjects effects revealed the main effect of group occurred only for the left prefrontal region $F(1, 48) = 7.44$, $p = .009$, partial $\eta^2 = .13$). Estimated marginal means were consulted, and EPP had significantly longer relaxation times in the region compared to HC with a mean difference of 118.67 (95% CI [31.16, 206.17]). No main effect of CUD status was observed (Pillai's Trace = .09, $F(4, 45) = 1.15$, $p = .344$, partial $\eta^2 = .09$).

The DESPOT1-HIFI values revealed no evidence of an interaction between group and CUD status (Pillai's Trace = .04, $F(4, 44) = 0.47$, $p = .760$, partial $\eta^2 = .04$). There was no main effect of group (Pillai's Trace = .12, $F(4, 44) = 1.56$, $p = .203$, partial $\eta^2 = .12$). No main effect occurred for CUD status (Pillai's Trace = .06, $F(4, 44) = 0.66$, $p = .624$, partial $\eta^2 = .06$).

3.4 Preliminary Discussion

Study 2 was tasked with providing additional evidence for if/how cannabis use influences cognitive performance in individuals with EPP (i.e., research question one) as a follow-up to the results of Study 1. Furthermore, Study 2 was designed to examine the overall effect of cannabis and EPP on cognition

individually (i.e., hypotheses one and three). Study 2 also allowed for a neuroimaging component to compare the effects of EPP and cannabis on white matter (i.e., hypotheses four and five, and research question two), with the ability to answer the final research question – whether white matter differences could help explain any differences found in the cognitive domains.

Hypothesis one, that HC would outperform EPP, was supported by a main effect of group. Tests of between-subjects effects found this effect was significant for all tasks but the CVLT-III. Therefore, the effect of group was significant for executive functioning, psychomotor speed, and working memory. The direction of the effect confirmed that for the tasks which reached significance, the HC group performed better than the EPP group. The results suggest that individuals with EPP have less intact working memory, executive functioning, and psychomotor speed, but do not differ from HC participants in verbal learning and memory. The impact of EPP on cognition observed in Study 2 fits with findings by Addington et al. (2003) and Fatouros-Bergman et al. (2014) in which working memory, executive functioning, and psychomotor speed were negatively impacted in individuals presenting with schizophrenia spectrum disorders. However, both studies found an effect on verbal learning and memory that the current study did not. Fioravanti et al. (2012) highlighted that memory was the most probable domain to observe a deficit in individuals with schizophrenia, and while Study 2 did not find evidence of an effect of EPP on verbal learning and memory, working memory was found to be reduced compared to controls.

Hypothesis two predicted that CUD status (i.e., + or -) would influence cognition, such that individuals without a CUD, regardless of EPP or HC status, would outperform individuals with a CUD. A main effect of CUD status supported hypothesis two. Tests of between-subjects effects indicated that the impact of CUD status was significant for executive functioning, working memory (in part, due to the non-significant finding for the W-DSST), and verbal learning and memory. Participants' CUD status did not impact psychomotor speed significantly. The direction of this effect demonstrated that having a CUD resulted in reduced cognitive functioning in the domains of executive functioning, working memory, and verbal learning and memory. This finding is consistent with findings by Broyd et al. (2016), Schoeler et al. (2016), and Scott et al. (2018), which all found executive functioning, working memory, and verbal learning and memory to be negatively impacted by cannabis use, though it is important to note the aforementioned studies did not collapse across healthy controls and EPP patients.

The non-significant interaction between group and CUD status suggests that the effect that CUD status has on cognition is consistent whether an individual has EPP or not. Concerning research question one, this translates to EPP+ and EPP- varying in the same respect that HC+ and HC- would vary. That is, having a CUD is detrimental to cognitive performance on tasks of working memory, executive functioning, and verbal learning and memory (though, recall the main effect of group which provided evidence for similar verbal learning and memory scores between the HC and EPP groups overall, while the remainder of

domains were already negatively impacted in the EPP group). In other words, the reduced performance observed in the EPP group was further influenced by CUD status. Hypothesis three (i.e., that HC- would have better cognitive performance than HC+) therefore, is supported, owing to the main effect of CUD status and its consistent influence regardless of group status. With respect to research question three, which pertained to how the four groups would vary, the insignificance of the interaction term and the significant main effects suggest that individuals vary similarly between groups (i.e., HC versus EPP) based on CUD status (which impacted all domains excluding psychomotor speed). The lack of interaction is contradicted by studies such as Rabin et al. (2011) and Yucel et al. (2012) which found that for individuals with schizophrenia, having a CUD positively affected performance on memory and executive functioning tasks. Verbal learning and working memory is the one domain that similar results have been described in, though the study included young adults and focused on regular use, not specifically having a CUD (Bogaty et al., 2018).

Hypothesis four predicted that EPP overall would have longer relaxation times in the left and right pars triangularis and the left and right prefrontal white matter compared to healthy controls. Results supported this prediction for only the DESPOT1-no values, as no significant main effect of group was found for DESPOT1-HIFI or MP3RAGE values. Inspection of the main effect from the DESPOT1-no values, however, indicated that the effect of group was only significant for the left prefrontal region, in which EPP had significantly longer relaxation times which would indicate less intact white matter in the region.

Reduced integrity of left prefrontal white matter was also found by Hao et al. (2009), though Study 2 showed this effect in only one method used (i.e., DESPOT-no).

The lack of a main effect of CUD status for any of the imaging methods shows that hypothesis five (i.e., that HC- would have reduced relaxation times compared to HC+) was not supported. In other words, having a CUD did not impact white matter integrity based on the MP3RAGE, DESPOT1-no, and DESPOT1-HIFI relaxation times. No differences in white matter based on cannabis use were found in a meta-analysis by Lorenzetti et al. (2019), however, most research shows that cannabis negatively impacts white matter integrity (Gruber et al., 2014; Epstein et al., 2014; Zalesky et al., 2012), and in prefrontal white matter in particular (Clark et al., 2012). Furthermore, based on the lack of a main effect of CUD status, EPP- and EPP+ did not differ significantly in longitudinal relaxation times (i.e., research question two, which sought to identify if CUD status had an impact on white matter in individuals with EPP). Evidence of abnormalities in prefrontal white matter in patients who use cannabis have been noted in individuals with schizophrenia (Rapp et al., 2012), though some evidence suggests that cannabis use does not affect white matter integrity in first-episode patients (Haller et al., 2014).

Finally, research question three probed how the four groups would vary in white matter integrity, and whether any differences in longitudinal relaxation times could provide an explanation for any differences found in the cognitive domains. Only one factor was found to impact white matter (i.e., the main effect

of group) in one single imaging procedure (i.e., DESPOT1-no), and this was for only one region – the left prefrontal region. A main effect of group was found for all cognitive domains excluding verbal learning and memory. This may suggest that the influence of EPP on working memory, executive functioning, and psychomotor speed is associated with reduced white matter in the left prefrontal region, however, if this were the case, a main effect of group would be anticipated in this region for the MP3RAGE and DESPOT1-HIFI relaxation times as well. However, neither the MP3RAGE nor DESPOT1-HIFI techniques have been used in individuals with EPP. The results of the imaging analyses as a whole reveal that white matter did not differ between the four groups for the four ROIs (i.e., the left and right prefrontal region and the left and right pars triangularis; with the exception of the left prefrontal region from the DESPOT1-no protocol). Therefore, the integrity of the white matter in the left and right pars triangularis and the left and right prefrontal region do not provide an explanation for differences in cognition based on group or CUD status, nor the effect of both.

One particular limitation of Study 2 is that the measure of cannabis use was a research diagnosis of a CUD. While binning participants based on a CUD versus no CUD provides certain strengths (e.g., less vague cut-offs defining cannabis use), it lends itself to limits in contextualizing the findings of the current study within the broader scope of the field. Another drawback particular to the use of simply differentiating based on CUD versus no CUD is that the absence or presence of a CUD is not entirely dichotomous. First, a participant can be a daily user of cannabis and not meet criteria for a CUD, while another participant may

use once weekly and meet CUD criteria. Furthermore, all participants who met the criteria for a CUD were binned together for the sake of statistical power. It may be the case that having a mild CUD could affect cognitive functioning and white matter integrity in different ways than having a moderate or severe CUD, however, the sample sizes in the present study were not conducive to testing for these effects.

Sample size is also a concern with respect to the findings in Study 2. In particular, there was a very small number of EPP participants who did not have a CUD (i.e., EPP-; $n = 5$). The minimum sample size requirement per group to properly carry out a two-way MANOVA is equal to the number of dependent variables in this analysis. This minimum was met for the MANOVAs used, but increased sample size (for the smaller EPP groups in particular) would have resulted in more statistical power, and therefore an increased ability to find between-group differences if and when such differences occurred. Uneven sample sizes between the groups were accounted for using Pillai's Trace which is robust to deviations from statistical assumptions, however, the uneven and small (though acceptable) sample sizes for the EPP groups are a limit of the current study.

Pillai's Trace is robust to other violations of the assumptions for two-way MANOVAs. For the cognitive tasks, there was a violation of the equality of variances for the TMT-A and the O-DSST. There were also several correlations between dependent variables which were non-significant (i.e., the W-DSST and TMT-A in the HC- group, and the W-DSST and TMT-A as well as the CVLT-III and the TMT-B in the HC+ group), though there was no multicollinearity found.

Ideally, all correlations would be significant and in the small to moderate range. For the neuroimaging data, nine total univariate outliers were identified as well as one multivariate outlier. These values were included in analyses because the present techniques have not been used within the context of cannabis use and EPP, and therefore the values cannot be discounted as abnormal. One final violation for the neuroimaging data was observed. Multicollinearity was observed for the MP3RAGE relaxation times in all combinations of group and CUD status excluding EPP-. These violations require that results be examined cautiously.

Chapter 4 General Discussion

4.1 Summarized Findings

4.1.1 Study 1

Results for Study 1 showed that for individuals with EPP, working memory and psychomotor speed were significantly better in the moderate/severe cannabis use group than the low/no use group, though effect sizes were very small (i.e., less than .1; see Table 1). Executive functioning and verbal learning and memory, however, did not significantly differ between the two groups, indicating that the effect of cannabis was not observed in the results of the ISL or TMT-B tasks.

4.1.2 Study 2

Study 2 demonstrated that overall, healthy controls differed significantly from EPP patients in cognitive functioning on working memory, executive functioning, and psychomotor speed, but not verbal learning and memory. Healthy controls performed significantly better on four of the five tasks (i.e., the O-DSST, W-DSST, TMT-A, and the TMT-B) with mostly small effect sizes (see Table 3).

Results also demonstrated that having a CUD significantly influenced cognitive functioning. Individuals with CUDs (overall) performed worse on all tasks excluding the W-DSST and TMT-A. These results indicate that having a CUD influences verbal learning and memory, working memory (on the O-DSST

only), and executive functioning, but not psychomotor speed. Small effect sizes were observed for these domains (see Table 3).

Study 2 was employed to further examine the influence of cannabis within the EPP and HC participants. A lack of significant interaction between CUD status and group indicated that the main effect of CUD did not depend on the level of group (i.e., EPP versus HC). In other words, the negative impact that having a CUD had on cognitive performance was not different between EPP patients and the control group. This means that reduced performance in HC+ would be seen relative to HC-, and in EPP+ relative to EPP-.

Findings from two of the three imaging measures for white matter indicated that the longitudinal relaxation time was not influenced by either CUD status or group, nor was there a differential influence of CUD status between groups. None of the four ROIs (i.e., left and right prefrontal region and left and right pars triangularis) were significantly different between the four groups for the MP3RAGE or DESPOT1-HIFI measures. However, DESPOT1-no values indicated a main effect of group for the left prefrontal white matter between the HC and EPP. The EPP group had significantly longer relaxation times in this region than the HC group with a small effect size.

Finally, two imaging methods did not provide any complementary evidence to the cognitive results of HC compared to EPP overall. Cognitive measures showed that overall, the HC group performed significantly better in all domains except for verbal learning and memory. Imaging measures showed no differences in white matter between the two groups, except for the left prefrontal

white matter for DESPOT1-no values, in which reduced white matter integrity was shown for the EPP compared to HC. However, this finding was not observed with MP3RAGE or DESPOT1-HIFI longitudinal relaxation times. Therefore, it is difficult to assert that complementary findings occurred between the imaging and cognitive parameters, as there was no consistent effect found between methods for the one ROI which reached significance for HC and EPP overall.

4.2 Evidence for Hypotheses and Research Questions

Hypothesis one predicted that overall, HC participants would outperform individuals with EPP (regardless of CUD status). Results from Study 2 partially supported this hypothesis, with HC participants outperforming EPP participants on tasks of working memory, executive functioning, and psychomotor speed – similar to Addington et al. (2003) – but not verbal learning and memory. The effects observed, however, were small. As highlighted in the preliminary discussion for Study 2, Fioravanti et al. (2012) and Fatouros-Bergman et al. (2014) noted that the most susceptible domain to deficits in individuals with schizophrenia in particular is memory. Almost half of the EPP participants in Study 2 had a diagnosis of schizophrenia and show significant reductions in working memory compared to controls, though this effect was not found for verbal learning and memory.

Hypothesis two predicted that individuals with no CUD would outperform individuals with a CUD. This hypothesis was supported by a main effect of CUD status in Study 2, followed up by significant between-subjects effects for each neuropsychological task except the TMT-A and W-DSST. The lack of a

significant difference in performance on the TMT-A and the significant difference on the TMT-B demonstrated that the two groups did differ in executive functioning, and not in psychomotor speed. Furthermore, the results indicated worse working memory and verbal learning and memory in individuals with a CUD compared to those without, though the effect on working memory was detected only on the O-DSST. The relative consistency of the effect of cannabis in the general population may account for the main effect of CUD status on executive functioning, working memory, and verbal learning and memory (Broyd et al., 2016; Curran et al., 2016; Scott et al., 2018), though no known study has assessed CUD status overall (i.e., collapsing healthy controls with EPP patients).

Relative to hypothesis three, that HC- would outperform HC+ on cognitive tasks, a main effect of CUD status was found for all domains excluding psychomotor speed with small effect sizes. Consultation of the estimated marginal means showed a significant reduction in scores for individuals with a CUD, and a lack of interaction indicated that this effect did not differ based on group (i.e., HC versus EPP). Therefore, HC- did have increased working memory, executive functioning, and verbal learning and memory abilities relative to HC+. These results were similar to results such as those by Broyd et al. (2016), Curran and colleagues (2016), and Scott et al. (2018) where working memory, executive functioning, and verbal learning and memory were reduced in individuals using cannabis.

Hypothesis four, that HC overall would have reduced relaxation times compared to EPP patients overall (i.e., regardless of CUD status) in the left and

right prefrontal region and left and right pars triangularis, was not supported for two of the three neuroimaging methods (i.e., the MP3RAGE and DESPOT1-HIFI methodologies). The DESPOT1-no measure did provide evidence of between-group differences for HC and EPP overall. This was significant for one region (i.e., the left prefrontal white matter), in which an increased relaxation time was observed for the EPP group, indicating reduced white matter integrity. Hao et al., (2009) did find reduced white matter integrity in left prefrontal white matter in individuals with schizophrenia as well as individuals with a genetic risk for the disorder. However, the MP3RAGE and DESPOT1-HIFI relaxation times did not reveal such a difference, as would be expected if this were a consistent effect between healthy individuals and individuals with psychosis. Hypothesis five predicted a significant difference would be found between HC- and HC+ in relaxation times in the left and right prefrontal region and left and right pars triangularis. This hypothesis was not supported by any evidence from the MP3RAGE, DESPOT1-no, or DESPOT1-HIFI measures of longitudinal relaxation time.

Research question one pertained to whether a CUD would impact cognitive performance within the EPP participants. Study 1 found that individuals with EPP who had moderate/severe cannabis use performed significantly better than those with low/no use on tasks of working memory task and psychomotor speed, while no significant difference occurred on the measures of verbal learning and memory and executive functioning. However, in Study 2, a main effect of CUD status was observed in the absence of an interaction between group and

CUD status. This finding indicated that for individuals with EPP (who had already reduced scores of working memory, executive functioning, and psychomotor speed overall), those in the EPP+ group would have even further reduced scores of working memory, and executive functioning, as well as verbal learning and memory compared to EPP-, owing to the main effect of CUD status. The results of Study 1 in relation to the wider literature are similar to those found by Rabin and colleagues (2011), where improved memory was found in individuals with schizophrenia who also had a CUD. Regular use in the EPP population in particular was shown by Yucel et al. (2012) to result in improved cognition on tasks of working memory, while the effect observed in Yucel et al. (2012) on verbal learning and memory and executive functioning was not found in Study 1. In Study 2, however, the opposite occurred – a finding which could be the result of having a small sample size in the EPP groups, with a particularly small sample size in the EPP- group. Furthermore, by collapsing across the HC and EPP groups, the specific effect in those with EPP with a CUD may have been lost.

Research question two also pertained to whether a difference would be found in longitudinal relaxation times for EPP- and EPP+, and if so, in what direction that difference would occur. No interaction effect and no main effect of CUD status were found in Study 2 with MP3RAGE, DESPOT1-no, and DESPOT1-HIFI relaxation times for any of the four ROIs (i.e., the left and right prefrontal region and left and right pars triangularis). This indicated no detectable difference in frontal white matter between EPP- and EPP+. A lack of evidence of

an effect of cannabis use on white matter integrity in EPP patients in particular was also noted by Haller et al. (2014).

Finally, the third research question aimed to probe the relationship between the four groups (i.e., HC-, HC+, EPP-, and EPP+) on cognitive tasks, as well as on MP3RAGE, DESPOT1-no and DESPOT1-HIFI measures in the four ROIs (i.e., the left and right prefrontal region and left and right pars triangularis). A lack of main effects and interaction indicated that the groups did not differ in white matter integrity, barring the one main effect of group observed for the left prefrontal region. Research question three also probed how all four groups would perform on the cognitive tasks in relation to one another. Study 2 revealed that the groups had similar differences depending on CUD status and that having a CUD or EPP resulted in reduced performance on the tasks described for the individual main effects. Studies such as Schoeler et al. (2016) and Yucel et al. (2012) also looked at four experimental groups but did not compare the four individually to compare differences/similarities in functioning, therefore these results are difficult to contextualize. As noted in the preliminary discussion for Study 2, MP3RAGE and DESPOT1-HIFI relaxation times provided no complementary evidence to the cognitive results. A main effect of group status from the DESPOT1-no values for the left prefrontal white matter may help explain the reduced executive functioning and working memory in the EPP group relative to controls, however, this finding was not replicated by the other measures of white matter integrity.

4.3 Implications

It has been posited that cognitive deficits that arise in EPP patients compared to healthy controls are actually overstated in the literature, as healthy control participants are typically recruited within the institutions conducting the research and therefore have potentially greater cognitive functioning than the general population (Wechsler, 1958). However, Study 2 ensured that the comparison groups had reasonably comparable premorbid functioning as estimated by the NART. Whether or not a participant had EPP explained 25% of the variance in cognitive functioning in Study 2. Those with EPP particularly struggled with executive functioning, working memory, and psychomotor speed. This could result in functional implications (e.g., an inability to effectively plan one's day). The deficits in cognitive functioning observed in EPP are important to note, as they predict general functioning, though it is through an additional variable – functional skills (Bowie & Harvey, 2006). Therefore, cognition is important to assess in EPP patients in conjunction with functional skills in order to have the best possible functional outcomes for patients.

While Studies 1 and 2 found different results in the cognitive functioning of EPP patients based on cannabis use, both studies suffered from small effect sizes in each domain. The enhanced working memory and psychomotor speed observed in individuals with EPP and cannabis use in Study 1 did not exceed .1, indicating that less than 10% of the variance in performance between the low/no group and moderate/severe was due the cannabis use. Study 2 found that cannabis use explained 23% of the variance in cognitive performance, though this was across EPP and HC groups. Functional implications could arise from the results

of Study 2 (e.g., increased difficulties with performing mental math for individuals with EPP who use cannabis) which could negatively impact an individual's life. Furthermore, there are external variables that may have an impact on cognitive functioning between users and non-users, such as lower levels of education, social and occupational functioning, and different cultural factors in continued users with psychosis (Rebgetz et al., 2014). However, Study 1 had antithetical results suggesting improvements with increased cannabis use. Therefore, no consensus can be made from the present results regarding the broader implications of cannabis use on cognition in individuals with EPP.

While it remains unclear whether EPP patients with cannabis use have enhanced or reduced verbal learning and memory, working memory, and executive functioning compared to their non-using counterparts, these results do reinforce the problematic cannabis use in the population. Of 152 total EPP participants (from both Study 1 and Study 2), only approximately 20% did not have a research diagnosis of a CUD. Therefore, 80% of the total EPP population in these two samples have problematic use of cannabis (i.e., probable CUDs). While cognitive deficits occurred in the sample overall, there were only small to moderate effect sizes. However, cannabis use in EPP is associated with increased relapse and rehospitalization, increased positive symptoms, reduced medication adherence, and general functioning (Flemenbaum & Zimmermann, 1973; Foglia et al., 2017; Setién-Suero et al., 2019; Zammit et al., 2008). Therefore, the high rate of cannabis dependence in these samples is cause for concern. Focused

treatment for CUDs in the EPP population is extremely important for improved outcomes for individuals in treatment for EPP.

No impact of cannabis on white matter integrity was found for any of the neuroimaging measures used. These results suggest that having a CUD may not influence the integrity of white matter in either EPP patients or healthy controls. However, DESPOT-no results did suggest an effect of EPP in the left prefrontal white matter. Differences in white matter integrity have been documented between individuals with psychotic disorders and healthy controls, and have been hypothesized to give rise to psychotic illnesses (Friston & Frith, 1995). Nearly one-quarter of the variation in longitudinal relaxation times in the left prefrontal white matter was explained by whether a participant had EPP or was a healthy control. While the present work is unable to assert that broad dysconnectivity occurred, it does lend evidence to aberrant white matter in EPP, which is has been posited to explain the presentation of psychotic disorders.

Another consideration is illness versus substance effects in white matter. Research by Bernier et al. (2016) indicated that duration of illness in an EPP group explained 22% of the variance in a white matter marker (i.e., choline-containing compounds, indicative of myelination/myelin integrity). In healthy controls with cannabis and/or alcohol use, glutamate levels in prefrontal white matter were reduced compared to healthy controls without substance use, with the severity of use accounting for 17% of the variance. Furthermore, several markers of white matter were implicated in the substance effects within EPP, and over one-third of the variance in the EPP group was explained by the severity of

substance use. While organic differences are noted in the EPP population (i.e., illness effects), a significant portion of variance is to be explained by substance use. The current research found only illness effects, as CUD status did not influence white matter integrity.

Regardless of the direction of the effect, cannabis use in the literature broadly as well as in the current studies is much less detrimental to cognitive functioning than it is to symptoms and outcomes in psychotic disorders. Small effect sizes are frequently noted when statistically significant effects do occur in cognitive domains between cannabis users and those who abstain (Bogaty et al., 2018; Rabin et al., 2011; Schoeler et al., 2016; Yucel et al., 2012). Cannabis use can significantly influence the course of a psychotic disorder, however, which can have a profound impact on an individual's life (Foglia et al., 2017; Setién-Suero et al., 2019; Zammit et al., 2008). For example, while an inability to efficiently plan a to-do list may not be benign, relapses, which have been associated with continued cannabis use, might affect employment. While it is known that cognitive abilities can predict functional outcomes, the effect of cannabis on psychotic symptoms and outcomes is profound.

4.4 Limitations

The generalizability of the present work is limited by several factors. In both Studies 1 and 2, there were uneven sample sizes between groups. While Pillai's Trace was used in statistical analyses to account for this, it is the case that effects in Study 2 in the small EPP+ and even smaller EPP- group, in particular, may not have been representative of cognition in these groups as a whole. This

could perhaps explain differing results in how cannabis influences cognition in EPP between Study 1 and Study 2. Although Study 1 had larger sample sizes, there was still a large variation in group size between the low/no and moderate/severe cannabis users.

Additionally, two different measures of cannabis use were used between studies. Study 1 used the WHO-ASSIST, and binned participants into low/no misuse and moderate/severe cannabis misuse, which reflect likely CUDs (Cookey et al., 2020; Hides et al., 2009). Study 2 used the SCID for substance use, and binned participants into CUD positive and CUD negative groups. WHO-ASSIST scores are more reflective of an estimate of misuse and dependence, while the SCID was selected for its more robust diagnostic abilities, though the CUD status was based on a research diagnosis from the SCID and not a clinical diagnosis. While both the WHO-ASSIST and SCID scores indicate problematic use, the measures are not identical, with the SCID being a diagnostic tool and the WHO-ASSIST designed to label substance misuse and dependence which may interfere with primary care. This distinction may help explain the opposing effects of cannabis use between Studies 1 and 2.

Different tasks were also used to estimate cognitive functioning in the two studies. Of the two tasks in Study 1 where a significantly better performance was observed in the moderate/severe group relative to the low/no use group, only one was used in Study 2 (i.e., the TMT-A), and Study 2 found CUD status did not impact psychomotor function. While the same executive functioning task was used for Studies 1 and 2 (i.e., the TMT-B), Study 1 found no significant

difference in executive functioning based on cannabis use in EPP, while Study 2 found CUD status reduced executive functioning. The working memory tasks and verbal learning and memory tasks differed between the two studies, as intentionally selected tasks that are validated in EPP and cannabis use were used in Study 2. While the results on tasks that measure the same functions should be similar, it must also be mentioned that two of the tasks (i.e., the ISL and ONB) in Study 1 were administered using a computerized cognitive battery already captured within a research database of EPP patients (i.e., a secondary analysis of archived data). Though the validity of all tasks in each study is good, and one can have confidence that the tasks are assessing the targeted function, it is possible that the difference in the tasks used had an impact on the different results within the EPP populations between Study 1 and Study 2.

Other factors known to influence cognitive functioning in EPP may have led to the antithetical results between Study 1 and 2. For instance, while all patients were within the first six months of illness onset (i.e., a similar duration of illness), illness severity, a factor known to influence cognition (Barder et al., 2013; Fitzgerald et al., 2004), between the EPP populations in Study 1 and 2 may have differed. Furthermore, individuals in Study 2 had to be well enough to undergo the MRI, a criterion not captured in Study 1. Continued use of cannabis is also dependent on the perceived impact on mental health, financial resources, and differences in social and cultural factors which likely differed between the using and non-using patients (Childs et al., 2011). It is also possible that the small improvements potentially afforded by second generation antipsychotic treatments

that have been reported in the literature may have contributed to the small improvements in the moderate/severe usage group in Study 1, though the scope of the present study did not address antipsychotic effects (Hill et al., 2010; Meltzer & McGurk, 1999). In contrast, there was no difference found for psychomotor speed between EPP- and EPP+ in Study 2, which confirmed expectations that there were not extrapyramidal symptoms from antipsychotic medications between EPP groups. Antipsychotics – particularly neuroleptics – can impact motor speed, a capacity which is already affected by EPP itself (Morrens et al., 2007; Walther, & Strik, 2012; Wang et al., 2019). It is possible that the two groups in Study 1 had a different proportion of patients taking neuroleptics, resulting in worse performance on the TMT-A for the low/no use group. Furthermore, improvements in motor speed have been observed in patients treated with second generation antipsychotics (Morrens et al., 2007), which may potentially explain improved psychomotor speed in the moderate/severe cannabis users in Study 1, if the two groups differed in antipsychotic treatments.

While moderate/severe cannabis use enhanced psychomotor speed and working memory in EPP in Study 1, there is no way of asserting that this group of participants did not have enhanced cognitive functioning to begin with due to the lack of a measure of premorbid functioning in Study 1. In EPP patients, it has been demonstrated that cannabis use is associated with higher premorbid intelligence (Ferraro et al., 2013), despite continued use being associated with lower levels of education, as well as social, occupational, and global functioning (Rebgetz et al., 2014). Specifically, Ferraro et al. (2013) demonstrated that

lifetime use of cannabis was associated with a premorbid IQ that was approximately 12 points higher than that of patients with no lifetime use. No significant difference occurred for lifetime use in the healthy control sample. Therefore, the results of Study 1 may be due to inherent differences in premorbid functioning in the two usage groups. In Study 2, where no such enhancement was found based on cannabis use, the findings may be the result of similar premorbid functioning in the patient sample, where the two patient groups (i.e., EPP- and EPP+) differed by less than one point in NART scores.

The results of the present study must be understood in the context of a unique subset of patients with psychosis. While some work has been done to look cognition and white matter integrity individually in those within the first episode, or early in the course of a psychotic disorder, little has looked at the combined effects of cannabis and EPP specifically (Yucel et al., 2012). Furthermore, the use of both cognitive and neuroimaging measures to investigate the individual and combined effects of cannabis and EPP in those with primary psychotic disorders and less than six months of clinically significant symptoms makes these results relatively unique within the literature. The specificity of the samples is a strength of Study 1 and 2 and may lend evidence to a timeline of illness and substance effects on cognition and white matter in primary psychoses.

A great deal of literature in this field fails to account for the effects of polysubstance use and age, which is one strength of the current studies. Age was not included as a covariate, but it was determined to be similar between all groups both within and between studies. While alcohol and tobacco use were not

controlled for in order to retain sample size, various other substances that are known to impact cognition (e.g., cocaine) were exclusion criteria for both studies. This provides some clarity on cannabis use and its effect on cognition. The effect of cannabis on cognition and white matter is extremely difficult to address, which also limits the generalizability of these results to the parameters that were used. There is extreme heterogeneity in cannabis use literature, with both acute and chronic effects, effects of a substance use disorder, effects of regular use, and effects of the age of onset of cannabis use being studied. Since the literature measures cannabis use variably, it can be expected that some discrepancies in findings would occur.

Regarding alcohol in particular, previous literature has indicated that alcohol use does have an impact on white matter as well as cognition. In a meta-analysis, Stavro and colleagues (2013) found that working memory, verbal learning and memory, and executive functioning were all reduced in individuals with alcohol dependency, even following periods of both short- and long-term abstinence. Furthermore, in individuals with schizophrenia with or without a comorbid alcohol use disorder, those with an alcohol use disorder had increasingly impaired working memory (Potvin et al., 2008). Ritter et al. (2004), however, did not find a difference in executive functioning in schizophrenia patients who had problematic alcohol use in the past versus those with no history of problematic use. The antithetical results therefore between Study 1 and Study 2 may be the effect of comorbid alcohol use, which the current studies did not use as exclusion criteria to retain statistical power. Furthermore, evidence from

Cookey et al. (2018) found that regular alcohol use was associated with decreased fractional anisotropy in an EPP population in individuals with earlier onset alcohol use, indicating that myelin integrity was reduced at the whole-brain level. The study failed to find a cannabis and alcohol interaction but did find that earlier onset of regular alcohol use explained more variance in white matter integrity than lifetime cannabis exposure. Indeed, future research should covary or exclude participants based on alcohol use for a clearer picture of how cannabis influences cognition, though for the purposes of this study the two were inextricably linked to retain sample size. Additionally, studies similar to the current one are warranted for alcohol use alone.

It has also been noted that there is an abstinence effect with cannabis use such that cognition improves after a period of abstinence in regular users (Broyd et al., 2016). The SCID used in Study 2 detects symptoms in the past 12 months to determine whether an individual has a CUD, but it is possible that a participant meeting the criteria for a CUD is not using at present. Similarly, the cannabis scores from the WHO-ASSIST in Study 1 were harvested as totals, with no ability to assess if patients had been abstinent at the time of testing. The tools used in the current studies capture substance use disorders, but the time of the last use was not taken into account, which may have impacted cognitive results.

Additionally, the potency of the cannabis that participants were using was not captured by the tools in Study 1 or 2, which has been alluded to in order to explain the effect of publication year in meta-analyses on cannabis' effect on cognitive abilities (Schoeler et al., 2016). One recent meta-analysis by Colizzi,

and Bhattacharyya (2017) found that in the common domains affected by cannabis use, strains of cannabis with high potency THC, and low potency cannabidiol (CBD) negatively impact cognition when administered acutely, or are used more chronically. While CBD does not particularly improve these cognitive domains, more even ratios of THC to CBD tend to result in a lower impact on cognition. Furthermore, it is predicted that the reduced effect seen with more even ratios occurs because of CBD acting as an antagonist at cannabinoid receptors (particularly CB1 receptors) working against THC's agonist effects. There are tools that can estimate these parameters, such as the Timeline Followback for cannabis use (Robinson et al., 2014), but the focus of the present studies was not aimed at addressing potency effects of cannabis on cognition and white matter, but to look at problematic use broadly.

Results for the imaging data in particular are a limitation of Study 2 and must be assessed cautiously, as several assumptions of the two-way MANOVA used in each measure were violated. In particular, several univariate outliers were identified in the data as well as one multivariate outlier. Multicollinearity was also detected for most regions in the MP3RAGE measure. While these assumptions were violated, continuing with the analyses was reasonable. It is possible that these violations could have impacted the results found. Furthermore, the sample size could simply be too small, particularly for the EPP- group, to detect any differences in white matter in these regions if they do in fact exist. Both the MP3RAGE and DESPOT1-HIFI techniques are new, and the MP3RAGE technique, in particular, has not yet been validated against other

measures of white matter integrity. The present study was unable to provide an indication of the validity of the method beyond the discrepant findings between it and the DESPOT1-no results. Additionally, the inconsistency between DESPOT1-HIFI and DESPOT1-no results suggest that the correction used for the B_1 field inhomogeneities in longitudinal relaxation time did not function properly. Finally, neither MP3RAGE nor DESPOT1-HIFI techniques have been used to assess white matter integrity in EPP or in cannabis users, while driven equilibrium single-pulse observations of relaxation times (though often for both T1 and T2) like DESPOT1-no have (Vanes et al., 2018; Vanes et al., 2019).

While there remains no consensus on the effect of cannabis use on cognitive functioning within the EPP population based on the results of the two current studies, as well as the prior literature, future research may be able to further disentangle the relationship with consistent methodology and increased sample sizes. Considerations such as the age of onset of cannabis use, the duration of regular use, as well as the relative potency of the cannabis individuals are using should be examined to see clearer effects of the substance. Furthermore, studies should continue to exclude individuals using other substances in addition to cannabis to assess the pure effect of cannabis. While sample size did not allow this for Study 1 and Study 2, alcohol use disorders should be treated as an exclusion criterion, again to parse out the effect of cannabis alone. Furthermore, future research should aim for no less than 50 participants per group, as is the recommendation for detecting differences in performance on neuropsychological tasks (Bridges, & Holler, 2007), a sample size which was unfortunately not

attainable for either Study 1 or 2 of the current work. Future research could also aim to correlate differences in neuropsychological functioning to structural and functional differences. Finally, white matter integrity may be used in larger studies in the future with the four groups to predict cognition, whereas the current study could only postulate differences between these groups.

References

Abdel-Baki, A., Ouellet-Plamondon, C., Salvat, É., Grar, K., & Potvin, S. (2017). Symptomatic and functional outcomes of substance use disorder persistence 2 years after admission to a first-episode psychosis program. *Psychiatry Research*, *247*, 113-119. https://doi.org/10.1016/j.psychres.2016.11.007

Addington, J., & Addington, D. (2002). Cognitive functioning in first-episode schizophrenia. *Journal of Psychiatry and Neuroscience*, *27*(3), 188. Retrieved from https://jpn.ca/

Addington, J., Brooks, B. L., & Addington, D. (2003). Cognitive functioning in first episode psychosis: initial presentation. *Schizophrenia Research*, 62(1–2), 59–64. https://doi.org/10.1016/S0920-9964(02)00340-7

Allott, K., Liu, P., Proffitt, T. M., & Killackey, E. (2011). Cognition at illness onset as a predictor of later functional outcome in early psychosis: Systematic review and methodological critique. *Schizophrenia Research*, *125*(2-3), 221-235. https://doi.org/10.1016/j.schres.2010.11.001

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. *Neuropsychology Review*, *16*(1), 17-42. https://doi.org/10.1007/s11065-006-9002-x

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: Author.

Anderson, V., Jacobs, R., & Anderson, P. J. (Eds.). (2010). *Executive functions and the frontal lobes: A lifespan perspective*. Psychology Press.

Anthony, J. (2006). The Epidemiology of Cannabis Dependence. In G. Marlatt (Author) & R. Roffman & R. Stephens (Eds.), *Cannabis dependence: Its nature, consequences and treatment* (pp. 58-105). Cambridge University Press. https://doi.org/10.1017/CBO9780511544248.006

Aron, A. R. (2007). The neural basis of inhibition in cognitive control. *The neuroscientist*, *13*(3), 214-228. https://doi.org/10.1177/1073858407299288

Arseneault L, Cannon M, Poulton R, et al. (2002) Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *British Medical Journal,* (325), 1212–1213. https://doi.org/10.1136/bmj.325.7374.1212

Baumann, N., & Pham-Dinh, D. (2001). Biology of oligodendrocyte and myelin in the mammalian central nervous system. *Physiological reviews*, *81*(2), 871-927. https://doi.org/10.1152/physev.2001.81.2.871

Bava, S., Thayer, R., Jacobus, J., Ward, M., Jernigan, T. L., & Tapert, S. F. (2010). Longitudinal characterization of white matter maturation during adolescence. *Brain Research*, *1327*, 38-46. https://doi.org/10.1016/j.brainres.2010.02.066

Benes, F. M., Turtle, M., Khan, Y., & Farol, P. (1994). Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. *Archives of General Psychiatry*, *51*(6), 477-484. https://doi.org/10.1001/archpsyc.1994.03950060041004

Bertelsen, M., Jeppesen, P., Petersen, L., Thorup, A., Øhlenschlæger, J., le Quach, P., ... & Nordentoft, M. (2008). Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: The OPUS trial. *Archives of General Psychiatry*, *65*(7), 762-771. https://doi.org/10.1001/archpsyc.65.7.762

Bernier, D., Bartha, R., McAllindon, D., Hanstock, C. C., Marchand, Y., Dillen, K. N., ... & Tibbo, P. G. (2016). Illness versus substance use effects on the frontal white matter in early phase schizophrenia: A 4 Tesla 1H-MRS study. *Schizophrenia Research*, *175*(1-3), 4-11. https://doi.org/10.1016/j.schres.2016.04.022

Barder, H. E., Sundet, K., Rund, B. R., Evensen, J., Haahr, U., ten Velden Hegelstad, W., ... & Melle, I. (2013). Neurocognitive development in first episode psychosis 5 years follow-up: Associations between illness severity and cognitive course. *Schizophrenia Research*, *149*(1-3), 63-69. https://doi.org/10.1016/j.schres.2013.06.016

Bogaty, S. E. R., Lee, R. S. C., Hickie, I. B., & Hermens, D. F. (2018). Meta-analysis of neurocognition in young psychosis patients with current cannabis use. *Journal of Psychiatric Research, 99,* 22–32. https://doi.org/10.1016/j.jpsychires.2018.01.010

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis?. *Schizophrenia Bulletin, 40*(4), 744-755. https://doi.org/10.1093/schbul/sbt085

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: Meta-analytic study. *The British Journal of Psychiatry*, *195*(6), 475-482. https://doi.org/10.1192/bjp.bp.108.055731

Bowie, C. R., & Harvey, P. D. (2006). Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatric disease and treatment*, *2*(4), 531. https://doi.org/10.2147/nedt.2006.2.4.531

Bridges, A. J., & Holler, K. A. (2007). How many is enough? Determining optimal sample sizes for normative studies in pediatric neuropsychology. *Child Neuropsychology, 13*(6), 528–538. https://doi.org/10.1080/09297040701233875

Broyd, S. J., van Hell, H. H., Beale, C., Yuecel, M., & Solowij, N. (2016). Acute and chronic effects of cannabinoids on human cognition—a systematic review. *Biological psychiatry*, *79*(7), 557-567. https://doi.org/10.1016/j.biopsych.2015.12.002.

Carletti, F., Woolley, J. B., Bhattacharyya, S., Perez-Iglesias, R., Fusar Poli, P., Valmaggia, L., ... & Williams, S. C. (2012). Alterations in white matter evident before the onset of psychosis. *Schizophrenia Bulletin*, *38*(6), 1170-1179. https://doi.org/10.1093/schbul/sbs053

Chadwick, B., Miller, M. L., & Hurd, Y. L. (2013). Cannabis use during adolescent development: susceptibility to psychiatric illness. *Frontiers in Psychiatry*, *4*, 129. https://doi.org/10.3389/fpsyt.2013.00129

Childs, H. E., McCarthy-Jones, S., Rowse, G., & Turpin, G. (2011). The journey through cannabis use: A qualitative study of the experiences of young adults with psychosis. *The Journal of Nervous and Mental Disease*, *199*(9), 703-708. https://doi.org/10.1097/NMD.0b013e318229d6bd

Clark, D. B., Chung, T., Thatcher, D. L., Pajtek, S., & Long, E. C. (2012). Psychological dysregulation, white matter disorganization and substance use disorders in adolescence. *Addiction*, *107*(1), 206-214. https://doi.org/10.1111/j.1360-0443.2011.03566.x

Cohen, J. D., Forman, S. D., Braver, T. S., Casey, B. J., Servan-Schreiber, D., & Noll, D. C. (1994). Activation of the prefrontal cortex in a nonspatial working memory task with functional MRI. *Human Brain Mapping*, *1*(4), 293-304. https://doi.org/10.1002/hbm.460010407

Colizzi, M., & Bhattacharyya, S. (2017). Does cannabis composition matter? Differential effects of delta-9-tetrahydrocannabinol and cannabidiol on human cognition. *Current Addiction Reports*, *4*(2), 62-74. https://doi.org/10.1007/s40429-017-0142-2

Cookey, J., Bernier, D., & Tibbo, P. G. (2014). White matter changes in early phase schizophrenia and cannabis use: an update and systematic review of diffusion tensor imaging studies. *Schizophrenia Research*, *156*(2-3), 137-142. https://doi.org/10.1016/j.schres.2014.04.026

Cookey, J., Crocker, C. E., Bernier, D., Newman, A. J., Stewart, S., McAllindon, D., & Tibbo, P. G. (2018). microstructural findings in white matter associated with cannabis and alcohol use in early-phase psychosis: A diffusion tensor imaging and relaxometry study. *Brain Connectivity*, *8*(9), 567-576. https://doi.org/10.1016/10.1007/s00415-002-0837-7

Cookey, J., McGavin, J., Crocker, C. E., Matheson, K., Stewart, S. H., & Tibbo, P. G. (2020). A Retrospective Study of the Clinical Characteristics Associated with Alcohol and Cannabis use in Early Phase Psychosis. *The Canadian Journal of Psychiatry, 65*(6), 426-435. https://doi.org/10.1177/0706743720905201

Correll, C. U., & Schooler, N. R. (2020). Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. *Neuropsychiatric Disease and Treatment*, *16*, 519. https://doi.org/10.2147/NDT.S225643

Crawford, J. R., Besson, J. A., Bremner, M., Ebmeier, K. P., Cochrane, R. H., & Kirkwood, K. (1992). Estimation of premorbid intelligence in schizophrenia. *The British Journal of Psychiatry, 161,* 69–74. https://doi.org/10.1192/bjp.161.1.69

Crawford, J. R., Deary, I. J., Starr J., & Whalley, L. J. (2001). The NART as an index of prior intellectual functioning: A retrospective validity study covering a 66-year interval. *Psychological Medicine*, *31*, 451-458. https://doi.org/10.1017/S0033291701003634

Crocker, C. E., Cookey, J., & Tibbo, P. G. (2017). Neuroimaging findings in adolescent cannabis use and early phase psychosis. In V. R. Preedy (Ed.), *Handbook of cannabis and related pathologies: Biology, pharmacology, diagnosis, and treatment* (p. 345–356). Elsevier Academic Press. https://doi.org/10.1016/B978-0-12-800756-3.00041-7

Cuesta, M. J., Peralta, V., & Zarzuela, A. (2001). Effects of olanzapine and other antipsychotics on cognitive function in chronic schizophrenia: a longitudinal study. *Schizophrenia Research*, *48*(1), 17-28. https://doi.org/10.1016/S0920-9964(00)00112-2

Cuesta, M. J., Peralta, V., & Zarzuela, A. (2007). Empirical validation of competing definitions of schizophrenia: A poly-diagnostic study of cognitive impairment in non-affective psychosis. *Schizophrenia Research*, *95*(1-3), 39-47. https://doi.org/10.1016/j.schres.2007.06.021

Curran, H. V., Freeman, T. P., Mokrysz, C., Lewis, D. A., Morgan, C. J., & Parsons, L. H. (2016). Keep off the grass? Cannabis, cognition and addiction. *Nature Reviews Neuroscience*, *17*(5), 293-306. Retrieved from https://www.nature.com/nrn/

Degenhardt, L., Hall, W., & Lynskey, M. (2003). Testing hypotheses about the relationship between cannabis use and psychosis. *Drug and Alcohol Dependence*, *71*(1), 37-48. https://doi.org/10.1016/S0376-8716(03)00064-4

Dekker, N., Schmitz, N., Peters, B. D., van Amelsvoort, T. A., Linszen, D. H., & de Haan, L. (2010). Cannabis use and callosal white matter structure and integrity in recent-onset schizophrenia. *Psychiatry Research: Neuroimaging*, *181*(1), 51-56. https://doi.org/10.1016/j.pscychresns.2009.06.003

Delis D.C., Kramer J.H., Kaplan E., & Ober B.A. (2017). *California Verbal Learning Test-3, Third Edition.* San Antonio, TX: The Psychological Corporation.

Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *Journal of Neuroscience*, *15*(9), 5870-5878. https://doi.org/10.1523/JNEUROSCI.15-09-05870.1995

Deoni, S. C. (2007). High-resolution T1 mapping of the brain at 3T with driven equilibrium single pulse observation of T1 with high-speed incorporation of RF field inhomogeneities (DESPOT1-HIFI). *Journal of Magnetic Resonance Imaging: An Official Journal of the International Society for Magnetic Resonance in Medicine*, *26*(4), 1106-1111. https://doi.org/10.1002/jmri.21130

Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., ... & Stilo, S. A. (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. *The Lancet Psychiatry*, *2*(3), 233-238. https://doi.org/10.1016/S2215-0366(14)00117-5

Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., ... & La Barbera, D. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. *The Lancet Psychiatry*, *6*(5), 427-436. https://doi.org/10.1016/S2215-0366(19)30048-3

Di Forti, M., Sallis, H., Allegri, F., Trotta, A., Ferraro, L., Stilo, S. A., ... & Dazzan, P. (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin*, *40*(6), 1509-1517. https://10.1093/schbul/sbt181

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of General Psychiatry*, *64*(5), 532-542. https://doi.org/10.1001/archpsyc.64.5.532

Dolan, R. J., & Fletcher, P. C. (1997). Dissociating prefrontal and hippocampal function in episodic memory encoding. *Nature*, *388*(6642), 582-585. https://doi.org/10.1038/41561

Edwards, J., & McGorry, P. D. (2002). *Implementing early intervention in psychosis: A guide to establishing psychosis services*. CRC Press.

Epstein, K. A., Cullen, K. R., Mueller, B. A., Robinson, P., Lee, S., & Kumra, S. (2014). White matter abnormalities and cognitive impairment in early-onset schizophrenia-spectrum disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*, *53*(3), 362-372. https://doi.org/10.1016/j.jaac.2013.12.007

Eranti, S. V., MacCabe, J. H., Bundy, H., & Murray, R. M. (2013). Gender difference in age at onset of schizophrenia: A meta-analysis. *Psychological Medicine*, *43*(1), 155-167. https://doi.org/10.1017/S003329171200089X

Fatouros-Bergman, H., Cervenka, S., Flyckt, L., Edman, G., & Farde, L. (2014). Meta-analysis of cognitive performance in drug-naïve patients with schizophrenia. *Schizophrenia Research*, *158*(1-3), 156-162. https://doi.org/10.1016/j.schres.2014.06.034

Ferraro, L., Russo, M., O'Connor, J., Wiffen, B. D., Falcone, M. A., Sideli, L., ... & Mondelli, V. (2013). Cannabis users have higher premorbid IQ than other patients with first onset psychosis. *Schizophrenia Research*, *150*(1), 129-135. https://doi.org/10.1016/j.schres.2013.07.046

Fields, R. D. (2010). Change in the brain's white matter. *Science*, *330*(6005), 768-769. https://doi.org/10.1126/science.1199139

Fioravanti, M., Bianchi, V., & Cinti, M. E. (2012). Cognitive deficits in schizophrenia: An updated metanalysis of the scientific evidence. *BMC Psychiatry*, *12*(1), 64. https://doi.org/10.1186/1471-244X-12-64

Fioravanti, M., Carlone, O., Vitale, B., Cinti, M. E., & Clare, L. (2005). A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology Review*, *15*(2), 73-95. https://doi.org/10.1007/s11065-005-6254-9

Fitzgerald, D., Lucas, S., Redoblado, M. A., Winter, V., Brennan, J., ... & Harris, A. (2004). Cognitive functioning in young people with first episode psychosis: Relationship to diagnosis and clinical characteristics. *Australian & New Zealand Journal of Psychiatry*, *38*(7), 501-510. https://doi.org/10.1080/j.1440-1614.2004.01403.x

Flemenbaum, A., & Zimmermann, R. L. (1973). Inter-and intra-rater reliability of the Brief Psychiatric Rating Scale. *Psychological Reports*, *33*(3), 783-792. Retrieved from https://journals-sagepub-com/home/prx

Foglia, E., Schoeler, T., Klamerus, E., Morgan, K., & Bhattacharyya, S. (2017). Cannabis use and adherence to antipsychotic medication: A systematic review and meta-analysis. *Psychological Medicine*, *47*(10), 1691-1705. https://doi.org/10.1017/S0033291717000046

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *Neuroimage, 54*(1), 313-327. https://doi.org/10.1016/j.neuroimage.2010.07.033

Fonov, V. S., Evans, A. C., McKinstry, R. C., Almli, C. R., & Collins, D. L. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage, 47*, S102. https://doi.org/10.1016/S1053-8119(09)70884-5

Friis, S., Sundet, K., Rund, B. R., Vaglum, P., & McGlashan, T. H. (2002). Neurocognitive dimensions characterising patients with first-episode psychosis. *The British Journal of Psychiatry*, *181*(S43), s85-s90. https://doi.org/10.1192/bjp.181.43.s85

Friston, K. J., & Frith, C. D. (1995). Schizophrenia: A disconnection syndrome. *Clinical Neuroscience*, *3*(2), 89-97.

Fujiki, R., Morita, K., Sato, M., Kamada, Y., Kato, Y., Inoue, M., ... & Uchimura, N. (2013). Reduced prefrontal cortex activation using the Trail Making Test in schizophrenia. *Neuropsychiatric Disease and Treatment*, *9*, 675. https://doi.org/10.2147/NDT.S43137

Gabrieli, J. D., Poldrack, R. A., & Desmond, J. E. (1998). The role of left prefrontal cortex in language and memory. *Proceedings of the national Academy of Sciences*, *95*(3), https://doi.org/906-913. 10.1073/pnas.95.3.906

Galderisi, S., Davidson, M., Kahn, R. S., Mucci, A., Boter, H., Gheorghe, M. D., ... & Peuskens, J. (2009). Correlates of cognitive impairment in first episode schizophrenia: The EUFEST study. *Schizophrenia Research*, *115*(2-3), 104-114. https:// doi.org/10.1016/j.schres.2009.09.022

Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., & Bebbington, P. E. (2001). A cognitive model of the positive symptoms of psychosis. *Psychological Medicine*, *31*(2), 189-195. https://doi.org/10.1017/S0033291701003312

Goeree, R., Farahati, F., Burke, N., Blackhouse, G., O'Reilly, D., Pyne, J., & Tarride, J. E. (2005). The economic burden of schizophrenia in Canada in 2004. *Current medical research and opinion*, *21*(12), 2017-2028. https://doi.org/10.1185/030079905X75087

Goldberg, T. E., Goldman, R. S., Burdick, K. E., Malhotra, A. K., Lencz, T., Patel, R. C., ... & Robinson, D. G. (2007). Cognitive improvement after treatment with second-generation antipsychotic medications in first-episode schizophrenia: Is it a practice effect?. *Archives of General Psychiatry*, *64*(10), 1115-1122. https://doi.org/10.1001/archpsyc.64.10.1115

Goldner, E. M., Hsu, L., Waraich, P., & Somers, J. M. (2002). Prevalence and incidence studies of schizophrenic disorders: A systematic review of the literature. *The Canadian Journal of Psychiatry*, *47*(9), 833-843. https://doi.org/10.1177/070674370204700904

Goldstein, G., Shemansky, W. J., & Allen, D. N. (2005). Cognitive function in schizoaffective disorder and clinical subtypes of schizophrenia. *Archives of Clinical Neuropsychology*, *20*(2), 153-159. https://doi.org/10.1016/j.acn.2004.03.008

Gould, A., DeSouza, S., & Rebeiro-Gruhl, K. L. (2005). And then I lost that life: A shared narrative of four young men with schizophrenia. *British Journal of Occupational Therapy, 68*(10), 467-473. https://doi.org./10.1177/030802260506801005

Green, M. F. (1998). *Schizophrenia from a neurocognitive perspective: Probing the impenetrable darkness*. Allyn & Bacon.

Green, B., Young, R., & Kavanagh, D. (2005). Cannabis use and misuse prevalence among people with psychosis. *The British Journal of Psychiatry: The Journal of Mental Science*, *187*, 306–313. https://doi.org/10.1192/bjp.187.4.306

Gruber, S. A., Dahlgren, M. K., Sagar, K. A., Gönenç, A., & Lukas, S. E. (2014). Worth the wait: Effects of age of onset of marijuana use on white matter and impulsivity. *Psychopharmacology*, *231*(8), 1455-1465. https://doi.org/10.1007/s00213-013-3326-z

Hall, W., & Pacula, R. L. (2003). *Cannabis use and dependence: public health and public policy*. Cambridge university press.

Haller, S., Curtis, L., Badan, M., Bessero, S., Albom, M., Chantraine, F., ... & Merlo, M. (2013). Combined grey matter VBM and white matter TBSS analysis in young first episode psychosis patients with and without cannabis consumption. *Brain Topography*, *26*(4), 641-647. https://doi.org /10.1007/s10548-013-0288-8

Hamilton, I., & Monaghan, M. (2019). Cannabis and psychosis: Are we any closer to understanding the relationship?. *Current Psychiatry Reports*, *21*(7), 48. https://doi.org/10.1007/s11920-019-1044-x

Hao, Y., Yan, Q., Liu, H., Xu, L., Xue, Z., Song, X., ... & Shan, B. (2009). Schizophrenia patients and their healthy siblings share disruption of white matter integrity in the left prefrontal cortex and the hippocampus but not the anterior cingulate cortex. *Schizophrenia Research*, *114*(1-3), 128-135. https://doi.org/10.1016/j.schres.2009.07.001

Hides, L., Cotton, S. M., Berger, G., Gleeson, J., O'Donnell, C., Proffitt, T., ... & Lubman, D. I. (2009). The reliability and validity of the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) in first-episode psychosis. *Addictive Behaviors*, *34*(10), 821-825. https://doi.org /10.1016/j.addbeh.2009.03.001

Hirst, R. B., Young, K. R., Sodos, L. M., Wickham, R. E., & Earleywine, M. (2017). Trying to remember: Effort mediates the relationship between frequency of cannabis use and memory performance. *Journal of Clinical and Experimental Neuropsychology*, *39*(5), 502-512. https://doi.org/10.1080/13803395.2016.1237617

Humeniuk, R., Ali, R., Babor, T. F., Farrell, M., Formigoni, M. L., Jittiwutikarn, J., ... & Nhiwatiwa, S. (2008). Validation of the alcohol, smoking and substance involvement screening test (ASSIST). *Addiction*, *103*(6), 1039-1047. 10.1111/j.1360-0443.2007.02114.x.

Hung, W., Chen, P., Chuang, T., Chang, H., & Wu, M. (2013, April). *High resolution volumetric T1 mapping using a novel MP3RAGE method* [Conference presentation abstract]. International Society for Magnetic Resonance in Medicine Annual Meeting, Salt Lake City, Utah, USA. Retrieved from http://archive.ismrm.org/2013/2353.html

Husa, A. P., Rannikko, I., Moilanen, J., Haapea, M., Murray, G. K., Barnett, J., ... & Jääskeläinen, E. (2014). Lifetime use of antipsychotic medication and its relation to change of verbal learning and memory in midlife schizophrenia—An observational 9-year follow-up study. *Schizophrenia Research*, *158*(1-3), 134-141. https://doi.org/10.1016/j.schres.2014.06.035

Jablensky, A. (1997). The 100-year epidemiology of schizophrenia. *Schizophrenia Research*, *28*(2-3), 111-125. https://doi.org/10.1016/S0920-9964(97)85354-6

Jaeggi, S. M., Buschkuehl, M., Perrig, W. J., & Meier, B. (2010). The concurrent validity of the N-back task as a working memory measure. *Memory*, *18*(4), 394-412. 10.1080/09658211003702171

James, A., Hough, M., James, S., Winmill, L., Burge, L., Nijhawan, S., ... & Zarei, M. (2011). Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS). *Schizophrenia Research*, *128*(1-3), 91-97. https://doi.org/10.1016/j.schres.2011.02.014

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage, 62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jones, P. B. (2013). Adult mental health disorders and their age at onset. *The British Journal of Psychiatry*, *202*(s54), s5-s10. https://doi.org/10.1192/bjp.bp.112.119164

Kloppenborg, R. P., Nederkoorn, P. J., Geerlings, M. I., & van den Berg, E. (2014). Presence and progression of white matter hyperintensities and cognition: a meta-analysis. *Neurology*, *82*(23), 2127-2138. https://doi.org/10.1212/WNL.0000000000000505

Koskinen, J., Löhönen, J., Koponen, H., Isohanni, M., & Miettunen, J. (2010). Rate of cannabis use disorders in clinical samples of patients with schizophrenia: A meta-analysis. *Schizophrenia Bulletin*, *36*(6), 1115-1130. https://doi.org/10.1093/schbul/sbp031

Kranzler, H. R., Kadden, R. M., Babor, T. F., Tennen, H., & Rounsaville, B. J. (1996). Validity of the SCID in substance abuse patients. *Addiction*, *91*(6), 859–868. https://doi.org/10.1046/j.1360-0443.1996.91685911.x

Ksir, C., & Hart, C. L. (2016). Cannabis and psychosis: A critical overview of the relationship. *Current Psychiatry Reports*, *18*(2), 12. https://doi.org/10.1007/s11920-015-0657-y

Large, M., Sharma, S., Compton, M. T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of General Psychiatry*, *68*(6), 555-561. https://doi.org/10.1001/archgenpsychiatry.2011.5

Leeson, V. C., Barnes, T. R., Harrison, M., Matheson, E., Harrison, I., Mutsatsa, S. H., ... & Joyce, E. M. (2010). The relationship between IQ, memory, executive function, and processing speed in recent-onset psychosis: 1-year stability and clinical outcome. *Schizophrenia Bulletin*, *36*(2), 400-409. https://doi.org/10.1093/schbul/sbn100

Leos-Toro, C., Rynard, V., & Hammond, D. (2017). Prevalence of problematic cannabis use in Canada: Cross-sectional findings from the 2013 Canadian Tobacco, Alcohol and Drugs Survey. *Canadian Journal of Public Health*, *108*(5-6), e516-e522. https://doi.org/10.17269/CJPH.108.5955

Liffick, E., Mehdiyoun, N. F., Vohs, J. L., Francis, M. M., & Breier, A. (2017). Utilization and cost of health care services during the first episode of psychosis. *Psychiatric Services*, *68*(2), 131-136. https://doi.org/10.1176/appi.ps.201500375

Lim, Y. Y., Prang, K. H., Cysique, L., Pietrzak, R. H., Snyder, P. J., & Maruff, P. (2009). A method for cross-cultural adaptation of a verbal memory assessment. *Behavior Research Methods*, *41*(4), 1190-1200. https://doi.org/10.3758/BRM.41.4.1190

Lorenzetti, V., Chye, Y., Silva, P., Solowij, N., & Roberts, C. A. (2019). Does regular cannabis use affect neuroanatomy? An updated systematic review and meta-analysis of structural neuroimaging studies. *European archives of psychiatry and clinical neuroscience*, *269*(1), 59-71. https://doi.org/10.1007/s00406-019-00979-1

Lutti, A., Dick, F., Sereno, M. I., & Weiskopf, N. (2014). Using high-resolution quantitative mapping of R1 as an index of cortical myelination. *Neuroimage*, *93*, 176-188. https://doi.org/10.1016/j.neuroimage.2013.06.005.

Lystad, J. U., Falkum, E., Haaland, V. Ø., Bull, H., Evensen, S., Bell, M. D., & Ueland, T. (2016). Neurocognition and occupational functioning in schizophrenia spectrum disorders: The MATRICS Consensus Cognitive Battery (MCCB) and workplace assessments. *Schizophrenia Research*, *170*(1), 143-149. https://doi.org/10.1016/j.schres.2015.12.002

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin*, *42*(5), 1262-1269. https://doi.org/10.1093/schbul/sbw003

Mathias, S. R., Knowles, E. E. M., Barrett, J., Leach, O., Buccheri, S., Beetham, T., … Glahn, D. C. (2017). The processing-speed impairment in psychosis is more than just accelerated aging. *Schizophrenia Bulletin*, *43*(4), 814–823. https://doi.org/10.1093/schbul/sbw168

McCleery, A., Ventura, J., Kern, R. S., Subotnik, K. L., Gretchen-Doorly, D., Green, M. F., ... & Nuechterlein, K. H. (2014). Cognitive functioning in first-episode schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) Profile of Impairment. *Schizophrenia Research*, *157*(1-3), 33-39. https://doi.org/10.1016/j.schres.2014.04.039

McGorry, P. D. (2015). Early intervention in psychosis: Obvious, effective, overdue. *The Journal of nervous and mental disease, 203*(5), 310. https://doi.org/10.1097/NMD.0000000000000284

Meltzer, H. Y., & McGurk, S. R. (1999). The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. *Schizophrenia Bulletin*, *25*(2), 233-256. https://doi.org/10.1093/oxfordjournals.schbul.a033376

Meule, A. (2017). Reporting and interpreting working memory performance in n-back tasks. *Frontiers in Psychology*, *8*, 352. https://doi.org/10.3389/fpsyg.2017.00352

Morrens, M., Hulstijn, W., & Sabbe, B. (2007). Psychomotor slowing in schizophrenia. *Schizophrenia Bulletin*, *33*(4), 1038-1053. https://doi.org/10.1093/schbul/sbl051

Myles, H., Myles, N., & Large, M. (2016). Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use. *Australian & New Zealand Journal of Psychiatry*, *50*(3), 208-219. https://doi.org/10.1177/0004867415599846

Nelson, H. E., & Willison, J. (1991). *National adult reading test (NART).* Windsor, BRK: Nfer-Nelson.

Nolin, M., Malla, A., Tibbo, P., Norman, R., & Abdel-Baki, A. (2016). Early intervention for psychosis in Canada: What is the state of affairs?. *The Canadian Journal of Psychiatry*, *61*(3), 186-194. https://doi.org/ 10.1177/0706743716632516

Orr, J. M., Paschall, C. J., & Banich, M. T. (2016). Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry. *NeuroImage: Clinical*, *12*, 47-56. https://doi.org/10.1016/j.nicl.2016.06.006

Ouellet-Plamondon, C., Abdel-Baki, A., Salvat, É., & Potvin, S. (2017). Specific impact of stimulant, alcohol and cannabis use disorders on first-episode psychosis: 2-year functional and symptomatic outcomes. *Psychological Medicine*, *47*(14), 2461-2471. https://doi.org/10.1017/S0033291717000976

Paolo, A. M., Tröster, A. I., & Ryan, J. J. (1997). Test–retest stability of the California Verbal Learning Test in older persons. *Neuropsychology, 11*(4), 613-16. https://doi.org/10.1037/0894-4105.11.4.613

Pérez-Iglesias, R., Tordesillas-Gutiérrez, D., Barker, G. J., McGuire, P. K., Roiz-Santiañez, R., Mata, I., ... & Crespo-Facorro, B. (2010). White matter defects in first episode psychosis patients: a voxelwise analysis of diffusion tensor imaging. *Neuroimage*, *49*(1), 199-204. https://doi.org/10.1016/j.neuroimage.2009.07.016

Peters, A. (2002). The effects of normal aging on myelin and nerve fibers: a review. *Journal of Neurocytology*, *31*(8-9), 581-593. https://doi.org/10.1023/A:1025731309829

Petersen, L., Jeppesen, P., Thorup, A., Abel, M. B., Øhlenschlæger, J., Christensen, T. Ø., ... & Nordentoft, M. (2005). A randomised multicentre trial of integrated versus standard treatment for patients with a first episode of psychotic illness. *British Medical Journal*, *331*(7517), 602. https://doi.org/10.1136/bmj.38565.415000.E01

Petker, T., Owens, M. M., Amlung, M. T., Oshri, A., Sweet, L. H., & MacKillop, J. (2019). Cannabis involvement and neuropsychological performance: findings from the Human Connectome Project. *Journal of Psychiatry & Neuroscience, 44*(6), 414. https://doi.org/10.1503/jpn.180115.

Petrides, M., & Pandya, D. N. (2012). The frontal cortex. In Mai, J. K., & Paxinos, G. (Eds.), The human nervous system. Academic Press.*The human nervous system* (3rd ed., pp. 988-1011). Academic Press. https://doi.org/10.1016/B978-0-12-374236-0.10026-4

Pietrzak, R. H., Olver, J., Norman, T., Piskulic, D., Maruff, P., & Snyder, P. J. (2009). A comparison of the CogState Schizophrenia Battery and the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Battery in assessing cognitive impairment in chronic schizophrenia. *Journal of Clinical and Experimental Neuropsychology*, *31*(7), 848-859. https://doi.org/10.1080/13803390802592458

Potvin, S., Joyal, C. C., Pelletier, J., & Stip, E. (2008). Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis. *Schizophrenia Research*, *100*(1-3), 242-251. https://doi.org/10.1016/j.schres.2007.04.022

Preedy, V. R. (Ed.). (2016). *Handbook of cannabis and related pathologies: biology, pharmacology, diagnosis, and treatment*. Academic Press.

Rabin, R. A., Zakzanis, K. K., & George, T. P. (2011). The effects of cannabis use on neurocognition in schizophrenia: a meta-analysis. *Schizophrenia research, 128*(1-3), 111-116. https://doi.org/10.1016/j.schres.2011.02.017

Rae, C. L., Davies, G., Garfinkel, S. N., Gabel, M. C., Dowell, N. G., Cercignani, M., ... & Critchley, H. D. (2017). Deficits in neurite density underlie white matter structure abnormalities in first-episode psychosis. *Biological Psychiatry*, *82*(10), 716-725. https://doi.org/10.1016/j.biopsych.2017.02.008

Rannikko, I., Haapea, M., Miettunen, J., Veijola, J., Murray, G. K., Barnett, J. H., ... & Jääskeläinen, E. (2015). Changes in verbal learning and memory in schizophrenia and non-psychotic controls in midlife: A nine-year follow-up in the Northern Finland Birth Cohort study 1966. *Psychiatry Research*, *228*(3), 671-679. https://doi.org/10.1192/bjp.181.43.s85

Rannikko, I., Paavola, L., Haapea, M., Huhtaniska, S., Miettunen, J., Veijola, J., ... & Jääskeläinen, E. (2012). Verbal learning and memory and their associations with brain morphology and illness course in schizophrenia spectrum psychoses. *Journal of Clinical and Experimental Neuropsychology*, *34*(7), 698-713. https://doi.org/10.1080/13803395.2012.668875

Rapp, C., Bugra, H., Riecher-Rossler, A., Tamagni, C., & Borgwardt, S. (2012). Effects of cannabis use on human brain structure in psychosis: a systematic review combining in vivo structural neuroimaging and post mortem studies. *Current Pharmaceutical Design*, *18*(32), 5070-5080. https://doi.org/10.2174/138161212802884861

Reininghaus, U., Priebe, S., & Bentall, R. P. (2013). Testing the psychopathology of psychosis: Evidence for a general psychosis dimension. *Schizophrenia Bulletin*, *39*(4), 884-895. https://doi.org/10.1093/schbul/sbr182

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, *8*(3), 271-276.

Rebgetz, S., Conus, P., Hides, L., Kavanagh, D. J., Cotton, S., Schimmelmann, B. G., ... & Lambert, M. (2014). Predictors of substance use reduction in an epidemiological first-episode psychosis cohort. *Early Intervention in Psychiatry*, *8*(4), 358-365.

Ritter, L. M., Meador-Woodruff, J. H., & Dalack, G. W. (2004). Neurocognitive measures of prefrontal cortical dysfunction in schizophrenia. *Schizophrenia Research*, *68*(1), 65-73. https://doi.org/10.1016/S0920-9964(03)00086-0

Roalf, D. R., de la Garza, A. G., Rosen, A., Calkins, M. E., Moore, T. M., Quarmley, M., ... & Shinohara, R. T. (2019). Alterations in white matter microstructure in individuals at persistent risk for psychosis. *Molecular psychiatry*, 1-14. https://doi.org/10.1038/s41380-019-0360-1

Robinson, S. M., Sobell, L. C., Sobell, M. B., & Leo, G. I. (2014). Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychology of Addictive Behaviors*, *28*(1), 154. https://doi.org/10.1037/a0030992

Rocchetti, M., Crescini, A., Borgwardt, S., Caverzasi, E., Politi, P., Atakan, Z., & Fusar-Poli, P. (2013). Is cannabis neurotoxic for the healthy brain? A meta-analytical review of structural brain alterations in non-psychotic users. *Psychiatry and Clinical Neurosciences*, *67*(7), 483-492. https://doi.org/10.1111/pcn.12085

Rossi, R., Zammit, S., Button, K. S., Munafò, M. R., Lewis, G., & David, A. S. (2016). Psychotic Experiences and Working Memory: A Population-Based Study Using Signal-Detection Analysis. *PLOS ONE, 11*(4). https://doi.org/10.1371/journal.pone.0153148

Savage, C. R., Deckersbach, T., Heckers, S., Wagner, A. D., Schacter, D. L., Alpert, N. M., ... & Rauch, S. L. (2001). Prefrontal regions supporting spontaneous and directed application of verbal learning strategies: Evidence from PET. *Brain*, *124*(1), 219-231. https://doi.org/10.1093/brain/124.1.219

Schoeler, T., Kambeitz, J., Behlke, I., Murray, R., & Bhattacharyya, S. (2016). The effects of cannabis on memory function in users with and without a psychotic disorder: Findings from a combined meta-analysis. *Psychological Medicine*, *46*(1), 177-188. https://doi.org/10.1017/S0033291715001646

Schoeler, T., Petros, N., Di Forti, M., Pingault, J. B., Klamerus, E., Foglia, E., ... & Bhattacharyya, S. (2016). Association between continued cannabis use and risk of relapse in first-episode psychosis: A quasi-experimental investigation within an observational study. *JAMA psychiatry, 73*(11), 1173-1179. https://doi.org/10.1001/jamapsychiatry.2016.2427

Schuster, R. M., Hoeppner, S. S., Evins, A. E., & Gilman, J. M. (2016). Early onset marijuana use is associated with learning inefficiencies. *Neuropsychology*, *30*(4), 405. https://doi.org/ 10.1037/neu0000281

Scott, J. C., Slomiak, S. T., Jones, J. D., Rosen, A. F., Moore, T. M., & Gur, R. C. (2018). Association of cannabis with cognitive functioning in adolescents and young adults: a systematic review and meta-analysis. *JAMA psychiatry*, *75*(6), 585-595. https://doi.org/10.1001/jamapsychiatry.2018.0335

Sembhi, S., & Lee, J. W. (1999). Cannabis use in psychotic patients. *Australian & New Zealand Journal of Psychiatry*, *33*(4), 529-532. https://doi.org/10.1080/j.1440-1614.1999.00588.x

Setién-Suero, E., Neergaard, K., Ortiz-García de la Foz, V., Suárez-Pinilla, P., Martínez-García, O., Crespo-Facorro, B., & Ayesa-Arriola, R. (2019). Stopping cannabis use benefits outcome in psychosis: Findings from 10-year follow-up study in the PAFIP-cohort. *Acta Psychiatrica Scandinavica*, *140*(4), 349-359. https://doi.org/10.1111/acps.13081

Shibuya-Tayoshi, S., Sumitani, S., Kikuchi, K., Tanaka, T., Tayoshi, S. Y., Ueno, S. I., & Ohmori, T. (2007). Activation of the prefrontal cortex during the Trail-Making Test detected with multichannel near-infrared spectroscopy. *Psychiatry and Clinical Neurosciences*, *61*(6), 616-621. https://doi.org/10.1111/j.1440-1819.2007.01727.x

Small, S. L., Hart, J., Nguyen, T., & Gordon, B. (1995). Distributed representations of semantic knowledge in the brain. *Brain*, *118*(2), 441-453. https://doi.org/10.1093/brain/118.2.441

Solowij, N., & Michie, P. T. (2007). Cannabis and cognitive dysfunction: Parallels with endophenotypes of schizophrenia? *Journal of Psychiatry & Neuroscience, 32*(1), 30–52. Retrieved from https://jpn.ca/

Solowij, N., & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: A review. *Current Drug Abuse Reviews*, *1*(1), 81-98. https://doi.org/10.2174/1874473710801010081

Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: A meta-analysis. *Addiction Biology*, *18*(2), 203-213. https://doi.org/10.1111/j.1369-1600.2011.00418.x

Stuss, D. T., Bisschop, S. M., Alexander, M. P., Levine, B., Katz, D., & Izukawa, D. (2001). The Trail Making Test: A study in focal lesion patients. *Psychological Assessment*, *13*(2), 230. https://doi.org/10.1037/1040-3590.13.2.230

Thames, A. D., Arbid, N., & Sayegh, P. (2014). Cannabis use and neurocognitive functioning in a non-clinical sample of users. *Addictive Behaviors*, *39*(5), 994-999. https://doi.org/10.1016/j.addbeh.2014.01.019

Thompson, T. A., Wilson, P. H., Snyder, P. J., Pietrzak, R. H., Darby, D., Maruff, P., & Buschke, H. (2011). Sensitivity and test–retest reliability of the international shopping list test in assessing verbal learning and memory in mild Alzheimer's disease. *Archives of Clinical Neuropsychology*, *26*(5), 412-424. https://doi.org/10.1093/arclin/acr039

Townsend, L. A., Malla, A. K., & Norman, R. M. (2001). Cognitive functioning in stabilized first-episode psychosis patients. *Psychiatry Research*, *104*(2), 119-131. https://doi.org/10.1016/S0165-1781(01)00302-X

Torniainen, M., Suvisaari, J., Partonen, T., Castaneda, A. E., Kuha, A., Suokas, J., ... & Tuulio-Henriksson, A. (2012). Cognitive impairments in schizophrenia and schizoaffective disorder: Relationship with clinical characteristics. *The Journal of Nervous and Mental Disease*, *200*(4), 316-322. https://doi.org/10.1097/NMD.0b013e31824cb359

Tsuang, M. T., Lyons, M. J., Meyer, J. M., Doyle, T., Eisen, S. A., Goldberg, J., ... & Eaves, L. (1998). Co-occurrence of abuse of different drugs in men: The role of drug-specific and shared vulnerabilities. *Archives of General Psychiatry*, *55*(11), 967-972. https://doi.org/10.1001/archpsyc.55.11.967

Tucker, P. (2009). Substance Misuse and Early Psychosis. *Australasian Psychiatry*, *17*(4), 291–294. https://doi.org/10.1080/10398560802657314

Van Mastrigt, S., Addington, J., & Addington, D. (2004). Substance misuse at presentation to an early psychosis program. *Social Psychiatry and Psychiatric Epidemiology*, *39*(1), 69–72. https://doi.org/10.1007/s00127-004-0713-0

Vanes, L. D., Mouchlianitis, E., Barry, E., Patel, K., Wong, K., & Shergill, S. S. (2019). Cognitive correlates of abnormal myelination in psychosis. *Scientific Reports*, *9*(1), 1-9. https://doi.org/10.1038/s41598-019-41679-z

Vanes, L. D., Mouchlianitis, E., Wood, T. C., & Shergill, S. S. (2018). White matter changes in treatment refractory schizophrenia: Does cognitive control and myelination matter?. *NeuroImage: Clinical*, *18*, 186-191. https://doi.org/10.1016/j.nicl.2018.01.010

Walther, S., & Strik, W. (2012). Motor symptoms and schizophrenia. *Neuropsychobiology, 66*(2), 77-92. https://doi.org/10.1159/000339456

Wang, S. M., Ouyang, W. C., Wu, M. Y., & Kuo, L. C. (2019). Relationship between motor function and psychotic symptomatology in young–adult patients with schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience*, *270*(3), 373-382. https://doi.org/10.1007/s00406-019-01004-1

Wechsler, D. (1958). *The measurement and appraisal of adult intelligence* (4th ed.). Williams & Wilkins Co. https://doi.org/10.1037/11167-000

Wechsler D. (2008). *Wechsler Adult Intelligence Scale—Fourth Edition*. Bloomington, MN: PsychCorp, an imprint of Pearson Clinical Assessment.

Weschler, D. (1999). *Wechsler abbreviated scale of intelligence*. San Antonio, TX: Psychological Corp.

Westerman, R., Darby, D. G., Maruff, P., & Collie, A. (2001). Computer-assisted cognitive function assessment of pilots. *ADF Health*, *2*, 29-36. Retrieved from https://www.awm.gov.au/collection/LIB50277

Whitman, D. (2010). *Cognition*. Wiley.

World Health Organization ASSIST Working Group. (2002). The alcohol, smoking and substance involvement screening test (ASSIST): Development, reliability and feasibility. *Addiction*, *97*(9), 1183-1194. https://doi.org/10.1046/j.1360-0443.2002.00185.x

Yoshida, T., Suga, M., Arima, K., Muranaka, Y., Tanaka, T., Eguchi, S., ... & Seo, T. (2011). Criterion and construct validity of the CogState Schizophrenia Battery in Japanese patients with schizophrenia. *PLoS One*, *6*(5). https://doi.org/10.1371/journal.pone.0020469

Yucel, M., Bora, E., Lubman, D. I., Solowij, N., Brewer, W. J., Cotton, S. M., … Pantelis, C. (2012). The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin*, *38*(2), 316–330. https://doi.org/10.1093/schbul/sbq079

Zabala, A., Rapado, M., Arango, C., Robles, O., de la Serna, E., González, C., … Bombín, I. (2010). Neuropsychological functioning in early-onset first-episode psychosis: Comparison of diagnostic subgroups. *European Archives of Psychiatry and Clinical Neuroscience*, *260*(3), 225–233. https://doi.org/10.1007/s00406-009-0046-9

Zalesky, A., Solowij, N., Yücel, M., Lubman, D. I., Takagi, M., Harding, I. H., ... & Seal, M. (2012). Effect of long-term cannabis use on axonal fibre connectivity. *Brain*, *135*(7), 2245-2255. https://doi.org/10.1093/brain/aws136

Zammit, S., Moore, T., Lingford-Hughes, A., Barnes, T., Jones, P., Burke, M., & Lewis, G. (2008). Effects of cannabis use on outcomes of psychotic disorders: Systematic review. *The British Journal of Psychiatry: The Journal of Mental Science, 193*(5), 357-63. https://doi.org/10.1192/bjp.bp.107.046375

Zorlu, N., Di Biase, M. A., Kalaycı, Ç. Ç., Zalesky, A., Bağcı, B., Oğuz, N., ... & Bora, E. (2016). Abnormal white matter integrity in synthetic cannabinoid users. *European Neuropsychopharmacology*, *26*(11), 1818-1825. https://doi.org/10.1016/j.euroneuro.2016.08.015

Appendix MRI Safety Criteria

Demographic Information

Research code: **Exam number:**

Name: **Scan date:**
(yyyy/mm/dd)

DOB: **Weight:** (pounds)

Sex: M / F **Hand:** R / L **Height:** (feet / in)

Email address: **Phone:** (cell or home?)

MR Safety Checklist: Please circle Yes or No

Pacemaker/biostimulator	Yes / No	Removable dentures	Yes / No
Cerebral aneurysm clip	Yes / No	Dental apparatus*	Yes / No
Joint replacement	Yes / No	Tattoos	Yes / No
Fracture treated with metal	Yes / No	Jewelry	Yes / No
Metal worker	Yes / No	Body piercings	Yes / No
History of ocular foreign body	Yes / No	Watches	Yes / No
	Yes / No	Eye/Makeup	Yes / No
Shrapnel wound	Yes / No	Wig	Yes / No
Chance of pregnancy	Yes / No	Artificial limb	Yes / No
Inner ear implant	Yes / No	Implants	Yes / No
Pump for medication	Yes / No	Checked for loose metal	Yes / No
Hearing aid		Valuables stored	Yes / No

*retainer, crowns, implants etc

Consent form to be explained and signed.

Washroom is strongly recommended - changing clothes if need be and check pockets for metal.

Safety check done by: _____

Scanning by: _____