CHARACTERIZING THE EFFECTS OF EXTENDED CANNABIS ABSTINENCE ON COGNITIVE FUNCTION IN PATIENTS WITH SCHIZOPHRENIA AND NON-PSYCHIATRIC CONTROLS WITH CANNABIS DEPENDENCE

by

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Abstract

**Background:** While chronic cannabis use impairs cognition in controls, paradoxically, cannabis-using patients with schizophrenia demonstrate better cognitive function than non-using patients. It has been proposed that this relationship is driven by a higher functioning patient subgroup (trait effect) that is cognitively less impaired than their non-using counterparts. A caveat, however, is that most studies employed cross-sectional designs making it difficult to draw firm conclusions regarding causality. **AIM:** Therefore, we used a 28-day cannabis abstinence period to investigate the state-dependent effects of cannabis on key cognitive outcomes (e.g., HVLT, SDR, Digit Span) in cannabis dependent schizophrenia patients versus non-psychiatric controls.
**Hypothesis:** We predicted that abstaining participants would experience improvements in working memory, and verbal memory and learning performance over time, and expected patients to have greater magnitude of change compared to controls. **Method:** Nineteen patients and 20 non-psychiatric male cannabis dependent participants underwent 28 days of cannabis abstinence. Cognition was assessed biweekly on Day 0, 14 and 28 using a comprehensive battery. Clinical symptoms were assessed weekly. Abstinence was encouraged using weekly therapy sessions and low cost contingency management confirmed by twice weekly urine assays. **Results:** Fort-two percent of patients and 55% of controls achieved end-point abstinence. This was biochemically verified by full cannabis elimination (Day28 urinary THC-COOH<20ng/mL). Schizophrenia-abstainers demonstrated significant improvements in HVLT performance over time [F(2,14)=4.73, p<0.03]; improvements were not observed on other cognitive test (SDR, CPT, TMT Digit Span) nor in control participants. PANSS symptoms remained stable, however, by Day28, schizophrenia-abstainers showed greater reductions in depressive scores compared to non-abstainers (d=1.56 versus d=0.49). **Conclusions:** Using a 28-day cannabis abstinence paradigm, we demonstrated that verbal memory and learning performance improved exclusively in schizophrenia-abstainers. This suggests that select cannabis-induced deficits in schizophrenia may be state-dependent and reversible. Recovery may favour cognitive processes facilitated by brain regions rich in cannabinoid 1 receptors, such as the hippocampus. Importantly, ceasing cannabis did not lead to any increased psychopathology or other adverse outcomes. Findings underscore the importance of developing effective treatment interventions for cannabis use disorders in patients with schizophrenia. Future research should investigate whether longer abstinence periods lead to further remediation of cognitive function.
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Abbreviations

11-hydroxy-Δ⁹-tetrahydrocannabinol (11-OH-THC)

Abnormal Involuntary Movement Scale (AIMS)

Addiction Severity Index (ASI)

Alcohol Use Identification Test (AUDIT)

Amino-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA).

Analysis of Covariance (ANCOVA)

Analysis of Variance (ANOVA)

Barnes Akathisia Rating Scale (BARS)

Benton Revised Visual Retention Test (BSRT)

Biobehavioural Addictions and Concurrent Disorders Research Laboratory (BACDRL)

Blood Oxygen Level Dependent (BOLD)

Cannabidiol (CBD)

Cannabinoid (CB)

Cannabis Dependence (CD)

Cannabis use disorder (CUD)

Carbon Monoxide (CO)

Catechol-O-Methyltransferase (COMT)

Centre for Addiction and Mental Health (CAMH)
Chlorpromazine (CPZ)

Cigarettes per day (CPD)

Cognitive Behavioural Therapy (CBT)

Continuous Performance Test (CPT)

Delta-9-tetrahydrocannabinol (THC)

Diagnostic and Statistical Manual of Mental Disorders (DSM)

Dopamine (DA)

Dorsolateral prefrontal cortex (DLPFC)

Duration of Untreated Psychosis (DUP)

Fagerstrom Test of Nicotine Dependence (FTND)

Fatty acid amide hydrolase (FAAH)

Full Scale Intelligence Quotient (FSIQ)

Gamma-aminobutyric acid (GABA)

Hamilton Rating Scale for Depression (HAM-D)

International Statistical Classification of Diseases and Related Health Problems (ICD)

Interviewer Severity Rating Scale (ISR)

Intelligence Quotient (IQ)

Iowa Gambling Task (IGT)

Kirby Delay Discounting Task (KDDT)

Loss of Consciousness (LOC)
Marijuana Craving Questionnaire (MCQ)

Marijuana Withdrawal Checklist (MWC)

Multivariate Analysis of Covariance (MANCOVA)

N-methyl-D-aspartate (NMDA)

Nucleus Accumbens (NAcc)

Orbitofrontal cortex (OFC)

Positive and Negative Syndrome Scale (PANSS)

Positron Emission Tomography (PET)

Prefrontal cortex (PFC)

Research Domain Criteria (RDoC)

Research Ethics Board (REB)

Simpson Angus Scale (SARS)

Spatial Delay Response (SDR)

Standard Deviation (SD)

Statistical Package for the Social Sciences (SPSS)

Structured Clinical Interview for the DSM-IV (SCID-IV)

Tardive Dyskinesia (TD)

Test of Memory Malingering (TOMM)

Timeline Follow Back (TLFB)

Trail Making Test A (TMT-A)
Trail Making Test B (TMT-B)

Ventral tegmental area (VTA)

Wisconsin Card Sorting Test (WCST)

Wechsler Test of Adult Reading (WTAR)
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Chapter 1

1 LITERATURE REVIEW

1.1 Schizophrenia

The human brain is a tremendously complex organ and exposing it to insult intrinsically or extrinsically may have devastating consequences at both the neurobiological and behavioural levels. Disruption of normal intact neural functioning may result in a myriad of mental health problems from psychiatric symptoms to full-blown syndromes. Understanding brain disorders has been one of the greatest challenges of modern medicine to date and schizophrenia, in particular, continues to be one of the most mysterious and perplexing illnesses of our time. While fundamental advances in genetics, neuroimaging, and environmental determinants of psychiatric illness have undoubtedly occurred, the precise neuropathophysiological nature of schizophrenia still remains unknown. While treatment of the disorder continues to improve with time, full functional recovery of all patients is yet to be the gold standard. Arguably the greatest success stories in medicine have come in the arena of prevention, and with continued dedication hopefully the same, one day, can be true for schizophrenia.

1.1.1 Nosology of Schizophrenia

Schizophrenia is characterized by positive symptoms, negative symptoms and cognitive impairment. Originally, the name for the illness was “dementia praecox,” coined by Emil Kraepelin, a German psychiatrist, whose description of the illness remains a guiding force for modern investigators.
The Diagnostic and Statistical Manual of Mental Disorders (DSM) published by the American Psychiatric Association offers a standardized approach for the classification of mental disorders (APA, 2000). The DSM uses a multidimensional approach for diagnosing. Thus, no single symptom is definitive for diagnosis; rather, the diagnosis encompasses a pattern of signs and symptoms, in conjunction with impaired occupational or social functioning. Given that there are no reliable biological markers for schizophrenia, diagnosis depends substantially on symptom endorsement by the patient.

In the DSM IV-TR, the criteria to diagnose schizophrenia is based on meeting two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated): (1) delusions, (2) hallucinations, (3) disorganized speech, (4) grossly disorganized or catatonic behavior, (5) negative symptoms (i.e. affective flattening, alogia, or avolition. Symptoms must lead to social or occupational dysfunction for a significant portion of time and disturbances must be continuous, persisting for at least 6 months. Symptoms may not be precipitants of other disorders or due to general medical conditions.

There is a high degree of heterogeneity in the clinical presentation of schizophrenia (Andreasen et al., 1995; Davidson & McGlashan, 1997). Substantial between-patient variation exists in terms of cluster of symptoms, degree of response to treatment and overall prognosis. This lack of phenotypic homogeneity has led to the proposition of schizophrenia subtypes (paranoid, catatonic, disorganized, and residual), which was a promising attempt to address etiologic variation within the disorder. However, scientific evidence provides little support for the validity, reliability, or stability of these constructs (Korver-Nieberg et al., 2011). This has been substantiated by the decreased mention of subtypes in the schizophrenia research literature over the past two decades (Braff et al., 2013).

The newly implemented DSM-V, published in 2013 makes several key changes to the category of schizophrenia (APA;, 2013), culminating a 14-year revision process. For one, the subtypes of schizophrenia have been eliminated from the classification system.
Secondly, in contrast to DSM-IV, in DSM-5 a patient is required to have at least two characteristic symptoms. In the DSM-IV that threshold was one if delusions were categorized as bizarre or if hallucinations included a running commentary on the individual’s thoughts/behaviour, and/or there were two or more voices conversing. This exception has been removed, again due to the lack of specificity and poor reliability (Flaum, Arndt, & Andreasen, 1991). The notion of what constitutes “bizarre” is rather vague, and its removal reduces cultural bias. In addition, now in DSM-V a patient is required to meet criteria for at least one of the following positive symptoms: delusions, hallucinations, or disorganized speech.

While the DSM-5 will likely show clear advantages over earlier versions, diagnostic categories as a whole fail to align with findings emerging from the clinical neurosciences and genetics as they do not capture fundamental underlying mechanisms of dysfunction. This has prompted The National Institute of Mental Health (NIMH) to initiate a new nosology altogether, the Research Domain Criteria (RDoC). This framework proposes moving away from the exclusivity of categorical dimensions based on descriptive phenomenology into one rooted in observable behaviours and neurobiology (Cuthbert, 2014). It is the hope that this new perspective leads to more scientifically informed conceptions of diagnosis and etiology that are not constrained or limited by sets of predefined symptom clusters.

### 1.1.2 Epidemiology

Schizophrenia inflicts approximately one per cent of the population worldwide (McGrath et al., 2008; Peralta et al., 2007). While some reports indicate that schizophrenia affects men and women to an equal degree (Wyatt et al., 1988), other data suggest that this is not the case. One meta-analysis concluded that approximately 60% of those who develop schizophrenia are men (Aleman, Kahn, & Selten, 2003). In support, an earlier study by Castle et al (1998) showed that while the incidence was relatively equal between the two sexes for mild schizophrenia, as the diagnostic criteria narrowed, a higher proportion of males than females emerged (Castle, Sham, & Murray, 1998). The finding of an earlier onset in men than in women supports this notion (McGrath et al., 2008; Saha et al., 2005).
The peak incidence for schizophrenia among males occurs between 15 and 24 years (Munk-Jorgensen, 1987). A later onset is observed among female patients, occurring between 29 and 32, (Kirkbride et al., 2006) followed by a second peak at menopausal age (Grigoriadis & Seeman, 2002). The earlier age of onset in males has been attributed to their brain's heightened vulnerability to neurodevelopmental disorders, the disproportionately high incidence of birth injury among boys, hormonal factors as well as heavy and chronic exposure to substances of abuse (Castle & Murray, 1991; Seeman & Lang, 1990; Van Mastrigt, Addington, & Addington, 2004).

1.1.3 Phenotype of Schizophrenia

1.1.3.1 POSITIVE & NEGATIVE SYMPTOMS

The positive symptoms of schizophrenia manifest as hallucinations, delusions, disorganized thinking, and thought disorder. They are complex and are often of a bizarre nature. In contrast, negative symptoms represent an absence of behaviours or deficit symptomatology. They refer to a reduction of emotional responsiveness, interest, motivation, socialization, speech, and movement. While negative symptoms are an intrinsic component of schizophrenia psychopathology, they can also be caused by secondary factors. Such symptoms may result from medication side effects or be consequences of other symptoms (i.e., depression).

Positive and negative symptoms follow independent trajectories over time (Eaton et al., 1995). During the acute phase of psychosis, positive symptoms often dominate, and then cycle through stages of relapse and remission (Harrow et al., 1995). In contrast, negative symptoms tend to be more persistent; they are present in the prodromal phase, during psychosis, and after the remission of positive symptoms (Lencz et al., 2004; Mason et al., 2004; Thorup et al., 2005). In addition negative symptoms are considered to be strong predictors of prognosis, social outcome, and quality of life (Kirkpatrick et al., 2006). Antipsychotic medications have proven relatively effective at targeting positive symptoms however both conventional antipsychotics and the
newer atypical antipsychotics have demonstrated limited effects for reducing the burden of negative symptoms (Arndt et al., 1995; Leucht et al., 2009; Leucht et al., 1999).

1.1.3.2 COGNITIVE DEFICITS

Cognitive deficits are a core feature of schizophrenia, and are present in approximately 80% of patients (Keefe, Eesley, & Poe, 2005). Although varying widely in severity from patient to patient, the degree of cognitive impairment can be substantial. Patients on average perform one to two standard deviations below the norms of healthy populations (Heinrichs & Zakzanis, 1998; Wilk et al., 2004). These impairments are broad-based and global rather than specific, and thereby affect various domains of cognition (Heinrichs & Zakzanis, 1998). Cognitive deficits in schizophrenia patients are most prominent in areas of verbal and working memory, spatial memory, attention, executive function and psychomotor speed (Heinrichs & Zakzanis, 1998).

Cognitive deficits in schizophrenia patients are generally more severe and pervasive compared to patients with other psychiatric and psychotic disorders (Reichenberg, 2010). Notably, there is no pathognomonic neuropsychological profile in schizophrenia, which is likely a reflection of the etiological heterogeneity of the disorder.

Cognitive deficits are relatively stable, enduring traits and are common across the lifespan of the patient (Heaton et al., 2001). While the classical positive symptoms of schizophrenia are cyclical in nature, undergoing periods of relapse and remission, cognitive deficits remain persistent over the course of the illness. Impairments predate the onset of the illness (Bilder et al., 2000; Cornblatt et al., 1992; Reichenberg et al., 2010), are not secondary to other symptoms (Green et al., 2004), and are not attributable to antipsychotic medications (Torrey, 2002). Cognitive dysfunction is also reported in high-risk individuals, and unaffected first-degree relatives of patients with schizophrenia display similar patterns of deficit in an attenuated form (Sitskoorn et al., 2004). This suggests that a significant genetic contribution may underlie these deficits (Cosway et al., 2000; Egan et al., 2001a). Moreover, this supports the role of cognitive dysfunction as putative endophenotypes in schizophrenia (Gonzalez-Blanch et al., 2007).
Manifestations of overall cognitive dysfunction may be a reflection of underlying aberrant neural synchronization within a single region of the brain, within a specific network or at the level of interconnected networks (Callicott et al., 2003; Fornito et al., 2012; Friston & Frith, 1995). Emerging evidence from neurophysiology studies indicates that abnormal gamma range (30–80 Hz) synchrony may be a biomarker, reflecting core pathophysiological features of schizophrenia related to cognition. Gamma oscillatory activity is thought to be a fundamental mechanism that integrates neural networks within and across brain structures; in particular, it is thought to be essential for working memory ability (Fries, 2009). Interestingly, disruption in gamma oscillatory activity has been well documented in patients with schizophrenia (Barr et al., 2010; Basar-Eroglu et al., 2007).

The most important rationale for focusing on cognitive deficits is that they have a substantial impact on the functional outcome of schizophrenia. In other words, key cognitive constructs are strongly associated with real-world daily functioning (Green, 1996). These functional impairments involve social, occupational, independent living activities, as well as lack of success in rehabilitation programs. Notably, the relationship between cognition and functional outcome is generally stronger than those observed between psychotic symptoms and functional outcome (Green et al., 2000). Therefore, remediation of disease-related cognitive dysfunction may provide the essential building blocks for rehabilitating patients suffering from the disorder.

Currently approved pharmaceutical treatments for schizophrenia typically have little or no effect on the cognitive features of the disorder (Keefe et al., 2008), rendering these impairments difficult to remedy. Therefore improving or at least preventing further deterioration of cognitive impairment, represents a promising target for intervention (Davidson & Keefe, 1995).

1.1.3.3  COURSE & OUTCOME

There is compelling evidence that signs of schizophrenia are present long before the illness is formally diagnosed. Most of these signs are subtle, and do not reach the severity of clinical significance. The onset of clinical symptoms of schizophrenia can be insidious or gradual, but for the majority of individuals escalating signs of behavioural abnormalities and subclinical
psychotic symptoms precede the first psychotic episode of schizophrenia. This period is referred to as the prodromal phase (Lieberman et al., 2001). The mean length of this period is 5 years, with early signs and symptoms often presenting as depressive and negative symptoms as well as cognitive dysfunction (an der Heiden & Hafner, 2000). The prodrome is clinically relevant as it offers a target for early diagnosis, management of symptoms and intervention (Yung & McGorry, 1996).

Often, the appearance or worsening of psychotic symptoms is what triggers the initial contact with mental health professionals. Therefore the first episode of schizophrenia is usually described by the presence of positive symptoms, such as fully formed delusions and hallucinations. However, studies examining the early course of illness have shown that about 70% of schizophrenia patients actually develop negative symptoms prior to the onset of positive symptoms (Hafner et al., 1992).

The gradual development of psychosis, combined with lack of insight, and the misunderstanding of symptoms, creates a critical window between the onset of symptoms and the onset of adequate treatment. This time period is known as the Duration of Untreated Psychosis (DUP). While DUP should be in minimal, it can often be quite lengthy with a mean of 1–3 years (Barnes et al., 2000; Ho et al., 2000; Loebel et al., 1992). This is unfortunate given that treatment effectiveness is most optimal when initiated early in the pathological process. Thus it follows that longer DUP is associated with worse prognosis (McGlashan, 1999; Ucok et al., 2004). Therefore a primary aim of initial treatment is to bring about accelerated remission of the acute psychotic episode.

Rates of symptomatic remission for schizophrenia patients experiencing a first episode of psychosis within the first year of treatment are in the range of approximately 70%–80% (Addington, Leriger, & Addington, 2003; Menezes et al., 2009). Evidence suggests that individuals who achieve remission after their first episode are, on average, able to maintain similar rates of remission over the longer-term as well. However, the majority of these patients (70-82%) will experience a relapse within 5-7 years, with comparable percentages of patients going on to have a second and third relapse (Robinson et al., 1999; Wiersma et al., 1998). Patients who become non-compliant with medication in the early course of the disorder are at an especially high risk of relapse (Gitlin et al., 2001). Thus, their course of schizophrenia is
characterized by irregularly alternating episodes of psychotic symptom exacerbation and symptom remission. Unfortunately, with subsequent psychotic episodes, patients may not respond to treatment as well as in prior episodes and may then fail to achieve symptom remission (Robinson et al., 1999). Notably, rates of functional recovery are much lower than rates of remission (Robinson et al., 2004). A study by Bertelsen et al (2009) found that less than 20% of patients with a first episode of schizophrenia were considered recovered after two years; similar rates were also reported at the five year mark (Bertelsen et al., 2009).

The traditional societal view of schizophrenia maintains that it is a disorder associated, in the long-term, with poor recovery and persistent hospitalization. However considerable longitudinal research has reformulated this outlook to one that is less negative, where at least some degree of symptomatic and functional recovery is increasingly the expectation (Jobe & Harrow, 2005). Such studies suggest that 10-15 years after initial diagnosis, approximately 25% of individuals with schizophrenia show complete remission or are improved to the point of being able to function independently. These individuals attain good outcomes on a range of clinical and functional measures (i.e., education, employment, and relationships) (Harrow et al., 2005). A larger proportion, about 50%, experience partial remission, characterized by episodic periods of symptoms, often with continual or chronic malfunctioning, adjustment difficulties, and some impairment in functioning between episodes (Harrow et al., 2005). Fifteen percent, however, remain unimproved and are typically grossly impaired and are permanently hospitalized (an der Heiden & Hafner, 2000; Ciompi, 1980; Harrison et al., 2001). Sadly, common estimates are that 10% of people with schizophrenia will eventually have a completed suicide attempt (Siris, 2001).

Continued research is dedicated to understanding what factors best predict better prognosis and produce more favourable outcomes for patients with schizophrenia. Positive long-term outcomes have been associated with better premorbid functioning, being married, higher IQ and education levels, and living in a developed country. In contrast, poorer outcome is related to insidious and early onset, having a family history of schizophrenia and the use of illicit substances (Geddes et al., 1994; Leff et al., 1992; Margolese et al., 2004; Murray & Van Os, 1998; Vaillant, 1978).

With further identification and greater understanding of these risk and protective factors, it is the hope that the prognosis will continue to improve and patients may strive to achieve premorbid levels of functioning.
1.1.4 A Public Health Concern

Given the chronic nature of schizophrenia, its severity, and its early onset, the financial costs to society far outweigh those of other more common illnesses. This complex illness generates overwhelming costs to the patient in terms of personal suffering, on the family and caregivers and to society as a whole. In Canada, schizophrenia is responsible for approximately 3% of the total social and economic burden of all human disease, which is disproportionately high given that the illness only affects 1% of the population (Public Health Agency of Canada, 2012). A Canadian study found that the direct health care and non-health care costs of schizophrenia were estimated to be at 2.02 billion Canadian dollars. This, combined with the high unemployment rate among patients, and morbidity and mortality loss, yields a total cost estimate of 6.85 billion dollars (Goeree et al., 2005).

Although schizophrenia is not in itself a fatal disease, death rates of people with schizophrenia are higher than those in the general population. These individuals have a shorter life span than the rest of the population by about 12–15 years (Saha, Chant, & McGrath, 2007). Suicide and cardiovascular disease are the two major contributors to this excess mortality rate (McGrath et al., 2008). Other factors include physical illnesses that are diagnosed late and/or treated insufficiently, side effects from antipsychotic medications, and unhealthy lifestyle choices (poor diet, smoking, excess alcohol consumption, and lack of exercise) (Laursen, Munk-Olsen, & Vestergaard, 2012). Schizophrenia exerts a significant impact on our country. The significant social and economic costs of the illness warrant the creation of a coordinated, multi-disciplinary approach that integrates healthcare practices, education, social support programs, pharmaceutical innovation and evidence-based public policy to combat the high expenditures associated with schizophrenia.

1.1.5 Pathophysiology of Schizophrenia

While the etiology of schizophrenia remains elusive, there is substantial evidence that suggests that there are changes in several neurotransmitter systems underlying the pathophysiological processes leading to the development of schizophrenia. Since the 1950s, scientists have largely
focused on dopamine, and two of its specific receptor subtypes. However, in more recent investigations there has been a shift, and currently close attention is now being paid to other potential neurochemical systems, such as glutamate, gamma-aminobutyric acid (GABA), and to neuromodulator systems such as the endocannabinoid system (eCB).

1.1.5.1 **DOPAMINE**

For more than 50 years, the classical dopamine hypothesis has been a dominant theory of schizophrenia (Van Rossum, 1967). This theory emerged with the discovery that (i) drugs that reduced dopamine activity also diminished psychotic symptoms, and (ii) drugs that heightened dopamine activity exacerbated or triggered psychotic episodes (Carlsson, 1988). Accordingly, excess dopamine transmission (at D2 receptors) in the mesolimbic system may be related to the core or "positive" symptoms (hallucinations, delusions) of schizophrenia. A later attempt to explain negative and cognitive symptomatology of schizophrenia led to the idea that co-occurring deficits may be present in dopamine transmission at D1 receptors in the prefrontal cortex (PFC) (Davis et al., 1991; Weinberger, 1987). Thus, dopamine transmission in schizophrenia may be characterized by an imbalance between subcortical and cortical systems.

Subsequently, with the advent of neuroimaging techniques, direct evidence of abnormalities in the dopamine system was documented from both preclinical and clinical studies. Post-mortem and functional MRI studies of the brains of schizophrenia patients, both medicated and unmedicated, showed greater dopamine D2 receptors in their brains compared to normal controls (Kestler, Walker, & Vega, 2001). In addition, dopamine synthesis and release have also been observed to be augmented in the brains of patients with schizophrenia (Lindstrom et al., 1999). Evidence supporting this comes from amphetamine challenge studies. When schizophrenia patients and normal controls are given amphetamine, a drug that enhances dopamine release, patients show enhanced dopamine release (Abi-Dargham et al., 1998). Other studies suggest abnormalities in dopamine storage, vesicular transport, release, and reuptake (Laruelle et al., 1999).
1.1.5.2 GLUTAMATE

Glutamate is the primary excitatory neurotransmitter in the brain and its excitatory effects are mediated by N-methyl-D-aspartic acid (NMDA) and amino-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. The ‘glutamate hypothesis’ of schizophrenia arose out of observations that NMDA antagonists such as phencyclidine (Halberstadt, 1995) and ketamine (Lahti et al., 1995) can trigger or exacerbate psychotic symptoms. Mechanisms proposed to explain glutamatergic involvement in schizophrenia centre on its interactions with dopamine (Carlsson & Carlsson, 1990), excitotoxicity (Olney & Farber, 1995) and abnormal pruning of glutamatergic innervation during neurodevelopment (Deakin & Simpson, 1997). NMDA receptor hypofunction can trigger excess compensatory release of glutamate that can overactivate other glutamate receptors subtypes (Moghaddam & Adams, 1998). This may also produce disturbances in neuroplasticity (Olney & Farber, 1995).

Moreover, this theory of glutamatergic dysfunction works in concert with the dopamine hypothesis of schizophrenia, as there are reciprocal connections between these two systems (Vasiliadis, Elie, & Dewar, 1999; Zheng et al., 1999). Converging data also suggests that dopamine has a modulatory role on glutamatergic transmission. Thus, it follows that changes in dopamine function might in turn affect NMDA activity (Jentsch & Roth, 1999).

1.1.5.3 GABA

GABA is the predominant inhibitory neurotransmitter in the brain and it was first proposed to be implicated in schizophrenia in 1972 (Roberts, 1972). Postmortem studies conducted in patients with schizophrenia demonstrated that GABAergic hypofunction in the PFC and the hippocampus may be important contributors to the pathophysiology and symptomatology, particularly in relation to cognitive symptoms, of the illness (Lewis, Hashimoto, & Volk, 2005). Reduced expression of GAD67 (the 67-kDA isoform of glutamate decarboxylase, a key enzyme in GABA synthesis) has been a well-replicated finding in post-mortem brains of schizophrenia patients (see (Gonzalez-Burgos, Hashimoto, & Lewis, 2010) for review). Similar decreases are also found in mRNA expression for the GABA membrane transporter (GAT1). This protein is responsible for
GABA reuptake that is released into nerve terminals (Volk et al., 2001). Accordingly, among patients, neuronal density and reuptake of GABA are reduced (Benes et al., 1991; Lewis & Moghaddam, 2006). Compensatory up-regulation of GABA_A receptor binding and down-regulation of GABA_B receptors have also been reported (Mizukami et al., 2002; Volk et al., 2002). Decreased GABAergic neurotransmission may also contribute to impaired dopamine (Goldman-Rakic, 1996) and glutamatergic activity (Lewis, Hashimoto, & Volk, 2005).

1.1.5.4 THE ENDOCANNABINOID SYSTEM

Accumulating evidence identifies disturbances in the eCB system as another contributor to the pathogenesis of schizophrenia. The highest densities of cannabinoid 1 receptors (CB1R) in the brain are found in regions that have been implicated in schizophrenia. This includes the PFC, basal ganglia, hippocampus and the anterior cingulate cortex (Mailleux & Vanderhaeghen, 1992). Post-mortem brain studies of patients with schizophrenia have shown increased CB1R density in these regions (Dean et al., 2001; Zavitsanou, Garrick, & Huang, 2004) and genetic studies have shown associations between polymorphisms in the gene encoding CB1R, (CNR1) and schizophrenia (Martinez-Gras et al., 2006; Ujike et al., 2002). De Marchi et al (2003) found significantly increased amounts of anandamide, a naturally occurring eCB. These authors also reported increased levels of the mRNA that encodes fatty acid amide hydrolase (FAAH), the enzyme responsible for degrading anandamide (De Marchi et al., 2003). It is thought that elevated FAAH levels, may be a compensatory mechanism to normalize circulating anandamide levels (De Marchi et al., 2003). Elevated levels of anandamide have also been documented in the cerebral spinal fluids of patient with schizophrenia. Interestingly, another study showed that elevated levels positively correlated with clinical symptoms severity in patients (Giuffrida et al., 2004; Leweke et al., 1999).

Behavioural, biochemical, and electrophysiological data demonstrate that endogenous cannabinoids are involved in regulating dopaminergic neurotransmission and GABAergic activity (Manzoni & Bockaert, 2001). Another important aspect for studying the relationship between the eCB system and schizophrenia is the putative role of chronic cannabis in the
development of the disorder, which has led to the eCB hypothesis of schizophrenia (Muller-Vahl & Emrich, 2008).

In sum, it is clear that dopamine, glutamate, GABA and the eCB systems contribute, in concert, to the dysfunctional neurochemical pathophysiology observed in patients with schizophrenia. In turn, it is also likely that the pathology of schizophrenia affects these neurotransmitter systems. Interventions that can remediate or tame aberrant functioning may result in bringing that dysfunction into a state of remission. To this end, better understanding of this complex neuropathophysiology is essential for exploiting compounds that act on these systems in order to develop novel therapeutic agents for the treatment of schizophrenia.

1.1.6 Pharmacotherapy for Schizophrenia Patients

The beginning of the pharmacological era in psychiatry began in the 1950’s with chlorpromazine, a “typical” antipsychotic. Its introduction led to a dramatic improvement in positive symptoms, decreased the length of hospital stays and if maintained, reduced the risk of relapse and re-hospitalization. The mechanism of action of a typical antipsychotic medication is linked to the blockade of dopamine receptors (Seeman & Lee, 1975). In fact, there is a strong correlation between the clinical potency of these drugs and their pharmacological ability at blocking the D2 receptor (Seeman & Lee, 1975). Currently, the first-line of treatment for schizophrenia is second-generation, or “atypical” antipsychotic drugs. This class of medications represents a critical effort to improve upon the management of symptoms (Beasley et al., 1996; Kane et al., 1988), reduce extrapyramidal symptoms associated with first-generation antipsychotics (Simpson & Lindenmayer, 1997), and ultimately better the quality of life and functioning of patients with schizophrenia. Clozapine was the first atypical antipsychotic to be FDA-approved and has proven effective not only at reducing positive symptoms of schizophrenia, but it has also been demonstrated to be successful at targeting negative and cognitive symptoms of the disorder (Lee, Thompson, & Meltzer, 1994; Lindenmayer, Grochowski, & Mabugat, 1994). Clozapine possesses a unique pharmacological profile that exhibits affinity for the dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors (Tamminga, 1997). However, despite clozapine’s remarkable efficacy its use has been reserved
exclusively for treatment-resistant individuals given that it is associated with severe adverse effects such as agranulocytosis (Alvir et al., 1993). Other atypical agents include risperidone, olanzapine, quetiapine and ziprasidone. These medications are accompanied by their own characteristic profile of side effects that include weight gain, diabetes, hyperglycemia and dyslipidemia (Allison & Casey, 2001; Goldstein et al., 1999; Osser, Najarian, & Dufresne, 1999). While this class of medications shows robust improvement in efficacy and tolerability, a significant proportion of patients still do not experience complete symptomatic remission. Further, cognitive symptoms remain largely unchanged, and functional recovery, though improved, is still far from optimal. However, medications alone are not the optimal solution. Antipsychotic drugs are best administered in the context of other psychological and social supports, such as cognitive behavioural therapy (CBT). New insights combined with the advent of novel technologies will hopefully lead to improved pharmacotherapies and overall outcome for patients suffering from schizophrenia.

1.2 Cannabis

1.2.1 History of Cannabis

Cannabis has a rich history that dates back over 5000 years. Cannabis has been used for centuries for both therapeutic and recreational purposes. The first formal report of cannabis used medicinally was in China when it was recommended for malaria, constipation, rheumatic pains childbirth, and as a surgical analgesic (Mechoulam, 1986). Psychoactive preparations of cannabis have been used for its euphoric properties for over 4000 years (Zias et al., 1993), and early recounts elude to the psychotic nature of the drug [See (Iverson, 2000)].

However, as the 20th century progressed the status quo of cannabis changed. Recreational use has become normalized to the extent that it is now regarded as a socially acceptable lifestyle choice and as a benign and non-hazardous drug ("Deglamorising Cannabis," 1995).
1.2.2 What is Cannabis?

The term ‘cannabis’ is used internationally; nevertheless cannabis is referred to by countless street names (i.e., pot, skunk, weed, reefer, Mary Jane, grass, yandi, gunja and dope). ‘Marijuana’ is mainly used in the USA, deriving from the Mexican name for the plant. In this thesis the term ‘cannabis’ will be used. Cannabis is derived from the Cannabis Sativa plant and refers to a mixture of cut, dried, and ground flowers, leaves, and stems of the hemp plant.

Herbal cannabis contains over 421 different compounds, including over 60 cannabinoids, which can be bred to yield hundreds of strains, each with a unique cannabinoid profile (Elsohly, 2002; Turner, Elsohly, & Boeren, 1980). The primary psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC) and it is this cannabinoid that is largely responsible for the psychoactive and physical effects of the plant (Dewey, 1986). However, the effects of THC do not work in isolation, but can be modulated by other cannabinoids such as cannabidiol (CBD), a non-psychoactive cannabinoid present in many cannabis products (McLaren et al., 2008; Morgan et al., 2010). Other plant cannabinoids include delta-8-tetrahydrocannabinol, cannabinol and Δ⁹-tetrahydrocannabivarin (Iversen, 2008). The concentrations of these and other cannabinoids vary enormously from preparations to preparation.

The potency of cannabis is usually expressed in terms of THC content and is highly variable. The type of plant, where it is grown, the season in which it was grown, and the quality and freshness of the plant all play a role in the strength of the cannabis preparation (Beshay et al., 2007). In recent years, likely a result of selective breeding and more advanced methods of cultivation, there have been substantial increases in the potency of cannabis. In the 1960s THC content was in the range of 1-3% while today concentrations may reach up to 20% (Adams & Martin, 1996). No data are currently available on changes in CBD content (Hall, 2015; Hall & Degenhardt, 2009). The impact of increased potency of cannabis use should be a research priority.

1.2.3 Epidemiology of Cannabis Use

After tobacco and alcohol, cannabis is the most commonly used recreational drug worldwide, (Iversen, 2003) and Canada has one of the highest rates (Health Canada, 2014). An estimated
10–13% of the general adult population have used cannabis in the past year (Health Canada, 2014) and sizable proportions report weekly (20.1%) and daily (18.1%) use (Health Canada, 2014). These rates are concerning given that about 9% of individuals who experiment with cannabis will go on to develop dependence (Anthony, Warner, & Kessler, 1994; Lopez-Quintero et al., 2011). Moreover, this number increases to 17% if cannabis is introduced during adolescence (Johnston, 2014). Despite that the rate of developing cannabis dependence is lower than that of other drugs of abuse (Anthony, Warner, & Kessler, 1994), the widespread prevalence of cannabis use results in a significant number of individuals with CUDs. In this regard, in 2014 approximately 1.3% of Canadians met for cannabis dependence, which is almost double that of other substance use disorders (0.7%) (Pearson C, 2013). The number of people seeking treatment for cannabis is steadily increasing (UNODC, 2012), however, similar to other drug treatments, the vast majority of patients seeking help for their cannabis use fail to achieve abstinence.

### 1.2.4 Changing Policies

Recreational cannabis use is currently criminalized in Canada. However, changes in legislation are currently being debated and legalization is no longer an abstract notion. This policy shift is in line with the attitudes of many Canadians who are in favour of legalization. In 2012, citizens in Colorado and Washington State voted to legalize recreational cannabis use and its commercial sale for adults and in the November 2014 election, Oregon, Alaska, and Washington D.C. followed suit. Projections predict that this number will continue to rise. With the recent inauguration of the Liberal government, it now appears that it not a question of “if” cannabis will be legalized in Canada but more a question of “when.” However, it should be underscored that the move towards cannabis legalization is premature given that cannabis research is still in its infancy and the full characterization of the pharmacological, behavioural, and health effects are far from complete. Given that impending legalization may lead to wider acceptance, availability, increased consumption and a greater number of individuals presenting with problematic use (Johnston, 2014; Substance Abuse and Mental Health Services Administration, 2014) (Gallup, 2013), developing a solid evidence base regarding the effects of cannabis beforehand is imperative.
1.2.5 Pharmacokinetics of Cannabis

Cannabis is usually smoked in a joint or with a water pipe, sometimes with tobacco added. A typical joint contains between 0.5 g and 1.0 g of cannabis. Smoking tends to be the preferred method of administration as it is the most efficient means of drug delivery. One reason for this is because experienced users can titrate the dose by modifying the frequency and the depth of inhalation (Iversen, 2008). Cannabis may also be ingested, usually in the form of food or tea. While the pharmacokinetics of THC varies with respect to the route of administration, it does not appear to differ between males and females (Wall et al., 1983), or as a function of frequency of use (Kelly & Jones, 1992).

THC is rapidly absorbed after cannabis inhalation and it is detectable in the plasma within seconds. Peak brain concentrations are reached within 15 to 30 minutes and effects seldom last longer than 2-3 hours (Grotenhermen, 2003). In contrast, if cannabis is ingested, absorption rates are more variable and slower with attenuated, more delayed peak of THC concentrations as compared to inhalation (1-5 hours) (Ohlsson et al., 1980). While oral administration may prolong the effects of cannabis, this route decreased the effectiveness of the cannabis by about 25-30% of the inhalation dose (Perez-Reyes et al., 1991).

THC is highly lipophilic and water-insoluble (Garrett & Hunt, 1974). It is initially taken up by highly perfused tissues, such as fatty tissue, the lungs, heart, liver and brain (Ho et al., 1970). More specifically, within the brain, THC and other cannabinoids are differentially distributed, with higher concentrations reaching neocortical, limbic, sensory and motor areas (Herkenham, 1995).

Initial metabolism of THC occurs in the lungs and liver, where it is converted to 11-hydroxy-Δ9-tetrahydrocannabinol (11-OH-THC) by cytochrome P450 2C9, 2C19, and 3A4 (Matsunaga et al., 1995). This metabolite is short-lived, psychoactive and equipotent to THC (Huestis, 2005). More extensive metabolism in the liver then converts 11-OH-THC to a host of inactive metabolites, including 11-nor-9-carboxy-THC (THC-COOH), the most abundant metabolite in plasma and urine. THC-COOH is the compound of interest for diagnostic purposes. It is excreted in urine.
mainly as a glucuronic acid conjugate (Musshoff & Madea, 2006). Notably, the elimination half-life for THC metabolites is longer than the elimination half-life of the parent molecule (THC). See Huestis et al 2005 for full review. The major reason for the slow elimination of THC is the slow re-diffusion of THC from body fat and other tissues into the blood (Leuschner et al., 1986).

THC plasma concentrations decrease rapidly after the end of smoking due to rapid distribution into tissues. This leads to increasing levels in fatty tissues over a period of hours to days (Maykut, 1985). It should be noted that the residual THC levels are maintained in the body for a long time following abuse. Therefore, with recurrent administration, THC can in effect accumulate and “build-up” in the body (Ashton, 1999). This storage of THC is then slowly re-released back into the blood for metabolism to THC-COOH. This is the reason for cannabis’ prolonged detection times. This may contribute to a type of “reverse tolerance” that is often associated with cannabis (Julien, 2001).

It is widely acknowledged that blood, and to a lesser extent saliva, offer the most accurate measurement of drugs currently active in the body, whereas urine, provides a broader time frame with less quantitative accuracy (Baumgartner, 1989). Urine analysis is the most common and routine drug testing conducted for detecting psychoactive substances of interest. Most urine tests detect the inactive metabolite THC-COOH. Concentration exceeding 50 ng/mL are suggestive of a positive result for documenting recent abstinence (Huestis, Mitchell, & Cone, 1995). Importantly, while detection of cannabinoids in the urine is indicative of previous cannabis use, the long excretion half-life of THC-COOH in the body makes it difficult to discern the exact timing of past drug exposure. For example, a single dose of THC may result in measurable metabolites in urine for up to 12 days (Law et al., 1984). Moreover, full elimination of THC from the body among regular users may take between two weeks (Law et al., 1984) and up to one month (Ellis et al., 1985; Goodwin et al., 2008). However, even longer periods of excretion have been documented in individuals with prolonged and heavy use. Ellis et al (1985) reported that in one case, it took up to 77 days of abstinence for one individual to produce 10 consecutive negative urine specimens using a 20ng/mL cutoff. Thus, in chronic cannabis users, it is especially difficult to determine whether a positive result for cannabis represents a new episode of drug use or continued excretion of residual THC (Musshoff & Madea, 2006). To make matters more complex, since urine excretion of metabolites does not decrease monotonously, urine
screenings may therefore fluctuate between positive and negative results for several days after cannabis use has been discontinued (Ellis et al., 1985).

Gas chromatography-mass spectrometry (GC-MS), offers a more expensive analytical method that provides quantitative levels of cannabinoid metabolites. This method allows for the normalization of THC-COOH concentrations to urinary creatinine which helps control for individual differences in hydration and urine output (Lafole et al., 1991). Another advantage of using this method is that noting the time interval between collected urine specimens, one can determine if new cannabis use has been introduced in a given time period despite high residual cannabinoid levels (Manno, 1984; Schwilke et al., 2011; Smith, Barnes, & Huestis, 2009). In this respect, using ratios calculated from creatinine-normalized urine specimens collected >24 hours apart (Urine2/Urine1), will allow one to distinguish new cannabis use from residual excretion. More, specifically, Manno et al. (1984) suggested that new cannabis use was indicated if the ratio of the creatinine normalized THC-COOH concentration (ng/mg) of a later specimen to an earlier specimen was greater or equal to 1.5 (Manno, 1984). A more recently published prediction model improves upon the validity of previous ones by taking into account the initial cannabinoid concentrations and the variable times between urine collections (Schwilke et al., 2011). These algorithms prove especially valuable for ensuring extended cannabis abstinence among chronic cannabis users.

1.2.6 The Endocannabinoid System

The eCB system is one of the most ubiquitous neuromodulatory systems in the brain and is responsible for the overall homeostatic control of synaptic transmission. The eCB system is comprised of two G protein-coupled receptor subtypes: cannabinoid 1 receptors (CB1R) and cannabinoid 2 receptors (CB2R). Cannabis, cannabis-related drugs and eCBs act primarily at these receptors. The cannabinoid receptor is a member of a large family of G-protein coupled receptors containing seven membrane-spanning domains (Glass & Northup, 1999; Howlett et al., 1991). CB1Rs are the most abundant G protein-coupled receptor in the human brain, with densities 10–50 fold above those of classical transmitters (i.e., dopamine or opioid receptors) (Herkenham, 1991). A high density of CB1R density has been documented in the striatum,
cerebral cortex, and hippocampus correlating with cannabinoid effects on perception, cognitive function, addiction, food intake, and body temperature regulation (Compton et al., 1993). Significant binding has also been found in the caudate nucleus and cerebellum consistent with the marked effects of cannabinoids on motor behaviour (Sanudo-Pena et al., 2000). Only modest binding is observed in the spinal cord and brain stem (Herkenham, 1991) which explains why cannabis is not a lethal substance. In contrast, the CB2R are located in the periphery and are localized in the spleen, thymus, tonsils, and on mast cells and plasmocytes. Thus these receptor subtypes play an important immunomodulatory role (Galiegue et al., 1995; Lynn & Herkenham, 1994). There is now accumulating evidence to suggest that a third cannabinoid receptor subtype exists as well (Baker et al., 2006; Begg et al., 2005).

The CB1R is linked to a large number of second messenger transduction mechanisms in the brain. The intracellular surface of the CB1R interacts with G proteins to regulate intracellular events, which vary by cell type. The majority of CB1Rs are expressed pre-synaptically. While found on both inhibitory and excitatory neurons (Auclair et al., 2000; Diana et al., 2002), CB1R predominate on the axon terminals of GABA basket neurons (Eggan & Lewis, 2007).

The discovery of specific cannabinoid receptors implies the presence of natural ligands in the body. In 1992, the first endogenous cannabinoid ligand was identified, anandamide (arachidonylethanolamide), which is Sanskrit for bliss (Devane et al., 1988). Anandamide binds to both CB1Rs and CB2Rs. It produces similar effects to THC but with reduced potency and is shorter acting (Fride & Mechoulam, 1993; Iversen, 2008). Anandamide is inactivated by FAAH (Deutsch & Chin, 1993) or by a specific transporter reuptake mechanism (Di Marzo & Deutsch, 1998). 2-arachidonoylglycerol (2-AG), a more abundantly present eCB, was subsequently discovered in 1995 (Mechoulam et al., 1995). Much less is understood about the enzymes that terminate its action. Taken together this suggests that eCbs function as a biological neurotransmitter. However, unlike most neurotransmitters, eCBs are produced “on-demand,” as a result of specific stimuli and are released in a non-vesicle manner rather than stored in vesicles.

Endocannabinoids act as retrograde neurotransmitters at particular synapses. They are synthesized and secreted from postsynaptic neurons upon membrane depolarization and then travel backwards across the synaptic cleft where they bind to CB1Rs located on pre-synaptic
neurons. The activation of CB1Rs decreases the production of cAMP and adenylate cyclase at both GABA and glutamate nerve terminals, resulting in a decrease in the release of neurotransmitter from the pre-synaptic neuron (Alger, 2002; Ohno-Shosaku & Kano, 2014; Schlicker & Kathmann, 2001). That is, this post-synaptic depolarization causes a transient suppression of either GABA or glutamate release. Therefore, the eCB effectively acts as a synaptic break, initiating a negative feedback mechanism that “calms” stimulated neurons after excitation (Chevaleyre, Takahashi, & Castillo, 2006; Schlicker & Kathmann, 2001; Wilson & Nicoll, 2002). As such, this system is essential in the maintenance and determination of synaptic plasticity (Freund, Katona, & Piomelli, 2003). In addition, a growing body of research suggests that the eCB system plays a highly specialized and functionally distinct role during neurodevelopmental periods, particularly during adolescence, that extends beyond the regulation of transmitter release (Bossong & Niesink, 2010). Therefore changes in eCB activity during this specific developmental phase, induced by exogenous cannabinoids, might lead to subtle but lasting neurobiological changes that can affect brain functions as well as behaviour (Malone, Hill, & Rubino, 2010).

1.2.6.1 CANNABIS AND THE ENDOCANNABINOID SYSTEM

THC acts as a partial agonist at the CB1R and CB2R, where it demonstrates modest affinity and low intrinsic activity (Compton et al., 1992; Pertwee, 1997). Pure THC may not entirely mimic the effects of cannabis, which as previously mentioned contains additional cannabinoid constituents, such as CBD. CBD, in fact, shows very little affinity for CB1R and CB2R and does not possess psychoactive properties (Pertwee, 2008). While the precise molecular mechanism of action of CBD remains unclear (Mechoulam et al., 2007), it has been shown that CBD influences the pharmacological activity of THC and therefore THC’s effects can be modulated by the presence of CBD (Pertwee, 2008).

Similar to the effects of endogenous cannabinoids, THC inhibits synaptic neurotransmitter release via activation of presynaptic CB1Rs, thereby disrupting the fine balance of the eCB system (Chevaleyre & Castillo, 2003; Mato et al., 2004). Chronic exposure to cannabis can lead to CB1R desensitization (G-protein receptor uncoupling) and down-regulation (loss of binding
sites), consequently rendering individuals tolerant to the central and peripheral effects of THC (Gonzalez, Cebeira, & Fernandez-Ruiz, 2005). Moreover, disturbances of the eCB system, such as alterations in brain eCB levels, or expression of CB1R, or of idiopathic origin may lead to long-term dysregulation of neuronal functions resulting in overwhelming neurobiological consequences (Bossong & Niesink, 2010; Zamberletti). Given the importance of the eCB system during neurodevelopment, it is likely that externally induced changes in eCB signalling during adolescence can have profound long-term consequences on the functioning of the adult brain (Renard et al., 2014).

1.2.6.2 CANNABIS AND THE REWARD SYSTEM

Cannabinoids enhance brain reward processes and reward-related behaviours in a similar fashion to other addictive drugs (Gardner & Vorel, 1998). For one, high densities of CB1Rs are found in brain structures associated with reinforcement processing, including the ventral tegmental area (VTA), the nucleus accumbens (NAcc), and the PFC (Ameri, 1999; Gardner, 2005).

Cannabinoids are thought to exert their effects directly and indirectly within the NAcc and VTA respectively on dopaminergic transmission through the glutamatergic and GABAergic systems (Filbey & DeWitt, 2012). Animal and human studies indicate THC and other CB1R agonists activate the mesolimbic dopamine system (Tanda, Pontieri, & Di Chiara, 1997). For example, microinjections of THC into the posterior VTA and posterior shell of the NAcc produced conditioned place preference in rats, a common behavioural model used to study the rewarding and aversive effects of a drug. Importantly, the cannabinoid antagonist SR141716A subsequently blocked this effect (Zangen et al., 2006) suggesting that many, if not all, of the psychological properties of cannabis are mediated by the CB1R (Huestis et al., 2001). Further support for the positive and reinforcing properties of cannabinoids comes from studies demonstrating that both mice and rats self-administer CB1R agonists in a dose-dependent fashion (Deiana et al., 2007; Fadda et al., 2006). Interestingly, this finding has been replicated in clinical settings. Active cannabis was self-administered significantly more than placebo (0% THC), and with a preference for preparations with higher THC concentrations over lower concentrations (Haney et al., 1997; Hart et al., 2001). In addition, recent human studies showed that THC administration
increased dopamine transmission in the striatum as measured by positron emission tomography (PET) (Bossong et al., 2009). Moreover, even cues (visual and tactile) associated with cannabis activate reward neurocircuitry (Filbey et al., 2009).

1.2.7 Effects of Cannabis

1.2.7.1 ACUTE EFFECTS OF CANNABIS

Cannabis intoxication is associated with acute euphoria, enhanced well-being, drowsiness, relaxation, perceptual alterations, time distortion, and the intensification of ordinary sensory experiences (Green, Kavanagh, & Young, 2003; Tart, 1970). With higher doses, memory impairments, depersonalization, mood alterations, decreased motor skills and coordination are observed (Jaffe, 1985). The most frequently reported side effects of cannabis are anxiety and panic reactions. Further, it is not uncommon for naïve users to report acute toxic psychosis (Ashton, 1999; Iversen, 2008). Several lines of evidence suggest that cannabis (and other cannabinoids) can produce a range of transient psychotic symptoms (D'Souza, 2007). In large community surveys, between 20% and 50% of individuals report acute transient psychotic experiences including paranoia, persecutory ideas, and hallucinations while under the influence of cannabis (Green, Kavanagh, & Young, 2003). It is important to note that commonly reported subjective effects of cannabis show significant overlap as well as variation across individuals. Cannabis tolerance, context and expectancies are factors that may, in part, help to explain this variation (Green, Kavanagh, & Young, 2003).

In addition, cannabis has well described physiological effects. For example cannabis use is associated with a dose-dependent increases in resting heart rate as much as 20-100% and modest increases in blood pressure (Aryana & Williams, 2007; Hart et al., 2001). In susceptible individuals, the additional stress of cannabis on the cardiovascular system may be severe (Jones, 2002; Mittleman et al., 2001). Dizziness or lightheadedness, dry mouth, sedation, amotivation,
muscle weakness, myalgia, and palpitations may also be experienced with acute use of cannabis (Pertwee, 2007).

1.2.7.2 LONG-TERM EFFECTS OF CANNABIS

Evidence indicates that frequent and prolonged use of cannabis can be detrimental to one’s mental and physical health. Chronic effects of cannabis use has been linked to an increased risk of developing psychiatric disorders such as anxiety, depression and schizophrenia (Degenhardt, 2003; Degenhardt, Hall, & Lynskey, 2003a; Kedzior & Laeber, 2014). Other probable effects include cannabis dependence and withdrawal, an amotivation syndrome as well as residual cognitive impairment (Anthony, 1994; DuPont, 2000; Hall & Degenhardt, 2009; Tennant & Groesbeck, 1972). Importantly, these consequences are compounded when introduced early in life. Moreover, heavy cannabis use in adolescence has also been associated with altered brain development, poor educational outcome, and poor psychosocial development (Solowij & Battisti, 2008; Volkow, Compton, & Weiss, 2014).

Further, there is evidence to suggest that chronic and heavy cannabis use can lead to a host of adverse physical outcomes. As with tobacco smoke, cannabis smoke contains harmful chemicals and given that users tend to inhale cannabis more deeply and for prolonged periods of times compared to tobacco cigarettes, there is a three-fold increase in the amount of tar and a five-fold increase in the carbon monoxide that is taken into the lungs (Wu et al., 1988). Therefore, it is not surprising that cannabis causes damage to the lungs, airways and respiratory system (Pletcher et al., 2012). Heavy cannabis consumption is also associated with a higher prevalence of bronchitis and a higher incidence of emphysema compared to non-smoking individuals (Ashton, 1999). While some of the constituents of cannabis smoke have been identified as carcinogenic, conflicting findings exist with respect to associations between heavy cannabis use and cancer (Pletcher et al., 2012).
1.2.8 Cannabis Use Disorders

1.2.8.1 CANNABIS DEPENDENCE

Cannabis dependence, as defined in the DSM-IV (APA, 2000), is a maladaptive pattern of substance use leading to clinically significant impairment or distress and is manifested by three or more of the following, occurring at any time in the same 12-month period:

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<td>1.</td>
<td>Tolerance</td>
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<td>2.</td>
<td>Withdrawal</td>
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<td>3.</td>
<td>Cannabis used in larger amounts or for longer than intended</td>
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<td>4.</td>
<td>Persistent desire or unsuccessful efforts to control use</td>
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<td>5.</td>
<td>Great deal of time spent in obtaining, using and recovering</td>
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<td>6.</td>
<td>Important activities given up or reduced</td>
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<td>7.</td>
<td>Continued use despite knowledge of physical or psychological problem</td>
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1.2.8.2 CANNABIS ABUSE

Cannabis abuse is defined as a maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1.) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home

2.) Recurrent substance use in situations in which it is physically hazardous

3.) Recurrent substance-related legal problems
4.) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

The symptoms have never met the criteria for Cannabis Dependence.

1.2.8.3 DSM-5

Since the publication of the fourth edition of the DSM, a substantial amount of research has examined the validity and performance of the manual’s diagnostic criteria for substance use disorders (SUDs). The DSM-5 now combines the DSM-IV categories of substance abuse and substance dependence into a single entity reflecting a unidimensional continuum of substance-problem severity. SUDs are measured on a continuum from mild to severe. While each specific substance in the manual is addressed separately, nearly all substances are diagnosed based on identical criteria.

A CUD is defined by the DSM-5 using the following:

• A problematic pattern of cannabis use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:
  • Cannabis is often taken in larger amounts or over a longer period than was intended.
  • There is a persistent desire or unsuccessful efforts to cut down or control cannabis use.
  • A great deal of time is spent in activities necessary to obtain cannabis, use cannabis, or recover from its effects.
  • Craving, or a strong desire or urge to use cannabis.
  • Recurrent cannabis use resulting in a failure to fulfill major role obligations at work, school, or home.
  • Continued cannabis use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of cannabis.
  • Important social, occupational, or recreational activities are given up or reduced because of cannabis use
  • Recurrent cannabis use in situations in which it is physically hazardous.
• Cannabis use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by cannabis.
• Tolerance, as defined by either a (1) need for markedly increased cannabis to achieve intoxication or desired effect or (2) markedly diminished effect with continued use of the same amount of the substance.
• Withdrawal, as manifested by either (1) the characteristic withdrawal syndrome for cannabis or (2) cannabis is taken to relieve or avoid withdrawal symptoms

Notably, drug craving has been included, and the item “problems with law enforcement” has been eliminated. Importantly, diagnostic criteria for cannabis withdrawal has been operationalized and incorporated.

Cannabis withdrawal is defined as follows:
• Cessation of cannabis use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months).
• Three or more of the following signs and symptoms develop within approximately 1 week after cessation of heavy, prolonged use:
  • Irritability, anger or aggression
  • Nervousness or anxiety
  • Sleep difficulty
  • Decreased appetite or weight loss
  • Restlessness
  • Depressed mood
  • At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache

The signs or symptoms of CUD must lead to clinically significant distress or impairment in social, occupational, or other important areas of functioning. The signs or symptoms cannot attributable to another medical condition and are not better explained by another mental disorder, including intoxication or withdrawal from another substance.
1.2.8.4 \textbf{ADDITION POTENTIAL}

The risk of progressing from recreational or occasional cannabis use to problematic use is lower for cannabis than it is for other substances of abuse (Anthony, Warner, & Kessler, 1994). Approximately 9% of those who ever use cannabis are estimated to meet criteria for dependence (DSM-IV criteria) at some point in their lives. This is relatively low in comparison to tobacco (32%), alcohol (15%), cocaine (16%), and heroin (23%). However, given the widespread number of individuals who try cannabis, implies that a substantial number of individuals will develop cannabis dependence (Anthony, Warner, & Kessler, 1994).

As with other addictive substances, the risk of developing dependence is influenced by multiple factors. It has been suggested that the earlier initiation of cannabis (Silins et al., 2014) as well as heavy and chronic use increases the risk of cannabis dependence (Hall, Solowij, & Lemon, 1994). The use of more potent cannabis (i.e. high THC levels), may also lead to a higher propensity for cannabis dependence (Hall, 2001). Lastly, vulnerability to the reinforcing effects of cannabis and to developing dependence has been shown to have a heritable component. That is, family and twin studies have demonstrated that genetic factors influence the risk of developing dependence, (Agrawal & Lynskey, 2006; Merikangas et al., 1998). In the literature, estimates of the proportion of variance in cannabis use accounted for by genetic influences hovers around 60% (Kendler et al., 2000; Verweij et al., 2010).

Converging evidence suggests that men have higher rates and greater severity of cannabis dependence compared to women (Coffey et al., 2003; Fergusson, Boden, & Horwood, 2006). In light of this, however, women are actually more susceptible to the development of cannabis dependence, have more severe withdrawal symptoms, and are more likely to relapse compared to men (Cooper & Haney, 2014; Craft, Marusich, & Wiley, 2013). One reason for these differences may be attributable to hormonal factors as they robustly affect the functioning of the eCB system (Craft, Marusich, & Wiley, 2013). Psychosocial factors may also play a role. For example, men may be driven to greater consumption of cannabis as a result of peer use, drug availability and because they are less sensitive to the perceived stigma associated with having an SUD (Coffey et al., 2000; Lex, 1991).
1.2.8.5  **CANNABIS WITHDRAWAL**

Once a controversial issue, a cannabis withdrawal syndrome (CWS) is now a well-documented, replicated and accepted component of cannabis dependence (Budney & Hughes, 2006). To this end, it has been incorporated into the latest edition of the DSM (APA;, 2013).

Cannabis withdrawal is a time-dependent, pharmacologically specific phenomenon associated with a constellation of clinically relevant symptoms (Budney, Novy, & Hughes, 1999; Copeland, Swift, & Rees, 2001; Kouri & Pope, 2000). The proportion of patients reporting cannabis withdrawal in recent treatment studies ranges from 50-95% (Budney & Hughes, 2006). Withdrawal symptoms usually appear approximately 24 hours after abstinence initiation, peak within two to six days and then gradually decline over the next three weeks (Allsop et al., 2011; Budney et al., 2004). Affective and behavioral, rather than physical, withdrawal symptoms are most often reported, and include irritability, anxiety, sleep difficulties, decreased appetite and cravings for cannabis (Budney et al., 2003; Haney et al., 1999; Hart et al., 2001). While this syndrome does not appear to include major medical or psychiatric consequences, symptoms have an additive effect and the severity of cannabis withdrawal is comparable to the withdrawal severity from other drugs of abuse, such as tobacco (Budney et al., 2008).

The CWS is of critical significance given that symptoms can impede normal daily functioning, cause significant distress and be sufficiently uncomfortable to persuade a return to use after cessation, thereby playing a significant role in maintaining dependence (Allsop et al., 2012; Budney et al., 2008; Haney et al., 2013b). Both laboratory and clinical studies demonstrate that withdrawal symptoms represent prominent risks factors that drive relapse among those trying to quit (Budney et al., 2001; Copersino et al., 2006a; Hart, 2005). Therefore, tailoring treatments to target withdrawal symptoms during a quit attempt may be one mechanism in which to maximize cannabis treatment outcomes.
1.2.9 Cannabis and Cognition

1.2.9.1 ACUTE CANNABINOID ADMINISTRATION

An abundance of evidence supports the acutely impairing effects of cannabis intoxication across a range of cognitive processes. THC-induced cognitive dysfunction appears to be most pronounced in the domain of verbal learning, and memory (Ranganathan & D’Souza, 2006). More specifically, cannabinoids have been found to impair memory encoding, consolidation, and retrieval of both verbal and nonverbal information (D’Souza et al., 2004; Ilan, Smith, & Gevins, 2004; Lane et al., 2005; Morrison et al., 2009).

For example, Hart et al (2010) found that acute intoxication resulted in significant working memory impairments, and participants who received higher doses of smoked THC (3.9%) took significantly longer to complete the task (Hart et al., 2010). Other investigators also reported worsening of memory performance following acute administration of vaporized THC (Bossong et al., 2012), oral THC (Curran et al., 2002b; D’Souza et al., 2008a) and intravenous THC (Morrison et al., 2009). Similarly, THC administered sublingually negatively affected visuospatial memory performance (Makela et al., 2006). Moreover, other evidence, in addition to that provide by Hart et al (2010), also supports a dose-dependent relationship between the amount of THC given and the magnitude of memory impairment (Curran et al., 2002a; D’Souza et al., 2008b).

Worsening of attention has also been consistently observed with the introduction of cannabis. Impairments in sustained, selective, focused, and divided attention have all been previously reported (Hunault et al., 2009; Morrison et al., 2009; Ramaekers et al., 2009). However, not all data supports this relationship. Other studies have reported no effect on auditory selective attention and concentration after of 20mg of THC was administered to regular users (O’Leary et al., 2007). Similarly, after ingesting 15mg of THC, occasional cannabis users demonstrated no worsening of sustained attention as compared to placebo (Sugarman, Poling, & Sofuoglu, 2011). Further, other research actually found significant improvements in sustained and divided attention.
attention following a dose of THC, relative to the other conditions (Haney et al., 1999; Hart et al., 2001)

In addition, impairments in inhibitory control and processing are known to occur under the influence of cannabis. This has been demonstrated using a variety of paradigms and outcomes such as increased stop reaction time, impulsive responding as well as decreased accuracy of responses (McDonald et al., 2003; Ramaekers et al., 2009; Theunissen et al., 2012). Further support comes from a 2005 study that demonstrated that acute THC administration produced measurable changes in risky decision-making under laboratory conditions (Lane et al., 2005). Contradictory evidence also exists. Two studies reported that cannabis had no behavioural effects on gambling tasks in recreational cannabis users (Ramaekers et al., 2006) or in heavy users (Vadhan et al. 2007).

The acute impairing effect of cannabis on cognition is generally a well-accepted phenomenon. Contradictory findings are likely attributable to differences in methodologies employed. One major inconsistency between studies is the drug-using history of the study sample. This is important because experienced cannabis users may be tolerant to the cognitive-impairing effects of cannabis. In line with this notion, studies have demonstrated no “further” impairing effect on cognitive function (D'Souza et al., 2008b; Hart et al., 2001). It must be mentioned that these studies did not include control samples; therefore the level of cognitive impairment of these regular cannabis users could not be quantified. This is in contrast to infrequent or naive users who may have a higher sensitivity to the cognitive-impairing effects of cannabis (Morrison et al., 2009).

1.2.9.2 LONG-TERM & NON-ACUTE EFFECTS OF CANNABINOIDS

Converging evidence supports the notion that long-term, heavy chronic cannabis use leads to cognitive dysfunction, and that these impairments persist beyond the period of acute intoxication. Chronic cannabis use is associated with deficits in verbal memory and learning, working memory, sustained attention, decrements in IQ, decision-making and inhibitory processing (Battisti et al., 2010; Harvey et al., 2007; Indlekofer et al., 2009; Pope et al., 2001; Verdejo-
Garcia et al., 2007). Other studies have failed to find differences in performance as a function of prolonged cannabis use (Gruber et al., 2012; Harvey et al., 2007; Jager et al., 2010). However these studies do provide evidence that cannabis users are working “harder” to achieve comparable performance levels to their non-using counterparts. Several neuroimaging studies demonstrate that cannabis users recruit additional brain resources as a compensatory mechanism to achieve adequate working memory performance (Jager et al., 2007; Kanayama et al., 2004).

It needs to be highlighted that the abovementioned studies are likely capturing the residual cognitive effects of cannabis or are confounded by symptoms of withdrawal. Accordingly, it is of critical importance to determine whether impairments associated with cannabis use are transitory in nature and remediate with protracted abstinence, or if dysfunction is non-reversible and permanent. To date, this remains a controversial subject. Given that cannabinoid metabolites remain detectable in urine for at least four days in light users (Fraser, Coffin, & Worth, 2002) and on average about one month in heavy users (Ellis et al., 1985), sufficient abstinence periods are required in order to bypass the residual effects of cannabinoids and assess the enduring long-term effects of use.

Pope and colleagues (2001) examined groups of former heavy cannabis users (n=45), current heavy cannabis users (n=63), and non-using controls (n=72). Participants completed a comprehensive cognitive battery at days 0, 1, 7, and 28 over a period of supervised abstinence. Findings revealed that current users performed more poorly than controls on the Buschke Selective Reminding Test, a measure of verbal learning and memory retention and retrieval. However, these differences were only observed on days 0, 1, and 7, with no significant differences detected at day 28. Findings suggest that cannabis-induced deficits may remediate with at least one month of abstinence (Pope et al., 2001). Notably, this study may have been confounded by lack of control for tobacco, as there were disproportionate numbers of cigarette smokers across the three groups, with controls reporting no use. Given that tobacco may influence cognitive performance (Levin & Rezvani, 2000), it is problematic that use across group was differed. In line with these results, Fried et al (2005) demonstrated that while increasing cannabis use correlated with a decline in global IQ, visual processing speed, and both immediate and delayed memory in current cannabis users, no such deficits were observable when individual remained cannabis-free for at least 3 months (Fried, Watkinson, & Gray, 2005). Lastly, in a
meta-analysis that included studies in which cannabis users had sustained abstinence for at least 25 days, reported that cannabis was not associated with persistent cognitive dysfunction (Schreiner & Dunn, 2012).

However, other investigators argue that cannabis-induced cognitive deficits are not reversible. Bolla et al (2002) examined a sample of 22 non-treatment-seeking heavy cannabis users who underwent 28 days of supervised abstinence (Bolla et al., 2002). The study concluded that memory deficits were persistent and dose-dependent, in that higher frequencies of cannabis use were correlated with poorer performance across executive functions, inhibitory control, and psychomotor speed. In line with these findings, a study examining cannabis users who were abstinent from 6 weeks to 2 years found significant impairments persisted in domains of selective attention and concentration (Solowij, 1995). In a study using an adolescent sample, cognitive functioning was assessed in 31 cannabis users and 34 non-using controls following ≥23 days of monitored abstinence (Medina et al., 2007). After controlling for alcohol use and depressive symptoms, abstinent adolescent cannabis users demonstrated poorer complex attention, sequencing ability, and verbal story memory, and slower psychomotor speed compared to controls. Moreover, greater lifetime cannabis use was associated with poorer performance in these cognitive domains, even after controlling for lifetime alcohol use. Similarly, Tapert and colleagues (2007) initiated a 28-day monitored abstinence period among cannabis-using adolescents and evaluated response inhibition and blood oxygen level dependent (BOLD) response using fMRI. Post-abstinence, results revealed deficits in select cognitive domains in cannabis users such as verbal fluency and memory (Tapert et al., 2007). While performance on inhibition and motor impulsivity tasks were intact in cannabis users, these individuals showed increased BOLD response during both inhibitory and non-inhibitory trials of a go/no-go task compared to controls. Therefore, adolescent cannabis users appear to recruit more neural tissue for executive control (dorsolateral prefrontal and parietal areas) in order to adequately perform the task, suggesting the use functional compensation processes (Tapert et al., 2007). In the largest prospective longitudinal study to date, Meier et al (2012) reported that individuals who began using cannabis early in their teenage years never fully returned to their predicted pre-drug exposure IQ trajectory following reduction of use or complete abstinence (>1 year cessation in some cases).
Taken together, evidence not only suggests that cognitive impairments develop as a result of prolonged cannabis use, but that deficits worsen with increasing years of use (Bolla et al., 2002; Fried, Watkinson, & Gray, 2005; Pope et al., 2001). Impairments tend to develop gradually and may only become clinically significant and detectable by standard neuropsychological tests after one to two decades of cannabis use (Solowij et al., 2002b), suggesting that duration of cannabis consumption is a significant determinant of cognitive impairment (Solowij et al., 2002b). An abundance of evidence also suggests that timing of cannabis onset is a critical factor. For one, earlier use is associated with greater propensity of persistent use and of developing dependence (Meier et al., 2012). In addition, specific structural and functional changes occur in the adolescent brain to produce greater cognitive efficiency, this includes synaptic pruning, increases in myelination and maturation of neurotransmitter systems (Durston et al., 2001; Eggan & Lewis, 2007). Further, preclinical data demonstrates that CB1R peak in adolescence in areas such as the PFC, hippocampus, basal ganglia and cerebellum (Rodriguez de Fonseca et al., 1993). Therefore, given that neurodevelopment continues throughout adolescence, teenagers may be more vulnerable and sensitive to certain neurological consequences associated with cannabis compared to adults namely altered brain development and enduring cognitive changes (Gruber et al., 2012; Pope et al., 2003).

As with studies assessing the acute cognitive effects of cannabis, there is also wide variation in the methodologies employed in studies assessing the cognitive effects of long-term cannabis use. For example, studies included heterogeneous sample, in which participants differed greatly in the severity of their cannabis use/misuse. In addition, there was a lack of control for confounding variables (i.e., co-morbid substance use, tobacco use). Lastly, the length of abstinence period was not consistent between studies. This is an important factor to explore in its entirety, as different durations of abstinence will help to characterize the window of cognitive recovery among individuals who discontinue use, and will help to clarify if and when cognitive remediation occurs.
1.2.10 Cannabis and Substance Co-Use

Studies report that up to 90% of cannabis users are also tobacco smokers (Agrawal, Budney, & Lynskey, 2012; Amos et al., 2004). Rates of co-use of other substances such as alcohol (33.3–45.7%), cocaine (37.5–42.9%), stimulants (30.0–51.7%), and hallucinogens (35.6–41.7%) occur at lower rates (Barrett, Darredeau, & Pihl, 2006; Richter et al., 2002). This suggests that tobacco and cannabis may possess unique properties that render them more likely to be used in combination as opposed to the co-use of other substances (Agrawal, Budney, & Lynskey, 2012; Coffey et al., 2003).

1.2.10.1 CANNABIS AND TOBACCO

Neurobiological mechanisms have been proposed to explain the link between tobacco and cannabis co-use, as outlined in a recent review from our laboratory (Rabin & George, 2015). For example, there is overlap in the distribution of nicotinic and cannabinoid receptors in the brain (Viveros, Marco, & File, 2006) and these receptors may interact to enhance reinforcement compared to that of each drug independently (Valjent et al., 2002). Furthermore, clinical studies suggest that tobacco use contributes to an increased number of cannabis dependence symptoms (Agrawal & Lynskey, 2009; Ream et al., 2008) and tobacco smokers have greater odds of cannabis relapse as compared to non-smokers (de Dios et al., 2009). Co-use may also serve to counterbalance aversive states induced by the other substance (Rabin & George, 2015). Common route of administration (inhalation) may also contribute to high rates of co-use (Agrawal & Lynskey, 2009) by “cuing” use of the other substance (Moore & Budney, 2001). Co-use is worrisome given that tobacco is a partial driver of cannabis dependence (Hindocha et al., 2015) and tobacco use can hinder cessation outcomes in individuals attempting to quit cannabis (Haney et al., 2013a).

Interestingly, results from a recent national U.S survey reported that co-use of cannabis and tobacco among adults increased between 2003–2012 (Schauer et al., 2015). It is thought that this rise reflects increases in the prevalence of cannabis use among tobacco users, rather than increases in tobacco use among cannabis users (Schauer et al., 2015). Therefore, in light of
pending policies to legalize cannabis, and predicted increases in cannabis consumption it will be
critical to monitor tobacco use in conjunction with cannabis use.

1.2.11 Cannabis Treatments

While cannabis is not popularly seen as addictive, there are an increasing number of cannabis
users seeking treatment for their use. Approximately 25% of patients presenting for substance
use treatment are those with problematic cannabis use (UNODC, 2012). Currently there are no
recognized or approved pharmacotherapies to treat cannabis dependence. Existing treatments for
cannabis use disorder involve psychosocial interventions. However, only ~20% of patients
achieve continuous abstinence (Allsop et al., 2014), thereby highlighting the need for improved
and more efficacious treatments

With respect to behavioural interventions, cognitive behavioural therapy (CBT), Motivational
Interviewing, Contingency Management and their combinations have received the most
attention. CBT focuses on providing the necessary skills to achieve abstinence, prevent relapse
and cope with various stressors and high-risk situations. Motivational Interviewing is a non-
confrontational approach that aims to build motivation to reduce drug use by addressing
ambivalent feelings which may in turn trigger and strengthen motivation for behavioural change
(Miller WR, 2002). Lastly, contingency management involves the systematic use of positive and
negative reinforcements, either monetary or voucher-based following the demonstration of a
“target” behaviour.

Evidence from a series of controlled clinical trials for CUDs suggests that the combination of
CBT and MET renders higher rates of abstinence compared to a delayed treatment option [See
(Budney et al., 2007)]. Even more successful outcomes are observed when abstinence-based
contingency management is added to MET-CBT. Five trials have demonstrated enhanced rates
of cannabis abstinence when integrating these approaches (Budney et al., 2000; Budney et al.,
2006; Carroll et al., 2006; Kadden et al., 2007; Stanger et al., 2009). A meta-analysis of 46
psychosocial treatments revealed that, while all interventions were modestly efficacious, no
intervention was particular superior to the others (Waldron & Turner, 2008).
The establishment and acceptance of the CWS and a better understanding of the eCB system has led to a surge in the number of medications being tested as potential pharmacotherapies for cannabis dependence. Many laboratory studies and a few clinical trials have been conducted to examine cannabinoid agonists, antagonists as well as other non-cannabinoid approaches to target cannabis dependence. For example, under laboratory conditions, bupropion, divalproex, and nefazodone were shown to worsen or had no effect on most cannabis withdrawal symptoms (Haney et al., 2004; Haney et al., 2003; Haney et al., 2001) while others (mirtazapine and quetiapine) substantially reversed withdrawal-related disruptions, but failed to reduce relapse rates (Cooper et al., 2013; Haney et al., 2010). Similarly, dronabinol, an oral synthetic agonist of delta-9-tetrahydrocannabinol (THC), reduced a subset of withdrawal symptoms but did not alter cannabis use (Haney et al., 2004). Notably, nabilone, a more potent THC analog, robustly decreased cannabis withdrawal symptoms as well as relapse rates without concurrently increasing sedation or intoxication. Moreover, among those who did relapse, nabilone reduced cannabis consumption (Haney et al., 2013b). Superior efficacy observed with nabilone over dronabinol may be due to its higher bioavailability and longer duration of action (Bedi, Cooper, & Haney, 2013). Some preliminary research using N-acetylcysteine, an antioxidant that has modulatory effects on glutamatergic transmission demonstrates promising results. N-acetylcysteine was evaluated in a randomized controlled study with adolescent cannabis users and was reported to be more effective than placebo in reducing cannabis use (Gray et al., 2012). Gabapentin is an alkylated analog of GABA and is an approved compound for the management of epileptic seizures and neuropathic pain, and has also shown promise in treating cannabis dependence. Mason et al (2012) demonstrated that individuals receiving gabapentin (1200 mg/day) over a 12-week period compared to placebo had decreased levels of cannabis as measured by self-report and negative urine toxicology. Gabapentin also reduced withdrawal symptoms including depressive symptoms, cravings and sleep. Moreover gabapentin was also associated with significantly greater improvement in overall performance on tests of executive function. Given that gabapentin was associated with an acceptable safety profile (Mason et al., 2012), suggests that it may be one of the most promising treatments for cannabis dependence studied to date.

Treatment of cannabis dependence is particularly challenging and unfortunately the demand for treatment has far outpaced the development of effective treatment strategies. Clearly more
research in the area of pharmacotherapies is warranted. Testing new treatment modalities is critical. One avenue of potential research is testing modifications to existing treatments and testing combinations of existing treatments in the hope that combining therapies might increase their efficacy.

1.3 Schizophrenia & Cannabis

1.3.1 The Cannabis-Psychosis Link

There is an extensive body of literature examining the link between cannabis use and the subsequent development of psychotic illnesses such as schizophrenia. While ample evidence supports the hypothesis that cannabis is a component cause of schizophrenia, this etiological theory remains a highly controversial topic.

One of the first, most comprehensive and largest study to investigate the link between cannabis use and schizophrenia was the Swedish Conscript Study, published in 1987 (Andreasson et al., 1987). The investigators found that men (N = 50,053) who had smoked cannabis by the age of 18 had double the risk of developing schizophrenia. In addition, individuals who had smoked cannabis on at least 50 occasions were six times more likely to receive a later diagnosis of schizophrenia. Further analysis of this data revealed that cannabis is indeed an independent risk factor for schizophrenia, and that this relationship is not mediated by the use of other psychoactive substances (Zammit et al., 2002). In another influential study, a birth cohort of 1,034 children born in Dunedin, New Zealand, were asked about their drug consumption at the ages of 15 and 18, and 26 (Arseneault et al., 2002). Among those who had used cannabis by the ages of 15 or 18 reported significantly more psychotic symptoms at 26 compared with non-users. Furthermore, at 26, 10% of those who used cannabis by the age of 15 had received a diagnosis of schizophreniform compared with 3% of non-cannabis-users. In a systematic review that included 7 cohort studies, Moore and colleagues (2007) reported an increased risk (odds ratio = 1.4) of any psychotic outcome in individuals who had ever used cannabis (Moore et al., 2007). Findings
were consistent with a dose-response relationship of cannabis, with greater risk in those who used cannabis more frequently. Notably, this meta-analysis only included studies that adjusted for confounding variables such as other substance use, personality traits, sociodemographic characteristics, intellectual functioning, and other mental health problems. Further, when two later studies were included into the analysis [(Gage et al., 2014; Rossler et al., 2012)], the updated pooled odds ratio remained comparable (odds ratio = 1.46) (Gage, Hickman, & Zammit, 2015).

Converging evidence suggests that the association between cannabis use and risk of psychosis is reported to be higher among those that initiate cannabis in early adolescence, when critical neurodevelopmental processes are occurring (Spear, 2000). For example, Arseneault et al (2002) showed that the onset of cannabis use before the age of 15 years was associated with a greater risk of developing schizophreniform at age 26 years compared with onset of cannabis use at a subsequent age. This finding was replicated in a prospective longitudinal study that found cannabis use at age 18 and 21 led to higher rates of psychotic symptoms, 3.7 and 2.3 respectively (Fergusson, Horwood, & Swain-Campbell, 2003). Moreover, results from a meta-analysis concluded that age of onset of psychosis was about 2.7 years earlier among cannabis users as compared to alcohol users (Large et al., 2011). In support, a later study that controlled for other substance use found that age at onset of cannabis use was directly associated with age at onset of psychosis and age at first hospitalization (Galvez-Buccollini et al., 2012). Furthermore, cannabis has also been shown to increase the rate of conversion to psychosis in individuals who are deemed to be at high clinical risk for psychosis (Kristensen & Cadenhead, 2007).

Lastly, a 2014 study suggested that earlier cannabis initiation, greater frequency of use, and the more potent the cannabis is, the greater the risk of psychosis (Di Forti et al., 2014).

A consistent pattern of association appears to emerge between cannabis use and psychosis, which could be indicative of a causal relationship. Findings suggest that regular cannabis use predicts an increased risk of developing schizophrenia, and the relationship persists after controlling for potential confounding variables. A common recurrent theme that appears in this thesis is that cannabis use introduced in adolescence may be more dangerous than adult onset cannabis use given that adolescence represents a critical phase of brain development (Bossong & Niesink, 2010). The eCB system plays an important role in fundamental neurodevelopmental and
neuromaturational processes such as progressive and regressive changes in myelination and synaptic pruning, as well as neurogenesis (Realini, Rubino, & Parolaro, 2009). Therefore cannabis-induced changes in eCB activity during adolescence, might lead to disrupted and enduring neurobiological changes that can alter neural circuitry, functions and behaviour.

This led to the proposition that alterations in the eCB system induced by cannabis during the adolescent developmental window might represent a salient risk factor for developing schizophrenia (Malone, Hill, & Rubino, 2010).

However, despite the robust link between cannabis use and psychosis, most cannabis users do not develop psychosis. If cannabis is in fact “causing” schizophrenia, then it would be expected that the incidence of schizophrenia would increase at the same rate as any increases in cannabis consumption. Given that no direct correlation is observed (Degenhardt, Hall, & Lynskey, 2003b) suggests the presence of a third variable. That is, cannabis may precipitate schizophrenia in persons who are susceptible to the disorder as a result of underlying vulnerabilities (Henquet et al., 2005; van Os et al., 2002; Verdoux et al., 2003). This hypothesis is consistent with a stress–diathesis model of schizophrenia (Der, Gupta, & Murray, 1990).

There is evidence to suggest that cannabis use interacts with an underlying genetic vulnerability to increase the risk for developing schizophrenia. For example, catechol-o-methyltransferase (COMT) is an enzyme involved in the metabolism of synaptic dopamine. A common single nucleotide polymorphism in COMT at codon 158, results in valine (Val) instead of methionine (Met). Notably, this variant is associated with a substantial decrease in enzymatic activity and has been associated with increased levels of dopamine in the PFC (Lachman et al., 1996; Lotta et al., 1995). Interestingly, in a study of over 800 individuals, Caspi et al (2005) found that those that were homozygous for the Val allele showed increased risk for developing schizophreniform disorder and exhibiting psychotic symptoms if they had used cannabis in adolescence (odds ratio =10.9) (Caspi et al., 2005). Variations in the AKT1 gene have also been proposed to interact with cannabis to mediate the effects of psychosis (Di Forti et al., 2012; van Winkel et al., 2011). In the absence of a well-defined etiology of schizophrenia, the identification of such component causes may help to elucidate the neurophathophysiology implicated in schizophrenia.
Taken together, this suggests that underlying genetic liability for schizophrenia may only become expressed in the context of exposure to relevant environmental risk factors, such as cannabis. In addition, dose, duration of exposure, and the age of first cannabis use may further moderate the risk of developing the disorder.

1.3.2 Prevalence of Cannabis in Schizophrenia

A history of cannabis use is more prevalent in schizophrenia than in the normal population. Lifetime use has been reported to be as high as 64.4% (Barnes et al., 2006), rendering it the most commonly used illicit drug among patients. In comparison to the estimated 2% of individuals in the general population, approximately 33% of patients with schizophrenia and other psychoses are daily cannabis users (Jablensky, 2000). A meta-analysis conducted in 2010, found that approximately one in four schizophrenia patients was diagnosed with a CUD (Koskinen et al., 2010). CUDs were especially common in younger and first-episode patient samples as well as in samples with high proportions of males.

1.3.3 Mechanisms by which Cannabis may Trigger Psychotic, Negative and Cognitive Symptoms

As previously mentioned, acute cannabis intoxication can produce a range of transient psychotomimetic effects, negative symptoms and cognitive deficits that strikingly resemble symptoms associated with schizophrenia (D'Souza et al., 2004; Solowij & Michie, 2007), thereby suggesting the involvement of similar and overlapping neurobiological substrates (Rabin et al., 2014). While the exact biological mechanisms by which cannabinoid exposure increases the risk of developing a psychotic disorder remain unknown, multiple hypotheses for such pathways have been proposed.

An abnormality in dopamine transmission, particularly in striatal regions, is considered to be a common and prominent abnormality that may explain the presence of psychotic symptoms in schizophrenia (Davis et al., 1991; Howes & Kapur, 2009). There are multiple lines of evidence
implicating and association of cannabinoid administration and dopaminergic functioning. For one, there are close interactions between the eCB and dopaminergic systems (Tanda, Pontieri, & Di Chiara, 1997). Accordingly, data suggests that CB1Rs and dopamine (D1 or D2) receptors are co-localized in several brain regions (Hermann, Marsicano, & Lutz, 2002), and can interact at the level of G-protein/adenylyl cyclase signal transduction in these regions (Meschler & Howlett, 2001). Moreover, psychotic disorders involve disturbances in dopamine neurotransmitter systems (Carlsson, 1988) and cannabis increases dopamine release (Pistis et al., 2001). Excessive cannabis-induced stimulation of CB1Rs can lead to increased dopamine synthesis, release, firing rate, receptor number and/or affinity, and turnover (Banerjee, Snyder, & Mechoulam, 1975; Pertwee, 2005). There is also evidence that exogenous cannabis disrupts the eCB system resulting in excess dopaminergic transmission in the mesolimbic tract (Cheer et al., 2004; Diana, Melis, & Gessa, 1998). Given that dopamine transmission in the mesolimbic region has been associated with transient worsening of positive symptoms (Laruelle & Abi-Dargham, 1999), provides an explanation for cannabis-mediated increases in psychotic symptoms in healthy individuals who use cannabis, and may also account for the increased sensitivity of schizophrenia patients to the psychotomimetic effects of cannabis (D'Souza et al., 2005; D'Souza et al., 2004).

The psychosis-inducing effects of cannabis have also been explained using an “abnormal salience theory” in which THC leads to an increase in strange experiences which are then often misinterpreted (Kapur, 2003). It is thought that the chaotic and stimulus-independent release of dopamine in the brain is linked to the formation of psychotic symptoms. The untimely firing of dopaminergic neurons to trivial everyday events results in increased attention and attribution of excessive motivational significance to these irrelevant stimuli (Kapur, 2003). Hallucinations and delusions may consequently arise from cognitive explanations for these altered experiences.

CB1R-expressing GABA neurons are instrumental in orchestrating pyramidal cell synchrony in the gamma (40 Hz) frequency range (Hoffman et al., 2001; Traub et al., 1996) and these oscillations mediate perceptual, as well as cognitive processes [see (Wilson & Nicoll, 2002)]. Activation of presynaptic CB1Rs on GABAergic hippocampal neurons lead to a decrease in GABA release (Freund, Katona, & Piomelli, 2003), causing a reduction in the power of hippocampal network oscillations (Hajos et al., 2000). Such events will disrupt the
synchronization of pyramidal cell activity and interfere with memory consolidation, and normal gating mechanisms, bringing about both cognitive and psychotic symptoms (D'Souza, Sewell, & Ranganathan, 2009; Hoffman & Lupica, 2000; Wilson & Nicoll, 2002). Notably, cannabis administration is also associated with changes in other neurophysiological measures that may, in part, facilitate these symptoms including P50 suppression, mismatch negativity and the P300 potential (Gallinat, Rentzsch, & Roser, 2012).

The mesocortical dopamine projection from the VTA to the PFC, is integral for the intact functioning of the PFC (Tzschentke, 2001). While acute cannabis administration can potently increase frontal cortical dopamine metabolism and release (Jentsch et al., 1997), repeated exposure to cannabis can trigger adaptive change that decreases dopamine release in the PFC, but not in other dopamine-rich areas such as the NAcc or dorsolateral striatum (Verrico, Jentsch, & Roth, 2003). This provides a conceivable mechanism for understanding how chronic cannabis use may induce cognitive and negative symptomatology. Negative symptoms are associated with disturbances in frontal networks as well as in striatal regions (Bloomfield et al., 2014; Wolkin et al., 1992). Cannabis-induced dopaminergic transmission irregularities are also thought to mediate negative symptoms. For example, a recent study examined the association of dopamine synthesis capacity with the Apathy Evaluation Scale in 14 heavy cannabis users. A significant inverse correlation emerged between dopamine synthesis capacity (measured using [18F]–DOPA PET scan) and apathy, a key feature of the ‘amotivational syndrome’ (Bloomfield et al., 2014). Interestingly, evidence suggests that there is an optimal level of dopaminergic activity for intact cognition, such that too much or too little activity in the PFC can compromise cognitive performance especially with respect to working memory (Goldman-Rakic, 1995; Goldman-Rakic, Muly, & Williams, 2000; Zahrt et al., 1997).

Taken together, these neurobiological mechanisms provide support for a causal link between cannabis use and the subsequent development of schizophrenia-like symptoms. The abundance of research examining the robust association between cannabis use and schizophrenia has led to the proposition of a “cannabinoid hypothesis” of schizophrenia (Muller-Vahl & Emrich, 2008).
1.3.4 Does Cannabis Exacerbate Schizophrenia Symptoms?

Given the range of adverse effects cannabis exerts in terms of brain functioning, and its role in precipitating a psychotic disorder, one may intuitively expect that cannabis further exacerbates positive, negative and cognitive symptoms in patients with schizophrenia. However, whether cannabis exposure exerts a negative impact on clinical outcomes is a key question that will be addressed in the remaining sections.

1.3.4.1 SELF-MEDICATION HYPOTHESIS

Self-medication has been one theory commonly proposed to explain the high rates of cannabis use among schizophrenia patients. The self-medication hypothesis posits that patients use substances in order to alleviate undesirable symptoms associated with the primary illness (i.e. depression, anxiety, negative symptoms) or attenuate side effects from medications used to treat the disorder (Khantzian, 1985). Nevertheless, existing data does not find strong support for this hypothesis (Chambers, Krystal, & Self, 2001). For example, an important argument against reversed causality is an “order-effect”. That is, cannabis use often occurs before the onset of psychotic symptoms and diagnosis of schizophrenia, rather than vice versa (Degenhardt et al., 2007; Linszen, Dingemans, & Lenior, 1994). In addition, cannabis use is associated with symptomatic exacerbation, rather than symptomatic relief (D'Souza et al., 2005; Linszen, Dingemans, & Lenior, 1994). Moreover, one study showed that daily fluctuations in positive, negative and dysphoric symptoms were not influenced by the extent of cannabis use in patients with schizophrenia (Hamera, Schneider, & Deviney, 1995). Further evidence comes from a cohort study from Greece that examined the self-medication hypothesis by testing whether subtle psychotic experiences with a distressing component would have stronger associations with cannabis than psychotic experiences without distress. Findings supported stronger associations between cannabis and psychotic experiences in the absence of distress, making self-medication an unlikely explanation (Stefanis et al., 2004). Lastly, a study that investigated reasons for cannabis use among patients using a longitudinal design also concluded that there is little evidence to support this theory. The data indicated that first episode patients at each time-point over the one-year follow-up endorsed ‘psychological enhancement’ as the principle reason for
their cannabis use, followed by social reasons (Kolliakou et al., 2015). These motives were rated higher than motives related to reducing positive symptoms and/or attenuating side effects associated with antipsychotic medication. In sum, there is little evidence to support the beneficial effects of cannabis used to self-medicate symptoms associated with schizophrenia.

1.3.4.2 CLINICAL COURSE, POSITIVE & NEGATIVE SYMPTOMS

Studies employing cross-sectional designs have shown that cannabis use is one of strongest predictors of a psychotic relapse in schizophrenia patients (Linszen, Dingemans, & Lenior, 1994). Non-compliance and reduced effectiveness of antipsychotic medication have also been associated with cannabis use in individuals with schizophrenia (Barrowclough et al., 2013; Bowers et al., 1990; Swartz et al., 2008). Other cross-sectional data indicate that cannabis users experience more severe psychotic and positive symptomatology than their non-using counterparts (Addington & Addington, 2007; Negrete et al., 1986; Peralta & Cuesta, 1992). In line with these results, a meta-analysis of cross-sectional studies by Yucel et al (2012) demonstrated that cannabis-using first episode patients and schizophrenia patients experienced higher positive symptom scores compared to non-using patients. A subsequent meta-analysis by our group replicated this finding, and given that we controlled for other SUDs, suggests that this association was indeed driven by cannabis use, and not a result of other drug use (Rabin, Zakzanis, & George, 2011). In contrast, in these meta-analyses, no differences in negative symptoms scores were found between cannabis users and non-users (Rabin, Zakzanis, & George, 2011; Yucel et al., 2012). Interestingly, other cross-sectional studies reported less severe disorganized symptoms and attenuated negative symptomatology in cannabis users compared to non-users (Bersani et al., 2002; Compton, Furman, & Kaslow, 2004; Peralta & Cuesta, 1992).

In 2008 Zammit and colleagues conducted a systematic review of 13 longitudinal studies to examine the strength of association between cannabis use and clinical outcomes (Zammit et al., 2008). The study concluded that cannabis use was consistently associated with increased rates of relapse, rehospitalisation, decreased treatment adherence and poorer psychosocial functioning. Associations between cannabis use and psychotic symptoms and other
psychopathology scores were more variable. Only three (of the included 8) studies presented
evidence of associations between cannabis use and increased positive symptoms (Caspari, 1999;
Degenhardt et al., 2007; Grech et al., 2005) and one study reported an association between
cannabis and decreased negative symptoms (Horcajadas, 2002).

Since 2008, many other researchers sought to disentangle the complex relationship between
cannabis and psychopathology. Foti et al (2010) examined the relationship between cannabis use
and the course of illness in schizophrenia over a 10-year period following first psychiatric
hospitalization. The authors observed that cannabis users suffer from more depressive and more
severe psychotic symptoms, with the latter relationship being bidirectional. That is, cannabis
exposure predicted severity of psychosis, and individuals with more severe psychotic
symptoms were more likely to use cannabis in the future (Foti et al., 2010). In another study,
不同的 patterns of cannabis use were identified in a large sample of patients diagnosed with a
psychotic disorder (N=678), and the impact of cannabis use on clinical and functional outcomes
was assessed (van der Meer et al., 2015). Persistent users were found to have more positive and
general symptoms, psychotic relapses and worse global functioning compared to non-users and
discontinued users. Notably, data also suggested that cannabis’ negative impact might be
reversible given that improvements were observed when patients ceased cannabis use (van der Meer et al., 2015). More recent data suggests that while level of cannabis use was not associated
with delusions, hallucinations, negative symptoms or daily functioning in first-episode patients,
those who reduced or stopped using cannabis experienced greater clinical symptom
improvements over a one-year follow-up period compared with continued users and non-users
(Stone et al., 2014).

In contrast, Barrowclough et al (2013) reported no association between changes in cannabis dose
and changes in severity of positive symptoms, even when patients became abstinent. However,
lack of an association may be due to the confounding use of other substances. While cannabis
use patterns may have changed, it is unclear whether alcohol or other illicit drug use followed
similar trajectories and thus may have prevented or masked symptom improvement. Other
studies also lacked support for a relationship between cannabis and symptomatology. A
prospective follow-up study demonstrated that while patients with schizophrenia with co-morbid
cannabis use were more frequently hospitalized than non-cannabis using patients, they two
groups did not differ with respect to severity of psychopathology (van Dijk et al., 2012).
Similarly, greater cannabis consumption was associated with worse psychosocial functioning,
but did not correlate with psychotic symptom severity (Barrowclough et al., 2013). In support,
other longitudinal studies also failed to find relationships between cannabis use and clinical
symptomatology, which included depression (Degenhardt et al., 2007; Faber et al., 2012;
Gonzalez-Pinto et al., 2011; Stirling et al., 2005).

Taken together, research to date on the effects of cannabis use on clinical outcomes in
schizophrenia presents a confusing picture as results reported are inconsistent (Zammit et al.,
2008). Reasons for the lack of consistent findings may be due to the methodological variation
between studies and failure to control for a host of confounding variables that are associated with
poor outcome and cannabis use (i.e., sex, sociodemographic factors, medication adherence). In
addition, most studies did not examine heavy, chronic cannabis consumption, but rather light or
inconsistent use, and most studies did not include a measure of biochemical verification of
cannabis use (or lack of use for non-users). Few studies adjusted for baseline illness severity and
level of functioning, and most made no adjustment for alcohol, or other illicit substance use
(Zammit et al., 2008). In addition, given that attrition rates in cohort studies tend to be greater for
individuals who have more severe mental health problems and for those with SUDs, results from
longitudinal data may in fact be an underestimation of cannabis’ true impact (Zammit et al.,
2008). To help clarify such relationships, well-controlled laboratory studies are needed.

In 2005, D’Souza et al (2005) conducted an elegant laboratory study to examine the effects of
THC in patients with schizophrenia who had minimal prior exposure to cannabis. Results
demonstrated increases in positive and general PANSS scores. Interestingly, negative PANSS
scores increased in a dose-dependent manner. Participants were reported to be more blunted, less
talkative, less spontaneous, and more internally preoccupied with higher doses (D'Souza et al.,
2005). While this study provides a clear presentation of the acute effects of THC, effects of long-
term and persistent cannabis use cannot be inferred from such a design.
While cognitive impairment is inherent to schizophrenia (Keefe, Eesley, & Poe, 2005), the moderating role of cannabis on cognitive function in patients remains unclear. This relationship is imperative to understand given that these impairments represent reasonable targets for treatment in order to improve functional outcome (Green, 1996).

Thus far, this thesis has reviewed evidence demonstrating cannabis’s influence on neurodevelopmental processes, neurochemical functioning and its role acting as a catalyst to precipitate the development of schizophrenia. Theoretically, one may then expect cannabis to exacerbate cognitive dysfunction in patients with schizophrenia. However, two recent meta-analyses, including one from our group (see Appendix A) demonstrated better cognitive function among cannabis-using patients with schizophrenia compared to non-using patients (Rabin, Zakzanis, & George, 2011; Yucel et al., 2012). Of note, the magnitude of the observed effect sizes was in the small to moderate range (0.00-0.67). A number of hypotheses have been put forward to explain these paradoxical pro-cognitive effects. First, cannabinoids may have the capacity to directly enhance cognition by increasing blood flow, metabolic processes, and neurotransmission in the PFC (Cohen, Solowij, & Carr, 2008; Coulston, Perdices, & Tennant, 2007a; Jentsch et al., 1997). While this theory may help to explain the acute effects of cannabis on cognition, it fails to extend support for the long-term effects associated with chronic and repeated cannabis administration (Verrico, Jentsch, & Roth, 2003). Clinical and non-clinical studies also provide evidence that cannabis may possess neuroprotective and neurogenerative properties, which may exert a positive effect on cognitive function (Hampson et al., 2000; Jiang et al., 2005). Solid evidence for these hypotheses is lacking.

Conversely, most scientists would agree that better cognitive performance among cannabis-using patients is a primary phenomenon, and not a result of cannabis use. That is, patients with comorbid CUDs may belong to a subgroup of schizophrenia whereby they encompass better premorbid adjustment and IQ, and overall prognosis (Dixon et al., 1991; Ferraro et al., 2013). These drug-seeking individuals may possess social skills that enable them to navigate in drug scenes and allow them to facilitate the purchase and acquisition of illegal substances (Arndt et al., 1992). These characteristics have been associated with better social cognition and higher
cognitive capacities among persons with schizophrenia (Arnold et al., 2015; Silverstein, Mavrolefteros, & Close, 2002). However, this theory may not be specific to cannabis per se but may extend to all illicit substances in general. It has also been proposed that the preserved cognitive performance of cannabis-using patients reflects a lower vulnerability for psychosis and represents a developmental trajectory in which cannabis use is required to trigger psychosis (Schnell et al., 2009). Thus, those who develop psychosis in the context of cannabis use have better cognition as a result of fewer neurodevelopmental risk factors and better prognostic features compared to individuals who develop the disorder from a different etiological pathway (Leeson et al., 2011; Loberg et al., 2014). In other words, cannabis may promote transition to psychosis that may not have otherwise occurred. Other support for this view comes from studies that demonstrate that patients who have used cannabis have fewer neurological soft signs (Ruiz-Veguilla, Callado, & Ferrin, 2012) and more intact MRI scans (Cunha et al., 2013) than those who have not.

Evidence for superior cognitive function among cannabis-using patients appears to outweigh the number of studies demonstrating negative effects of cannabis use on cognition in schizophrenia, yet the data for a further deteriorating effect is considerable. For example, a well-controlled laboratory study by D’Souza and colleagues (2005) characterized the effects of intravenous THC using a double-blind, randomized, placebo-controlled design. The effects of 0 mg, 2.5 mg and 5 mg of THC were compared in 13 stabilized patients with schizophrenia and 22 healthy controls. Cognitive assessments began 30 min after the administration of THC or placebo. Patients with schizophrenia as well as healthy controls demonstrated dose-dependent impairments in verbal memory and attention compared to those on placebo. Moreover, the schizophrenia group performed worse than the control group in these domains, demonstrating an increased sensitivity to the effects of THC on cognition. These results are in line with other studies that report deficits in verbal memory and attention in cannabis-using patients as compared to non-using patients (Lev-Ran et al., 2012; Ringen et al., 2010). Another study using a first-episode sample concluded that cannabis abuse is associated with decision-making impairment, but not working memory and executive function impairment (Mata et al., 2008). In another study, cannabis use was associated with deficits in social cognition, however other cognitive outcomes were independent of patterns of cannabis use (Sanchez-Torres et al., 2013). Other studies too support the absence of significant difference between cannabis-using and non-using patients (Bahorik, Newhill, &
Eack, 2013; Scholes & Martin-Iverson, 2010; Sevy et al., 2007). Power et al 2015 posited that any observed association between cannabis and cognition might be accounted for by residual confounding factors. In their study of 1237 patients diagnosed with a psychotic disorder, they found that there were no differences in current cognitive performance between non-cannabis users and those with a lifetime history of cannabis use or dependency, after controlling for age and age at onset of illness (Power et al., 2015). However, it should be noted that the study only assessed a limited number of cognitive domains (premorbid IQ and information processing). In line with this notion, after adjusting for premorbid functioning, Ringen et al (2013) found that the presence of cannabis in urine was not associated with levels of cognitive functioning.

The studies reviewed here differ greatly in the methodologies employed and many failed to statistically control for potential confounding variables. There is clearly no consistency between studies and there is even a lack of internal consistency within studies (i.e. between participants). The following variables represent potential sources of variability and likely account for the contradictory findings reported in the literature.

**Defining a Cannabis User**

The approach in which cannabis-users and non-users are characterized in this body of literature is diverse and varied. Several researchers define the cannabis-using group according to the diagnostic standards of the DSM wherein all participants enrolled met for a diagnosis of a CUD (DeRosse et al., 2010; Kumra et al., 2005; Schnell et al., 2009). However, many of the other studies characterized the cannabis-using sample according to simple and arbitrary cut-off parameters. Some studies’ inclusion criteria for the cannabis-using group had minimum usage requirements that ranged from weekly use in the last year (Mata et al., 2008), up to a 0.5g per day minimum over the last two years (Jockers-Scherubl et al., 2007). While other studies defined their cannabis-using groups using a binary approach. That is, participants were classified as either users or non-users without any other refining criteria (Ringen et al., 2010; Scholes & Martin-Iverson, 2010). No other variable (such as impact on functioning, amount of cannabis, frequency or duration of use) was taken into account.

The comparative cannabis-naïve group was more uniform across studies. In most studies, they were defined as the absence of a DSM CUD diagnosis. Yet, using this term alone may be
misleading as it is apt to include occasional cannabis users and more frequent or heavy users whose functioning is not affected (DeRosse et al., 2010). Jockers-Scherubl et al. (2007) overcame this inadequacy by further stipulating that participants in the non-using group could not have used cannabis on more than five occasions in their lifetime. Others have since adopted this criteria as well (Schnell et al., 2009).

What is most troubling and problematic about this lack of consistency is that the manner in which some authors defined a “user” corresponded to how other studies defined their non-using group. For example, Ferraro et al (2013) examined premorbid IQ among ever users, in other words patients who had used cannabis at least one time. Yet, such criteria would be used to classify many non-users among other studies [i.e. (Jockers-Scherubl et al., 2007; Rabin et al., 2013; Yucel et al., 2012)].

The practice of combining current and former cannabis users to comprise the cannabis-using group seems to be the rule rather than the exception in this body of literature. This is concerning given that cannabis may have divergent acute, residual and long-term cognitive effects (D'Souza et al., 2005; Pope et al., 2001). In the meta-analysis by Yucel et al (2012), the authors concluded that the observed superior cognitive function among cannabis-using patients was largely driven by studies including samples with lifetime histories of use rather than current or recent use (Yucel et al., 2012). Therefore, given that these studies are cross-sectional, it may prove useful and advantageous to parse lifetime cannabis users into current cannabis-users and those with a history of cannabis use. In accordance with the abovementioned theories, it would be expected that both current and former-using patients would demonstrate enhanced cognitive performance as compared to non cannabis-using patients.

**Nicotine**

Cannabis and tobacco use are highly comorbid (Aad et al., 2012). Cannabis is the most frequently used drug among tobacco users (Smart & Ogborne, 2000), and similarly, tobacco use often co-occurs among active cannabis users (Amos et al., 2004). Neurobiological mechanisms have been proposed to explain the robust link between cannabis and tobacco co-use [For review see Rabin & George, 2015]. Given that tobacco is the most commonly abused drug among patients with schizophrenia, one may expect analogous associations between cannabis and
tobacco to extend to this patient population. In support of this, a study by Margolese et al (2004) reported that patients with concurrent substance use disorders, including cannabis, were more likely to smoke cigarettes (88.9%) compared to those diagnosed with schizophrenia alone (49.6%) (Margolese et al., 2004). Other studies directly comparing schizophrenia cannabis users to non-users also report higher average cigarettes per day among the former group versus the latter (Jockers-Scherubl et al., 2007; Schnell et al., 2009; Sevy et al., 2007). Similarly, another study found that the proportion of smokers was higher among cannabis patients compared to non-using patients (Scholes & Martin-Iverson, 2010).

Nicotine, one psychoactive component of tobacco, has been demonstrated to possess pro-cognitive effects in patients with schizophrenia, and hence cigarette smoking in schizophrenia is associated with better cognitive performance (Adler et al., 1993; Sacco et al., 2005). Given that tobacco smokers are likely to be over-represented in the cannabis-using group compared to the non-using group, it is essential that studies control for tobacco use. However, while few studies did control for cigarette use in their analyses (Jockers-Scherubl et al., 2007; Sanchez-Torres et al., 2013; Schnell et al., 2009), most studies did not (DeRosse et al., 2010; Kumra et al., 2005; Mata et al., 2008; Stirling et al., 2005; Yucel et al., 2012). In the study by Scholes et al (2010), cigarettes per day were surprisingly higher among schizophrenia non-cannabis users, however again this may be a result of their definition of a “cannabis user”.

**Abstinence**

Another critical source of inter-study variation is the period of time elapsed between the last use of cannabis and the administration of cognitive testing. Depending on this interval, studies may be assessing the impact of acute cannabis intoxication (D'Souza et al., 2005), withdrawal, or the longer-lasting, residual effects of cumulative cannabis exposure (Jockers-Scherubl et al., 2007; Schnell et al., 2009). Coulston et al (2007) and DeRosse et al (2010) mandated that patients refrain from cannabis use for at least 24 hours prior to testing so as to capture the narrow window between intoxication and withdrawal (Budney et al., 2003). In addition, some studies failed to report whether or not there was a hiatus from cannabis use (Loberg & Hugdahl, 2009; Sevy et al., 2007; Stirling et al., 2005). In effect these studies are measuring completely different phenomena associated with cannabis use. Researchers should clearly define what effects of
cannabis they attempt to capture, and biochemical verification, in addition to self-report, is critical for the reliability and validity of findings.

**Sex**

The research literature suggests that individuals suffering from psychotic disorders with comorbid SUDs are predominantly male (Kavanagh et al., 2004), and this gender distribution phenomenon extends to CUDs as well (Koskinen et al., 2010). Males are also thought to have an earlier onset of schizophrenia, a more severe course of the disorder, suffer from greater cognitive impairment, and have worse premorbid function than female patients (Goldstein et al., 1994). Given that the non-using cannabis group is more likely to be populated by females, and males and females present with different symptomatic profiles, underscores the significance of controlling for sex in these studies.

**Co-morbid SUDs (other than cannabis)**

Polysubstance use is common among the schizophrenia population, and other substances of abuse including alcohol, cocaine, stimulants and hallucinogens are associated with altered cognitive performance [see (Coulston, Perdices, & Tennant, 2007b)]. As such the presence of co-morbid substance use needs to be considered. However, a great deal of the research conducted to date did not control for effects of co-use (Mata et al., 2008; Sevy et al., 2007; Stirling et al., 2005; Yucel et al., 2012), thereby making it is impossible to attribute cognitive effects to a specific substance.

The primary goal of my Master’s thesis was to address the limitations of these previous studies. In 2013, we published, “Effects of cannabis use status on cognitive function, in males with schizophrenia” in Psychiatry Research (Rabin et al., 2013) (Appendix B). This study conferred several advantages over previous research examining this relationship. First, we employed strict criteria in which to define our cannabis using and non-using groups. In attempt to elucidate the effects of heavy use that lead to functional impairment, a cannabis user was defined according to DSM-IV cannabis dependence criteria. Second, in this cross-sectional study, we clustered participants according to their current cannabis use status: patients with current cannabis
dependence and patients not currently cannabis dependent, the latter group was further parsed into patients with former cannabis dependence (>6month of remission) and those with minimal/no lifetime use. This type of classification is commonly used in the tobacco literature (Hughes et al., 2000) and is important as it may help to elucidate whether effects of cannabis on cognition are best characterized as state or trait phenomena. Third, this study controlled for other substance use by only including current tobacco smokers and excluded those presenting with concurrent SUDs (e.g., alcohol, cocaine, stimulants and hallucinogens). Lastly, all participants enrolled were male, to overcome any sex-based effects that may occur with co-morbid cannabis dependence.

Findings from my Master’s thesis were consistent with the abovementioned meta-analyses (Rabin et al., 2011; Yucel et al., 2012) and the preponderance of research suggesting that lifetime cannabis users (i.e., ever meeting cannabis dependence) do indeed have superior cognitive function as compared to non-using patients. However, these effects were modest and selective for psychomotor speed as assessed by the Continuous Performance Test (CPT) and the Trailmaking Test A (TMT-A). Both current and former cannabis users performed better than never-dependent patients on CPT reaction time and on the TMT-A, and former-using patients performed significantly better than never-dependent patients. In support of these results, other studies have also found subtle but enhanced performance in psychomotor speed among lifetime cannabis users versus non-users (Coulston et al., 2007a; DeRosse et al., 2010; Yucel et al., 2012).

In short, this supports the concept that lifetime cannabis-using patients represent a subgroup of schizophrenia patients with higher cognitive capacities than never dependent schizophrenia patients. Moreover, the never-dependent group may consist of patients who developed the disorder from different etiopathology and as such psychomotor deficits may denote vulnerability markers for this subgroup. Given the small sample size of the study, other between group differences may not have emerged due to lack of statistical power. Furthermore, given that effects of cannabis on cognition are likely subtle and that schizophrenia is a highly heterogeneous disorder (Davidson & McGlashan, 1997) which also extends to cognition (Joyce & Roiser, 2007), large variation of cognitive outcomes within each subgroup may have masked differences and reduced the likelihood of obtaining significance, irrespective of sample size.
In sum, while findings lend support for cannabis-users belonging to a higher functioning subgroup, these studies fail to directly assess the impact of cannabis on cognitive performance. So while the “trait” effects associated with cannabis use are a well-replicated finding, the “state” effects of cannabis remain equivocal. Therefore a secondary aim of my Master’s study was to examine the relationship between cumulative cannabis exposure and cognition among current and former dependent patients. If cannabis use has a neurotoxic effect, then conceivably the more cannabis one uses, the more severe the resulting deficits will be. While studies have examined the effects of frequency, quantity and duration of cannabis use on cognition (i.e., Coulston et al. 2007; Schnell et al 2010; Solowij et al 2007; Bolla et al 2002), no previous study has considered lifetime cumulative exposure, an index that accounts for all these factors. The term joint-year, borrowed from the cancer literature (Aldington et al., 2007), offers a standardized approach to assess cumulative cannabis exposure where one joint-year of cannabis is equivalent to using on average one joint per day for one year.

Using an exploratory approach, we examined correlations between joint-years and cognitive performance in current and former dependent patients. Findings revealed that patients with current cannabis dependence demonstrated robust relationships between greater cumulative cannabis use and poorer performance across various cognitive domains namely attention (CPT), visuospatial working memory (SDR), verbal memory and learning (HVLT) and executive function (WCST); [See Figure 1.1]. Tests that mediate these cognitive processes are thought to recruit the PFC, particularly the DLPFC, and the hippocampus (Berman et al., 1995; Cohen et al., 1987; Nagahama et al., 1996; Williams & Goldman-Rakic, 1995). In contrast, performance on tests of emotional cognition such as the Kirby Delay Discounting Task (KDDT) and the Iowa Gambling Task (IGT), revealed no association with cumulative cannabis use. These measures are thought to be functionally dependent on the orbitofrontal and ventromedial cortices, respectively (Bechara et al., 2000; Mobini et al., 2002). Remarkably, when these relationships were assessed in former dependent patients (who self-reported no CUD for at least six months prior to study enrollment) no significant correlations emerged. See Figure 1.1
Cumulative Effects of Cannabis on Cognition

Increasing joint-years significantly correlated with worse VSWM performance as measured by the SDR in current dependent patients, but not in former dependent patients. This suggests that greater cannabis exposure is associated with poorer cognitive function, however deficits may be reversible with sustained abstinence of at least six months.

While these data are preliminary, the specificity of this association to current dependent patients is intriguing and lends support for “state-dependent” effects of cannabis on select cognitive outcomes. Moreover, this relationship appears to exist for cognitive processes facilitated by brain regions rich in CB1 receptors, such as the PFC (SDR) and hippocampus (HVLT). Further, this suggests that while cannabis may have detrimental effects on cognition, remediation of these deficits may be possible with at least 6 months of abstinence. This is quite promising from a treatment perspective as cognitive deficits are notoriously difficult to treat (Spaulding et al., 1996). These findings should also encourage investigators to conduct prospective studies that evaluate the reversibility of cannabis-induced cognitive deficits in patients with schizophrenia.

Taken together, these findings do not challenge the ‘subgroup’ theory of cannabis-using patients,
but in fact serve to compliment it. That is, cannabis-using patients who achieve sustained abstinence may subsequently demonstrate improvements to their (already superior) cognitive function. Such findings underscore the importance of developing effective treatment interventions for CUD in patients with schizophrenia.

1.4 Study Objectives and Hypotheses

Given that all research studies to date examining the relationship between cannabis and cognition in schizophrenia have employed cross-sectional designs, we proposed an alternative paradigm. We posit that the proper investigation to isolate the state-dependent effects of cannabis on cognitive function warrants a longitudinal, within- and between-subject (mixed) design in cannabis dependent patients with schizophrenia and cannabis dependent non-psychiatric controls. Therefore, the present study used a prospective, longitudinal highly-controlled laboratory approach to examine the state-dependent effects of 28 days of cannabis abstinence on cognitive outcomes in cannabis dependent patients with schizophrenia.

Given results from Rabin et al (2013), primary cognitive outcomes included tasks facilitated by brain regions rich in CB1R, such as the hippocampus (HVLT) and PFC (SDR, Digit Span Forwards). Other cognitive domains were also examined (attention, executive function, decision-making, motor control). These secondary domains are facilitated by brain regions with varying levels of CB1R, and thus may not exhibit the same degree of change as those with the highest concentrations of CB1R.

Non-psychiatric controls acted as our diagnostic comparison group. Enrolling this population enabled us to determine if cognitive change was diagnostic-specific. In other words, these comparison samples offered us the possibility to determine if cannabis exerts differential effects in patients compared to controls. Evidence from D’Souza et al (2005) suggests that while both patients with schizophrenia and controls experience THC-induced cognitive decrements, the magnitude of impairment in patients was greater than that of controls, suggesting enhanced sensitivity to THC compared to controls.
A 28-day abstinence period was chosen given that this is the duration needed to rid the body of residual cannabinoids and thus achieve biochemically confirmed abstinence (20ng/mL cut-off) (Ellis et al., 1985; Smith-Kielland, Skuterud, & Morland, 1999). This abstinence time period was also consistent with previous studies that examined the effects of cannabis abstinence on cognitive outcomes in non-psychiatric controls (Bolla et al., 2002; Pope et al., 2001).

A non-abstinent control group was inherently embedded within the study. Given that not all participants were predicted to achieve sustained abstinence for the full 28-day period, these individuals were intended to act as the appropriate within-group cannabis using time controls.

Moreover, this study would help to determine if cannabis-induced deficits in patients with schizophrenia are state-dependent and reversible. If cognitive recovery occurs with sustained abstinence, findings would help to establish the magnitude and at what time point remediation of these cognitive deficits occur.

### 1.4.1 Primary Aim and Hypothesis

**Primary Aim:** To investigate the state-dependent effects of 28-days of cannabis abstinence on working memory (i.e., SDR, Digit Span) and verbal memory and learning performance (i.e., HVLT) in cannabis dependent schizophrenia patients and cannabis dependent non-psychiatric controls.

**Primary Hypothesis:** We predicted that abstaining participants would experience improvements over time in tasks assessing working memory (SDR, Digit Span), and verbal memory and learning (HVLT) performance, and expected that patients would have a greater magnitude of improvement compared to controls.
1.4.2 Secondary Aims and Hypotheses

i.) To investigate whether contingency management was a useful intervention to initiate and sustain 28-days of cannabis abstinence in cannabis dependent patients with schizophrenia and non-psychiatric controls.

We predicted that 50% of cannabis dependent patients with schizophrenia and 50% of cannabis dependent non-psychiatric controls would achieve sustained cannabis abstinence for the full 28-day period.

ii.) To investigate the state-dependent effects of 28-days of cannabis abstinence on secondary cognitive outcomes (CPT, Digit Span Backwards, Trail Making Test, Grooved Pegboard, BART, KDDT).

We predicted that secondary cognitive outcomes would demonstrate a lesser degree of change with abstinence compared to primary cognitive outcomes in patients with schizophrenia and controls.

iii.) To investigate the state-dependent effects of 28-days of cannabis abstinence on psychotic and affective symptoms in cannabis-dependent patients with schizophrenia.

We predicted that among patients with schizophrenia who achieve cannabis abstinence, psychotic and affective symptoms would decrease in severity over time compared to baseline assessments and to those patients who relapse.

iv.) To investigate the withdrawal trajectory in abstaining cannabis-dependent patients with schizophrenia and non-psychiatric controls.

We predicted that among patients with schizophrenia and non-psychiatric controls, withdrawal symptoms would peak in severity within the first week of abstinence and then decrease in severity over the following three weeks. Severity of symptoms would be greater in patients with schizophrenia versus non-psychiatric controls.
Given that patients with schizophrenia possess high rates of CUDs and suffer from already compromised cognition, underscores the importance of determining the true effects of cannabis on cognitive function in this population. A longitudinal study of cannabis abstinence will provide the definitive approach necessary to test these hypotheses. Given that improved cognition leads to better functional outcomes in schizophrenia, a careful examination of cannabis’ effects may encourage and foster the development of novel treatments for CUDs in patients with schizophrenia.
2 METHODS

This study was approved by the Centre for Addiction and Mental Health’s (CAMH) Research Ethics Board (REB #169/2011) and in accordance with the declaration of Helsinki. Written informed consent was obtained for each participant enrolled as approved by REB of CAMH (see Appendix C).

2.1 Design Overview

A standardized phone interview was conducted to prescreen individuals who were interested in study participation. All potential participants were invited into the Biobehavioural Addictions and Concurrent Disorders Laboratory (BACDRL) located at 33 Russell Street of CAMH to complete consent, a comprehension quiz on study procedures, and a screening session to assess eligibility. Once eligibility was confirmed, a cognitive training session followed on a different day. Participants attended weekly study visits that included clinical assessments, urine toxicology, and supportive therapy session. The comprehensive cognitive battery was administered at Day0 (baseline), 14, and 28. Twice weekly urine analysis was used to confirm abstinence, which later was tested by gas chromatography-mass spectrometry (GC-MS) to obtain quantitative cannabis metabolite levels (THC-COOH). A $300 bonus was awarded to patients who successfully abstained from cannabis for the full 28-day period, confirmed via biochemical verification. A one-month follow-up visit ensued that included both clinical and cognitive assessments. Figure 2.1 demonstrates an overview of the study design.
Figure 2.1 Study Design

Study Design
Outline of the overall study design including screening and training visit, weekly assessments and biweekly urine collections.
2.2 Participants

Patients with schizophrenia were recruited through CAMH via flyers, word-of-mouth, various outpatient clinics, and referrals. Non-psychiatric controls were recruited through flyers, referrals from other studies and online advertisements such as Craigslist, and Kijiji.

2.2.1 Power Analysis

Our primary outcome was cognitive performance on tests of verbal memory and learning (HVLT) and working memory (SDR, Digit Span Forward). Power for this study was determined based on findings from the Pope et al 2001 study given that no longitudinal abstinence study has been conducted in schizophrenia. The investigators observed a 30% recovery of cognitive performance on a test of verbal memory and learning, the Benton Revised Visual Retention Test (BSRT) in heavy cannabis-using non-psychiatric controls. Therefore we estimated a medium effect size (Cohen’s d=0.70) on HVLT performance between cannabis dependent controls that would achieve abstinence compared to those who would relapse. We predicted that cannabis-using patients with schizophrenia would be more sensitive to the effects of cannabis on cognition and thus would demonstrate a >30% change over the 28-days. Thus we powered both groups for 30% change.

Given that we were primarily interested in within group change rather than between group differences, our power analysis did not reflect between group differences (i.e., SCZ versus CTL). Therefore, a sample size of n=10 completers (total N=20, based on a 50% abstinence rate) would allow sufficient power to detect the hypothesized within diagnostic group differences for this study.

2.2.2 Sample

Male participants between the ages of 18 and 55 were recruited for the study. All participants met for current cannabis dependence based on the DSM-IV-TR (APA, 2000). A positive urine
test for THC-COOH was required to confirm current and recent cannabis use. To control for the effects of tobacco on cognition, all participants were daily cigarette smokers, consuming a minimum of five cigarettes per day. In addition, all participants had to achieve Full Scale Intelligent Quotient (FSIQ) scores \( \geq 80 \).

Psychiatric participants met diagnostic criteria for either schizophrenia or schizoaffective according to DSM-IV-TR criteria. Patients were psychiatrically stable at the time of interview with a score \(< 70\) on the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay, Fiszbein, & Opler, 1987). Patients had to be on a stable dose of antipsychotic medication for at least one month prior to the study assessments, with no hospitalizations in the previous 3 months due to psychiatric instability.

Non-psychiatric controls were excluded if they met for a current or past DSM-IV Axis I diagnosis (except for major depression in remission \( >1 \) year;). Controls were also excluded if they were taking psychotropic medications.

All participants were excluded if they were actively seeking treatment for their cannabis use. Additionally, individuals with a current or past (in remission \(< 6\) months) DSM-IV SUD (other than cannabis, nicotine, caffeine) or those testing positive on urine toxicology for illicit drug use other than cannabis (i.e., cocaine, opiates, amphetamine, phencyclidine, barbiturates) were also excluded. Head injury with loss of consciousness (LOC) for \( >30 \) minutes or a neurological/medical condition affecting cognitive function was also exclusionary.

2.3 Measures

2.3.1 Clinical Interview Assessments

Structured Clinical Interview for the DSM-IV-TR (SCID)

The SCID (APA;, 2000) (First, 2002) is a semi-structured interview used to diagnose a current or lifetime axis I disorder. In this study, the SCID was used to verify a diagnosis of schizophrenia or schizoaffective disorder in our patient group as well as confirm that controls did not have any
axis I disorders. The SCID also ensured that all participants met criteria for cannabis dependence. The SCID was completed at the screening visit.

**Addiction Severity Index (ASI)**

The ASI 5\textsuperscript{th} Edition (McLellan et al., 1992b) is a semi-structured interview designed to assess 7 potential problem areas in substance-using patients: medical status, employment and support, drug and alcohol use, legal status, family/social status, and psychiatric status. Information is gathered relating to two time references, the past 30 days and lifetime. Using a ten-point scale (0-9), interviewer severity ratings (ISR) indicate the degree of the patients’ problems in each of the seven problem domains in the last 30 days. These ISRs indicate the need for new or additional treatment based on the amount, duration, and intensity of symptoms. The ASI assesses current problem severity by calculating composite scores ranging from 0 (no problem) to 1 (extreme severity) in each of the 7 domains. Scores are based on the patient’s responses and correspond to the last 30 days. The ASI was completed at the screening visit.

**The Positive and Negative Syndrome Scale (PANSS)**

The PANSS (Kay, Opler, & Lindenmayer, 1988) is a 30-item inventory assessing the absence or severity of schizophrenia symptoms across three subscales: positive symptoms (items P1–P7, including hallucinatory behavior, delusions, and conceptual disorganization), negative symptoms (items N1–N7, including blunted affect, social and emotional withdrawal, and lack of spontaneity), and general psychopathology symptoms (items G1–G16, including mannerisms and posturing, unusual thought content, and lack of insight). Each item is scored on a scale ranging from 1 (absent) to 7 (extreme), with item ratings incorporating the behavioural effect of symptoms as well as their severity. The PANSS was only administered to patients. It was used to assess patients’ stability at screen; for eligibility participants must have a total score below 70. The PANSS was then used to evaluate changes in symptoms over the course of abstinence. Thus it was administered at Day0 (baseline), Day7, Day14, Day28 and at the one-month follow-up visit.

**Calgary Depression Scale for Schizophrenia**

The CDSS (Addington, Addington, & Maticka-Tyndale, 1993) is semi-structured interview, developed to assess the severity of depressive symptoms in individuals with schizophrenia
(McLellan et al., 1992a). It compensates for the presence of negative symptoms and extrapyramidal side effects of medication in patients. The CDSS is a 9-item measure rated from 0 (absent) to 3 (severe). A total score $>4$ suggests the presence of minor depression, whereas scores $>7$ are indicative of major depression. The CDSS was administered in only patients. It was completed at the screening visit, Day0 (baseline), Day7, Day14, Day28 and at the one-month follow-up visit, and assessed symptoms of the previous week.

**Hamilton Rating Scale for Depression (HAM-D)**

The HAM-D (Hamilton, 1967) is a 17-item scale that is useful for determining the level of depression in the previous week. Its ratings are based on the clinician's interview with the patient, and probes symptoms such as depressed mood, guilty feelings, suicide, sleep disturbances, anxiety levels and weight loss. Severity levels of symptoms are scored on a scale that ranges from 0 (not present) to 4 (extreme symptoms). The HAM-D was administered to both patients and controls at the screening visit, Day0 (baseline), Day7, Day14, Day28 and at the one-month follow-up visit.

### 2.3.2 Intelligence Scales

**Wechsler Test of Adult Reading (WTAR)**

The WTAR (Wechsler, 2001) was developed to assess premorbid intellectual functioning. This assessment is comprised of 50 irregularly spelled words, and each correctly pronounced word is given a score of 1. The irregularity of the words makes them difficult to correctly pronounce without having previous knowledge of the words. Thus, the participants vocabulary, and by extension IQ, can be assessed. Raw scores were standardized by age and then converted to Full Scale IQ (FSIQ) estimates. This test was administered at the screening visit, participants with FSIQ $<80$ were excluded from study participation.

**SHIPLEY-2**

Shipley-2 (Shipley et al., 2009) offers a measure of both crystallized and fluid intelligence. It is composed of two subscales. (1) The Vocabulary Test is composed of 40 items asking participants to underline one out of the four words that is most similar to the prompting word. (2)
The Abstract Thinking Test is composed of 25 items asking participants to fill in each blank with a letter or number to complete the pattern. The Shipley takes a maximum of 22 minutes to complete and produces standard scores for the scales administered that estimate an FSIQ score (Zachary, Paulson, & Gorsuch, 1985). This test was administered at the screening visit.

2.3.3 Extrapyramidal Side Effects

**Simpson Angus Rating Scale (SARS)**
The SARS (Simpson & Angus, 1970) is used to assess neuroleptic-induced parkinsonism. This is a 10-item rating scale that consists of one item measuring gait (hypokinesia), six items measuring rigidity and three items measuring glabella tap, tremor and salivation. Items are rated on a 4-point scale.

**Abnormal Involuntary Movement Scale (AIMS)**
The AIMS (Guy & Cleary, 1976) was designed to measure dyskinetic symptoms, a common side effect associated with long-term antipsychotic treatment in schizophrenia. The AIMS allows for early detection and ongoing surveillance of tardive dyskinesia (TD). This 12-item assessment of involuntary movements is rated on a 5-point scale ranging from 0 (none) to 4 (severe), except for items 11 and 12 (dental care) which are answered with either a “yes” or a “no”.

**Barnes Akathisia Rating Scale (BARS)**
The BARS (Barnes, 1989) is used to assess neuroleptic-induced akathisia, a syndrome of motor restlessness in individuals with schizophrenia. The BARS incorporates subjective reports of awareness and distress related to akathisia, along with objective motor restlessness observations. These items are rated using a 4-point scale, while global clinical assessment is rated using a 5-point scale.

All three of these scales are completed at the screening visit and then again at Day28 in schizophrenia patients only.
2.3.4 Substance Use Assessments

Timeline Follow Back (TLFB)
The Timeline Follow Back (TLFB) (Sobell & Sobell, 1995) while originally developed to assess frequency of alcohol use, has now been validated for collecting information on other substances of abuse (Carey & Correia, 1998; Fals-Stewart et al., 2000). The frequency of the substance is assessed on a day-by-day basis, using a calendar whereby participants provide a retrospective estimate of their daily consumption of use over a 7-day period. Cannabis, tobacco cigarettes, alcohol and caffeine use were assessed using this scale. Cannabis use was recorded in grams per day, and was used as self-reported corroboration of abstinence. This scale was administered at the screening visit, Day0 (baseline), Day7, Day14, Day28 and also at the one-month follow-up visit.

Fagerstrom Test of Nicotine Dependence (FTND)
The FTND (Heatherton et al., 1991) is a brief, 6-item scale that yields scores between 0 and 10 to assess the level of nicotine dependence. Individuals respond to multiple-choice type questions, with each answer corresponding to a score. Higher scores indicate more severe levels of dependence. The FTND is one of the most commonly used measures to assess nicotine dependence, and has acceptable reliability for use among smokers with and without schizophrenia (Weinberger et al., 2007). This questionnaire was administered only at the screening visit in both patients and controls.

The Alcohol Use Disorders Identification Test (AUDIT)
The AUDIT (Saunders et al., 1993) is a simple ten-question test developed by the World Health Organization to assess excessive drinking. Questions 1-3 rate alcohol consumption, 4-6 relates to alcohol dependence and 7-10 considers alcohol related problems. A score of 8 or more in men (7 in women) indicates a strong likelihood of hazardous or harmful alcohol consumption. A score of >20 is suggestive of alcohol dependence. Questions one through eight are scored from zero to four while questions 9 and 10 are scored zero, two or four. The maximum score one can achieve on the AUDIT is 40. Participants completed this measure at the screening visit.

Contemplation Ladder
The Marijuana Ladder (Slavet et al., 2006) is an adapted version of the Contemplation Ladder
(Biener & Abrams, 1991), a measure that assesses readiness for smoking cessation. The Marijuana Ladder is a visual analog scale comprised of 10 rungs, each accompanied by a corresponding statement. A higher score on the ladder indicates that the participant is more interested in behavioural change, while a lower score on the ladder indicates that the participant is less interested in behavioural change (i.e., cessation). Participants completed this measure at the screening visit, and at Day 28, post-abstinence.

**Marijuana Withdrawal Checklist (MWC)**

The MWC (Budney et al., 2003) is used to assess the incidence and severity of perceived cannabis withdrawal symptoms. The revised 15-item version of the MWC is comprised of the most frequently endorsed withdrawal symptoms (Budney et al., 2003). Participants rate each symptom experienced based on a 4-point scale where 0 = none, 1 = mild, 2 = moderate, and 3 = severe. At screen and Day 0, participants rate severity of these symptoms retrospectively based on the last time they used cannabis, and once abstinence is initiated, participants rate the presence of symptoms during the previous week. This questionnaire is completed weekly and also at Day 3, when participants come to the laboratory to drop off a urine sample.

**The Marijuana Craving Questionnaire (MCQ)**

The MCQ (Heishman et al., 2009) assesses cannabis craving along four dimensions: factor 1: Compulsivity; factor 2: Emotionality; factor 3: Expectancy, and factor 4: Purposefulness. We employed a shorted version (12-item) of the original 47-item questionnaire, which is shown to exhibit high internal reliability and validity. The MCQ is scored on a 7 point likert scale of 1 = Strongly Disagree and 7 = Strongly agree, and participants rate how they are feeling “right now”. This scale is completed weekly and also at Day 3.

**Joint-Years**

The term joint-year, borrowed from the cancer literature (Aldington et al., 2007), offers a standardized approach to assess cumulative cannabis exposure. One joint-year of cannabis is defined as smoking on average one joint per day for 1 year (e.g., 1 joint year = one joint smoked per day in one year) (Rabin et al., 2013). This term was calculated at the screening visit.

**Urine Drug Screen**

MEDTOX™ urine toxicology assays (7-panel) were used to test for the presence of cannabis,
opiates, amphetamines, cocaine, phencyclidine, barbiturates, and benzodiazepines. This test was administered at screen to ensure that no other illicit substances other than cannabis were being used. We also used this test at Day28 to biochemically verify cannabis abstinence at study endpoint.

Narcocheck® is a semi-quantitative urine drug-screening test that assesses the presence of 5 different concentrations levels of THC-COOH in the urine. Detection ranges are as follows: >25ng/mL; 25-50ng/mL; 50-150ng/mL; 150-300 ng/mL; 300-500ng/mL; <500ng/mL. Narcocheck was used weekly to assess cannabinoid levels in the body. This test allowed for the monitoring of decreasing cannabinoid levels expected with cannabis abstinence.

Results for both these tests are given in 5 minutes, and thus were performed at the investigative site. Urine samples were then sent to CAMH clinical laboratory for GC-MS testing in order to obtain quantitative THC-COOH and creatinine concentrations. A sensitive cut-off of 20ng/mL at Day28 was used to parse abstainers from non-abstainers (Ellis et al., 1985).

**Vitals**

Blood pressure, heart rate and temperature were assessed at every visit (except for the cognitive training session). Weight and Height was assessed at Day0, and a Body Mass Index score was calculated. Weight was then monitored at the weekly study visits. Expired breath carbon monoxide (CO) levels), a byproduct of cigarette and cannabis smoke, were also assessed at these visits.

### 2.4 Cognitive Battery

**The Test of Memory Malingering (TOMM)**

The TOMM (Tombaugh, 1997) is a visual recognition test designed to distinguish between malingering and true memory impairments. The TOMM was rated as having the best classification accuracy in discriminating between insufficient versus adequate effort (Sharland & Gfeller, 2007) and thus was used as a measure of motivation and effort in the current study. The
TOMM is a 50-item recognition test that includes two trials and a retention trial. During the two learning trials participants are shown 50 target pictures, followed by 50 recognition panels. Each recognition panel contains one of the target pictures and a novel one. The participant is to correctly identify the correct picture. The same paradigm is used for the retention trial, yet the target pictures are not re-administered. The retention trial is only administered if the Trial 2 score is less than 45. Scores range from 0 to 50 for each trial, and 5 or more errors on trial 2 or the retention trial indicates the possibility of malingering. This test was only administered once at the cognitive training visit.

**Wisconsin Card Sorting Task (WCST)**

The WCST (Heaton et al., 1993) is an extensively used measure that assesses executive function, including planning and set-shifting. We utilized the computerized version (WCST-version 5, PAR inc). Outcome measures include percent total errors, percent perseverative errors, percent non-perseverative errors, number of categories completed, and number of trials to complete first category. Performance on this task has been linked to activation of the DLPFC (Egan et al., 2001b). Reliability of the WCST, inter-scorer and intra-scorer agreements have been found to be excellent. This WCST is administered once at the cognitive training visit given that performance on this test is susceptible to practice effects (Basso et al., 2001).

**Iowa Gambling Task (IGT)**

The IGT (Bechara et al., 1994) is a widely used computerized measure that assesses decision-making impairments associated with a variety of neurological and psychiatric conditions, including schizophrenia (Bechara et al., 1994). The IGT was initially created to assess individuals with ventromedial prefrontal cortex damage (Bechara et al., 1994). All participants sat facing a computer screen which displayed four decks of cards (A, B, C, and D) and were told to pick a card from the decks one at a time. They were informed they would receive a monetary reward or penalty for every card they choose, and that the goal of the game is to maximize profits on a $2000 loan they will receive before they begin the task. Participants were permitted to pick from any deck and to switch decks at any time. Participants were allowed to take as much time as they needed to complete this task. The four decks in the IGT vary in the amount and ratio of reward to penalty that each provides. Decks A and B initially offer large monetary rewards,
but are disadvantageous because some selections from these decks are accompanied by large monetary penalties. Decks C and D offer smaller monetary rewards, but also involve smaller penalties. The game ends after 100 trials. Participants do not know the contingencies and the duration of the game in advance; participants are told simply that their goal is to have the best possible net outcome in the game. Overall performance on this task is the difference between choices in advantageous decks (C and D) minus choices in disadvantageous decks (A and B), total net score. Net scores for each block of 20 cards/trials. In addition, you can examine the total number of cards selected from each deck and the total amount of money won. This test was administered once at the cognitive training visit as with re-administration of this test, practice effects are likely (Bechara, Damasio, & Damasio, 2000).

The Continuous Performance Test II (CPT-II)
The CPT-II (Conners, 2000) is a computerized test designed to measures sustained and selective attention as well as impulsivity. Respondents are required to press the space bar when any letter except the target “X” appears on the screen. The inter-stimulus intervals (ISIs) are 1, 2 and 4 seconds with a display time of 250 milliseconds. The following outcomes indices were used: CPT Hit rate (100-% of Omissions), % of Commission, Hit Reaction Time, CPT and Variability, and D-prime. D-prime is a measure of attentiveness/distractibility in which higher scores are indicative of worse performance.

Hopkins Verbal Learning Test-Revised (HVLT-R)
The HVLT-R (Benedict, 1998; Brandt & Benedict, 2001) is a measure of verbal memory, learning, retrieval and recognition. Participants are asked to learn and recall a list of 12 words presented three times, and then following a delay of 20-25 minutes. A recognition trial then presents the participant with 24 words, of which 12 are from the target list. The participant is to identify all target words by responding “yes” and all 12 non-target words by responding “no.” Six distinct forms are available, eliminating practice effects with repeated administrations. A number of indices were used as outcome measures: List 1, 2, and 3 free recall, Total recall, Delayed Recall, Number of Repetitions, Number of Intrusions, True Positives, False Positives, Percent Retention (calculated as the number of spontaneously recalled items divided by the maximum number of items learned), and Discrimination Index (number of true-positives minus
false-positives on the recognition trial).

**Digit Span-Forward and Backward**
The Digit Span (Wechsler, 1997) is a subtest of the WAIS-III. The task consists of two trials: one where the participant is to repeat a length of digits aloud in the forward direction and a second trial where they repeat the string of numbers in the reverse direction. The Digit Span Forward assesses short-term working memory, while backwards is a measure of executive function. The total number of correctly repeated strings of numbers is summed for a forward score, backwards score and a total score (forwards + backwards). Higher scores are indicative of better performance.

**Trail Making Test A (TMT-A) and Trail Making Test B (TMT-B)**
The Trail Making Test is a test of speed for visual search, attention, executive function, mental flexibility and motor function (Lezak, 2004). Using a pencil, the participant is required to connect 25 encircled numbers that are randomly arranged in the appropriate numerical order (Part A). Part B includes both randomly arranged numbers and letters and the participants is to connect the circles alternating between number and letter, in consecutive and alphabetical order. The participant was instructed to complete the task as quickly as possible, but also as accurately as possible and without lifting the pencil off the page. When an error occurred, the participant was notified and instructed to correct their mistake(s) and continue until the test was completed. A sample trial was presented prior to test administration for both parts A and B. Raw scores for the TMT-A and TMT-B were obtained by measuring the length of time required to complete the tasks in seconds. A third score was computed by subtracting TMT-A time from TMT-B, a common method for partialining out effects of general processing speed difficulties (Strauss, 2006).

**Spatial Delayed Response (SDR)**
The SDR (Hershey et al., 1998) is a measure of visuospatial working memory (VSWM). In this task participants must focus on a central fixation cross on the computer screen. While fixated, a cue (dot) appears in one of many possible locations. A delay period (5, 15 or 30 seconds) is then imposed where a series of geometric shapes appear in place of the fixation cross. The participant
must press the spacebar whenever the diamond shape appears. After the delay, the fixation cue returns, and the participant must point on the computer screen where they remember seeing the dot. Mean error in mm (distance between recall and actual target) is calculated for each of the three time delay trials. Higher scores reflect worse performance.

**Grooved Pegboard**

The Grooved Pegboard (Lafayette Instrument Company, 1989) is used to measure manual dexterity and fine motor movement. It consists of 25 slotted holes angled in different directions arranged in a 5x5 array. Participants are instructed to use their dominant hand to insert the pegs one at a time in the holes in sequence as quickly as possible. After completion, participants are instructed to complete the same task with their non-dominant hand. When participants use their right hand, pegs are inserted from left to right; when using their left hand, participants are to insert pegs from right to left. Raw scores are calculated by measuring the length of time required to complete the task with the dominant and non-dominant hand respectively. A total time score is also computed where dominant and non-dominant scores were summed. The number of pegs dropped during each trial and both trials is also recorded. Higher scores are indicative of worse performance.

**Balloon Analog Risk Task (BART)**

The BART (Lejuez et al., 2002) is a computerized measure of risk taking behaviour. The BART models real-world risk behaviour through the conceptual frame of balancing the potential for reward versus loss. In the task, the participant is presented with 30 balloons and offered the chance to earn money by pumping up each balloon by clicking on a button. Each click causes the balloon to incrementally inflate and money ($0.02) to be added to a counter up until some threshold, at which point the balloon is overinflated and explodes. Thus, each pump confers greater risk, but also greater potential reward. If the participant chooses to cash-out prior to the balloon exploding then they collect the money earned for that trial, but if balloon explodes earnings for that trial are lost. Participants are not informed about the balloons’ breakpoints; the absence of this information allows for testing both participants' initial responses to the task and changes in responding as they gain experience with the task contingencies. The primary score used was the adjusted average number of pumps on unexploded balloons, with higher scores
indicative of greater risk-taking propensity (Lejuez et al., 2002). Other outcome measures for the BART include: money earned and the number of balloon explosions. Participants were entitled to take home cash winnings on this task, which usually range from $7.00-22.00.

The Kirby Delay Discounting Task (KDDT)
The KDDT (Kirby, Petry, & Bickel, 1999) is a 27-item questionnaire that assesses discounting of hypothetical monetary amounts across three different delayed-reward magnitudes: small ($25 - $35), medium ($50 - $60), and large ($75 - $85). Each question asked participants to choose between money delivered today and a larger amount of money delivered following delays ranging from 7 to 186 days. Participants were instructed to answer all questions by circling their preferred outcome. As such, this task assesses future-orientated decision-making and impulsivity. Examples of items include “Would you prefer $100 today or $101 in 300 days?” and “Would you prefer $20 today or $55 in 7 days?” K-values are calculated and are based on the extent to which the respondents choose the hypothetical smaller immediate rewards rather than larger delayed rewards. Separate k-values are obtained at small- ($25–35), medium- ($50–60), and large-delayed rewards ($75–85). An average score is also computed. Higher delay discounting scores reflect more impulsive performance.

2.5 Abstinence Paradigm

2.5.1 Urine Collection and Analysis

Given cannabis’ pharmacological profile, an abstinence period of 28-days was chosen. Twenty-eight days is the estimated time needed for chronic, heavy users to yield a negative urine result on a traditional immunoassay for cannabinoids. THC-COOH <50ng/mL is the accepted cut-off for documenting recent abstinence (Huestis, Mitchell, & Cone, 1995). Therefore, if cannabis-dependent participants successfully abstain from cannabis for the 28-day period, in-laboratory biochemical verification of abstinence using MEDTOX is achievable.
Urine was collected and stored at every study visit starting at Day0, and on one other occasion during the week (every 3-4 days). Weekly abstinence was assessed using self-reported TLFB scores and a semi-quantitative urine assay (NarcoCheck®, Villejuif, France) that was able to detect decreasing (or increasing) THC levels at five interval levels as described above. End-point abstinence was biochemically verified using MEDTOX urine assays.

Individuals were classified as “abstainers” if they self-reported no cannabis use over the 28-day period as well as provided urine with THC-COOH levels below 50ng/mL, at Day28 (Huestis, Mitchell, & Cone, 1995). If participants did not meet these criteria, they were classified as “relapsers.”

Stored urine was then subsequently sent to CAMH clinical laboratory for GC-MS analysis to obtain quantitative concentrations levels of THC-COOH and creatinine. In order to account for varying levels of hydration over time, THC-COOH was normalized to creatinine. These THC-COOH:creatinine ratios were used as the basis for abstinence assessment following the Schwilke prediction model (Schwilke et al., 2011). These data allowed for definitive confirmation that participants were indeed classified correctly with respect to their abstinence status.

### 2.5.2 Contingency Management

Given that participants were non-treatment seeking individuals, abstinence was encouraged through the implementation of contingency management procedures. Contingency management is a behavioural intervention that promotes behavioural change using positive or negative contingencies in a progressive manner. It is based on the idea that behaviors that are rewarded or reinforced will increase in frequency. Robust data support the use of contingency management for increasing attendance and retention rates in substance use treatment programs and decreasing drug use. Notably, there is evidence for the efficacy of contingency management in treating cannabis dependence in control populations (Budney et al., 2000), in those with serious mental illness (Sigmon et al., 2000) as well as in populations with low motivation for behavioural change in drug-using samples (Sinha et al., 2003).
The “Fishbowl” technique is a low cost contingency management technique that delivers equivalent efficacy with a significant reduction in cost (Petry et al., 2000). Patients are reinforced, but not all of the time, and the value of reinforcements that they receive may vary. The “Fishbowl” technique was implemented as follows: Participants who provided evidence of adhering to abstinence by demonstrating decreasing levels of THC-COOH, were invited to select a slip of paper from a fish bowl. The bowl contained 250 slips of paper. Half of the slips were non-winning slips labeled “Good Job!” The other half were winning slips that could be exchanged for prizes that varied in value: small, large, and jumbo. Of the winning slips, 109 were for small prizes (i.e., $5 gift card for Tim Horton’s). Fifteen of the winning slips were exchangeable for large prizes, worth up to a maximum of $20 in value (gift card to iTunes, and fast food chains). The jumbo prize was valued at $100 (gift card for restaurants, Best Buy). Slips were returned to the bowl following each draw so that probabilities remained constant. The chance to draw from the fishbowl was initiated on Day14 and 21. This delay was to account for the amount of time needed to allow THC-COOH levels to fall below <50ng/ml, if abstinence was maintained since from Day0 (Law et al., 1984). Moreover, if on Day 28, urine results were indicative of sustained cannabis abstinence (Huestis, Mitchell, & Cone, 1995), participants were rewarded with a $300 cash bonus.

### 2.5.3 Therapy

As a means to maximize abstinence behaviors, individual therapy sessions were administered weekly over the 4 weeks. While therapy adopted a supportive therapy platform it included a combination of motivational interviewing, psychoeducation, and coping skills therapy. Sessions were approximately 20 minutes long, and conducted by trained clinical staff in the Schizophrenia Division at CAMH.

Early sessions focused on building rapport with participants and exploring their feelings and thoughts about cannabis. Given that participants were non-treatment-seekers, motivational interviewing was used to help overcome any ambivalence participants may have had towards quitting as well as to increase their willingness to cease cannabis use for the 28-day study period. Reasons for their use were reviewed, and advantages and disadvantages for maintaining
abstinence were discussed. Subsequent sessions provided psychoeducation in order to heighten awareness of the risks and personal consequences associated with cannabis use. Time was spent helping participants understand cannabis dependence, and what may be expected with abstinence (i.e., the presence of withdrawal symptoms and cravings). There was also a focus on general coping strategies and relapse prevention techniques. Problem-solving and emotional management practices were emphasized throughout. See Appendix D for the Therapy Manual.

### 2.6 Study Procedures

Once potential participants were identified via phone-screen, they were invited into BACRDL for additional assessments to confirm eligibility; Principal Investigator: Dr. Tony P. George, M.D., FRCPC at CAMH. First, research staff thoroughly reviewed the study consent form with participants, who then signed it and received a copy. A post-consent quiz followed to verify participants’ understanding of the study procedures. Subsequently, demographic information, vitals and urine sample (tested with MEDTOX) were collected. Diagnoses were made using the SCID, and patients’ medical records were accessed for confirmation. We tested for IQ, completed substance use scales (ASI, TLFB, AUDIT, Contemplation Ladder), and clinical assessments (HAM-D, CDSS, PANSS). Schizophrenia patients were further evaluated using the AIMS, SARS, and BARS. If participants were deemed eligible, they were invited back to the lab for the Cognitive Training session. Participants were instructed to abstain from cannabis use for the 12 hours prior to this visit so as to minimize the presence of cannabis intoxication as well as withdrawal symptoms during cognitive testing (Budney et al., 2003). The purpose of this visit was to habituate participants to the laboratory and to introduce cognitive testing procedures. By familiarizing participants with these tasks, neuropsychological practice effects are minimized (Sacco et al., 2006). All cognitive tests of the comprehensive battery were completed at this training session. The TOMM, WCST and IGT were completed at this visit only. This study visit took a total of 3 hours to complete. A quit date was then set. Participants quit cannabis the night before (a minimum of 12 hours) coming into the lab for the Day0 (baseline) visit. During the baseline, Day14 visits, all clinical measures were completed and the cognitive battery administered. Urine was collected, tested with the semi-quantitative assay and stored in the -80°C
The visit ended with a one-on-one therapy session. Three days later, participants came to the lab to drop off a urine sample that was stored in the freezer, and complete the MWC and MCQ. At the Day7 and 21 visits, clinical assessments were administered, urine was collected, tested and stored, and individual therapy session was given. Urine samples were also collected and stored on Day10, Day17, and Day24. At Day28, all clinical measures were completed and the cognitive battery re-administered. Urine was collected, tested with MEDTOX to evaluate abstinence status and then stored in the -80C freezer for future GC-MS testing. At the one-month follow-up, were interested to see if abstinent participants continued with cannabis cessation, or whether they relapsed. Given that participants were non-treatment seekers, we expected that most would not be motivated to remain cannabis-free. In this respect, this provided the opportunity to capture patients in an “on-cannabis/off-cannabis/on-cannabis” model. Thus, at this visit, urine toxicology was completed and all clinical and cognitive assessments were administered. Low-cost contingency management (the fishbowl draw) was implemented on Day14 and Day21. Participants were not eligible for the $300 bonus until Day 28. Participants were compensated for their time at a rate of $10 per hour, which they received in cash at the end of each study visit. See Table 2.1 for the schedule and timing of study assessments.

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AIMS, Abnormal Involuntary Movement Scale; ASI, Addiction Severity Index; AUDIT, Alcohol Use Identification Test; BARS, Barnes Akathisia Rating Scale; Calgary Depression Scale for Schizophrenia; FTND, Fagerstrom Test of Nicotine Dependence; FU, Follow-up; HAM-D, Hamilton Depression Rating Scale; MCQ, Marijuana Craving Questionnaire; MWC, Marijuana Withdrawal Checklist; PANSS, Positive and Negative Symptom Scale; SARS, Simpson Angus Rating Scale; TLFB, Timeline Follow Back; WTAR, Wechsler Test of Adult Reading
2.7 **Data Analysis**

Data were analyzed using the Statistical Program for Social Sciences (SPSS) version 24.0 (SPSS Inc., Chicago, Ill). All tests were two-tailed and the level of significance was set at p< 0.05. Trend level significance was set at p-values between 0.05-0.09.

2.7.1 **Demographics, Sample Characteristics and Baseline Outcomes**

Independent t-tests and chi-square tests were used to analyze group differences between cannabis dependent patients with schizophrenia and cannabis dependent non-psychiatric controls. Relationships between cannabis use and baseline clinical and cognitive symptoms were analyzed using Pearson Product Moment correlations. Between group differences were analyzed using t-tests.

2.7.2 **Clinical and Cognitive Measures**

Repeated Measures Analysis of Variance (RM-ANOVA) was used to assess change over time for clinical (withdrawal, craving, depression and psychotic) symptoms and cognitive performance in controls and patients. Time was the within factor, and the between factor was abstinence status (abstainer versus non-abstainer). Significant effects were followed up with one-way ANOVAs to determine which group was driving the effect. Pairwise T-tests were used to determine between which two time-points there was a significant difference.

Repeated Measures Analysis of Variance (RM-ANOVA) were also conducted with time as the within factor, and diagnostic group as the between factor (SCZ versus CTL). These analyses would help to determine if change followed a similar trajectory in abstaining patients and abstaining control participants.

We did not correct for multiple comparison in our analyses given that data was preliminary and exploratory.
Chapter 3

3 RESULTS

3.1 Study Sample

In order to achieve our total sample (N=39), a total of 213 individuals were pre-screened over the telephone and 78 of these individuals were invited into BACDRL to complete a screening visit. Thirty-one individuals did not meet study inclusion criteria and were thus excluded from study participation. Of these, 14 patients were excluded. Reasons included not meeting SCID-IV diagnosis for schizophrenia or schizoaffective disorder (n=1) or cannabis dependence (n=3); not on a stable dose of antipsychotic medication (n=1); and two patients were deemed unstable due to >70 PANSS scores. Other patients were excluded due to illicit drug use or SCID SUD diagnosis other than cannabis (n=4) or because they smoked less than five CPD (n=1). Lastly two patients had a previous head injury with LOC (n=1) or FSIQ < 80 (n=1).

Seventeen controls were excluded during the screening visit. Reasons were as follows: The majority of exclusions were based upon not meeting SCID diagnosis for current cannabis dependence and/or being negative for THC-COOH on the urine toxicology screen (n=9). Others were excluded due to illicit drug use or SCID SUD diagnosis other than cannabis (n=3) or because they smoked less than five CPD (n=1). One participant met for current depression, and another met for a current eating disorder. One participant was excluded because he had a previous head injury with LOC (n=1) and one due to an FSIQ < 80 (n=1).

Seven controls dropped out of the study, six were lost to follow-up, and one got a job while enrolled in the study and could no longer participate. One patient dropped out because he relapsed within the first 3 days of beginning abstinence and chose to not continue participating. Participants were not considered drop-outs if they missed the one-month follow-up visit, given that this data was treated as exploratory as our primary interest was in changes over the one-
month abstinence period. Thus, the final study sample consisted of 39 participants: 19 patients with schizophrenia and 20 non-psychiatric controls. See Figure 3.1

**Figure 3.1 Consort Diagram**

CD, cannabis dependent; CPD, cigarettes per day; CTL, control; IQ, intelligent quotient; SCZ, schizophrenia; SUD, substance use disorder;

**Consort Diagram**
*Details of recruitment, screening, drop-outs and completion rates of participants for this study*
3.1.1 Sample Characteristics

Our sample was comprised of all male participants (N=39) with a current diagnosis of cannabis dependence according to the Structural Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders for Axis I disorders (DSM-IV) (APA, 2000).

Nineteen schizophrenia patients completed the study, of which 14 met for a DSM-IV diagnosis of schizophrenia and 5 with a diagnosis of schizoaffective. There was a nearly even split between first-episode patients (n=10) and more chronic cases of the illness (n=9). Patients were primarily taking atypical antipsychotic medication (n=17). Of these, patients were prescribed olanzapine (n=4), risperidone (n=4), risperdione consta (n=3), paliperidone (n=3), quetiapine (n=1) and clozapine (n=1). One patient was on a combination of an atypical and typical medication (quetiapine + fluphenazine). Lastly, one patient was taking flupentixol, a typical antipsychotic. The mean chlorpromazine (CPZ) equivalents of these medications are listed in table 3.1.

Three non-psychiatric controls had a history of depression, but not in the previous two years.

Patients and controls were comparable on age and race, but differed on FSIQ and years of education. That is, non-psychiatric controls had higher IQ scores (t(37) = -3.64, p =0.001) and had completed more years of education (t(37) = -3.45, p =0.001) than schizophrenia patients.

With respect to clinical scores, baseline means are provided so as to control for recency of cannabis use. Given that participants were instructed to not use cannabis 12 hours prior to the baseline visit, minimizes the possibility that these assessments reflect cannabis’ intoxicating effects. The mean PANSS and CDSS scores at baseline are listed in Table 3.1. Group differences on the HAM-D approached significance with patients demonstrating higher, more depressed scores than non-psychiatric controls (t(37) = 1.98, p =0.055).

The TOMM was completed at the cognitive training session to assess motivation. Given that all participants scored ≥ 45 on trial 2 indicates that patients and controls were exerting sufficient motivation and effort during the cognitive battery. In addition, no difference was observed between patients and controls on the TOMM trial 2 performance; (t(37) = -0.53 p =0.600). The retention trial did not have to be used on any participant.
### Table 3.1 Demographic and Clinical Characteristics

<table>
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<th>SCZ (n=19)</th>
<th>CTL (n=20)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Age (years)</td>
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<td>30.80 ±8.1</td>
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<tr>
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<td>FSIQ</td>
<td>91.21 ±8.6</td>
<td>101.60 ±9.2</td>
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<td>Education (years)</td>
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<td>13.35 ±2.4</td>
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<td>CPZ Equivalents</td>
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<td>n/a</td>
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<td>Duration of Illness</td>
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<tr>
<td>TOMM (trial 2)</td>
<td>49.53 ±1.2</td>
<td>49.70 ±0.8</td>
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</tr>
</tbody>
</table>

Values given in Mean ±Standard deviation; a, values are in numbers; * p<0.05
A, African; C, Caucasian; CDSS, Calgary Depression Scale for Schizophrenia; CPZ, chlorpromazine; HAM-D, Hamilton Depression Rating Scale; O, Other race; PANSS, Positive and Negative Symptom Scale

Substance-using characteristics of the two groups are listed in Table 3.2. Groups were well-matched on all cannabis-using variables such as cumulative use (joint-years), grams of cannabis used in the previous week (GPD) and money spent on cannabis in the prior week. Baseline THC-COOH levels were characterized in a subset of participants (SCZ, n=13; CTL, n=13), and did not significantly differ between diagnostic groups. The age of first initiation and age of regular (at
least weekly) cannabis use was similar between both diagnostic groups. The number of quit attempts between patients and controls did not differ between groups, nor did the mean baseline scores for MCQ and MWC.

According to the FTND, patients demonstrated higher levels of nicotine dependence compared to controls \([t(37) = 1.98, p=0.046]\). Despite this, the average number of cigarettes per day over the prior week did not differ between groups. Problematic alcohol use as indexed by the AUDIT, as well as alcoholic drinks consumed over the previous week did not differ between groups. Similarly, caffeinated beverages were comparable between patients and controls. Lastly, patients and controls reported similar levels of motivation to quit cannabis as measured by the contemplation ladder.

While participants with current SUDs (including alcohol) were excluded from the study, individuals who had been in remission for at least 6 months were included in the sample. Nine patients and 10 controls had previous diagnoses of SUDs. The proportion of these individuals did not differ between groups \([\chi^2 (1) = 0.03, p=0.56]\).

<table>
<thead>
<tr>
<th>Table 3.2 Substance-using Characteristics</th>
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</tr>
<tr>
<td>9.76 ±6.6</td>
</tr>
<tr>
<td>0.88</td>
</tr>
<tr>
<td>GPD</td>
</tr>
<tr>
<td>1.22 ±0.8</td>
</tr>
<tr>
<td>1.63 ±1.2</td>
</tr>
<tr>
<td>0.21</td>
</tr>
<tr>
<td>Baseline THC-COOH:Creatinine levels</td>
</tr>
<tr>
<td>49.00 ±47.7</td>
</tr>
<tr>
<td>100.26 ±104.2</td>
</tr>
<tr>
<td>0.12</td>
</tr>
<tr>
<td>($)/Week on Cannabis</td>
</tr>
<tr>
<td>43.95 ±36.2</td>
</tr>
<tr>
<td>64.75 ±58.6</td>
</tr>
<tr>
<td>0.19</td>
</tr>
<tr>
<td>Age of First Use of Cannabis</td>
</tr>
<tr>
<td>15.00 ±2.5</td>
</tr>
<tr>
<td>15.05 ±2.9</td>
</tr>
<tr>
<td>0.95</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td><strong>Age of Onset of Regular Cannabis Use</strong></td>
</tr>
<tr>
<td><strong># of Quit Attempts</strong></td>
</tr>
<tr>
<td><strong>MCQ</strong></td>
</tr>
<tr>
<td><strong>MWC</strong></td>
</tr>
<tr>
<td><strong>CPD</strong></td>
</tr>
<tr>
<td><strong>% of Tobacco Mixed with Cannabis</strong></td>
</tr>
<tr>
<td><strong>CO Level</strong></td>
</tr>
<tr>
<td><strong>FTND</strong></td>
</tr>
<tr>
<td><strong>AUDIT</strong></td>
</tr>
<tr>
<td><strong>Alcoholic Drinks/week</strong></td>
</tr>
<tr>
<td><strong>Caffeinated Beverages/week</strong></td>
</tr>
<tr>
<td><strong>Contemplation Ladder</strong></td>
</tr>
</tbody>
</table>

Values given in Mean ± Standard deviation; a, values are in numbers; * p<0.05
AUDIT, Alcohol Use Identification Test; CO, carbon monoxide; CPD, cigarettes per day; FTND, Fagerstrom Test of Nicotine Dependence; GPD, average grams of cannabis per day; MCQ, Marijuana Craving Questionnaire; MWC, Marijuana Withdrawal Checklist: THC-COOH:Creatinine, carboxy-tetrahydrocannabinol normalized to creatinine.

The majority of patients smoked cannabis using a joint (68.4%). The next preferred method of cannabis administration was a bong (15.8%). An equal number of patients stated that they routinely used more than one method of administration. Among controls, 50% of participants reported their preferred method of administration was using a joint, while 15% reported using a
bong and 15% using a pipe. Other less common routes were using a vaporizer (5%) and using a blunt (5%). The distribution of method used to deliver cannabis did not differ between groups; $[\chi^2=7.371 \text{ (df=6); } p=0.288]$. 

### 3.1.2 Associations between Clinical Symptoms and Cannabis Use

Baseline assessments, rather than screening assessments, were used to assess relationships between cannabis use and clinical outcomes in order to control for time of last use of cannabis.

Pearson correlations were conducted to assess for relationships between cumulative use (joint-years) and PANSS and depressive (CDSS, HAM-D) scores among patients. No associations emerged as significant. MWC also showed no relationship with joint-years. While the total MCQ score and Factor 1, 2 and 3 did not significantly correlate with joint-years; Factor 4 demonstrated a significant negative association with joint-years ($r=-0.459, n=19, p=0.048$).

To assess the effects of recent consumption of cannabis use in patients, correlations between GPD and clinical outcomes were evaluated. No significant associations were present between GPD and the subscales (positive, negative or general) of the PANSS or total PANSS scores. Interestingly, significant associations emerged between GPD and individual items on the positive subscale of the PANSS: conceptualization ($r=0.497, n=19, p=0.030$) and suspiciousness ($r=-0.563, n=19, p=0.012$). With respect to depression in schizophrenia patients, significant associations emerged between GPD and CDSS total score ($r=0.537, n=19, p=0.018$), and approached significance with HAM-D total score ($r=0.456, n=19, p=0.050$). In contrast, there was no significant relationship present in controls between GPD and HAM-D scores ($r=-0.211, n=20, p=0.373$). See Figure 3.2.

There was no significant association between GPD and craving outcomes or total score from the MWC in patients. However, individual items on the MWC demonstrated significant positive associations with GPD: sleep ($r=0.508, n=19, p=0.018$) and sweating ($r=0.788, n=19, p<0.01$). Relationships between PANSS scores and withdrawal and craving scores were also examined. Positive associations between PANSS scores and MWC total score emerged, for PANSS positive ($r=0.689, n=19, p<0.001$), negative ($r=0.493, n=19, p=0.031$), general ($r=0.553, n=19, p=0.014$)
and total scores \((r=0.711, n=19, p<0.001)\). MWC also significantly correlated with CDSS \((r=0.556, n=19, p=0.013)\) and HAM-D \((r=0.523, n=19, p=0.022)\) scores in patients. In controls, a positive correlation was found between HAM-D and MWC \((r=0.743, n=20, p<0.001)\).

Positive correlations were also found between CDSS and PANSS positive \((r=0.583, n=19, p<0.001)\), general \((r=0.722, n=19, p<0.001)\) and total score \((r=0.648, n=19, p<0.001)\). Similarly, positive correlations were also found between HAM-D and PANSS positive \((r=0.714, n=19, p<0.001)\), general \((r=0.742, n=19, p<0.001)\) and total score \((r=0.718, n=19, p<0.001)\). The negative PANSS subscale score did not significantly correlate with the CDSS or HAM-D.

Among control participants, no significant associations were present between cumulative cannabis use and clinical symptoms (HAM-D, MCS, MWC). With respect to GPD, only one relationship emerged as significant: a positive association between GPD and MCS Factor 4 \((r=0.532, n=20, p=0.016)\).
Figure 3.2 Association between Cannabis Use and Depression

Association between Cannabis Use and Depression

A significant correlation was observed between GPD and CDSS total score in patients, in that increasing cannabis use was associated with higher depressive scores on the CDSS. There was no significant relationship between cannabis use and negative symptomatology.

CDSS, Calgary Depression Scale for Schizophrenia; CTL, Controls, HAM-D, Hamilton Depression Scale; SCZ, schizophrenia

*p = 0.05; **p < 0.05
3.1.3 Baseline Cognitive Performance

When comparing the baseline cognitive function of patients with schizophrenia to controls no group differences emerged on any of the WCST or IGT outcomes. However, there were differences in select cognitive tasks when comparing baseline cognitive performance between schizophrenia patients and controls. As expected controls performed better than patients on the HVLT, the Digit Span, and on the Grooved Pegboard. There were no differences on any of the CPT outcomes, TMT (both A and B and B-A), SDR, KDDT, or BART. See Table 3.3

In order to determine if cannabis affected cognitive impairment in a dose-dependent manner, Pearson Product-Moment correlations were conducted between joint-years and cognitive function at baseline. Both patients and controls demonstrated significant correlations with increasing cannabis use and worse performance on the WCST and the HVLT. Patients demonstrated opposite relationships as well in that higher cannabis use correlated with better performance in the CPT. Among controls, significant correlations were also observed between joint-years and the TOMM, CPT and TMT. All significant and non-significant relationships are presented in Table 3.3

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>Subtest</th>
<th>SCZ (n=19): Joint-Years</th>
<th>CTL (n=20): Joint-years</th>
<th>Between group Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOMM</td>
<td>Trial 2</td>
<td>NS</td>
<td>r=-0.661, p=0.001**</td>
<td>NS</td>
</tr>
<tr>
<td>WCST</td>
<td># Trial</td>
<td>NS</td>
<td>r=0.584, p=0.007**</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td># Correct</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>% Error</td>
<td>r=0.476, p=0.040**</td>
<td>r=0.536, p=0.015**</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>% Perseverative Response</td>
<td>r=0.411, p=0.080*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>% Perseverative</td>
<td>r=0.435, p=0.063*</td>
<td>r=0.448, p=0.063*</td>
<td>NS</td>
</tr>
<tr>
<td>Error</td>
<td>% Non Perseverative Error</td>
<td>Categories Completed</td>
<td>Conceptual Response</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----------------------------</td>
<td>----------------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$r=0.448$, $p=0.054^*$</td>
<td>$r=0.407$, $p=0.083^*$</td>
<td>$r=0.469$, $p=0.043^{**}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$r=0.471$, $p=0.036^*$</td>
<td>$r=0.460$, $p=0.041^{**}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

| IGT                                        | Net Total                  | NS                   | NS                  |
|                                            | Total Money                | NS                   | NS                  |

| CPT                                        | % Hits                     | NS                   | NS                  |
|                                            | % Commission              | $r=-0.582$, $p=0.009^{**}$ | NS                  |
|                                            | Hit Rate                   | NS                   | NS                  |
|                                            | Variability                | NS                   | NS                  |
|                                            | Attentiveness              | $r=0.636$, $p=0.003^{**}$ | $r=-0.046$, $p=0.034^{**}$ |

<p>| HVLT                                       | Trial 1                    | $r=0.583$, $p=0.007^{<strong>}$ | t(37) = -2.69, $p=0.01$ |
|                                            | Trial 2                    | $r=0.521$, $p=0.019^{</strong>}$ | t(37) = -2.76, $p &lt; 0.01$ |
|                                            | Trial 3                    | $r=0.651$, $p=0.002^{<strong>}$ | t(37) = -2.42, $p = 0.02$ |
|                                            | Sum of Trial 1-3           | $r=0.639$, $p=0.002^{</strong>}$ | t(37) = -2.95, $p &lt; 0.01$ |
|                                            | Delayed Recall            | $r=0.464$, $p=0.039^{<strong>}$ | t(37) = -2.74, $p &lt; 0.01$ |
|                                            | Repetitions                | $r=0.625$, $p=0.004^{</strong>}$ | NS                  |
|                                            | Intrusions                 | $r=0.426$, $p=0.061^*$  | NS                  |
|                                            | True Positives             | $r=0.472$, $p=0.041^{**}$ | NS                  |
|                                            | False Positives            | NS                   | NS                  |
|                                            |                            | NS                   | t(35) = 3.08, $p &lt; 0.01$ |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>NS Retention</th>
<th>NS</th>
<th>t(35) = 1.73, p=0.09</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrusions</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Discrimination Index</td>
<td>NS</td>
<td>NS</td>
<td>t(35) = -2.80, p&lt;0.01</td>
</tr>
<tr>
<td><strong>Digit Span</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forwards</td>
<td>NS</td>
<td>NS</td>
<td>t(37)= -2.32, p&lt;0.03</td>
</tr>
<tr>
<td>Backwards</td>
<td>NS</td>
<td>NS</td>
<td>t(37)= -2.80, p&lt;0.01</td>
</tr>
<tr>
<td>Total</td>
<td>NS</td>
<td>NS</td>
<td>t(37)= -2.86, p&lt;0.01</td>
</tr>
<tr>
<td>TMT A (seconds)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>TMT B (seconds)</td>
<td>NS</td>
<td></td>
<td>r=0.481, p=0.032**</td>
</tr>
<tr>
<td>TMT B minus A (seconds)</td>
<td>NS</td>
<td></td>
<td>r=0.502, p=0.024**</td>
</tr>
<tr>
<td>SDR 5-second delay</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SDR 15-second delay</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>SDR 30-second delay</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>KDDT Geomean</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BART Avg. Adjusted Pumps</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Grooved Pegboard</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Time</td>
<td>NS</td>
<td>NS</td>
<td>t(37)= -2.42, p&lt;0.02</td>
</tr>
<tr>
<td>Total Pegs Dropped</td>
<td>NS</td>
<td>NS</td>
<td>t(37)= 3.23, p&lt;0.01</td>
</tr>
</tbody>
</table>

BART, Balloon Analog Risk Task; CPT, Continuous Performance Test; HVLT, Hopkins Verbal Learning Test; KDDT, Kirby Delay Discounting; SDR, Spatial Delay Response; TOMM, Test of Memory Malingering; TMT, Trail Making Test; WCST, Wisconsin Card Sorting Test; **p<0.05; *p<0.09
Correlations between Recent Cannabis Use and Cognition

With respect to recent use (GPD) among patients, the more cannabis used in the previous week, the worse the performance on the CPT and KDDT. GPD positively correlated with CPT variability ($r=0.542$, $n=19$, $p=0.017$); KDDT small reward ($r=0.613$, $n=19$, $p=0.005$) and geomean and ($r=0.553$, $n=19$, $p=0.014$). In contrast, no significant relationships were observed between recent cannabis use (GPD) and cognitive outcomes in control participants.

Associations between Clinical Symptoms and Cognitive Performance

Relationships between clinical symptoms and cognition were assessed at baseline. The majority of correlations that emerged as significant were between negative symptoms and cognitive performance. The higher the negative symptoms the worse patients performed cognitively: [WCST % perseverative responses ($r=0.577$, $n=19$, $p=0.010$) and errors ($r=-0.526$, $n=19$ $p=0.020$); CPT % hits ($r=-0.633$, $n=19$, $p=0.004$); Digit Span Forwards ($r=-0.545$, $n=19$, $p=0.016$); and Total ($r=-0.516$, $n=19$, $p=0.024$); TMT-B errors ($r=0.474$, $n=19$, $p=0.040$); and KDDT large reward ($r=0.646$, $n=19$, $p=0.003$).

The positive symptom subscale only correlated with one cognitive outcome: TMT-B errors ($r=0.682$, $n=19$, $p=0.001$). General and total scales correlated with overlapping cognitive test outcomes, which suggests that the more symptoms present, the worse patients performed: CPT % hits ($r=-0.497$, $n=19$, $p=0.003$) and ($r=-0.596$, $n=19$, $p=0.007$) respectively; HVLT intrusions ($r=0.643$, $n=19$, $p=0.003$) and ($r=0.624$, $n=19$, $p=0.004$) respectively; TMT-B errors ($r=0.571$, $n=19$, $p=0.011$) and ($r=0.652$, $n=19$, $p=0.002$) respectively.

In patients, higher levels of depressive symptoms correlated with select cognitive outcomes. WCST nonperseverative errors demonstrated negative relationships with both the CDSS ($r=0.577$, $n=19$, $p=0.010$) and HAM-D ($r=0.577$, $n=19$, $p=0.010$). HVLT intrusions positively correlated with the CDSS ($r=0.751$, $n=19$, $p<0.001$) and HAM-D ($r=0.623$, $n=19$, $p=0.004$). As did TMT-B errors [CDSS ($r=0.599$, $n=19$, $p=0.007$); HAM-D ($r=0.534$, $n=19$, $p=0.019$)]; and KDDT medium reward [CDSS ($r=0.496$, $n=19$, $p=0.031$); HAM-D ($r=0.466$, $n=19$, $p=0.044$)]. The GPB only correlated with the CDSS ($r=-0.541$, $n=19$, $p=0.017$), not the HAM-D. In controls, depression scores as measured by the HAM-D, only correlated with HVLT total repetitions ($r=0.600$, $n=20$, $p=0.005$).
3.2 Was the Abstinence Paradigm Successful?

3.2.1 Defining Abstainers and Non-Abstainers

Weekly subjective data from the TLFB-cannabis, demonstrated that 68.4% schizophrenia patients and 95% of control participants self-reported sustained abstinence for the full 28-day study period. See Table 3.4. When sustained abstinence was assessed according to biochemical verification (MEDTOX) at Day28, abstinence rates differed. That is, 47.4% of schizophrenia patients and 40% of controls yielded urine THC-COOH levels <50ng/mL using. See Table 3.5

<table>
<thead>
<tr>
<th>Table 3.4 Self-Reported Weekly Abstinence Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Control</td>
</tr>
</tbody>
</table>

Self-reported weekly abstinence was determined using TLFB score =0 at visits: Day0, Day7, Day21, and Day28

<table>
<thead>
<tr>
<th>Table 3.5 Biochemical Confirmation at Day 28 using MEDTOX</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Control</td>
</tr>
</tbody>
</table>

Negative results were determined with biochemically-verified in laboratory MEDTOX testing at Day 28. Negative results were determine by THC-COOH <50ng/mL. Positive results were determined by THC-COOH levels >50ng/mL
There is an obvious discrepancy between self-reported abstinence and biochemical verification of abstinence. Despite producing positive results on urine toxicology for THC-COOH, some participants claimed that they did indeed remain abstinent for the full 28-day period [SCZ: (CAN107, CAN116, CAN121, CAN126); CTL:(CAN204, CAN206, CAN211, CAN213, CAN215, CAN220, CAN224, CAN228, CAN231, CAN234)]. Therefore GC-MS, a sensitive quantitative urine analysis was employed on 9 samples from these individuals (baseline + 2 samples per week, for 4 weeks) (N=26). A THC-COOH: creatinine ratio was calculated for each sample in ng/mg. Following, each quotient calculated was divided by the previously collected sample quotient (urine2/urine1). The prediction model developed by Schwilke et al (2011) was applied to these quotients to biochemically determine whether new cannabis use was introduced during the 28-day abstinence period (Schwilke et al., 2011). Therefore, from this data, we can confidently determine which participants successfully abstained from cannabis for the full 28-day period. Table 3.6 presents re-calculated abstinence rates using GC-MS data to resolve discrepancies between participants’ self-report and urine analysis. Using this data we can now conclude that CAN107, CAN116, CAN204, CAN206, CAN215, CAN220, CAN224, CAN228 did not relapse during the abstinence period. Conflicting results are a product of two limitations of our study protocol: 1.) MEDTOX and other traditional immunoassay screens, do not take into consideration hydration level of the individual and 2.) 28-days of abstinence may not be sufficient to rid the body of below cut-off levels of THC-COOH. The latter point is especially applicable in cases of very heavy and prolonged cannabis use. Notably, even after sustained abstinence these individuals still possess detectable and quite substantial levels of THC. GC-MS elimination curves are presented in Figure 3.3 and Figure 3.4.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>No introduction of Cannabis</th>
<th>Relapse to Cannabis</th>
<th>Percent Abstinent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>19</td>
<td>10</td>
<td>9</td>
<td>52.6%</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>14</td>
<td>6</td>
<td>65%</td>
</tr>
</tbody>
</table>

Sustained cannabis abstinence was determined according to the Schwilke et al 2011 model.
Figure 3.3 THC-COOH Elimination Curves in Schizophrenia

Creatinine normalized THC-COOH Elimination Curves are presented in a subset of schizophrenia patients (n=13). Abstainers are plotted in blue; Relapsers are plotted in green.

THC-COOH Elimination Curves in Schizophrenia

Creatinine normalized THC-COOH Elimination Curves are presented in a subset of schizophrenia patients (n=13). Abstainers are plotted in blue; Relapsers are plotted in green.
Figure 3.4 THC-COOH Elimination Curves in Controls

THC-COOH Elimination Curves in Controls
Creatinine normalized THC-COOH Elimination Curves are presented in a subset of control participants (n=13). Abstainers are plotted in blue; Relapsers are plotted in green.
Importantly, with GC-MS, THC-COOH we were able to quantify THC-COOH levels at Day28 in ng/mL. Accordingly, participants with THC-COOH levels >20ng/mL at Day28 were considered to be positive for THC (Ellis et al., 1985). Only individuals who did not introduce new cannabis during the 28-day abstinence period AND achieved THC-COOH levels <20ng/mL at Day 28 were classified as “abstainers.” Study analyses were conducted using the classification presented in Table 3.7. Chi-square analyses revealed that there were no significant differences in rates of abstinence between patients and controls [$\chi^2=0.648$ (df=1), $p=0.527$].

What is also evident from Figure 3.3 and Figure 3.4 is that our binary abstinence classification can be broken down into more specific subgroups, which further details individual trajectories of cannabis use over the 28-day abstinence period. For example, there were two types of abstainers—those that remained abstinent and completely rid the body of THC, and those that did not (i.e., Reducing Abstainers with Day28 THC-COOH >20ng/mL). With respect to the latter group, these individuals may be heavier users and/or alternatively rid THC at a slower rate. Of individuals who relapsed, some participants classically relapsed demonstrating a short period of abstinence followed by continued use of cannabis throughout the 28 days. On the other hand, a small proportion of participants demonstrated one “lapse” at only one time point over the 28 days. Therefore, while abstainers demonstrated a mean % decrease in THC-COOH, non-abstainers did as well. The percent decrease between abstainers and non-abstainers was only significant in schizophrenia patients, not in controls. See Table 3.8. Figure 3.5 demonstrates the varied number of days of sustained abstinence achieved by our participants.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Abstainers</th>
<th>Non-Abstainers</th>
<th>% Abstinent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>19</td>
<td>8</td>
<td>11</td>
<td>42.1%</td>
</tr>
<tr>
<td>Control</td>
<td>20</td>
<td>11</td>
<td>9</td>
<td>55.0%</td>
</tr>
</tbody>
</table>

There were no differences in rates of abstinence between patients and controls [$\chi^2=0.648$ (df=1), $p=0.527$].
Individuals who did not introduce new cannabis during the 28-day abstinence period AND achieved THC-COOH levels <20ng/mL at Day 28 were classified as “abstainers.” Study analyses were conducted using this classification.

### Table 3.8 Percent Change of THC-COOH

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Abstainers</th>
<th>Non-Abstainers</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>13</td>
<td>94.17 ±5.3</td>
<td>57.74 ±42.9</td>
<td>0.048*</td>
</tr>
<tr>
<td>Control</td>
<td>13</td>
<td>97.17 ±2.0</td>
<td>72.35 ±40.5</td>
<td>0.19</td>
</tr>
</tbody>
</table>

*p<0.05

All four groups: patient abstainers and non-abstainers and control abstainers and non-abstainers demonstrate a decrease in THC-COOH from baseline to Day 28. However, the percent decrease between abstainers and non-abstainers was only significant in schizophrenia patients, not in controls.

### Figure 3.5 Days of Sustained Abstinence

This graph demonstrates the percentage of participants that achieved various lengths of sustained abstinence over the 28-day abstinence period.
3.3 **Withdrawal**

3.3.1 **What is the Time Course of Withdrawal in Abstinent Participants?**

In patients, there was no significant change in the total MWC severity score over time (Day0, Day7, Day14, Day21, Day28); \[F(4, 68) =1.607, p=0.182\]. However, in controls there was a trend towards change in MWC severity; \[F(4, 72) =2.172, p=0.080\]. This trend for change was driven by abstaining controls; \[F(4, 40) =3.944, p=0.009\]. No significant change was observed in non-abstaining controls; \[F(4, 32) =0.346, p=0.845\]. Post-hoc analyses revealed that a significant change was observed between Day0 and Day7; \[t(10) =2.335, p=0.042\], with symptoms peaking at Day7. Graphically, compared to baseline, patient abstainers had a peak in symptom severity at Day7 with another slight increase in symptoms at Day21. See **Figure 3.6**

We then compared abstaining participants between patients and controls. Mauchly’s test of sphericity was violated \(p=0.002\), thus Greenhouse-Geisser statistics are reported and results show no change in withdrawal symptoms over time in abstaining participants; \[F(4, 68) =2.306, p=0.095\].
**Trajectory of Withdrawal Symptoms over Time**

*In abstaining controls, withdrawal severity changed over time. There was no significant change in abstaining patients. Non-abstaining controls and non-abstaining patients also demonstrated a lack of change in symptom severity over time.*

\[\text{p<0.05 for the One-way ANOVA}\]
There is a noticeable peak in symptom severity at Day7, followed by a decrease in symptoms by Day14. As a result we wanted to see if we could detect a more robust change if we examined withdrawal symptoms during the first 2 weeks of abstinence only. Therefore we conducted RM-ANOVAs using just 3 time-points: (Day0, Day7, and, Day14) in patients and controls (abstainers versus non-abstainers). The time effect in both groups did not achieve significance.

Given that withdrawal symptoms peak within the first week, we also collected data at the midpoint (Day3) of week1. However, there was missing MWC at Day 3 for four patients and four controls. Six of these participants did not complete this measure as it was added to the protocol after they began the study; one participant missed the Day 3 visit.

A RM-ANOVA now using 6 time-points (Day0, Day3, Day7, Day14, Day21, Day28) demonstrated a non-significant time effect in patients; [F(5, 65) =1.155, p=0.341]; but a significant main effect of time in controls. A Greenhouse Geisser correction was applied; [F(2, 28.1) =7.243, p=0.003]. Post-hoc analyses revealed that there was a significant change in withdrawal symptoms in abstaining controls; [F1.4, 11.2) =7.121, p=0.015], but not in non-abstaining controls. When comparing diagnostic groups, a RM-ANOVA in abstainers, yielded a significant time effect, [F2.(5, 32.9) =3.271, p=0.040]. See Figure 3.7

Taken together, we can conclude that MWC severity scores in abstaining controls significantly changed over time, while patients’ withdrawal symptoms remained relatively stable with abstinence. Symptoms in controls peaked at Day 3 while the peak in patients was delayed in comparison, and occurred at Day7.
Figure 3.7 Trajectory of Withdrawal Symptoms over Time (6 Time-Points)

*\( p < 0.05 \), RM-ANOVA in abstainers main effect of time and one-way ANOVA in abstaining controls

**Trajectory of Withdrawal Symptoms over Time (6 Time-Points)**

*Withdrawal severity scores in controls significantly changed over time, with symptom severity peaking at Day3. There was no significant change in patient withdrawal scores over the 28-day abstinence period. In addition, among patients there was a lag in the onset of peak symptom severity (Day7) compared to controls.*

We were also interested in determining withdrawal curves in participants that did not introduce cannabis over the 28-days, as even if participants did not achieve <20ng/mL THC-COOH levels, there was a dramatic drop in THC-COOH observed in the first urine analysis done at Day 3 compared to baseline levels (Day0). However, findings remained comparable to the previous classification.

Participants for whom we had quantitative THC-COOH data, Pearson correlations were conducted to determine if there was an association between change in THC-COOH levels from baseline to Day7 and change in withdrawal symptom severity. No significant correlations emerged in either diagnostic group or when group together.
3.3.2 What are the Most Prevalent Withdrawal Symptoms?

Frequency of withdrawal symptoms at Day0 (baseline) after a minimum of 12 hours of abstinence was evaluated. The mean number of hours of abstinence did not differ between patients, (M= 18.76±8.9) and controls, (M= 15.97±8.0); [t(33) =0.977, p=0.336]. Among patients, the most frequently reported withdrawal symptoms, experienced by almost three-quarters of patients, were cravings (73.7%) and restlessness (73.7%). Sleep problems were also frequently reported (68.42%). Among controls, the most frequently reported symptoms were cravings for cannabis (65.0%), sleep problems (45.0%), and decreased appetite (45.0%).

At Day7 when withdrawal symptoms peaked\(^1\), among abstaining patients the most frequently reported symptoms was sleep problems (87.5%). Seventy-five percent of patients reported decreased appetite, cannabis cravings, as well as restlessness. Strange dreams (62.5%) and irritability (50%) were also commonly experienced. Among abstaining controls, similarly strange dreams (81.82%), cannabis cravings (72.7%), irritability (63.6%) and aggression (54.5%) were the most frequently reported withdrawal symptoms. The symptom rated as most severe on the CWS among patients was craving, and among controls, strange dreams was rated the most severe withdrawal symptom. See Figure 3.8

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\(^{1}\) Day7 data was used as opposed to Day3 data given that all participants had data at this time point
Figure 3.8 Prevalence of Cannabis Withdrawal Symptoms at Day7

Profile of withdrawal symptoms in abstaining schizophrenia patients and controls reported after 7-days of cannabis abstinence.

3.3.3 Do Withdrawal Symptoms Fully Remit with 28-days of Abstinence?

Symptoms that were present in >50% of abstaining patients or controls (decreased appetite, sleep problems, craving, restlessness, aggression and strange dreams) were individually analyzed to identify their time course and determine if they remitted by Day28 (i.e., returned to baselines levels). Decreased Appetite, sleep problems, restlessness and aggression all returned to baseline levels by Day28. In contrast, strange dreams among controls did not return to baseline levels by Day28; [F(1, 18) =13.157, p=0.002]. Post-hoc analysis revealed that among abstainers, there was a trend towards significance in the severity level of strange dreams between Day0 and Day28; t(10) =-1.896, p=0.087]. See Figure 3.9
Figure 3.9 Trajectory of Prevalent Withdrawal Symptoms Over Time

Strange Dreams

Decreased Appetite
Sleep Problems

### SCZ

- Abstainer (n=8)
- Non-Abstainer (n=11)

### CTL

- Abstainer (n=11)
- Non-Abstainer (n=9)

Restlessness

### SCZ

- Abstainer (n=8)
- Non-Abstainer (n=11)

### CTL

- Abstainer (n=11)
- Non-Abstainer (n=9)
Trajectory of Prevalent Withdrawal Symptoms over Time

Most reported withdrawal symptoms reported in patients and controls are plotted. Strange
dreams, appetite and sleep problems in abstaining SCZ appear to follow a bimodal trajectory,
with a peak in symptoms at Day7 and then followed by an attenuated peak at Day21. Strange
dreams was the only symptom that persisted beyond the one-month abstinence period in control
participants.
3.4 Craving

3.4.1 What is the Time Course of Craving?

In patients, a RM-ANOVA demonstrated that there was no significant change in the total MCQ severity score over time. Sphericity was violated ($p=0.011$), therefore Greenhouse-Geisser statistics were used; $[F(2.6, 68) =2.110, p=0.119]$. Among controls, with a correction for a violation of sphericity, a significant change in total craving symptom scores across time emerged; $[F(2.1, 72) =3.328, p=0.045]$; however the interaction term (time x abstinence status) was not significant. While, abstaining and non-abstaining controls (appear to graphically) decrease in craving symptoms over time, post-hoc analyses failed to achieve statistical significance. Subsequently, we wanted to determine if we could detect a more robust change if we examined craving symptoms during the first 2 weeks of abstinence only. Therefore we conducted RM-ANOVAs using just 3 time-points: (Day0, Day7, and, Day14) in patients and controls (abstainers versus non-abstainers). The time effect in controls achieved significance; $[F(2, 36)=6.046, p=0.005]$. Post-hoc analyses showed a significant time effect in non-abstainers; $[F(2, 16)=4.617, p=0.026]$, but not abstainers. See Figure 3.10

Using Day3 data and thus 6 time points, total craving scores remained stable over time in patients. Similar to when using 5-time point, among controls, severity scores changed significantly over time; $[F(5, 70)=7.142, p<0.000]$, and no significant change over time emerged in patients. However, post-hoc analyses revealed that severity craving scores of abstaining controls significantly changed over time; $[F(5, 40)=5.792, p<0.000]$, while there was no change in non-abstaining controls.
Figure 3.10 Trajectory of Cannabis Cravings over Time

** p<0.05 for time effect in controls across 28 days and within the first 14 days; *p<0.05 for post-hoc time effect within the first 14 days in non-abstaining controls

**Trajectory of Craving Symptoms over Time**

*No significant changes in craving scores were observed in schizophrenia patients. A significant time effect was observed in craving scores in controls. Craving scores decreased in severity from Day0 to Day14 in non-abstaining controls. Craving scores among abstaining controls did not change over time.*
**Trajectory of Craving Symptoms Over Time in Controls (6 Time-Points)**

Among controls, there was a significant change in the severity of craving scores across 6 time-points. This effect was driven by decreasing craving scores in abstaining controls over time.

Scores from factor 1, 2, and 4 did not show any significant change over time in patients or controls. Among controls, Mauchly’s test of sphericity was violated (p<0.05), therefore Greenhouse-Geisser statistics are reported and results are significant for main effect of time; [F(2.4, 42.8) =4.736, p=0.010] and the interaction of time by group was not significant. Post-hoc analyses revealed that abstaining controls factor 3 craving severity significantly decreased over time with abstinence; [F(4, 40) =3.553, p=0.014]. This was not significant in non-abstaining controls. See Figure 3.12. Among schizophrenia patients, there was no change in factor 3 craving scores over time.
Figure 3.12 Trajectory of Cannabis Cravings over Time in Controls (Factor 3)

** MCQ-Factor 3 significantly decreased in controls over time. Post-hoc analyses revealed that this effect was driven exclusively by decreasing craving scores among abstaining controls.

3.5 Clinical Symptoms

3.5.1 PANSS

RM-ANOVAs were conducted in order to detect whether PANSS subscales and total scores changed over time according to abstinence status in schizophrenia patients. No significant main effects of time were observed in the positive; [F(4, 68) =1.430, p=0.234], negative subscore; [F(4, 68) =0.882, p=0.480], general subscore; [F(4, 68) =1.229, p=0.307], or the total symptoms score; [F(4, 68) =1.112, p=0.358]. Interaction terms were also non-significant. See Figure 3.13
Trajectory of PANSS Symptoms over Time in Patients

The PANSS positive, negative and general symptom subscales as well as total PANSS scores did not significantly change over time in either in schizophrenia patients.
3.5.2 Depression Scales

In patients, at baseline, there was no significant difference in depression scores on the CDSS between abstainers and non-abstainers, \([t(18) = 1.430, p=0.145]\). Further, RM-ANOVAs demonstrated a significant change in the total CDSS severity score over time in patient abstainers and non-abstainers; \([F(4, 68) = 4.436, p=0.003]\). The interaction \([F(4, 68) = 0.337, p=0.882]\) and between group effects \([F(1, 17) = 1.877, p=0.189]\) were not significant. When one-ANOVAs were conducted within each group both abstainers \([F(4, 28) = 2.697, p=0.051]\) and non-abstainers \([F(4, 28) = 2.200, p=0.086]\) showed trends for a reduction in depressive symptoms. See Figure 3.14. A large effect size was observed in abstainers for the difference between depressive symptoms at baseline compared to depressive symptoms at Day28 \((d=1.56)\), while a small effect size was found in non-abstainers \((d=0.49)\). Given that the confidence intervals of these effect sizes did overlap suggests that there was no statistical difference between these two effect sizes; \([\text{Abstainers; (0.44, 2.67); Non-Abstainers (-0.48, 1.47)}]\).

Both patients and controls completed the HAM-D. RM-ANOVAs demonstrated that there was no significant change in HAM-D scores over time in patients \([F(4, 68) = 0.823, p=0.515]\) or in controls; \([F(4, 72) = 1.360, p=0.256]\).
3.5.3 Extra-pyramidal symptoms

Among patient abstainers, there was no difference on SARS, BARS, AIMS scores between baseline and week 4; [SARS: (t(6) =0.0, p=1.0)); BARS: (t(6) =1.0, p=0.356); AIMS: (t(6) =1.0, p=0.356)]. Similarly there was no difference in scores between patients who abstained and patient non-abstainers on these assessments at baseline and at Day28.
3.6 Trajectory of Substance Use with Abstinence

3.6.1 Tobacco

In patients, there was a significant change in CPD over time, even when applying a Greenhouse-Geisser correction for violation of sphericity; [F(2.37, 68) = 3.254, p = 0.041], however, one-way ANOVAs in patient abstainers and non-abstainers were not significant. Among controls, there was no significant change in CPD over time; [F(4,72) = 0.513, p = 0.726]. See Figure 3.15

3.6.2 Alcohol

Among patients, RM-ANOVAs demonstrated that there was no significant change in alcohol use over time; [F(4, 68) = 1.279, p = 0.287]. In controls, however, there was a significant main effect of time. Greenhouse-Geisser statistics are reported; [F(2.1, 72) = 3.325, p = 0.034]. Post-hoc analyses revealed no significant change over time in alcohol use in either abstainers or non-abstainers. See Figure 3.16

3.6.3 Caffeine

Among patients, RM-ANOVAs demonstrated no significant change in caffeine over time; [F(4, 68) = 0.641, p = 0.635]. In controls, similarly, RM-ANOVAs showed no significant change in caffeine over time; [F(4, 72) = 1.388, p = 0.247].
Figure 3.15 Trajectory of Tobacco Use over Time

There was an overall significant change over time in CPD in patients with schizophrenia. CPD peaked at Day7 in patients and then tapered off over the next 21 days, returning to baseline levels by Day28. Among controls, there was no significant change in CPD over time.

Interestingly, among patients, correlations were present between CPD and MWC scores ($r=0.499$, $n=19$, $p=0.029$) and MCQ scores ($r=0.712$, $n=19$, $p=0.001$). These relationships were not significant in controls.

*p<0.05; CPD; cigarettes per day
There was no significant change in alcohol use over time in either patients or controls. However, both controls abstainers and non-abstainers non-significantly appeared to increase their alcohol intake at Day7. This slight increase in both groups likely explains why there was a significant time effect in controls.
3.7 Trajectory of Cognitive Symptoms with Abstinence

3.7.1 Attention

CPT % Hits
Among patients, there was no significant change in CPT % hits over time; $[F(2, 34) =1.315, p=0.282]$. There was a significant interaction of time by abstinence status; $[F(2, 34) =5.529, p=0.008]$. A one-way ANOVA was not significant in abstainers; $[F(2, 14) =2.237, p=0.144]$, but was significant among non-abstaining patients $[F(2, 20) =4.217, p=0.019]$. A significant improvement was seen between Day14 and Day28; $[t(10) =2.252, p=0.048]$

Controls showed no significant main effect of time or interaction of time by abstinence status; $[F(2, 36) =0.247, p=0.782]$ and $[F(2, 36) =0.822, p=0.448]$ respectively.

Abstainers, demonstrated no significant main effect of time in CPT% hits; $[F(2, 34) =0.238, p=0.789]$. However, the time by group interaction term was significant; $[F(2, 34) =3.886, p=0.030]$. Post-hoc analyses revealed that performance significantly differed between Day0 and Day28; $F(1,17) =8.089, p=0.011$. See Figure 3.17
**Figure 3.17 Trajectory of CPT % Hits over Time**

Both patient and control abstainers did not show any change in CPT % hits over time. However, schizophrenia non-abstainers demonstrated improved performance over time.
CPT % Commission Errors

Among patients, there was no significant change in CPT % commission errors over time; [F(2, 34) =1.282, p=0.291]; however, the interaction, time by abstinence status, was significant; [F(2, 34) =3.965, p=0.028]. A one-way ANOVA was not significant in abstainers; [F(2, 14) =2.237, p=0.144], but was significant among non-abstaining patients [F(2, 20) =4.217, p=0.019]. Improvement occurred between Day0 and Day28; [t(10) =2.293, p=0.045].

Among Controls, there was no significant main effect of time; [F(2, 36) =1.304, p=0.284] or interaction effect with respect to abstinence status; [F(2, 36) =0.911, p=0.411].

Among abstainers, Mauchly’s test of sphericity was violated (p<0.05), therefore Greenhouse-Geisser statistics are reported and results are non-significant for main effect of time; [F(1.5, 34) =2.595, p=0.106] and the interaction of time by group [F(1.5, 34) =0.388, p=0.682]. See Figure 3.18
Both patient and control abstainers did not show any change over time in CPT % commission errors. However, schizophrenia non-abstainers demonstrated improved performance over time.
**Trail Making Test A**

Among patients, Mauchly’s test of sphericity was violated (p=0.011), thus Greenhouse-Geisser statistics are reported and results are non-significant for main effect of time; [F(1.4, 34) =0.049, p=0.898] as well as for the interaction of time by group [F(1.4, 34) =0.365, p=0.697].

Similarly, among controls, RM-ANOVAs; within factor: time; between factor: abstinence status, showed no significant main effect of time or interaction of time by abstinence status; [F(2, 36) =0.790, p=0.461] and [F(2, 36) =0.494, p=0.614] respectively. The between group effect was also non-significant; [F(1, 18) =0.017, p=0.899].

Among abstainers, Mauchly’s test of sphericity was violated (p=0.004), therefore Greenhouse-Geisser statistics are reported and results for main effect of time; [F(1.3, 34) =0.910, p=0.412] and the interaction of time by group [F(1.3, 34) =0.845, p=0.755] are non-significant.

### 3.7.2 Verbal memory and Learning

**HVLT sum of trials 1-3**

Among patients there was no significant main effect of time on HVLT sum of trials 1-3; [F(2, 34) =0.002, p=0.998] or time by group; [F(2, 34) =0.1916, p=0.410].

Controls, showed a trend towards significance for the main effect of time; [F(2, 34) =2.687, p=0.082]. However, the time by abstinence interaction was non-significant [F(2, 34) =0.908, p=0.911]. One-way ANOVAs conducted in control abstainers and non-abstainers both emerged as non-significant; F(2, 20) =1.572, p=0.232] and F(2, 20) =1.300, p=0.303].

Among abstainers, there was no significant main effect of time HVLT sum of trials 1-3; [F(2, 34) =1.495, p=0.239] or time by group; [F(2, 34) =0.166, p=0.847].
**HVLT Delayed Recall**

Patients demonstrated no significant main effect of time for HVLT delayed recall; [F(2, 34) =1.844, p=0.174] or time by group; [F(2, 34) =2.117, p=0.136].

Among controls, no significance emerged for the main effect of time; [F(2, 34) =1.707, p=0.197], however, the time by abstinence interaction was significant [F(2, 34) =3.715, p=0.035]. Post analyses revealed that the interaction effect was both significant between Day0 and Day14; [F(1, 18) =9.913, p=0.006] and Day14 and Day28; [F(1, 17) =4.597, p=0.047].

Among abstainers, there was a significant main effect of time HVLT delayed; [F(2, 34) =5.455, p=0.009]. The interaction effect was not significant; [F(2, 34) =0.276, p=0.760]. One-way ANOVAs in patient and control abstainers did not achieve significance. See Figure 3.19
Figure 3.19 Trajectory of HVLT Delayed Recall over Time

**p<0.05 for time effect; **p<0.05 for time x group interaction effect
HVLT, Hopkins Verbal Learning Test

**Trajectory of HVLT Delayed Recall over Time**

Abstainers demonstrated improved performance on the HVLT delayed recall over time. In controls, there was a significant interaction effect between time and abstinence status.
**HVLT % Retention**

Patients demonstrated a significant main effect of time for HVLT percent retention; \( [F(2, 34) = 7.740, p=0.002] \) but not time by group; \( [F(2, 34) = 1.397, p=0.261] \). Post-hoc analyses demonstrated significant improvement over time in patient abstainers; \( [F(2, 14) = 4.73, p=0.021] \), but not non-abstainers; \( [F(2, 20) = 2.198, p=0.137] \).

Among controls, no significant main effect of time emerged; \( [F(2, 34) = 0.650, p=0.528] \), but time by group interaction was significant; \( [F(2, 34) = 3.391, p=0.045] \). One-way ANOVAs demonstrated that both control abstainers and non-abstainers had no significant change in performance over time \( [F(2, 20) = 2.268, p=0.129] \) and \( [F(2, 14) = 1.770, p=0.206] \).

Among abstainers, there was a significant main effect of time for HVLT % retention; \( [F(2, 34) = 6.901, p=0.003] \). Time by diagnosis was not significant; \( [F(2, 34) = 0.894, p=0.418] \). A one-way ANOVA in patient abstainers demonstrated a significant improvement over time in performance; \( [F(2, 14) = 4.733, p=0.027] \). Post-hoc analyses revealed that significant changes occurred between Day 0 and Day28; \( [t(7) = 2.450, p=0.044] \). Control abstainers had no significant change in performance over time \( [F(2, 20) = 2.268, p=0.129] \). Notably, there was a 39.28% improvement in SCZ-abstainers and a 12.33% improvement in CTL. See Figure 3.20
**Figure 3.20 Trajectory of HVLT % Retention over Time**

Schizophrenia abstainers demonstrated improved performance on the HVLT delayed recall over time, between Day0 and Day28; this effect was not significant in controls.

*p<0.05 for time effect; **p<0.05 for time x group interaction effect
HVLT, Hopkins Verbal Learning Test
While exploratory in nature, given that HVLT % retention improved in patients with schizophrenia with abstinence, we sought to determine what happened after abstinence ceased, and participants relapsed. Cannabis was resumed in all participants immediately after the abstinence period ended. Six abstaining patients (out of the 8) completed the one-month follow-up. Thus, we examined HVLT performance across the 56-day period using four time-points (Day0, Day14, Day28 and Day56). RM-ANOVAs revealed a significant change in HVLT % retention performance over time; [F(3, 15) =5.026, p=0.013]. Post-hoc analyses revealed that a significant change occurred between Day 0 and Day28; [t(5) =2.797, p=0.038, and between Day28 and Day56; [t(5) =3.3013, p=0.030. See Figure 3.21

**Figure 3.21 Trajectory of HVLT % Retention with Relapse in Patients**

**p< 0.05 overall time effect; *p< 0.05 significant change between Day0 and Day28 and Day 28 and Day56; HVLT, Hopkins Verbal Learning Test**

**Trajectory of HVLT % Retention with Relapse in Patients**

A significant change in HVLT % retention occurred over time in patient abainers who relapsed at Day28.
It is important to determine if cannabis use returned to baseline levels after the abstinence period ended, therefore we assessed cannabis consumption at the one-month follow-up, Day 56 in comparison to baseline levels of cannabis use. While average cannabis use (number of grams per day and number of days in the last 30 participants reported using cannabis) did not significantly differ between the baseline visit and the one-month follow-up, Figure 3.22 demonstrates graphically that a reduction clearly occurred.

**Figure 3.22 Change in Cannabis Between Baseline and Follow-up in Patients**

*Change in Cannabis Consumption Between Baseline and Follow-up in Patients*

*There was a non-significant decrease in cannabis consumption between Day 0 and Day 56, among abstaining patients who relapsed.*
In contrast, cannabis resumption among non-psychiatric controls (N=4) had little effect on HVLT performance, akin to cannabis abstinence. RM-ANOVAs revealed no significant change in HVLT % retention performance over time (Day 0 until Day 56); [F(3, 9) =1.820, p=0.214]. See Figure 3.23

Figure 3.23 Trajectory of HVLT % Retention with Relapse in Controls

Trajectory of HVLT % Retention with Relapse in Controls
No significant change in HVLT % retention occurred over time in control abstainers who relapsed at Day28.
3.7.3 Working Memory

**Digit Span Forward**

Among patients, there was a non-significant main effect of time and a non-significant interaction effect of time by abstinence status for performance on the Digit Span Forward; \[F(2, 34) =1.046, p=0.362\] and; \[F(2, 34) =0.541, p=0.587\] respectively.

Similar findings were found in controls: A non-significant main effect of time for performance; \[F(2, 36) =1.594, p=0.217\] and for time by group interaction; \[F(2, 36) =0.546, p=0.584\].

Among abstainers, RM-ANOVAs; within factor: time; between factor: group, demonstrated a non-significant main effect of time for performance on the Digit Span Forward; \[F(2, 34) =1.424, p=0.255\]. Time by diagnosis was also non-significant; \[F(2, 34) =0.246, p=0.784\].

**Digit Span Total**

Among patients, no significance emerged for a main effect of time on the Digit Span Total score; \[F(2, 34) =1.527, p=0.232\] or for time by abstinence status; \[F(2, 34) =1.421, p=0.255\].

Results in control also demonstrated no main effect of change over time; \[F(2, 36) =1.383, p=0.264\] or for the interaction of time by abstinence status; \[F(2, 36) =0.253, p=0.778\].

Among abstainers, RM-ANOVAs: there was a non-significant main effect of time for performance on the Digit Span Total score; \[F(2, 34) =1.964; p=0.456\]. Time by diagnosis was also non-significant; \[F(2, 34) =0.341, p=0.713\].

**SDR-5 sec delay**

A RM-ANOVA in patients demonstrated a violation of Mauchly’s test of sphericity (\(p=0.040\)), thus Greenhouse-Geisser statistics are reported. Results were non-significant for both the main and interaction effects on the SDR 5-second delay; \[F(1.5, 34) =2.643, p=0.103\]; \[F(1.5, 34) =0.138, p=0.812\] respectively.

Likewise, among controls there was a non-significant main effect and interaction effect for performance on the SDR-5 second delay; \[F(2, 36) =0.083, p=0.921\] and for time by group interaction; \[F(2, 36) =0.798, p=0.459\].
Among abstainers, RM-ANOVAs; within factor: time; between factor: group, demonstrated a non-significant main effect of time for performance on the SDR-5 second delay; [F(2, 34) =0.104, p=0.901]. Time by diagnosis was also non-significant; [F(2, 34) =1.076, p=0.353].

**SDR-15 sec delay**

A RM-ANOVAs in patients: showed no significant change for both the main and interaction effects on the SDR 15-second delay; [F(2, 34) =0.249, p=0.781]; [F(2, 34) =1.928, p=0.161] respectively.

Similarly for controls, RM-ANOVAs, there was a non-significant main effect and interaction effect for performance; [F(2, 36) =1.406, p=0.258]; [F(2, 36) =0.352, p=0.706], respectively.

Among abstainers, RM-ANOVAs; there was a trend towards a significant main effect of time for performance on the SDR-15 second delay; [F(2, 34) =2.880, p=0.070]. Time by diagnosis was not significant; [F(2, 34) =0.549, p=0.583]. When one-way ANOVAs were conducted in both patient abstainers and control abstainers, change in performance over time did not achieve significance.

**SDR-30 sec delay**

Among patients, there was a non-significance for both main and interaction effects on the SDR 30-second delay; [F(1, 34) =0.408, p=0.668]; [F(1, 34) =0.166, p=0.842] respectively.

For controls, RM-ANOVAs: also demonstrated a significant main effect [F(2, 36) =3.766, p=0.033]; and a non-significant interaction effect for performance on the SDR-30 second delay; [F(2, 36) =0.573, p=0.569].

Among abstainers, RM-ANOVAs; within factor: time; between factor: group, demonstrated a non-significant main effect of time for performance on the SDR-30 second delay; [F(2, 34) =2.185, p=0.137]. Time by diagnosis was also non-significant; [F(2, 34) =1.777, p=0.184].
3.7.4 Executive Function

Trail Making Test B

RM-ANOVAs in patients showed a non-significant main and interaction effect on the TMT-B; [F(2, 34) = 2.292, \( p = 0.116 \)]; [F(2, 34) = 0.744, \( p = 0.483 \)] respectively.

For controls, there was a significant main effect of time [F(2, 36) = 4.281, \( p = 0.021 \)]; and a non-significant interaction effect for performance on the TMT-B; [F(2, 36) = 0.527, \( p = 0.595 \)]. However, post-hoc analyses in control abstainers and non-abstainers were both non-significant.

Among abstainers, RM-ANOVAs; there was a non-significant main effect of time for performance on the TMT-B; [F(2, 34) = 2.175, \( p = 0.129 \)]. Time by diagnosis was also non-significant; [F(2, 34) = 0.204, \( p = 0.817 \)].

Digit Span Backwards

Among patients, both the main and interaction effects on the Digit Span Backwards were not significant; [F(2, 34) = 0.821, \( p = 0.470 \)]; [F(2, 34) = 1.868, \( p = 0.170 \)] respectively.

For controls, a RM-ANOVAs also demonstrated a non-significant main effect [F(2, 36) = 0.198, \( p = 0.821 \)]; and a non-significant interaction effect for performance; [F(2, 36) = 0.011, \( p = 0.989 \)].

Among abstainers, RM-ANOVAs; there was a non-significant main effect of time for performance on the Digit Span Backwards; [F(2, 34) = 0.778, \( p = 0.467 \)]. Time by diagnosis was also non-significant; [F(2, 34) = 0.607, \( p = 0.551 \)].

3.7.5 Motor Function

Grooved Pegboard

A RM-ANOVA in patients violated Mauchly’s test of sphericity (\( p = 0.020 \)), therefore Greenhouse-Geisser statistics are reported and reflect non-significant results for the time and interaction effects for performance on the Pegboard (total time); [F(1.4, 34) = 1.692, \( p = 0.208 \)]; [F(1.2, 34) = 0.873, \( p = 0.398 \)] respectively.
Controls, demonstrated a significant main effect of time \([F(2, 36) = 6.391, p=0.004]\); and a non-significant interaction effect; \([F(2, 36) = 1.555, p=0.225]\). Post-hoc analyses showed that while a one-way ANOVA was not significant in abstainers, non-abstainers significantly improved in performance over time; \(F(1,16) = 8.239, p=0.003\).

Among abstainers, a RM-ANOVA demonstrated a violation of Mauchly’s test of sphericity (\(p<0.001\)), therefore Greenhouse-Geisser statistics are reported; results approach significance \([F(1.2, 34) = 3.480, p=0.070]\). The interaction effect of time by diagnosis was not significant \([F(1.2, 34) = 0.525, p=0.596]\) respectively.

### 3.7.6 Impulsivity

**KDDT Average Ln**

A RM-ANOVA in patients demonstrated a non-significant main and interaction effect on the KDDT; \([F(2, 34) = 0.949, p=0.397]\); \([F(2, 34) = 1.240, p=0.302]\) respectively.

Similarly, for controls the main effect; \([F(2, 36) = 0.973, p=0.388]\); and the interaction effect; \([F(2, 36) = 0.305, p=0.739]\) were both non-significant.

Among abstainers, a RM-ANOVA revealed a non-significant main effect of time for performance on KDDT; \([F(2, 34) = 0.778, p=0.467]\). However, the time by diagnosis interaction effect was significant; \([F(2, 34) = 3.420, p=0.044]\).

**BART Average Adjusted Pumps**

A RM-ANOVAs in patients demonstrated were non-significant for both the main and interaction effects on the BART; \([F(2, 24) = 0.560, p=0.579]\); \([F(2, 24) = 0.471, p=0.630]\) respectively.

Likewise, for controls, a RM-ANOVA demonstrated a non-significant main effect; \([F(2, 28) = 0.668, p=0.520]\); and a non-significant interaction effect; \([F(2, 28) = 0.199, p=0.820]\).

Among abstainers, a RM-ANOVA revealed a non-significant main effect of time on BART performance; \([F(2, 24) = 0.016, p=0.984]\). However, the time by diagnosis interaction effect was significant; \([F(2, 24) = 0.857, p=0.437]\).
3.8 Factors Associated with Sustained Abstinence

Lastly, we were interested in determining if baseline characteristics or clinical variables were associated with abstinence status in patients and controls. While these analyses were exploratory, results may help to identify potential risk factors that hinder successful abstinence.

3.8.1 Are Baseline Characteristics Associated with Abstinence Status?

Age, IQ and education did not significantly differ between abstainers and non-abstainers in patients or among control participants. Most clinical variables including baseline MWC and MCQ, PANSS severity and depression did not show a difference between patient abstainers and non-abstainers. Similarly, among patients, chlorpromazine equivalents were comparable between the two groups. However, among controls there was a trend for non-abstainers to have higher baseline depressive scores on the HAM-D.

Self-reported cannabis consumption at baseline trended towards significance among patients. Not surprisingly, non-abstainers had (non-significantly) greater baseline cannabis use compared to patient abstainers. Scores on the contemplation ladder at baseline also trended towards significance among patients. That is, abstainers had elevated scores on this measure compared to non-abstaining patients. After 28-days of abstinence, scores on the contemplation ladder did not significantly change from baseline scores in patients. Similarly, in controls, baseline contemplation ladder scores did not differ between abstainers and non-abstainers. However after 28-days of abstinence, motivation levels to quit cannabis were significantly higher than compared to baseline; \[t(19)=-2.610, p=0.017\].

See Table 3.9 for all demographic and clinical comparisons between abstainers and non-abstainers in patients and controls.
### Table 3.9 Sample Characteristics by Abstinence Status

<table>
<thead>
<tr>
<th></th>
<th>SCZ (n=19)</th>
<th>CTL (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abstainers (n=8)</td>
<td>Non-Abstainers (n=11)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.6 ±8.8</td>
<td>30.8 ±9.6</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.1 ±2.2</td>
<td>10.9 ±1.6</td>
</tr>
<tr>
<td>FSIQ</td>
<td>91.5 ±10.3</td>
<td>91.0 ±7.8</td>
</tr>
<tr>
<td>CPZ Equivalents</td>
<td>376.86 ±238.9</td>
<td>336.87 ±170.4</td>
</tr>
<tr>
<td>PANSS +</td>
<td>14.13 ±4.3</td>
<td>13.64 ±3.8</td>
</tr>
<tr>
<td>PANSS -</td>
<td>12.38 ±2.9</td>
<td>13.64 ±4.7</td>
</tr>
<tr>
<td>PANSS General</td>
<td>25.75 ±3.2</td>
<td>25.91 ±5.1</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>52.25 ±8.4</td>
<td>53.18 ±11.3</td>
</tr>
<tr>
<td>CDSS</td>
<td>1.75 ±1.2</td>
<td>3.27 ±3.4</td>
</tr>
<tr>
<td>HAM-D</td>
<td>4.00 ±2.1</td>
<td>4.64 ±3.5</td>
</tr>
<tr>
<td>MWC</td>
<td>10.25 ±7.2</td>
<td>10.82 ±6.8</td>
</tr>
<tr>
<td>MCQ</td>
<td>40.63 ±21.0</td>
<td>43.09 ±11.4</td>
</tr>
<tr>
<td>Cannabis grams/day</td>
<td>0.81 ±0.4</td>
<td>1.41 ±0.8*</td>
</tr>
<tr>
<td>Joint-years</td>
<td>10.8 ±9.1</td>
<td>9.57 ±6.1</td>
</tr>
<tr>
<td>Contemplation Ladder</td>
<td>5.75 ±2.1</td>
<td>3.91 ±2.0*</td>
</tr>
</tbody>
</table>

Values given in Mean ±Standard deviation; a, values are in numbers; **p<0.05; *p<0.09
CDSS, Calgary Depression Scale for Schizophrenia; CPZ, Chlorpromazine; FSIQ, Full Scale Intelligent Quotient; HAM-D, Hamilton Depression Rating Scale; MCQ, Marijuana Craving Questionnaire; MWC, Marijuana Withdrawal Checklist; PANSS, Positive and Negative Symptom Scale
3.8.2 Baseline Cognitive Function

Independent t-tests were conducted within each diagnostic group to determine if cognition at baseline differed between abstainers and non-abstaining participants. Among patients, differences emerged in select cognitive tasks demonstrating that abstainers possessed better cognitive performance compared to non-abstainers. For example, abstainers demonstrated better scores on the CPT: CPT % Hits; \[t(17) = 3.501, p = 0.008\] and CPT variability; \[t(17) = -2.092, p = 0.033\]. Given that GPD trended towards significance, we re-ran analyses adding GPD to the model as a covariate. Results remained significant for CPT % Hits; \[F(2, 16 = 4.522, p = 0.028)\], but not variability. See Figure 3.24

In addition, there was a trend towards better IGT performance among patient abstainers versus non-abstainers; IGT (total money \[t(17) = 2.027, p = 0.059\]. No other group differences were observed. When t-tests were conducted in controls, there were no differences in performance between abstainers and non-abstainers emerged on any cognitive task.

For exploratory purposes, binary logistic regressions were conducted to determine whether there are cognitive predictors of abstinence in patients and controls. Notably, CPT % hits trended as a significant predictor of abstinence in patients; \([b = -4.064 \text{ Wald } \chi^2(1) = 3.715, p = 0.054]\). This relationship was not significant in control participants.
Among patients, baseline CPT performance differed between patients who were able to successfully abstain from cannabis compared to non-abstaining patients. Among controls baseline CPT performance was not associated with abstinence status.
There is an abundance of data available investigating the effects of cannabis on cognitive function in schizophrenia. Studies report inconsistent findings, and to date results are contradictory and confusing. Notably, the cross-sectional designs employed by previous studies have not allowed for the appropriate assessment of whether better cognition is attributed to cannabis itself (a state-effect) or if it is a reflection of cannabis-using patients being a higher functioning subgroup (a trait-effect) than non-users. Thus, the primary goal of this study was to introduce a novel longitudinal paradigm to specifically examine the state-dependent effects of 28-days of cannabis abstinence on memory and learning performance (i.e., HVLT, SDR, Digit Span Forward) in cannabis dependent schizophrenia patients versus non-psychiatric controls. At study end, 19 schizophrenia patients and 20 controls completed the study. Abstinence rates were approximately on par with predicted rates: 42% of patients (8/11) and 55% of non-psychiatric controls (11/20) successfully met abstinence criteria at Day 28.

4.1.1 Longitudinal Cognitive Findings

The main finding from this study suggests that cannabis may exert state-dependent effect on select cognitive outcomes in patients with schizophrenia. With 28-days of sustained cannabis abstinence, cannabis dependent schizophrenia patients demonstrated significant improvements in cognitive performance on tests of verbal memory and learning (HVLT). The greatest change in performance occurred within the first 14 days of abstinence, and improvement continued, although of lesser magnitude, over the following two weeks. Improvements on other cognitive
tests (SDR, CPT, Digit Span, TMT, KDDT, BART) were not observed. Overall, these results suggest that chronic cannabis use may be associated with worse cognitive performance in schizophrenia, and more importantly that specific cannabis-induced deficits may resolve with one-month of abstinence. Conversely, deficits in other cognitive domains may be more persistent and resistant to change or facilitated by a different mechanism (i.e., not CB1R-mediated), as they did not improve with cannabis cessation.

This finding was further substantiated by data from a subset of patient abstainers. Preliminary data was collected at a one-month follow-up visit (Day56). Six of the eight patients who had successfully abstained from cannabis had relapsed one-month post abstinence (the other two were lost to follow-up). On average these patients consumed 0.5 grams per day on approximately 17.4 (12.0) days in the month between abstinence end-point and the one-month follow-up. While cannabis abstinence led to significant improvements in verbal memory and learning performance, cannabis relapse overturned these effects. That is, there was reversal of abstinence-related improvements. This “on-off-on” cannabis effect provides additional support for the notion that cannabis may exert state-dependent effects on select cognitive outcomes in patients with schizophrenia.

While some studies have attributed greater cognitive capacities of cannabis-using patients to cannabis itself (Coulston, Perdices, & Tennant, 2007a, 2007b), others have proposed that cannabis users belong to a subgroup of higher functioning patients (Schnell et al., 2009; Yucel et al., 2012). Our data contradicts the former hypothesis, however, it works in concert with the latter. Thus, we posit that cannabis exerts a deleterious effect on cognition (state-effect), and it is tempting to speculate that these deficits are superimposed upon a higher functioning subgroup of patients (trait-effect). Findings are in line with our previous study that reported robust associations between increasing cannabis use and progressive cognitive impairment in current, but not former (>6 months abstinent) cannabis-using patients (Rabin et al., 2013).

While select deficits may improve with one-month of abstinence, other cognitive domains may do so at differential rates. Thus, continued abstinence may be warranted for full cognitive recovery. It is possible that specific brain regions are more vulnerable and/or resilient to cannabis compared to others; therefore recovery of one cognitive domain does not necessarily predict
recovery of others. In other words, while verbal learning and memory appears to improve with abstinence, it is conceivable that permanent damage may occur in other cognitive processes, such as attention, executive function, psychomotor speed and impulsivity. Alternatively, lack of change in performance on other cognitive tests may reflect that these processes are not mediated by CB1R, and thus, remains constant irrespective of cannabis abstinence status or duration.

The lack of a time by abstinence status effect observed likely reflects that non-abstainers on average decreased their consumption of cannabis use over time. This is not surprising given that non-abstainers collectively included (1) abstainers whose THC-COOH levels did not drop below 20ng/mL by Day28; (2) individuals who relapsed, even just once (3) non-quitters who reduced cannabis use from baseline use (4) Individuals who relapsed and then continuously used cannabis throughout the study.

In contrast to patients with schizophrenia, no cognitive improvements were seen in cannabis dependent non-psychiatric controls following 28-day of cannabis abstinence across any of the cognitive tasks assessed.

4.1.2 Clinical Symptomatology

4.1.2.1 PSYCHIATRIC SYMPTOMS (PANSS)

To date, research on the effects of cannabis on psychiatric symptomatology is equivocal. While longitudinal studies examining this relationship have been conducted, this is the first study to implement a prospective, well-controlled laboratory paradigm to address this question. A significant finding from this study, and contrary to expectation, there was no change in the severity of psychiatric symptoms in schizophrenia patients with sustained cannabis abstinence. Severity levels on PANSS subscales (positive, negative and general) and total score remained unchanged over time in both abstaining and non-abstaining patients. While, symptoms did not improve with abstinence, it is of equal significance to note that psychiatric symptoms did not get worse.
Our findings are consistent with other longitudinal studies examining the relationship between cannabis use and schizophrenia psychopathology. Barrowclough et al (2013) similarly reported that change in cannabis dose did not significantly predict change in symptoms on the PANSS positive, negative or general subscales in patients with non-affective psychosis. Results remained non-significant even when patients became completely abstinent. However, the authors did find that greater cannabis exposure was associated with worse psychosocial functioning, according to the Global Assessment of Functioning (Barrowclough et al., 2013). A follow-up study was conducted to determine if cannabis’ effects on measures of psychopathology scores were more pronounced among those with recent onset of psychosis. Again, there was no evidence of a specific association between cannabis and positive symptoms, or negative symptoms. However, a greater dose of cannabis was associated with subsequent higher scores on depression and anxiety assessments (Barrowclough et al., 2015). Earlier studies reported similar results. For example, Faber et al (2012) reported that after a 2-year follow-up, cannabis use was associated with social functioning (economic and social activities), but was not associated with psychopathology in 124 patients with non-affective first-episode psychosis. Lastly, in a prospective cohort study of male patients with schizophrenia patients, cannabis use was not associated with symptom scores on the PANSS. However, the number of hospitalizations, an index of relapse, was significantly higher among cannabis-using patients compared to non-cannabis using patients (van Dijk et al., 2012).

In contrast, however, three longitudinal studies found that change in cannabis use was associated with improved psychotic outcomes. Clausen et al (2014) observed that first-episode patients who stopped using cannabis within a five-year follow-up period had significantly lower levels of psychotic symptoms compared to those who continued using cannabis (Clausen et al., 2014). In another study that used clinical data from 502 first-episode patients reported that cannabis users who reduced or stopped using cannabis demonstrated the greatest improvement in symptoms at a 1-year follow-up compared with both continued users and non-users. Interestingly, these patients had lower severity scores on items of aggression and disinhibition rather than the more traditional positive symptoms of delusions and hallucinations (Stone et al., 2014). Lastly, in a very recent study using a 3-year follow-up period, patients who used cannabis persistently had less improvement in positive and, general symptomatology compared to discontinued cannabis users (van der Meer et al., 2015).
An important finding from our data worth emphasizing is that in comparison to abstinent patients, non-abstaining patients did not show worsening of psychiatric symptoms. Furthermore, at baseline no associations were found between cumulative cannabis use or recent (in the last week) cannabis use and PANSS scores. Our findings suggest that patients with schizophrenia are not consuming cannabis as a form of ‘self-medication’ to mitigate negative symptoms associated with the illness.

Moreover, while PANSS symptomatology appears relatively immune to cannabis consumption, many of the abovementioned studies found significant relationships between cannabis use and worse outcomes in terms of number of hospitalizations and psychosocial functioning (Barrowclough et al., 2013; Barrowclough et al., 2015; Faber et al., 2012; Schoeler et al., 2015; van Dijk et al., 2012). This may suggest that cannabis use is more closely associated with functional outcomes rather than severity of psychiatric symptomatology. Unfortunately the current study did not include measures of global functioning. However, we can comment on the general functioning of our sample. For example during the 28-day abstinence period, no participant relapsed to psychosis, nor was anyone hospitalized; patients remained compliant with medications and antipsychotic doses were maintained.

There are several explanations for the lack of change observed in PANSS symptom scores. It has been hypothesized and generally well-accepted that THC induces neurobiological changes that are implicated in the development of psychotic symptoms, especially among those with pre-existing vulnerabilities (van Os et al., 2002). Dopaminergic hyperactivity in the striatum is one mechanism thought to be responsible for the psychotogenic effects associated with cannabis (Kuepper et al., 2013). To date, the exact mechanism by which cannabinoid exposure results in schizophrenia has not yet been established, but it is likely that the eCB system is implicated in the development and the pathophysiology of the disorder (Muller-Vahl & Emrich, 2008). While acute administration of cannabinoids leads to an array of transient positive symptoms in both non-cannabis-using healthy controls and schizophrenia patients (D'Souza et al., 2005; D'Souza et al., 2004), whether chronic cannabis exposure continues to produce increases in psychotic symptoms in those who have already transitioned to schizophrenia is a matter of contention.
All patients enrolled in the study reported initiating cannabis use prior to the onset of schizophrenia. Accordingly, cannabis may have played a role in the transition to psychosis in these individuals. The combination of long-standing cannabis use (Joint-years, M=10.10 years) and an established diagnosis of schizophrenia (duration of illness, M= 8.9), rather than early psychosis, may have precluded even gradual improvement in psychiatric symptoms over the course of the month. To this end, a meta-analytic study reported that discontinuation of cannabis use was associated with a decline in positive symptoms, but only in first-episode patients; this relationship was not significant in patients with an established psychotic illness (Mullin et al., 2012). This suggests individuals early in the course of the disorder may be more susceptible to the effects of cannabis and its discontinuation, compared to chronically ill patients. Accordingly, with repeated psychotic episodes and the presence of persistent symptoms, features of schizophrenia become crystallized (i.e., delusions and hallucinations) and as a result these patients may be more resistant to symptomatic change. Simply put, quitting cannabis may only have beneficial effects on psychopathology for those in the early course of the disorder (Mullin et al., 2012). This provides another reason to encourage early intervention, when cannabis cessation may have its greatest effect. Given that our study only enrolled patients with established schizophrenia, we speculate that one reason for lack of change in PANSS scores may be due to the chronicity of our sample.

Additionally, because a PANSS score >70 was exclusionary for participation, the patients enrolled in this study were markedly stable. Thus, as a result floor effects on PANSS scores may have been observed thereby preventing detection of a greater magnitude of change over time. Other studies that did detect change in the severity of psychopathology did not employ cut-offs to account for the stability of participants at the time of enrollment (Clausen et al., 2014; Stone et al., 2014; van der Meer et al., 2015). In addition, many studies reporting changes in symptoms enrolled patients that did not exclusively use cannabis but engaged in other substance use. Failure to appropriately control for other confounding drug use may in part account for discrepant findings (Clausen et al., 2014; van der Meer et al., 2015). Given that the use of alcohol and other drugs is associated with worsening of mental health outcomes, may have led to an overestimation of the effects of cannabis (Zammit et al., 2008).
Lastly, one-month of abstinence may not have offered patients sufficient time to exhibit a shift in their symptomatic profiles. Of note, previous studies that detected improvements in psychopathology severity observed participants over longer periods of time, such as three (van der Meer et al., 2015) and five-year periods (Clausen et al., 2014).

Findings from this study demonstrate that abstaining cannabis-dependent patients with schizophrenia may not be susceptible to changes in psychiatric symptoms over a one-month abstinence period. Perhaps the stability of patients in this sample supersedes the negative effects that cannabis acutely exerts on psychotic symptoms. However, it would be worthwhile to explore whether longer abstinence periods under laboratory conditions would trigger symptomatic improvements. Moreover, while cannabis may not exert a direct influence on psychiatric symptomatology, there is an abundance of data to suggest that outcomes of other prognostic and functional sequelae (i.e., relapse to psychosis, hospitalizations, duration of hospital stays and psychosocial functioning) may be more closely associated with cannabis use.

4.1.2.2 DEPRESSION

The association between cannabis and depression has received much less attention than the relationship between cannabis use and psychotic symptomatology. In this study, we explored this relationship both cross-sectionally at baseline and longitudinally over the course of abstinence. In line with our hypothesis, schizophrenia patients demonstrated associations between recent cannabis use (grams per day; GPD) and severity of depressive symptoms on the CDSS and HAM-D. This suggests that the more cannabis consumed in the previous week, the greater the severity of depression, as assessed at baseline. The well-controlled nature of this study and its prospective design also allowed for the proper temporal evaluation of cannabis use on depressive symptoms. Over the 28-day abstinence period, patients experienced an overall reduction in the severity of their depressive symptoms on the CDSS. By Day28, schizophrenia abstaining participants demonstrated greater improvement in the CDSS compared to schizophrenia non-abstaining patients. Of note, the magnitude of the effect size was three times larger in abstaining versus non-abstaining patients.
While a link between heavy cannabis use and depression over time has been observed in the general population (Degenhardt, 2003), this relationship has not been well documented in schizophrenia patients. Results presented here are novel and exciting as they suggest that daily cannabis use in schizophrenia worsens depression in a dose-dependent fashion and that this effect may be reversible with cessation. Given that the level of depression in our patient sample is indicative of sub-clinical depression, it would be of interest to determine if this relationship exists in patients with clinical depression such as major depressive disorder. Barrowclough et al (2015) similarly reported that when cannabis levels were higher, patients were experiencing greater affective symptoms. The authors argue that their results are especially robust given that they accounted for various potencies of cannabis. At odds with our findings, when the authors conducted a change analysis results suggested that reducing cannabis was unlikely to lead to improvements in depressive symptoms (Barrowclough et al., 2015).

Early studies reporting on the association between cannabis and depression found that cannabis had a positive effect on affective symptoms associated with schizophrenia (Addington & Duchak, 1997; Johns, 2001; Linszen, Dingemans, & Lenior, 1994; Schuck et al., 2013); data was collected using self-reports from cross-sectional studies. This evidence led findings to be discussed within the context of the self-medication theory (Khantzian, 1985). Therefore it was proposed that individuals who experience negative emotional states might seek out cannabis to alleviate specific symptoms. However, findings presented here as well as other more recent research suggests that there is little support for cannabis to alleviate dysphoric states (Lev-Ran et al., 2014). Moreover, given that abstaining patients showed reductions in severity and not worsening of depressive symptoms with abstinence provides further evidence against the self-medication hypothesis.

Given that our non-abstaining patients also had better CDSS ratings over time, suggests that it may not be cannabis abstinence in its entirety that is resolving depressive symptoms. Decreasing scores among both abstaining and non-abstaining patients may be attributable to the therapy platform employed in the study. In addition, given that the study required dedicated engagement, social contact, and financial gains may have, in part, contributed to overall effect of improved mood. However, given that individuals classified as non-abstainers decreased their cannabis use over time, may help also to explain why their CDSS scores decrease in severity over time as well.
Interestingly, these relationships were exclusively observed among the patient group. Controls demonstrated no associations between cumulative cannabis use and depression nor did they show reduced depressive symptoms with abstinence. Other studies similarly report on the lack of relationship between cannabis use and changes in depressive symptoms among non-psychiatric controls (Degenhardt et al., 2007; Feingold et al., 2014).

### 4.1.3 The Cannabis Withdrawal Syndrome

While studies have characterized the time course of cannabis withdrawal in non-psychiatric controls (Budney et al., 2003), there has been no documentation of the time course of cannabis withdrawal in psychiatric patients. Therefore this is the first study to report on the pattern and trajectory of the CWS in patients with schizophrenia. Cannabis withdrawal is an important component of cannabis dependence. The presence, time course and significance of the CWS are well documented, validated and are clinically significant phenomena (Allsop et al., 2012; Budney et al., 2004). Accordingly, withdrawal data from this study provides further confirmation, in addition to biochemical verification, that participants did indeed achieve extended cannabis abstinence under our imposed laboratory conditions.

Consistent with previous reports (Budney et al., 2003), abstaining participants, both patients and controls, demonstrated a classic withdrawal trajectory. That is, abstainers experienced a peak in the severity of their withdrawal symptoms within the first week following cessation, and subsequently, symptoms decreased over the following 21 days. By Day 14 most, but not all, symptoms had remitted and returned to baseline levels. Further, in a subsample of participants, we demonstrated that while controls’ withdrawal symptoms were most severe on Day3, patients experienced peak severity of symptoms on Day7. It has been proposed that a reduction in THC levels in the extracellular brain fluid is central to the formation of the withdrawal syndrome (Vandrey et al., 2005). As we can see from the THC-COOH elimination curves presented in Figure 3.3 and Figure 3.4, the plummeting levels of cannabis metabolites likely triggered the quick onset of withdrawal symptoms. Specifically, abstaining controls demonstrated a significant change in the severity of their withdrawal symptoms over the 28-day abstinent period. However, this change was not significant in patient abstainers. See Figure 3.6
Greater variation in symptom severity may account, in part, for the lack of significant change observed in patients. That is, patients may be more variable in how they experience withdrawal. Withdrawal symptoms are non-specific and may overlap with the primary and secondary symptoms associated with schizophrenia. In support of this, at baseline PANSS (positive, negative, general and total), CDSS and HAM-D scores correlated with the total score on the MWC. In other words, the more psychopathology patients endorsed, the greater the severity level of their withdrawal symptoms. Therefore, it may just appear as though patients are in a constant state of withdrawal. Thus, developing and validating a cannabis withdrawal scale for specific psychiatric populations (akin to the CDSS for depression) may help to better characterize the etiologic basis of presenting symptoms. Moreover, a recent study found that while the majority of schizophrenia patients in their sample (N=113) endured withdrawal symptoms when trying to quit cannabis without formal treatment, not all experienced a full-blown CWS (Boggs et al., 2013). This suggests that some schizophrenia patients may experience an attenuated and less severe CWS compared to non-psychiatric controls.

Antipsychotic medications may have attenuated or masked specific cannabis withdrawal symptoms (Boggs et al., 2013; Hesse & Thylstrup, 2013; Schnell et al., 2014). A recent review reported that antipsychotic treatment was effective at reducing cannabis-using behaviours among psychotic patients with co-morbid CUDs (Wilson & Bhattacharyya, 2016). In addition, it has been suggested that clozapine and olanzapine specifically, may decrease cravings associated with cannabis use (Machielsen et al., 2012). Because many antipsychotics can trigger increased appetite and/or weight gain (Bhuvaneswar et al., 2009), medication effects may have counteracted specific withdrawal symptom in patients. Given our small sample and the various antipsychotics prescribed, we unfortunately could not explore the effects of medication on severity of withdrawal symptoms or abstinence status. Additional research in this area is warranted.

Compared to what has previously been reported in the literature (Budney et al., 2008), non-psychiatric controls demonstrated withdrawal trajectories spanning a reduced range in severity. One reason for this is that baseline assessment of withdrawal symptoms followed a minimum of 12 hours of abstinence. While the onset of withdrawal is said to generally occur approximately 24 hours post-cessation (Budney et al., 2003), there are reports that symptoms may emerge as
early as 4 hours after last use of cannabis (Jones, Benowitz, & Bachman, 1976). Therefore, our baseline levels may not reflect true cannabis satiation, but instead may depict early withdrawal symptoms. As a result fluctuations in symptom severity over time were minimized. In addition, weekly therapy sessions may have also attenuated withdrawal symptom severity given that planning and developing appropriate strategies to manage cannabis withdrawal were addressed. Likewise, therapy may have also played a role in lessening withdrawal symptoms in schizophrenia patients.

In line with previous research, we observed that affective and behavioral symptoms, rather than physical symptoms, were the most frequently reported withdrawal symptoms (Budney et al., 2003; Haney et al., 1999; Hart et al., 2001). Sleep problems, strange dreams, cannabis cravings, and irritability were the most common symptoms reported at Day7 in both patients and controls. Further, restlessness and decreased appetite were more widespread among patients compared to controls. In contrast, aggression was more frequently reported among controls. A study using an objective assessment of aggression reported increased aggression within the first week of cannabis abstinence and proposed that elevated levels may be related to withdrawal-related changes in mood (Kouri, Pope, & Lukas, 1999). Notably, the greatest risk of violence from a cannabis user is within the first week of abstinence (Hoaken & Stewart, 2003).

The symptom rated as most severe among abstaining patients was craving. Among controls strange dreams was rated the most severe withdrawal symptom and was the only withdrawal symptom that did not return to baseline severity levels by Day28 (at trend level). These reports are consistent with data from earlier studies (Budney et al., 2003; Lee et al., 2014; Vandrey et al., 2005).

Findings lend support for the recent inclusion of the cannabis withdrawal syndrome in the DSM-5. However, of note, frequently reported symptoms in this study do not entirely overlap with those symptoms listed in the revised manual (APA;, 2013). For example, depressed mood and nervousness are listed in the DSM-5, but were infrequently reported as withdrawal symptoms among our abstaining participants. In addition, strange dreams, which is not currently included as a DSM-5 withdrawal symptom, was highly prevalent among cannabis abstainers in this study. Hesse & Thylstrup (2013) assessed the validity of the DSM-5 cannabis withdrawal
syndrome in sample of detoxifying patients and their findings support that strange dreams should be included as a DSM-5 withdrawal symptom (Hesse & Thylstrup, 2013).

Withdrawal data presented here adds to the growing body of research confirming the presence as well as characterizing the time course of cannabis withdrawal in psychiatric and non-psychiatric populations. Given that withdrawal symptoms are strong predictors of relapse, i.e., serve as negative reinforcement for relapse during a quit attempt (Allsop et al., 2011; Budney et al., 2004), targeting these symptoms may lead to more favourable cessation outcomes in treatment-seeking individuals. Numerous pharmacotherapy trials addressing cannabis withdrawal have already been conducted [See (Vandrey & Haney, 2009)] with unfortunately no proven success. Therefore with improved understanding of the CWS, better intervention strategies that effectively treat CUDs will likely follow.

4.1.4 Contingency Management & Study Retention

This study was conceptualized as a natural stepping-stone from the questions generated from the findings of my Master’s thesis (see Rabin et al., 2013; Appendix B). At its initial conception, clinicians and scientists were skeptical of how we would see this study to fruition. Concerns stemmed from our ability to get schizophrenia patients, in particular, to quit cannabis and remain cannabis-free for one-month. In addition, while study attrition is an issue with all research utilizing longitudinal designs, it was thought that retention would be especially challenging within our study context. The target recruitment goal for this study was to enroll 20 cannabis-dependent schizophrenia patients and 20 cannabis-dependent non-psychiatric controls. Four years later, we have completed the study. Moreover participants lost to follow-up were minimal. Once abstinence was initiated, remarkably only one patient and two controls dropped-out, rendering a 92% completion rate. While contingency management was predominantly used to encourage abstinence, it also inevitably contributed to study retention and completion. However, given that our non-abstainers had equally good retention rates compared to abstaining participants suggests that it was not the abstinence rewards alone that single-handedly maintained study participation and prevented attrition. We attribute the above average retention rates to a well-developed protocol, good rapport with study staff, financial compensation, and to
participants feeling a sense of valued commitment, contribution and productiveness. Other experimental studies employing >21 days of cannabis abstinence paradigms had much higher drop-out rates than ours. However, it is difficult to compare our methods to theirs as they failed to report on the methods they used to initiate and sustain abstinence (Pope et al., 2001; Urban et al., 2012).

4.1.5 Biochemical Data

The current paradigm utilized very strict criteria in which to define abstinence. Self-reported cannabis abstinence over the 28-day abstinence period was corroborated with in-lab MEDTOX urine analysis and later verified with sensitive GC-MS testing (in a subset of participants). Abstinence criteria were based on two phenomena (1) no new cannabis could be introduced over the 28-day period (Schwilke et al., 2011) and (2) THC-COOH metabolite levels at Day28 had to be less than 20ng/mL. If either of these criteria were violated, participants were characterized as “non-abstainers.” While most laboratory abstinence studies examining cognitive outcomes adopt the first criteria [i.e., (Medina et al., 2007; Pope et al., 2001), this is the first study to use a biochemical cut-off criteria in tandem. Applying these two criteria ensures not only complete and true “behavioural” abstinence, but in addition, aims to eliminate the possibility of lingering residual levels of cannabinoids that may affect clinical and/or cognitive outcomes. Participants’ Elimination Curves are presented in Figure 3.3 and Figure 3.4.

Also evident from these graphs, the scale used for the Y-axis in the control graph (Figure 3.4) was 2.5X greater than the range of the scale used in the patient graph (Figure 3.3). Therefore, while diagnostic groups were well-matched according to subjective reports of cannabis use (i.e., joint-years and average cannabis consumption per day), using an objective measure of quantitative baseline THC-COOH levels, controls demonstrated a much larger range of use. Despite this, statistically, there were no between group differences in THC-COOH metabolite levels, likely a reflection of the large variation present within each group. However, it is important to note, that cannabis is difficult to quantify given the various methods in which it may be consumed, that it is commonly shared, and that its potency can be highly variable (Gray, Watson, & Christie, 2009).
Among participants who did not use cannabis over the course of the 28-day period, THC-COOH levels fell drastically within the first 7 days of abstinence and then tapered off over the following 21 days. While the majority of these participants achieved THC-COOH levels <20ng/mL, not all did. Two patients and two controls, despite no introduction of new cannabis during this time frame (Schwilke et al., 2011), failed to produce urine samples meeting this elimination cut-off. Given that such individuals possessed residual THC-COOH, which may impact clinical and/or cognitive outcomes, these participants were classified as “non-abstainers”. Therefore, we posit that longer abstinence periods are needed to completely rid the body of cannabinoids in select cannabis-using individuals.

Unlike other abused drugs, such as alcohol, the relationship between THC concentrations and its pharmacodynamic properties is complex and nonlinear. Substantial intra- and inter-subject variability exists in the patterns of THC-COOH absorption, metabolism and excretion (Huestis, 2007). While factors affecting the rate of THC-COOH elimination have been proposed, such as frequency and duration of use, factors governing the release of THC from fat stores are still unclear (Huestis, 2007). Unfortunately, our sample size was too small to explore variables that may have played a role in the pharmacokinetics of THC.

By adhering to these stringent principles we were able to produce a very “clean” abstinent sample of schizophrenia patients and controls. Approaching our predicted abstinence rates, 42% of cannabis-dependent schizophrenia patients and 55% of non-psychiatric cannabis-dependent controls met established criteria for cannabis abstinence. Accordingly, cannabis-dependent patients can indeed achieve 28-days of cannabis abstinence and, moreover, at comparable rates to non-psychiatric controls.

### 4.1.6 Craving

Findings from the present study indicated that cannabis abstinence did not precipitate significant cravings in either schizophrenia patients or controls according to the MCQ. This is in contrast to many previous studies that showed cravings to be the most intense and prevalent withdrawal
symptom, among all psychological symptoms (Budney et al., 2001; Budney, Novy, & Hughes, 1999; Lee et al., 2014).

While we expected cravings to follow a similar trajectory to other withdrawal symptoms, craving in controls showed a significant decrease from baseline levels within the first week, which then plateaued over the following 21 days. Other studies report more of a steady decline in craving symptom severity. An earlier study examining non-treatment seeking-participants engaging in up to 28-days of cannabis abstinence showed that MCQ total scores significantly decreased over time (Lee et al., 2014). Similarly, Preuss et al (2010) demonstrated that craving decreased (almost) linearly over a period of 10 days of sustained abstinence (Preuss et al., 2010). Using a 45-day abstinence period, Budney et al (2003) observed that craving severity 3-weeks post-abstinence was significantly lower than baseline intensity levels. In contrast, schizophrenia patients showed no change over time in craving severity. Given that this is the first study to examine cannabis cravings over time in abstinent patients, replication studies are warranted. Thus, cannabis craving in patients did not follow the same time course as other psychological symptoms associated with cannabis withdrawal. Moreover, substantial individual variability exists in levels of reported craving intensity (Budney, Novy, & Hughes, 1999; Lee et al., 2014). Numerous factors have been shown to influence the intensity of cravings such as race (Copersino et al., 2010) genotype (Haughey et al., 2008) and expectancy (Sayette et al., 2000). Furthermore, there is evidence that exposure to cannabis cues increase cravings above and beyond levels that are associated with withdrawal (Haughey et al., 2008). Taken together, while craving is often thought of as a withdrawal symptom, it may be better regarded as a related, but independent construct with respect to cannabis.

4.1.7 Concurrent Substance Use

Given that tobacco use is known to modulate cognitive function in psychiatric and non-psychiatric populations (Heishman, Kleykamp, & Singleton, 2010; Sacco et al., 2005), it was critical to control for cigarette smoking in this study. In doing so, we were provided with a unique opportunity to systematically explore what happens to tobacco use when daily cigarette smokers quit cannabis. This is an important area to address given the high prevalence of tobacco
use among cannabis smokers (Agrawal, Budney, & Lynskey, 2012) and that cannabis cessation may result in compensatory changes in other substances of abuse.

On average, patients and controls smoked 12 and 11 cigarettes per day (CPD) respectively. Cigarette use significantly changed over the course of the 28-day abstinence period in patients with schizophrenia but not in controls. Among patients, peak CPD was observed at Day7 and by Day28, use normalized back to baseline levels. Interestingly, peak consumption of CPD in patients coincided with peak severity of withdrawal symptoms. Moreover, at baseline, patients demonstrated a significant relationship between CPD and craving and withdrawal symptoms, in that the greater the intensity of withdrawal and craving, the higher the number of cigarettes consumed. We have previously posited that nicotine and cannabis may be used in combination to attenuate each other’s undesirable and/or aversive effects (Rabin & George, 2015). Other research also suggests that tobacco use helps to mitigate symptoms of cannabis withdrawal. For example, Levin et al (2010) found that in a minority of participants (37.7%), tobacco use increased during quit attempts, often to relieve specific withdrawal symptoms, such as cannabis cravings, sleep problems, and irritability (Levin et al., 2010). Similarly, in another study cannabis cessation was accompanied by increased tobacco use, and the authors interpreted this as a mechanism to overcome states of withdrawal (Copersino et al., 2006b).

In 2014, our group published a cross-sectional study that reported on elevated CPD and higher levels of nicotine dependence in never cannabis dependent schizophrenia patients compared to former and current cannabis dependent patients (Rabin, Giddens, & George, 2014). These results are in line with findings from the current study and suggest a state-dependent effect of cannabis use status on tobacco consumption. Current cannabis-using patients may be deriving similar beneficial effects from cannabis that renders them less interested in excessive cigarette consumption. This is consistent with other studies that suggest the presence of a “substitution phenomenon”, whereby quitting or decreasing the use of one substance triggers increased use of another substance (Akre et al., 2010; Amos et al., 2004). That is, increases in tobacco use may represent attempts to substitute for the effects of cannabis not being used. Therefore, in the absence of cannabis, patients may be more prone to elevate their cigarette use. While the principle psychoactive constituents of cannabis and tobacco differ, their subjective, neurobiological and behavioural effects in patients with schizophrenia may be analogous. For
example, patients may be attempting to replace the euphoric and reinforcing properties of cannabis with those that can be derived from tobacco. It should be noted that among our sample tobacco was commonly mixed and smoked with cannabis. Hence, when cannabis was ceased, participants were inevitably exposed to less tobacco. Therefore, it would be expected that cigarette use would increase to compensate for the reduced exposure over the full course of abstinence. However this was not the case for either diagnostic group.

Given that the elevated consumption of CPD in this study appears to be a time-limited phenomenon and corresponds to increased withdrawal symptoms renders it likely that patients are managing aversive withdrawal symptoms by adjusting their cigarette use rather than using it as a “substitute”. In controls, however, increased withdrawal symptoms during the first 7 days of abstinence did not coincide with increased tobacco consumption. This is consistent with results from a previous study (Preuss et al., 2010) and suggests that controls may employ other strategies to cope with symptoms of withdrawal.

Lastly, recent research suggests that tobacco use is associated with high rates of cannabis relapse and poor CUD treatment outcomes (Haney et al., 2013a; Peters, Budney, & Carroll, 2012). Notwithstanding, we achieved our predicted cessation rates. Whether success rate would have been higher among non-tobacco using participants remains to be determined.

Other substances monitored over time were alcohol and caffeine. In line with previous research, there was no evidence that cannabis abstinence led to increases in alcohol use (Budney et al., 2001; Hughes et al., 2008; Marijuana Treatment Project Research, 2004). In contrast, in a small retrospective study of untreated daily cannabis users, about one third of abstainers reported elevated alcohol consumption during a quit attempt (Copersino et al., 2006b). Notably, alcohol use in our study was modest to begin with, and it may be that reductions in cannabis use do not substantially enhance drinking in non alcohol-dependent users. However, this may not be the case among individuals with problematic drinking behaviours. Similar to alcohol, the use of caffeine did not fluctuate with cannabis abstinence in either patients or controls. This is congruent with the few studies in the literature that have examined this relationship (Budney et al., 2001; Copersino et al., 2006b; Hughes et al., 2008).
In sum, alcohol and caffeine use did not change with abstinence and while cigarette use transiently increased in patients, it returned to baseline levels within 14 days. Importantly, no participant reported initiating new substance use during the trial. Taken together, while substance substitution may be a conceivable concern for clinicians treating drug addiction, it does not appear to be relevant for psychiatric and non-psychiatric patients ceasing cannabis. However, whether modifications in substance use may occur among those presenting with other co-morbid SUDs (such as alcohol), rather than merely recreational use, warrants investigation. Nevertheless, clinicians should be advised to monitor substance use behaviours in cannabis treatment settings in order to promptly detect individuals that may fall outside these norms and exhibit increases in other abusive substances.

4.1.8 Cross-sectional Cognitive Findings

There is evidence that chronic cannabis use in non-psychiatric controls generates deficits that resemble the cognitive profile of patients with schizophrenia (Solowij et al., 2002a). That is, cognitive domains disrupted by cannabis use in controls overlap with the core cognitive deficits observed in patients with schizophrenia. Therefore, by comparing the cognitive performance of cannabis-dependent patients and cannabis-dependent controls at baseline, we can determine if and/or which cognitive deficits in schizophrenia patients are further exacerbated by cannabis use. Alternatively, if the preserving effects of cannabis on cognition in schizophrenia patients are true (Jockers-Scherubl et al., 2007; Stirling et al., 2005) or if cannabis exerts a positive effect on cognitive function, then we may not expect patients to perform worse than cannabis-dependent controls. At baseline, controls performed significantly better than patients on tests of verbal memory and learning (HVLT), working memory (DSF, DST), executive function (DSB) and motor function (Grooved Pegboard). These cognitive domains are commonly impaired in schizophrenia (Heinrichs & Zakzanis, 1998). Moreover, these tasks are facilitated by areas rich in CB1Rs, suggesting that schizophrenia cannabis users may have enhanced sensitivity to abnormalities within these brain regions, particularly the hippocampus, PFC and cerebellum with the use of cannabis.
We also examined relationships between cumulative use and cognition. In patients, increasing years of cannabis exposure was associated with worse performance in verbal memory and learning (HVLT) and executive function (WCST). Findings are in line with our previous study that reported cumulative cannabis exposure dose-dependently impaired tasks facilitated by the hippocampus and PFC in cannabis-dependent patients (Rabin et al., 2013). Unexpectedly, we also found an association between increasing cannabis use and better CPT outcome (% commission errors). Notably, other studies have also observed a negative relationship between greater cannabis use and attentional outcomes. Coulston et al (2007) found that increased frequency of cannabis use in schizophrenia patients predicted better performance, predominantly in the domains of attention and executive functions. The authors posited that, in the short-term, cannabinoids could stimulate prefrontal neurotransmission to enhance cognitive functions (Coulston, Perdices, & Tennant, 2007a, 2007b). Schnell et al (2009) also found a higher frequency of cannabis use was associated with better outcomes on the CPT. However this study employed a long abstinence period making the theory proposed by Coulston et al (2007) unlikely. Another interpretation is that high frequency of cannabis use reflects a lower vulnerability to transition to psychosis (Schnell et al., 2009), which may correspond to a higher level of attentional functioning.

Among controls, increasing years of cannabis exposure was associated with poorer performance across various cognitive domains such as verbal memory and learning (HVLT), attention (CPT), and executive function (WCST, TMT-B). These observations are in line with previous findings reported in the literature. That is, long-term heavy cannabis use results in cognitive deficits that increase as a function of dose and duration and resemble those classically observed in patients with schizophrenia (Bolla et al., 2002; Jacobsen et al., 2004; Solowij & Michie, 2007).
4.1.9 Putative Mechanisms to Explain Study Findings

4.1.9.1 CANNABIS-INDUCED COGNITIVE IMPAIRMENT

The neural mechanisms responsible for the lack of cognitive improvement in controls are discussed below. While such studies are limited in psychiatric samples, we postulate that similar mechanisms are likely implicated in cannabis-induced cognitive impairment in patients with schizophrenia.

**Neuroadaptation**

Precise neurobiological mechanisms underlying cannabis-induced cognitive impairment, and recovery with abstinence are unknown, but may be associated with changes in CB1R functioning. Accumulating evidence suggests that chronic cannabis exposure induces CB1R down-regulation and desensitization of CB1R-mediated G-protein activation. Notably, both down-regulation and desensitization develop at varying rates and magnitudes in different regions of the brain (Sim-Selley & Martin, 2002; Sim-Selley et al., 2006). More specifically, down-regulation occurs more rapidly and is greater in cortical regions, such as the hippocampus and cerebellum compared to subcortical regions namely the basal ganglia and midbrain (Sim-Selley, 2003). Accordingly, a human post-mortem study showed that CB1R down-regulation in cannabis smokers was greatest in the hippocampus and least in the globus pallidus and substantia nigra (Villares, 2007). Regional differences are thought to reflect the distribution of markers of CB1R signaling, such as G-protein subunits, subtypes of adenylyl cyclase, receptor kinases, arrestins and other proteins associated with receptor signalling (Martin, Sim-Selley, & Selley, 2004). Therefore ability to cognitively recover and/or time to cognitively recover may correlate with CB1R density in the brain region responsible for facilitating the specific cognitive task. That is, improved cognitive function (with 28-days of abstinence) may first occur in tasks facilitated by areas of very high CB1R concentrations, such as the hippocampus (Herkenham, 1991). In contrast, tasks mediated by areas of lower CB1R concentration may require longer abstinence periods for recovery. This mechanism supports findings from the current study in that schizophrenia patients demonstrated improvements in the HVLT, a task predominantly mediated by the hippocampus.
A recent PET study by Hirvonen et al (2012) observed that at baseline individuals with chronic, heavy cannabis use had 20% lower CB1R availability in cortical, but not subcortical, regions compared to control participants, excluding the cerebellum. Cannabis users then participated in a period of sustained cannabis abstinence (13–32 days) on a monitored inpatient unit. At endpoint, an increase in CB1R availability was observed in select cortical regions; however, the hippocampus did not show this reversal of down-regulation after abstinence (Hirvonen et al., 2012). This suggests that some, but not all, alterations in the eCB recover with abstinence. This prolonged down-regulation in the hippocampus might contribute to the long-term cognitive impairment in chronic daily cannabis smokers (D'Souza, 2007). Notably, these results may help to explain why in the current study cannabis-dependent non-psychiatric demonstrated no cognitive improvement with a 28-day cannabis abstinence period.

Prolonged CB1R activation leads to down-regulation and desensitization of CB1R and is associated with tolerance, which attenuates this inhibition and has been reported to make the cells relatively more susceptible to neurotoxicity (Deshpande, Blair, & DeLorenzo, 2011).

**Neurotoxicity**

It has been suggested that cannabis itself is neurotoxic. Converging data posits that chronic cannabis use results in permanent brain damage in areas that overlap with those that facilitate cognitive function. Therefore, among controls and perhaps pertaining to certain domains for schizophrenia patients, cognitive deficits may persist as a result of cell damage and may be non-reversible. There is a wealth of data to support such a phenomenon in controls. The literature reports that the most consistent deficits associated with long-term cannabis use are found on measures of memory, specifically verbal learning and memory (Grant et al., 2003). This cognitive process is facilitated by the hippocampus (Kelley et al., 1998). Furthermore, there is consistent pharmacological evidence from animal studies supporting the notion that THC is particularly neurotoxic to hippocampal neurons (Chan et al., 1998; Kim & Thayer, 2001). At a pharmacological level, the hippocampus is particularly enriched with CB1Rs (Mackie, 2005). Namely, there is significant overlap between the neuroanatomical structures affected by cannabis use and the sites of high-density concentrations of CB1R in the brain. Accordingly, most studies found structural anomalies within the hippocampus, a region containing one of the highest densities of CB1Rs in the brain (Glass, Dragunow, & Faull, 1997). Reports from the literature
suggest that chronic cannabis exposure is associated with neuroanatomic abnormalities such as reduced volumes and gray matter density, and altered shape, in several brain regions (i.e., orbitofrontal cortex, parietal cortex, insular cortex, and cerebellum), but most consistently within the hippocampus (Lorenzetti, Solowij, & Yücel, 2016). A meta-analysis that included 14 studies sought to estimate the magnitude of the putative neurotoxic effect of cannabis in otherwise healthy cannabis users (Rocchetti et al., 2013). The authors concluded that among cannabis users, grey matter in the hippocampus was significantly reduced compared to non-users. Results from a later study were in agreement with these findings and showed localised neuroanatomical reductions in hippocampal volume in individuals with chronically high cannabinoid exposure (Lorenzetti et al., 2015). In contrast, other regions such as the orbitofrontal and anterior- and paracingulate cortices, and the pituitary gland were relatively spared from damage. A critical review of the topic published in 2016, stated that there “appears to be an intriguing link between the concentration of CB1R density in the brain and the consistency with which studies detect abnormal neuroanatomy in regular cannabis users” (Lorenzetti, Solowij, & Yücel, 2016). In sum, chronic administration of cannabis may lead to alterations in brain morphology, and the hippocampus may be exceptionally susceptible to such THC-induced neurotoxicity.

Putative mechanisms and pathways have been proposed to explain cannabis-induced atrophy to cannabinoid receptor rich regions. Prolonged cannabis use may lead to an accumulation of THC and its metabolites in brain tissue causing toxicity (Monnet-Tschudi et al., 2008). Neurotoxicity may be expressed as shrinkage of neuronal cell nuclei and bodies (Heath et al., 1980; Scallet et al., 1987), neuronal death (Chan et al., 1998), a reduction in synapses (Scallet et al., 1987), or decreased pyramidal cell density (Scallet, 1991) These have been associated with decreased gray matter volume (Herning et al., 2005). Lastly, connectivity, both functional (i.e., synchrony of activity) and structural (i.e., white matter tracts), between different brain regions may be compromised with continued cannabis use leading to neural network dysfunction (Harding et al., 2012; Zalesky et al., 2012).

Whether this functional or structural damage can be reversed to restore brain functions remains inconclusive at this point. Within the framework of our data, we can neither decisively conclude whether deficits are repairable or permanent. We can however, hypothesize that 28 days of abstinence may not have provided sufficient time to initiate cognitive recovery among control
participants. Longer cessation periods may be warranted for restoration to pre–cannabis use integrity and functionality. Alternatively, if cannabis-induced neurotoxicity is not reversible, the brain, given its plastic nature, may implement compensation mechanisms that will translate into restored function.

**Compensatory Strategies**

Neuroplasticity is an intrinsic property of the human brain and thus neurons have the remarkable ability to reorganize themselves after insult or injury (Pascual-Leone et al., 2005). Hence it is plausible that compensatory cerebral mechanisms are initiated as a means to cope with the burden of sustained cannabis use. That is, cannabis users may employ alternate strategies such as recruiting additional brain region or “working harder” to obtain comparable performance to non-cannabis-using individuals. This suggests functional inefficiency as a means to meet the demands of the task. In line with this theory, functional imaging studies have reported altered brain response patterns in cannabis users compared to non-users despite the two groups demonstrating similar task performance. This phenomenon may be explained by increased neural effort as well as the use of alternative cortical strategies put forth by cannabis users (Eldreth et al., 2004; Jager et al., 2006). In light of this, it is possible that irrespective of change in cognitive performance, patterns of functional activation may have normalized over the course of 28-day abstinence period. Given that this study did not include an imaging component, this is simply conjecture. However, moving forward cognitive function should be assessed in conjunction with neuroimaging methods during cannabis abstinence paradigms to test this definitively.

**4.1.10 Factors Affecting Reversal of Cannabis-Induced Deficits**

Recovery of function even after prolonged abstinence remains contentious and several factors may play a role in the ability to restore the brain to pre-cannabis function.

**Sensitivity to Cannabis**

Differential effects of one-month of abstinence on cognitive function were observed between cannabis-dependent patients versus cannabis-dependent controls. This finding adds to the already available evidence that cannabis-dependent schizophrenia patients possess heightened sensitivity
to the psychoactive properties of cannabis. For example, D'Souza et al (2005) previously reported that patients with schizophrenia who were administered THC intravenously were more vulnerable to its effects, specifically on a test of learning and recall compared to controls. Several mechanisms in isolation, in conjunction and synergistically might account for schizophrenia patient’s heightened sensitivity to the effects of THC.

Dysfunction in the neurotransmitter systems of patients with schizophrenia may play a role in their enhanced sensitivity to cannabis by disrupting the balance of cognitive-dependent neurotransmitters (Abi-Dargham et al., 2002; Lewis & Hashimoto, 2007). These may be pre-existing or may be due to genetic predispositions associated with the development of schizophrenia. With respect to the latter, these may manifest as polymorphisms in genes that code for COMT (Caspi et al., 2005; Henquet et al., 2006), AKT1 (van Winkel et al., 2011) and DAT1 (Bhattacharyya et al., 2012).

Notably, gamma oscillations play a key role in sensory registration, integration and binding of perceptual features, associative learning, conscious awareness and in the organization of brain networks (Uhlhaas & Singer, 2010). GABAergic interneurons are the generators of these neural oscillations in the gamma range (30-80Hz). Moreover, there is evidence to suggest that cannabinoid activity may exert neuromodulatory control of GABA-ergic dependent network oscillations and as a result cause disruption to gamma-oscillations. Given that schizophrenia has been conceptualized as a disorder of abnormal neural oscillations and neural synchronization (Uhlhaas & Singer, 2010), may make these patients increasingly sensitive to the neurobehavioural effects of cannabis.

In addition, there are well-documented functional and structural alterations in the eCB system of schizophrenia patients (Cohen, Solowij, & Carr, 2008; Muller-Vahl & Emrich, 2008) that likely produce further sensitization to cannabis’ effects. For example, a recent study reported that in comparison to healthy controls, male schizophrenia patients had reduced CB1R availability. Further, the magnitude of this reduction was of a medium effect size and the pattern of reduction was global rather than localized (Ranganathan et al., 2015). Contrasting this, other studies observed greater CB1R availability (Dean et al., 2001; Volk et al., 2014; Wong et al., 2010). Nevertheless, each of these studies documents abnormal CB1R availability. Associations
between the gene encoding CB1R (CNR1) and schizophrenia have also been reported (Ujike et al., 2002) and may account for such abnormalities. There is accumulating evidence of other eCB dysfunction in schizophrenia such as increased anandamide levels (Giuffrida et al., 2004), and increased levels of FAAH (De Marchi et al., 2003).

Taken together, this evidence supports the notion that patients may be more susceptible to the cognitive-impairing effects of exogenous cannabinoids compared to controls, and henceforth may also be more apropos for recovery of cognitive functions.

**Amount of Cannabis Consumed**

One simplistic reason for the lack of cognitive change among abstinent controls versus schizophrenia patients may be because control participants were heavier cannabis users than patients. While subjectively patients and controls did not differ on measures of recent or cumulative use, biochemical (objective) data suggests otherwise. Baseline THC-COOH levels spanned a much larger range in controls; the mean THC-COOH level in controls was twice as large as the baseline THC-COOH levels of patients. While admittedly speculative this may imply that controls are smoking higher quality cannabis, with higher levels of THC than schizophrenia patients. Given that more potent cannabis is associated with greater cognitive impairment (Morgan et al., 2012) may imply that controls have incurred greater deterioration. Alternatively, patients may consume less cannabis compared to controls given that it has more adverse outcomes on their symptoms and clinical course (Linszen, Dingemans, & Lenior, 1994). However, because there is high inter-individual variability in the elimination half-lives of THC (Johansson et al., 1989), association with objective THC-COOH data should be interpreted with caution.

Further evidence for the significance of amount of cannabis on recovery comes from PET imaging abstinence studies. Hirvonen et al (2012) reported that after approximately one-month of cannabis abstinence, CB1R up-regulation occurred in regions that had shown decreases at baseline; this happened in cortical regions except for the hippocampus. A later study with a comparable abstinence period supported the reversal of down-regulation in cortical region, which included the hippocampus (D’Souza et al., 2016). The discrepant findings between the studies may be attributable to differences in cannabis exposure between the two samples. In the former
study, participants smoked an average of 10 ± 6 joints or blunts per day while in the latter study subjects consumed approximately 1–2 joints per day. Given that the hippocampus possesses a high density of CB1Rs, reversal of cannabis-induced impairment may be (partly) dependent on the quantity of cannabis consumed.

A recent study by Yucel et al (2016) suggested that hippocampus volume is reduced in long-term cannabis users, and found that this atrophy may be restored following abstinence. Interestingly, these investigators demonstrate for the first time that it is not just the amount of cannabis consumed, but also the composition of cannabinoids within the cannabis that may differentially affect the brain. In this study, prolonged cannabis exposure or abstinence on hippocampal integrity was examined in current and former cannabis users, respectively (Yucel et al., 2016). Results suggested that hippocampus volume was indeed reduced in long-term cannabis users exposed to THC. Moreover, given that the hippocampal integrity of former users was comparable to that of controls suggests that this atrophy was restored following prolonged abstinence. One of the most intriguing findings from this study was that among current cannabis users those using cannabis containing CBD showed no hippocampal differences compared to controls. Cannabis users not exposed to CBD had 11% reduced volumes and 15% lower concentrations of N-acetylaspartate, a measure of neuronal viability. Thus, CBD may exert neuroprotective properties and therefore oppose the neurotoxic effects induced by THC in regions that are high in CB1R (Bhattacharyya et al., 2010; Martin-Santos et al., 2012). CBD may counteract THC-induced damage to neuroanatomy, as it has been shown to alleviate neurodegeneration and modulate the effects of THC by blocking CB1Rs (McPartland et al., 2015). The lack of behavioural measures in this study makes it impossible to determine whether performance on hippocampus-mediated cognitive tasks would have shown a similar pattern of intactness corresponding to the integrity of the hippocampus. Therefore, in sum, it is the amount of cannabis used, cumulative exposure and its potency that together play a critical role in the resulting damage and dysfunction incurred from prolonged cannabis use.

**Length of Abstinence Period**

There is evidence from some, but not all, studies that impairment in specific cognitive domains may recover with sufficient abstinence periods. However, evidence for permanent cognitive dysfunction continues to emerge in parallel. Given the abovementioned mechanisms proposed to
underlie cannabis-induced dysfunction, significant time may be required to restore the brain to pre–cannabis use integrity and functionality. Studies examining abstinence periods of varying time continue to accumulate and yet the length of time needed for recovery remains undetermined. Pharmacologically, regular cannabis users require approximately 28-days to rid the body of THC and its metabolites. As such, abstinence periods of 28-days readily assess the true effect that cannabis has exerted on the brain rather than detecting the effects of lingering cannabinoids in the body. Thus, studies employing less than 28-days may be subject to the confounding effects of residual THC metabolites.

Pope et al (2001) monitored heavy cannabis users over 28-days of abstinence. Cognitive function was evaluated at Day 0, 1, 7 and 28. Decrements in verbal memory were found at 7 days of abstinence but not after 28 days of abstinence. The authors therefore concluded that cognitive deficits are a product of recent use, rather than cumulative, and are reversible following 28 days of abstinence (Pope et al., 2001). This finding is similar to what was observed in our sample of abstaining schizophrenia patients. In line with these results, abstinence studies in adolescents with relatively brief histories of regular cannabis use showed verbal memory significantly improved following three to six weeks of abstinence (Hanson et al., 2010; Schwartz et al., 1989). Others have also suggested that recovery does occur but may require as long as three months (Fried, Watkinson, & Gray, 2005). Again the participants included in this study had a relatively short period of regular cannabis use (mean =2.6 years). One recent study of heavy cannabis-using participants who self-reported smoking on average 10.9 joints per day for the last 10.5 years showed partial recovery of psychomotor function with three weeks of abstinence (Bosker et al., 2013).

However, other studies observed cognitive impairments that did not reverse with abstinence periods of 28-days or greater. Bolla et al (2002) reported a persistent dose-related association between increasing number of joints used per week and greater decrements in cognitive performance that persisted following one-month of abstinence. In the largest prospective longitudinal study to date, Meier et al (2012) reported that individuals who began using cannabis early in their teenage years never fully returned to their predicted pre-drug exposure IQ trajectory following reduction of use or complete abstinence (>1 year cessation in some cases). In line with these findings, a study examining cannabis users who were abstinent from 6 weeks to 2 years
also found that significant impairments persisted in selective domains such as attention and concentration (Solowij, 1995).

Thus, while some studies demonstrate that select cognitive domains are more susceptible to (faster) recovery than other domains, other studies have found that deficits do not remit even with prolonged periods of abstinence, suggesting permanency of these impairments. Large methodological variation exists between studies and diverse testing paradigms are employed, preventing direct between-study comparisons. Some studies employed cross-sectional designs (Schwartz et al., 1989; Solowij, 1995), however, between-group analyses may not be sensitive enough to pick up subtle cognitive differences (Rabin et al., 2013). Additionally, residual THC may confound cognitive performance in the current cannabis-using group (Fried, Watkinson, & Gray, 2005; Solowij, 1995). Laboratory models of abstinence arguably offer the most controlled means of testing cognitive recovery among chronic cannabis users. However, being continuously monitored on an inpatient unit (Bolla et al., 2002; Bosker et al., 2013; Pope et al., 2001) may yield different effects than utilizing a twice-weekly outpatient approach as in this study and others (Hanson et al., 2010; Medina et al., 2007). Lastly, the number of years and severity of cannabis use differs greatly between studies. If a relationship exists between lifetime duration of cannabis use and reversibility this would represent another confounding factor. One group of investigators suggested that impairments develop gradually and may only become clinically significant after one or two decades of chronic cannabis use (Solowij et al., 2002a). Therefore, cannabis-induced impairments or change may be too subtle to detect in some of these studies where participants used for less than ten years.

The parameters of recovery are far from being elucidated. From the studies conducted thus far, there is little consensus on whether or not cannabis-induced cognitive impairments reverse with abstinence. And if it recovery does occur for how long does one need to be abstinent before change may occur? The current study findings add to the conflicting literature suggesting that cognitive recovery if it is possible does not occur within one month of abstinence in non-psychiatric controls. The time course and potential moderators of potential recovery of cognitive function with abstinence warrant more precise characterization.
Age of Onset of Cannabis

The neurodevelopmental stage at both the onset and cessation of cannabis use may be an important predictor of the magnitude of effect that cannabis exerts on cognitive function. Cannabis use is often initiated in adolescence, a time when recreational use often proceeds to more chronic and problematic consumption (Coffey et al., 2000). Moreover, adolescence refers to the developmental time period between childhood and adulthood (Spear, 2000) and represents a critical window for brain development, maturational processes and neuronal remodeling. Such processes include myelination, synaptic pruning and dendritic plasticity (Lundqvist, Jonsson, & Warkentin, 2001; Realini, Rubino, & Parolaro, 2009). In particular, the expression of CB1Rs dramatically increase from infancy to young adulthood (Mato, Del Olmo, & Pazos, 2003), with peak levels occurring during early adolescence (Belue et al., 1995). These changes are largely seen in the hippocampus and PFC (Spear, 2000), notably brain areas that are responsible for mediating cognitive function.

Many of these fundamental brain developmental processes such as neuronal cell proliferation, migration and differentiation (Harkany et al., 2008) are dependent on the eCB system. Thus, through its action on CB1R, cannabis may interfere with these normal physiological processes resulting in a host of neurobiological abnormalities. [For review see (Bossong & Niesink, 2010)]. Taken together, this evidence suggests that cannabis use during adolescence may exert graver consequences on brain function and intactness compared to exposure during adulthood (O'Shea et al., 2004).

Studies have provided evidence that a relatively immature brain is more susceptible to the impact of cannabis exposure compared to an adult’s fully developed brain (Ehrenreich et al., 1999; Fontes et al., 2011; Pope et al., 2003; Sagar et al., 2015). There is no definitive age in which development of the adolescent brain ceases, however investigators have arbitrarily set this cutoff to before 15 (Fontes et al., 2011)16 (Sagar et al., 2015) and 17 (Ehrenreich et al., 1999). Conceivably, early chronic cannabis use may have more of an enduring non-reversible effect compared to individuals who begin using in adulthood. Therefore, disruption of normative eCB signaling during adolescence may permanently alter neurodevelopmental trajectories, particularly in CB1R-rich areas. This corollary also prompted the hypothesis that cannabis-induced alterations in the eCB system during adolescence might represent a risk factor for later
development of schizophrenia (Arseneault et al., 2002; Moore et al., 2007; van Os et al., 2002). Research suggests that cannabis use typically precedes the onset of schizophrenia, and acts as a catalyst in hastening the onset of the disorder (Cunha et al., 2013; Linszen, Dingemans, & Lenior, 1994; Sugranyes et al., 2009).

Among our sample the average age of onset of regular cannabis use (at least weekly) in patients and controls began at 17 and 18 respectively. Notably, this surpasses the age some investigators describe as early onset cannabis use (Ehrenreich et al., 1999; Fontes et al., 2011; Pope et al., 2003; Sagar et al., 2015). Thus the “later” initiation of cannabis use in our participants may have afforded them with less severe and/or less permanent cognitive deficits. Perhaps with longer abstinence periods and/or the implementation of more sensitive cognitive tests, greater magnitude of improvements would be seen.

4.1.11 Factors Associated with Abstinence

While not an a priori aim of this study, this was the first cannabis abstinence study to concurrently follow abstaining participants as well as those who relapsed before study end-point. One of the advantages of this is that it allowed for the exploration of factors associated with both the ability and inability to successfully quit cannabis. Examining predictors associated with cannabis cessation in schizophrenia is an understudied area of research and thus to our knowledge this is the first study to investigate if cognitive function is associated with the ability to maintain one-month of cannabis abstinence in patients with schizophrenia.

Among patients with schizophrenia, baseline attentional performance as assessed by the CPT, was significantly lower in patient non-abstainers compared to patients who were able to abstain from cannabis for the 28-day study period. Similarly, IGT performance was greater (at trend level) among abstainers versus non-abstainers, suggesting that the latter group possesses impairments in complex decision-making processes. Thus, pre-existing cognitive deficits may be associated with cannabis cessation failure in patients with schizophrenia. Our results are in line with studies conducted in tobacco smokers that noted that cognitive dysfunction was a
significant predictor of tobacco treatment failure in patients with schizophrenia (Dolan et al., 2004; Moss et al., 2009).

Attention refers to an individual’s ability to selectively concentrate on one aspect of the environment while ignoring potential distracters. CPT (percent hits) is a measure of inattentiveness and there is evidence of a reciprocal relationship between sustained attention and drug addiction. For example, drug cravings demand attentional resources that keep the individual focused on drug cues and away from non-drug relevant stimuli (Field, Munafo, & Franken, 2009). This “attentional bias” results in compromised performance on sustained attention tasks (Sayette, Schooler, & Reichle, 2010) and may contribute to poor cessation outcomes. For example, heightened awareness of drug availability combined with strong drug cravings, experienced early in cessation, may undermine abstinence attempts and result in relapse (Copersino et al., 2004; Marissen et al., 2006; Waters et al., 2003). Among these individuals, the craving state may go unnoticed and create a context in which drug users are likely to engage in relapse and not even notice (Sayette, Schooler, & Reichle, 2010). Therefore sustained attention is continuously required in order to suppress drug-seeking responses.

Attention is also an integral component of decision-making processes. Decision-making reflects a process in which attention is focused and a choice is made after reflecting on the expected outcomes of possible actions and/or inactions. Hence, it is not surprising that non-abstaining patients demonstrated worse IGT performance compared to patients who were successful at abstaining. Poor performance on this task suggests that these individuals tend to guide their behaviour according to short-term gains rather than carefully considering what the effects may be in the long-term (Bechara, 2005; Kirby, Petry, & Bickel, 1999). Accordingly, such cognitive deficits may increase the likelihood of relapse.

In contrast to schizophrenia patients, among control participants, cognitive function at baseline did not differ between individuals who were successful at abstaining compared to those who were not. Results are consistent with previous research. For example, Aharonovich et al (2008) found that cognitive function did not significantly predict treatment outcome at the end of a 12-week trial examining behavioural interventions on cannabis cessation outcomes. However, cognitive function did significantly distinguish completers from dropout. That is, better cognitive
impairments at treatment entry were associated with reduced treatment retention among cannabis-dependent individuals.

In sum, attentional and decision-making deficits may contribute to difficulty associated with cannabis cessation attempts and to the maintenance of sustained cannabis use among schizophrenia patients. This suggests that these deficits may provide a means of identifying individuals who may be at the highest risk for relapse. Moreover, these measures of cognitive functioning may serve as potential treatment targets in substance use interventions for patients (Sofuoglu et al., 2013). Among controls, cognitive function may be more relevant for treatment retention purposes. As such, perhaps clinicians should tailor their interventions with these factors in mind.

4.2 Study Strengths

The current study demonstrated several strengths over other studies that have attempted to characterize the effects of cannabis on cognitive function.

Firstly, while laboratory-controlled longitudinal approaches have been employed to study this relationship in controls, this is the first study to adopt such a paradigm in cannabis-dependent schizophrenia patients. Thus, a major methodological limitation of previous studies in patients is that results were generated from cross-sectional data. A more reliable and robust method is employing a prospective abstinence design, to assess within-subject differences rather than between-subject effects. Moreover, given that the primary purpose of this study was to examine the state-dependent effects of cannabis in schizophrenia, this design overcomes the causality issue, and is able to elucidate directionality of the relationship.

We believe that we have implemented a feasible, operational and effective study design. Other investigators have suggested that studies using highly controlled THC or cannabis administration may be more advantageous to study the cognitive effects associated with cannabis use. However, we disagree. For one, THC is not analogous to cannabis. The effects of cannabis are due to a
composite of various cannabinoids that may modulate the effects of THC (Hollister, 1988). Secondly, and most importantly, chronic cannabis users develop tolerance to the drug (Gonzalez, Cebeira, & Fernandez-Ruiz, 2005; Green, Kavanagh, & Young, 2003). Thus, with acute THC administration in cannabis dependent users lack of a significant effect on cognitive performance would be expected (D'Souza et al., 2008b; Hart et al., 2010).

In addition this study used a naturalistic approach as opposed to having participants reside on a closed secure inpatients unit. Outpatient studies are more relevant because inpatient studies do not include many of the environmental stimuli (i.e., cues) that can produce conditioned effects. As a result, inpatient studies may underestimate the severity of drug consequences such as withdrawal or craving. Moreover, attrition may be greater in residential settings. In one 33-day inpatient study, approximately half of participants (50%) withdrew by day 21 of the experimental period (Karschner et al., 2015). This is extremely high in comparison to our 8% dropout rate. On the other hand, a caveat of our design is that we cannot completely discount the possibility that some subjects might have surreptitiously smoked very small amounts of cannabis that went undetected with twice weekly urine tests, which may have been less likely to occur on a continuously monitored unit.

As demonstrated by the current study, despite no introduction of cannabis use over the 28-day abstinence period, complete elimination of THC may not occur. This is concerning given that many related studies have used decreasing cannabis metabolites as a marker of abstinence [e.g., (Hanson et al., 2010; Medina et al., 2007; Pope et al., 2001), without acknowledging levels of cannabinoids at abstinence end-point. Thus investigators attempting to not capture the residual effects of cannabis may inadvertently be doing so. Therefore, a novel feature of this study was that we not only characterized abstinence according to lack of introduction of cannabis, but also according to residual levels of cannabinoids present in the body at end-point (20ng/mL). We felt that this was essential to truly capture the state dependent effects of cannabis on cognition, especially given that the effects of residual cannabinoids on cognition are poorly characterized. Hence our abstainers were truly "clean" of cannabis, and thus removed the possibility of lingering THC as a confounding factor.
The principal intervention employed to encourage cannabis abstinence was contingency management. This was the ideal method to employ given that it targets reward processes rather than cognitive control processes, such as CBT (Petry, 2012; Sofuoglu et al., 2013). This was fundamental given that control participants from the outset have superior cognitive function compared to schizophrenia patients, and behavioural interventions targeted at cognition would provide controls a greater advantage in achieving abstinence over patients. Moreover, a supportive therapy platform was incorporated into the present study as a means to help participants cope with cannabis cessation and encourage abstinence. In addition, this also helped to satisfy ethical considerations (Street & Luoma, 2002) and perhaps assist with study retention. The counseling provided was brief and of low-intensity and thus not expected to have a robust effect on outcomes. Furthermore, adding a behavioural component is a conventional practice in pharmacotherapy trials and is not believed to undermine the test variable if used appropriately (Carroll, Kosten, & Rounsaville, 2004). However, we were unable to determine the degree of effect of the individual therapy session, if any, on study findings.

Lastly, this study took a rigorous approach to control for the confounding effects of other substances of abuse. This was especially critical for tobacco use as nicotine has been associated with increased cognitive performance in both patients with schizophrenia and healthy controls. (Adler et al., 1993; Sacco et al., 2005). Because many cannabis users also use tobacco (Agrawal, Budney, & Lynskey, 2012), it was advantageous to enroll only participants who were also daily cigarette smokers into this study. While participants were allowed to engage in cigarette and alcohol use during the study their use was closely monitored over the one-month. Participants with current SUDs, other than cannabis and nicotine, were excluded from this study so as to isolate and clarify the specific effects of cannabis. However, exclusion of participants with poly-substance use from the study may have resulted in an underestimation of symptom severity that would have been observed if these participants were included (Hughes, Higgins, & Hatsukami, 1990).
4.3 Study Limitations

Findings from the current study must be interpreted within the context of several limitations.

First, we did not include (non-contingent) yoked control groups: schizophrenia and non-psychiatric control cannabis users who continued to use cannabis over the 28-day study period. This would have allowed for the appropriate time control, exposing participants to the same experimental conditions as our cannabis abstaining participants.

In addition we did not enroll non-cannabis using control groups (i.e., non-cannabis-using non-psychiatric controls or non-cannabis using schizophrenia patients). The lack of these comparison groups makes it difficult to define the magnitude of cannabis-induced deficits at baseline. While unlikely, it is plausible that these cannabis-users may not be significantly cognitively impaired, and thus putative improvements would be trivial and/or unnecessary and therefore unfeasible to detect with cognitive testing. However, given that both patients and controls demonstrated robust relationships between cumulative use and cognitive deterioration provides strong rationale against this notion.

In the current study, a non-abstinent time control was inherently embedded in the study. That is, our relapsing participants, predicted to be 50% of the sample, were designed to act as our time-matched non-abstinent control group in both schizophrenia and healthy control groups. However, we now acknowledge the limitations of using such a control group. For one, we did not expect that these non-treatment seekers would decrease their cannabis consumption to the extent that they did. Additionally, it is plausible that individuals who relapse may be dissimilar from individuals who are able to successful abstain from cannabis. Thus, pre-existing difference may drive differences between these two groups.

Second, ceiling effects on specific cognitive tests at baseline may have prevented the detection of cognitive change with abstinence among control participants. This was observed on HVLT performance. It is critical to avoid both ceiling and floor effects on cognitive outcomes. An alternative to the HVLT is the California Verbal Learning Test (CVLT) (Delis et al., 2000),
which contains 15 words per list rather than 12. These additional items and trials on the CVLT would serve to avoid ceiling effects in controls and thus, may be more sensitive to alterations in memory performance. However, the CVLT does not have alternate forms, which makes it vulnerable to significant practice effects.

Third, cannabis use is associated with amotivational syndromes, characterized by laziness, social withdrawal, lethargy and apathy (DuPont, 2000). Given the intensive nature of this study, these individuals were likely not interested in participating and were thus underrepresented in the current sample. Motivation and effort exerted in this study were measured using the TOMM, and was found to be intact in both patients and controls. Therefore, the sample recruited likely reflects a higher functioning, less severe subgroup of cannabis users. Further, while all of our participants met criteria for DSM-IV cannabis dependence, they only smoked on average one gram of cannabis per day. Perhaps a more severe and heavily cannabis-using sample would exhibit greater magnitude of change with sustained abstinence in measures of psychopathology and cognitive performance.

Fourth, given that 28-days of abstinence was not a sufficient time period to achieve negligible levels of cannabinoids in the body in all users, we set a cut-off level to parse abstainers from non-abstainers. However, this may have unintentionally been biased towards heavier cannabis users, as they may have not been able to eliminate cannabinoids to levels below 20ng/mL within the study timeframe (Ellis et al., 1985; Goodwin et al., 2008). However other studies suggested that frequent cannabis smoking can induce THC metabolism, (Lemberger et al., 1971), thereby actually increasing the rate of elimination among chronic users. In contrast, other research proposes that frequent and infrequent cannabis users are in fact similar in the way that they metabolize cannabis (Agurell et al., 1986). If symptomatology and cognitive function are most likely to show the greatest magnitude of change in heavier users then lengthier abstinence periods are warranted. One study suggested that it may in fact require up to 46 days for cannabinoids to become undetectable (Ellis et al., 1985). However, we believe that there may be a trade-off as a longer duration of abstinence may be proportional to the number of study participants who drop out. Perhaps with the implementation of contingency management and adequate incentives, increasing the length of abstinence would be feasible.
These limitations should be addressed in future studies.

4.4 Conclusions

To our knowledge, this is the first study to employ a longitudinal prospective design to characterize the state-dependent effects of cannabis on cognition in patients with schizophrenia. Accumulating research suggests that cannabis-using patients possess superior cognitive function compared to non-using patients. This has led to the hypothesis that schizophrenia cannabis-using patients represent a higher functioning subgroup with inherently better cognition. While this trait effect has been demonstrated in two recent meta-analyses, including one from our own group (Rabin, Zakzanis, & George, 2011; Yucel et al., 2012), evidence that cannabis may have a deteriorating effect is likewise, quite convincing (D'Souza et al., 2005; Rabin et al., 2013). Yet, a major caveat of these studies is their cross-sectional nature and the tendency for investigators to group current and former patients together.

Using a 28-day cannabis abstinence paradigm, we were able to provide evidence that cannabis exerts a deleterious state-dependent effect on verbal memory and learning performance in patients with schizophrenia. Moreover, these cannabis-induced deficits may be reversible with sustained abstinence and recovery of cognitive function may favour cognitive processes facilitated by brain regions rich in CB1 receptors, such as the hippocampus. These results are in line with both our previous meta-analysis (Rabin, Zakzanis, & George, 2011) and cross-sectional study (Rabin et al., 2013). Taken together, findings support the notion that cannabis has a negative impact on cognitive functioning (state-effect). While admittedly speculative, we posit that these cannabis-induced impairments are likely superimposed upon a high functioning subgroup of schizophrenia patients (trait-effect).

Moreover, cognitive change was not observed with abstinence among cannabis dependent control participants. It has been suggested that schizophrenia patients demonstrate enhanced sensitivity to the cognitive-impairing effects of cannabis compared to control individuals (D'Souza et al., 2005). One reason for this is that cannabis appears to exacerbate dysfunction that is already present in schizophrenia patients, such as in the eCB system and in GABAergic
neurotransmission (Lewis & Hashimoto, 2007; Ranganathan et al., 2015). Moreover, genetic polymorphisms common in schizophrenia may interact with cannabis exposure to play a role in moderating sensitivity to cannabis (Henquet et al., 2005). Furthermore, studies consistently report that hippocampus-mediated cognitive domains such as verbal memory and learning are particularly vulnerable to the deleterious effects of THC. This has been demonstrated in both patient samples (D'Souza et al., 2005) and controls (Bolla et al., 2002; Grant et al., 2003; Pope et al., 2001). Effects of cannabis may be compounded in the hippocampus given the high concentration of CB1R in this brain region (Herkenham, 1991). Other cognitive tasks facilitated by brain areas less densely populated with CB1R and therefore may be less sensitive to the effects of cannabis. Thus, if hippocampus-mediated tasks are most susceptible to cognitive impairment, and schizophrenia patients have increased susceptibility to these effects, then it follows that this brain region may also be most vulnerable to the reversal of deficits in patients. This, in part, recovery of function was exclusive to verbal learning and memory within the 28-day abstinence period. Perhaps with longer duration of abstinence, performance on other tests included in our comprehensive battery would exhibit functional recovery. Among controls, it is possible that recovery of cognitive function may not be as forgiving as in patients. Their lack of improvement in cognitive function may be attributed to cannabis exerting a deteriorating effect that is more resistant to amelioration than in schizophrenia. However, we cannot fully exclude the possibility that cannabis exposure might not have impaired cognitive function in control participants.

Most other studies examining the non-acute effects of cannabis on cognitive function have also employed abstinence periods ranging up to one-month (Bolla et al., 2002; Hanson et al., 2010; Medina et al., 2007; Pope et al., 2001), however 28-days of abstinence may not provide a sufficient window to allow for full neurobiological recovery. One reasons for this may be because 28-days of abstinence did not allow for select users to completely rid their body of THC and its metabolites.

Findings presented here in schizophrenia support the notion that clinicians should actively intervene and help patients to quit cannabis. While cannabis may be thought of as a benign drug with low addiction potential, we demonstrated that it might have cognitive-impairing effects. Moreover, while cannabis cessation may be difficult, this study showed that it is certainly
possible. Comprehensive psychotherapeutic approaches, such as CBT and motivational interviewing, ought to be implemented and integrated into patients’ current and ongoing treatment plans. Cognitive improvement is especially essential in schizophrenia patients given that cognitive function is one of the strongest predictors of functional outcomes (Green et al., 2000). Cognitive deficits contribute to vocational difficulties, lack of success in rehabilitation programs and diminished quality of life. Thus reducing the severity of cognitive impairment will likely translate into better everyday functioning in schizophrenia.

Importantly, cannabis cessation did not lead to any adverse effects. According to the self-medication hypothesis cannabis is used to alleviate symptoms associated with the disorder. Our results do not provide support for this theory. That is, psychiatric symptoms and extra-pyramidal symptoms did not worsen with abstinence. Moreover, among schizophrenia abstainers depressive severity scores were reduced over time and by Day28, these patients demonstrated a sizeable improvement in their mood. Other studies agree that cannabis use is not associated with beneficial or favourable effects in patients with schizophrenia (Henquet et al., 2010; Ringen et al., 2013). The only adverse outcomes observed with cannabis abstinence were withdrawal symptoms, which tended to dissipate within the first week of cessation.

We demonstrated that contingency management was indeed effective at retaining study participants as well as facilitating abstinence, however the latter was only at about a 50% success rate across diagnostic groups. Unfortunately to date there are no approved medications to treat CUDs and behavioural interventions are only mildly satisfactory. Our data provides preliminary evidence that targeting specific cognitive deficits may offer a more effective approach for treating SUDs. More specifically, we found that attentional performance was superior amongst abstaining patients with schizophrenia compared to non-abstaining patients. Thus, it follows that pre-existing cognitive impairments in schizophrenia may be associated with cannabis cessation failure. In fact, poor attention may be a marker of poor treatment outcomes. Therefore, targeting attentional deficits through cognitive remediation may be a valuable strategy to overcome challenges (i.e., cravings) and enhance the effectiveness of behavioral treatments. Therefore, normalizing attentional deficits may improve overall treatment outcomes as well as protect against later risk of relapse. In addition, modifying behavioural interventions to address these attentional difficulties may prove equally effective.
4.5 Future Directions

The effects of cannabis on cognitive function in individuals with and without schizophrenia is complex, and only partially understood, and thus requires further investigation. While this study adds valuable knowledge to this growing body of literature, questions remain unanswered and new ones have emerged thereby providing subject matter for future studies to tackle.

For one, this study needs to be replicated using a larger sample set. While this study was powered to detect differences in specific cognitive tasks (HVLT), we may have lacked statistical power to detect subtle differences in other cognitive tasks and in clinical symptoms that may have emerged over the 28-day study period. An increased sample size would also allow for more sophisticated analyses to be conducted such as multiple regression and model building in order to identify predictors of abstinence and/or risk factors for relapse. In addition, it would be necessary to add in the appropriate control groups.

Future studies examining the effects of cannabis on cognition in schizophrenia should incorporate additional assessment measures. This study lacked a specific evaluation of anxiety. Anxiety is important to assess given that while acute cannabis use may quell symptoms of anxiety, the long-term effects of cannabis use may involve increased levels of anxiety (Crippa et al., 2009). Therefore it would be of interest to determine the trajectory of anxiety over a period of cannabis abstinence. In addition, it would be important to determine if improvement in cognitive performance correlated with overall functioning. Estimates of psychosocial functioning, and quality of life scales should also be included.

Additionally, with greater samples we would then be able to stratify our non-abstaining groups. The lack of a time by abstinence status effect likely reflects that non-abstainers on average decreased their consumption of cannabis use over time. This is not surprising given that non-abstainers collectively included those whose THC-COOH levels did not drop below 20ng/mL by Day 28 even if they did not use cannabis over the study period, individuals who lapsed, even just once, as well as those who did not quit but were nevertheless inspired to cut down on their current use. Needless to say non-abstainers also encompassed participants who relapsed after minimal cessation and then continued to use cannabis throughout the study period. It would be of
great interest to study these subgroups individually, in order to investigate how decreasing cannabis use, residual cannabis use, and immediate relapers compare to each other and compare to abstainers.

Given that there is considerable heterogeneity in schizophrenia and large intra-individual variability in the psychological reactions to THC (Atakan et al., 2013), one approach to try and reduce variability may be to study specific subgroups:

i.) First, while we only enrolled individuals who met for cannabis dependence, our participants were not overly heavy users. Testing individuals who consume greater amounts of daily cannabis may have differential effects in terms of impairments and the ability to reverse these impairments compared to lighter users. Heavier use has been defined as using up to five joints per day (Ashtari et al., 2009), or even 10 joints per day (Hirvonen et al., 2012). Thus, our study participants were moderate users given that they consumed on average about one gram per day. Pattern of use may play a critical role in how cannabis affects the brain. This tenet should be explored in futures studies. Moreover, this should extend beyond just the amount of cannabis consumed. That is, it may be important to determine if cannabis use is associated with differential effects on brain functioning according to frequency or duration of use. In other words is using cannabis in a concentrated time-period more harmful than using the same amount of cannabis spread out over years or decades? What about recreational use? Additionally, is there a threshold of cannabis use that once surpassed consequences are more likely to result in permanent effects?

ii.) Second, it would be important to determine if cognitive recovery is equally likely across all stages of schizophrenia: prodromal, first-episode and chronic patients. If timelier cessation is associated with better outcomes, then cannabis prevention and early intervention strategies need to be a priority at first admission for patients presenting with co-morbid cannabis use.

iii.) Another question of interest is whether cannabis use is associated with differential effects on brain function according to the age of consumption. As previously mentioned, adolescence represents a sensitive time period when the brain undergoes complex and extensive neurodevelopmental and neuromaturational processes that are essential for intact brain function.
(Paus et al., 1999). Therefore, it is necessary to determine if age of onset is predictive of the durability of deficits. In other words, does the use of cannabis during adolescence lead to the same magnitude and permanency of changes in brain function as cannabis exposure later in life?

iv.) Future studies should assess whether findings extend to female cannabis users. This is especially important because despite the lower rates of cannabis use among women, females are more susceptible to the development of CUDs, have more severe withdrawal symptoms, and are more likely to relapse compared to men (Cooper & Haney, 2014; Craft, Kandasamy, & Davis, 2013; Fergusson, Boden, & Horwood, 2006). Moreover recent research provides evidence that sex differences influence the effects that cannabis exerts on cognition (Crane et al., 2013). Moreover, sex-dependent effects should be examined in concert with reference to timing of onset of cannabis use given that males and females have differential neurodevelopmental trajectories, regional CB1R densities, as well as endocrinological and behavioral contributions [For review see (Crane et al., 2013)].

v.) Another important focus for future research and a logical extension of the current work is to employ longer abstinence periods. For one, in our sample of users, 28-days of abstinence was not a sufficient time period to achieve negligible levels of cannabinoids in the body for all users. Thus extending this period may allow all participants who do not introduce new cannabis use over the abstinence period, speculatively either because they are heavier users and/or eliminate cannabinoids at slower rate) to be classified as “abstainers” as opposed to “non-abstainers”.

In addition, prolonging the abstinence period would provide valuable information regarding the permanency of cognitive deficits, in patients in domains other than verbal memory and learning, and in controls for all cognitive domains. However what this time frame should be is highly uncertain. From this study, because we characterized our abstainers according to such stringent criteria, we can conclude that the lack of cognitive improvement was not a result of residual cannabinoids still present in the body. Thus perhaps mechanisms of neurobiological recovery are needed for restoring cognition. While we know this includes CB1R down-regulation, other processes required to “undo” neuroadaptation may be at work and need to be elucidated. In a similar respect, whether clinical symptoms, as assessed by the PANSS, ameliorate with longer abstinence periods should be studied in parallel. Studies using well-controlled laboratory
paradigms, similar to the one employed in the current study, but with longer abstinence periods will help to identify at what point beyond 28-days, clinical and cognitive symptoms begins to improve, if ever. That is to say, recovery of cognitive function necessitates more precise delineation.

vi.) Future studies should also incorporate imaging techniques into the study design such as fMRI or PET. This will allow one to determine the relationship between functional neural changes and changes in cognitive performance. It may also detect whether compensatory mechanisms have hijacked the brain to perform at “normal” levels.

vii.) A universal effort should be made to report the type or strain of cannabis being consumed by study participants (Hagerty et al., 2015). Such information should include the potency (i.e., percent THC), and the composition (i.e., ratio) of various constituents within the cannabis. Given that many countries are moving towards legalization, this may be an easier feat than once assumed. Differential and opposing effects of THC and CBD have been elucidated and may underlie complex effects of cannabinoids on underlying neural networks and this may ultimately help to explain some of the discrepancies in the literature.

viii.) In this study we used low-cost contingency management to facilitate abstinence. It would be of interest to determine if increasing the monetary gains would correlate to greater rates of abstinence. Extrapolating where the extrinsic reward outweighs the desire to engage in drug use may be of interest when designing such studies and for the use of contingency management in treatment approaches as well. However, sustained abstinence would eventually require continued application of the incentive or development of intrinsic motivation to remain drug-free. While this study speaks to the effectiveness of contingency management in initiating and sustaining short periods of abstinence, how this would translate to treatment-seeking populations for long-term cessation warrants exploration.

ix.) Lastly, this study offers preliminary evidence that specific cognitive impairments may be robust predictors of cannabis relapse. Therefore, targeting cognitive impairment associated with chronic cannabis use may be a promising novel strategy for the treatment of CUDs. Therefore, cognitive enhancement may offer a valuable alternative to pharmacotherapy, which has proven
unsuccessful to date. Future research should directly assess the capacity for cognitive enhancing treatments to improve cannabis use outcomes via their modulation of cognitive function.

4.6 Final Comment

In sum, we demonstrated that despite that cannabis-using schizophrenia patients may possess better cognitive function than non-using patients, chronic cannabis use may exert a state-dependent, deleterious effect on verbal memory and learning performance. Fortunately, these additive deficits may be reversible with sustained abstinence. While only specific deficits improved with 28-days of abstinence, other cognitive domains may do so at protracted rates. Alternatively, these cognitive tasks may be facilitated by other neural mechanisms. Thus, conceivably, accelerated recovery of cognitive deficits may favour cognitive processes facilitated by brain regions rich in CB1R.

Our findings are exciting from a treatment perspective given that these deficits are tightly linked to functional outcomes in schizophrenia patients. As such, cannabis use should be discouraged among patients and targeting cognitive impairment, specifically attention, may be a promising approach to treat this addiction. Cannabis use has also been independently associated with medication non-adherence, psychotic relapse, and number and duration of hospitalizations (Schoeler et al., 2016; Zammit et al., 2008), thereby reinforcing that cannabis is indeed harmful and is associated with serious consequences. It is plausible that remedying cannabis-related cognitive dysfunction may provide the building blocks needed for rehabilitation in schizophrenia.

Cannabis is the most widely used illicit substance worldwide. Unfortunately, rates of cannabis use continue to rise, and perceived risks associated with its use continues to decrease (Johnston, 2014). The changing legal landscape surrounding recreational and medicinal cannabis use worldwide is undoubtedly a contributing factor (Cerda et al., 2012; Hall & Weier, 2015; SAMHSA, 2014). Unfortunately, this rapid societal change is far outpacing our knowledge and understanding of the long-term effects associated with cannabis use. Thus, scientific evidence is contributing little to the debate on legalization. Findings from the current study draw a corollary
between cannabis use and cognitive outcomes in schizophrenia, thus supporting the notion that cannabis is not a benign drug. More well-controlled laboratory designs are needed to elucidate the effects of chronic cannabis use across all cognitive domains. Neuroimaging techniques should be incorporated into these paradigms to assess brain activity in parallel with cognitive testing. The understanding of how the human brain may recover, or partially recover, as a function of extended cannabis abstinence has important implications for both the neurobiology of co-morbid disorders as well as for the treatment of substance use disorders.
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6 Appendices
The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis

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ABSTRACT

Patients with schizophrenia frequently report cannabis use, yet its effects on neurocognitive functioning in this population are still unclear. This meta-analysis was conducted to determine the magnitude of effect of cannabis consumption on cognition in schizophrenia without the confounding effects of other co-morbid substance use disorders. Eight studies met inclusion criteria yielding a total sample of 942. Three hundred and fifty six of these participants were cannabis users with schizophrenia, and 586 were patients with no cannabis use. Neuropsychological tests were grouped into seven domains (general cognitive ability and intelligence; selective, sustained and divided attention; executive abilities; working memory and learning; retrieval and recognition; receptive and expressive language abilities and visuo-spatial and construction abilities). Effect sizes were computed for each cognitive domain between cannabis-using patients and patients with no history of cannabis use. Effect size differences in cognitive performance in the schizophrenia group as a function of cannabis use were in the small to medium range, denoting superior performance in cannabis-using patients. Explanations for these findings are discussed and suggestions for future research in this area are recommended.

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1. Introduction

With lifetime use reported to be as high as 64.4%, cannabis is the most commonly used illicit drug among patients with schizophrenia (Barnes et al., 2006). Further, approximately 25% of individuals with the illness have been diagnosed with a comorbid cannabis use disorder (CUD) (Koskinnen et al., 2010). While cognitive impairment is common in this disorder, wherein approximately 80% of patients will present with global, rather than specific, deficits across cognitive domains (Keefe et al., 2005), the moderating role of cannabis use on intelligence, attention, learning and memory, executive functioning, and spatial abilities remains unclear (Keefe et al., 2005).

While research reliably illustrates cognitive impairment in schizophrenia, very little is known about the cognitive function of patients suffering from the combined effects of schizophrenia and cannabis use. Intuitively, one may expect cannabis to have a deteriorating effect on cognitive performance as cannabis use has been associated with higher rates of psychotic symptoms (Fergusson et al., 2003), aberrant brain functioning (D’Souza et al., 2004) and is thought to hinder prognosis (Linszen et al., 1994). Nevertheless, to date inconsistent findings of the effects of cannabis on neurocognition have been reported. While the majority of studies examining the effects of cannabis on cognition in schizophrenia report superior neuropsychological functioning (Schnell et al., 2009), others have observed poorer cognitive performance (Mata et al., 2008), or fail to find a difference in some cognitive tasks when comparing patterns of cannabis use (Jockers-Scherubl et al., 2007; Sevy et al., 2007). Furthermore, studies conducted in otherwise healthy cannabis users report either poorer neuropsychological functioning (Bolla et al., 2002) or observe comparable cognitive performance between users and non users (Pope et al., 2001). These findings suggest that cannabis may have differential effects on a vulnerable schizophrenia brain as compared to a healthy brain.

In 2008, Potvin and colleagues conducted a meta-analysis to determine to which extent better neuropsychological functioning might be found among patients with schizophrenia and substance use disorders (Potvin et al., 2008). Their findings are in support of superior cognitive capacities in substance using patients compared to schizophrenia patients without an SUD. They further concluded that these schizophrenia patients do not represent a homogeneous group and that future investigations should consider intermediate factors to define subgroups such as preferred drug of abuse.

Recently, Yucel et al. (2010) published a meta-analysis focusing on the effects of cannabis on cognition in patients with established schizophrenia. Studies were included as long as cannabis was the...
most preferred substance of the sample. As such, their analyses included studies where not all patients in the substance-using group were abusing cannabis, and as a result the cannabis-using subgroup contained patients who did not use cannabis (e.g. Potvin et al., 2005). Moreover, the effects of cannabis use were confounded by concurrent drug use, as patients with current comorbid diagnoses of drug abuse and dependence other than cannabis were not excluded (e.g. Lobberg and Hugdahl, 2009; Sevy et al., 2007).

Thus, in the present meta-analysis, our goal was to conduct a further refined analysis to emphasize the direct effects of cannabis on cognition in schizophrenia without the confounding influence of other comorbid substance use disorders. More specifically, we wanted to determine the magnitude of effect of cannabis consumption on neuropsychological performance in schizophrenia.

2. Methods

2.1. Meta-analysis

We employed standard meta-analytic techniques to our review of the literature (Cooper and Hedges, 1994; Hedges and Olkin, 1985; Rosenthal, 1991, 1995). In addition to solving problems with traditional narrative reviews (Wolf, 1986), meta-analysis provides tools for the analysis of magnitude. Magnitude can be indexed with the effect size estimate \( d \) that is meant to reflect the degree to which the dependent variable is present in the sample group or the degree to which the null hypothesis is false (Cohen, 1988). In mathematical terms, \( d \) is the difference between two group means calibrated in pooled standard deviation units. Eligible research studies comprising a common dependent variable as well as statistics that can be transformed into effect sizes are viewed as a population to be systematically sampled and surveyed. Individual study results (typically means and standard deviations from each group) and relevant moderator variables can be abstracted, quantified and coded, and assembled into a database that is statistically analyzed (Lipsey and Wilson, 1993). The main statistic presented in a meta-analysis is the mean effect size, which is meant to reflect the average individual effect across the sample of studies included in the synthesis. Given the small sample size of studies available, we were unable to correlate moderator variables to the effect size. As a result subject characteristics that may have influenced the magnitude of the effect size could not be teased out. However, to ascertain how robust our findings were, Orwin’s fail safe N formula was also utilized so to provide an index of how many studies would be theoretically needed to overturn the obtained effect size and yield an insignificant effect (i.e., \( d = 0.1 \)) (Orwin, 1983). The effect sizes were also transformed into a non-overlap percentage using (Cohen, 1988) idealized distributions, which can be further transformed into an overlap percentage (OL%) to articulate the meaningfulness of an effect size (Zakzanis, 1998, 2001). The OL% statistic represents the degree of overlap by subtracting the non-overlap from 100. In the present context, this hypothetical overlap statistic used represents cognitive test sensitivity, or the percentage of patients who perform unlike any normal control participant in terms of cognitive impairment on a given cognitive test measure.

2.2. Search strategy, selection criteria, and effect size analysis

Articles for consideration were identified through extensive literature searches using online databases, which included Psychinfo, Medline, and PubMed. The search was limited to published English-language articles with human participants. The keywords used were schizophrenia, psychosis, cannabis, tetrahydrocannabinol (or THC), marijuana, in combination with a number of neuropsychology-related terms including: neuropsych, neurocog, and cognitive impairment. A secondary search involved checking the reference sections of relevant review and meta-analytic papers for articles that may have been missed in the computerized search. Studies meeting the following criteria were included: (i.) Studies had to compare a schizophrenia (or schizophrenia spectrum disorder) cannabis-using group to an appropriate control group i.e. schizophrenia nonusers, control users or healthy controls; (ii.) Each study had to provide sufficient information in which effect sizes could be calculated, which implies that sample size, means and standard deviations, and exact p values, t values, or exact should be reported; (iii.) The use of validated measures of neuropsychological performance must have been used; (iv.) Participants must not have any other concurrent drug or alcohol use disorders. A description of included studies is presented in Table 1.

This analysis focused on studies that have either looked solely at the association between cannabis and cognition or those who have properly parsed out the effects of cannabis from other drugs of abuse and/or dependence. Given that other substances including alcohol, cocaine, and stimulants are associated with altered cognitive performance, studies in which participants met for poly-substance use disorders, even if there was preferential use towards cannabis, were excluded.

To this end specifically, effect sizes were derived whenever means and standard deviations were reported. Effect sizes were calculated from inferential statistics based on formulas provided by Wolf (1986) when primary studies did not report central tendency and dispersion data. The statistical software Meta-Analysis 5.3 was used to calculate effect sizes.

2.3. Recorded variables

Recorded variables from each study used in our meta-analysis included the full study reference and any moderator variables reported (e.g., age, duration of illness, and psychotic symptoms). Effect sizes were calculated for each neuropsychological test that measured some aspect of cognitive functioning. To this end, a total of 75 neuropsychological test variables were categorized into 7 cognitive domains. Table 2 illustrates the specific neuropsychological tests that were aggregated into each neurocognitive category. Individual effect sizes for each reported cognitive test score in the literature were calculated and placed under the appropriate domain. If multiple scores were reported for the same measure (e.g., WCST) an aggregate effect size was computed so to not bias the weight that each individual study had on the final average effect size.

3. Results

A total of 8 studies, published between 2005 and 2010, met inclusion criteria and were incorporated into the meta-analysis. These studies yielded a total sample of 942 of which 356 were cannabis-using patients (mean age 28.7 years, 81.9% male, mean education 11.4 years), and 586 were patients with no cannabis use or current substance use disorders (SUD) (mean age 32.4 years, 65.8% male, mean education 12.2 years).

The schizophrenia cannabis-using patients had mean PANSS positive and negative scores of 18.66 (5.6) and 17.97 (5.0) respectively, while the non-using comparison group achieved a mean positive score of 14.61 (6.2) and mean negative score of 18.47 (2.6). While schizophrenia cannabis-using patients had higher positive symptom scores than nonusers \([t (1, 191) = 4.73, p < .05] \), there were no differences in the negative symptoms profile between the two groups \([t (1, 191) = 0.82, p > .05] \).

The effect sizes and related statistics of differences in performance between cannabis-using patients and non-using patients on several neurocognitive domains are presented in Table 3. Most effect sizes were in the small to medium range (Cohen’s \( d = 0.06–0.48 \)), and all suggest superior cognitive functioning in cannabis-using patients as compared to non-using patient. Due to the limited presentation of data on control samples, relevant effect size between schizophrenia...
Table 1
Description of included studies.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Scz-spectrum</th>
<th>Scz *</th>
<th>Scz +</th>
<th>Past substance use disorders</th>
<th>Abstinence period</th>
<th>Clinical measures</th>
<th>Neurocognitive tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumra et al. (2005)</td>
<td>Inpatients with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>DSM-IV cannabis abuse; n = 12</td>
<td>No chart dx of cannabis abuse; n = 16 cannabis nonusers, undefined; n = 41</td>
<td>SUD history with no current use</td>
<td>n/a</td>
<td>BPRS, CGI</td>
<td>Full-scale WAIS, performance score and verbal scores from WAIS-III, WAIS-R or WISC</td>
</tr>
<tr>
<td>Coulston et al. (2007)</td>
<td>Outpatient males with schizophrenia or schizoaffective disorder</td>
<td>CUD in past week; n = 11; Non-dependent cannabis use in past wk; n = 7</td>
<td>No SUD dx within three months</td>
<td>24 h</td>
<td>SAPS, SANS, CDS, DAS</td>
<td>Shipley, RAVLT, WCST, Trailmaking Test, Color–Word Interference test, Verbal Fluency, Tower Test, Hooper Visual Organization test, Gollin Incomplete Pictures Test – adapted version; Visual Object and Space Perception Battery</td>
<td></td>
</tr>
<tr>
<td>Jockers et al. (2007)</td>
<td>Outpatients with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>History of &gt;0.5 g cannabis/day, min. of 2 years; n = 19</td>
<td>Lifetime cannabis use &lt;5x; n = 20</td>
<td>No hx of SUDs</td>
<td>28 days</td>
<td>PANSS, CGI</td>
<td>WAI-R: Comprehension, Picture, arrangement, Block design, Digit symbol, WMS-R-verbal and visual memory, Trailmaking Test, CPT, WCST</td>
</tr>
<tr>
<td>Schnell et al. (2009)</td>
<td>In- and outpatient males with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>Lifetime DSM-IV dx of CUD; n = 35</td>
<td>No lifetime SUD; n = 34</td>
<td>No hx of SUDs</td>
<td>21 days</td>
<td>PANSS, MADRS</td>
<td>MWT-B, AVLT, Letter Number span, WAIS III: Digit-symbol, Trailmaking A and B, CPT, Dual Tasking,</td>
</tr>
<tr>
<td>Scholes and Martin-Iverson, 2009</td>
<td>In- and outpatient males with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>Current cannabis use; n = 22</td>
<td>No lifetime SUD treatment; n = 49</td>
<td>No hx of SUD treatment</td>
<td>No abstinence period</td>
<td>Not assessed</td>
<td>WMS-III (LNS, SS), STROOP, WCST</td>
</tr>
<tr>
<td>DeRosse et al. (2010)</td>
<td>Schizophrenia or schizoaffective (DSM-IV)</td>
<td>Comorbid cannabis abuse or dependence; n = 175</td>
<td>No recent (within 1 month) SUD; n = 280</td>
<td>No SUD dx within one month</td>
<td>At least 24 h</td>
<td>Derived from SCID</td>
<td>WRAT-3, CVLT, COWAT, WAIS-R, Digit Span forwards and backwards, Trailmaking A and B</td>
</tr>
<tr>
<td>Ringen et al. (2010)</td>
<td>Schizophrenia, schizophreniform, or schizoaffective (DSM-IV)</td>
<td>Cannabis use in the last 6 months; n = 117</td>
<td>No substance use in the last 6 months; n = 23</td>
<td>No substance use in the last 6 months.</td>
<td>n/a</td>
<td>PANSS</td>
<td>NART, WAIS-III: Digit Symbol Coding, Digit Span, WMS-MA, Verbal fluency test, D-KEFS: Color–Word Interference test, CVLT-II, Trailmaking A and B</td>
</tr>
<tr>
<td>Yucel et al. (2010)</td>
<td>FEP patients</td>
<td>&gt;2 g cannabis/week; n = 59</td>
<td>No history of regular cannabis use; n = 26</td>
<td>SUD history</td>
<td>No abstinence period</td>
<td>PANSS, GAF</td>
<td>NART, WAIS-R: Block Design, Digit Symbol Coding, WMS-R, spatial and pattern recognition, and spatial span, spatial working memory, Trailmaking A, RAVLT, ToL,</td>
</tr>
</tbody>
</table>

Note: Scz*, Cannabis user with schizophrenia; Scz+, Non-user with schizophrenia; CI*, Control cannabis user; CI+, Control non-user; BPRS, Brief Psychotic Rating Scale; CGI, Clinical Global Impression; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative symptoms; CDS, Calgary Depression Scale; DASS, Depression Anxiety Stress Scales; PANSS, Positive and Negative Syndrome Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; GAF, Global Assessment of Functioning Scale; WAIS, Wechsler Adult Intelligence Scale; WAIS-R, Wechsler Adult Intelligence Scale Revised; WISC, Wechsler Intelligence Scale for Children; WMS, Wechsler Memory Scale; WMS-R, Wechsler Memory Scale Revised; CPT, Continuous Performance Task Identical Pairs; WCST, Wisconsin Card Sorting Task; MWT-B, Mehrfachwahl-Wortschatztest From B; AVLT, Auditory Verbal Learning Task; WRAT-3, Wide Range Achievement Test-3; CVLT, California Verbal Learning Task; COWAT, Controlled Oral Word Association Task; NART, National Adult Reading Test; WM-MA, Working Memory-Mental Arithmetic; Delis-Kaplan Executive Function System; RAVLT, Rey Auditory Verbal Learning Task; ToL, Tower of London; D-KEFS, Delis-Kaplan Executive Function System.

cannabis users and healthy controls, schizophrenia non-users and healthy controls, and between patient users and cannabis-using controls could not be computed.

4. Discussion

To our knowledge, this is the first quantitative synthesis of neurocognition in patients with schizophrenia with lifetime cannabis use and no other current comorbid substance use disorder. While deficits in various domains of cognition in schizophrenia compared to healthy controls have been reported (Heinrichs and Zakzanis, 1998), our main findings demonstrate superior neurocognitive performance in cannabis-using patients compared to non-using patients.

In clinical neuropsychology effect sizes of 0.50 or greater are considered to be of clinical significance (Lezak et al., 2004). The magnitudes of these effect sizes were only in the small to medium range, which calls into question the clinical significance of the effects of cannabis on neurocognition in this sample of patients with schizophrenia. Our findings are in line with those of Yucel et al. (2010), who observed similar magnitudes of effect, ranging from 0.00 to 0.47. Given that all studies that met inclusion criteria employed a cross-sectional methodological design, poses a challenge and limits the interpretation of our findings. That is, it is difficult to determine whether...
it is cannabis itself that triggers alterations in neuropsychological functioning or if drug-using patients represent a subset of the schizophrenia population who exhibit better neurocognitive performance. Longitudinal designs studying the effects of cannabis abstinence or acute challenges are needed to parse the effects of cannabis per se on cognition in schizophrenia.

It has been proposed that the endocannabinoid system serves to regulate neuronal circuits and pathways involved in neurocognition (Gerdeman et al., 2003). Research suggests that exposure to cannabinoids can result in functional changes in CB1-rich brain regions, changes in cerebral blood flow perfusion and alterations in cognitively relevant neuromodulator systems, such as dopamine, GABA, and glutamate (Cohen et al., 2008). The neurochemical mechanisms by which cannabis may ameliorate cognitive dysfunction in schizophrenia have recently been reviewed (Coulston et al., 2011).

Alternatively, patients with comorbid cannabis use disorders may belong to a subgroup of schizophrenia whereby they encompass better premorbid adjustment, social skills and prognosis (Dixon et al., 1991). Drug-seeking individuals may possess social skills that enable them to socialize in drug scenes and allow them to facilitate the purchase and acquisition of illegal substances. These characteristics have been associated with higher cognitive capacities among persons with schizophrenia (Silverstein et al., 2002).

While not included in the analysis due to its methodological study design, it is important to comment on the work of D’Souza et al. (2005). They characterized the dose-related effects of intravenous THC in 13 patients with no history of a CUD and controls. Both patients and control participants demonstrated impairments in verbal memory and attention compared to those on placebo. Moreover, the schizophrenia group performed worse than controls in these domains, demonstrating an enhanced sensitivity to the effects of THC on cognition in schizophrenia (D’Souza et al., 2005). It is important to note that the patient sample of the study was comprised of schizophrenia subjects with at least one exposure to cannabis but no lifetime CUD, a divergence from the sample examined in this study. In keeping with the results of our analyses, one would expect such individuals to perform worse than healthy controls and patient users.

While our findings lend support for better cognitive functioning in cannabis-using patients, it must be stressed that this does not imply that cannabis improves cognition in schizophrenia. Cannabis may very well impair cognition in a dose-related fashion in both healthy controls and those with a diagnosis of schizophrenia. In lieu of this, patients who use cannabis who then achieve abstinence may then demonstrate even further improvements in their cognitive functioning. Future research may opt to include an additional comparison group of patients with former CUDs in order to help determine and clarify cannabis’ role and neurobiological mechanism of action in the brain.

The current study has several limitations. First, as this is a relatively understudied area of research, only 8 studies met inclusion criteria and were able to be incorporated into our analyses. Thus, these findings are preliminary and will need to be replicated with larger number of studies to help articulate the nature of this relationship as well as to determine the influence of any potential moderating variables. The low fail safe Ns are supportive of our general findings that cannabis use has little to no detrimental effect on most aspects of cognition in schizophrenia. And while the fail safe N is to be taken to articulate the robustness of an obtained effect as a function of sample size, other meta-analyses have demonstrated that in the instance of a large effect size based on a similar very few number of studies, results in very high fail safe Ns (e.g. McKay and Zakzanis, 2010; Zakzanis et al., 2010).

Second, while we were able to compute effect sizes as a function of cannabis use in schizophrenia (SczT vs SczC), we were unable to calculate effect size differences due to psychotic diagnosis (SczT vs CtrlT), the combined effects of cannabis use and schizophrenia (SczT vs CtrlC) nor the effects of cannabis use alone (SczT vs CtrlT). Not enough data was presented to isolate these more specific effects of cannabis use as only 3 of the 8 studies included a healthy control sample, and only 2 studies had a non-psychiatric cannabis comparison group. The inclusion of a control group with CUDs would allow for a more comprehensive understanding of the effects of cannabis on the brain, and determine whether it acts similarly in healthy users vs patient users.

Third, only a subgroup of studies reported moderator data regarding variables like age of illness onset, duration of illness and cannabis use disorder and affective and psychiatric symptoms. This information is critical in order to precisely examine the influence of potential moderators on effect size as a number of authors have emphasized the role of symptom severity, and chronicity in the cognitive functioning of patients with schizophrenia (Bornstein et al., 1990; Strik, 1996).

Fourth, a meta-analysis is only as good as the studies it includes. Limitations and lack of control over potential confounding variables exemplified in the 8 studies are likely responsible for the inconsistent findings reported in the literature. While our study excluded cannabis-using patients with other concurrent substance use disorders, future studies may benefit from examining the cognitive effects of cannabis with very limited lifetime use of any other drug. This may help

### Table 2

<table>
<thead>
<tr>
<th>Domain</th>
<th>Recorded test variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>General cognitive ability and intelligence</td>
<td>MWT-B (IQ), NART, Full-scale IQ WAIS, Verbal score (WAIS), Performance score (WAIS), WAIS Picture</td>
</tr>
<tr>
<td>Selective, sustained and divided attention</td>
<td>WAIS Digits Symbol, Trailmaking A, CPT d’ symbol, CPT d’ digit, CPT digits LogB, CPT symbols LogB, Dual Tasking (auditory hits, auditory false alarms, auditory misses, visual hits, visual false alarms, and visual misses), CopStat</td>
</tr>
<tr>
<td>Executive abilities</td>
<td>WCST (total correct, total errors, trials to complete first category, perseverative errors, perseverative responses, nonperseverative errors, conceptual level response, other errors, categories completed, failure to maintain set), Tower of London, Trailmaking B, Color–Word Interference Test, Color–Word Set Shifting</td>
</tr>
<tr>
<td>Working memory and learning</td>
<td>WAIS digit span Forwards and Backwards, Letter Number (Sequencing, Span Sum, Span Maximum, CVLT Total, RAVLT Total, AVL Total, and WM-MA)</td>
</tr>
<tr>
<td>Retrieval and recognition</td>
<td>WMS (spatial span, spatial span forwards, spatial span backwards, verbal, visual, learning, recall, logical, visual paired associates, visual reproduction, spatial recognition, and pattern recognition), Spatial working memory (strategy and errors), AVL immediate, AVL delayed recall, recognition, and immediate memory), CVLT recall, RAVLT recall</td>
</tr>
<tr>
<td>Receptive and expressive language abilities</td>
<td>WAIS comprehension, COWAT (semantic, phonemic/lexical) Verbal Fluency Test (lexical, semantic, and sum), D-KEFS (phonetic, semantic, and set-shifting)</td>
</tr>
<tr>
<td>Visuo-spatial and construction abilities</td>
<td>WAIS Block design, Perceptual Organization, Hooper Visual Organization test, Gollin Incomplete Pictures Test — adapted version, Visual Object and Space Perception Battery</td>
</tr>
</tbody>
</table>

Note: Abbreviations are explained in the table note of Table 1.

### Table 3

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Mean d</th>
<th>SD</th>
<th># of studies used in ES</th>
<th>Overlap %</th>
<th>NFs</th>
<th>ES, effect size; NFs, Orwin’s fail safe N formula</th>
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</thead>
<tbody>
<tr>
<td>1. General cognitive ability and intelligence</td>
<td>0.48</td>
<td>0.51</td>
<td>4</td>
<td>64</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2. Selective, sustained and divided attention</td>
<td>0.35</td>
<td>0.23</td>
<td>6</td>
<td>75</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>3. Executive abilities</td>
<td>0.14</td>
<td>0.49</td>
<td>7</td>
<td>88</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4. Working memory and learning</td>
<td>0.07</td>
<td>0.40</td>
<td>5</td>
<td>94</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>5. Retrieval and recognition</td>
<td>0.12</td>
<td>0.50</td>
<td>6</td>
<td>90</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>6. Receptive and expressive language abilities</td>
<td>0.06</td>
<td>0.30</td>
<td>4</td>
<td>95</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>7. Visuo-spatial and construction abilities</td>
<td>0.33</td>
<td>0.27</td>
<td>3</td>
<td>76</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>
to further clarify the role of cannabis in cognitive performance as lifetime alcohol and drug use has been associated with altered cognition (Allen et al., 1999; Liraud and Verdoux, 2002; Pencer and Addington, 2003; Serper et al., 2000). Several other caveats to note are a heterogeneous sample population, varying cannabis abstinence period before neurocognitive testing, and failure to control for smoking status.

Finally, in addition to confounds, methodological variability between the studies presents itself as another source of discrepancy. For example, the approach in which cannabis users vs non-users were characterized differed greatly between studies. While some researchers defined it according to diagnostic standards of cannabis abuse or dependence using the Structured Clinical Interview for the DSM-IV (SCID-IV), (DeRosse et al., 2010; Kruma et al., 2005; Schnell et al., 2009) others declared a minimum arbitrary amount and duration (Jockers-Scherubl et al., 2007; Yucel et al., 2010), whereas other investigators failed to provide any diagnostic criteria whatsoever (Ringen et al., 2010; Scholes and Martin-Iverson, 2009). The comparative cannabis-naive group is more uniform across studies, mostly defined as the absence of a SCID CUD diagnosis. Employing this binary classification system can be misleading as it is apt to include occasional cannabis users or more frequent and heavy users whose functioning is unaffected to the extent in which an SUD diagnosis is made. Jockers-Scherubl et al. (2007) overcame this inadequacy by defining abuse as lifetime consumption of at least 5 times; others have followed and adopted this criteria as well (Schnell et al., 2009).

The importance of clearly assessing and defining comparison groups cannot be stressed enough, as the way in which one proposes overcoming this inadequacy by de

frequent and heavy users whose functioning is unaffected to the extent in which an SUD diagnosis is made. Jockers-Scherubl et al. (2007) overcame this inadequacy by defining abuse as lifetime consumption of at least 5 times; others have followed and adopted this criteria as well (Schnell et al., 2009).

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In conclusion, cannabis use likely has modest and possible clinically

quantitative review of the evidence. Neuropsychology 12, 426

The importance of clearly assessing and defining comparison groups cannot be stressed enough, as the way in which one proposes to characterize a “cannabis user” or “non-user” can significantly influence results. For example Scholes and Martin-Iverson, 2009 and Ringen et al. (2010) defined the cannabis-using group according to a binary system, classifying participants as either users or non-users. No other criteria such as impact on functioning, amount, frequency or duration was taken into account. Interestingly, it was these studies that reported null findings or observed cannabis use to have a detrimental effect on cognition. In contrast, studies which mandated a diagnosis of a CUD or stipulated a minimum amount and duration of use reported superior neuropsychological functioning among the cannabis-using group. This highlights the importance of patterns of cannabis consumption, rather than bisecting a spectrum of use.

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Contributors

Miss Rachel Rabin performed the literature search and analyses, as well as wrote the manuscript. Dr. Zakzanis helped with analyses and methods section and Dr. George assisted with the preparation of the manuscript. All authors contributed to and have approved the final manuscript for submission.

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgments

No acknowledgments to report.

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Cannabis abuse is associated with decision-making impairment among first-episode patients with schizophrenia-spectrum psychosis. Psychol. Med. 38, 1257–1266.


Effects of cannabis use status on cognitive function, in males with schizophrenia

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A B S T R A C T

Cognitive impairment and cannabis use are common among patients with schizophrenia. However, the moderating role of cannabis on cognition remains unclear. We sought to examine cognitive performance as a function of cannabis use patterns in schizophrenia. A secondary aim was to determine the effects of cumulative cannabis exposure on cognition. Cognition was assessed in male outpatients with current cannabis dependence (n = 18) and no current cannabis use disorders (n = 29). We then parsed non-current users into patients with lifetime cannabis dependence (n = 21) and no lifetime cannabis dependence (n = 8). Finally, as an exploratory analysis, we examined relationships between cumulative cannabis exposure and cognition in lifetime dependent patients. Cross-sectional comparisons suggest that lifetime cannabis users demonstrate better processing speed than patients with no lifetime dependence. Exploratory analyses indicated that patients with current dependence exhibited robust negative relationships between cumulative cannabis exposure and cognition; these associations were absent in former users. Cannabis status has minimal effects on cognition in males with schizophrenia. However, cumulative cannabis exposure significantly impairs cognition in current, but not former users, suggesting that the state dependent negative effects of cannabis may be reversed with sustained abstinence. Prospective studies are needed to confirm these findings.

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1. Introduction

Cognitive dysfunction is a core feature of schizophrenia, and these deficits are closely linked to functional outcomes in this disorder (Green, 1996). While the classical symptoms that diagnostically define the illness are episodic in nature (e.g., positive symptoms such as thought disorder, hallucinations and delusions), functional disability secondary to cognitive deficits, develops early in the illness, is stable and persists throughout the disorder (Heaton et al., 2001). Impairments are broad-based and affect various cognitive dimensions such as attention, memory, executive function and motor abilities (Heinrichs and Zakzanis, 1998). Cognitive deficits are strongly linked to functional outcomes such as employment difficulties, social and community problems and lack of success in rehabilitation programs in schizophrenia. These relationships are generally stronger than those observed between psychotic symptoms and functional outcome (Green et al., 2000) and therefore remediation of these deficits in schizophrenia is clearly needed.

A history of cannabis use is more common in schizophrenia than in the general population, rendering it the most commonly used illicit drug among these patients (Barnes et al., 2006). Moreover, approximately 16% of patients with schizophrenia are diagnosed with a current cannabis use disorder, while 27% of patients meet this criteria over their lifetime. Cannabis use disorders are especially common in younger and first-episode patients, and in males (Koskinen et al., 2009). Clinical reports suggest that patients with schizophrenia who use cannabis experience increased psychotic symptomatology (Fergusson et al., 2003), respond poorly to antipsychotic medication (Bowers et al., 1990) and have a worse clinical course than patients who do not use cannabis (Linszen et al., 1994). However, there is a growing body of literature that suggests similar symptom profiles between cannabis-using and non-using patients (Makkos et al., 2011; van Dijk et al., 2012). While other studies report less anxiety and fewer depressive and negative
symptoms in schizophrenia patients using cannabis as well as fewer negative symptoms (Bersani et al., 2002; Johns, 2001; Koskinen et al., 2009).

Similarly, the effects of cannabis on cognitive function in schizophrenia are inconclusive due to heterogeneous findings reported from research conducted to date. D'Souza et al., 2005 sought to characterize the acute dose-related effects of intravenous THC, and found that verbal memory and attention were disrupted in schizophrenia patients (D’Souza et al., 2005). These results are in line with other studies that report deficits in verbal memory and attention in cannabis-using patients as compared to non-using patients (Lev-Ran et al., 2012; Rening et al., 2010). Another study using a first episode sample concluded that cannabis abuse is associated with decision-making impairment, but not working memory and executive function impairment (Mata et al., 2008). Other studies report similar as well as better performance in cannabis-using patients when comparing patterns of cannabis use in select cognitive tasks (Jockers-Scherubl et al., 2007; Sevy et al., 2007).

Furthermore, two recent meta-analyses that investigated the magnitude of effect of cannabis on cognition in schizophrenia reported better cognitive function (e.g., effect sizes of $d = 0.04$–0.90) among lifetime cannabis users compared to their non-using counterparts (Rabin et al., 2011; Yucel et al., 2012). This may, in part, be a reflection of a clinically distinct and more intact (i.e., in terms of cognition) subgroup of patients, who additionally misuse cannabis.

Methodological variability between studies, including patient selection, cannabis use indices and cognitive tests administered likely contribute to the inconsistent findings reported. Lack of control over potential confounding factors within studies may be another source of discrepancy. Comorbid substance use disorders and concurrent drug use, including tobacco, were not considered or controlled for in many of the abovementioned studies. In control populations, long-term heavy cannabis use results in impairments that increase as a function of frequency, duration and dose (Bolla et al., 2002; Jacobsen et al., 2004; Solowij et al., 2002) and impairments resemble those which are classically observed in patients with schizophrenia (Solowij and Michie, 2007). Other studies report weak, if any, effect of chronic cannabis consumption on cognition (Grant et al., 2003), while other research suggests that cannabis-induced deficits may be reversible after a 28-day abstinence period (Pope et al., 2001). In contrast to studies conducted in schizophrenia patients, there is no evidence in otherwise healthy users that cannabis is associated with improved cognitive performance.

Given that patients with schizophrenia already suffer from compromised cognition and that these impairments represent reasonable treatment targets to improve functional outcome, understanding the relationship between cannabis and cognition is imperative. Therefore, the primary goal of the present study was to examine cognition and psychiatric symptomatology as a function of cannabis use patterns in schizophrenia while addressing previous inconsistencies in the literature.

This study conferred several advantages compared to previous research in this area. First, we employed strict criteria in which to characterize our cannabis using and non-using groups. Second, in this cross-sectional study, we clustered participants according to their current cannabis use status: patients with current cannabis dependence and patients not currently cannabis dependent. Subsequently, not currently dependent patients were parsed into those with former cannabis dependence and those with minimal/no lifetime use. This type of classification is commonly used in the tobacco literature (Hughes et al., 2000) and is important as it may help to elucidate whether effects of cannabis on cognition are best characterized as state or trait phenomena. Third, given that cannabis users are more likely to be cigarette smokers (Margolese et al., 2004) and that cigarette smoking is associated with better cognitive performance in schizophrenia (Sacco et al., 2005; Smith et al., 2006), this study controlled for daily tobacco use by only including current tobacco smokers. Likewise, poly-substance abuse is common among this population and these substances (e.g., alcohol, cocaine, stimulants and hallucinogens) are associated with altered cognitive performance (Coulston et al., 2007b), and as such their level of use was considered. Participants meeting criteria for an alcohol or substance use disorder were excluded from this study, as were those who tested positive for illicit substances by urinalysis.

Lastly, as an exploratory analysis, we examined the relationship between cumulative cannabis exposure and cognition in current and former dependent patients. While studies have examined the effects of frequency of cannabis use on cognition (Coulston et al., 2007a; Schnell et al., 2009) no study has considered cumulative exposure. Given that Solowij and Michie (2007) concluded that duration of cannabis use is a more salient contributor to the development of cognitive impairment than quantity or frequency of use, an index that encompasses frequency, quantity and duration of cannabis exposure may be a useful correlate variable for these studies (Solowij and Michie, 2007).

2. Methods

Written informed consent was obtained from all subjects seeking participation as approved by Research Ethics Board at the Centre for Addiction and Mental Health (CAMH). Patients were recruited from outpatient clinics at CAMH via flyers, word-of-mouth, and referrals from psychiatrists, case managers and research staff.

2.1. Participants

Recruitment yielded 130 phone calls from people interested in participating in the study. Fifty-eight of these individuals were invited in for a screening visit. The remaining 72 did not meet basic inclusion criteria that could easily be assessed over the telephone (i.e., gender, no psychiatric diagnosis, not a cigarette smoker)

Participants enrolled in the study were male outpatients who met diagnostic criteria for either schizophrenia or schizoaffective disorder based on the Structural Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders for Axis I disorders (DSM-IV) (First, 1994). Participants were psychiatrically stable, had a Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al., 1987) total score $\leq 70$, and were maintained on a stable dose of antipsychotic medication for at least 1 month with no hospitalizations in the last month. Chlorpromazine (CPZ) equivalents of antipsychotics were calculated (APA, 2000; Woods, 2003).

All participants were daily cigarette smokers. Tobacco smoking status was assessed via self-report (cigarette smoked per day; CPD) and biochemically verified with expired breath carbon monoxide (CO).

All enrolled subjects tested negative for illicit substances using urine toxicology (Medtox; Wilmington, NC; except cannabis for current dependent participants) and could not have a DSM-IV diagnosis of a substance use disorder in the 6 months prior to study enrollment (other than current dependent patients for cannabis dependence).

Premorbid IQ was assessed using the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001); a Full Scale Intelligence Quotient (FSIQ) $< 80$ was exclusionary. Participants were also excluded if they had a serious medical condition, neurological illness, developmental disorder or head injury with loss of consciousness > 5 min.

Eleven patients failed to meet study criteria and were excluded from study participation due to FSIQ $< 80$ (n=2), current substance use disorder and/or positive urine drug screen (n=6) other than cannabis for current dependent patients, inpatient status (n=1) and because of psychiatric instability (n=2). A total of N=47 male outpatients between the ages of 18 and 54 were included in the final study sample.

2.2. Substance use measures

Current cannabis dependence and former cannabis dependence (in remission for at least 6 months) were diagnosed according to DSM-IV criteria for cannabis dependence.
dependence. Current cannabis use was further confirmed with a positive urinalysis for THC. Never dependent patients were defined as having no lifetime diagnosis of a cannabis use disorder; additionally, individuals were excluded if they consumed cannabis on five or more occasions.

Cumulative cannabis exposure was measured in joint-years derived from exposure constructs from the tobacco literature e.g., pack-years (Benowitz et al., 2002). One joint-year is the equivalent of smoking on average one joint per day for 1 year (e.g., 1 joint-year = 365 joints smoked in 1 year). This measure is commonly used in the cancer and pulmonary respiratory literature as a retrospective measure (Alexis et al., 2007, Hancor et al., 2016). Information was collected through a semi-structured interview and corroborated with medical records when available that included variables such as age of onset of regular cannabis use and number of days cannabis was used in past month.

Past alcohol use disorders and substance use disorders were also diagnosed according to DSM-IV criteria. The Timeline Follow-back (TFB) is a self-report measure of substances used (cannabis, cigarettes, alcohol and caffeine) in the past 7 days. The Timeline Follow-back has good reported reliability and validity in dual diagnosis populations (Carey, 1997). Level of nicotine dependence was measured using the Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton & Kozlowski, 1987). patch use in the cancer and pulmonary respiratory literature as a retrospective measure (Alexis et al., 2007, Hancor et al., 2016). Information was collected through a semi-structured interview and corroborated with medical records when available that included variables such as age of onset of regular cannabis use and number of days cannabis was used in past month.

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### Table 1
Demographic and clinical means and standard deviations of the sample by historical cannabis status.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>CD (n=18)</th>
<th>FD (n=21)</th>
<th>ND (n=8)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>31.6 (9.6)</td>
<td>34.8 (9.2)</td>
<td>45.5 (6.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>African</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0.53</td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Education(y)</td>
<td>12.5 (2.1)</td>
<td>12.1 (2.2)</td>
<td>14.1 (3.3)</td>
<td>0.13</td>
</tr>
<tr>
<td>BDI</td>
<td>11.3 (9.4)</td>
<td>10.5 (7.9)</td>
<td>14.0 (13.6)</td>
<td>0.68</td>
</tr>
<tr>
<td>PANSS</td>
<td>25.2 (3.7)</td>
<td>25.0 (3.4)</td>
<td>25.0 (4.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>TOMM</td>
<td>46.50 (7)</td>
<td>46.50 (6)</td>
<td>46.50 (5)</td>
<td>0.94</td>
</tr>
<tr>
<td>WCST</td>
<td>16.00 (4)</td>
<td>15.53 (3)</td>
<td>15.29 (4)</td>
<td>0.91</td>
</tr>
<tr>
<td>SCWT</td>
<td>2.05 (8.9)</td>
<td>1.06 (6.5)</td>
<td>1.06 (6.5)</td>
<td>0.27</td>
</tr>
<tr>
<td>SDT</td>
<td>21.28 (7.9)</td>
<td>23.22 (7.9)</td>
<td>0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Joint years</td>
<td>11.9 (8.2)</td>
<td>7.7 (7.4)</td>
<td>-</td>
<td>0.10</td>
</tr>
<tr>
<td>Age at onset of regular cannabis use</td>
<td>16.2 (3.1)</td>
<td>16.5 (2.8)</td>
<td>-</td>
<td>0.94</td>
</tr>
<tr>
<td>BDI</td>
<td>11.3 (9.4)</td>
<td>10.5 (7.9)</td>
<td>14.0 (13.6)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Values are expressed as mean (S.D.). Significant findings are indicated in bold font.

**Abbreviations**: CD, current dependent patients; FD, former dependent patients; ND, never dependent patients; BDI, Beck Depression Inventory; TOMM, Test of Memory Malingering; WCST, Wisconsin Card Sorting Test; SCWT, Stroop Color Word Test; SDT, Spatial Delay Response; IGDT, Iowa Gambling Test; IGT, Iowa Gambling Test; KDDT, Kirby Delay Discounting Task.

### Table 2
Mean scores and standard deviations [M (S.D.)] for the cognitive variables for schizophrenia patients as a function of current and lifetime cannabis dependence.

<table>
<thead>
<tr>
<th>Cognitive measures</th>
<th>Current cannabis use status</th>
<th>Lifetime cannabis use status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD (n=18)</td>
<td>NCD (n=29)</td>
</tr>
<tr>
<td>TOMM</td>
<td>46.50 (7.9)</td>
<td>49.60 (0.6)</td>
</tr>
<tr>
<td>CPT</td>
<td>98.00 (5.7)</td>
<td>97.77 (3.9)</td>
</tr>
<tr>
<td>% Hits</td>
<td>42.90 (23.1)</td>
<td>39.89 (24.7)</td>
</tr>
<tr>
<td>% Commissions</td>
<td>419.24 (85.1)</td>
<td>41.70 (159.1)</td>
</tr>
<tr>
<td>Reaction time</td>
<td>43.27 (11.2)</td>
<td>39.86 (18.3)</td>
</tr>
<tr>
<td>TMT-A</td>
<td>105.14 (50.9)</td>
<td>92.96 (50.8)</td>
</tr>
<tr>
<td>TMT-B</td>
<td>195.50 (89.4)</td>
<td>179.84 (48.5)</td>
</tr>
<tr>
<td>Grooved pegboard</td>
<td>16.00 (4.0)</td>
<td>15.53 (3.9)</td>
</tr>
<tr>
<td>Digit span total</td>
<td>0.25 (6.9)</td>
<td>-1.06 (6.5)</td>
</tr>
</tbody>
</table>

**Abbreviation**: CD, current dependent patients; NCD, not currently dependent; FD, former dependent patients; ND, never dependent patients; TOMM, Test of Memory Malingering; CPT, Continuous Performance Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; SCWT, Stroop Color Word Test; WCST, Wisconsin Card Sorting Test; CVLT, California Verbal Learning Test; SDR, Spatial Delay Response; IGDT, Iowa Gambling Test; KDDT, Kirby Delay Discounting Task.
cognitive tests employed. See Table 2. In contrast, when parsed according to lifetime cannabis status, CPT reaction time was significantly different across groups, F (2, 44) = 4.43; p < 0.02. Bonferroni post-hoc tests revealed ND (M = 552.16, S.D. = 264.9) patients performed more poorly than current dependent (M = 419.24, S.D. = 85.1); p = 0.04, and former dependent patients (M = 399.62, S.D. = 64.4); p = 0.01. Age and CPD were then treated as covariates; the main effect of group remained significant (p = 0.03). TMT-A scores also differed across groups, F (2, 44) = 3.23; p < 0.05. Applying a Bonferroni post-hoc test, never dependent patients (M = 50.98, S.D. = 26.1) had worse performance than former dependent patients; a difference that approached significance (M = 35.62, S.D. = 12.8); p = 0.06. When age and CPD were treated as covariates, results trended towards significance (p = 0.08). No group differences were observed on other cognitive tests. Given the small sample size in the never dependent group, Kruskal–Wallis non-parametric statistical tests were also applied to these outcomes. Analyses for CPT trended towards between group significance Kruskal–Wallis = 4.53, p = 0.10 as did TMT-A Kruskal–Wallis = 5.21; p = 0.07. The varied df-values are a reflection of 1 missing data and 2) The IGT, Pegboard and TOMM were added into the cognitive battery after the initiation of the study. As a result IGT had n = 35, TOMM n = 24 and Grooved Pegboard n = 23 completers.

3.3. Correlations: cumulative cannabis use and cognitive performance

Current dependent patients demonstrated robust correlations between joint-years and cognitive function. In general, we found that joint-years was associated with poorer performance across various cognitive domains. Correlations are presented in Table 3. In current dependent patients, significant negative correlations were observed between joint-years and CPT % hits (r = -0.52, p = 0.03) and Digit Span Forwards (r = -0.51, p = 0.03). Joint-years also associated with WCST subcores (% nonperseverative errors (r = 0.64, p < 0.01) and categories completed (r = -0.54, p = 0.02) and CVLT subcores (sum of trial 5 (r = -0.50, p = 0.03) and long-delay cued recall (r = -0.47, p = 0.05)). Lastly, correlations between joint-years and SDR performance at the 5- (r = 0.54, p = 0.02) and 30-s (r = 0.61, p < 0.01) delay were evident.

When relationships were assessed in former dependent patients the only association to achieve significance was between joint-years and CPT reaction time. This relationship appeared to be driven by an outlier, and upon removal, the association was not significant (r = 0.20, p = 0.41).

4. Discussion

The present study suggests modest and selective effects of lifetime cannabis dependence on cognitive performance in patients with schizophrenia. Data are consistent with prior meta-analytic reports suggesting that lifetime cannabis use has minimal effects on cognitive function in schizophrenia (Rabin et al., 2011; Yucel et al., 2012). When patients were characterized as a function of current cannabis status, no group differences emerged on cognitive outcomes. However, when parsed according to historical cannabis dependence, lifetime cannabis users demonstrated better psychomotor speed of completion (CPT reaction time and speed on the TMT-A) than patients without lifetime dependence, in line with previous reports (Coulston et al., 2007a; DeRosse et al., 2010; Yucel et al., 2012). Group effects were exclusive to this cognitive domain.

It has been proposed that better cognition represents a risk factor for the development of problematic cannabis use in schizophrenia (DeRosse et al., 2010) and data suggest a link between cannabis use and the later development of schizophrenia.

Table 3

<table>
<thead>
<tr>
<th>Cognitive test</th>
<th>Outcome measure</th>
<th>CD patients (n = 18)</th>
<th>FD patients (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>TOMM</td>
<td>Trial 2</td>
<td>-0.60</td>
<td>0.12</td>
</tr>
<tr>
<td>CPT</td>
<td>% Hits</td>
<td>-0.52</td>
<td>0.03**</td>
</tr>
<tr>
<td>CPT</td>
<td>% Commission Errors</td>
<td>0.10</td>
<td>0.71</td>
</tr>
<tr>
<td>CPT</td>
<td>Reaction Time</td>
<td>-0.04</td>
<td>0.86</td>
</tr>
<tr>
<td>Trail making A</td>
<td></td>
<td>0.22</td>
<td>0.38</td>
</tr>
<tr>
<td>Trail making B</td>
<td></td>
<td>0.35</td>
<td>0.15</td>
</tr>
<tr>
<td>Grooved pegboard</td>
<td>Total time</td>
<td>0.57</td>
<td>0.14</td>
</tr>
<tr>
<td>Digit span Forwards</td>
<td></td>
<td>-0.51</td>
<td>0.03**</td>
</tr>
<tr>
<td>Digit span Backwards</td>
<td></td>
<td>-0.20</td>
<td>0.43</td>
</tr>
<tr>
<td>Digit span total</td>
<td></td>
<td>-0.42</td>
<td>0.08</td>
</tr>
<tr>
<td>SCWT</td>
<td>Interference score</td>
<td>0.06</td>
<td>0.80</td>
</tr>
<tr>
<td>WCST</td>
<td>% Perseverative responses</td>
<td>0.45</td>
<td>0.06</td>
</tr>
<tr>
<td>WCST</td>
<td>% Perseverative errors</td>
<td>0.44</td>
<td>0.07</td>
</tr>
<tr>
<td>WCST</td>
<td>% Nonperseverative errors</td>
<td>0.64</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>WCST</td>
<td># Categories completed</td>
<td>-0.54</td>
<td>0.02**</td>
</tr>
<tr>
<td>CVLT</td>
<td>Total trials 1–5</td>
<td>-0.40</td>
<td>0.10</td>
</tr>
<tr>
<td>CVLT</td>
<td>Trial 5</td>
<td>-0.50</td>
<td>0.03**</td>
</tr>
<tr>
<td>CVLT</td>
<td>Long-delay cued recall</td>
<td>-0.47</td>
<td>&lt;0.05**</td>
</tr>
<tr>
<td>SDR</td>
<td>5 s delay</td>
<td>0.54</td>
<td>0.02**</td>
</tr>
<tr>
<td>SDR</td>
<td>15 s delay</td>
<td>0.27</td>
<td>0.28</td>
</tr>
<tr>
<td>SDR</td>
<td>30 s delay</td>
<td>0.61</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td>IGT</td>
<td>Net total score</td>
<td>-0.22</td>
<td>0.44</td>
</tr>
<tr>
<td>KDDT</td>
<td>Geomean k</td>
<td>0.01</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Abbreviations: CD, current dependent patients; FD, former dependent patients; TOMM, Test of Memory Malingering; CPT, Continuous Performance Test; SCWT, Stroop Color Word Test; WCST, Wisconsin Card Sorting Test; CVLT, California Verbal Learning Test; SDR, Spatial Delay Response; IGT, Iowa Gambling Test; KDDT, Kirby Delay Discounting Task.

*p < 0.05; relationship was driven by an outlier, and upon its removal r = 0.195, p = 0.41.

** p < 0.05.
in those with underlying predispositions (Arseneault et al., 2004). Taken together, cannabis may promote transition to psychosis that may not have otherwise occurred. These individuals may confer lower vulnerability for schizophrenia compared to patients who develop the illness without an additional trigger (Schnell et al., 2009). The observation that our cannabis-using patients (both current and former) began using cannabis before the onset of illness supports these hypotheses.

In contrast, never dependent patients may reflect a more severe subgroup of schizophrenia and developed the illness as a result of different etiological processes (e.g., neurodevelopmental abnormalities) than lifetime cannabis-using patients, which may be reflective of their later illness onset as compared to lifetime cannabis-using patients. As such motor deficits may constitute vulnerability markers for this subgroup. However, findings in relation to the never dependent group should be interpreted with caution, as the sample size of this patient subgroup was about 80% less than that of lifetime cannabis users.

This is the first study to examine correlations between cumulative cannabis exposure and cognitive performance in current and former dependent patients using an exploratory approach. Patients with current cannabis dependence demonstrated robust relationships between years of daily cannabis use and cognitive function. Increasing years of cannabis exposure were associated with poorer performance across various cognitive domains such as attention, memory, learning and executive function. Tests that assess these cognitive processes are thought to recruit the prefrontal cortex (PFC), particularly the dorsolateral prefrontal cortex, and the hippocampus (Berman et al., 1993; Cohen et al., 1987; Goldman-Rakic, 1999; Nagahama et al., 1996; Williams and Goldman-Rakic, 1995). Interestingly, performance on tests of emotional cognition or risky decision-making, namely the KDDT and IGT, revealed no association with cumulative cannabis use. These measures are thought to be functionally dependent on the orbitofrontal and ventromedial cortices, respectively (Becerra et al., 2000; Moini et al., 2002).

Cannabinoid receptor CB1 receptors are present in high densities in the PFC and the hippocampus. Cannabis-induced CB1 receptor activation in these regions may be, in part, responsible for the dose-related cognitive impairments observed in our current dependent patients. Cannabinoids have been shown to modulate dopamine (DA) and gamma-aminobutyric acid (GABA) in the PFC and hippocampus respectively (Cohen et al., 2008; Herkenham, 1991; Yang et al., 1999). Chronic and repeated cannabis exposure is thought to produce adaptive changes that decrease DA release in the PFC (Verrico et al., 2003). In the hippocampus, CB1 is expressed mainly by GABA-mediated inhibitory interneurons. Cannabinoids act at these receptors to attenuate GABA release (Hajos et al., 2000), disrupt synchronization of pyramidal cells (Wilson and Nicoll, 2002) and inhibit the formation of new synapses between neurons (Kim and Thayer, 2001).

Given that a PFC hypodopaminergic state and abnormalities in the GABA neurotransmitter system are involved in both the pathophysiology of schizophrenia (Lewis and Moghaddam, 2006) and cognitive dysfunction (Davis et al., 1991; Lewis et al., 2005; Lewis and Moghaddam, 2006), these patients may be exceedingly sensitive to the cognitive effects of cannabis. Moreover, cannabinoid receptor alterations present in schizophrenia may also contribute to this enhanced sensitivity (Solowij and Michie, 2007).

Given that both impulsivity and poor decision-making have been implicated as behavioral markers for the propensity to take addictive drugs (Grant et al., 2000; Kirby et al., 1999), it was surprising that no relationship emerged between these constructs and cumulative cannabis exposure in current dependent patients. While these traits are implicated with an increased risk for addictive behaviors (e.g., initiating drug use), cumulative cannabis use appears to have no direct effects on these cognitive outcomes. Notably, all participants were cigarette smokers, and cigarette smoking has been linked to higher delay discounting rates in schizophrenia (Wing et al., 2012), perhaps overwhelming any effects of cannabis dependence on this measure.

Correlations between cumulative cannabis exposure and cognitive performance were absent in former dependent patients who self-reported no cannabis use for at least six months prior to study enrollment. The specificity of this association to current dependent patients is intriguing. This finding may lend support for state- versus trait-dependent effects of cannabis on cognition in schizophrenia. While studies in healthy controls have observed that cognitive impairments in psychomotor speed, attention, memory and executive functions do not fully recover following one month of cannabis cessation (Bolla et al., 2002; Medina et al., 2007), our study suggests that cognitive remediation is possible in schizophrenia patients with at least 6 months of abstinence. This is quite promising from a treatment perspective as cognitive deficits are notoriously difficult to remediate (Spaulding et al., 1996).

There are several limitations to this study. First, this study employed a cross-sectional design, limiting interpretation of findings. Second, the overall sample size was small, considering the outcomes analyzed. Despite the adequate corrections for multiple comparisons, future studies encompassing larger samples are warranted. Further, parsing non-cannabis dependent patients into those with former dependence versus patients never meeting dependence yielded small subsamples, and low power may be responsible for lack of observed group differences. However, it should be emphasized that our inclusion criteria characterizing our never dependent group was highly restrictive and while small, is representative of a “clean” subsample.

Alternatively, given that schizophrenia is a highly heterogeneous disorder (Davidson and McGlashan, 1997), which also extends to cognitive function (Joyce and Roiser, 2007), the large variation in each group may mask group differences regardless of sample size. Therefore, future studies should adopt longitudinal designs, using within- and between-subjects paradigms to examine effects of cannabis on cognition in schizophrenia versus controls.

Third, absence of non-psychiatric control groups prevents establishing whether cognition of our patients was indeed impaired compared to that of normal controls, however, performance was observed to be in the deficient range based on the schizophrenia cognitive literature. Fourth, while exclusion of women from this study limits findings to males with schizophrenia, it is also an acknowledgment of the clear gender difference present in this comorbid population, with the majority of cannabis dependent subjects with schizophrenia being males (Koskinen et al., 2009).

While we attempted to control for tobacco consumption, never dependent patients smoked more cigarettes per day than both current dependent and former dependent patients. This was unexpected given that previous research reports that patients with comorbid substance use disorders are more likely to smoke cigarettes compared to patients with a single diagnosis (Margolese et al., 2004). While higher tobacco smoking rates in dually diagnosed patients may be true of most abused drugs, cannabis may be the exception. Further research exploring this relationship is warranted.

Since sample size is limited and the study has an exploratory nature, findings presented here are preliminary. Despite this, results suggest that while lifetime cannabis users may represent a better functioning subgroup of patients with schizophrenia, cannabis does disrupts cognitive function in that increasing years of cannabis use are associated with worse cognitive performance.
Given the high prevalence of cannabis misuse combined with the persistence and significance of cognitive deficits in schizophrenia, large-scale longitudinal investigations determining the true effects of cannabis on cognition are necessary. Such research may assist in the development of better treatment approaches for both cannabis dependence and remediation of cognitive deficits in schizophrenia.

Acknowledgments

This work was supported in part by operating grants from the Canadian Institutes for Health Research (CIHR MOP#115145) to T.P.G., the Ontario Mental Health Foundation (to T.P.G.) and the Chair in Addiction Psychiatry (to T.P.G.) from the University of Toronto. Ms. Rabin was supported by a CIHR Frederick Banting and Charles Best Master's Studentship. Dr. Daskalakis reports that he has received grant support from Brainsway, Inc., travel support through Pfizer, Inc. and Merck, Inc., and has received speaking honoraria through Pfizer, Inc. and Lundbeck, Inc. Dr. George reports that he has received grant support from Pfizer, Inc., and has received consulting fees from Pfizer, Evotec, Eli Lilly, Janssen-Ortho, Astra-Zeneca and Novartis in the past two years. Ms. Rabin and Dr. Zakzanis have no conflicts to report.

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All in-text references underlined in blue are linked to publications on ResearchGate, letting you access and read them immediately.

STUDY INFORMATION AND CONSENT FORM:

Effects of Cannabis Abstinence on Neurocognition in Schizophrenia

Investigators
Tony P. George, MD, FRCPC  416-535-8501 x 34544
Rachel A. Rabin MSc  416-535-8501 x 36115

Rachel Rabin is a PhD student in Medical Science at the University of Toronto and the Centre for Addiction and Mental Health, Schizophrenia Program, and this study is part of her graduate research program. Rachel Rabin will lead the project and be responsible for recruitment, enrolment and screening of participants, as well as assessments and cognitive testing.

Study Purpose:
The use of cannabis has been observed to affect people’s ability to think, concentrate, pay attention, reason and remember. Collectively these are known as cognitive functions. Patients with schizophrenia suffer from cognitive impairments as part of their illness. Therefore the purpose of this study is to observe what happens when both patients and control participants who are cannabis dependent stop using it for a period of one-month. We will examine cognitive function, withdrawal symptoms and any changes in psychiatric symptoms. This study is not part of any treatment plan.

Procedures:
You are being asked to provide informed consent. After reading through this form, you will be given a chance to ask questions. All study procedures will be completed at Dr. George’s BACDRL lab at the Centre for Addiction & Mental Health (1st floor, 33 Russell Street, Toronto, ON, Room 1910A).

The study will take place over a 1-month period, where you will be asked to come into the lab twice weekly, once for a study visit and once to provide a urine sample, followed by a one-month follow-up session.

The first assessment will be a screening session where we will ensure that you meet all eligibility criteria. You will be asked to provide details of your medical history and drug behaviour via questionnaires and undergo a psychiatric assessment with one of our research staff. A urine drug screen and carbon monoxide (CO) indicator will be used to check for the presence of substances (including tobacco and cannabis smoking) in your
system. Please note that urine will be stored for future quantification of THC metabolites. This screening visit will take approximately 5 hours.

A second screening day will then be booked. This session will include measures that assess cognitive function. Cognitive function will be assessed with paper and pencil tests and computer tasks. Then on a weekly basis you will be come in to complete questionnaires regarding psychiatric symptoms and report any cannabis withdrawal symptoms that you may be experiencing. At these weekly visits you will be asked to provide urine and CO samples. Individual therapy sessions will be given weekly to aid in cannabis abstinence. These sessions will include education regarding cannabis use and misuse, coping skills for cravings and withdrawal symptoms, increase motivation to abstain and preventing relapse. The total visit will last approximately 2 hours.

Cognitive function will be assessed on the 2nd screening day and then again on days 1, 15, 29 and therefore these visits will be 2 hours longer.

The one-month follow-up visit will include questionnaires, CO and urine testing and cognitive testing.

**Genetics and Blood Sampling:**

During the study approximately 20 ml of blood will be collected at the baseline visit which is the equivalent of about 1 teaspoon, and approximately 10ml at the week 4 visit. Risks associated with having blood drawn include bruising, swelling, or infection at the site where the needle is inserted, and light-headedness or feeling faint. If you feel faint, notify study staff. If you must stand up, please do so slowly. Precautions will be taken to avoid these difficulties.

Blood samples will be used to assess cannabis levels as well as for genetic purposes and to measure biochemical changes. Research shows that individuals with a certain genetic make-up who use cannabis may be at higher risk for developing schizophrenia and more susceptible to cognitive impairment. Control subjects will act as a comparison group to those with schizophrenia. Therefore we will be collecting blood to determine specific genotypes and see if they have an effect on outcomes such as abstinence and cognitive performance. Your genetic information will only be used for these purposes and no other.

**Benefits:**

This study might not be of any direct benefit to you. However, the information you provide will improve our knowledge about the effects of cannabis abstinence in individuals with schizophrenia, and might encourage you to want to quit using cannabis.

**Risks:**
There are no risks associated with the completion of the questionnaires and tasks; however, you might feel slight fatigue during the testing sessions. While a cannabis withdrawal syndrome has been reported it does not include significant physical, medical, or psychiatric problems. You may experience irritability, anger, depression, difficulty sleeping, craving, and decreased appetite. Headaches, physical tension, sweating, stomach pain, and general physical discomfort have also been observed during cannabis withdrawal, but are less common.

**Voluntary Participation & Subject Obligations:**
You are free to choose not to participate, and may withdraw from this study at any time. If you withdraw, it will not affect your ability to receive treatment at CAMH. Study staff/investigators may, at their discretion, end your participation in this study at any time. If you are an existing CAMH client, you will also be asked to give the research team permission to access your medical records for the purpose of confirming your medication and treatment status.

**Study Provisions:**
You will be paid for attending and completion of each study visit at a rate of $10/ hour. If all visits are attended, you will be compensated a total of $260.

Each week cannabis abstinence will be assessed using urine toxicology screening. If you provide a negative specimen you will be eligible to draw a slip of paper from the “fishbowl.” The fishbowl contains slips of paper in which 50% of draws are winners. Prizes vary in value from $1 (small prizes) to $20 large prizes to one jumbo prize valued at $100. The remaining 50% of draws consist of slips of paper with “sorry, try again.” Draws will not begin until week 2 of the study. In addition to the draws, on day 28 if urine results are indicative of cannabis abstinence, you will be entitled to a $300 bonus.

**Payment Schedule**

<table>
<thead>
<tr>
<th></th>
<th>Assessment Length (UP TO; h)</th>
<th>Assessment Completion (UP TO)</th>
<th>Abstinence Bonus (confirmed with urine tox screen)</th>
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<tbody>
<tr>
<td>Screen I</td>
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</tr>
<tr>
<td>Screen II</td>
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<td>$0</td>
</tr>
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<td>$0</td>
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<tr>
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<td>Fishbowl draw</td>
</tr>
<tr>
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<td>TOTAL</td>
<td>26 h</td>
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</table>

**Confidentiality:**
If you decide to take part in this research study, you will be required to answer some questions about your drug use and problems you may be having relating to drug use. Your answers to these questions, as well as other data collected will only be used by the study investigators and their designates and will remain confidential to the extent permitted by law.

- As part of continuing review of the research, your study records may be assessed on behalf of the Research Ethics Board. A person from the research ethics team may contact you to ask you questions about the research study and your consent to participate. The person assessing your file or contacting you must maintain your confidentiality to the extent permitted by law.
- In accordance with federal requirements, CAMH will maintain archived study records for 10 years. However, those documents that contain personal identifiers (i.e. consent forms) will be stored separately from data files.
- General results of this study might be published, but will not identify you by name.

As part of the Research Services Quality Assurance role, studies may be audited by the Manager of Quality Assurance. Your research records and CAMH records may be reviewed during which confidentiality will be maintained as per CAMH policies and to the extent permitted by law.

Contacts:
If you have any further questions or desire further information about this study, you may contact Rachel Rabin at 416-535-8501 x36115. If you have any questions about your rights as a study participant, you may contact Dr. Padraig Darby, Chair of the Research Ethics Board, Centre for Addiction & Mental Health, at 416-535-8501 (x36876).
AGREEMENT TO PARTICIPATE

I, ______________________________ have read (or had read to me) the information form for the study named *Effects of Cannabis Abstinence on Neurocognition in Schizophrenia*. I understand that my role is that of a participant in this study. I have been given an opportunity to ask questions about this study. Any questions that I have had, have been answered to my satisfaction, so that I now understand the study procedures, the potential risks of participating, and my right to the confidential treatment of the information that is collected about me. I also understand that my participation in this study is entirely voluntary, and that I may refuse to participate or withdraw from the study at any time, without any consequences for my continuing care. By signing this consent form, I do not waive any of my legal rights nor relieve the investigators/institution from legal responsibilities. If I have any questions about my rights as a study participant, I may contact Dr. Padraig Darby, Chair of the Research Ethics Board, Centre for Addiction and Mental Health, at 416- 535 8501, extension 6876.

☐ I have received a copy of this consent form for my own record.
Participant’s Initials:_______

☐ I give the research team permission to access my CAMH medical records to determine whether I am eligible to participate in this study (*Effects of Cannabis Abstinence on Neurocognition in Schizophrenia*). Study staff will confirm diagnoses, medication types and dosages with this information.
Participant’s Initials:___

☐ You may be invited to participate in more than one research study in the schizophrenia program at CAMH. Very often the researchers use the same assessments as the ones in the study you are considering. To avoid repeating the same assessments and reduce your time commitment, the researchers may share the results of common assessments completed within the past 6 months. Sharing results will be limited to research studies in the Schizophrenia Program which have research ethics review and approval. Results will only be shared if you consent to participate in another study. You may indicate your decision to agree or decline sharing the results of the assessments by checking your choice below. If you decline sharing information, you can still consent to study participation.
Participant’s Initials:___
CONSENT TO FOLLOW-UP FOR FUTURE RESEARCH

By signing below, I grant permission to be contacted by a member of the research team regarding future research opportunities related to treatment and Schizophrenia. For instance, this could involve being contacted about your experiences in the current treatment program or other prospective studies.

If you do not agree to be re-contacted, this will not impact your treatment or your participation in the current study. Your consent can be withdrawn at any time.

Participant Name:          Person who conducted informed consent discussion:

__________________________________________    ________________________________
Print name                                      Print name

__________________________________________    ________________________________
Signature of Participant                        Signature of Witness

Date:                                          Date:

__________________________________________    ________________________________
Appendix D

BRIEF ADDICTION COUNSELING
Effects of Cannabis Abstinence on Neurocognition
Brief Addiction Counseling

**Session 1:**
Informed consent  
What to expect from therapy  
Motivational interviewing  
Goal setting

**Session 2:**
Psychoeducation – cannabis withdrawal  
Relapse Prevention and management  
Coping strategies

**Session 3:**
Problem solving  
Emotional management

**Session 4:**
Termination

It is important to recognize that not all people are the same and that everyone will experience the process of ceasing their cannabis use in a different way. Therefore, these sessions may not follow this exact order. The therapist must meet the client where they are at and use whatever technique is most fitting to the particular circumstance.
Session One

1. Informed Consent and what to expect from therapy:

Therapist to complete informed consent with the participant. Provide explanation of the nature and purpose of therapy; role of the therapist; length of sessions; frequency of visits; and clearly outline limits of confidentiality and conditions under which information will be released to others; and allowing time for a questions period.

2. Motivational Interviewing

For the purpose of the current study, a major motivating factor will be monetary gains for cannabis abstinence. It may therefore be helpful for looking at the next month only while using MI strategies. Reviewing the “good” and the “less good”

a) The good things about cannabis use of the next month:

The good things about cannabis use can be explored using questions such as:

“What are some of the things you like about using cannabis?”
“What is it about using cannabis that keeps you doing it?”

Acknowledge each of the good things before moving on and ask the client if there are any other good things that they have not yet mentioned. Keep in mind that you want more detail about the less good things rather than the good things, as the goal is cessation.

b) The less good things about cannabis use for the next month:

This is the area in which you want to get as much detail as possible. Possible question to start this part of the discussion off are:

“We have talked about some of the good things about using cannabis, now could you tell me some of the less good things?”
“How would using cannabis during the course of this study negatively affect you?”

c) This should lead into a discussion regarding the monetary gains of not using cannabis throughout the next month. Some questions you may wish to ask are:

“What could that extra money allow you to do/take part in?”
d) Summarizing:

It is important to summarize what the participant has said throughout this discussion, placing particular emphasis on the costs of using and the gains of not using. It is also important that you ask the participant for their opinion of your summary.

d) The decision

After exploring the above, a participant may still require assistance in making the final decision about their cannabis use. The aim of the summarizing is to tie together as many reasons for change as possible. For the current study, the decision should be abstinence.

Goal Setting

Since for the current study, the goal should be abstinence, below is a goal setting exercise you may complete with the participant.

I am going to……

Advantages of achieving this goal are…. 

*It is here that you would discuss the compensation structure from the CM procedure, especially the abstinence bonus if the subject achieves 30 day study endpoint abstinence.*

Things they may stop me from achieving this goal are…..

Things that I can do to overcome these obstacles are…..

I will start achieving this goal by…..
Session 2

Psychoeducation – Withdrawal Symptoms

Although cannabis withdrawal is not dangerous, it can be uncomfortable. Over the past week, the participant may have experienced symptoms that include:

- irritability, anger, or aggression
- nervousness or anxiety
- sleep difficulties (e.g., insomnia, disturbing dreams)
- decreased appetite or weight loss
- restlessness
- depressed mood
- physical symptoms (e.g., stomach pain, shakiness/tremors, sweating, fever, chills, headache)

If the participant has experienced withdrawal symptoms, it is helpful to normalize the experience. Let the participant know that these feeling are normal and that they will pass. Here is where some coping strategies (listed below) may also be helpful to introduce as a way to deal with uncomfortable feelings. If the withdrawal symptoms have caused the participant to use cannabis, relapse prevention exercise should be conducted.

Relapse Prevention

When someone first take action to change their cannabis use, it is usually best to avoid high-risk situations as much as possible. A high-risk situation involves people, places, thoughts, and feelings that may trigger an individual to use. Often times, common themes run through an individual’s high-risk situations. For example, someone may be at high-risk of using when they feel unhappy or anxious, or when they are in the presence of people with whom they normally use. It is helpful to explore these themes with the individual to help them become aware of their high-risk situations so that they may avoid relapse. The following is an example of an exercise to complete with a participant:
FEELINGS:
Feelings can include both positive and negative emotions as well as boredom and loneliness. For example:
“I had such a stressful day, I just needed to chill out.”
“I was at home alone and felt bored”
Have the participant write down his/her high risk feelings.

THOUGHTS
These include things you would say to yourself that make you want to use cannabis. For example:
“I am nothing but a pothead loser.”
“It’s just one puff. It won’t hurt.”
Have the participant write down his/her high risk thoughts.

PEOPLE
People include anyone who someone hangs out with that makes them want to use cannabis. They can include people with positive or negative affiliations. For example:
“When I hang out with my friend Mike, I want to use.”
“When I’m near my parole officer, I get so stressed out that I want to smoke.”
Have the participant write down his/her high risk people below.

Review these so that client gains insight to his/her high-risk situations. Devise a plan using coping strategies (see below).

Coping Strategies

Once the participant has identified high risk situations, provide them with coping strategies that they can use when they experience cravings or triggers. This will be different for ever and needs to explored with each participant individually but some examples may include:
• Go for a run
• Listen to your favorite album
• Take a warm bath
• Go for a walk in the park
• Write in a journal
• Cook a new dish
• Call a supportive friend
• Paint/Draw
• Read
• Create other personalized coping strategies
It is helpful if the coping strategy is pleasant so that it is a viable and realistic alternative. This conversation can begin with asking the participant what they like to do or what makes them happy, besides using cannabis. If this is difficult for them to answer, you may ask them what they used to enjoy doing before they began using cannabis.
Session 3

Problem Solving

Problem solving may be about using cannabis or not. It may the case that when clients cease use, they encounter problems in their everyday life that they used to cope with by smoking cannabis. If client have ceased use, they may become more aware of everyday problems. Below is a step-by-step strategy to help participants solve problems that may arise during the course of the study.

1. The first part of problem solving is to have the participant step back from the problem so that they can view it more objectively. Have the participant define the problem as specifically as possible.

2. Brainstorm solutions. It is important to remember that when brainstorming, anything goes.

3. Evaluate the brainstormed solutions. It may be helpful to cross out any that immediate appear impractical or unhealthy. From the remaining list, weigh out the pros and cons of the each solution.

4. Make a decision. Determine what needs to be done in order to implement the solution.

5. Try out the solution.

Emotional Management

Some people may use cannabis to help them manage their emotions. When they cease using cannabis, emotions may arise that cause them to feel uncomfortable or unpleasant. It is important to ensure the participant that this is a very normal and common occurrence. Teaching a client alternative ways to cope with unpleasant emotions is crucial for the continuation of their cessation. Examples of grounding, which involves detaching from unpleasant emotions by focusing on the outside, are listed below. Explore each one with the participant to determine which techniques mat be useful to him/her.

- Describe your surroundings in detail, using all your senses - sight, sound, smell, taste, touch.
- Describe what you are doing such As eating or walking.
- Think of something funny.
- Press your heels into the floor and notice how it feels.
- Put your hands under running water
- Make encouraging statements to yourself
- Think of a place where you feel calm and peaceful
- Go to a safe place you have created in your imagination
- Create your own grounding techniques.
Session 4

Termination

At this point of the study, therapy will come to an end. It is important to review the participant progress throughout the study. Allow the participant to ask any questions or raise any concerns that they have regarding the end of the study/therapy.

You may wish to ask the participant about their plans regarding their cannabis use after the study. If a participant notes that they plan to use, you should provide some psychoeducation around this. Notably, that their tolerance may have decreased over the past month and that they should be aware that this could impact their use by causing them to become more intoxicated than they are used to. This is something to be mindful of as paranoia and other negative effects could result.

If a participant states that they wish to continue with abstinence or minimal use, it may be helpful to review high-risk situations and coping strategies that were discussed throughout therapy. You may also wish to encourage them to seek support through one of the concurrent groups run in the Schizophrenia program or to contact an outside addiction service.
References


