Effects of Cannabis Dependence on Cognitive Function in Males with Schizophrenia

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2011

Abstract

**Background:** Cognitive impairment and cannabis use are common among patients with schizophrenia. However, the moderating role of cannabis on cognition remains unclear.

**Aim:** We sought to examine cognition and symptomatology as a function of cannabis use patterns in schizophrenia.

**Methodology:** Cognition was assessed in male outpatients with current cannabis dependence (n=18), historical cannabis dependence (n=21) and patients with no lifetime use (n=8). In addition, we explored the relationship between cumulative cannabis exposure and cognition among lifetime users.

**Results:** Lifetime cannabis users demonstrated better processing speed than patients with no lifetime use. Notably, patients with current dependence exhibited robust relationships between cumulative cannabis exposure and cognition; associations were absent in former users.

**Conclusions:** Cannabis status has minimal effects on cognition in 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.
Acknowledgments

I would like to express my sincere and utmost gratitude to my supervisor, Dr. Tony P. George, for his constant guidance, support and confidence in my academic performance. I thank him for providing me with the foundation and myriad of opportunities to grow as both a scientific researcher and critical thinker. Without his expertise, dedication and mentorship this work would not be possible.

I am grateful to my dedicated committee members, Dr. Konstantine Zakzanis and Dr. Jeff Daskalakis for their time, knowledge and invaluable feedback throughout the course of this project. I would also like to express my appreciation for the support of past and current BACDRL members.

To my family and friends: Thank you for your unconditional love & enthusiasm!!
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List of Abbreviations

Abnormal Involuntary Movement Scale (AIMS)
Addiction Severity Index (ASI)
Alcohol Use Identification Test (AUDIT)
Analysis of Covariance (ANCOVA)
Analysis of Variance (ANOVA)
Auditory-Verbal Learning Test (AVLT)
Barnes Akathisia Rating Scale (BARS)
Beck Depression Inventory- Second Edition (BDI-II)
Biobehavioural Addictions and Concurrent Disorders Research Laboratory (BACDRL)
California Verbal Learning Test (CVLT)
Cannabidiol (CBD)
Cannabinoid (CB)
Cannabis use disorder (CUD)
Carbon Monoxide (CO)
Catechol-O-Methyltransferase (COMT)
Centre for Addiction and Mental Health (CAMH)
Chlorpromazine (CPZ)
Cigarettes per day (CPD)
Continuous Performance Test (CPT)
Currently dependent (CD)
Delta-9-tetrahydrocannabinol (THC)
Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition (DSM-IV)
Digit Symbol Substitution Test (DSST)
Dopamine (DA)
Dorsolateral prefrontal cortex (DLPFC)
Fagerstrom Test of Nicotine Dependence (FTND)
First Episode Psychosis (FEP)
Formerly dependent (FD)
Full Scale Intelligence Quotient (FSIQ)
Gamma-aminobutyric acid (GABA)
Interviewer Severity Rating Scale (ISR)
Intelligence Quotient (IQ)
Iowa Gambling Task (IGT)
Kirby Delay Discounting Task (KDDT)
Multivariate Analysis of Covariance (MANCOVA)
Never dependent (ND)
Not currently dependent (NCD)
Orbitofrontal cortex (OFC)
Positive and Negative Syndrome Scale (PANSS)
Prefrontal cortex (PFC)
Research Ethics Board (REB)
Rey Auditory Verbal Learning Test (RVLT)
Simpson Angus Scale (SARS)
Spatial Delay Response (SDR)
Standard Deviation (SD)
Statistical Package for the Social Sciences (SPSS)

Stroop Colour Word Test (SCWT)

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

Test of Memory Malingering (TOMM)

Timeline Follow Back (TLFB)

Trail Making Test A (TMT-A)

Trail Making Test B (TMT-B)

Wechsler Adult Intelligence Scale (WAIS)

Wisconsin Card Sorting Test (WCST)

Wechsler Test of Adult Reading (WTAR)
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Chapter 1: LITERATURE REVIEW

1.1 Schizophrenia

Schizophrenia is a severe, pervasive and debilitating brain disorder. With a lifetime morbidity risk close to 1% (Lewis and Lieberman 2000), it is one of the world’s leading causes of disability (Murray and Lopez 1996). This neuropsychiatric illness is characterized by positive symptoms (delusions, hallucinations, thought disorganization), negative symptoms (blunted affect, social dysfunction, amotivation) and cognitive impairment. The criteria of the Diagnostic and Statistical Manual of Mental Disorders IV-TR (DSM IV-TR) (APA 2000) requires symptoms to have been present for at least 6 months (including prodromal and residual phases), and not precipitants of another disorder. In addition, functional deterioration must be present in major arenas of life such as social and occupational functioning.

There is a high degree of heterogeneity in the clinical presentation of schizophrenia (Andreasen, Arndt et al. 1995; Davidson and McGlashan 1997). Substantial between-patient variation exists in terms of age of onset, cluster of symptoms, degree of response to treatment interventions, and overall prognosis. This phenotypic heterogeneity has led to the proposition of diagnostic subtypes: a promising attempt to address the aetiologic variation of the disorder. However, efforts to validate stable and meaningful subtypes have been met with limited success.

The aetiology of schizophrenia is poorly understood. Prevailing theories suggest a biological vulnerability with both environmental and psychological stressors as
contributing factors. Heritability in this disorder is high, in that genetics contribute to about 80% of the disorder’s liability (Gottesman 1991). No one gene appears to be either sufficient or necessary for the development of schizophrenia, in effect a large number of candidate susceptibility genes are likely involved (Tandon, Keshavan et al. 2008). Neurobiological evidence plausibly link these genes to relevant pathophysiological processes in schizophrenia such as abnormalities in neurotransmitter systems, for example Catechol-O-methyltransferase (COMT) and dopamine (DA) (Harrison and Weinberger 2005). Gene-environment interactions in schizophrenia are common (van Os, Rutten et al. 2008). Systematic reviews have identified and emphasised a broad range of environmental exposures that may cause further insult to an already vulnerable brain, such as viral infections (Mednick, Machon et al. 1988), substance abuse (Moore, Zammit et al. 2007) and urbanization (Krabbendam and van Os 2005). Researchers agree that it appears increasingly probable that a large proportion of incidences of schizophrenia can be accounted for by the interaction between genetics and the environment as well as by other mechanisms involving the subtle interplay between them.

1.2 Cognitive Deficits in Schizophrenia

Cognitive deficits have been a neglected aspect of schizophrenia, and only in recent years has their clinical importance been appreciated. These deficits are key factors contributing to the patient’s failure to rehabilitate despite attenuation of psychotic symptoms (Green 1996). Subsequently, cognitive impairment is emerging as a reputed and important therapeutic target for treatment (Davidson and Keefe 1995).
Cognitive deficits are a core feature of schizophrenia, and are present in approximately 80% of patients (Keefe, Eesley et al. 2005). Patients with schizophrenia perform 1 to 2 standard deviations below the norm of healthy populations on various neurocognitive tests (Heinrichs and Zakzanis 1998; Wilk, Gold et al. 2004). These impairments are broad-based and global rather than specific, thereby affecting various domains of cognition such as attention, verbal, working and spatial memory, executive function, motor abilities and social cognition (Heinrichs and Zakzanis 1998). Cognitive deficits are common across the lifespan of schizophrenia patients. They can often be identified in childhood, well before psychotic symptoms appear (Reichenberg, Caspi et al.; Cornblatt, Lenzenweger et al. 1992). They are present at illness onset (Saykin, Shtasel et al. 1994), and can even progress beyond what is expected with normal aging (Sponheim, Jung et al. 2009). Neurocognitive impairment is not simply the result of the clinical symptoms of schizophrenia, institutionalization nor is it due to antipsychotic medication (Green, Nuechterlein et al. 2004). Moreover, cognitive dysfunction may indeed represent a potential endophenotype of the disorder (Gonzalez-Blanch, Crespo-Facorro 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. Cognitive deficits have been linked to 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, Kern et al. 2000). Therefore improving, or in the least preventing further deterioration of cognitive impairment, represents promising targets for intervention.
1.3 Cannabis

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 more than 400 compounds, including over 60 cannabinoids. The primary and most potent psychoactive constituent of cannabis is delta-9-tetrahydrocannabinol (THC). THC is found in all parts of the plant, with the highest concentration in the flowers followed by the leaves. Other plant cannabinoids include delta-8-tetrahydrocannabinol, cannabinol and cannabidiol (CBD) (Iversen 2008). The concentrations of these and other cannabinoids vary enormously in preparations of cannabis. The potency of cannabis is usually expressed in terms of THC content; however no reliable information exists about the concentration of THC and other cannabinoids (eg, cannabidiol) in commonly used cannabis products. More importantly, concerns over the putative increase in cannabis’ potency have been expressed. In the 1960s the THC content was thought to be in the range of 1-3 % while today concentrations can reach up to 20% (Adams and Martin 1996). It is unclear whether increases in other cannabinoids have accompanied changes in THC.

1.3.1 Pharmacokinetics of Cannabis

Cannabis is usually smoked as a joint, which is the size of a cigarette or a water pipe. A typical joint contains between 0.5 g and 1.0 g of cannabis. Tobacco may be added to assist burning. Smoking remains to be the preferred method of administration as this is the most efficient means of drug delivery. Further, experienced users can titrate the dose by modifying the frequency and the depth of inhalation (Iversen 2008). Cannabis can also
be ingested, usually in the form of food or tea. The pharmacokinetics of THC varies with respect to the route of administration. THC is rapidly absorbed after cannabis inhalation and it is detectable in the plasma within seconds. Peak brain concentrations and thus psychotropic effects reach a maximum within 15 to 30 minutes and effects seldom last longer than 2-3 hours (Grotenhermen 2003). In contrast, if the drug is ingested absorption rates are more variable. Oral application causes prolonged effects with decreased effectiveness of about 25-30% of the inhalation dose (Perez-Reyes, White et al. 1991). Cannabinoids are highly lipophilic and thus accumulate in fatty tissue and quickly cross the blood-brain barrier.

Initial metabolism takes place in the lungs and liver to 11-OH-THC. This metabolite is short-lived, psychoactive and somewhat more potent than THC. More extensive metabolism in the liver converts 11-OH-THC to many inactive metabolites, including THCCOOH, the most abundant metabolite in plasma and urine. THCOOH is non-psychoactive and can remain detectable in the blood anywhere from days to weeks (Adams and Martin 1996; Hawksworth and McArdle 2004). The plasma elimination half-life of THC is approximately 56 hours in occasional users and as short as 8 hours in chronic users (Busto, Bendayan et al. 1989). The tissue half-life is 7 days and complete elimination of a single dose of THC can take up to 30 days (Maykut 1985). Further, recurrent cannabis use can lead to an accumulation of cannabinoids in the body including the brain (Ashton 1999), and can contribute to a type of “reverse tolerance” to the drug (Julien 2001). No simple relationship exists between the level of THC and its metabolites in the blood and behavioural effects (Agurell, Halldin et al. 1986).
1.3.2 Acute Psychological Effects of Cannabis

Cannabis produces characteristic behavioural, cognitive and motor effects. The subjective effects of cannabis in humans vary between individuals and are dose-related. Mild cannabis intoxication can lead to acute euphoria, drowsiness, perceptual alterations, time distortion, and the intensification of ordinary sensory experiences (Tart 1970). With higher doses, short-term memory impairments, depersonalization, mood alterations, decreased motor skills and coordination are observed (Jaffe 1985). The most common unpleasant side-effects of cannabis use are anxiety and panic reactions such as paranoia and acute toxic psychosis (Ashton 1999; Iversen 2008). The acute toxicity of cannabinoids is very low; there are no confirmed published cases of human deaths from cannabis poisoning (Hall, Solowij et al. 1994).

1.3.3 Adverse Health Effects of Cannabis

The smoke from cannabis contains all the same constituents as tobacco smoke, except for the nicotine, and thus one could expect similar side-effects (Gold 1989). Chronic cannabis smoking has been associated with cancer, bronchitis and emphysema (Ashton 1999). Immunosuppression and clinical observations of increased risk of acute infections of the nose, sinuses, pharynx and bronchi are also common (Tennant 1983). The full long term health risks associated with chronic cannabis use are still under investigation and the breadth of them may not be revealed for another decade.

1.4 The Endogenous Cannabinoid System

The endogenous cannabinoid system is comprised of two types of G-protein-coupled
receptors: cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors. Cannabis, cannabis-related drugs and endogenous ligands act primarily through these receptors. CB1 receptors are primarily located on central and peripheral neurons (Tsou, Brown et al. 1998) and CB2 receptors predominantly on immune cells (Galiegue, Mary et al. 1995).

One important role of the CB1 receptor is to modulate neurotransmitter release in a manner that maintains homeostasis by preventing excessive neuronal activity in the central nervous system (Pertwee 2008). CB1 receptors are located presynaptically on inhibitory and excitatory neurons (Auclair, Otani et al. 2000; Diana, Levenes et al. 2002), but predominate on axon terminals of Gamma-aminobutyric acid (GABA) inhibitory interneurons (Eggan and Lewis 2007). It is these interneurons that are thought to mediate most of the effects of cannabinoids (Freund, Katona et al. 2003). Other neurotransmitters that are involved include L-glutamate, noradrenaline, DA, serotonin and acetylcholine (Iversen 2003).

CB1 receptors are highly concentrated in brain regions implicated in cognition, namely the hippocampus, prefrontal cortex (PFC), anterior cingulate, basal ganglia, cerebellum and cortex. The presence of these receptors in the limbic system suggests that the endocannabinoid is implicated in emotional cognitive tasks. Only modest binding is observed in the spinal cord and brain stem (Herkenham 1991).

THC acts as a partial agonist at the CB1 receptors, where it has modest affinity and low intrinsic activity (Compton, Johnson et al. 1992; Pertwee 1997). In contrast, CBD shows
very little affinity for these receptors (Pertwee 2008). Moreover, the precise molecular
mechanism of action of CBD remains unclear and it may involve a variety of
mechanisms (Mechoulam, Peters et al. 2007). Further, it has been demonstrated that CBD
influences the pharmacological activity of THC and therefore THC’s effects can be
modulated by CBD (Pertwee 2008). THC and CBD have been demonstrated to have
divergent properties. In patients with schizophrenia, THC may exacerbate existing
psychotic and affective symptoms (D'Souza, Abi-Saab et al. 2005); effects not associated
with CBD (Zuardi, Shirakawa et al. 1982). CBD may actually attenuate some of the
unwanted psychological precipitants of THC and counteract its adverse effects, as it is
thought to possess anxiolytic (Crippa, Zuardi et al. 2004) and antipsychotic properties
(Zuardi, Crippa et al. 2006). CB1 receptors also respond to anandamide, an endogenous
ligand. Anandamide produces similar effects to THC but is less potent and shorter acting
(Iversen 2008). This and other endogenous ligands are present in the brain and other
tissues in minimal amounts (Iversen 2003).

Evidence suggests a reliable relationship between the endogenous cannabinoid system
and brain dopaminergic circuitry. D2 receptors are co-expressed in similar brain regions
as CB1 receptors (Hermann, Marsicano et al. 2002). Psychoactive cannabinoids increase
the activity of mesolimbic dopaminergic neurons that terminate in the striatum and PFC
via CB1 receptor activation (Gardner 2005; D'Souza, Braley et al. 2008). They lead to
enhanced DA synthesis, release and turnover (Chen, Paredes et al. 1990; Pistis, Porcu et
al. 2001; Gardner 2005; Bossong, van Berckel et al. 2009), which is thought to underlie
the reinforcing and abusive properties of cannabis (Ameri 1999).
Recurrent cannabis use produces prolonged and excessive stimulation of the CB1 receptor and this is thought to lead to disruption of the endocannabinoid system (Murray, Morrison et al. 2007). Further, CB1 receptor overstimulation may be a contributing factor in triggering THC-induced psychosis (Morrison and Murray 2009).

1.5 Cannabis Use in the General Population

With nearly 150 million people worldwide reporting annual use, cannabis has become the most widely used illicit drug (Cohen, Solowij et al. 2008). Cannabis is the third most commonly used recreational drug, after tobacco and alcohol (Iversen 2003). The United Nations Office on Drugs and Crime report that 3.3 to 4.4% of the world’s population aged 15-64 have used cannabis at least once in their lifetime (United Nations Office on Drugs and Crime 2009). Within the framework of a large North American population study, an attempt has been made to determine the rate of cannabis dependence. Among the 20,000 people surveyed, 4.4% showed signs of cannabis abuse and approximately 60% of these cases met criteria for dependence (Hall, Solowij et al. 1994). More specifically among the Canadian population, increasing rates in cannabis use have been found. Lifetime use increased from 23.2% in 1989 to 44.5% in 2004 and use in the past year from 6.5% in 1989 to 14.1% in 2004. Lastly, approximately 3% of Canadians are daily cannabis users (Adlaf 2005).

1.6 Effects of Cannabis on Cognition: Healthy Populations

Given the widespread use of cannabis, concerns regarding the adverse consequences of its use continue to grow, especially in the realm of cognitive function. The literature examining the effects of cannabis on cognition in control participants is of abundance and
remains mixed. There is good evidence that long-term heavy cannabis use results in cognitive deficits that have been shown to increase as a function of frequency, duration and dose (Bolla, Brown et al. 2002; Solowij, Stephens et al. 2002; Jacobsen, Mencl et al. 2004). There is growing recognition that cannabis users are impaired in many of the same cognitive domains as patients with schizophrenia (Solowij and Michie 2007). In contrast, another study that followed long-term, heavy cannabis found that cognitive deficits were reversible after a 28-day abstinence period (Pope, Gruber et al. 2001). Further, the results of a meta-analytic study demonstrated a weak, if any, effect of chronic cannabis consumption on cognitive (Grant, Gonzalez et al. 2003). While memory and learning were the only domains to yield significant effect sizes, they were quite small, 0.27 and 0.24 respectively.

1.7 Cannabis use in Schizophrenia

A history of cannabis use is more common in schizophrenia than in the normal population, with life-time use as high as 64.4% (Barnes, Mutsatsa et al. 2006), rendering it the most commonly used illicit drug among this population. In comparison to the estimated 2% of individuals in the general population, approximately one-third of persons with schizophrenia and other psychoses in the USA and Australia are daily users of cannabis (Jablensky 2000). Koskinen and colleagues (2010) conducted a meta-analysis and found that approximately one in every four patients diagnosed with schizophrenia had a cannabis use disorder (CUD), either cannabis abuse or cannabis dependence. CUDs were especially common in younger and first-episode patient samples as well as in samples with high proportions of males (Koskinen, Lohonen et al. 2010).
1.8 Effects of Cannabis on Cognition in Schizophrenia

Clinical reports suggest that patients with schizophrenia who use cannabis experience increased psychotic symptomatology (Fergusson, Horwood et al. 2003), respond poorly to antipsychotic medication (Bowers, Mazure et al. 1990) and have a worse clinical course than patients who do not use cannabis (Linszen, Dingemans et al. 1994). Accordingly, one may expect cannabis to have a detrimental effect on cognitive performance. However, the literature provides inconsistent evidence of the effects of cannabis on cognitive function in schizophrenia - a relationship proving to be more complex than initially considered. Given that these patients already suffer from compromised cognition, it is necessary to determine whether cannabis use causes added impairments, remedies core deficits, or whether the effects are inconsequential.

Accordingly, the following literature review will focus on studies in patients with schizophrenia that have either examined the association between cannabis and cognition or those who have properly parsed out the effects of cannabis from other drugs of abuse.

Polysubstance abuse is common amongst patients with schizophrenia (Regier, Farmer et al. 1990), and studies examining the relationship between cannabis and cognition at times fail to isolate the specific effects of cannabis use on cognitive function by including participants who abuse or are dependent on other drugs. Given that there is evidence that other substances of abuse, including alcohol, cocaine and stimulants are associated with altered cognitive performance (Potvin, Joyal et al. 2008), studies in which participants met for poly-substance use disorders were excluded from this review.
1.8.1 Effects of Cannabis on Cognition: Evidence of Enhancement in Users

A surprising number of studies report better cognitive function in cannabis-using schizophrenia patients and psychosis groups compared to non drug-using groups. This difference remains significant even after controlling for confounding factors such as age, years of education, premorbid IQ, and psychiatric symptoms (Coulston, Perdices et al. 2007).

Schnell and colleagues (2009) investigated the residual impact of cannabis use disorders and patterns of consumption on cognitive performance in a large sample of schizophrenia patients (Schnell, Koethe et al. 2009). A cognitive test battery was administered to 35 patients with schizophrenia with a comorbid lifetime diagnosis of a cannabis use disorder with no additional substance use disorder and to 34 patients who had no present or previous history of a substance use disorder. The former group performed better in tests of verbal memory [Auditory Verbal Learning Test (AVLT)], working memory (letter-number span), visuomotor speed (Digit Symbol Test) and executive function (Trail Making Test Part B). More frequent cannabis use was associated with better performance in attention and working memory tasks.

Similar results were found in a study that examined the relationship between cognitive performance and three different indices of cannabis use in schizophrenia (Coulston, Perdices et al. 2007). Within the schizophrenia group, a larger proportion of participants with lifetime cannabis abuse/dependence demonstrated better performance than those without lifetime abuse/dependence on a component of psychomotor speed. Frequency
and recency of cannabis use were also associated with better neurocognitive performance, predominantly in the domains of attention/processing speed and executive functions.

One hundred and twelve consecutively admitted patients experiencing their first episode of psychosis were followed up 10–12 years later and assessed on a neurocognitive battery (Stirling, Lewis et al. 2005). Cannabis use was documented at time of admission. Those with a history of cannabis use performed significantly better than those without cannabis use on measures of memory, verbal fluency, visual spatial construction, sequencing, and face recognition. Further, patients with some level of sustained cannabis use during the follow-up period exhibited better cognitive performance on several measures, than those with no use during this time.

In another sample comprised of first-episode psychosis (FEP), Yucel et al. (2010) examined the effects of regular cannabis use on cognition. They concluded that FEP patients who used cannabis (especially those who used prior to the age of 17) performed better than non-using patients in select cognitive domains such as tests of visual memory, working memory, and executive functioning.

Rodríguez-Sánchez et al. (2010) examined cognitive function in both a cross-sectional and longitudinal manner in a FEP sample (N=104) in cannabis users (n=47) and nonusers (n=57). The authors reported that cannabis-using patients had better attention and executive function than non-using patients at baseline and after one year of treatment. However, both groups exhibited superior cognitive performance at follow-up compared
Jockers-Scherubl et al. (2007) evaluated the effects of chronic cannabis consumption on cognitive function in patients with schizophrenia (n=39) and healthy controls (n=39) after a minimum abstinence period of 28 days (Jockers-Scherubl, Wolf et al. 2007). Cannabis abuse was defined as an average of at least 0.5 grams of cannabis per day for a minimum of 2 years (this level of cannabis use was required prior to disease onset for schizophrenia participants). With regards to cannabis use, schizophrenia patients performed significantly better than controls in the Digit Symbol Substitution Test (DSST), a measure of psychomotor speed. This is in contrast to what was observed in otherwise healthy controls, where their performance deteriorated as a result of cannabis abuse. As in the Yucel et al. (2010) study, results were even more pronounced when patients started regular cannabis consumption before the age of 17.

A more recent study retrospectively examined a large cohort of patients with schizophrenia (N=455), who were classified as either having a lifetime CUD (n=280) or no history of CUD (n=175) (DeRosse, Kaplan et al. 2010). Compared to the cannabis-naïve group, lifetime users demonstrated significantly better performance on measures of processing speed (Trail Making Tests A and B), verbal fluency and verbal learning and memory (California Verbal Learning Test).

Kumra et al. (2005) also adopted a retrospective approach to examining the effects of having a historical cannabis use on intellectual functioning in inpatients with
schizophrenia (Kumra, Thaden et al. 2005). They reported that a history of cannabis abuse/dependence was associated with better full scale intelligence quotient (FSIQ) scores and verbal intelligence quotient (IQ) scores.

Two recent meta-analyses addressed the relationship between cannabis use and cognition in schizophrenia. In 2010, Yucel et al. published a meta-analysis that focused 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 (Potvin, Briand 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 (Sevy, Burdick et al. 2007; Loberg and Hugdahl 2009). The authors concluded that patients with a lifetime history of cannabis use had superior cognitive functioning.

In a more recent meta-analysis (Rabin, Zakzanis et al. 2011) (see Appendix B), we conducted a quantitative review of the literature so to examine more specifically the direct effects of cannabis on cognition in schizophrenia without the confounding influence of other comorbid substance use disorders. Eight studies were incorporated into the analyses and 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 visuospatial and
construction abilities) of cognitive function were assessed. Findings demonstrated superior cognitive performance in cannabis-using patients compared to non-using patients, albeit the magnitude of effect sizes were in the small to medium range (0.00-0.48). Zakzanis (2001) proposed that it is effect sizes between patient and control samples of greater than 3.0 that may be a useful criterion for evaluating the sensitivity of neuropsychological tasks and for determining specific test markers of neurocognitive disorders (Zakzanis 2001). Therefore this calls into question the clinical significance of the effects of cannabis on neurocognition in this sample of patients with schizophrenia.

Possible explanations for better cognitive performance amongst cannabis users may be attributable to the neurobiological and neurochemical effects of cannabis on the brain. To this end, it has been proposed that the endocannabinoid system serves to regulate neuronal circuits and pathways involved in neurocognition (Gerdeman, Partridge 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 DA, GABA, and glutamate (Cohen, Solowij et al. 2008). The neurochemical mechanisms by which cannabis may ameliorate cognitive dysfunction in schizophrenia have recently been reviewed (Coulston, Perdices 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 overall prognosis (Dixon, Haas et al. 1991; Rodriguez-Sanchez, Ayesa-Arriola et al.
Drug-seeking individuals may possess the necessary 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, Mavrolefteros et al. 2002).

Previous longitudinal studies have established that cannabis can act as a component cause leading to psychosis in vulnerable individuals (Arseneault, Cannon et al. 2004; Henquet, Krabbendam et al. 2005). It has been hypothesized that patients with schizophrenia and comorbid CUDs possess a lower vulnerability for psychosis as compared to those with schizophrenia alone (Schnell, Koethe 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 than individuals who became psychotic without an additional trigger in the form of cannabis use (Leeson, Harrison et al. 2011).

1.8.2 Effects of Cannabis on Cognition: Evidence of Impairment in Users
D’Souza and colleagues at Yale University conducted a study characterizing the dose-related effects of intravenous THC (D'Souza, Abi-Saab et al. 2005). 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. Both patients with schizophrenia and control participants given THC demonstrated 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 enhanced sensitivity to the effects of THC on cognition.

Using a cross-sectional approach, Ringen et al (2010) examined the relationship between cannabis use in the last six months and neurocognitive function in 140 patients with schizophrenia (Ringen, Vaskinn et al. 2010). Findings from this study were consistent with the D’Souza et al. (2005) study such that poorer verbal learning and memory and attention were associated with the acute effects of THC.

Mata et al. (2008) examined the association between cannabis use prior to illness onset and impairment in cognitive tasks associated with the orbitofrontal cortex (OFC) and the dorsolateral prefrontal cortex (DLPFC) (Mata, Rodriguez-Sanchez et al. 2008). One hundred and thirty-two patients experiencing their first-episode of a schizophrenia-spectrum disorder completed a cognitive battery comprised of the Iowa Gambling Task (IGT), Trail Making Test, a fluency test and the Wechsler Adult Intelligence Scale (WAIS)’ Backwards Digits. The performance on these tasks was compared between cannabis abusing patients to those with no history of abuse. While no differences in DLPFC-related task performance were observed, cannabis-abusing patients did demonstrate poorer performance on the gambling task as well as lower improvement scores compared to non-abusers.

The Wisconsin Card Sorting Test (WCST) is another task thought to be sensitive to the dysfunction of the DLPFC. In contrast to the findings of the abovementioned study,
another study found that cannabis-using schizophrenia patients had increased non-preservative errors on the WCST as compared to non-using patients (Scholes and Martin-Iverson 2010).

Akin to the positive effects of cannabis, neurobiological and neurochemical explanations have been proposed to account for the detrimental effects of cannabis. Dopaminergic transmission is tightly linked to intact neurocognitive performance, such that the hypodopaminergic state in the PFC characteristic of schizophrenia patients (Howes and Kapur 2009) has been proposed to contribute to the cognitive deficits associated with the illness (Davis, Kahn et al. 1991). Given that cannabis use can also produce dopaminergic modulation in the brain, specifically in the prefrontal cortex (Pistis, Porcu et al. 2001), provides a plausible mechanism for further impairment in cognitive function in cannabis-using patients (D'Souza, Sewell et al. 2009).

1.8.3 Effects of Cannabis on Cognition: Evidence of No Effects in Users

It is important to note that each of the aforementioned studies also noted no differences in certain domains of cognitive functioning when comparing patterns of cannabis use. Cannabis had no effect on executive functioning as measured by the WCST (Stirling, Lewis et al. 2005), the Backwards Digits (Mata, Rodriguez-Sanchez et al. 2008) and Trail Making B (Sevy, Burdick et al. 2007; Mata, Rodriguez-Sanchez et al. 2008). Verbal fluency remained unaffected by cannabis use (Mata, Rodriguez-Sanchez et al. 2008; Schnell, Koethe et al. 2009), as was psychomotor speed, (Mata, Rodriguez-Sanchez et al. 2008), and attention as measured by the Continuous Performance Test (CPT) (Jockers-
Scherubl, Wolf et al. 2007; Sevy, Burdick et al. 2007). It is plausible that concurrent use of cannabis may have no compounding effect on cognitive function in patients with schizophrenia. On the other hand, lack of group differences may be a result of a combination of the aforementioned reasons. To this end, cannabis may very well impair cognition in patients and drug-users may be representative of a subpopulation of schizophrenia. Thus, when these higher functioning individuals engage in cannabis use their cognitive function becomes compromised to the level of a non-using patient, rendering similar test performance among cannabis users and non-users.
<table>
<thead>
<tr>
<th>Authors</th>
<th>SCZ-Spectrum</th>
<th>Cann +</th>
<th>Cann −</th>
<th>Abstinence Period</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Souza et al. (2005)</td>
<td>DSM-IV diagnosis of schizophrenia or schizoaffective</td>
<td>Used cannabis at least once; no CUD to characterized dose-dependent effects of THC on cognition; N=13</td>
<td>30 minutes</td>
<td>THC increased learning and recall deficits in a dose-dependent fashion</td>
<td></td>
</tr>
<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 diagnosis of cannabis abuse; n=16</td>
<td>N/A</td>
<td>Cann+ had better full scale IQ score, and performance and verbal score than Cann−</td>
</tr>
<tr>
<td>Stirling et al. (2005)</td>
<td>First episode psychosis patients</td>
<td>self-reported cannabis use cross-referenced with a co-habitee; n=38</td>
<td>No report of cannabis use; n=25</td>
<td>N/A</td>
<td>Cann+ performed better on tests of memory, verbal fluency, object assembly, block design, picture completion and arrangement and face recognition memory</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 Non-dependent cannabis use in past month; n= 7</td>
<td>undefined; n=41</td>
<td>≥24 hours</td>
<td>Cann+ had better psychomotor speed than Cann−. Cannabis frequency and recency were associated with better performance in domains of attention and processing speed and executive functions</td>
</tr>
<tr>
<td>Jockers-Scherubl et al. (2007)</td>
<td>Outpatient with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>History of &gt;0.5g cannabis /day, min. of 2 years; n=19</td>
<td>Lifetime cannabis use &lt;5X; n=20</td>
<td>≥ 28 days</td>
<td>Cann+ was associated with better psychomotor speed</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Description</td>
<td>Inclusion Criteria</td>
<td>Exclusion Criteria</td>
<td>Findings</td>
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<tr>
<td>Sevy et al.</td>
<td>Inpatients and outpatients with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>Current DSM-IV diagnosis for cannabis abuse or dependence; n=14</td>
<td>≥ 1 week</td>
<td>No difference in IGT performance, intelligence, memory, learning, fluency, and problem solving. Working memory was better in Cann+ compared to Cann-</td>
<td></td>
</tr>
<tr>
<td>Mata et al.</td>
<td>First episode patients with a schizophrenia-spectrum psychosis (DSM-IV)</td>
<td>At least weekly cannabis use in previous year, n=61</td>
<td>Not defined; n=71</td>
<td>Cannabis use prior to illness is associated with greater impairments in decision-making and IQ, but not working memory or executive function</td>
<td></td>
</tr>
<tr>
<td>Schnell et al.</td>
<td>In- and outpatients with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>Lifetime DSM-IV dx of CUD; n=35</td>
<td>≥ 21 days</td>
<td>Cann+ had lower vocabulary scores, better verbal and working memory, executive function and visuomotor speed. More frequent cannabis use was associated with better performance in attention and working memory tasks.</td>
<td></td>
</tr>
<tr>
<td>Scholes et al.</td>
<td>In- and outpatients with schizophrenia or schizoaffective disorder (DSM-IV)</td>
<td>Current cannabis use; n=22</td>
<td>No lifetime SUD treatment; n=49</td>
<td>Cannabis had no effect on attentional control, working memory, executive function (other than perseverative errors). No significant correlations between cannabis use and cognition.</td>
<td></td>
</tr>
<tr>
<td>DeRosse et al.</td>
<td>Schizophrenia or schizoaffective (DSM-IV)</td>
<td>Comorbid cannabis abuse or dependence; n=175</td>
<td>≥ 24 hours</td>
<td>Cann+ is associated with better processing speed and verbal skills.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Diagnosis</td>
<td>Cannabis use in last 6 months; n=</td>
<td>No substance use in last 6 month; n=</td>
<td>N/A</td>
<td>Cannabis using patient; Cannabis-using patient; Non Cannabis-using patient; N/A, not available, SCZ-spectrum, schizophrenia spectrum disorder</td>
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</tr>
<tr>
<td>Ringen et al (2010)</td>
<td>Schizophrenia, schizophreniform, or schizoaffective (DSM-IV)</td>
<td>117</td>
<td>23</td>
<td>N/A</td>
<td>Cann+ performed worse in verbal memory and attention</td>
</tr>
<tr>
<td>Rodríguez-Sánchez et al. (2010)</td>
<td>First episode patients with non-affective psychosis (DSM-IV)</td>
<td>At least weekly cannabis use in year prior to first-episode, n=47</td>
<td>Non-users: not defined, n=57</td>
<td>N/A</td>
<td>Cann+ patients had better attention and executive functions than Cann- patients at baseline and after 1 year of treatment</td>
</tr>
<tr>
<td>Yucel et al. (2010)</td>
<td>First episode patients with a schizophrenia-spectrum psychosis (DSM-IV)</td>
<td>&gt;2g cannabis/week; n=59</td>
<td>No history of regular cannabis use; n=26</td>
<td>No abstinence period</td>
<td>Cann+ performed better on domains of visual memory, working memory, planning, and reasoning No correlation between cognition and other cannabis use parameters</td>
</tr>
<tr>
<td>Leeson et al. (2011)</td>
<td>In and outpatients experiencing their first episode (DSM-IV)</td>
<td>Used cannabis at all in lifetime</td>
<td>No lifetime cannabis use</td>
<td>N/A</td>
<td>Cann+ had better verbal learning, and planning than Cann-, but there were no differences in working memory Low-frequency users had higher current IQ than non-users</td>
</tr>
</tbody>
</table>
1.9 Reasons for Conflicting Findings in the Literature

The observed conflicting results may be in part due to limitations, methodological variations between studies and failure to statistically control for potential confounding variables within studies.

1.9.1 Defining Cannabis Use

The approach in which cannabis-users and non-users are characterized in this body of literature varies greatly. Several researchers define the cannabis-using group according to the diagnostic standards of the Structured Clinical Interview for the DSM-IV (SCID-IV), wherein all participants in this sample group merit diagnosis of a cannabis use disorder (Kumra, Thaden et al. 2005; Schnell, Koethe et al. 2009; DeRosse, Kaplan et al. 2010). Other studies characterized the cannabis-using sample according to arbitrary cut-off parameters. These parameters are far from consistent across studies, and range from cannabis used on a weekly basis in the last year (Mata, Rodriguez-Sanchez et al. 2008), to 2 gram minimum per week in the last two years (Yucel, Bora et al. 2010) to 0.5g minimum amount per day over the last two years (Jockers-Scherubl, Wolf et al. 2007). Further, Scholes et al. (2010) and Ringen et al. (2010) defined their cannabis-using groups according to a binary system. They classified participants as either users or non-users; the exact criteria used to define these groups remains suspect (Ringen, Vaskinn et al. 2010; Scholes and Martin-Iverson 2010).

The comparative cannabis-naïve group is more uniform across studies, mostly defined as the absence of a SCID-IV CUD diagnosis. Yet, using this term alone may be misleading
as it is apt to include occasional cannabis users or more frequent and heavy users whose functioning is unaffected (DeRosse, Kaplan et al. 2010). Jockers-Sherbl 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, Koethe et al. 2009).

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 may be problematic as research demonstrates divergent acute, residual and long-term cognitive effects of cannabis (Pope, Gruber et al. 2001; D'Souza, Abi-Saab et al. 2005). Given that these studies are cross-sectional, it may prove useful and beneficial to consider current cannabis-users as a discrete group from those patients with a history of cannabis use. To date, no study examining the effects of cannabis use on cognitive function have parsed lifetime users into distinct comparable groups.

1.9.2 Measuring Exposure: Parameters of Cannabis Use

Two studies examined the relationship between frequency of cannabis use and cognitive performance in currently-using patient groups. Coulston et al. (2007) examined frequency of cannabis use in the past year and sought out to determine the extent to which it correlated to cognitive performance. Cannabis users were organized into three groups: patients who reported using at least weekly were deemed “high” frequency users, patients who used between two and four times per month, were classified as “medium” frequency users and those with either no (or virtually) no cannabis use were deemed “low” frequency users. The authors concluded that high frequency cannabis use was associated
with the best level of performance on tests of attention, and planning efficiency compared to the two other groups. Schnell et al. (2009) also investigated the association between patterns of cannabis use and cognitive function in patients with schizophrenia. They observed findings in line with Coulston et al. (2007). Average frequency of cannabis use and maximum frequency of cannabis use, both measured in joints per month, were correlated to cognitive performance. High scores on both these indices were as associated with better performance on tests of attention and memory. In contrast, Yucel et al (2010) examined cognitive functioning in first-episode patients with a lifetime history of cannabis use and explored relationships between cognition and cannabis use parameters. No associations were found between cannabis frequency, quantity, or duration of use and cognitive performance. Despite this lack of finding in the first-episode sample, age of onset of cannabis use and duration of cannabis use has also been shown to be associated with neuropsychological test performance in the general population (Pope, Gruber et al. 2001; Solowij, Stephens et al. 2002).

Lifetime patterns of cannabis use should be determined along with CUD as DSM-IV diagnoses provide no information on duration, frequency, or quantity of the substance at hand. Further, assessing these parameters in isolation is insufficient for acquiring an individual’s exposure to cannabis. For example, frequency of cannabis use refers to a specific isolated period and fails to capture fluctuating use over time. Thus a standardized approach that converged frequency, duration and quantity of cannabis use into one term would serve as an informative index of *cumulative cannabis exposure*. The term Joint-years is a familiar measure in the realm of cancer research and the Cannabis literature
may benefit from borrowing such a term. A joint-year of cannabis is defined as smoking on average one joint per day for 1 year.

1.9.3 Nicotine

Tobacco is commonly mixed with cannabis to ensure it burns smoothly. Further, many studies report a strong relationship between cannabis use and nicotine dependence (Patton, Coffey et al. 2005; Patton, Coffey et al. 2006). A study by Margolese et al. (2004) reported that patients with current substance abuse/dependence and a psychotic disorder were more likely to smoke cigarettes (88.9%) compared to those with a single diagnosis (49.6%) (Margolese, Malchy et al. 2004). Preliminary research in an adolescent population suggests that nicotine may attenuate memory deficits induced by cannabis use (Jacobsen, Pugh et al. 2007). Further, it has been suggested that the relationship between cannabis use and nicotine addiction may be due to common genetic vulnerability (Agrawal, Lynskey et al. 2008). Therefore, given that cannabis users are more likely to be cigarette smokers and that cigarette smoking is associated with better cognitive performance in schizophrenia (Adler, Hoffer et al. 1993; Sacco, Termine et al. 2005), controlling for nicotine use is essential.

1.9.4 Abstinence Period

Another source of inter-study variation is the period of time elapsed between the last use of cannabis and administration of cognitive testing. Depending on this interval, studies may be assessing the impact of cannabis intoxication, acute withdrawal or the longer-lasting, possibly, neurotoxic effects of cannabis exposure. The studies included in this
literature review span an abstinence period ranging from none at all to those of at least 28 days. For example, in one study cognitive testing was initiated 30 min after THC administration (D'Souza, Abi-Saab et al. 2005), thereby examining the acute, intoxicating effects of cannabis. Coulston et al. (2007) and DeRosse et al. (2010) mandated that patients refrain from cannabis for at least 24 hours prior to testing so as to capture the narrow window between intoxication and withdrawal as most withdrawal symptoms have their onset during the first day of abstinence (Kouri and Pope 2000), and peak between two and six days (Budney, Moore et al. 2003). Further, given the long elimination time of cannabis from the body, two studies investigated the residual effects by instigating abstinence periods of at least 21 days (Jockers-Scherubl, Wolf et al. 2007; Schnell, Koethe et al. 2009), thus minimizing any acute pharmacological effects of cannabis. Lastly, some studies failed to report whether or not there was a hiatus from cannabis use. In effect these studies are measuring completely different phenomena associated with cannabis use and thus researchers should clearly define what effects of cannabis they attempt to investigate. Furthermore, these abstinence periods should be confirmed with the appropriate objective screening measure i.e. urine drug testing.

1.9.5 Co-morbid Substance Use Disorders (other than cannabis)

Given that polysubstance abuse is common among this population, and that other substances of abuse including alcohol, cocaine, stimulants and hallucinogens are associated with altered cognitive performance (Coulston, Perdices et al. 2007), their level of use needs to be considered. Controlling for the effects of substances other than cannabis in this literature has generally been poor. Much research investigating the
relationship between cannabis and cognition is confounded by concurrent drug use, as patients with current comorbid diagnoses of drug abuse and dependence other than cannabis are not excluded from the sample (Stirling, Lewis et al. 2005; Sevy, Burdick et al. 2007). This is problematic when interpreting results, as parsing out what cognitive effects are attributed to what substance remains questionable.

1.9.6 Gender

The research literature suggests that individuals suffering from psychotic disorders with comorbid substance use disorders are predominantly male (Kavanagh, Waghorn et al. 2004), and this gender distribution phenomenon extends to CUDs (Koskinen, Lohonen et al. 2010). Further, males are also thought to have an earlier illness onset, a more severe course of the disorder, suffer from greater cognitive impairment, and have better premorbid function (Goldstein, Seidman et al. 1994). Given that the non-using group is more likely to be populated by females, and males and females present with different symptomatic profiles, gender must be treated as a confounding factor. The lack of control of gender, to date, may account for discrepancies present in the literature.

1.9.7 Premorbid Intellect and Level of Education

Certain studies have suggested that either better or preserved cognitive functioning observed among patients with schizophrenia with comorbid substance use disorders may be explained by higher premorbid intellectual functioning and level of education (Sevy, Robinson et al. 2001; Thoma, Wiebel et al. 2007). Therefore it is essential to control for
these factors as to determine the true effects of cannabis on cognition in patients. Accordingly several studies either controlled for differences in premorbid IQ (Stirling, Lewis et al. 2005; Jockers-Scherubl, Wolf et al. 2007; Mata, Rodriguez-Sanchez et al. 2008; Leeson, Harrison et al. 2011), for level of education (Scholes and Martin-Iverson 2010) or controlled for both when analysing differences in cognitive performance between cannabis users and non-users (Sevy, Burdick et al. 2007; Rodriguez-Sanchez, Ayesa-Arriola et al. 2010). But while Yucel et al. (2010) reported a significant difference between the cannabis-using groups with respect to education, they did not control for this in their analyses. DeRosse et al. (2010) found no differences in premorbid IQ as a function of cannabis use and thus these variables were not entered into analyses as covariates. Other studies failed to mention or consider premorbid intellect or level of education as potential confounding variables (Kumra, Thaden et al. 2005; Schnell, Koethe et al. 2009). The lack of consistency in treating these variables as possible confounds may in part explain contradictory results presented in the literature.

1.10 Current Study Design and Predictions

The current study employed a cross-sectional design to compare cognition and symptomatology as a function of cannabis use in schizophrenia outpatients while conferring several advantages to previous research. For the current study we borrowed an approach from the tobacco literature in which to characterize our sample groups (Hughes, Rose et al. 2000). Given the cross-sectional nature of the study, we proposed to cluster participants according to their current cannabis status: patients with current cannabis dependence (CD) and patients who were not currently cannabis dependence (NCD).
Subsequently, we categorized NCD users into patients with former cannabis dependence (FD) and those with minimal/no lifetime use (ND). This comparison may help to elucidate whether effects of cannabis on cognition are best characterized as state or trait phenomena.

A secondary aim of the study was to examine the relationship between cumulative cannabis exposure and cognition among current and former dependent patients. While studies have examined the effects of frequency of cannabis use on cognition (eg Coulston et al. 2007 and Schnell et al 2010), no previous study has considered lifetime cumulative exposure. Given that Solowij et al. (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, such as joint years, that encompasses frequency, quantity and duration of cannabis use is essential.

Consistent with the results from our meta-analysis we predicted that patients with current dependence would demonstrate poorer cognitive function across all cognitive domains than patients with no current dependence. Further when patients are classified according to lifetime cannabis status, patients with FD would outperform CD and ND patient groups, with ND patients presenting with the most severe of deficits. In line with results from the aforementioned laboratory study by D’Souza et al. (2005), we predicted that patients with current cannabis dependence would demonstrate robust negative relationships between years of daily cannabis use and cognitive function, in that higher
number of years of use would be related to poorer performance across various cognitive domains; these relationships will be less robust in former cannabis dependent patients.
Chapter 2: METHODS

The study was approved by the Centre for Addiction and Mental Health’s (CAMH) ethics committee (REB# 303/2009). All participants provided written informed consent (see Appendix A). A convenience sample of outpatients with schizophrenia was recruited through CAMH via flyers, word-of-mouth, and referrals at CAMH.

2.1 Participants

2.1.1 Power Analysis

We modeled a power analysis on the effect size of the detected differences in cognitive performance on several domains between cannabis users and non-users with schizophrenia using results from primary studies mentioned in our literature review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cognitive Domain</th>
<th>Cognitive test</th>
<th>Effect Size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jockers-Scherubl et al. (2007)</td>
<td>Processing Speed</td>
<td>Trail Making A</td>
<td>0.45</td>
</tr>
<tr>
<td>Jockers-Scherubl et al. (2007)</td>
<td>Attention</td>
<td>CPT</td>
<td>0.40</td>
</tr>
<tr>
<td>Ringen et al. (2010)</td>
<td>Working Memory</td>
<td>Digit Span Forwards</td>
<td>0.51</td>
</tr>
<tr>
<td>Schnell et al. (2010)</td>
<td>Executive Function</td>
<td>Trail Making B</td>
<td>0.63</td>
</tr>
<tr>
<td>Leeson et al. (2011)</td>
<td>Verbal learning</td>
<td>RVLT</td>
<td>0.46</td>
</tr>
</tbody>
</table>

CPT, Continuous Performance Test; RVLT, Rey Verbal Learning Test
Effect sizes from the literature derived from various cognitive domains range from 0.40-0.63. Thus we would need a total sample size ranging from 82 - 198 to produce 80% power at the .05 level of significance to detect such a range of effect size between CD and NCD groups. Given that our study controlled for confounding variables that previous studies overlooked and because we parsed lifetime users into current and former dependent patient groups, we predicted our differences to be more robust and yield effect sizes in the medium to large range. To power our study to render an effect size of 0.7, we would thus need a total sample of 66. Additionally, we considered the time constraints for a Master’s project (2 years duration) and that this study was exploratory in nature and thus we concluded that recruiting a sample size of 50-60 was reasonable to explore our primary and secondary study hypotheses.

2.1.2 Total Sample

A total sample of N=54 patients with schizophrenia outpatients were recruited over a 24-month period. Eighteen patients met for current cannabis dependence (CD; n=18) and 36 patients were without a current cannabis dependence diagnosis (NCD; n=36).

Psychiatric participants met diagnostic criteria for either schizophrenia or schizoaffective disorder based on the Structural Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV-TR) (American Psychiatric Association 2000). Current cannabis dependence and former cannabis dependence (in remission for at least 6 months) was also diagnosed according to DSM-IV-TR criteria.
Given that age has a non-linear effect on many neuropsychological tests (Capitani and Laiacona 1988), we confined the age range of included patients to 15 and 55 in order to minimize these effects.

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 et al. 1987), and on a stable dose of medication for at least one month prior to the study assessments. Chlorpromazine (CPZ) equivalents of antipsychotics were calculated (APA 2000; Woods 2003).

All participants recruited were current 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) levels (Vitalograph, Lenexa, KS). Level of nicotine dependence was measured using the Fagerstrom Test of Nicotine Dependence (FTND) (Heatherton, Kozlowski et al. 1991).

Subjects were excluded if they were using illicit drugs other than cannabis as were those with diagnoses of substance use disorders (other than cannabis) in the past six months prior to study enrolment. Medtox urine toxicology screens (7-panel) were used to screen for illicit drugs (Cannabinoids, Opiates, Amphetamine, Cocaine, Phencyclidine, Barbiturates, and Benzodiazepines). The Alcohol Use Disorders Identification Test (AUDIT) (Saunders, Aasland et al. 1993) was included to assess hazardous and harmful patterns of alcohol consumption. Premorbid intelligence was assessed using the Weschler
Test of Adult Reading (WTAR; (Wechsler 2001)). Individuals who scored the equivalent of a FSIQ score of < 80 were excluded from the study. Exclusion criteria also included evidence of a developmental disorder, history of a serious medical disorder or neurological illness that might affect cognitive performance. Participants were also excluded if they had a history of acquired brain injury, or suffered from loss of consciousness. While there is insufficient data to establish a definite threshold of severity for loss of consciousness, we adopted specific criteria as noted in the DSM-IV (First 1994).

2.2 Measures

2.2.1 Clinical Interview Measures

*SCID-IV*

The SCID-IV is a semi-structured interview that assesses current and lifetime diagnoses of axis I disorders. This allowed for definitive psychotic and substance use disorder diagnoses of the sample participants.

*Addiction Severity Index (ASI)*

The ASI (McLellan, Kushner et al. 1992) is a semi-structured interview designed to assess 7 potential problem areas in substance-using patients: medical status, employment and support, drug use, 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 patient 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 gauges problem severity by calculating composite scores ranging from 0 (no problem) to 1 (extreme severity) in each of 7 domains. Scores on based on the patient’s responses and correspond to the last 30 days.

**PANSS**

The PANSS is a widely used medical scale that measures symptoms severity of patients with schizophrenia. This 30-item rating instrument evaluates the presence or absence and severity of positive, negative and general psychopathology of schizophrenia. All items are rated on a 7-point scale (1=absent; 7=extreme). The PANSS has good inter-rater reliability (Kay, Opler et al. 1988), adequate construct validity (Kay, Fiszbein et al. 1987; Kay, Opler et al. 1988), and high internal reliability.

**2.2.2 Self-Report Symptom Inventory**

**Beck Depression Inventory – Second Edition (BDI-II)**

The BDI-II (Beck, Steer, & Brown, 1996) is a 21-item self-report questionnaire used measure the severity of current depressive symptomatology. Each answer is scored on a scale value of 0 to 3. The cutoffs used differ from the original: 0–13: minimal depression; 14–19: mild depression; 20–28: moderate depression; and 29–63: severe depression. Higher total scores indicate more severe depressive symptoms.

**2.2.3 Pre-morbid Intelligence**

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

The WTAR was developed to estimate premorbid intellectual ability. This reading test is
composed of a list of 50 words that have atypical grapheme to phoneme translations. The intent in using words with irregular pronunciations is to minimize the current ability of the client to apply standard pronunciation rules and assess previous learning of the word, without have to provide the definition of the word. The WTAR has the added advantage of being co-normed with the widely-used The Wechsler Adult Intelligence Scale Third Edition (WAIS–III). This co-development enables the WTAR to be an effective method for predicting full-scale IQ and memory performance, with prediction equations available for WAIS–III index scores.

2.2.4 Substance Use Assessments

The Alcohol Use Disorders Identification Test (AUDIT)

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

Timeline Follow Back (TLFB)

The Timeline Follow Back (TLFB) (Sobell and Sobell 1995) while originally developed to assess frequency of alcohol use, it has now been validated for collecting information
on drug use, in addition to alcohol consumption (Carey and Correia 1998; Fals-Stewart, O'Farrell et al. 2000). The frequency of the substance of abuse is assessed on a day-by-day basis, using a calendar where participants provide retrospective estimates of their daily substance use over a 7-day period. The TLFB was used as an effective tool for measuring the use of alcohol, marijuana, tobacco and caffeine over the previous week.

**Fagerstrom Test of Nicotine Dependence (FTND)**

The FTND (Heatherton, Kozlowski et al. 1991) is a brief, 6-item scale that yields a score between 0 and 10, assessing smokers’ level of nicotine dependence. Individuals respond to multiple-choice type questions, with each answer corresponding to a score and higher scores indicating higher 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, Reutenauer et al. 2007).

**Joint-Years**

Cumulative exposure to cannabis was measured in joint years. A joint-year of cannabis was defined as smoking on average one joint per day for 1 year (e.g., 1 joint year = 365 joints smoked in one year).

2.2.5 Extrapyramidal Side-effects

**Simpson Angus Rating Scale (SARS)**

The SARS (Simpson and Angus 1970) is a scale used to measure 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.

Abnormal Involuntary Movement Scale (AIMS)
The AIMS (Guy 1976) is a scale designed to assess tarditive dvskinesia associated with long-term treatment of antipsychotic medication. The AIMS test has a total of twelve items that rate involuntary movements of various areas of the patient's body. These items are rated on a five-point severity scale from 0–4.

Barnes Akathisia Rating Scale (BARS)
BARS (Barnes 1989) is used to measure drug-induced Akathisia. Akathisia is a syndrome of motor restlessness, principally seen in association with antipsychotic medication. The BARS was designed to assess the characteristic objective motor phenomena as well as the subjective aspects of akathisia. Objective akathisia, subjective awareness of restlessness and distress related to restlessness are rated on a 4-point scale, while global clinical assessment employs a 5-point scale.

2.3 Neurocognitive 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 and Gfeller 2007) and thus was used as a measure of 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 the participant is shown 50 target pictures, followed by 50 recognition panels. Each recognition panel contains one of the target pictures and a novel one. The patient 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 was administered only if the Trial 2 score was less than 45. Scores range from 0 to 50 for each, and 5 or more errors on trial 2 or the retention trial indicates the possibility of malingering.

*The Continuous Performance Test II (CPT-II)*

The CPT-II (Conners 2000) is a computerized psychological test which measures a person's sustained and selective attention and 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, % of Omissions, % of Commission, Hit Reaction Time, CPT Variability, and measure of Attentiveness/Distractibility.

*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 them alternating between number and letter, in
consecutive and alphabetical order. The participant was instructed to complete the task as quickly as possible, and as accurately as possible. 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.

**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. Raw scores are calculated by measuring the length of time required to complete the task with the dominant and non-dominant hand respectively.

**Digit Span-Forward and Backward**

The Digit Span (Wechsler 1997) is a subtest of the WAIS-III, and is a measure of short-term verbal memory, concentration and attentional skills. 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 total number of correctly repeated strings of numbers is summed for a forward score, backwards score and a total score (forwards + backwards).
**Stroop Color Word Test (SCWT)**

The SCWT (Golden 1978) is a measure of executive function and response inhibition. Participants are required to read 100 black colour words (word card), to name the ink-coloured XXXXs (colour card), and to name the colours of 100 incongruent colour words (colour–word card) as fast as possible within a 45 second time limit. The test yields three scores based on the number of items completed on each of the three stimulus pages with higher scores reflecting better performance. An interference score is also calculated. This score reflects the extent of delay in naming the colour of an incongruent colour word (RED) relative to naming the colour of a congruent colour word (RED).

**Wisconsin Card Sorting Task (WCST)**

The WCST (Heaton, Chelune et al. 1993) is an extensively used measure that assesses executive functions, including planning and set-shifting. Outcome measures include number of categories completed, percent total errors, percent perseverative errors, percent non-perseverative errors, and number of trials to complete first category. Performance on this task has been linked with activation of the dorsolateral prefrontal cortex (Egan, Goldberg et al. 2001). Reliability of the WCST, inter-scorer and intra-scorer agreements have been found to be excellent. Since this task assesses decision-making ability, poor performance on this task should be consistent with high levels of delay discounting.

**California Verbal Learning Test--Second Edition (CVLT-II)**

The CVLT-II (Delis, Kramer et al. 2000) is a measure of verbal memory, learning, retrieval and recognition. Participants are asked to learn and recall a list of 16 words presented five times. A total of nine indices were used as outcome measures (List A Free

**Spatial Delayed Response (SDR)**

The SDR (Hershey, Craft et al. 1998) is a measure of visuospatial working memory. In this task participants must focus on a central fixation cross on a computer screen. While fixated, a cue (dot) appears for in one of many possible locations on. 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 subject must press the spacebar whenever the diamond shape appears. After the delay, the fixation cue returns, and the subjects must to point on the computer screen where they remember seeing the cue. Mean error in mm (distance between recall and actual target) is calculated for each of the three time delay trials.

**Iowa Gambling Task – Computerized (IGT)**

The IGT (Bechara, Damasio et al. 1994) is a widely used measure that is highly sensitive to measuring impaired decision-making in a variety of neurological and psychiatric conditions, including schizophrenia (Bechara, Damasio 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. The subjects were permitted to pick from any deck and to switch decks at any time. Subjects
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 variable that measures overall performance on this task is the difference between choices in advantageous decks (C and D) minus choices in disadvantageous decks (A and B). Previous research has suggested that individuals with schizophrenia are significantly impaired on IGT in comparison to healthy controls, as they earn significantly lower scores and make more disadvantageous picks (Beninger, Wasserman et al. 2003; Kester, Sevy et al. 2006), resulting in less hypothetical monetary winnings by the end of the task.

**The Kirby Delay Discounting Task (KDDT)**

The KDDT (Kirby, Petry et al. 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). 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 smaller immediate rewards rather than larger delayed rewards.

**2.4 Procedure**

Once potential participants were identified, a telephone screen was completed and those
eligible were invited to the Biobehavioural Addictions and Concurrent Disorders Research Laboratory (BACDRL; Principal Investigator: Tony P. George, M.D., FRCPC) at CAMH for a screening session. Assessments took place over two occasions. Both the screening and cognitive visits were conducted by the candidate Rachel Rabin (R.R). RR was trained on all clinical interview measures as well as on the administration and scoring of all cognitive assessments included in the battery.

On the first occasion, consent was completed, demographic information recorded followed by administration of the SCID-IV, PANSS, ASI, TLFB, AUDIT, Carbon Monoxide (CO) level, and Medtox™ urine toxicology screening. Participants who met eligibility criteria were invited back for a cognitive-testing session at the earliest convenience of the patient.

The PANSS was re-administered along with the BDI-II on the day of the second visit to assess the symptom severity at the time of cognitive testing. Other time-sensitive measures were also re-administered: TLFB, CO levels, and Medtox™ urine toxicology screen.

The cognitive test battery included the 11 aforementioned tests administered in a counterbalanced manner across study groups. CD patients were asked to refrain from using cannabis 24 hours before the time of their cognitive visit. This is in accordance with Coulston et al. (2007) and DeRosse et al. (2010). This minimal abstinence period was instigated as to prevent patients from being tested while actually intoxicated and
before the onset of withdrawal symptoms (Budney, Moore et al. 2003). However, no objective measure was utilized in order to ensure compliance with this abstinence period. All subjects were instructed to refrain from consuming caffeinated beverages within one hour of commencing the assessment (Coulston, Perdices et al. 2007). All participants were given 10 minute cigarette breaks before testing sessions began and throughout testing ad libitum prior to the testing session, in order to reduce the likelihood of nicotine withdrawal affecting cognitive performance (George, Vessicchio et al. 2002).

After completion of each session, participants were compensated at a rate of $10 per hour. Completion time was approximately two to three hours for the screening visit and an additional three hours for the cognitive session. Participants’ compensation ranged from $50- $60.

2.4.1 Statistical Analysis

All statistical calculations were completed using the Statistical Package for the Social Sciences (SPSS) for Windows version 15.0. Initially groups were compared as a function of current cannabis status (CD versus NCD) on demographic and clinical factors. Chi-square tests were used to detect differences in categorical variables and independent samples t-tests for continuous variables. Two-tailed t-tests were then employed to analyze differences in cognitive performance between these two groups. Comparison of groups on neurocognitive domains were carried out using Multivariate Analysis of Covariance (MANCOVA)s that covaried for any differences observed in demographic or symptom variables. Analyses were repeated to observe group differences as a function of historical
(or lack thereof) cannabis dependence (CD versus FD versus ND). In these analyses
Analysis of Variance (ANOVA)s were used to in place of t-tests. For multiple
comparisons, Bonferroni post-hoc tests were employed in order to conservatively control
for type-1 errors. Cognitive scores that showed between-group differences were further
analysed using ANCOVAs with respect to the impact of potential confounding factors
(CPD and age). Kruskal-Wallis Tests and ANOVAs were conducted to explore
differences in ASI interviewer severity ratings and composite scores respectively between
the 3 groups: CD, FD and ND. Effect sizes were computed for cognitive outcomes as a
function of current cannabis status (CD and NCD) and as a function of historical cannabis
status (CD and FD, CD and ND and FD and ND). Effect sizes were defined as the mean
difference divided by the pooled SD. Pearson product moment correlation coefficients
were used to examine relationships between cumulative cannabis exposure and cognitive
test battery performance outcomes. Education and IQ were examined as covariates using
partial correlations (see Appendix C). The study adopted the conventional 0.05 alpha
level as evidence of statistical significance (p<0.05).
Chapter 3: RESULTS

3.1 Demographic Characteristics of Study Sample

One hundred and thirty people were assessed for study eligibility via phone screening, and 65 of these individuals were invited to BACDRL to complete a screening visit. Eleven patients failed to meet study criteria and were thus excluded from further participation due to Full Scale Intelligence Quotient (FSIQ) < 80 (n=2), current SUD and/or positive urine drug screen (n=6), other than cannabis for CD patients, inpatient status (n=1) and because of psychiatric instability (n=2). A total sample of 54 male and female outpatients with schizophrenia between the ages of 15 and 55 were recruited over a 24-month period. Eighteen of these patients met study criteria for current cannabis dependence (CD; n =18 patients) and 36 patients were classified as non-currently dependent, (NCD; n=36). There were a disproportionate number of females in the two groups. Of the 18 CD patients, all were male; no females were represented in this subsample (0%). In the NCD group 7 of the 36 (19.4%) patients were female. Given this uneven gender distribution in our sample groups, we opted to exclude all female participants (n=7) from analyses and confine our sample to male patients. Limiting our sample to males prevents us as having to treat gender as a confounding factor and allows us to focus on those most representative of the target population (Goldstein, Seidman et al. 1994). Therefore the final sample was comprised of 47 male outpatients with schizophrenia, 18 of these patients met study criteria for current cannabis dependence, and 29 were classified as not currently dependent. The latter group could be further divided into those who were formerly cannabis dependent (FD; n= 21) and those with no or minimal cannabis use (ND; n=8).
Figure 1

Consort Diagram

- Assessed for eligibility via phone screen (N= 130)
- Total Sample (N = 54)
  - Excluded (n = 11)
    - Not meeting inclusion criteria:
      - Concurrent SUD or drug use (n=6)
      - PANSS > 70 (n=1)
      - FSIQ < 80 (n=2)
      - Inpatient status (n=1)
  - Females (N = 7)
    - CD; n= 0
    - NCD; n= 7
  - Males (N = 47)
    - CD; n= 18
    - NCD; n= 29
  - Males (N = 47)
    - CD; n= 18
    - FD; n= 21
    - ND; n= 8
- Enrolled (N = 65)
3.1.1 Current Cannabis Status

The demographic and clinical characteristics as a function of current cannabis dependence: patients with current dependence (n=18) and patients with no diagnosis of current dependence (n=29) are presented in Table 3. The two groups were comparable on racial background, years of education and premorbid functioning as measured by FSIQ. However there was a significant difference in age $t (45) = -2.11, p = .04$, with NCD patients being significantly older than CD patients. There were no differences in psychiatric or depressive symptomatology as a function of cannabis use. Patients all scored similarly on the PANSS total score, its subscores and on the BDI-II. Antipsychotic levels (based on chlorpromazine equivalents; CPZ Eq.) were also consistent across groups. There were no significant group differences in AUDIT scores. While expired carbon monoxide breath levels and FTND scores were consistent across groups, CPD differed $t (44) = -3.38, p < .01$. NCD patients smoked more cigarettes per day than CD patients. Further, there was also a significant difference in cumulative cannabis exposure between CD and NCD patient groups $t (45) = 2.79, p < .01$. 
Table 3
Demographic and clinical means and standard deviations of the sample by current cannabis status

<table>
<thead>
<tr>
<th></th>
<th>CD (n=18)</th>
<th>NCD (n=29)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31.6 (9.6)</td>
<td>37.8 (9.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
<td>19</td>
<td>0.41</td>
</tr>
<tr>
<td>African-American</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Education (y)</td>
<td>12.5 (2.1)</td>
<td>12.7 (2.6)</td>
<td>0.84</td>
</tr>
<tr>
<td>FSIQ</td>
<td>95.4 (8.2)</td>
<td>96.9 (9.3)</td>
<td>0.58</td>
</tr>
<tr>
<td>CPZ Eq.</td>
<td>304.7 (195.9)</td>
<td>482.7 (335.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>CPD</td>
<td><strong>11.3 (6.7)</strong></td>
<td><strong>20.8 (10.2)</strong></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CO level (ppm)</td>
<td>19.8 (12.1)</td>
<td>22.4 (11.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>FTND score</td>
<td>5.3 (1.8)</td>
<td>5.9 (2.0)</td>
<td>0.47</td>
</tr>
<tr>
<td>AUDIT</td>
<td>5.1 (3.5)</td>
<td>5.6 (5.4)</td>
<td>0.67</td>
</tr>
<tr>
<td>Joint Years</td>
<td><strong>11.9 (8.2)</strong></td>
<td><strong>5.7 (7.2)</strong></td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>PANSS +</td>
<td>13.9 (3.2)</td>
<td>13.6 (3.5)</td>
<td>0.72</td>
</tr>
<tr>
<td>PANSS -</td>
<td>13.9 (3.3)</td>
<td>12.3 (2.3)</td>
<td>0.47</td>
</tr>
<tr>
<td>PANSS General</td>
<td>25.8 (3.7)</td>
<td>24.3 (3.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>53.6 (6.6)</td>
<td>51.1 (7.6)</td>
<td>0.28</td>
</tr>
<tr>
<td>BDI</td>
<td>11.3 (9.4)</td>
<td>11.2 (9.7)</td>
<td>0.97</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD)

3.1.2 Historical Cannabis Status

The demographic and clinical characteristics of the three groups: patients with current dependence (n=18), patients with former dependence (n=21) and patients with no history of cannabis dependence (n=8) are presented in Table 4. The three groups were comparable on racial background, years of education and premorbid functioning.
Age differed across the groups $F(2, 44) = 6.66, p < .01$. Bonferroni post hoc revealed that ND patients were significantly older than both CD and FD patient groups. There were no differences in psychiatric or depressive symptomatology as a function of cannabis use as patients all scored similarly on the PANSS total score, its subscores and on the BDI-II. Antipsychotic levels (based on chlorpromazine equivalents; CPZ Eq.) were also consistent across groups. Expired CO levels and FTND and AUDIT scores were similar across groups. However, CPD differed $F(2, 43) = 10.62, p < .01$. ND smoked more cigarettes per day than CD and FD patients. Independent-samples $t$-tests revealed similar cumulative cannabis exposure between CD and FD patient groups. Lastly, movement scale total scores of extrapyramidal side-effects (SARS, AIMS and BARS) did not differ between the groups.

ASI Interview Severity Ratings (ISR) for CD, FD and ND groups are detailed in Table 5. Severity scores on medical, employment, alcohol, legal, social and psychiatric domains did not differ between the three groups. However, drug severity scores were significantly different, $H(2) = 39.50; p<0.01$. Mann-Whitney tests revealed that severity scores were higher in CD patients as compared to FD, $U = 0; p< 0.01$, and ND patients, $U = 0; p<0.01$.

ASI composite scores across the 7 domains are outlined in Table 6. Family/social composite scores differed between the groups, $F(2, 43) = 3.43 p= .04$, but when a Bonferroni correction was applied, between group differences were no longer observed.
Table 4  
**Demographic and clinical means and standard deviations of the sample by historical cannabis status**

<table>
<thead>
<tr>
<th></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>Age (y)</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>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>8</td>
<td>14</td>
<td>5</td>
<td>0.51</td>
</tr>
<tr>
<td>African</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td></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>FSIQ</td>
<td>95.4 (8.2)</td>
<td>97.1 (9.7)</td>
<td>96.5 (9.0)</td>
<td>0.86</td>
</tr>
<tr>
<td>CPZ Eq.</td>
<td>304.7 (195.9)</td>
<td>543.4 (375.0)</td>
<td>338.5 (151.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>CPD</td>
<td>11.2 (6.7)</td>
<td>18.0 (7.2)</td>
<td>28.6 (15.3)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CO level (ppm)</td>
<td>19.8 (12.1)</td>
<td>23.0 (10.7)</td>
<td>20.7 (12.4)</td>
<td>0.69</td>
</tr>
<tr>
<td>FTND score</td>
<td>5.3 (1.8)</td>
<td>5.5 (1.6)</td>
<td>7.3 (3.1)</td>
<td>0.25</td>
</tr>
<tr>
<td>AUDIT</td>
<td>5.1 (3.5)</td>
<td>6.1 (5.7)</td>
<td>4.5 (4.8)</td>
<td>0.69</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>PANSS +</td>
<td>13.9 (3.2)</td>
<td>14.2 (3.4)</td>
<td>11.8 (3.2)</td>
<td>0.23</td>
</tr>
<tr>
<td>PANSS -</td>
<td>13.9 (3.33)</td>
<td>13.1 (2.5)</td>
<td>13.4 (1.6)</td>
<td>0.71</td>
</tr>
<tr>
<td>PANSS General</td>
<td>25.8 (3.7)</td>
<td>24.9 (3.2)</td>
<td>22.8 (2.4)</td>
<td>0.11</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>53.6 (6.6)</td>
<td>52.5 (7.7)</td>
<td>48.0 (6.5)</td>
<td>0.19</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 (SD)
### Table 5
**ASI ISRs as a function of historical cannabis status**

<table>
<thead>
<tr>
<th></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>Medical</td>
<td>0.39 (1.4)</td>
<td>0.38 (1.0)</td>
<td>0.86 (1.2)</td>
<td>0.22</td>
</tr>
<tr>
<td>Employment</td>
<td>0.56 (1.0)</td>
<td>0.29 (0.7)</td>
<td>0.00 (0.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.67 (1.2)</td>
<td>1.00 (1.5)</td>
<td>0.43 (1.1)</td>
<td>0.32</td>
</tr>
<tr>
<td><strong>Drug</strong></td>
<td><strong>5.39 (1.1)</strong></td>
<td><strong>0.19 (0.6)</strong></td>
<td><strong>0.00 (0.0)</strong></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Legal</td>
<td>0.50 (1.5)</td>
<td>0.00 (0.0)</td>
<td>0.00 (0.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Family/Social</td>
<td>0.22 (0.5)</td>
<td>0.57 (1.2)</td>
<td>0.29 (0.80)</td>
<td>0.72</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>3.67 (1.3)</td>
<td>2.95 (1.7)</td>
<td>2.29 (1.3)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD)

### Table 6
**ASI composite scores as a function of historical cannabis status**

<table>
<thead>
<tr>
<th></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>Medical</td>
<td>0.13 (0.2)</td>
<td>0.13 (0.2)</td>
<td>0.20 (0.3)</td>
<td>0.78</td>
</tr>
<tr>
<td>Employment</td>
<td>0.87 (0.2)</td>
<td>0.82 (0.3)</td>
<td>0.84 (0.2)</td>
<td>0.55</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0.07 (1.0)</td>
<td>0.09 (1.0)</td>
<td>0.08 (0.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>Drug</td>
<td>0.16 (0.1)</td>
<td>0.06 (0.2)</td>
<td>0.03 (0.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Legal</td>
<td>0.04 (1.0)</td>
<td>0.00 (0.0)</td>
<td>0.00 (0.0)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Family/Social</strong></td>
<td><strong>0.07 (1.0)</strong></td>
<td><strong>0.15 (0.2)</strong></td>
<td><strong>0.01 (0.0)</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>0.28 (0.1)</td>
<td>0.33 (0.2)</td>
<td>0.24 (0.1)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Values are expressed as mean (SD)

### 3.2 Group Differences in Cognitive Performance

Effect sizes as a function of current cannabis status (CD and NCD) and as a function of historical cannabis status (CD and FD, CD and ND and FD and ND) are presented in Table 7.
**Table 7**  
*Effect size differences in cognitive performance as a function of current and historical cannabis status*

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>subtest</th>
<th>Effect sizes (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CD-NCD</td>
</tr>
<tr>
<td>Groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOMM</td>
<td>trial 2</td>
<td>-0.70</td>
</tr>
<tr>
<td>CPT</td>
<td>% hits</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>hit reaction time</td>
<td>0.16</td>
</tr>
<tr>
<td>Trail Making</td>
<td>A</td>
<td>-0.19</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>-0.27</td>
</tr>
<tr>
<td>Pegboard</td>
<td>total time</td>
<td>-0.20</td>
</tr>
<tr>
<td>Digit Span</td>
<td>digit span total</td>
<td>0.12</td>
</tr>
<tr>
<td>STROOP</td>
<td>interference score</td>
<td>0.16</td>
</tr>
<tr>
<td>WCST</td>
<td>% perseverative errors</td>
<td>-0.12</td>
</tr>
<tr>
<td></td>
<td># categories complete</td>
<td>-0.21</td>
</tr>
<tr>
<td>CVLT</td>
<td>total trials 1-5</td>
<td>0.19</td>
</tr>
<tr>
<td>SDR</td>
<td>30s delay</td>
<td>-0.23</td>
</tr>
<tr>
<td>IGT</td>
<td>net total score</td>
<td>-0.21</td>
</tr>
<tr>
<td>KDDT</td>
<td>Geomean k</td>
<td>0.08</td>
</tr>
</tbody>
</table>
**The Test of Memory Malingering (TOMM)**

Two tailed independent t-tests revealed that CD and NCD performance on trial 2 of the TOMM did not differ, \( t (20) = -1.50; p = .15 \). A one-way ANOVA demonstrated comparable TOMM performance across CD, FD and ND groups, \( F (2, 19) = 1.09; p = .36 \). Therefore, there were no group differences in effort exerted.

**Figure 2**

*TOMM scores across historical cannabis status*

![Motivation and Effort](image)

**The Continuous Performance Test II (CPT-II)**

Two tailed independent t-tests revealed that CD and NCD performed similarly on all subtests of the CPT [percent hits, \( t (44) = 0.10; p = .92 \), percent commissions, \( t (44) = 0.45; p = .69 \), and reaction rate, \( t (44) = -0.51; p = .61 \)]. Therefore selective attention, impulsivity, and hit reaction time did not differ between CD and NCD groups.
One-way ANOVAs revealed that CD, FD and ND had similar performance on percent hits, $F(2, 43) = 1.41; p = .26$ and percent commission, $F(2, 43) = 0.70 \ p = .50$, of the CPT-II. However hit reaction time was significantly different across groups, $F(2, 43) = 4.48; p < .02$. Bonferroni post-hoc tests revealed that ND (M=562.47, SD= 284.4) performed more poorly than both CD patients (M=419.24, SD= 85.1); $p= 0.04$, and FD patients (M=399.62, SD= 64.4); $p=0.01$. Age and cigarettes per day were then treated as covariates, and while they did impact CPT hit reaction time, the main effect of group remained significant ($p=.03$). Therefore lifetime cannabis users had better reaction time than ND patients, but groups did not differ in CPT measures of attention and impulsivity.

Figure 3a
CPT percent hits across cannabis
Figure 3b
CPT hit reaction time across historical cannabis status

---

**TMT-A and TMT-B**

Two tailed independent t-tests suggest that CD and NCD groups did not differ on time to complete TMT-A, $t(44) = 0.60; p < .55$, or TMT-B, $t(44) = 0.88; p < .39$. Therefore neither processing speed nor executive function differed as a function of current cannabis status. While one-way ANOVAs revealed that CD, FD and ND had similar performance on the TMT-B, $F(2, 43) = 0.74; p < .49$, TMT-A scores differed significantly across groups, $F(2, 43) = 4.50; p < .02$. When a Bonferroni post-hoc correction was applied, ND patients ($M=54.57$, $SD= 26.0$) were found to have performed significantly worse than FD patients ($M=35.62$, $SD= 12.8$); $p<0.02$. When age and cigarettes per day were treated as covariates, results were still significant ($p<.05$). Results suggest that while executive function is similar between the 3 groups, former cannabis users demonstrated better speed of processing as compared to nonusers.
**Figure 4a**  
*Trail Making Test A across historical cannabis status*  

**Figure 4b**  
*Trail Making Test B across historical cannabis status*
**Grooved Pegboard**

Speed to complete the grooved pegboard did not differ as a function of current $t(20) = 0.43; p = .67$, or historical cannabis status $F(2, 19) = 0.44; p = .65$. Manual dexterity and fine motor movement did not differ as a result of cannabis use.

**Figure 5**
*Grooved pegboard performance across historical cannabis status*

![Motor Movement Chart]

**Digit Span**

The Digit Span total score was similar between CD and NCD groups, $t(44) = 0.39; p = .70$, and between CD, FD and ND patients, $F(2, 19) = 0.09; p = .91$. Verbal and working memory did not differ as a function of current or historical cannabis use.
Figure 6  
*Digit Span total score across historical cannabis status*

![Memory & Attention](image)

---

**Stroop Color Word Test (SCWT)**

Two tailed independent t-tests revealed that CD and NCD had similar interference scores $t (44) = 0.52; p = .61$. Likewise, CD, FD and ND performance did not differ $F (2, 43) = 0.49; p < .62$. Therefore cannabis had no effect on executive function/response inhibition as assessed by the SCWT.
Wisconsin Card Sorting Task (WCST)

None of the WCST subscores differed between CD and NCD patients, such as on percent perseverative responses, $t(44) = 0.67; p = .51$; percent perseverative errors, $t(44) = 0.37; p = .71$; percent non-perseverative errors $t(44) = 0.08 p = .94$; categories completed, $t(44) = -0.85; p = .40$. Similar performance was seen across CD, FD and ND patients on all subscores of the WCST [percent perseverative responses, $F(2, 43) = 2.16; p = .13$; percent perseverative errors, $F(2, 43) = 2.26; p = .12$; percent non-perseverative errors $F(2, 43) = 0.12 p = .34$; categories completed, $F(2, 43) = 1.71; p = .19$]. Therefore all groups had comparable performance on the WCST, a test of executive function.
Figure 8a
WCST perseverative errors across historical cannabis status

Figure 8b
WCST categories completed across historical cannabis status
California Verbal Learning Test--Second Edition (CVLT-II)

Similar performance between CD and NCD was observed on the CVLT. Subscores such as total trials correct, $t(44) = 0.62; p=.54$; short-delay free recall, $t(43) = -2.29; p=.82$; short-delay cued-recall, $t(43) = -0.32 p=.75$; long-delay free recall $t(43) = -0.34; p=.74$; long-delay cued recall $t(43) = -1.26; p=.22$; long-delay recognition $t(43) = -0.82; p=.42$ was comparable between the 2 groups. Performance on the CVLT did not differ across CD, FD and ND patients. Similar CVLT subscores were observed for all groups [total trials correct, $F(2, 43) = 0.41; p=.67$; short-delay free recall, $F(2, 42) = 0.04; p=.96$; short-delay cued-recall, $F(2, 43) = 0.15 p=.86$; long-delay free recall $F(2, 43) = 0.07; p=.93$; long-delay cued recall $F(2, 43) = 0.81; p=.45$; long-delay recognition $F(2, 41) = 0.33; p=.72$]. Therefore verbal memory and learning did not differ across groups.

Figure 9
CVLT total trials across historical cannabis status
**Spatial Delayed Response Task (SDR)**

Similar performance was observed between CD and NCD patients at the 5s delay, $t(44) = 0.03; p = .97$, the 15s delay $t(44) = 0.42; p = .68$, and the 30s delay $t(44) = 0.73; p = .47$. Group differences were not seen on the SDR at the 5s delay, $F(2, 43) = 0.08; p = .92$, the 15s delay $F(2, 43) = 0.56; p = .57$, or the 30s delay $F(2, 43) = 1.77; p = .19$. Therefore visuospatial working memory performance was similar as a function of current and historical cannabis status.

**Figure 10**
*SDR 30 second delay across historical cannabis status*

![Figure 10](image)

**Iowa Gambling Task (IGT) – Computerized**

IGT net total did not differ as a function of current cannabis status $t(32) = -0.59; p = .56$ or historical cannabis status $F(2, 31) = 0.91; p = .41$. Therefore no differences on the IGT, a measure of impulsivity and decision making was observed across groups.
**Figure 11**
*IGT net total across historical cannabis*

The Kirby Delay Discounting Task (KDDT)

Two tailed independent t-tests revealed that CD and NCD had similar scores on the geomean K of the KDDT $t(44) = 0.29$ $p = .77$. One-way ANOVAs revealed that CD, FD and ND performance did not differ on geomean k scores of the KDDT $F (2, 19) = 1.16; p = .33$. Therefore, future-orientated decision-making and impulsivity did not differ across CD and NCD groups or CD, FD or ND groups.
3.3 Correlations: Cumulative Use and Cognitive performance

Patients with current cannabis dependence demonstrated robust correlations between cumulative cannabis exposure, measured in joint years and cognitive function, in that higher number of years of use were associated with poorer performance across various cognitive domains. Correlations are presented in Table 5. Further, when relationships were assessed in patients with former dependence, the only relationship to achieve significance was between CPT reaction time and joint years. This relationship appears to be driven by an outlier, and upon removal, this relationship no longer remains significant (r=0.195, p=.41). No other significant correlations between joint-years and cognitive test performance were observed.
Table 8
*Relationship between cognitive performance and cumulative cannabis use (joint-years) in current and former dependent patients*

<table>
<thead>
<tr>
<th>Cognitive Test</th>
<th>subtest</th>
<th>CD patients</th>
<th></th>
<th>FD patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>TOMM</td>
<td>trial 2</td>
<td>-0.60</td>
<td>0.12</td>
<td>0.15</td>
<td>0.67</td>
</tr>
<tr>
<td>CPT</td>
<td>% hits</td>
<td>-0.52</td>
<td>0.03**</td>
<td>0.04</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>% commissions</td>
<td>0.10</td>
<td>0.71</td>
<td>-0.32</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>hit reaction time</td>
<td>-0.04</td>
<td>0.86</td>
<td>0.47</td>
<td>0.03**</td>
</tr>
<tr>
<td>Trail Making</td>
<td>A</td>
<td>0.22</td>
<td>0.38</td>
<td>0.04</td>
<td>0.88</td>
</tr>
<tr>
<td>Trail Making</td>
<td>B</td>
<td>0.35</td>
<td>0.15</td>
<td>-0.06</td>
<td>0.79</td>
</tr>
<tr>
<td>Pegboard</td>
<td>total time</td>
<td>0.57</td>
<td>0.14</td>
<td>-0.37</td>
<td>0.27</td>
</tr>
<tr>
<td>Digit Span</td>
<td>forwards</td>
<td>-0.51</td>
<td>0.03**</td>
<td>-0.07</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>backwards</td>
<td>-0.20</td>
<td>0.43</td>
<td>-0.13</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>digit span total</td>
<td>-0.42</td>
<td>0.08</td>
<td>-0.12</td>
<td>0.61</td>
</tr>
<tr>
<td>STROOP</td>
<td>interference score</td>
<td>0.06</td>
<td>0.80</td>
<td>-0.37</td>
<td>0.10</td>
</tr>
<tr>
<td>WCST</td>
<td>% perseverative responses</td>
<td>0.45</td>
<td>0.06</td>
<td>-0.08</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>% perseverative errors</td>
<td>0.44</td>
<td>0.07</td>
<td>-0.07</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>% nonperseverative errors</td>
<td>0.64</td>
<td>&lt;0.01**</td>
<td>0.10</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td># categories complete</td>
<td>-0.54</td>
<td>0.02**</td>
<td>-0.09</td>
<td>0.70</td>
</tr>
<tr>
<td>CVLT</td>
<td>total trials 1-5</td>
<td>-0.40</td>
<td>0.10</td>
<td>0.02</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td>trial 5</td>
<td>-0.50</td>
<td>0.03**</td>
<td>0.04</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>long-delay cued recall</td>
<td>-0.47</td>
<td>&lt;0.05**</td>
<td>0.10</td>
<td>0.67</td>
</tr>
<tr>
<td>SDR</td>
<td>5s delay</td>
<td>0.54</td>
<td>0.02**</td>
<td>-0.27</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>15 s delay</td>
<td>30 s delay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.27</td>
<td>0.61</td>
<td>0.61</td>
<td>&lt;0.01**</td>
<td></td>
</tr>
<tr>
<td>IGT net total score</td>
<td>-0.22</td>
<td>0.44</td>
<td>-0.18</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>KDDT Geomean k</td>
<td>0.01</td>
<td>0.98</td>
<td>0.17</td>
<td>0.47</td>
<td></td>
</tr>
</tbody>
</table>

** p<0.05
Figure 13

*Relationship between WCST % perseverative errors and cumulative cannabis exposure*

**Current Dependent Patients**

![Graph showing the relationship between WCST perseverative errors and joint years for current dependent patients.](image1)

$r = 0.44; p = 0.07$

**Former Dependent Patients**

![Graph showing the relationship between WCST perseverative errors and joint years for former dependent patients.](image2)

$r = -0.07; p = 0.78$
Figure 14

Relationship between Spatial Delayed Response (SDR; in mm) and cumulative cannabis exposure

**Current Dependent Patients**

$r = 0.61; p < 0.01$

**Former Dependent Patients**

$r = -0.18, p = 0.43$
Chapter 4: DISCUSSION

This main aim of this study was to facilitate a greater understanding of the modulatory role of cannabis use on cognitive function in individuals with schizophrenia. The literature examining this relationship is inconsistent, yielding contradictory findings likely due to variation in methodological design between studies and failure to control for potential confounding factors within studies. In the current study, we sought to address previous inconsistencies by employing stricter definitions of the cannabis-using and non-using groups, controlling for concurrent tobacco use and SUDs, and restricting analyses to male participants.

We interpret data to represent modest and limited effects of current and historical cannabis dependence on cognitive function. These data are consistent with prior meta-analytic reports (Rabin, Zakzanis et al. 2011) suggesting that lifetime cannabis use has nominal effects on neurocognitive function in schizophrenia. Specifically, when patients were characterized as a function of current cannabis status (CD vs NCD), no significant differences emerged on any of the cognitive tests assessed. Lifetime cannabis users (CD and FD) demonstrated better performance on tests of psychomotor speed than patients with no or minimal lifetime cannabis use and yielded a large effect size difference. Effects of historical cannabis use were exclusive to this cognitive domain.

Recent studies support this finding of better psychomotor speed in lifetime cannabis users (Yucel, Bora et al. 2010) (Coulston, Perdices et al. 2007; DeRosse, Kaplan et al. 2010; Yucel, Bora et al. 2010), others report no performance differences (Sevy, Burdick et al.
This finding provides evidence that patients with comorbid cannabis use characterize a clinically distinct subgroup of schizophrenia with better cognitive abilities than their non-using counterparts. Perhaps, cannabis use triggers the onset of psychosis in people who otherwise have good prognostic features such as premorbid adjustment and social skills. These patients may encompass lower vulnerability for schizophrenia compared to patients who developed the illness devoid of an additional trigger such as cannabis use (Schnell, Koethe et al. 2009). Hence, ND patients may have developed psychosis due to different aetiological processes, such as e.g. neurodevelopmental abnormalities, and thus represent a more severe subgroup of schizophrenia. Moreover, motor deficits in particular may constitute vulnerability markers of schizophrenia. This finding should be interpreted with caution as the ND group was one third less populated than lifetime users. Future research should focus on teasing apart these subgroups and establishing characteristics, other than cognitive performance, to distinguish between them.

While ND patients may be more compromised cognitively, one may still expect them to have less psychotic symptoms given that patients with cannabis users present with a more severe symptomatic profile (Caspari 1999; Grech, Van Os et al. 2005). Therefore the lack of observed PANSS score difference between the three groups is counterintuitive. Nonetheless this result is consistent with other studies comparing cannabis using and non-using patients (Jockers-Scherubl, Wolf et al. 2007; Mata, Rodriguez-Sanchez et al.

2007; Mata, Rodriguez-Sanchez et al. 2008; Schnell, Koethe et al. 2009), and no investigators observed deficient motor performance as a result of cannabis use.
2008; DeRosse, Kaplan et al. 2010). However, it is important to acknowledge that lack of statistical power could also account for this finding.

To our knowledge this is the first study to examine the relationship between cumulative exposure to cannabis (e.g., joint-years), and cognitive performance in both currently and formerly dependent patients. Patients with current cannabis dependence demonstrated robust relationship between years of daily cannabis use and cognitive function, in that increasing cumulative cannabis use was associated with poorer performance across various cognitive domains. In other words, poor cognitive function is directly associated with being in a current dependent state, and worsens with increasing years of daily cannabis use. The detrimental effects of cannabis were observed on cognitive domains such as attention, working and visuospatial memory, verbal learning and executive function; tests mediated by the prefrontal cortex, specifically the DLPFC and the hippocampus (Cohen, Semple et al. 1987; Berman, Ostrem et al. 1995; Williams and Goldman-Rakic 1995; Nagahama, Fukuyama et al. 1996; Goldman-Rakic 1999).

Interestingly, performance on tests of emotional cognition, namely the KDDT and IGT, revealed no association with cumulative cannabis use. These measures are thought to be more functionally dependent on the OFC and VmPFC respectively.

Both impulsivity and poor decision-making have been implicated as behavioural markers of the propensity to take addictive drugs (Kirby, Petry et al. 1999; Grant, Contoreggi et al. 2000). While these traits may have made cannabis-using patients more susceptible to initiate drug use, cumulative cannabis use in and of itself appears to have no further
compounding effect on theses cognitive processes. Further, if this explanation were true then conceivably by increasing power, group differences on IGT performance between lifetime cannabis users and ND patients should emerge. Data from Mata et al. (2008) support poorer total gambling performance in patients with cannabis abuse prior to the onset of psychosis as compared to non-abusers. Unfortunately, the question about the direction of causality between cannabis abuse and decision-making impairments cannot be answered from our results. No other study has explored the relationship between delay discounting and cannabis use in schizophrenia.

Unlike current dependent patients, relationships between cumulative cannabis exposure and cognitive performance were almost completely absent in former cannabis dependent patients. The only association that achieved significance was between joint years and CPT hit rate reaction time.

Previous studies that report superior cognitive performance among cannabis-using patients have proposed that cannabis may offer acute pharmacological benefits via prefrontal neural stimulation (Coulston, Perdices et al. 2007; Coulston, Perdices et al. 2007). Conversely, our data suggests that exogenous cannabinoids trigger further disruption to the already compromised cognitive function of patients with schizophrenia. Given that CB1 receptors are densely populated in the PFC and the hippocampus, the cannabinoid system plays an integral role in modulating prefrontal cortical neurotransmission (Herkenham 1991; Coulston, Perdices et al. 2011). Thus cannabis induced CB1R activation in the PFC may be, in part, responsible for the
dose-related impairment in prefrontal cortex-mediated tasks in our sample of currently dependent patients.

Cannabinoids have been shown to modulate DA PFC (Herkenham 1991; Yang, Seamans et al. 1999), and it has been suggested that long-term cannabis use potentiates a neurochemical deficit in the dopaminergic pathway (Verrico, Jentsch et al. 2003). Preclinical research suggests that chronic cannabinoid exposure can produce adaptive changes that lead to decreased DA release in the PFC, while preserving levels in other DA-rich areas (e.g., nucleus accumbens) (Verrico, Jentsch et al. 2003). Further these dopaminergic deficits were observed following an abstinence period of up to 14 days (Verrico, Jentsch et al. 2003). This PFC hypodopaminergic state has been thought to underlie cognitive disturbances in schizophrenia (Davis, Kahn et al. 1991). Additionally, imaging studies suggest that cannabis administration in long-term users is associated with decreased perfusion in the PFC (Lundqvist, Jonsson et al. 2001), both while cognitively engaged and at rest (Cohen, Solowij et al. 2008). Research findings suggest that frontal regional cerebral blood flow correlates positively with cognitive performance, therefore decreased prefrontal cerebral blood flow associates with poorer cognitive performance in schizophrenia (Hazlett, Buchsbaum et al. 2000). Further, stimulation of CB1 receptors may lead to nonspecific activation of the PFC, which may in turn disrupt normal signal processing leading to poor integration of cortical inputs (Pistis, Porcu et al. 2001).

Evidence for structural damage associated with cannabis use in schizophrenia is less clear and warrants further investigation (DeLisi 2008). While PFC dysfunction has been well
established in schizophrenia, at present there is still no clear overall mechanistic explanation for the compounded effects of cannabinoids in this brain region. Lastly, it is important to acknowledge that only DA pathways were considered here as their behavioural functions and relation to schizophrenia are more obvious than those of other neurotransmitters.

Given that cumulative cannabis use exclusively affects cognitive function in CD patients suggests that the negative effects of cannabis on cognition is a state, rather than a trait feature. These cannabinoid-induced alterations whether functionally or structurally mediated seem to be reversible or overcome with sufficient cannabis abstinence. This is very exciting and promising from a treatment perspective since cognitive deficits observed among patients with schizophrenia are notoriously difficult to remediate (Spaulding, Reed et al. 1996). Psychotherapeutic and pharmacological interventions should stress and exploit the timely manner in which cognitive deficits may be minimized as improving cognitive function will have a direct and substantial impact on functional outcome and prognosis. This information should be used as a focal point in motivating patients to relinquish their drug habit and achieve cannabis abstinence. Given that interview severity scores according to the ASI were significantly higher for current than former dependent patients implies that this may be a useful tool for clinicians to incorporate in their treatment plan to assess patient progress.

It is also important to comment on the genetic mediation of the relationship between cannabis use, psychosis and cognition, as this too contributes to reduced dopaminergic activity in the frontal lobes (Egan, Goldberg et al. 2001). The COMT gene is located on
chromosome 22q11 and codes for an enzyme that is essential for the metabolic
degradation of DA. Interestingly, the region of chromosome 22q11 that contains COMT
is also the site of a relatively common deletion syndrome that has been associated with
cognitive impairments and linked to schizophrenia (Scambler 2000). While widely
expressed in the human brain, the importance of COMT in DA clearance varies with
respect to brain region. Whereas little relevance of this enzyme has been observed in the
nucleus accumbens, pre-clinical research has confirmed the significance of COMT for
dopaminergic clearance in the PFC (Huotari, Santha et al. 2002; Tunbridge, Bannerman
et al. 2004). In 2005, Caspi et al demonstrated that a functional polymorphism involving
a Met to Val substitution at codon 158 altered DA breakdown by COMT in the synapse.
Two common variants of the enzyme Val and Met correspond to high and low activity,
respectively (Lotta, Vidgren et al. 1995). The increased activity associated with the Val
allele leads to a reduction of dopaminergic neurotransmission in the PFC and has been
associated with impairments in working memory, attention and executive functioning
(Egan, Goldberg et al. 2001; Goldberg, Egan et al. 2003; Henquet, Rosa et al. 2006).
Therefore any study examining the relation of cognitive function and cannabis use should
consider genetic variation and its influence on brain neurochemistry.

It may seem contradictory to have a lack of between group effects coexist with robust
within group differences. This incongruence may be attributed to low power, a result of
our small sample size, especially when examining differences across 3 subgroups.
Additionally the large variance observed within each subgroup may have obscured any
cognitive difference that existed in the data and reduced the likelihood of achieving
significance.

The observation of a within-subject detrimental effect of cannabis does not negate the theory of drug-using patients belonging to a subgroup of schizophrenia. In view of this, cannabis-using patients who then achieve abstinence may then demonstrate improved cognitive performance. Thus, while our results lend support for the state-related effects of cannabis on cognitive function, we cannot rule out that lifetime cannabis users as a whole encompass better cognitive function.

Further research is warranted to determine whether patients with schizophrenia derive any benefit from cannabis on cognitive function as cannabis may have differential effects on a vulnerable schizophrenia brain as compared to a healthy brain. There is evidence to suggest that cannabis has neuroprotective effects on the brain (Sarne and Mechoulam 2005) which may serve to counteract a putative neurotoxic process related to the illness (Jockers-Scherubl, Wolf et al. 2007; Potvin, Joyal et al. 2008). Given that cognitive dysfunction in schizophrenia is associated with reduced blood flow, metabolic processes, and neurotransmission in the PFC (Velakoulis and Pantelis 1996; Kim, Mohamed et al. 2000; Vance, Velakouls et al. 2000), and cannabinoids mediate increases in prefrontal neurotransmission (Jentsch, Andrusiak et al. 1997; Acquas, Pisanu et al. 2001; Pistis, Ferraro et al. 2002), may provide an account for the observable enhancements in cognitive function in these patients. Research supporting the favourable action of cannabis may lead to pharmacological interventions that can be tailored to enhance the cognitive functioning of special populations. Whether it be adjunctive medication added
to already prescribed antipsychotics, or new drug candidates altogether, the endocannabinoid system, its neural circuits and pathways may potentially hold promise for the treatment and remediation of cognitive impairment in schizophrenia.

4.1 Limitations

These results should be interpreted in light of several limitations. This study employed a cross-sectional methodological design, which poses a challenge and limits the interpretation of findings.

While exploratory in nature, partitioning the NCD group into FD and ND samples yielded small patient subsamples and low power may be responsible for failure to detect between group differences. Further, lack of a control group prevents establishing whether the cognitive performance of our patient sample was indeed impaired compared to that normal controls. Additionally, not having a healthy and cannabis using control group limits the generalizability of the study.

While exclusion of women from this study also limits generalizability of the findings, it is also an acknowledgment of the clear sex differences present in this comorbid population. Thus it only seemed fitting to restrict the study sample to men. The literature substantiates why this may be the case. There is overwhelming evidence in the general population that males are more prone to substance use disorders than are females (Smith 1989). It has also been suggested that cannabis use may cause a psychotic disorder that would not have occurred in the absence of its use (Hall, Degenhardt et al. 2004).
Further, results from a study by Veen et al. (2004) indicate a strong association between cannabis and earlier age at first psychotic episode in male schizophrenia patients. Taken together, these findings help elucidate the difficulties in recruiting female patients with current cannabis dependence.

While we attempted to control for nicotine, our ND subjects smoked more cigarettes per day than both CD and FD patients. This was surprising given that previous research has established that patients with comorbid SUDs were more likely to smoke cigarettes compared to those patients with a single diagnosis (Margolese, Malchy et al. 2004). While higher smoking rates in concurrently diagnosed patients may be true of most drugs of abuse, cannabis may be the exception. Support for this stems from the hypothesis proposed by researchers that have observed better cognition amongst lifetime cannabis users compared to nonusers (Jockers-Scherubl, Wolf et al. 2007; Schnell, Koethe et al. 2009). They concluded that perhaps cannabis increases the risk for developing psychosis, thereby facilitating the transition to psychosis that might otherwise not have occurred. That is, early cannabis use may induce psychosis onset in less cognitively vulnerable individuals. Thus, patients with minimal or no lifetime cannabis use may be more cognitively impaired than those with lifetime cannabis use. Evidence that nicotine ameliorates cognitive deficits associated with schizophrenia (Sacco, Termine et al. 2005; George 2007) may explain why higher co-morbid rates of smoking appear among these patient subtypes.

No reliable information exists about the concentration of THC and other cannabinoids in
commonly used cannabis products. Oral THC has been reported to impair several aspects of cognitive function in a dose-dependent fashion in healthy individuals, deficits in memory seems to be the most consistent finding (Curran, Brignell et al. 2002; D'Souza, Perry et al. 2004). This effect has also been demonstrated in patients with schizophrenia (D'Souza, Abi-Saab et al. 2005). Further, as previously discussed, cannabis is a composite of many cannabinoid compounds, some with differing neuropharmacological effects and the ratio of cannabis’ constituents serves to further complicate the investigation of the effects of cannabis on cognition. THC and cannabidiol have divergent properties and to further complicate matters, the effects of THC may be modulated by CBD (Bornheim, Kim et al. 1995). A study by Morgan et al demonstrated that people who smoke different strains of cannabis (i.e. variations in THC: CBD ratios) manifest different psychological symptomatology (Morgan and Curran 2008). But as with THC, the CBD content of cannabis varies greatly, with some samples of cannabis being completely devoid of CBD (Pitts, Neal et al. 1992). Therefore the specific chemical make-up of cannabis presents scientists with another source of variation that is difficult to control in this area of research.

4.2 Future Directions

Future studies ascertaining the effects of cannabis on cognition in schizophrenia are warranted. This study highlights the need for employing the appropriate paradigm in which to investigate these effects. Between-group analysis in our study did not appear sensitive enough to illustrate the detrimental effects of cannabis. Increasing the sample size may overcome this barrier. 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 the sample size. Therefore future studies should adopt longitudinal designs, using within-subjects paradigms to examine the effects of cannabis on cognition in this population. Researchers ought to examine the ensuing cognitive performance in current dependent patients who achieve drug abstinence. This will help delineate the time course of when cannabis exerts a change in cognitive function or alternatively if cognitive performance remains stable over time with abstinence. Given that our results suggest that former dependent patients may recover from cognitive impairment associated with cumulative cannabis use, it would be of importance to clarify at what time point and at what rate recovery occurs.

Further, by employing a within-subjects paradigm we overcome the confounding factor of genetic heterogeneity between participants. Given that COMT is important in regulating PFC DA, and DA has been shown to be a key factor in PFC-mediated cognition, genotyping these individuals is of essence to determine the role of allelic variation in this realm of research. Elucidating the effects of genetic variation may provide clues to the exact neurobiological mechanisms underlying cannabis-induced cognitive impairment (Egerton et al., 2006).
4.3 Conclusions

Given that lifetime users demonstrated better performance in tests assessing speed of processing combined with the observation that ND patients have higher smoking consumption supports the notion that drug-users belong to a subgroup of schizophrenia. Importantly, this does not imply that cannabis improves cognition in schizophrenia, but simply the opposite. Cannabis indeed impairs cognitive function in schizophrenia, in that more cumulative exposure is directly related to the level of impairment in prefrontal-mediated tasks in patients who present with current dependence. The finding that robust relationships between cognitive performance and cumulative cannabis exposure exist exclusively in current dependent patients is of clinical relevance and has profound treatment implications. The high prevalence of cannabis use among patients with schizophrenia highlights the need for further research investigating the relationship between cannabis use and cognition in this population. Given that cognitive impairment in schizophrenia is so tightly linked to functional outcomes, provides clinicians with optimal treatment targets in which to drive their clients to best possible clinical outcome.
Literature Cited:


George, T. P., J. C. Vesciochio, et al. (2002). "Effects of smoking abstinence on visuospatial working memory function in schizophrenia."

Neuropsychopharmacology 26(1): 75-85.


Appendix

Appendix A: Study Information and Consent Form

Effects of Cannabis Dependence on Cognitive Functioning in Schizophrenia

Investigators
Tony George, MD, FRCPC  416-535-8501 x 4544
Rachel Rabin BSc  416-535-8501 x 6115
Ofer Agid, MD
Crystal Baluyut, MD
Diana Blank, MD

Study Purpose: The primary objective of this study is to compare neurocognitive performance in schizophrenia with or without co-morbid cannabis dependence. Second, we will examine the interactive effects of co-morbid cannabis dependence and schizophrenia on positive and negative symptoms and outcomes. Three groups of subjects will be studied: 1) Subjects with schizophrenia and current cannabis dependence; 2) Subjects with schizophrenia with historical cannabis dependence; 3) Subjects with schizophrenia with no history of cannabis use (< 5 lifetime use). You are being asked to participate in this study because we think you may meet criteria for one of these groups.

Procedures: You are being asked to provide informed consent. After reading through this form, you will be given a chance to ask questions. You will be asked to provide details of your medical history and smoking behaviour via questionnaires and undergo a psychiatric assessment/interview with one of our research staff. 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. A urine drug screen and carbon monoxide indicator will be used to check for the presence of substances in your system. You will complete tasks that include both “paper-and-pencil” and computerized measures of memory, attention, and concentration. All study procedures will be completed via a telephone screen and two on-site sessions (approximately 2-3.5 hours each) at Dr. George’s lab at the Centre for Addiction & Mental Health (1st floor, 33 Russell Street, Toronto, ON).

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 using marijuana in individuals with schizophrenia.

Risks: There are no risks associated with the completion of the questionnaires and tasks; however, you might feel slight fatigue during the testing sessions.
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 adversely affect your ability to receive treatment at CAMH.

Study Provisions: You will be compensated $10.00/hr for completing the study. The study is expected to take about 5 hours, so if you finish the study, you will receive a minimum of $50. If you do not complete both sessions, payment will be based on a pro-rated scale (directly related to the number of hours you complete). Study staff/investigators may, at their discretion, end your participation in this study at any time.

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 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.

Contacts:
If you have any further questions or desire further information about this study, you may contact Rachel Rabin at 416-535-8501 x6115. 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 (x6876).
AGREEMENT TO PARTICIPATE

I, ___________________________________ have read (or had read to me) the information form for the study named *Effects of Cannabis Dependence on Cognitive Functioning 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 Dependence on Cognitive Functioning Schizophrenia*).
Participant’s Initials: ___

Participant Name: ____________________________  Person who conducted informed consent discussion: ____________________________

Print name ____________________________  Print name ____________________________

Signature of Participant ____________________________  Signature of Witness ____________________________

Date: ____________________________ ____________________________
Appendix C: Age and IQ-adjusted correlations between cognition and cumulative cannabis use in current cannabis dependent patients

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<th>Cognitive Test</th>
<th>subtest</th>
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