LONG TERM COGNITIVE SEQUELAE OF ADOLESCENT CANNABIS USE IN INDIVIDUALS WITH PSYCHOSIS

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DEDICATION

I would like to thank the members of my Graduate Committee and my mother, Dolly Miller, for all of their support.

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by

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THESIS

Presented to the Faculty of the School of Health Professions

The University of Texas Southwestern Medical Center

Dallas, Texas

In Partial Fulfillment of the Requirements

For the Degree of

MASTER OF REHABILITATION COUNSELING

Abstract

BACKGROUND: Cognitive deficits are well established in schizophrenia and there is evidence of an association between adolescent cannabis use and cognitive function in schizophrenia. This study examined the relationship between age of cannabis use and cognition in individuals within the psychosis domain, including those with schizophrenia, schizoaffective disorder and bipolar disorder with psychosis.

SUBJECTS: Archival data from the University of Texas Southwestern Medical Center (UTSW) site of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Participants included probands with schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, and healthy controls with and without a history of cannabis use.

METHOD: The psychosis (N=97) and control (N=64) groups were divided into six groups: control with no cannabis use (CCB-; N=38), control with adolescent cannabis use (CCB+; N=16), control with late cannabis use (N=10), psychosis with no cannabis use (PCB-; N=48), psychosis with adolescent cannabis use (PCB+; N=33), and psychosis with late cannabis use (N=16). All participants completed the Brief Assessment of Cognition in Schizophrenia (BACS) neuropsychological battery, the Birchwood Social Functioning Scale, Structured Clinical Interview for DSM-IV diagnosis, Positive and Negative Symptom Scale, as well as a detailed record of patterns of substance use including age of onset, period and frequency of greatest consumption, and most recent use.

RESULTS: Regarding cognitive function, this thesis found that age of cannabis use impacted the BACS total score. Specifically, the control and psychosis adolescent cannabis use groups

were not significantly different in cognitive functioning. PCB+ performed better than the other psychosis groups, and CCB+ performed worse than the other control groups. Additionally, PCB+ and PCB- were significantly different, with the PCB+ performing better cognitively. DISCUSSION: There is previous evidence suggesting that individuals with schizophrenia and adolescent cannabis have less neuropsychological impairment compared to individuals with schizophrenia who do not have a cannabis use history. In this thesis, we extended these findings to psychosis as a spectrum, finding that individuals with psychosis and adolescent cannabis use had better overall cognition as measured by a brief neurocognitive test battery compared to those with psychosis and no cannabis use history.

Keywords: adolescent, adult, cannabis, humans, marijuana abuse/ complications, psychotic disorders.

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LIST OF ABBREVIATIONS

ACU: Adolescent cannabis use

CB: Cannabis

LCU: Late-onset cannabis use

PCB+: Patients with psychosis and adolescent cannabis use

PCB-: Patients with psychosis and no adolescent cannabis use

CCB-: Controls with no cannabis use

CCB+: Controls with adolescent cannabis use

BACS: Brief Assessment of Cognition in Schizophrenia

SFS: Social Functioning Scale

CHAPTER ONE

Introduction

Is cannabis a risk factor for schizophrenia?

Psychotic disorders are brain-based neuropsychiatric illnesses of which schizophrenia is the prototype. Individuals with schizophrenia may have different brain development patterns that lead to both structural and functional abnormalities. Neuroimaging studies have indicated that there are subtle decreases in gray matter volume and abnormal connectivity in the brains of those with schizophrenia (Pantelis et al., 2005). Cognitive deficits are a core feature of schizophrenia, manifesting in more than 80% of patients (R. S. Keefe, Eesley, & Poe, 2005). Neuropsychological studies have indicated that memory, attention, and executive functioning are most often the main areas affected by schizophrenia. The etiology of schizophrenia and psychotic disorders in general is unknown, although there is substantial evidence that genetic and environmental factors play a role in the development of schizophrenia. Genetic studies have indicated several genes are associated with an increased risk of developing schizophrenia, but they do not directly cause it. Additionally, there have been a multitude of environmental factors such as obstetric complications (Dalman, Allebeck, Cullberg, Grunewald, & Koster, 1999), maternal influenza (Brown et al., 2004), and social class (Kohn, 1976) that have been suggested to contribute to the development of schizophrenia.

Cannabis use during adolescence is one environmental factor implicated in the development of schizophrenia as suggested by several epidemiologic studies that report an association between adolescent cannabis use and schizophrenia. Cannabis appears to be a risk

factor for some individuals, which may interact with other risk factors in the development of psychosis. However, because the cause(s) of psychosis is/are not known, exploration of potential component factors is important. Research that looks at this association includes: anecdotal accounts, survey studies of cannabis users, epidemiological studies, and pharmacological studies.

Association between cannabis use and neuropsychological performance.

Recent research has indicated that individuals with schizophrenia and adolescent cannabis use history (SCB+) have been shown to exhibit different neuropsychological profiles compared to affected individuals with no cannabis use history. Specifically, SCB+ individuals have shown better performance on certain neuropsychological tasks when compared to SCB-, including visual measures of declarative memory, attention, and processing speed; however, the most consistent findings have been in executive functioning and working memory (Jockers-Scherubl, 2007; Leeson, Harrison, Ron, Barnes, & Joyce, 2012; Loberg & Hugdahl, 2009; Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009; Stirling, Lewis, Hopkins, & White, 2005; Yucel et al., 2012). Theories, such as cannabis having a protective influence on cognition in schizophrenia, have been offered to explain this unexpected finding (Loberg & Hugdahl, 2009). However, the literature does not support this theory or any other theory at this time. In regards to this paradoxical finding, it is not known whether cannabis use is associated with unique cognitive deficits in people with psychosis in general, or whether this is specific to schizophrenia. Therefore, it would be valuable to research the cognitive functioning of people with psychosis in general as it may relate to a history of adolescent cannabis use and potentially allow better characterization of these individuals and define their treatment needs.

Psychosis as a domain. The psychosis spectrum includes schizophrenia, schizoaffective disorder, and bipolar disorder. Phenotypic and neuroimaging research studies have endeavored to find similarities in clinical features and brain structure among these different types of psychotic disorders (Keshavan et al., 2011). Additionally, genetic studies have attempted to find biomarkers that link or separate the psychotic disorders. However, conclusive biological data to link or separate diagnoses has not been found. The clinical diagnostic criteria (i.e., DSM-IV, DSM-V) for the psychotic disorders are based solely on clinical symptoms. Therefore, the research that suggests that cannabis may be a component cause of schizophrenia can be expanded by replicating and extending the association to psychosis as a spectrum rather than separating out the various psychotic disorders.

One of the ways that research on the risk association between cannabis and psychosis has been limited is that the studies have only included participants with a diagnosis of schizophrenia. Clinicians and researchers have been using the Kraepelinian dichotomy (i.e., schizophrenia or bipolar disorder) to diagnose patients for over a century (Craddock & Owen, 2010). However, there is a considerable number of patients with psychotic symptoms that do not fit neatly into these two categories (Keshavan et al., 2011). Schizoaffective disorder, for example, involves significant mood symptoms, but also psychotic symptoms that are too prominent for a bipolar diagnosis. Clinicians typically diagnose patients that do not fit into the Kraepelinian dichotomy as *schizoaffective* and therefore create a dimensional concept indirectly. However, basic characteristics of the disorder are poorly defined and reliability is low for schizoaffective disorder as defined by DSM IV (Kane, 2010). Diagnoses of schizophrenia, schizoaffective

disorder, and bipolar disorder tend to overlap because there is no clear discontinuity between the disorders (Keshavan et al., 2011). Therefore, there appears to be a dimensional, rather than categorical distribution of psychotic and mood symptoms. Additionally, family studies and genome-wide association studies have illustrated that schizophrenia and bipolar disorder have overlapping genes and share genetic vulnerabilities (Craddock & Owen, 2010; Ivleva, Thaker, & Tamminga, 2008). Because these three disorders overlap genetically and clinically, it is beneficial to replicate the reported association between cannabis use and schizophrenia using the three disorders as a psychosis spectrum. Using the dimensional approach, the research can be expanded to include an investigation of cognitive and social functioning.

Specific Aims. The goal of this study was to determine if adolescent cannabis use is associated with cognitive function in individuals with a psychotic disorder. Thus, we proposed to extend the demonstrated association between adolescent cannabis use and cognitive function in schizophrenia to the domain of psychosis. Using archival data of participants with various well-characterized psychotic disorders, including schizophrenia, bipolar disorder with psychosis, and schizoaffective disorder, the association between adolescent cannabis use and cognitive deficits and social functioning later in life was explored. It was hypothesized that those with psychosis who have a history of adolescent cannabis use (PCB+) would perform better cognitively than patients with psychosis and no adolescent cannabis use (PCB-). Additionally, it was predicted that the PCB+ group would perform better on measures of social functioning. Finally, it was predicted that indices of cognitive functioning and social functioning would have a stronger correlation in the PCB+ group.

CHAPTER TWO

Review of the Literature

Cannabis

Cannabis is the third most commonly used recreational drug, following closely behind alcohol and tobacco. Research on the make up of cannabis has found Delta 9-tetrahydrocannabinol (THC) to be the major psychoactive drug in cannabis. Psychological effects of THC are elicited by stimulating the cannabinoid 1 receptor (CB1) in the brain (Murray, Morrison, Henquet, & Di Forti, 2007). The ability of cannabis to induce paranoia was first noted in 1845 by French psychiatrist Moreau de Tours. He was a user of cannabis who also studied the effects of cannabis on his students. He noted "acute psychotic reactions, generally lasting but a few hours, but occasionally as long as a week" (Moreau, 1973). While the acute effects of cannabis have been widely noted, there are additional long-term effects that can have significant impact on otherwise healthy controls.

Long-term effects of cannabis on otherwise healthy individuals. Long-term cannabis use has been associated with cognitive impairments in a variety of investigations, although there is disagreement regarding how long the deleterious effects can last. Meier et al. (2012) conducted a 38-year follow up study using the 1,037 participants from the Dunedin Longitudinal Study. Participants were followed from birth to age 38 and information on cannabis use was ascertained through interviews at ages 18, 21, 26, 32, and 38. Baseline neuropsychological testing was conducted at age 13, before cannabis use had been initiated, and follow up neuropsychological testing was conducted at age 38. The investigators found that persistent

cannabis use was associated with broad cognitive declines, affecting multiple domains of neurocognitive functioning. Furthermore, participants with adolescent onset of cannabis use had cognitive deficits that persisted more than a year after cessation of cannabis use (Meier et al., 2012). Results suggested that persistent use of cannabis that is initiated while the brain is still developing might have a broad lasting impact on cognition even after cessation of cannabis use.

Lyons et al. (2004) conducted a study examining the long-term effects of cannabis use by evaluating 54 monozygotic twins discordant for history of cannabis use. Neurocognitive testing was conducted a minimum of one year after cessation of cannabis use, but the mean of abstinence was 20 years. The investigators found that across a comprehensive test battery that included 50 different measures, only one test of perceptual reasoning was found to be significantly different between the twin-pairs, with the CB+ twin performing worse. In contrast to the Meier et al. (2012) investigation, this study suggests that the cognitive effects of cannabis do not last for extended periods of time after abstinence. However, part of the discrepancy in findings may be due to the age that drug use was initiated. For example, Pope et al. (2003) examined 122 long-term heavy cannabis users and 87 subjects with minimal cannabis exposure. All subjects underwent a 28-day abstinence from cannabis and were evaluated at the end of the 28 days with a battery of 10 neuropsychological tests assessing verbal and visuospatial memory, attention, and executive functions. Neurocognitive functioning of early onset users, late onset users, and controls was compared, with results showing that long-term cannabis users had a lower verbal IQ than the control group. However, this effect was limited to subjects who started using before the age of 17; those that initiated cannabis use after adolescence did not show an

affected IQ (Pope et al., 2003). Similarly, in a nonhuman animal study, O'Shea, Singh, McGregor, and Mallet (2004) found lasting memory impairment in adolescent rats exposed to a cannabinoid receptor (CB1) agonist, but no such effect was seen in adult rats that were exposed to the same CB1 agonist. Since the brain is still developing in adolescence, it is possible that cannabis can have its strongest effects on cognitive function during this time.

Psychotic disorders and symptoms. Previous research has studied cannabis' ability to induce psychotic *symptoms* as well as the more severe implications of cannabis inducing psychotic *disorders*. Psychotic symptoms can occur without the presence of a full-blown psychotic disorder. For schizophrenia to be diagnosed, the DSM-IV requires that two or more of the following symptoms be present: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. These must also be accompanied by social or occupational dysfunction and these symptoms must persist for at least 6 months. Symptoms cannot be due to schizoaffective disorder, which we will address shortly or be due to a substance or general medical condition. For schizoaffective disorder to be diagnosed, the DSM-IV states that it must be "an uninterrupted period of illness during which, at some time, there is either a Major Depressive Episode, a Manic Episode, or a Mixed Episode concurrent with symptoms that meet Criterion A for Schizophrenia," which includes delusions, hallucinations, disorganized speech, etc. Schizoaffective disorder can be bipolar type or depressive type. In both schizophrenia and schizoaffective disorder there are positive and negative symptoms. Positive symptoms are symptoms that are "added" by the disorder, like hallucinations, delusions, a thought disorder, or paranoia. Negative symptoms are things that are

"taken away" by the disorder, like social withdrawal, blunted affect, or decreased motivation. While the DSM-IV attempts to clearly define these disorders, there is still overlap in psychotic symptoms. Therefore, it is valuable to include study participants that meet criteria for both of these disorders in research that endeavors to understand psychosis.

Cannabis and psychotic symptoms. The acute effects of cannabis are readily observable, and various studies have been conducted to look at cannabis-induced psychotic symptoms. Mayor's C (as cited in D'Souza, Sewell, & Ranganathan, 2009) conducted one of the earliest studies in 1944 on cannabis in prisoners, wherein 12.5 % of the participants experienced psychotic reactions. In 2004, D'Souza and colleagues conducted a double-blind study with 22 healthy controls, noting that THC produced positive symptoms, negative symptoms, euphoria, anxiety, and working memory problems (D'Souza et al., 2004). While the acute effects of cannabis have been well documented, less is known about the potential long-term connections between cannabis history and a full-blown psychotic disorder.

Cannabis and psychotic disorders. Many researchers have hypothesized that cannabis is likely a component cause of psychotic disorders that interacts with other risk factors (Andreasson, Allebeck, Engstrom, & Rydberg, 1987; Arseneault et al., 2002; van Os et al., 2002; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). It is not implied that cannabis is a direct cause, nor a necessary factor for psychosis to develop. However, since the cause of psychosis remains unknown, all potential component risk factors are important. Research that looks at the risk association of cannabis and psychotic disorders includes: anecdotal accounts, survey studies of cannabis users, epidemiological studies, and pharmacological studies.

Andreasson, Allebeck, Engstrom, and Rydberg (1987) conducted a large Swedish study of 45,570 males ages 18-20. The investigators utilized the population going into the military as study participants, obtaining self-reports of cannabis use as they enlisted. They compared these self-reports with schizophrenia incidence over the next 15 years and found a dose-response relationship. Specifically, those that used cannabis more then 50 times were 6 times more likely to be hospitalized for schizophrenia. Zammit, Allebeck, Andreasson, and Lundberg (2002) conducted a follow up on Andreasson's Swedish participants and found that heavy cannabis users were 6.7 times more likely to develop schizophrenia in the 27 years after the original baseline analysis. Results remained significant after controlling for potential confounding factors like IQ, SES, stimulant use, etc. Additionally, Zammit et al. excluded incidents of schizophrenia that developed in the following 5 years after the baseline assessment to control for those that were already developing psychosis before the cannabis use.

Arseneault et al. (2002) followed a population of 1,037 people from New Zealand from birth to 26 and found a higher risk for schizophrenia in cannabis users. The researchers obtained self-report cannabis use at 15 and 18 years old. Self-reported psychotic symptoms were obtained at age 11 to control for those that were already developing psychosis before the cannabis use. Van Os et al. (2002) studied 59 participants with psychosis and 4,045 without psychosis in the Netherlands. Those that used cannabis were 3 times more likely to manifest psychotic symptoms. A dose response was seen in which the more cannabis that was used, the higher the risk of psychotic symptoms. Those already with psychotic disorders were more likely to have it develop into full-blown schizophrenia if they used cannabis.

A recent meta-analysis of 35 studies found a 40% risk increase for psychosis in cannabis users, with the level of risk rising in a dose-response manner. As a result of the review, the authors suggested that cannabis might be responsible for triggering 8%-14% of cases of schizophrenia (Moore et al., 2007). However, because there is no single cause of schizophrenia, it is possible that cannabis was the proverbial "straw that broke the camel's back" in the 8%-14% of cases as Moore et al. suggested, i.e., that individuals at risk for psychosis may be particularly susceptible to the deleterious effects of cannabis. Along these lines, Arendt, Mortensen, Rosenberg, Pedersen, and Waltoft (2008) studied a group of subjects at risk for psychosis, which were identified as individuals with a history of psychiatric treatment in a first degree relative. Results suggested that cannabis-induced psychotic symptoms mainly occurred in those already at risk for psychosis. Additionally, Kristensen and Candenhead (2007) found that those already at risk for schizophrenia, as defined by CARE (Cognitive Assessment and Risk Evaluation) criteria (Seeber and Cadenhead, 2005), who used cannabis were 10 times more likely to manifest psychosis.

Henquet et al. (2005) addressed the idea of the "chicken and the egg" with a study of cannabis use in 2,437 14-24 year old participants at risk and not at risk for psychosis followed for 4 years. They also found a dose-response, with more frequent cannabis use associated with a higher risk for psychosis. However the converse was not seen, i.e., risk for psychosis was not found to be a predictor of future cannabis use. Therefore, results suggested that cannabis was a risk factor for psychotic disorders, rather than psychotic disorders being a risk factor for future cannabis use.

The effect of cannabis on an already psychotic population has also been of empirical interest. Corcoran et al. (2008) found that cannabis made symptoms much worse in already psychotic patients, and the effects of cannabis have become more pronounced over the years. Di Forti found a dose-response to THC levels; therefore as common cannabis starts to have more THC in it, the risk for developing psychosis increases (Di Forti et al., 2009). The change in THC levels could explain why there was not a significant outbreak of psychosis in the 1960's and 70's.

Schizophrenia and cognitive deficits. Cognitive deficits are a core feature of schizophrenia, manifesting in more than 80% of patients, although some investigations have reported larger percentages of patients to fall within normal limits (Bryson, Silverstein, Nathan, & Stephen, 1993; Palmer et al., 1997). For example, based on their research, Palmer estimated 27% and Bryson estimated 55% of those with schizophrenia were free of cognitive deficits. Some such estimates may not take into account premorbid cognitive functioning, however. That is, it is possible that patients with schizophrenia suffer a decline in cognitive functioning compared to their "expected" level of functioning if they had not developed schizophrenia, even if they maintain a "normal" level of cognitive functioning compared to standardized norms. This concept was illustrated by a monozygotic twin study, which found that the affected twin performed worse on multiple cognitive domains than the unaffected twin (Goldberg et al., 1990). Thus, it may be useful to include measures of estimated premorbid intelligence to identify current vs. expected level of cognitive functioning (R. S. Keefe et al., 2005; Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000). Given this method of defining cognitive decline, it is

estimated that as high as 98% of those with schizophrenia experience cognitive decline (R. S. Keefe et al., 2005).

Neuropsychological studies have indicated that memory, attention, and executive functioning are the main cognitive areas affected by schizophrenia. Weickert et al. (2000) administered a detailed neuropsychological battery to 117 patients with schizophrenia and 27 healthy controls. A reading measure was administered to estimate premorbid IQ, and current IQ was also assessed. It was found that while IQ decline was variable in schizophrenia, executive functioning and attention deficits appeared to be a core feature of schizophrenia.

While certain cognitive deficits may be a core feature of schizophrenia, introducing cannabis use into the equation has elicited interesting findings. The most significant findings have been that participants with schizophrenia and adolescent cannabis use actually have better cognitive functioning than those without adolescent cannabis use (Jockers-Scherubl, 2007; Lesson, Harrison, Ron, Barnes, & Joyce, 2012; Loberg & Hugdahl, 2009; Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009; Stirling, Lewis, Hopkins, & White, 2005; Yucel et al., 2012).

Schizophrenia and social functioning. Social functioning deficits are a prominent factor of schizophrenia (Couture, Penn, & Roberts, 2006). In fact, it has been noted that poor social functioning can be more devastating to patients in terms of overall adjustment than the positive symptoms of schizophrenia (Addington, 2008). Social withdrawal in people with schizophrenia is hypothesized to be predominantly due to negative symptoms of schizophrenia. Negative symptoms include 1) anhedonia, a condition involving an inability to experience pleasure from

normally enjoyable acts, 2) avolition: a lack of general motivation, 3) asociability, 4) a lack of emotional reactivity, 5) blunted affect, and 6) alogia: poverty of speech (Milev, Ho, Arndt, & Andreasen, 2005). While cognitive as well as social functioning deficits have been recognized in schizophrenia, the relationship between the two has not been thoroughly examined.

In summary, there is a substantial body of evidence suggesting that adolescent cannabis use may be associated with an increased risk of schizophrenia. Further, these individuals appear to have specific neuropsychological function when compared to individuals with schizophrenia who do not have a cannabis use history. In this thesis, we will determine if this association between adolescent cannabis use cognition extends beyond the schizophrenia diagnosis to all individuals with psychosis.

CHAPTER THREE

Method

Hypotheses

Hypothesis 1: It was predicted that subjects with psychosis who have a history of adolescent cannabis use (PCB+) would obtain higher scores on the global composite score from a brief neurocognitive test battery [i.e., the Brief Assessment of Cognition in Schizophrenia, (BACS)] when compared to subjects with psychosis and no adolescent cannabis use (PCB-).

Hypothesis 2: PCB+ subjects would perform better in terms of social functioning as indicated by total scores on the Social Functioning Scale (SFS), a self-report measure.

Subjects. This study used archival data from the University of Texas Southwestern Medical Center (UTSW) site of the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. The study was approved by the Institutional Review Board at UTSW. Written informed consent was obtained from all subjects after a detailed explanation of experimental procedures.

Individuals with schizophrenia, schizoaffective disorder, bipolar disorder with psychotic features, and healthy controls were included. Patient volunteers were recruited from the local Dallas-Fort Worth metropolitan area, referred from inpatient units and outpatient clinics at UTSW Medical Center, Parkland Memorial Hospital, the Dallas Veteran's Administration Medical Center, and community outpatient clinics. Additionally, participants were recruited from the local National Alliance on Mental Illness (NAMI) chapter and through advertisements in a local newspaper. Patient volunteers were eligible if they were between 15 and 65 years old,

had a DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder with psychotic features and were medically stable. Healthy volunteers met inclusion criteria if they were in the same age range and had no psychiatric illness themselves or in their immediate family. All subjects provided sufficient information on substance use history to allow characterization of subjects by onset of cannabis use. All subjects must have completed cognitive testing for study inclusion. Exclusion criteria for both groups were (1) neurologic disorder, including history of seizures, head injury with loss of consciousness over 30 minutes, encephalopathy, and neurological malignancy; (2) intellectual disability; (3) diagnosis of DSM-IV substance abuse within the past month, substance dependence (excluding nicotine) within the past 3 months, or an extensive history of substance dependence[1]; (4) unstable medical illness; (5) positive urine drug screen for illicit substance, and (6) the inability to read and speak English.

Subjects were divided by diagnosis (psychosis vs. controls) and cannabis use history. Non-users of cannabis (CB-) were defined as having used CB on less than five occasions during their lifetime, Adolescent-onset CB use (ACU), defined as use that began before 18 years old, and Late-onset CB use (LCU) beginning at or after age 18.

Procedures. Subjects participated in a clinical diagnostic interview as well as the following: Structured Clinical Interview for DSM-IV diagnosis (SCID I), Positive and Negative Symptom Scale (PANSS), and Birchwood Social Functioning Scale (SFS) (Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990). In addition to the substance abuse module of the SCID,

[1] An extensive history of substance dependence was defined as a past history of severe substance dependence that could cause detrimental effects on CNS function. This was determined by three independent clinicians during the diagnostic consensus procedure.

a detailed record of patterns of substance use including age of onset, period and frequency of greatest consumption, and most recent use, were collected. As noted, information about CB use history determined the subject's group assignment. Subjects were considered to have significant non-cannabis substance use if they used illicit drugs other than CB on more than four occasions or met DSM-IV criteria for an alcohol use disorder (Meier et al., 2012; Jockers- Scherubl et al., 2007).

Cognitive testing was comprised of the Wide Range Achievement Test-Fourth Edition (WRAT-4) Reading subtest, which is considered an estimate of premorbid IQ (Gladsjo, Heaton, Palmer, Taylor, & Jeste, 1999) and the Brief Assessment of Cognitive Function in Schizophrenia (BACS). The BACS is a brief assessment (i.e., 30-35 minutes) that has good reliability and sensitivity to cognitive deficits (Keefe et al., 2004). The BACS includes six subtests: Verbal memory (word list learning), Working memory (digit sequencing task), Motor speed (token motor task), Verbal fluency (category fluency and controlled oral word association test), Attention and speed of processing (symbol coding), and Executive function (Tower of London). Social functioning was assessed using the Social Functioning Scale (SFS), a self-report questionnaire that has good psychometric properties and was developed to be used with an outpatient schizophrenic population (Birchwood et al., 1990). The SFS has a total score (range = 80-170) and 7 sub-scores that tap into Withdrawal/social engagement, Interpersonal communication, Independence-performance, Independence-competence, Recreation, Prosocial, and Employment/Occupation.

Statistical analysis. Demographic data was compared using Analysis of Variance (ANOVA) for continuous variables, and χ^2 for categorical variables. Analysis of Covariance (ANCOVA) with 2-by-3 factorial design (Diagnosis [Psychosis vs. Con] x CB [CB- vs. ACU vs. LCU]) was used for the BACS composite score, reported as an age- and gender-corrected z-score. Exploratory analyses of the BACS domain scores between groups were determined using t-tests. Continuous demographic variables that correlated with the primary outcome for either diagnostic group (Psychosis or Control), and also categorical variables that differed across groups, were evaluated for inclusion as covariates. The significance level was set at $p<0.05$. All analyses were performed in Statistica (Statsoft, Inc, version 9.1).

CHAPTER FOUR

Results

Demographics

A total of 161 participants met study criteria out of the 264 controls and probands at the Dallas site. The psychosis group consisted of 97 individuals and the control group had 64 individuals. The sociodemographic variables of the two broad diagnostic groups and the groups divided by cannabis use history are presented in Table 1 and Table 2, respectively. The continuous variables included age, education, and WRAT-4 reading test score. The categorical variables included gender, race, alcohol use disorder, and drug use other than cannabis.

Psychosis vs. Controls. *Age and gender*. The two groups were similar in age, with mean ages of 39.5 and 39.8 for the psychosis and control groups respectively. Regarding gender, 47% of the control group and 47.4% of the psychosis group were male.

Ethnicity and race. Race differed across the groups, with African Americans and Caucasians making up the majority. The psychosis group was 49.5% Caucasian and 43.3% African American, compared to 79.7% Caucasian and 18.8% African American in the control group. Because of the limited number of subjects in each group, the potential effects of race on cannabis use-by-group could not be statistically analyzed.

Education and WRAT-4 Scores. Education differed across groups, with the control group being more educated. The control group also performed better on the WRAT-4 reading test, consistent with expectation and a higher level of education and intellectual functioning.

Alcohol and other drug use disorders. The rate of alcohol use disorders and non-cannabis drug use differed across the groups. The psychosis group was significantly higher in both alcohol use disorders and other drug use, with 43% of the psychosis group having an alcohol use disorder, compared to 19% of the control group. Similarly, 40% of the psychosis group had a history of other drug use, compared to only 13% among controls.

Groups by diagnosis and cannabis use history (Table 2). *Age and gender*. Age was generally similar across the six subgroups. When the groups were divided by diagnosis and cannabis use history there were differences in gender composition across the groups. Adolescent cannabis users were more frequently male regardless of diagnosis.

Ethnicity and race. Race differed across the six groups, but most were Caucasian except for the psychosis late cannabis use. Ethnicity percentages across the groups can be found in Table 2.

Education and WRAT-4 Scores. Education remained fairly consistent when the diagnoses were split into the three cannabis use history groups. WRAT-4 reading scores were similar across groups, except that controls with no cannabis use performed lower than the other control groups. Education and WRAT-4 scores can be found in Table 2.

Alcohol and other drug use disorders. There was a considerable difference across the six groups in terms of the percentage of alcohol and other drug use disorders (See Table 2). Regardless of diagnosis, the adolescent cannabis use groups had the highest percentage of alcohol and drug use, and the groups that never used cannabis had the lowest.

Neurocognitive results. To conservatively analyze the BACS total score, a two way ANCOVA, correcting for education, WRAT-4 reading score, alcohol use disorder and other drug use was utilized. Education and WRAT-4 scores were corrected because they were both significantly different between the groups (education: F=, df=157, p=0.005 and WRAT-4: F=, df=159, p=0.02). We found an effect of diagnosis (F=18.5, df=1, p<0.001), no effect of age of cannabis use (F=1.39, df=2, p=0.25) or of group x age of cannabis use interaction on the BACS total score (F=2.5, df=2, p=0.08). A post hoc analysis (Tukey's test) between the six subgroups showed that the CCB+ and PCB+ groups were not significantly different (see Figure 1). Per our *a priori* hypothesis, we found that PCB+ performed significantly better on the BACS composite score than PCB- (t =2.19, df=79, p = 0.03). The significant group differences remained (F=5.54, df=76, p = 0.02) even after including WRAT-4, education, and other drug use as covariates.

Tables 3 and 4 and Figures 2 and 3 illustrate the percentage of BACS total z scores by different levels of performance across groups. As expected, controls performed better on the BACS than the psychosis group. The tables and figures also illustrate the association between cannabis use and cognition between the groups.

Exploratory analysis of detailed cognitive results. A two way ANCOVA was used for exploratory analyses of each of the BACS subtests. These analyses were conducted to determine if specific cognitive domains were affected by history of cannabis use. There were significant differences between groups on the processing speed subtest (F=24.5, df=1, p<0.001) and the working memory subtest (F=20.83, df=1, p<0.001). No differences were found on the executive function (F=2.54, df=1, p=0.11) or verbal memory (F=2.22, df=1, p=0.14) subtests. There were

no effects of age of cannabis in processing speed (F=2.31, df=2, p=0.102), executive function (F=0.17, df=2, p=0.84), verbal memory (F=1.57, df=2, p=0.212), or working memory (F=0.25, df=2, p=0.78) subtests. There were also no significant differences across diagnoses by age of cannabis use for processing speed (F=1.33, df=2, p=0.27), executive function (F=2.34, df=2, p=0.1), verbal memory (F=1.68, df=2, p=0.19), or working memory (F=1.82, df=2, p=0.17) subtests.

Results of social functioning assessment. We found an effect of diagnosis (F=30.74, df=1, p<0.001), with the controls scoring higher, as expected, but no effect of age of cannabis use (F=0.06, df=2, p=0.94), or diagnosis x age of cannabis use interaction (F=2.48, df=2, 139, p=0.09). Post hoc Tukey tests revealed that every psychosis subgroup was significantly different than the control groups, suggestive of a diagnosis effect. The CCB+ subgroup scored the lowest of the controls and PCB+ subgroup scored the highest of the psychosis groups (Figure 4). Comparisons between our primary target groups (PCB+ and PCB-) did not show any difference on total SFS (F=0.21, df=77, p=0.83). Inclusion of the WRAT-4, education, and other drug use as covariates did not affect this non-significant result (F=0.23, df=74, p=0.63).

CHAPTER FIVE

Discussion

It was hypothesized that subjects with psychosis and adolescent cannabis use would perform better both in overall cognition and social functioning than subjects with psychosis and no history of cannabis use. Regarding cognitive testing results, there was a clear difference between control and psychosis group scores, with controls performing significantly better, as expected. There was, however, no overall diagnosis by age of cannabis use interaction. When we examined the target groups defined in an *a priori* manner (PCB+ vs. PCB), we found that there was a difference between these groups, with the PCB+ group performing better cognitively as reflected by the BACS composite score. When the six groups were examined more closely, there were significant differences between all of the groups except for the two adolescent cannabis use groups. Specifically, controls with adolescent cannabis use had the lowest BACS total scores of all the controls, and the psychosis with adolescent cannabis use group had the highest BACS total scores out of the three psychosis groups (Figure 1). Importantly, these findings remained significant even when controlling for education, WRAT-4 reading scores, alcohol and other drug use, further strengthening these findings. These findings supported our primary hypothesis where it was predicted that PCB+ would obtain higher total scores on the BACS than PCB-. The seemingly paradoxical effect of adolescent cannabis use negatively impacting cognition in controls but being positively associated with cognition in the psychosis group is consistent with prior studies focused on schizophrenia. This study lends further support

to this paradoxical effect by finding that adolescent cannabis use is associated with better cognition in a broader group of psychotic disorders.

There are several theories as to why people with schizophrenia and adolescent cannabis use (SCB+) might perform better cognitively than those without cannabis use. The first is that social functioning is associated with higher cognitive functioning and that the SCB+ group may have a higher level of social functioning in order to obtain cannabis, based on the rationale of obtaining an illegal substance requires a certain level of social skills, such as the ability to network. A study conducted in Netherlands, however, does not support this notion (Meijer, Dekker, Koeter, et al., 2012). Since cannabis is a legal substance in Netherlands, it is more easily obtained and would not require better social functioning. SCB+ subjects in the Meijer study demonstrated better cognition, suggesting that the superior cognitive functioning in the SCB+ group might be independent from social functioning.

A second theory offered to explain why SCB+ might perform better cognitively than SCB- is that cannabis has a neuroprotective effect (Coulston, Perdices, & Tennant, 2007). If cannabis did have a general neuroprotective effect on the brain the effect would be expected to be seen in the otherwise healthy brain. There is, however, no evidence that cannabis has a neuroprotective effect in healthy controls. In a variety of investigations, long-term cannabis use has been associated with cognitive impairments in otherwise healthy controls. The investigators found that persistent cannabis use was associated with broad cognitive declines, affecting multiple domains of neurocognitive functioning. Furthermore, participants with adolescent onset of cannabis use had cognitive deficits that persisted more than a year after cessation of cannabis

use (Meier et al., 2012). However, a possible defense for this theory is that there are fundamental differences between an at-risk brain and a normal brain. Therefore, adolescent cannabis might affect a psychosis-predisposed brain differently than it affects a healthy brain.

The third theory to explain the cognitive differences between SCB+ and SCB- incorporates the research that suggests that cannabis is a contributing factor to the development of schizophrenia. Cannabis appears to be a risk factor for some individuals, which may interact with other risk factors in the development of schizophrenia. The theory is that some people may have some genetic risk factors for schizophrenia but not enough to trigger the disorder. The additional CNS insult of adolescent cannabis use may be what induces the development of schizophrenia. It is possible that the population that had less genetic loading and required the additional risk factor of cannabis to develop schizophrenia has more intact cognitive functioning.

Exploratory analysis of the BACS subtests resulted in no significant findings for diagnosis by age of cannabis use. It is unclear whether this is an indication of cognitive decline being global, or another possible explanation could be that this finding was a reflection on the sensitivity of the BACS subtests. The BACS has been shown to be a reliable measure of cognitive functioning (Keefe et al., 2004); however, it may be that because it is a brief measure, the psychometric properties of the subtests are weaker because they lack the sensitivity of more detailed cognitive measures. Keefe et al. (2004) examined the reliability of both the composite score and the subtests but only assessed the validity of the composite score. Therefore, the validity of the BACS subtests is something that requires further research.

Regarding social functioning findings, controls scored higher than the psychosis group, as expected. The interaction between diagnosis and cannabis use was not significant but revealed a p value of .09. This raises the possibility that a significant interaction might be found if sample sizes were larger. Controls with adolescent cannabis use had the lowest social functioning scores among all control subjects, and the psychosis with adolescent cannabis use group had the highest social functioning scores among the psychosis groups (Figure 4). To our knowledge, the relationship between cannabis use and social functioning in a psychosis population has not been studied before. While the findings were not statistically significant for social functioning, the paradoxical effects of PCB+ performing the best of the psychosis probands and the CCB- performing the worst of the controls seen in the cognitive functioning results were seen in a lesser degree in terms of social function ratings. A similar effect in cognitive functioning and social functioning would support the notion that these two elements are positively correlated. Future research with larger sample sizes will be important to explore whether PCB+ consistently score higher on social functioning than PCB-. Previous research found that at-risk subjects for psychosis that engaged in lifetime cannabis use had higher social functioning and less negative symptoms (Auther et al., 2012). However, these subjects had higher social functioning at baseline, indicating that the cannabis use did not affect social functioning. This might suggest that adolescents with higher social functioning are more likely to use cannabis.

Implications of findings. Adolescent cannabis use has been associated with long-term lowered cognitive functioning in healthy controls. Meier et al. (2012) found that persistent

cannabis use was associated with broad cognitive declines, affecting multiple domains of neurocognitive functioning in healthy controls. Furthermore, those with adolescent-onset of cannabis use had cognitive deficits that persisted more than a year after cessation of cannabis use. Pope et al. (2003) found that long-term cannabis users had a lower verbal IQ than the control group. However, this effect was limited to subjects who started using before the age of 17; those that initiated cannabis use after adolescence did not show evidence of reduced IQs. The current findings were consistent with previous research in that the CCB+ showed lower cognitive functioning compared with the other control groups. However, it is important to note that they were still within the normal range and therefore most would not meet criteria for cognitive impairment. A possible explanation for this is that while we collected information on age of cannabis use onset, we did not have sufficient information to characterize length of active use, length of sobriety periods, or what kind of cannabis was used. Therefore, it is possible that our controls were cognitively affected by adolescent cannabis use, but they may not have used enough during adolescence to result in cognitive impairment per se.

Cognitive deficits are a well-established feature of schizophrenia. Weickert et al. (2000) found that while IQ decline was variable in schizophrenia, executive functioning and attention deficits appeared to be a core feature. In a twin study of schizophrenia, Goldberg et al. (1990) found that the affected twin had deficits that were especially severe on tests of vigilance, memory, and concept formation. Park and Holzman (1992) found working memory deficits to be a core feature of schizophrenia. In a meta-analysis, processing speed deficit was indicated (Dickinson, Ramsey, & Gold, 2007); however, a separate meta-analysis found this result to be

affected by multiple moderators, including anti-psychotic medication dosage (Knowles, David, & Reichenberg, 2010). Consistent with Park and Holzman (1992) and Dickinson et al. (2007), the current study found that processing speed and working memory were the most impaired domains for the psychosis group. These were also the two areas that were significantly different between the psychosis and control groups. However, these findings did not remain consistent when the groups were divided by cannabis use, in that there were no significant differences between the six subgroups on any cognitive subtest. Although there were no statistically significant differences between the psychoses by cannabis use subgroups, the mean value of the tasks for the PCB+ group was consistently higher than the other psychosis groups. It is possible that there may be differences between the groups that we did not pick up because of the small number per group. Further research would be necessary to determine if there are clinically relevant subgroups.

The finding of better cognitive functioning among patients with psychosis and a history of adolescent cannabis use is consistent with previous research looking at the association between cannabis use and cognition in schizophrenia. Specifically, SCB+ individuals have shown better performance on certain neuropsychological tasks when compared to SCB-, including measures of visual declarative memory, attention, and processing speed; however, the most consistent findings have been in executive functioning and working memory (Jockers-Scherubl, 2007; Lesson, Harrison, Ron, Barnes, & Joyce, 2012; Loberg & Hugdahl, 2009; Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009; Stirling, Lewis, Hopkins, & White, 2005; Yucel et al., 2012). In this thesis we find evidence that cognitive differences associated

with adolescent cannabis use pertains not only to schizophrenia but also extends to other psychotic diagnoses. By finding that the psychosis group with adolescent cannabis use had the best cognitive performance of the psychsosis groups, we illustrated that the previous findings from schizophrenia research extend to psychosis as a spectrum. Other, larger, studies have proposed viewing psychosis as a dimensional domain (Craddock & Owen, 2012; Hill et al., 2012; Tamminga et al., 2013). Clinicians using conventional psychiatric nomenclature typically attempt to fit patients into the Kraepelinian dichotomy, and if patients do not fit into these two categories they are frequently diagnosed as *schizoaffective.* In addition to implications for diagnosis, it could be that attempting to fit patients with psychosis into specific groups limits their treatment options. Viewing psychosis as a spectrum could open up future research avenues and treatment options. A dimensional approach to analyze schizo-bipolarity, rather than overt illness categories, is more likely to be productive when examining the genome and other etiological factors. An alternative to the traditional bipolar vs. schizophrenia diagnoses could be to characterize subjects with psychosis by their history of cannabis use to understand disease pathophysiology, considering treatment options and even while conducting research. History of cannabis use and the age of onset of cannabis use seem to have a clear impact on the cognition of people with psychosis. Dividing psychosis probands by cannabis history could be particularly helpful when addressing cognition, specifically, clinical trials designed to improve cognition in individuals with psychosis. If PCB+ probands consistently have higher cognitive functioning than the other psychosis groups, this could confound the results of future clinical trials by

masking cognitive responses to medication. Excluding the PCB+ group from clinical trials would likely result in clearer findings.

In addition to replicating previous cognitive findings in schizophrenia, this thesis further emphasized the impact that adolescent cannabis use has on cognition in individuals with psychosis. One of the theories mentioned earlier explaining more intact cognitive functioning in PCB+ is that this population has better cognitive functioning because they might not have developed psychosis without the additional insult of cannabis use. It is possible that these people had less genetic risk factors and therefore had more intact cognitive functioning compared with the probands that were genetically at risk to develop psychosis. The previous research indicating that ACU is a risk factor for the development of schizophrenia may have important public health implications. Incorporating this research into education awareness, etc. could be valuable, especially with the new rulings legalizing recreational cannabis use in states such as Colorado and Washington. Additional longitudinal research will be needed to determine if cannabis is a risk factor for the development of the entire psychosis spectrum.

Limitations and future directions. While the number of subjects in the psychosis and controls groups were reasonable for detecting groups differences, dividing subjects into six groups led to smaller sample sizes in each cell, which may have limited our ability to determine subgroup differences. The study sample was a generally high functioning sample (Mean estimated IQ psychosis = 96; control = 101), which may have skewed findings. A high functioning psychosis group may have minimized the differences between control and psychosis groups and may limit generalizability. Additionally, the data on cannabis use were collected

through self-report measures. While this is common practice in most clinical research settings, the retrospective approach is reliant on memory, and participants may over- or under- report cannabis use. A longitudinal prospective study may allow more accurate characterization of cannabis use patterns and allow assessment of cognition at different time points. One confound that would still remain, however, is the accuracy of self-reporting cannabis use.

Another potential limitation is that subjects were characterized by age of onset of cannabis use rather than by how much they used. This approach did not take into account length of active use, length of sobriety periods, or what kind of cannabis was used. It is possible that quantity of use and THC potency could account for cognitive effects, although this would be challenging to measure with any accuracy. However, Di Forti found a dose-response to THC levels, with increased THC levels correlating to increased incidence of psychosis (Di Forti et al., 2009). Additionally, K2 (or "spice") is a synthetic cannabinoid that acts on the CB1 receptor, like THC. K2 is more potent than THC (Vardakou, Pistos, & Spiliopoulou, 2010) and is known to have acute effects on psychosis, with reports of use causing psychosis lasting weeks (Pierre, 2011). Regarding length of active use and sobriety periods, as discussed in the review of the literature, the cognitive deficits that were found in healthy controls did not last after periods of sobriety. Cognitive deficits only persisted if the onset of cannabis use was in adolescence. In concordance with these findings, age of onset has been the most commonly used distinction between study groups in previous schizophrenia research.

The effects of antipsychotic medications could be a potential limitation in this study. The majority of the probands were on medication; therefore a differential effect would seem unlikely.

However, a meta-analysis found processing speed result to be affected by multiple moderators, including anti-psychotic medication dosage (Knowles, David, & Reichenberg, 2010). This study did not take into account dosage of antipsychotic medications, raising the possibility of an effect on processing speed or other subscores.

Finally, this study utilized the BACS, which is a useful cognitive assessment measure for schizophrenia. However, because it was designed to measure the specific cognitive areas that have been shown to be impacted by schizophrenia, there might be other cognitive domains that are impacted by cannabis use that the BACS does not measure. Additionally, previous literature has found the BACS provides a meaningful measure of global cognition (BACS total) but may not be as useful for assessing individual domains. A more detailed neuropsychological battery may be needed to elucidate specific areas of cognitive inefficiency between the groups.

Future directions might include a larger prospective study designed to examine correlations of adolescent cannabis use amongst study participants. A larger sample size could possibly allow confirmation of the apparent paradoxical effects found in this study. A future study designed to have larger sample sizes in the subgroups divided by diagnosis and cannabis use would be likely to have more definitive correlations on the association between adolescent cannabis use and long-term cognitive function and social functioning. The fact that this study found similar findings as previous schizophrenia research while broadening the research to psychosis spectrum prompts the future question: what other “schizophrenia only” findings would also apply to the entire psychosis spectrum? We know that there is no clear biological distinction between the disorders. Other correlational studies researching schizophrenia could be

replicated using a sample of psychosis as a spectrum to determine if the findings remain consistent in the broader sample. If similar results are found then it could further support the abandonment of the Kraepelinian dichotomy. A particularly important area of the research that should be expanded is the research on cannabis being a component cause of schizophrenia. Future research should examine if cannabis is also a component cause of bipolar disorder with psychosis and schizoaffective disorder. Positive findings could lead to more etiological studies on the psychotic spectrum.

Additional directions could include brain-imaging studies, such as structural and functional imaging (fMRI) and EEG, to help determine if the PCB+ group has regional brain abnormalities compared to PCB- group. Findings could possibly help to explain the paradoxical effects that have been found between adolescent cannabis use and cognition. Also, future treatment trials designed to improve cognition in schizophrenia through medication could utilize cannabis use criteria to define subgroups of volunteers. By separating groups by cannabis use the trials may be more definitive without the paradoxical cognitive effect weakening the findings. In other words, the PCB+ group is likely to be less impaired, so they may not show as much cognitive improvement as the PCB- group with treatment. Separating the groups allows more detailed examination of the effect that the medication is having. Finally, future investigations could capitalize on the unique study sample in states that have legalized cannabis. Setting up prospective studies to examine the long-term effects of CB legalization on the incidence of psychosis provides an invaluable opportunity.

In summary, there is previous evidence suggesting that individuals with schizophrenia

and adolescent cannabis use have less neuropsychological impairment compared to individuals with schizophrenia who do not have a cannabis use history. In this thesis, we extended these findings to psychosis as a spectrum, finding that individuals with psychosis and adolescent cannabis use performed better cognitively than those with psychosis and no cannabis use history. Whereas the reasons for this finding remain unclear, results lend additional support to the growing literature that there is a unique interaction between adolescent cannabis use and psychosis, specifically in cognitive functioning. Results also support the abandonment of the Kraepelinian dichotomy by illustrating that previous findings are not specific to schizophrenia but apply to other disorders in the psychosis spectrum. This study provides results that could stimulate future psychosis research to examine the effect that ACU has on its development and cognitive function.

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Table 1

Sociodemographic Variables in Psychosis and Control Groups

	Psychosis Group (N=97)		Control Group (N=64)	
	Mean	SD	Mean	SD
Age (years)	39	11	40	12
Education (years)	13	2	14	2
WRAT-4, reading test, standard score	96	13	101	15
	%		%	
Male	47		47	
Race				
Caucasian	49		80	
African American	43		19	
Asian	2		5	
Mixed Race	0		2	
Other	2		0	
Alcohol Use Disorder	43		19	
Other Drug Use	40		13	

Table 2

Sociodemographic Variables in Subgroups by Diagnosis and Cannabis Use

PSYCHOSIS

	No Cannabis Use Group (N=48)		Adolescent Cannabis Use Group (N=33)		Late Cannabis Use Group (N=16)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	40	12	38	11	41	9
Education (years)	14	2	13	2	12	2
WRAT-4, reading test, standard score	96	14	96	14	95	13
	%		%		%	
Male	38		67		38	
Race						
Caucasian	50		61		44	
African American	42		39		56	
Asian	6		0		0	
Mixed Race	2		0		0	
Other	0		0		0	
Alcohol Use Disorder	21		73		50	
Other Drug Use	15		73		50	
Antipsychotics	92		90		91	

Sociodemographic Variables in Subgroups by Diagnosis and Cannabis Use Cont.

CONTROLS

	No Cannabis Use Group (N=38)		Adolescent Cannabis Use Group (N=16)		Late Cannabis Use Group (N=10)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	41	12	37	12	40	12
Education (years)	14	2	14	2	14	2
WRAT-4, reading test, standard score	99	14	104	19	104	12
	%		%		%	
Male	37		63		60	
Race						
Caucasian	71		75		90	
African American	24		13		10	
Asian	3		6		0	
Mixed Race	0		0		0	
Other	3		6		0	
Alcohol Use Disorder	8		44		20	
Other Drug Use	0		44		10	

Table 3

BACS Z Score Percentages by Diagnosis

	< -2	**-2 t o -1**	**0 to -1**	**1 to 0**	**>1**
	%	**%**	**%**	**%**	**%**
Controls	8	14	25	36	17
Psychosis	35	33	22	9	1

Table 4

BACS Z Scores Less than -1 for Psychosis Subgroups

Psychosis No Cannabis Use Group (N=48)		Psychosis Adolescent Cannabis Use Group (N=33)		Psychosis Late Cannabis Use Group (N=16)	
N	%	N	%	N	%
37	77	16	48	12	75

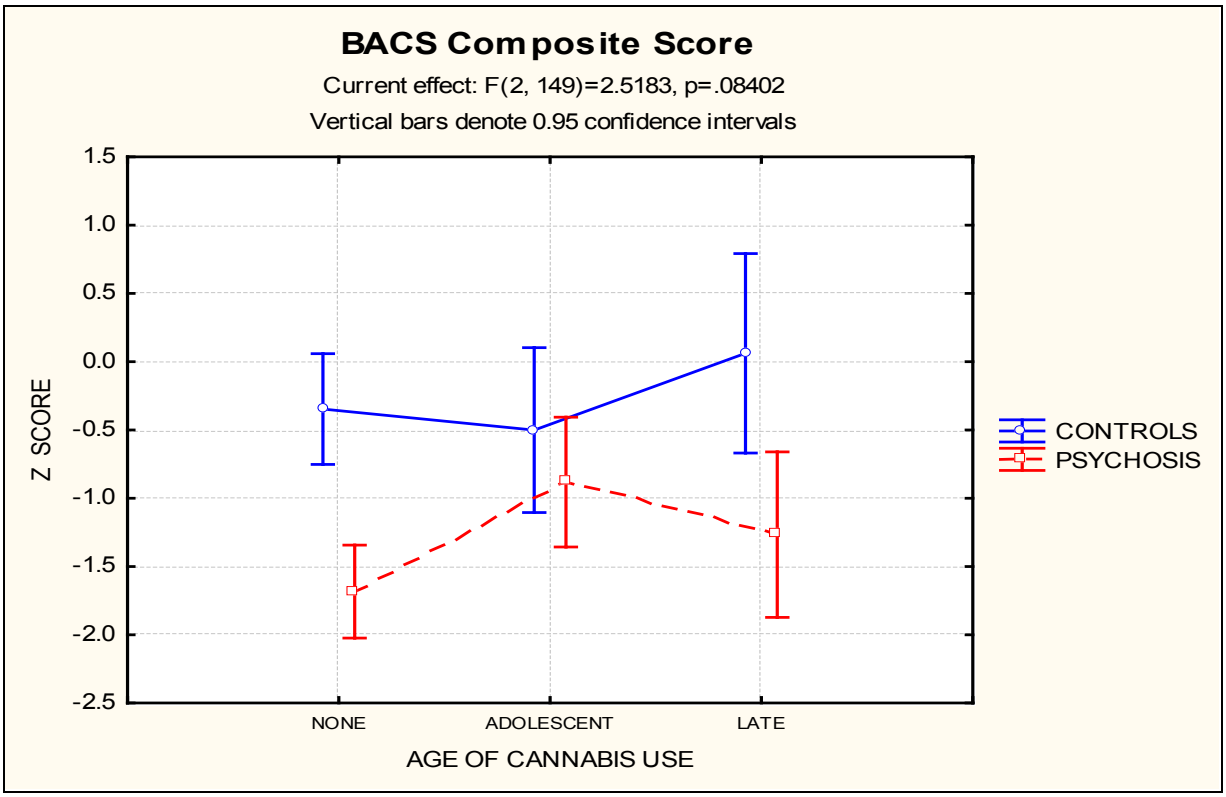

Figure 1. Representation of BACS Total Score in six subgroups.

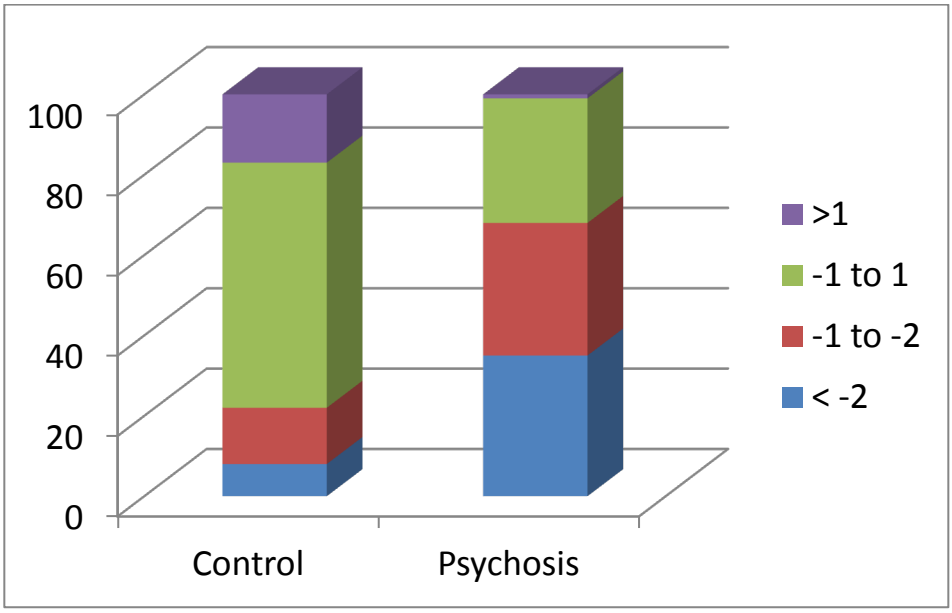

Figure 2. BACS Z Score Percentages by Diagnosis

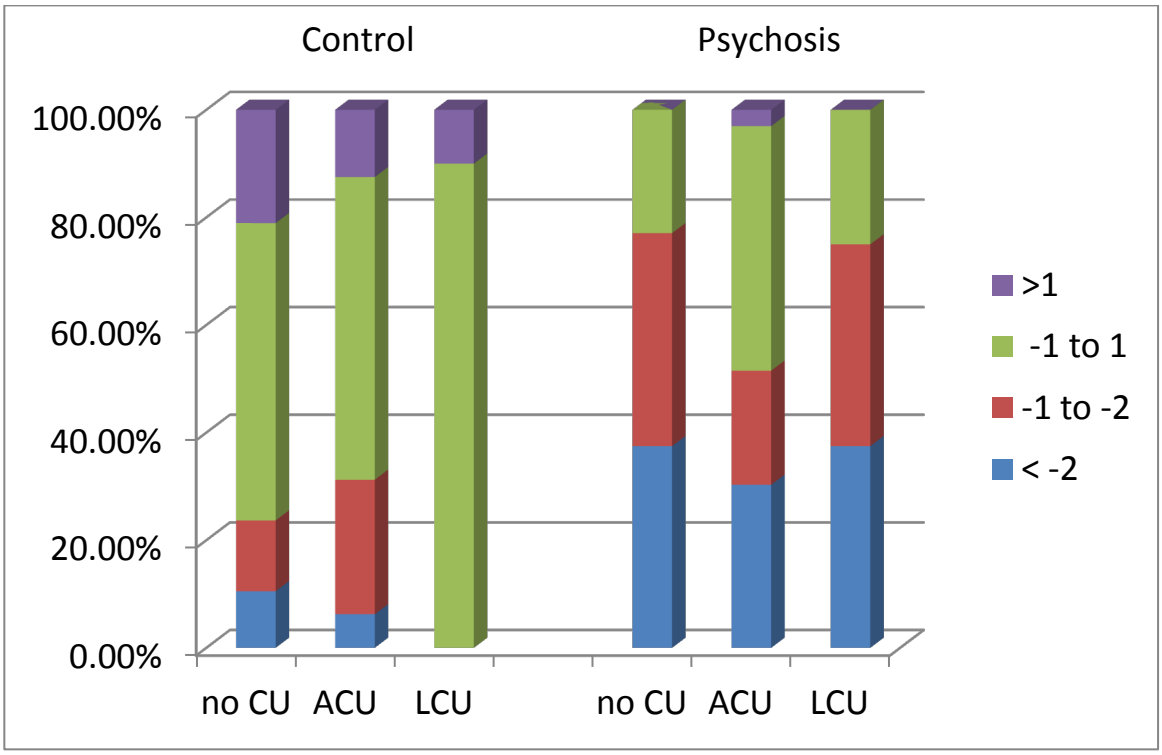

Figure 3. BACS Z Score Percentages by Diagnosis and Cannabis Use

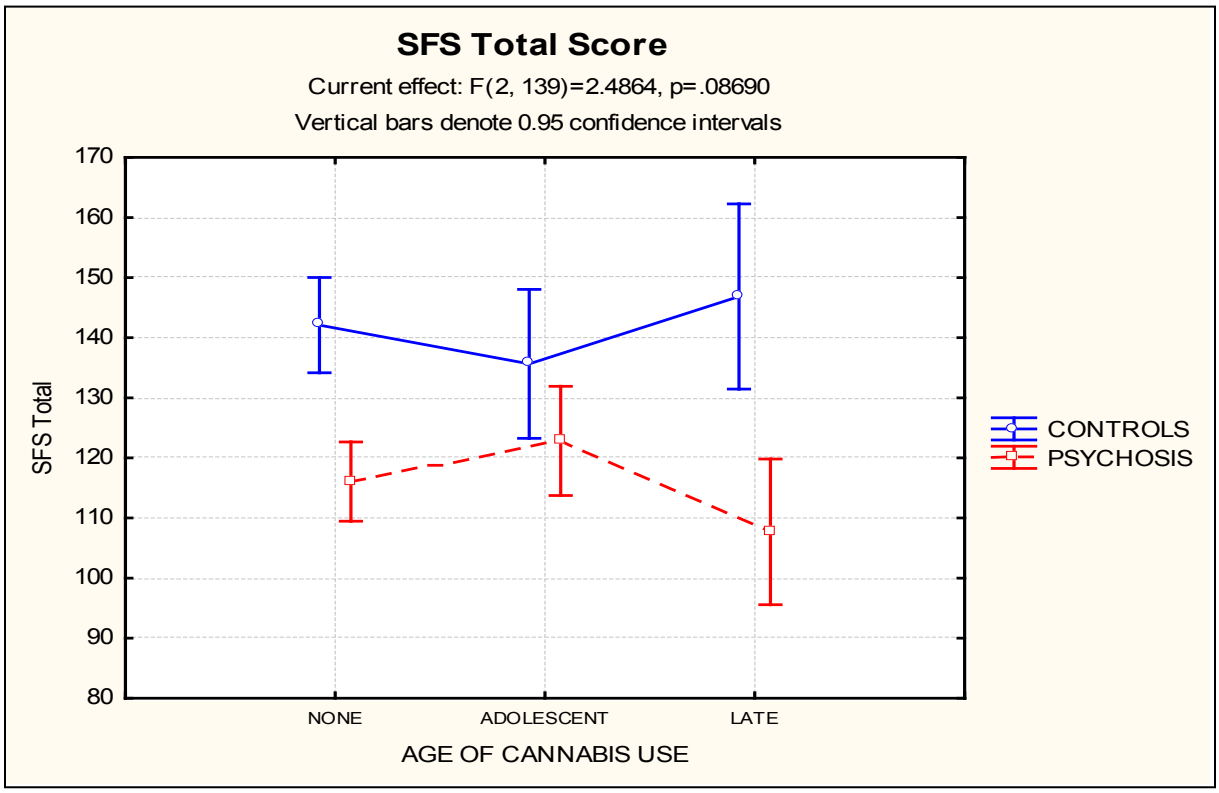

Figure 4. Representation of SFS Total Score in six subgroups

BIOGRAPHICAL SKETCH

Alexandra Shalvoy
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EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR	FIELD OF STUDY
Southern Methodist University Dedman College	B.A.	2008	Psychology
The University of Texas Southwestern School of Allied Health Sciences	M.R.C.	2014	Rehabilitation Counseling Psychology

Positions and Employment

UT Southwestern Medical Center

May 2008 – July 2011 *Research Assistant II, Department of Psychiatry, Division on Addictions*

- Study Coordinator for multiple studies involving Institution Review Board coordination
- Recruited patients and healthy controls; conducted screening, baseline, and follow-up research visits with participants
- Administered neurocognitive assessments and semi-structured interviews
- Trained and supervised study team members; reported communicable diseases to health department; VA liaison between study and treatment team; checked data for quality assurance

Clinical Experience

UT Southwestern Medical Center

Feb 2013 – Aug 2013 *Psychology Intern, Zale Lipshy Inpatient Psychiatry*

- Conducted personality assessments, neuropsychological assessments, group therapy, and individual therapy
- Participated in patient feedback on assessment results, participated in team meetings, and wrote clinical reports

Aug 2012 – Aug 2013
Practicum Counselor, University Rehabilitation Services

- Conducted individual therapy, utilizing Person-Centered, Motivational Interviewing, and Cognitive Behavioral Therapy techniques

Aug 2012 – Feb 2013
Practicum Testing Administrator, Psychology Assessment Service, Parkland Behavioral Health

- Conducted clinical interview and neuropsychological assessments with Parkland patients
- Conducted eligibility assessments for renal transplant candidates

Presentations and Publications

2010 Shalvoy, A.M., Leachman, L.L., Fielding, S., Walker, N.R., Minhajuddin, A., North, C.S., Rao, U., Xiao, H., & Adinoff, B. (2010, June 27). Antisocial Personality Characteristics and Alcohol Use as a Predictor of Cortisol Reactivity to a Behavioral Stressor. Poster presentation, Research Society on Alcoholism Meeting, San Antonio, TX, USA.