CANNABIS USE AND ATTENUATED POSITIVE PSYCHOTIC SYMPTOMS: A MULTIPLE MEDIATION MODEL

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ABSTRACT

Cannabis use has been associated with various psychosis outcomes, including psychotic disorders, the clinical high risk period of psychosis, and subthreshold measures of psychotic symptoms in non-clinical samples, such as attenuated positive psychotic symptoms (APPS). The present study examined whether individual- and contextual-level factors account for the relationship between cannabis use and psychosis. Specifically, we hypothesized that the relationship between cannabis and psychosis would be mediated by social functioning; negative, depression, anxiety, and aggression symptoms; context of cannabis use; and motivations for cannabis use. Nine hundred and forty-five young adults ages 18-35 years ($M = 20.1$ years, 24.4% male) completed self-report questionnaires: the Prodromal Questionnaire, Marijuana Use Form, Social Functioning Scale, Center for Epidemiologic Studies Depression Scale, State-Trait Anxiety Inventory-Trait Form-Anxiety Subscale, Social Phobia Scale, Life History of Aggression Scale, Reasons for Use scale, and Drug Use Frequency questionnaire. Psychosis outcomes included a dimensional measure of APPS and a dichotomous measure indicating potential higher/lower risk for psychosis, based on number of distressing symptoms endorsed (i.e., D-APPS status). A multiple mediation framework was used, and significance of mediators was evaluated through estimating the significance of indirect effects using bootstrapped confidence intervals. Increases in negative and aggression symptoms mediated the relationship between higher cannabis use and increases in APPS. Negative and aggression symptoms, context of cannabis use, and using cannabis to cope with unpleasant affect mediated the relationship between cannabis use and high-D-APPS
status. Results indicate that individual and contextual-level characteristics may contribute to the relationship between cannabis use and psychosis.
This dissertation is dedicated to:

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My husband, Pete, for your never-ending pursuit of keeping me laughing, nourished, and confident over the years.

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CHAPTER 1
EXTENSIVE LITERATURE REVIEW

The Psychosis Spectrum

Overview

Psychotic disorders are chronic and debilitating neuropsychiatric disorders with severe individual, family, and societal burdens. Although only a small segment of the population is diagnosed with schizophrenia (approximately one percent), its effects have a large impact (Wu et al., 2005). Psychotic disorders impose significant costs on society for direct treatment and for reduced or lost productivity (Wu et al., 2005), and also on personal costs for individuals with the disorders and their primary caregivers (Solomon & Draine, 1995). Understanding the etiology of psychotic disorders, such as schizophrenia, is critical for treatment as well as for preventative measures to improve outcomes for at risk individuals. One approach to improve understanding of the etiology of psychotic disorders is to investigate the period prior to the onset of psychosis. This period, known as the psychosis prodrome, involves the early manifestation of psychotic symptoms, but is prior to onset of a clinical disorder (Yung & McGorry, 1996). One method of identifying individuals in this prodromal, or clinical high risk (CHR), phase is by meeting one or more of three criteria outlined in the Structured Interview for Psychosis-Risk Syndromes, the gold standard interview for diagnosing those potentially in the prodrome of psychosis: (1) recent onset or worsening of attenuated psychotic symptoms, (2) very brief periods of fully psychotic positive symptoms, or (3) deterioration in role functioning within the past year, in addition to either schizotypal personality disorder or having a first-degree relative with psychosis (Miller et al., 2002, 2003). Approximately 20-40 percent of individuals at CHR for psychosis will
convert to a clinical psychotic disorder (Cannon et al., 2008; Mittal et al., 2010; Ruhrmann et al., 2010; Woods et al., 2009). Therefore, this group of individuals has a greater likelihood of developing psychosis compared with the general population. Investigating populations in which psychosis has not yet been fully developed, either by studying individuals at CHR for psychosis and/or individuals from the general population with subthreshold psychotic symptoms, is crucial to understanding the onset of psychosis and may allow for more targeted preventive interventions.

One method by which to study the period prior to a prodromal disorder is by measuring psychotic symptoms dimensionally. Research indicates that although a high number of individuals within the general population experience subthreshold psychotic symptoms, they are not diagnosable according to current criteria (van Os & Linscott, 2012). Although the manifestation of subthreshold psychotic symptoms is transitory in the general population (Dominguez, Wichers, Lieb, Wittchen, & van Os, 2011), for certain individuals, they may predict the development of a clinical psychotic disorder (Cannon et al., 2008; Poulton et al., 2000). Attenuated positive psychotic symptoms (i.e., APPS) are common, yet brief, attenuated, or limited symptoms that are not in themselves clinically significant, and occur in the absence of current substance use (Loewy, Johnson, & Cannon, 2007). Typically, only the most debilitating or frequent psychotic symptoms are considered to be of diagnostic relevance (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009); however, constraining the definition of psychotic symptoms to only those of diagnostic relevance may underrepresent the contribution of these symptoms to the liability for psychotic disorders. An extended psychosis phenotype is supported by results that suggest that subclinical and clinical psychosis share many of
the same risk factors (Griffith-Lendering et al., 2012; Kelleher & Cannon, 2011; van Os & Kapur, 2009). Further, APPS experienced by the general population may have relevance for individuals at risk for psychotic disorders (van Os & Kapur, 2009; van Os & Linscott, 2012), as individuals endorsing APPS are at 3.5 times increased risk of developing a psychotic disorder (van Os & Linscott, 2012). These findings strongly support the use of dimensional measurement of psychotic symptoms via APPS. The following review will focus on a specific environmental risk factor for psychosis, cannabis use, with an emphasis on typical patterns of cannabis use within healthy young adults, as well as individuals representing the entire spectrum of psychosis. As we review the literature we highlight gaps and conflicts in the cannabis and psychosis knowledge base, identify important individual and contextual factors to consider, and suggest future directions.

Cannabis Use and the Psychosis Spectrum

Although genetic factors appear to be substantially related to the etiology of psychotic disorders, evidence suggests that the environment also influences the development and course of psychosis (Schlosser, Pearson, Perez, & Loewy, 2012). Among the environmental contributors to psychotic disorders, cannabis use has been repeatedly associated with risk of psychosis (Caspari, 1999; Corcoran et al., 2008; Kuepper et al., 2011; Linszen, Dingemans, & Lenior, 1994). Exploring this association is particularly critical, as cannabis use is potentially one of the few psychosis risk factors that is modifiable, and it is amenable to targeted interventions. Further, evidence suggests that approximately eight percent of the attributable risk for schizophrenia is accounted for by cannabis use (Arseneault, Cannon, Witton, & Murray, 2004). Cannabis use has repeatedly been associated
with various psychosis outcomes, including risk for psychotic disorders, CHR for psychosis, and subthreshold psychotic symptoms in non-clinical samples (Caspari, 1999; Corcoran et al., 2008; Kuepper et al., 2011; Linszen et al., 1994). High rates of substance use are prevalent in individuals diagnosed with schizophrenia or schizophrenia-related disorders, and such individuals have an increased likelihood of having a substance use disorder compared to non-psychotic individuals (Boyd et al., 1984). Alcohol and cannabis are the most commonly used substances in psychotic populations (Kessler et al., 1997; Weaver et al., 2003), and approximately 42 percent have used cannabis in their lifetime, and 23 percent demonstrate lifetime cannabis misuse (Green, Young, & Kavanagh, 2005). Such associations between increased rates of cannabis use and psychosis are not limited to only individuals with a diagnosable disorder. Cannabis use is temporally associated with positive psychotic symptoms (i.e., hallucinatory phenomena) in prodromal samples (Corcoran et al., 2008), and rates of lifetime cannabis use in individuals at CHR for psychosis are higher than for healthy controls (Auther et al., 2012; Buchy et al., 2015). Even general population studies demonstrate that cannabis use is related to psychotic-like experiences (Reeves et al., 2014; Schubart et al., 2011; Stefanis et al., 2004; van Gastel et al., 2012; Verdoux, Gindre, Sorbara, Tournier, & Swendsen, 2003). This relationship has also been demonstrated experimentally: studies indicate that injecting doses of delta-9-tetrahydrocannabinol (THC), the main psychoactive component of cannabis, in a non-clinical sample resulted in transient increases in schizophrenia-like positive and negative symptoms (D’Souza et al., 2000; Morrison et al., 2009; Morrison & Stone, 2011). Further, cannabis use during adolescence in the presence of genetic polymorphisms, such as the Val/Val catechol-O-methyltransferase (COMT) genotype, is associated with being at least ten times more likely to develop
schizophreniform disorder (Caspi et al., 2005). Thus, the relation between psychosis and cannabis is supported by experimental and genetic evidence, and it has been replicated in patient populations, as well as in the general population.

Further, there is a clear dose-response relationship between the frequency of cannabis consumption and increased risk for psychosis (Moore et al., 2007; van Os et al., 2002) and this has been replicated in non-clinical samples with the frequency of cannabis use corresponding to the number of APPS endorsed (Reeves et al., 2014). Specifically, among cannabis-abusing individuals with schizophrenia, those with heavier consumption experience relapses more frequently and earlier than their non-cannabis abusing counterparts (Linszen et al., 1994). Similarly, within prodromal samples cannabis use is temporally associated with subthreshold hallucinations in a dose-dependent fashion, even when accounting for use of alcohol, cocaine, or medications (Corcoran et al., 2008). This dose-response relationship is evident in general population and conscription studies to the extent that as the number of lifetime cannabis use increases, the risk of schizophrenia increases linearly (Andreasson, Engstrom, Allebeck, & Rydberg, 1987a; van Os et al., 2002), and heavier and more frequent cannabis use is related to increases in APPS in the general population (Binbay et al., 2012; Kuepper et al., 2011; Ruiz-Veguilla et al., 2013).

Despite these repeated, well-established associations, the causality of the cannabis-psychosis relationship remains unclear. Specifically, cannabis consumption may act as a risk factor for the subsequent development of schizophrenia-spectrum disorders, as well as symptoms along the psychosis continuum (Arseneault et al., 2002; van Os et al., 2002), or cannabis use may represent an attempt to self-medicate against already established psychiatric symptoms, or to counteract the side-effects of psychiatric medications (Siris,
A third potential direction of causality proposed by Hambrecht and Häfner (2000) is that the concurrence of cannabis and psychotic symptoms may be coincidental, and causality is attributed to an unknown mediator. However, the majority of empirical, longitudinal studies indicate that cannabis consumption precedes the onset of schizophrenia and other psychotic disorders by several years in the majority of individuals, and that it strongly predicts risk of psychosis for individuals who initially present without psychosis (Allebeck, Adamsson, Engstrom, & Rydberg, 1993; Andreasson et al., 1987a; Caspi et al., 2005; Cleghorn et al., 1991; Linszen et al., 1994; van Os et al., 2002). Further, there is evidence indicating that once subthreshold psychotic symptoms increase in frequency, individuals begin to use less cannabis (Fergusson, Horwood, & Ridder, 2005; Valmaggia et al., 2014), suggesting that cannabis is not an attempt to self-medicate against psychotic symptoms.

Yet, the evidence that cannabis is an independent risk factor for psychosis becomes less clear when evaluating individuals at CHR for psychosis. The first study to examine the relation between cannabis use and psychosis used a CHR for psychosis sample and failed to find an association between self-reported cannabis use or dependence and conversion to psychosis after one year (Phillips et al., 2002). Later studies echoed the findings of a lack of association between substance use severity and transition to psychosis (Auther et al., 2012; Buchy, Perkins, Woods, Liu, & Addington, 2014; Compton, Broussard, Ramsay, & Stewart, 2011; Corcoran et al., 2008; Ruhrmann et al., 2010; Thompson, Nelson, & Yung, 2011; Valmaggia et al., 2014; Yung, Phillips, Yuen, & McGorry, 2004), and this was further supported by a review of the CHR literature (Addington et al., 2014), although not all studies are in agreement (Cannon et al., 2008; Kristensen & Cadenhead, 2007). For those studies not
in agreement, it is noted that an overall history of substance use predicted conversion to psychosis, but multivariate analyses indicated that no specific substance class (including cannabis) was significantly associated with risk (Cannon et al., 2008). In sum, the data are mixed for whether substance use, specifically cannabis use, is related to increased likelihood of being at CHR for psychosis. Further, there are methodological concerns with these studies, as some examining CHR populations excluded individuals with current drug or alcohol abuse/dependence diagnoses (Auther et al., 2012; Kristensen & Cadenhead, 2007), and only one study used a healthy comparison group (Auther et al., 2012). While there is abundant evidence that cannabis is a risk factor for psychosis, the vast majority of cannabis users do not experience psychotic symptoms or develop clinically relevant psychotic disorders (Caspi et al., 2005). Yet, given the high rates of cannabis use in individuals with or at risk for psychosis, as well as the debilitating nature of schizophrenia and other psychotic disorders, it is imperative to understand what distinguishes these at risk individuals from other cannabis users.

**Risk Factors for Psychosis Among Cannabis Users**

The following section examines factors among cannabis users that are associated with increased likelihood of developing psychosis. The focus is primarily on social and psychological risk factors, including age of cannabis initiation, frequency of cannabis use, presence of a comorbid cannabis use disorder, and genetic factors/pre-existing vulnerabilities.

*Age of Cannabis Initiation and Frequency of Cannabis Use*

Research highlights the importance of (1) the age of cannabis use initiation, and (2) the extent of cannabis used, when examining risk for psychosis. Several studies point to the
significance of using cannabis for the first time around the age of 15 years or younger as indicating particularly high risk of psychosis (Arseneault et al., 2002; McGrath et al., 2010; Stefanis et al., 2004; Valmaggia et al., 2014). Specifically, a longitudinal general population study assessed 759 individuals at age 11, and follow up data were obtained regarding drug use, psychiatric symptoms, and DSM-IV diagnoses at ages 15, 18, and 26 (Arseneault et al., 2002). This study found that individuals who initiate cannabis use by age 15 are at increased risk for schizophrenia outcomes compared to those who initiated cannabis use at age 18, even when accounting for childhood subthreshold psychotic symptoms (Arseneault et al., 2002).

Another general population cohort study used a cross-sectional design to assess 3,500 individuals, all aged 19, and measured subthreshold psychotic symptoms using the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2004). This study found that using cannabis for the first time at or before age 15 was associated with a much stronger effect than first use after age 15, and this was independent of lifetime frequency/amount of cannabis use (Stefanis et al., 2004). Finally, Valmaggia et al. (2014) assessed 182 CHR individuals, and although the age range is not specified, the average age of participants was 22, individuals were followed for two years, and results indicated that among cannabis users, those whose first use was prior to the age of 15 had higher rates of transition to psychosis. Although these studies (Arseneault et al., 2002; Stefanis et al., 2004; Valmaggia et al., 2014) utilized some of the same age categories (i.e., comparing cannabis use at or by age 15), it is unclear why these ages were chosen and whether other meaningful differences would emerge if ages at first use were analyzed more broadly, or if different categories were used. Finally, McGrath and colleagues (2010) analyzed 3,801 individuals aged 18-23 and found that compared to individuals who never used cannabis, those who
began using around 15 years or younger were twice as likely to later develop a nonaffective psychosis, and were four times as likely to have high scores on a measure of subthreshold delusional-like experiences (i.e., the Peters et al. Delusions Inventory; PDI) (McGrath et al., 2010). Other studies have also indicated that the age of onset of cannabis use is linearly associated with age of onset of psychosis (Galvez-Buccollini et al., 2012; Leeson, Harrison, Ron, Barnes, & Joyce, 2012). The former study, which analyzed 57 individuals between the ages of 18 and 39, only examined (1) individuals that used cannabis prior to the development of psychosis, and (2) heavy cannabis users, defined as using cannabis 50 or more times within one year (Galvez-Buccollini et al., 2012). Thus, this limits results to only individuals with substantial use and relies on retrospective self-report data that may be biased (Galvez-Buccollini et al., 2012). The latter study assessed 99 individuals between the ages of 16 and 60, and although data were included for all cannabis users (i.e., not just heavy users), individuals who used other drugs or alcohol on more than a monthly basis were excluded, which may limit generalizability (Leeson et al., 2012). Although not all studies support the relationship between earlier age of cannabis use and risk for psychosis (Schimmelmann et al., 2012), numerous findings from the CHR and psychosis literature indicate that earlier age of cannabis initiation is a critical factor for psychosis development.

Frequency of cannabis use also has been highlighted as an important indicator of risk (Stefanis et al., 2004). Research from one study indicates that using cannabis daily or on five or more occasions (the time period is not specified but is assumed to be lifetime use) is associated with all four categories of positive psychotic symptoms: hallucinations, paranoia, grandiosity, and first-rank (e.g., thought withdrawal, thought broadcasting, thought insertion, etc.) symptoms (Stefanis et al., 2004). A dose-response relationship was found, whereby
using cannabis on 2-4 occasions is related to paranoia, grandiosity, and first-rank symptoms (measured using the CAPE, a self-report assessment of subthreshold psychotic experiences), and single use is associated with paranoia and grandiosity (Stefanis et al., 2004). Further, a large cross-sectional general population study found that heavier cannabis consumption (measured by amount of Euros spent per week) is associated with increases in subthreshold positive psychotic symptoms, with the highest consumption category (spending more than 25 Euros per week) associated with being three times as likely of having a top 10 percent score on subthreshold psychotic experiences, measured using the CAPE (Schubart et al., 2011). This study included 17,698 participants aged 18-25, and their measurement of cannabis consumption reflected an attempt to capture the role of high-potency cannabis (i.e., THC exposure) that may be used less frequently (Schubart et al., 2011). Similarly, progression to daily cannabis use is associated with increased risk of psychotic symptoms, although this was determined retrospectively in a sample of individuals with first episode psychosis (FEP), ages 18-40 (Compton et al., 2009). Longitudinal studies show further support that using cannabis more frequently during the premorbid period is associated with greater risk for developing a psychotic disorder (Henquet et al., 2004; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002), with lifetime use of 50 or more times associated with the highest likelihood (Zammit et al., 2002). In summary, substantial evidence exists to support the finding that cannabis users who initiate use at a young age (i.e., at or before age 15) and/or use at a high frequency are more likely to experience subthreshold psychotic symptoms or be at risk for psychosis. Yet, it is important to note that the majority of studies required individuals to recall age of first use (i.e., data were not necessarily collected close to the time of first use), which for many individuals, may have occurred at least six years prior to data collection (e.g.,
Compton et al., 2009; Kristensen & Cadenhead, 2007; Stefanis et al., 2004; Valmaggia et al., 2014).

*Cannabis Use Disorders*

Individuals at CHR for psychosis with a comorbid cannabis use disorder (i.e., cannabis abuse, cannabis dependence) have a higher rate of conversion to psychosis within one-year of baseline assessments as compared to their non-cannabis abusing counterparts (individuals with no cannabis use and cannabis use without impairment were grouped together for this study) (Kristensen & Cadenhead, 2007). This suggests that the level of impairment caused by cannabis may be an indicator of increased risk of psychosis, and even if the reverse were driving the relationship (i.e., individuals at risk for psychosis are more likely to abuse/be dependent upon cannabis), it is still a potential marker that distinguishes cannabis users. Yet, many CHR studies fail to collect data on and/or report substance use; indeed, a recent review of the CHR literature reported that only ten studies exist that (1) were published in English-language peer-reviewed journals, (2) included information on substance use, and (3) reported effects of substance use on conversion rates to psychosis (Addington et al., 2014). Further, a number of CHR studies exclude participants that either developed symptoms shortly after substance use and/or are heavy substance users, due to difficulties in determining whether the reported symptoms are merely due to the short-term psychological consequences of psychoactive substances (Dragt et al., 2012; Leeson et al., 2012; Meyer et al., 2005; Niendam et al., 2007). Therefore, it is unclear whether many, if not most, CHR populations are underrepresenting the influences of substance use on risk for being at CHR for psychosis.
Genetic Factors/Pre-existing Vulnerabilities to Psychosis

Individuals with schizophrenia are at greater risk for developing alcohol and substance abuse disorders compared to the general population (Regier et al., 1990). In addition, family and twin studies indicate that the heritable risk for schizophrenia does not overlap with the heritable risk for alcohol and substance abuse (e.g., Abi-Dargham et al., 2000; see Krystal et al., 2006 for review; Martinez et al., 2005). Indeed, for individuals with diagnoses of schizophrenia and a substance use disorder, it appears that they may have heritable vulnerabilities to both disorders (Cantor-Graae, Nordström, & McNeil, 2001). Studies have suggested that cannabis use has a higher likelihood of being associated with psychotic symptoms when an individual has a family history of psychosis (Miller et al., 2001; Stowkowy & Addington, 2013), and the CHR literature suggests there may be an interaction between cannabis consumption and genetic vulnerability in determining risk for psychosis (Kristensen & Cadenhead, 2007). Yet, this is not always found: a second study using a CHR for psychosis cohort found that cannabis use was not related to psychosis transition in individuals with a family history of psychosis (Valmaggia et al., 2014). However, this study may have been underpowered to detect this effect, as only 14 percent ($n = 25$) of the CHR participants had a family history of psychotic disorders (Valmaggia et al., 2014).

Cannabis users with a pre-existing vulnerability for psychosis may be more susceptible to the psychosis-inducing effects of cannabis than users without a pre-existing vulnerability. Synergistic effects between cannabis and other traits may increase the likelihood that a young cannabis user will be more likely to develop psychosis. Several findings from general population studies indicate that when determining the likelihood of
psychotic symptoms, the joint effect of cannabis use and predisposition for psychosis, measured either using self-report questionnaires assessing subthreshold psychotic- or delusional-like experiences (Henquet et al., 2004; Verdoux et al., 2003) or by a positive family history of schizophrenia (Giordano, Ohlsson, Sundquist, Sundquist, & Kendler, 2014), is greater than measuring either of those variables individually, thus suggesting that cannabis may be more of a component risk factor. Indeed, a four-year longitudinal study compared individuals with and without a predisposition for psychosis, measured using the paranoid ideation and psychoticism subscales of the Symptom Checklist (i.e., SCL-90-R), and found that the effect of baseline cannabis use on psychosis outcome was much greater in those with the predisposition (Henquet et al., 2004). There is also evidence that a functional polymorphism in the COMT gene may interact with cannabis use during adolescence to predict later psychosis (Caspi et al., 2005); however, most studies have failed to support this finding (Costas et al., 2011; van Winkel, 2011; Zammit et al., 2007; Zammit, Owen, Evans, Heron, & Lewis, 2011).

Similarly, cannabis use and the presence of other environmental risk factors may further increase risk of psychosis either interactively or additively. The combined presence of cannabis use and childhood trauma among adults is associated with higher rates of psychosis (Wu, Schairer, Dellor, & Grella, 2010), and individuals dependent on cannabis are five times more likely to endorse psychotic symptoms (measured using a brief screener from the Structured Clinical Interview for DSM-IV-TR) if they were abused as children (Banducci, Hoffman, Lejuez, & Koenen, 2014). Further, Harley and colleagues (2010) reported that the joint presence of cannabis use and childhood trauma increases the likelihood of experiencing psychotic symptoms, and this joint effect is greater than the individual effects of each risk.
factor, suggesting a greater than additive interaction between the two environmental risk factors. Overall, there is substantial evidence suggesting that pre-existing vulnerabilities (i.e., family history, predisposition, or trauma history) may be a factor that differentiates young cannabis users who will and will not experience subthreshold psychotic symptoms and/or be at risk for psychosis. Yet, despite the empirical support, few studies collect data on these variables, or, they have controlled for pre-existing vulnerabilities (e.g., Arseneault et al., 2002; Caspi et al., 2005) or history of trauma (Kuepper et al., 2011), but do not examine whether they account for or better explain the relationship between cannabis and psychosis.

**Neurobiology of Cannabis**

Cannabis has a vast number of chemical constituents: THC is its most active constituent, and cannabidiol is one of several other cannabinoids (ElSohly & Slade, 2005). Whereas THC is the major psychoactive constituent, cannabidiol is believed to have anxiolytic and antipsychotic effects (Leweke, Schneider, Radwan, Schmidt, & Emrich, 2000). THC exerts its psychogenic effects via stimulation of the cannabinoid 1 (CB1) receptor (Huestis et al., 2001), which is the most prevalent G-protein-coupled receptor in the brain (Di Marzo, Bifulco, & De Petrocellis, 2004) with high concentrations found in the frontal cortex, basal ganglia, hippocampus, and cerebellum, all brain regions that have been associated with the neural circuitry of psychosis (see D’Souza, Sewell, & Ranganathan, 2009). The CB1 receptor then inhibits pre-synaptic neurotransmitter release, the targets of which are GABA and glutamate terminals, and influences the dopamine system and other neurotransmitter systems (Chevaleyre, Takahashi, & Castillo, 2006). While the acute effect of THC in animals and humans has been demonstrated and associated with transient positive and negative psychotic-like symptoms (D’Souza et al., 2000) and increases in extracellular
dopamine in the brain, repeated and heavy THC exposure may ultimately decrease dopamine
levels in the prefrontal cortex (see Kuepper et al., 2010).

Evidence from the psychosis literature suggests the presence of genetic
polymorphisms that may increase an individual’s risk of psychosis with cannabis exposure.
The COMT gene, which plays a role in the breakdown of dopamine, may regulate the
association between cannabis and psychosis. The COMT gene contains a functional
polymorphism, and the Val allele of this polymorphism is related to greater COMT activity,
and therefore decreased levels of prefrontal dopamine (Akil et al., 2003). Research suggests
that individuals with the Val/Val COMT genotype are at increased odds of developing
psychosis after adolescent cannabis exposure, compared to those with the Met/Met or
Val/Met genotypes (Caspi et al., 2005). This polymorphism, however, was not associated
with proneness to earlier use of cannabis or heavier use of cannabis (Caspi et al., 2005).
Zammit and colleagues (2007) investigated whether variations within the cannabinoid
receptor (CNR1) gene (which may modulate striatal dopamine) were associated with
schizophrenia, and whether there is a differential effect with cannabis use. However, they
failed to find any associations between schizophrenia and a polymorphism in the CNR1 gene
(Zammit et al., 2007), and other studies have failed to find an association between CNR1 and
substance use (Martinez-Gras et al., 2006). There is also a possibility that interactions
between the cannabinoid and gamma-aminobutyric acid (GABA) systems, and the
cannabinoid and glutamatergic systems may also explain the psychotomimetic effects of
THC (see D’Souza et al., 2009 for review; Fernandez-Espejo, Viveros, Núñez, Ellenbroek, &
Rodriguez de Fonseca, 2009). It is likely that multiple variations within numerous genes,
rather than single genetic polymorphisms, play a role in the interaction between cannabis and psychosis risk.

**Prevalence of Cannabis Use in the General Population**

It is widely established that alcohol and nicotine are generally the most commonly used substances among adolescents and young adults, and this is closely followed by cannabis (Bauman & Phongsavan, 1999). The popularity of cannabis as a recreational drug began in the early 1970s and the proportion of young adults using cannabis has steadily increased since this time, while the age of first use has declined (Degenhardt et al., 2008; Hall & Pacula, 2003). Cannabis is the most commonly used illicit substance around the world (Bauman & Phongsavan, 1999; Johnston, O’Malley, Bachman, & Schulenberg, 2011), and fewer adolescents consider cannabis use to be associated with significant health risks (Johnston et al., 2011). Males typically use and abuse cannabis more often than females (Kandel, Chen, Warner, Kessler, & Grant, 1997; von Sydow et al., 2001), and females may have a lower cumulative lifetime incidence of use (von Sydow et al., 2001). The majority of people initiate cannabis use during mid-adolescence (Chen & Kandel, 1995; Hall & Pacula, 2003), and recent cannabis use is highest among 18 to 25 year-olds, with 16 percent of this age group reporting use within the past month (Vicente, Olszewski, & Matias, 2008). According to the Substance Abuse and Mental Health Services Administration (2013), approximately seven percent of adolescents/young adults aged 12 to 17 are current cannabis users. Another national survey, the Monitoring the Future study (2013), reported a history of cannabis use in approximately 45 percent of twelfth graders, with 6.5 percent reporting current daily use (Johnston, O’Malley, Miech, Bachman, & Schulenberg, 2014). Further, the likelihood of trying cannabis increases from adolescence to young adulthood, from 29
percent at age 14, to 33 percent at age 16, and to 54 percent at age 22 (Brook, Brook, Zhang, Cohen, & Whiteman, 2002). Such findings suggest that a large percentage of young adults have a lifetime history of using cannabis, and a smaller percentage are using at a high frequency.

Many researchers agree that for the majority of cannabis users, their pattern of use is relatively transient and recreational, showing no major risks or problems and a high rate of spontaneous remission (Chen & Kandel, 1998; von Sydow et al., 2001). Few lifetime cannabis users will actually go on to develop clinically significant symptoms and patterns of cannabis abuse or dependence (Perkonigg et al., 1999; Weinberg, Rahdert, Colliver, & Glantz, 1998). Problematic use is typically associated with poor academic achievement, antisocial behavior, poor parental relationships, use of other illicit substances, and psychological health problems (Coffey, Carlin, Lyskey, Li, & Patton, 2003; Hall & Solowij, 1998; Macleod et al., 2004). Although there is variability in patterns of cannabis use and escalation to disorder over time, a substantial proportion of cannabis users eventually discontinue use (typically in their mid-20’s), even after sustained and heavy use, due to transition to new responsibilities such as jobs, relationships, and/or parenthood (Chen & Kandel, 1995; von Sydow et al., 2001). Thus, for the majority of young cannabis users, use is short-term and without major disturbance.

**Characteristics of Cannabis Use in Healthy Adolescent and Non-Psychotic Populations**

Cannabis use initiation in healthy, non-psychotic adolescents and young adults has been extensively researched, as has the more global pattern of cannabis use in these populations. An extensive analysis of this literature is beyond the scope of this review (but see: Flory, Lynam, Milich, Leukefeld, & Clayton, 2004; Hawkins, Catalano, & Miller, 1992;
Verweij et al., 2010); thus, herein is a brief discussion of the many years of research into the profiles of cannabis users in non-psychotic populations. Later, it will be determined whether many of the characteristics associated with cannabis users in non-psychotic populations extend to: (1) individuals at risk for psychosis or individuals from the general population with variations in APPS, and/or (2) psychotic populations.

Role of Peer Influences and Social Functioning

There are numerous factors that contribute to substance use initiation during adolescence/early adulthood. Among these include factors within the individual and their environments, including influences from families and peers (Chabrol et al., 2006; Ellickson, Bird, Orlando, Klein, & McCaffrey, 2003; Hawkins et al., 1992). Supporting sibling or parent use and peer influence as important factors in drug initiation is social learning theory (Bandura, 1977). Social learning theory posits that a behavior is more likely to occur when (1) an individual is exposed to the behavior, and (2) the behavior is reinforced by valued others. As this relates to drug use, an individual’s drug use behavior is largely influenced by the behaviors of their family and peers. Indeed, adolescents who report parental use of cannabis are twice as likely to use cannabis, although this was not parsed apart from genetic liability (Li, Pentz, & Chou, 2002). Additionally, social learning theory postulates that certain beliefs about the environment will be formed based on perceptions of others’ behavior (Kandel, 1978; Maisto, Carey, & Bradizza, 1999). This is illustrated by research indicating that adolescents’ overestimation of peer substance use contributes to increased substance use behaviors, indicating that the perceived level of drug usage is often more impactful than actual usage (Ellickson et al., 2003). Hence, when an adolescent is exposed to drug-using behaviors by friends, siblings, or parents, or if their perception is that these individuals use,
the adolescent is more likely to initiate drug use. Yet, practically, it is difficult to parse apart an adolescent modeling parental use of cannabis from genetic liability of cannabis use.

Peer influences have been found to substantially contribute to and exacerbate substance use behaviors in healthy adolescents and young adults. Although genetic liability plays a major role in susceptibility to drug use, abuse, and dependence (Gruber & Pope, 2002), the role that peers play in influencing initiation of drug use in healthy adolescents has long been thought to be the strongest proximal influence on substance use behaviors (Steinberg, Fletcher, & Darling, 1994). Support for the critical role of peers in drug initiation comes, in part, from the observation that adolescents who use illicit substances typically have friends who also use, and adolescents that do not use drugs tend to have friends who also do not use (Allen, Chango, Szwedo, Schad, & Marston, 2012; Blount & Dembo, 1984; Chabrol et al., 2006; Hawkins, Lishner, Catalano, & Howard, 1986; Huba, Wingard, & Bentler, 1979; Kandel, 1978; Kandel, 1973; Needle et al., 1986). Some of the observed similarity in substance use patterns among friends is the result of selection, or the propensity for substance-using adolescents to seek out friendships with like-minded individuals (Kandel, 1973). Yet, research also indicates that peers impact each other’s behavior beyond their initial similarity (Allen et al., 2012; Billy & Udry, 1985; Dishion, Reid, & Patterson, 1988; Kandel, 1973), pointing to the importance of the role of socialization. Both selection and socialization are important processes for initiation of drug use: adolescents who share particular characteristics are more likely to become friends, and as peers spend more time with one another, they become more similar over time (Kandel, 1985). With socialization, similarity among peer groups evolves over time due to association and interpersonal influence (Kandel, 1985). Evidence from animal research indicates that the impact of peers on adolescent
alcohol use is hard-wired, and not simply a result of peer pressures or desire to gain group inclusion or admiration of peers (Logue, Chein, Gould, Holliday, & Steinberg, 2014). Logue and colleagues (2014) found that the presence of peers increased alcohol consumption in adolescent, but not adult, mice, indicating that the impact of peers on reward seeking exists across species and is particularly salient during adolescence.

Interestingly, there is evidence to suggest that specifically for cannabis use, the influence of peers, or the socialization effect, may slightly outweigh that of selection (Kandel, 1978; Pearson, Steglich, & Snijders, 2006). Indeed, perception of peers’ behaviors may be more important in predicting initial cannabis use than the peers’ actual use of cannabis (D’Amico & McCarthy, 2006; Kandel, Kessler, & Margulies, 1978). Not surprisingly, these peer influences include the adolescents’ values and attitudes towards cannabis use (i.e., that it is a benign substance and/or should be legalized) and these are critical predictors of initiation of cannabis use (Kandel et al., 1978; Pearson et al., 2006). Overall, Kandel and colleagues (1978) suggest a multitude of ways in which peer influence contributes to cannabis use: healthy adolescents are more likely to initiate use of cannabis if (1) their friends also use, (2) they believe that their friends are using, and/or (3) they share beliefs with their friends that promote cannabis use and are counter to adult standards.

Motivations for Cannabis Use

The self-reported reasons for cannabis use are critical to examine as they may play a role in the development of cannabis abuse or dependence (Patrick, Schulenberg, O’Malley, Johnston, & Bachman, 2011). Within healthy, non-psychotic adolescents, motivations for using cannabis often involve the desire to ‘get high,’ relax, and increase pleasure (Pencer & Addington, 2008), and this has been consistent across studies with others identifying social
motives, enhancement, coping, and conformity as reasons for cannabis use, measured using the Marijuana Motives Measures (Zvolensky et al., 2007). Other motivations for cannabis use include a desire to manipulate perceptions (this study allowed recent high school graduates to provide self-generated reasons) (Lee, Neighbors, & Woods, 2007) or expanding awareness (Zvolensky et al., 2007). Indeed, a predictor of initiation of use in healthy young adults is the desire to experience its effects (Kandel et al., 1978). Reasons for cannabis use that involve conformity and desire to experiment is associated with fewer substance use problems, while being motivated to use in order to alleviate negative affect predicts future cannabis use disorder symptoms (Patrick et al., 2011).

**Context of Cannabis Use**

Research indicates that the majority of adolescent drug use takes place within social settings (Kandel et al., 1978; Newcomb & Bentler, 1989; Tucker et al., 2014), which may provide further support that healthy adolescents learn patterns of drug use from socializing agents (i.e., peer groups). Further, whether an adolescent uses substances alone or with others can be an important predictor for later problematic substance use (e.g., King & Chassin, 2007; Swift, Coffey, Carlin, Degenhardt, & Patton, 2008). One study assessed a sample of eighth-grade substance users, and those that used by themselves were more likely than those who used in social settings to report a substance abuse problem by the age of 23 (Tucker, Ellickson, Collins, & Klein, 2006), and a second longitudinal study indicated that solitary alcohol drinkers had more alcohol use disorder symptoms within the past year compared to social drinkers (Creswell, Chung, Clark, & Martin, 2013). Further, drinking alcohol in isolation may indicate that an individual is using to self-medicate against negative affect, which has been indicated by increased levels of mood symptoms among solitary drinkers and
reported reasons for drinking (Creswell et al., 2013; Tomlinson & Brown, 2012). Thus, evidence suggests that the context in which a young adult uses alcohol or substances may be a key indicator of substance use severity or other psychopathology, although most non-psychotic individuals are using with peers (Tucker et al., 2014).

**Negative, Mood, and Anxiety Symptoms**

In non-psychotic young adults, studies have shown strong relationships between mood/anxiety symptoms and cannabis use (Buckner, Heimberg, Schneier, et al., 2012; Wittchen et al., 2007). Specifically, major depression may predict increased rates of cannabis use and dependence (Wittchen et al., 2007), although a number of longitudinal studies of children and adolescents have failed to find this association (see Degenhardt, Hall, & Lynskey, 2003 for review; Hofstra, van der Ende, & Verhulst, 2002). Further, heavy, but not infrequent, cannabis use is associated with increased likelihood of experiencing depression (Degenhardt et al., 2003). Similarly, compared to the other anxiety disorders, social anxiety disorder is robustly associated with cannabis abuse and dependence and may be uniquely related to cannabis dependence (Buckner, Heimberg, Schneier, et al., 2012). Indeed, individuals with clinically significant levels of social anxiety are more likely to use cannabis to cope in a social situation, and they are more likely to avoid a social event if cannabis is unavailable (Buckner, Heimberg, Matthews, & Silgado, 2012).

**Characteristics of Cannabis Use in Individuals With or at Risk for Psychosis**

Despite a large body of research on processes contributing to the initiation of cannabis use among non-psychotic adolescents and young adults, many of these factors have yet to be comprehensively investigated in psychosis research. The following section seeks to determine whether many of the risk factors that have been associated with cannabis use in
non-psychotic populations have been associated with CHR individuals who use cannabis, and individuals with psychosis, or whether this has yet to be explored.

Role of Peer Influences and Social Functioning

Although it is clear from decades of research that peers play an important role in influencing cannabis use in young adults, it is presently unknown whether peers play a critical role in initiation of cannabis use in young adults at CHR for psychosis, individuals with psychosis, or those experiencing APPS. However, there has been abundant research on social functioning in these populations. Deficits in social functioning are among the most robust behavioral correlates of genetic risk for psychotic disorders, and are present in many at risk individuals from childhood (at risk based on parental history of schizophrenia or schizoaffective disorder: Dworkin, Lewis, Cornblatt, & Erlenmeyer-Kimling, 1994; Hans, Auerbach, Asarnow, Styr, & Marcus, 2000; Tyrka et al., 1995; at risk based on CHR criteria: Cannon et al., 2008). Social deterioration is a pronounced feature of the initial stages of schizophrenia (Birchwood, Todd, & Jackson, 1998; Grant, Addington, Addington, & Konnert, 2001), and studies investigating individuals with FEP indicate that they experience marked difficulty sustaining any relationships outside of their immediate family, and thus often remain financially dependent upon their parents or public assistance (Gillberg, Hellgren, & Gillberg, 1993; Lay, Blanz, Hartmann, & Schmidt, 2000; Vyas, Hadjulis, Vourdas, Byrne, & Frangou, 2007). As the onset of psychosis typically occurs during late adolescence, disruptions in an individual’s ability to function socially at this developmental phase can have a harmful impact on the long-term duration of untreated psychosis (Malla et al., 2002; Norman, Malla, & Manchanda, 2007) and long-term clinical outcomes (Couture, Lecomte, & Leclerc, 2007). Thus, the role of social functioning appears to be a critical
element of outcome for individuals with or at risk for psychosis. Substance-using individuals with schizophrenia may have better social functioning compared to non-substance users, but they report a greater number of problems with their family relationships (Salyers & Mueser, 2001). In this study, social functioning was assessed from both the patient and a close relative using the Social Adjustment Scale, and this includes social/leisure, interpersonal/family relations, romantic, and role functioning domains (Salyers & Mueser, 2001). A study with FEP individuals indicated that those who continued using cannabis over time had worse functioning (measured using the Global Assessment of Functioning; GAF) than cannabis users that stopped smoking at onset of psychosis, but had better functioning than individuals who never used cannabis (Baeza et al., 2009). These results may extend to individuals with FEP, as another study found that cannabis users had better social functioning (measured using the Social Function Scale, which assesses various areas of social and daily functioning) at psychosis onset than those who never used (Leeson et al., 2012). On the other hand, cannabis use in individuals with schizophrenia has also been associated with worse psychosocial functioning, measured with the Global Assessment Scale (GAS), compared to non-users (Caspari, 1999). Despite the strong correlates of social functioning and schizophrenia outcomes, there is less clarity on how social functioning compares in individuals with and without a history of cannabis use. Further, several of the studies that have examined this used measures of overall functioning (i.e., GAF and GAS), and are not specific to social functioning (Baeza et al., 2009; Caspari, 1999).

Preliminary findings suggest that CHR populations that use cannabis may, in fact, have better social functioning than their non-cannabis using counterparts. A study on FEP individuals evaluated premorbid (i.e., more than one year prior to onset of prodromal
symptoms) use of cannabis and social functioning, measured using the Premorbid Adjustment Scale (Compton et al., 2011). This study found better social functioning, characterized by sociability and withdrawal, peer relationships, and social-sexual functioning, during early adolescence (but not late adolescence) in those that used cannabis, compared to non-cannabis users (Compton et al., 2011). Ather and colleagues (2012) found that CHR adolescents with comorbid cannabis use had significantly higher social functioning at baseline and follow-up than non-cannabis users. Further, CHR individuals who met DSM-IV criteria for cannabis abuse also had superior social functioning, measured using the Global Functioning: Social Scale, a scale that takes into account contact with friends, family and intimate relationships, when compared to non-cannabis abusers at a two-year follow-up (Auther et al., 2012). Coupled with the finding that cannabis use was not related to later onset of psychosis in this study and that the cannabis users reported fewer negative symptoms and lower social anhedonia, it is possible that increased sociability leads to more opportunities to be exposed to cannabis (Auther et al., 2012). However, this study did not have information regarding rates of using cannabis alone compared to using cannabis in social groups. Lacking in the majority of these studies (with the exception of Auther et al., 2012) is inclusion of a healthy comparison sample, composed of cannabis users and non-users. Cumulatively, there are contrasting results between the psychosis literature and data from the CHR literature regarding social functioning and cannabis use.

Motivations for Cannabis Use

Similar to healthy young adults and non-psychotic individuals, research suggests that patients with schizophrenia also use cannabis to increase pleasure and improve mood, as well as for social motives that include being accepted by their peers (Spencer et al., 2002), or to
relieve boredom and provide stimulation (Mueser, Bellack, & Blanchard, 1992; Noordsy et al., 1991; Test, Wallisch, Allness, & Ripp, 1989). An additional motive for using cannabis found in patient populations is to relieve positive psychotic symptoms and medication side effects, although these are not endorsed as often (Spencer et al., 2002). Similar reasons are endorsed by patients with FEP: they report using cannabis for the same reasons as their non-psychotic peers, including to ‘get high,’ to increase pleasure, and to relax (Kolliakou et al., 2015; Pencer & Addington, 2008). Although FEP adolescents are not as likely to use substances like alcohol and cannabis to self-medicate positive psychotic symptoms, they do use cannabis to alleviate other concerns related to psychosis, specifically to relieve depression, to concentrate better, to feel more emotions, and to go along with their peer group (Pencer & Addington, 2008).

Overall, there are only three studies to date that compare the reasons for cannabis use between cannabis-using individuals with psychosis and cannabis-using individuals without psychosis (Green, Kavanagh, & Young, 2004; Saddichha, Prakash, Sinha, & Khess, 2010; Schaub, Fanghaenel, & Stohler, 2008). According to these studies, cannabis users with and without a psychotic disorder diagnosis endorse many of the same reasons for using cannabis, including for positive mood alteration, coping with negative affect, and for social activity reasons (Green et al., 2004; Saddichha et al., 2010; Schaub et al., 2008). However, there are some differences in the expectations and reasons for use between the two cannabis-using groups: individuals with psychosis are less likely to report relaxation as the most important effect experienced after using, and are less likely to expect to feel relaxed compared to cannabis users without a psychosis history (Green et al., 2004). When examining factors for initiating cannabis use, there were no significant differences between individuals with only
cannabis dependence compared to individuals with schizophrenia and cannabis dependence (Saddichha et al., 2010). Yet, the same study found that the two cannabis-using groups reported different reasons for continued use. The cannabis-use only group attributed their cannabis dependence to external factors (e.g., nature of work, social setting, pressure from peers), whereas the individuals with a dual diagnosis of schizophrenia and cannabis dependence were more likely to attribute it to internal factors (e.g., cope with negative affect, improve self-esteem) (Saddichha et al., 2010; Schofield et al., 2006). Further, reasons generated for cannabis use relapse significantly differed between the substance dependence-only and dual diagnosis individuals. Typically, individuals with a substance-only diagnosis attribute cannabis relapse to external factors: watching peers use, wanting to use after eating or drinking, or taking it with other substances (Chandrasekaran, Sivaprakash, & Chitraleka, 2001; Fowler, Carr, Carter, & Lewin, 1998; Herkenham, 1992; Iversen, 2003; Saddichha et al., 2010; Test et al., 1989). On the other hand, the dual-diagnosis patients attributed their cannabis relapse to internal factors: for increased concentration, to improve positive affect, and to alleviate withdrawal symptoms (Saddichha et al., 2010). This pattern of results suggests that the course of cannabis dependence is experienced differently by individuals with and without psychosis, and those with comorbid diagnoses may differ in their expectations that cannabis will elevate their mood (Herkenham, 1992; Iversen, 2003; Saddichha et al., 2010; Tupala & Tiihonen, 2004). Interestingly, the reasons why some FEP individuals report using cannabis (i.e. to reduce internal psychopathology such as depression or anxiety levels) are incongruent with the reported effects of the drug; that is, individuals often do not describe feeling relief from these symptoms after using (Addington & Duchak, 1997; Green et al., 2004; Swendsen, Ben-Zeev, & Granholm, 2011).
Only one study to date has researched motivations for cannabis use in individuals at CHR for psychosis (Gill et al., 2013). According to that study, CHR individuals most commonly endorse using cannabis for enhancement of mood (e.g., to get high or for fun); however, this study measured cannabis use only within the past month, only 24 participants (23 percent of the sample) used cannabis, the sample was primarily male (approximately 75 percent), and did not include a same-aged cannabis users comparison group (Gill et al., 2013). In order to differentiate young cannabis users who are and are not at risk for psychosis, the motivations for use are best understood when evaluating all cannabis-using individuals, not only patient populations. Yet, no study to date has examined motivations for use in a non-clinical, general population study that measures psychotic symptoms dimensionally and reasons for use comprehensively.

Context of Cannabis Use

Despite the findings that the majority of adolescent drug use takes place within social settings (Newcomb & Bentler, 1989), it is unclear whether these findings apply to young adults with APPS and/or at CHR for psychosis. One study observed that individuals with a dual diagnosis of a psychotic illness and cannabis dependence tended to use cannabis more often alone, compared to individuals with only a cannabis dependence diagnosis (Saddichha et al., 2010). This was attributed to the internal factors that the dual-diagnosis individuals gave for maintaining cannabis use and reasons for relapse (i.e., to help concentrate, increase positive affect) (Saddichha et al., 2010). One study examined the social context of cannabis use among schizophrenia patients (who used multiple substances, including alcohol), and found that most of these individuals used substances with others (Test et al., 1989), but this finding may be inflated by use of alcohol in bars and restaurants. There is a long-standing gap
in the literature regarding the social contexts in which individuals with schizophrenia use
drugs and alcohol, and further examination is warranted, as it may help explain the high rates
of comorbidity with substance use disorders (Phillips & Johnson, 2001). The context of
cannabis use for young adults with increases in APPS is presently unknown, and only one
study to date has examined context of cannabis use in individuals at CHR for psychosis, and
found that they are more likely to use cannabis alone compared to healthy controls (Buchy et
al., 2015). Determining whether context of cannabis use (i.e., using alone or in social
settings) is related to severity of psychotic symptoms or likelihood of psychosis may assist in
differentiating cannabis users who may be at greater risk for psychosis.

**Negative, Mood, and Anxiety Symptoms**

Negative symptoms are common features of schizophrenia, and are characterized by
avolition or diminished emotional expression (American Psychiatric Association, 2013).
Individuals with significant negative symptoms are typically characterized as having
particularly poor functioning and quality of life (Wegener et al., 2005), and negative
symptoms have not been as amenable to psychopharmacological treatment as positive
symptoms (Leucht, Pitschel-Walz, Abraham, & Kissling, 1999). Endorsement of negative
symptoms has been researched in relation to cannabis use in individuals with psychosis, but
findings are mixed. Numerous studies using psychosis populations have found that cannabis
users experience fewer negative symptoms compared to non-users (Baeza et al., 2009;
Bersani, Orlandi, Kotzialidis, & Pancheri, 2002; Compton, Whicker, & Hochman, 2007;
Salyers & Mueser, 2001), although other studies have found no differences in the number of
negative symptoms experienced between cannabis users and non-users with schizophrenia
(Addington & Addington, 2007; Caspari, 1999; Grech, van Os, Jones, Lewis, & Murray,
However, some of these studies combined cannabis users with other drug users (Salyers & Mueser, 2001), making it difficult to parse apart the individual role of cannabis, others analyzed only males (Bersani et al., 2002), thus limiting generalizability, and many studies grouped all negative symptoms together (Addington & Addington, 2007; Baeza et al., 2009; Grech et al., 2005; Stirling et al., 2005). Further, the time course in which the cannabis use takes place is critical to note, as one study of individuals with schizophrenia indicated the presence of fewer negative symptoms in only those who used cannabis prior to the onset of psychosis (Dubertret, Bidard, Adès, & Gorwood, 2006).

The literature from general population studies also indicates varied results regarding the association between cannabis use and negative symptoms. Cannabis use in the general population has been associated with increases in subthreshold negative symptoms, measured using items from the CAPE (Schubart et al., 2011; Stefanis et al., 2004). Schubart and colleagues (2011) found that young adults who use cannabis excessively, measured by spending more than 25 Euros per week on cannabis, are more likely to experience negative symptoms, and another large general population study found that cannabis use was positively associated with negative symptoms in a dose-response manner, and this held when adjusting for positive and depressive symptoms (Stefanis et al., 2004). Those with an earlier age of first cannabis use had a greater likelihood of experiencing negative symptoms compared to individuals who used after the age of 15 (Schubart et al., 2011). However, it is unclear whether cannabis use was associated with any negative symptoms in particular, and/or whether there are other factors, in addition to age of first use, that differentiate cannabis users that are more likely to experience negative symptoms (Schubart et al., 2011; Stefanis et al.,
In contrast to the findings that cannabis use is positively associated with negative symptoms, at least one study found that increases in cannabis use in individuals at CHR are related to decreases in negative symptoms, measured using the negative symptom dimension from the Scale of Prodromal Symptoms (Auther et al., 2012). Although the evidence in psychosis populations indicates that cannabis use is typically associated with fewer or no difference in negative symptoms (Addington & Addington, 2007; Baeza et al., 2009; Bersani et al., 2002; Caspari, 1999; Compton et al., 2007; Grech et al., 2005; Salyers & Mueser, 2001; Stirling et al., 2005), the evidence is less clear in the CHR literature. Clarification of the association between negative symptoms and cannabis use among those with APPS or at CHR for psychosis may be useful for improving diagnosis and treatment of individuals at CHR for psychosis.

Symptoms of depression and anxiety commonly occur prior to the onset of psychosis (Myles-Worsley, Weaver, & Blailes, 2007; Rosen, Miller, D’Andrea, McGlashan, & Woods, 2006; Yung et al., 2004), and they are associated with subthreshold psychotic symptoms in the general population (Reeves et al., 2014; Wigman et al., 2012). The relationship between cannabis, mood/anxiety symptoms, and psychosis is complex. FEP patients with cannabis abuse and subthreshold depressive symptoms have poorer clinical and functional outcomes during a five-year follow-up compared to their counterparts without depressive symptoms (González-Ortega et al., 2015). Continuing to experience subthreshold depressive symptoms during the follow-up period was associated with maintained use of cannabis, which together may be associated with poorer functional outcomes (determined by the Global Assessment of Functioning) (González-Ortega et al., 2015). One general population study suggests that symptoms of generalized anxiety mediate the relation between cannabis use and APPS.
(Reeves et al., 2014), and another found that social anxiety moderates the relationship between schizotypy symptoms and frequent cannabis use (Najolia, Buckner, & Cohen, 2012). Further, depression and trait anxiety may moderate the relationship between positive schizotypy traits and cannabis use frequency (Najolia et al., 2012). Therefore, it is possible that the association between cannabis use and psychotic symptoms may be related, at least in part, to premorbid and/or prodromal mood and anxiety symptoms. It is clear that further understanding of the mood and anxiety symptomatology of cannabis users with and without increases in APPS is warranted. One study suggesting that heavy cannabis use is associated with the development of psychotic symptoms in a non-clinical sample controlled for diagnoses of anxiety and depression, rather than subthreshold anxiety/depressive symptoms (Fergusson, Horwood, & Swain-Campbell, 2003). Yet, individuals experiencing APPS may not yet have developed a clinical disorder, and their experiences may be best represented using a dimensional approach (Wigman et al., 2012).

**Remarks**

As is evident from the research discussed thus far, there is no single profile of young adults who are cannabis users. Healthy adolescents and non-psychotic individuals who use cannabis likely have different profiles from cannabis-using young adults at CHR for psychosis, individuals from the general population with variations in APPS, and cannabis-using individuals with chronic psychotic disorders.

Although there are variations of this profile, quite generally, healthy adolescents typically use cannabis for experimentation and for social motives, their use is transient, occurs within social settings, and is largely due to peer influences (e.g., Pearson et al., 2006; Pencer & Addington, 2008; Tucker et al., 2014; von Sydow et al., 2001). The research on
individuals at CHR for psychosis is more mixed: cannabis users at CHR for psychosis appear to have good social functioning (e.g., Auther et al., 2012), and only one study has evaluated their motivations for use and they appear similar to their non-psychotic counterparts (Gill et al., 2013). Further, only one study has examined whether cannabis users at CHR for psychosis are more likely to use cannabis alone or with others compared to their healthy control counterparts, and found that they typically use in isolation (Buchy et al., 2015). In addition, it is unclear whether they experience a greater number of negative symptoms than non-users. Even less is known about the general population: cannabis-using individuals who vary on levels of APPS appear to have greater negative and anxiety symptoms compared to non-cannabis users (Schubart et al., 2011), but their context of use, motivations of use, and social functioning is currently unknown.

Individuals with a psychotic disorder and comorbid cannabis use may have better social functioning, although this has not been extensively reviewed, they use cannabis for many of the same reasons as non-psychotic individuals, but also to relieve symptoms associated with psychosis (i.e., depression), they may use cannabis alone more often than with others, and they may have fewer negative symptoms compared to non-users (e.g., Baeza et al., 2009; Pencer & Addington, 2008; Saddichha et al., 2010; Salyers & Mueser, 2001). In sum, there is a large body of research on the processes that contribute to cannabis use, and the characteristics of cannabis users, in non-psychotic populations. Many of these factors and processes have not yet been examined in psychosis studies, or, there are major variations in the measures used that make comparison between studies difficult.

Further, there is a dearth of research delineating the characteristics that differentiate young, cannabis-using individuals who have increases in APPS and/or who may be at risk for
psychosis from those with fewer APPS and/or who are not at risk for psychosis. No study has systematically evaluated young cannabis users to (1) identify variations in the experiences of cannabis use, in order to (2) parse apart which cannabis users are most at risk for psychosis. In order to do so, young cannabis users at risk for psychosis should be compared to other cannabis users who are not at risk. One method to evaluate varying risk levels is by measuring psychotic symptoms dimensionally, such as by APPS, in the general population. It is likely that there are variations of individual and contextual-level characteristics of cannabis users who endorse APPS, and/or who are at CHR for psychosis. It is currently unknown whether subgroups of cannabis users who differ by patterns of social functioning, internalizing psychopathology, and/or cannabis use characteristics, can be identified, with subgroups differing on psychosis outcomes. Yet, such research would greatly inform identification of risk factors and treatment for those at risk for psychosis. For example, it is possible that certain motivations for cannabis use (e.g., coping with mood or anxiety symptoms) are associated with increases in APPS and/or being at CHR for psychosis, and that other motivations for use (e.g., social motives, conformity, or acceptance) are associated with fewer APPS and low risk for psychosis. The elucidation of individual characteristics of cannabis users with and without APPS is a novel approach to understanding the role of cannabis use in psychosis, and improved understanding of these characteristics may inform treatment via social skills training or other psychosocial interventions to address the mood, anxiety, or negative symptoms that could be part of initial motivations for using cannabis.

Determining the role of cannabis in the etiology of psychosis has become increasingly critical with the legal standing of the drug at a turning point in the United States.
With three states and the District of Columbia passing legislation to legalize the commercial production and sale of cannabis (Colorado Amendment 64, 2012, Washington Initiative 502, 2012), understanding its role in psychosis is paramount. With the recent trend of individuals initiating use at a younger age (Monshouwer, Smit, De Graaf, Van Os, & Vollebergh, 2005) and evidence indicating that fewer adolescents consider cannabis use to be associated with significant health risk (Johnston et al., 2011), further research on the association between cannabis use and psychological health is needed to inform public health policy. Additionally, given findings that both cannabis (van Os et al., 2002) and lower social functioning (Cannon et al., 2008) are important contributors to the development of psychotic disorders, and that peer influence and socialization are important to the initiation of cannabis use in healthy young adults (Kandel, 1978), it is imperative to understand how these factors relate to individuals with increases in APPS. Clarification of whether these peer processes operate similarly among those with and without APPS may help identify cannabis users at higher risk of psychosis. There is also a need to examine various individual and contextual-level factors that may differentiate young cannabis users who are and are not at risk for psychosis. Even if the association is non-causative between cannabis use and risk for psychosis (i.e., cannabis causes psychosis or cannabis is used for self-medication reasons), characterizing subgroups of cannabis users who are at increased risk for psychosis will aid in improving early identification and detection of at risk youth.
CHAPTER 2
INTRODUCTION

Cannabis use has continually been associated with a wide range of psychosis outcomes. At the severe end of the psychosis spectrum, cannabis use is highly prevalent in individuals diagnosed with schizophrenia or schizophrenia-related disorders (Arseneault et al., 2002; McGrath et al., 2010) and comorbid cannabis use has been associated with a worse course of the disorder, evidenced by greater impairments in psychosocial functioning (Caspari, 1999) and frequent and earlier psychotic relapses (Linszen et al., 1994). Similarly, escalation to daily cannabis use is associated with increased risk of psychotic symptoms among those with first-episode psychosis (Compton et al., 2009), while cannabis abuse (but not alcohol or cocaine abuse/dependence) (Kristensen & Cadenhead, 2007) and frequent or early-onset use (Valmaggia et al., 2014) is related to conversion to psychosis in individuals at clinical high risk. At the less severe end of the psychosis spectrum, early exposure to cannabis (Schubart et al., 2011; Stefanis et al., 2004) or heavy use (Schubart et al., 2011) is associated with increases in subthreshold psychotic symptoms in nonclinical populations. Thus, associations between cannabis use and psychosis are apparent in individuals with and without diagnosable disorders, they are supported by experimental and genetic evidence (Caspi et al., 2005; D’Souza et al., 2000), and have been replicated in both patient and general populations.

Hundreds of studies have examined the association between cannabis and psychosis, some by evaluating patterns of drug use and psychosis symptoms over time (e.g. Andreasson, Engstrom, Allebeck, & Rydberg, 1987a; Linszen et al., 1994; van Os et
al., 2002) and others by using prospective designs (e.g., Henquet et al., 2005). Yet, its precise temporal nature is ambiguous; consequently, there are several proposed hypotheses. Cannabis use may be a causal factor in the development of psychosis (e.g., Arseneault et al., 2002; van Os et al., 2002), cannabis (or other substances) may be used to self-medicate against already established psychiatric symptoms (Khantzian, 1996), the concurrence of cannabis and psychotic symptoms may be coincidental, and causality is attributed to an unknown mediator (Hambrecht & Häfner, 2000), or they may be related due to a shared vulnerability (Ksir & Hart, 2016). Further illustrating the ambiguity in the cannabis-psychosis relationship, numerous studies with clinical high risk individuals fail to find any association between cannabis and conversion to psychosis (Auther et al., 2012; Buchy, Perkins, Woods, Liu, & Addington, 2014; Compton, Broussard, Ramsay, & Stewart, 2011; Corcoran et al., 2008; Phillips et al., 2002; Ruhrmann et al., 2010; Thompson, Nelson, & Yung, 2011; Valmaggia et al., 2014; Yung, Phillips, Yuen, & McGorry, 2004), and some research has found that cannabis users with first-episode psychosis have better premorbid functioning and attention/executive functions compared to non-users (Rodríguez-Sánchez et al., 2010). Given data suggesting that approximately 8% of the attributable risk for schizophrenia is explained by cannabis use (Arseneault, 2004), coupled with the notion that cannabis is a modifiable risk factor, the importance of elucidating the cannabis-psychosis association is paramount.

An alternative approach to evaluate the relationship between cannabis and psychosis is to examine attenuated positive psychotic symptoms (APPS) in young adults from the general population. In younger individuals who may not have yet developed a clinical disorder, examination of APPS may assist in understanding subthreshold
symptomatology that indicate risk. APPS are commonly experienced phenomena that are generally transitory and occur in the absence of current substance or alcohol use (e.g., hearing one’s name being called when there is no one around). Indeed, an extended psychosis phenotype has been proposed and suggests that vulnerability to psychotic disorders is behaviorally expressed in the general population (van Nierop et al., 2011; van Os & Linscott, 2012). Further, the persistence and severity of subclinical psychotic symptoms has been associated with risk of transitioning to a psychotic disorder (Kaymaz et al., 2012; Kelleher & Cannon, 2011; van Os & Linscott, 2012). Expanding the scope to young adult, non-clinical populations is therefore a valid method for evaluating psychosis, and may increase our understanding of early risk factors, such as cannabis use.

Additionally, although previous studies have controlled for variables that may impact the cannabis-psychosis relationship (e.g., minor or previous psychotic symptoms, intelligence, and use of psychostimulants) (Arseneault et al., 2002; van Os et al., 2002; Zammit et al., 2002), a variety of other variables have not been explored, despite their links to increased cannabis use in non-clinical populations. These include individual- and contextual-level variables such as affective symptoms, aggression symptoms, negative psychotic symptoms, social functioning, motivations for cannabis use, and the context of cannabis use (described further below).

Affective, aggression, and negative psychotic symptoms

Past work has indicated that affective symptoms are useful in understanding psychosis risk and cannabis use. For example, depression and anxiety symptoms are present prior to the onset of psychosis (Rosen et al., 2006; Yung et al., 2004), they are found among individuals with psychotic symptoms in the general population (Wigman et
and they are highly associated with cannabis use (Buckner, Heimberg, Schneier, et al., 2012; Reeves et al., 2014; Wittchen et al., 2007). Limitations in the current literature include controlling for diagnoses of anxiety and depression, rather than examining symptoms in a mediational model. In our previous study, we found that symptoms of generalized anxiety mediated the relationship between cannabis use and subthreshold psychotic symptoms, which points to the importance of considering clinical characteristics when evaluating the cannabis-psychosis relationship (Reeves et al., 2014).

Aggression is another factor to examine, as it is related to psychotic disorders (Douglas, Guy, & Hart, 2009; Spidel, Lecomte, Greaves, Sahlstrom, & Yuille, 2010), psychosis proneness (Fanning, Berman, Mohn, & McCloskey, 2011), and cannabis abuse and dependence symptoms (Oshri, Rogosch, Burnette, & Cicchetti, 2011; Tarter, Kirisci, Ridenour, & Vanyukov, 2008). Aggression also is a proxy of externalization symptoms, which have strong associations with substance use in non-psychosis (Griffith-Lendering, Huijbregts, Mooijaart, Vollebergh, & Swaab, 2011; Oshri et al., 2011) and psychosis populations (Scott et al., 2009; Tarbox & Pogue-Geile, 2008). Yet, no study has examined whether aggression is an explanatory variable in the cannabis-psychosis association.

Endorsement of negative symptoms has been researched in relation to cannabis use in individuals with psychosis, but findings are mixed. Some studies have found that cannabis-using patients with psychotic disorders and individuals at high risk have fewer negative symptoms compared to non-users (Auther et al., 2012; Bersani, Orlandi, Kotzalidis, & Pancheri, 2002; Compton, Whicker, & Hochman, 2007; Dubertret, Bidard, Adès, & Gorwood, 2006), whereas others have found no difference in negative symptoms
(Addington & Addington, 2007; Caspari, 1999; Grech, van Os, Jones, Lewis, & Murray, 2005; Stirling, Lewis, Hopkins, & White, 2005). However, there is some evidence that substance use may occur as a response to specific negative symptoms (e.g., anhedonia) in psychosis samples (Baigent, Holme, & Hafner, 1995; Noordsy et al., 1991; Pristach & Smith, 1996). Clarification of the association between negative symptoms and cannabis use among those with APPS or at potential risk for psychosis may prove useful for improving diagnosis and treatment of individuals at risk for psychosis.

Social functioning and context of use

Deficits in social functioning are among the most robust behavioral correlates of genetic risk for psychotic disorders, and are present in many at-risk individuals from childhood (Cannon et al., 2008; Dworkin et al., 1993; Hans et al., 2000; Tyrka et al., 1995). Less is known about social functioning in non-clinical samples where psychosis is measured dimensionally, and only one study to date has examined social functioning in relation to cannabis use and risk for psychosis (Auther et al., 2012). Given findings that lower social functioning is an important contributor to the development of psychotic disorders (Cannon et al., 2008), it is feasible that social functioning may explain, at least in part, the relationship between cannabis and psychosis.

Additionally, the context of cannabis use may be an important explanatory factor in the relationship between cannabis and psychosis, but this has been a largely untested variable. Despite findings that the majority of adolescent drug use takes place within social settings (Newcomb & Bentler, 1989; Tucker et al., 2014), it is unclear whether these findings apply to young adults with APPS and/or at potential higher risk for psychosis. Only one study has examined context of use and found that individuals at
clinical high risk for psychosis are more likely to use cannabis alone compared to healthy controls (Buchy et al., 2015). Thus, determining whether context of cannabis use is related to APPS and frequency of cannabis consumption may further clarify the cannabis-psychosis relationship.

**Motivations for cannabis use**

Few studies have examined the reasons why individuals with psychosis use cannabis (e.g., Green, Kavanagh, & Young, 2004; Swendsen, Ben-Zeev, & Granholm, 2011). Non-psychiatric adolescent participants endorse using cannabis to ‘get high’ or to increase pleasure (Pencer & Addington, 2008), and patients with first-episode psychosis and schizophrenia may have similar motives, but also use for social reasons (e.g., to reduce social awkwardness), or to improve mood (Pencer & Addington, 2008; Spencer et al., 2002). Only one study to date has researched motivations for cannabis use in individuals at clinical high risk for psychosis, but was limited to a small sample size of cannabis users (Gill et al., 2013), and no study has examined reasons for use in a non-clinical, general population study that measures psychotic symptoms dimensionally. It is possible that certain motivations for use (for example, coping with mood/anxiety symptoms) are associated with increases in cannabis use and APPS.

In sum, there are numerous variables related to both cannabis use and psychosis that have yet to be explored in a non-clinical population with a continuous measurement of psychosis. Based on the mixed findings from the literature regarding the cannabis-psychosis relationship, particularly from numerous clinical high risk studies that fail to find any association between cannabis and conversion to psychosis, it is possible that
these premorbid contextual and individual-level factors partially or wholly explain the relationship between cannabis consumption and psychotic symptoms.

The current study examined whether the aforementioned individual and contextual factors mediate the relationship between cannabis use and subthreshold psychotic symptoms, and potential higher risk for psychosis, in a nonclinical population. Further, this study will expand upon current literature by including a wide range of domains relevant to both cannabis use and psychosis, and examining this relationship in a mediational model. This mediational model does not preclude cannabis as a causal factor in psychosis, but rather, it may identify additional variables that are involved in the cannabis-psychosis relationship. It was hypothesized that there would be a dose-response relationship between the frequency of cannabis use and increases in APPS, and that this association would be mediated by affective symptoms (i.e., depression, social anxiety, and generalized anxiety), aggression symptoms, negative psychotic symptoms, social functioning, motivations for using cannabis, and context of cannabis use. Additionally, an exploratory aim was to determine whether this relationship persisted when examining individuals at potential higher risk for psychosis, a measure of greater clinical relevance.
CHAPTER 3

METHODS

Participants and procedure

The protocol was approved by the Institutional Review Board at Temple University and a Certificate of Confidentiality was obtained from the National Institutes of Health. Participants (N = 945) were recruited across a variety of academic disciplines through the university’s online research study listing. Participants had the option to receive course credit for their participation in one or more of the available research studies, or to complete an alternative assignment in lieu of obtaining research participation credit. Men and women eligible for inclusion (a) had to be able to read and speak proficient English such that they could complete the required assessments, (b) were between ages 18-35 at time of enrollment, and (c) had normal or corrected vision. After consent procedures, participants completed the battery of self-report questionnaires.

Measures

Psychotic symptoms

The Prodromal Questionnaire (PQ) (Loewy, Bearden, Johnson, Raine, & Cannon, 2005; Loewy et al., 2007) was used to evaluate APPS, potentially higher and lower risk for psychosis based on number of distressing-APPS endorsed (i.e., D-APPS status), and negative symptoms. This 92-item self-report screen evaluated the frequency of positive, negative, disorganized, and general symptoms in the past month while not under the influence of drugs, alcohol, or other medications, and asked participants to indicate whether endorsed symptoms were distressing. The PQ has moderate concurrent validity, strong sensitivity, and moderate specificity with semi-structured interviews that assess
risk for psychotic disorders, including the Structured Interview for Psychosis-Risk Syndromes (SIPS) (Kline et al., 2012; Miller et al., 2002). Endorsing eight or more positive symptoms has been found to have 90% sensitivity and 49% specificity with those identified as CHR using the SIPS in a clinical population (Loewy et al., 2007; Loewy, Therman, Manninen, Huttunen, & Cannon, 2012). APPS were examined dimensionally (calculated as the sum of the 45 positive symptom PQ items), and D-APPS was dichotomized into low-D-APPS (i.e., those who endorse three or fewer APPS as distressing in the past month) and high-D-APPS (i.e., those who endorse eight or more APPS as distressing in the past month), consistent with previous studies from our lab (Gibson et al., 2014; Reeves et al., 2014). Negative symptoms were calculated as the sum of the 19 negative symptom PQ items.

Social functioning

The Social Functioning Scale (SFS) (Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990) was used to assess social functioning. This questionnaire is a 79-item self-rating scale normed on a sample of individuals with schizophrenia and healthy individuals from the general population. It assessed several areas of social functioning, including withdrawal/social engagement, interpersonal communication, performance in independent activities, competence in independent activities, recreation, prosocial activities, and engagement in daily activity/occupation. Total scores were summed to provide an overall score, with higher scores indicating better social functioning. The SFS has high internal reliability and consistency, with strong power to discriminate between criterion groups (Birchwood et al., 1990). Alpha for the current sample was 0.89.
Cannabis use

The Marijuana Use Form (MUF) (Buckner, Bonn-Miller, Zvolensky, & Schmidt, 2007) is a self-report questionnaire used to assess cannabis use. Participants reported whether they have ever used cannabis, and for those who have used, their average frequency of cannabis use (past three-month use was analyzed for the present study), ranging from “less than once or never” (0) to “21+ times per week” (9). An additional question addressing the context of cannabis use (i.e. whether the individual typically uses cannabis alone or with others) was added to the original questionnaire.

The Reasons for Use (RUS) scale (Spencer et al., 2002) is composed of 26-items that probe for five categories for reasons of/motivations for cannabis use: (1) enhancement (three items, e.g. “Because it’s fun”); (2) social motives (four items, e.g. “To be sociable”); (3) coping with unpleasant affect (11 items, e.g. “To forget your worries”); (4) conformity and acceptance (five items, e.g. “To be liked”); and (5) relief of positive symptoms and side effects of medication (three items, e.g. “To feel less suspicious/paranoid”). Each item assessed how often an individual uses cannabis for that reason, and was rated using a scale ranging from “never/almost never” (0) to “almost always/always” (4). Each category was scored as the mean score of all applicable items, and alphas ranged for each subscale (enhancement $\alpha = 0.91$; social motives $\alpha = 0.88$; coping with unpleasant affect $\alpha = 0.90$; conformity and acceptance $\alpha = 0.77$; relief of positive symptoms $\alpha = 0.51$).

Affective and aggression symptoms

Symptoms, rather than clinical diagnoses, were included because late adolescents/young adults experiencing APPS may not have yet developed any clinical
disorders. Thus, this dimensional approach may offer a more accurate characterization of an individual’s affective (e.g., mood, anxiety) and psychosis symptoms (Wigman et al., 2012).

Depression symptoms were measured with the Center for Epidemiologic Studies-Depression Scale (CES-D) (Kohout, Berkman, Evans, & Cornoni-Huntley, 1993; Radloff, 1977): A 10-item shortened version of the CES-D was used to assess the presence and severity of depression symptoms in the past week, ranging from “rarely or none of the time/less than one day” (0) to “all of the time/5-7 days” (3). This scale has been found to be reliable and valid (Radloff, 1977; Roberts, Vernon, & Rhoades, 1989). The total score was calculated as the sum of all items, and alpha was 0.81 for the present sample.

Generalized anxiety symptoms were measured with the State-Trait Anxiety Inventory- Trait Form- Anxiety Subscale (STAI-Trait) (Bieling, Antony, & Swinson, 1998). The STAI-Trait ascertained the frequency of seven symptoms of generalized anxiety, ranging from “almost never” (1) to “almost always” (4). This version contained only items that loaded onto the anxiety factor (e.g., “I feel nervous and restless”) and excluded those loading on a depression factor. It has been found to be psychometrically sound (Peterson & Heilbronner, 1987; Rule & Traver, 1983). The total score from the STAI-Trait was used, and alpha was 0.86 for the current sample.

Symptoms of social anxiety were measured with the Social Phobia Scale (SPS) (Mattick & Clarke, 1998). This 20-item scale assesses fears of scrutiny related to social anxiety (e.g., “I become anxious if I have to write in front of other people”), and possesses sound psychometric properties (Mattick & Clarke, 1998). Items were rated on a
4-point scale ranging from “not at all characteristic or true of me” (0) to “extremely characteristic or true of me” (4), and the total score was used. For the current sample, alpha was 0.92.

Aggression symptoms were measured with the aggression subscale from the Life History of Aggression (LHA) Scale (Coccaro, Berman, & Kavoussi, 1997). The five self-report items (assessing angry outbursts, physical fighting, verbal aggression, assaults, and aggression toward objects) were rated by how many times the individual has engaged in the specified behavior ranging from “never happened” (0) to “happened so many times I couldn’t give a number” (5), and these items were summed for an overall aggression score. This subscale correlates with both laboratory and self-reported measures of aggression (Berman, McCloskey, Fanning, Schumacher, & Coccaro, 2009; Coccaro, Berman, Kavoussi, & Hauger, 1996). The LHA has adequate internal consistency ($\alpha = 0.87$), and test-retest reliability ($r > 0.80$) (Coccaro et al., 1997). For the current sample, alpha was 0.81.

**Other drug use**

Drugs that are associated with psychosis, including opiates, cocaine, and amphetamines (Hall & Degenhardt, 2000; Smith, Thirthalli, Abdallah, Murray, & Cottler, 2009; Van Dam, Earleywine, & DiGiacomo, 2008), were examined with the Drug Use Frequency (DUF) self-report questionnaire (O’Farrell, Fals-Stewart, & Murphy, 2003). These drug use variables were coded as present, indicating that an individual has used the drug within the past three months, or absent. The original questionnaire was altered to include further description about each of the aforementioned drug categories for purpose of clarity.
Family history

Family history of excessive substance and/or alcohol use was assessed using two questions adapted by one of the study authors (L. Ellman) from the screening questions of the family interview for genetic studies (Maxwell, 1992). Participants were asked whether anyone in their family used alcohol or drugs so much that it caused problems, or went to treatment due to it, and they were asked whether anyone in their family was hospitalized for drug or alcohol problems. Responses were dichotomized into yes/no for family history of excessive alcohol/substance use.

Statistical analyses

The continuous APPS dependent variable was inspected for normality by visual inspection and skewness/kurtosis values. Initial analyses were conducted with SPSS, version 23 (SPSS Inc., Chicago, IL, USA). Bivariate analyses were conducted to assess whether potential covariates, including use of other drugs (specifically, opiates, cocaine, and amphetamines), age, sex, ethnicity/race, and family history of excessive alcohol/substance use, were associated with main study dependent and independent variables.

Tests of mediation may provide the most useful framework for understanding the main study hypotheses, as this approach considers the overall and individual effect of multiple mediators simultaneously, and also accounts for the potential inter-correlations among mediators. In order to test for mediation, bivariate analyses were first conducted to examine the association between all potential mediator variables with cannabis use, APPS, and D-APPS status. Only variables significantly associated with cannabis use and psychosis variables were entered into multiple mediation analyses. The robust weighted
least squares means and variance adjusted estimator was specified (WLSMV), in order to accommodate the combination of continuous and categorical variables. This approach provides more accurate estimates of direct, indirect, and total effects and allows for the use of bias-corrected bootstrapping (MacKinnon, 2008; Preacher & Hayes, 2008). Multiple mediation analyses were conducted in Mplus, version 7.4 (Muthén & Muthén, 1998-2015). Data were assumed to be missing at random, which allowed for inclusion of the full sample using WLSMV estimators. Mediators and covariates that met the aforementioned criteria were added to the model simultaneously (see Figures 1 and 2 for model depictions), and mediators were allowed to covary. Mediation was evaluated by estimating the significance of indirect effects of cannabis use and APPS/D-APPS status through each potential mediator using bootstrapped bias-corrected 95% confidence intervals based on 500 bootstrap draws. If confidence intervals did not include zero, then the mediating/indirect effect was considered statistically significant (Preacher & Hayes, 2008).
Figure 1. Cannabis use and APPS mediation model.

Figure 2. Cannabis use and D-APPS mediation model. A priori proposed multiple mediation model of cannabis use frequency and (Figure 1) attenuated positive psychotic symptoms and (Figure 2) D-APPS status. Potential mediators include five reasons for cannabis use categories (relief of positive symptoms, coping with unpleasant affect, conformity, social motives, and enhancement), context of cannabis use, aggression symptoms, affective symptom domains (depression, social anxiety, and generalized anxiety), negative psychotic symptoms, and social functioning.
CHAPTER 4

RESULTS

Demographic and descriptive statistics

Demographic and descriptive statistics are presented in Table 1, and main study variable inter-correlations are included in Appendix A. The APPS dependent variable was positively skewed and was subsequently log transformed (log10 after adding 1) for all analyses. Analyses to determine potential covariates indicated that age was not related to any of the main study independent or dependent variables (cannabis use: \( p = .41 \); APPS: \( p = .09 \); D-APPS status: \( p = .18 \)). Gender was neither related to D-APPS status (\( p = .08 \)) nor APPS (\( p = .17 \)), although males were more likely to use cannabis at a higher frequency (\( F = 21.15, df = 1, 939, p < .0001 \)). Because gender was not related to either of the main study dependent variables, it was not used as a covariate. Race was neither related to D-APPS status (\( p = .13 \)), APPS (\( p = .54 \)), nor cannabis use (\( p = .67 \)). Individuals who used amphetamines in the past three months were more likely to use cannabis at a higher frequency (\( F = 55.69, df = 1, 936, p < .0001 \)), they had a higher number of APPS that approached significance (\( F = 3.83, df = 1, 940, p = .051 \)), and they were more likely to be at high-D-APPS status (\( \chi^2 = 11.70, p < .001 \)) compared with those who had not used amphetamines in the past three months. Finally, individuals with a positive family history of excessive substance use were more likely to use cannabis at a higher frequency (\( F = 12.61, df = 1, 939, p < .001 \)), endorse a higher number of APPS (\( F = 10.61, df = 1, 943, p = .001 \)), and were more likely to be at high-D-APPS status (\( \chi^2 = 14.20, p < .001 \)). Therefore, amphetamine use and family history of excessive alcohol/substance use were included as covariates in both mediation models.
<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Low D-APPS</th>
<th>High D-APPS</th>
<th>( p )-value</th>
</tr>
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<tbody>
<tr>
<td>( N )</td>
<td>945</td>
<td>568</td>
<td>175</td>
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<td><strong>Demographics</strong></td>
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<tr>
<td>Male, ( n ) (%)</td>
<td>231 (24.4)</td>
<td>147 (25.9)</td>
<td>34 (19.4)</td>
<td>.082</td>
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<td>Age, mean (SD) [range]</td>
<td>20.1 (2.5) [18-34]</td>
<td>20.2 (2.6) [18-34]</td>
<td>19.8 (2.0) [18-30]</td>
<td>.100</td>
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<td>Race, ( n ) (%)</td>
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<td>Non-hispanic white</td>
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<td>21 (12.0)</td>
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<td>82 (14.4)</td>
<td>27 (15.4)</td>
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<td>22 (3.9)</td>
<td>14 (8.0)</td>
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<td>Other</td>
<td>63 (6.7)</td>
<td>41 (7.2)</td>
<td>10 (5.7)</td>
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<td><strong>Clinical characteristics, mean (SD) [range]</strong></td>
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<tr>
<td>Attenuated positive psychotic symptoms(^1)</td>
<td>9.9 (7.7) [0-44]</td>
<td>5.7 (4.6) [0-30]</td>
<td>20.4 (6.7) [9-44]</td>
<td>&lt;.001</td>
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<td>Negative psychotic symptoms</td>
<td>7.7 (4.9) [0-19]</td>
<td>5.4 (3.8) [0-18]</td>
<td>12.9 (3.8) [2-19]</td>
<td>&lt;.001</td>
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<td>Social anxiety symptoms</td>
<td>14.7 (13.0) [0-64]</td>
<td>10.0 (9.4) [0-58]</td>
<td>27.4 (15.1) [0-64]</td>
<td>&lt;.001</td>
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<td>Generalized anxiety symptoms</td>
<td>12.7 (4.9) [7-28]</td>
<td>10.4 (3.3) [7-24]</td>
<td>18.1 (4.8) [8-28]</td>
<td>&lt;.001</td>
</tr>
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<td>Depression symptoms</td>
<td>7.8 (5.1) [0-27]</td>
<td>5.6 (3.7) [0-22]</td>
<td>13.1 (5.1) [4-27]</td>
<td>&lt;.001</td>
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<td>Aggression symptoms</td>
<td>6.3 (4.7) [0-24]</td>
<td>5.0 (4.2) [0-20]</td>
<td>8.9 (4.9) [0-21]</td>
<td>&lt;.001</td>
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<td>Social functioning</td>
<td>141.7 (19.6) [70-209]</td>
<td>144.4 (19.7) [70-209]</td>
<td>135.9 (19.6) [81-185]</td>
<td>&lt;.002</td>
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<td>Family history of psychosis, ( n ) (%)</td>
<td>196 (20.7)</td>
<td>99 (17.4)</td>
<td>57 (32.6)</td>
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<td>Family history of excessive alcohol/substance use, ( n ) (%)</td>
<td>407 (43.1)</td>
<td>217 (38.2)</td>
<td>95 (54.3)</td>
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</tr>
<tr>
<td><strong>Drug use characteristics, mean (SD) [range]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use cannabis for enhancement, mean (SD) [range]</td>
<td>1.8 (1.4) [0-4]</td>
<td>1.7 (1.4) [0-4]</td>
<td>1.9 (1.4) [0-4]</td>
<td>.327</td>
</tr>
<tr>
<td>Use cannabis for social motives, mean (SD) [range]</td>
<td>1.2 (1.2) [0-4]</td>
<td>1.1 (1.2) [0-4]</td>
<td>1.4 (1.2) [0-4]</td>
<td>.013</td>
</tr>
<tr>
<td>Use cannabis for coping with unpleasant affect, mean (SD) [range]</td>
<td>0.8 (0.8) [0-4]</td>
<td>0.6 (0.7) [0-3.1]</td>
<td>1.2 (1.0) [0-3.7]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use cannabis for conformity and acceptance, mean (SD) [range]</td>
<td>0.3 (0.5) [0-3.2]</td>
<td>0.2 (0.5) [0-3.2]</td>
<td>0.5 (0.7) [0-2.4]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Use cannabis for relief of positive symptoms and side effects, mean (SD) [range]</td>
<td>0.1 (0.3) [0-2.7]</td>
<td>0.1 (0.3) [0-2]</td>
<td>0.2 (0.5) [0-2.7]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>First used cannabis age 15 years or younger, ( n ) (%)</td>
<td>186 (29.8)</td>
<td>108 (29.2)</td>
<td>37 (31.4)</td>
<td>.641</td>
</tr>
<tr>
<td>Typically use cannabis alone, ( n ) (%)</td>
<td>52 (8.3)</td>
<td>18 (4.9)</td>
<td>15 (12.7)</td>
<td>.003</td>
</tr>
</tbody>
</table>
Table 1. (continued)

<table>
<thead>
<tr>
<th>Frequency of past 3 month cannabis use, mean (SD) [range]</th>
<th>Total</th>
<th>Low D-APPS</th>
<th>High D-APPS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of past 1 month cannabis use, mean (SD) [range]</td>
<td>1.6 (2.5) [0-10]</td>
<td>1.4 (2.3) [0-10]</td>
<td>2.0 (2.9) [0-10]</td>
<td>.006</td>
</tr>
<tr>
<td>Used amphetamines in past 3 months, n (%)</td>
<td>69 (7.3)</td>
<td>33 (5.8)</td>
<td>24 (13.7)</td>
<td>.001</td>
</tr>
<tr>
<td>Used cocaine in past 3 months, n (%)</td>
<td>60 (6.3)</td>
<td>33 (5.8)</td>
<td>12 (6.9)</td>
<td>.619</td>
</tr>
<tr>
<td>Used opiates in past 3 months, n (%)</td>
<td>15 (1.6)</td>
<td>8 (1.4)</td>
<td>4 (2.3)</td>
<td>.423</td>
</tr>
</tbody>
</table>

¹APPS means and SD shown in table derived from raw data; log-transformed APPS was used in all analyses and in calculating p-value shown in table; p-value reflects differences between high- and low-D-APPS groups
²n = 625 for full sample, as only participants who endorsed using cannabis answered cannabis-related questions; n = 488 for sample at high/low-D-APPS status
Incomplete data were collected for four participants due to study protocol interruptions

**Bivariate Analyses**

Data from bivariate analyses are presented in Table 2. The RUS category assessing use of cannabis for relief of positive symptoms and side effects of medication was removed from analyses due to poor internal consistency (α = .51) and a very low rate of endorsement (approximately 1% of individuals, n = 7, endorsed using cannabis for these reasons half of the time or more, on average). As Table 2 indicates, cannabis use was significantly related to both APPS and D-APPS status. APPS was significantly related to all potential mediators. D-APPS status was significantly related to all potential mediators with the exception of one of the reasons for use domains (enhancement). Cannabis use was related to all but four potential mediators, which included social anxiety symptoms, generalized anxiety symptoms, using cannabis for reasons of conformity, and social functioning.
Table 2. Bivariate analyses for cannabis use, APPS, and D-APPS status.

<table>
<thead>
<tr>
<th>Dependent Variables</th>
<th>APPS$^{1,2}$</th>
<th>D-APPS status$^3$</th>
<th>Cannabis use$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPS</td>
<td>--</td>
<td>--</td>
<td>.15, &lt;.0001</td>
</tr>
<tr>
<td>D-APPS status</td>
<td>--</td>
<td>--</td>
<td>7.52, .006</td>
</tr>
<tr>
<td>Independent Variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Potential Mediator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>.70, &lt;.0001</td>
<td>536.67, &lt;.0001</td>
<td>.10, .004</td>
</tr>
<tr>
<td>Social anxiety symptoms</td>
<td>.45, &lt;.0001</td>
<td>333.73, &lt;.0001</td>
<td>-.02, .55</td>
</tr>
<tr>
<td>Generalized anxiety symptoms</td>
<td>.54, &lt;.0001</td>
<td>584.40, &lt;.0001</td>
<td>.05, .30</td>
</tr>
<tr>
<td>Depression symptoms</td>
<td>.55, &lt;.0001</td>
<td>457.86, &lt;.0001</td>
<td>.10, .002</td>
</tr>
<tr>
<td>Aggression symptoms</td>
<td>.33, &lt;.0001</td>
<td>106.72, &lt;.0001</td>
<td>.22, &lt;.0001</td>
</tr>
<tr>
<td>Reasons for cannabis use - enhancement</td>
<td>.12, .004</td>
<td>.961, .33</td>
<td>.58, &lt;.0001</td>
</tr>
<tr>
<td>Reasons for cannabis use - social motives</td>
<td>.11, .005</td>
<td>6.27, .013</td>
<td>.51, &lt;.0001</td>
</tr>
<tr>
<td>Reasons for cannabis use - coping with negative affect</td>
<td>.24, &lt;.0001</td>
<td>35.95, &lt;.0001</td>
<td>.66, &lt;.0001</td>
</tr>
<tr>
<td>Reasons for cannabis use - conformity</td>
<td>.11, .006</td>
<td>22.98, &lt;.0001</td>
<td>.07, .09</td>
</tr>
<tr>
<td>Reasons for cannabis use - relief of positive symptoms</td>
<td>.16, &lt;.0001</td>
<td>24.20, &lt;.0001</td>
<td>.26, &lt;.0001</td>
</tr>
<tr>
<td>Social functioning</td>
<td>-.17, &lt;.0001</td>
<td>24.13, &lt;.0001</td>
<td>.04, .21</td>
</tr>
<tr>
<td>Context of cannabis use</td>
<td>18.42, &lt;.0001</td>
<td>8.74, .003</td>
<td>45.01, &lt;.0001</td>
</tr>
</tbody>
</table>

Data presented as test statistic, $p$-value

1 Log-transformed APPS variable used for all analyses

2 Test statistics in columns represent Pearson correlation coefficient (with exception of context of cannabis use and D-APPS status, $F$ statistic)

3 Test statistics in column represent $F$ statistics (with exception of context of cannabis use, $X^2$)

Mediation Analyses

1. Cannabis use and APPS

For the model including APPS as the dependent variable, the mediators entered into the model included negative, depression, and aggression symptoms; use of cannabis for reasons of enhancement, social motives, and coping with negative affect; and context of cannabis use. Amphetamine use and family history of excessive alcohol/substance use were included as covariates. Figure 3 displays the standardized estimates between study variables in the APPS model, as well as the unstandardized estimates of direct and specific indirect effects. Direct effects between cannabis use and APPS were not
significant ($\beta = .005, [-.007, .018], p = .39$) (see Figure 3). However, cannabis use exerted a significant indirect effect on APPS ($\beta = .014, [.001, .027], p = .038$, as indexed by the sum of indirect effects. Examination of the point estimates and 95% confidence intervals of the indirect effects indicated that the relationship between cannabis use and APPS was statistically mediated by both increases in negative psychotic symptoms ($\beta = .006, [.001, .011], p = .021$) and increases in aggression symptomatology ($\beta = .002, [.001, .005], p = .016$), such that higher cannabis use was associated with increased negative and aggression symptoms, which in turn, were associated with increases in APPS. Context of cannabis use ($\beta = .006, [-.002, .016], p = .188$), depression symptoms ($\beta = .001, [.000, .002], p = .226$), and the three RUS categories (i.e., enhancement: $\beta = -.001, [-.010, .007]$, **p** < .05, **p** < .01, ***p** < .0001; standardized estimates reported (standardization on dependent and independent variable). Unstandardized indirect effects (based on 500 bootstrapped samples) appear in parentheses: bold indicates significant indirect effect based on 95% bias-corrected bootstrapped confidence interval. Numbers to the left of the slash are the unstandardized direct effects and numbers on the right of the slash are the sum of the indirect effects. 

![Figure 3. Cannabis use and APPS mediation results. Mediation model with only mediators related to cannabis use and APPS included. Note: **p** < .05, **p** < .01, ***p** < .0001; standardized estimates reported (standardization on dependent and independent variable). Unstandardized indirect effects (based on 500 bootstrapped samples) appear in parentheses: bold indicates significant indirect effect based on 95% bias-corrected bootstrapped confidence interval. Numbers to the left of the slash are the unstandardized direct effects and numbers on the right of the slash are the sum of the indirect effects.](image-url)
social motives: \( \beta = .003, [-.005, .011], p = .576 \); and coping with unpleasant affect: \( \beta = -.003, [-.015, .006], p = .554 \) were not found to be significant mediators. As a covariate in the mediation model, family history of excessive alcohol/substance use (but not amphetamine use) was significantly associated with APPS, after other variables were entered in the model.

2. Cannabis use and D-APPS status

For the model with D-APPS status as the dependent variable, negative, depression, and aggression symptoms; use of cannabis for social motives and coping with negative affect; and context of cannabis use were included as mediators. Amphetamine use and family history of excessive alcohol/substance use were included as covariates. Figure 4 contains the standardized estimates between study variables in the D-APPS model, and the unstandardized estimates of direct and specific indirect effects. Direct effects between cannabis use and D-APPS status were not significant (\( \beta = .164, [1.108, 1.002], p = .756 \)), nor was the total indirect effect of cannabis use on D-APPS status (\( \beta = .212, [-.550, 1.539], p = .683 \)). However, there were five significant specific indirect effects, suggesting mediation by several variables. Increased negative psychotic symptoms (\( \beta = .293, [.066, .625], p = .041 \)) and increases in aggression symptomatology (\( \beta = .199, [.070, .385], p = .011 \)) significantly mediated the relationship between higher cannabis use and high-D-APPS status. Context of cannabis use also mediated this relationship (\( \beta = -.873, [-1.516, -.521], p = .021 \)), in that increased cannabis use was associated with using cannabis alone, which in turn, was associated with high-D-APPS status. The relationship between cannabis use and D-APPS status was also statistically mediated by the two reasons for use variables, respectively: using cannabis for social
motives ($\beta = -1.091, [-1.923, -.486], p = .017$) and using cannabis for coping with unpleasant affect ($\beta = 1.634, [.885, 2.701], p = .002$). Specifically, increased cannabis use was associated with greater endorsement of using cannabis for social motives, which in turn was associated with low-D-APPS status. Increased cannabis use was also associated with greater endorsement of using cannabis to cope with unpleasant affect, and this was related to high-D-APPS status. Depression symptoms did not act as a significant mediator ($\beta = .049, [-.023, .237], p = .409$). As covariates in the mediation model, family history of excessive alcohol/substance use and amphetamine use were significantly associated with D-APPS status, after the other variables were entered into the model.

Additional analyses were conducted that are included in Appendices B-E, but are not included in the present chapter/manuscript.

![Figure 4. Cannabis use and D-APPS mediation results. Mediation model with only mediators related to cannabis use and D-APPS status included. Note: *p < .05, **p < .01, ***p < .001; standardized estimates reported (standardization on independent variable for Fig. 2b). Unstandardized indirect effects (based on 500 bootstrapped samples) appear in parentheses: bold indicates significant indirect effect based on 95% bias-corrected bootstrapped confidence interval. Numbers to the left of the slash are the unstandardized direct effects and numbers on the right of the slash are the sum of the indirect effects.]

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CHAPTER 5
DISCUSSION

This is the first study to determine that increased negative psychotic and aggression symptoms mediate the relationship between higher cannabis use and increases in APPS, and that this relationship exists even when controlling for potential confounding variables (i.e., family history of excessive alcohol/substance use; amphetamine use). Although bivariate analyses indicated a positive relationship between higher frequency of cannabis use and increases in APPS, this association did not hold when mediators were entered into the model. In addition, analyses indicated that context of cannabis use, depression symptoms, and using cannabis for reasons of enhancement, social motives, and coping with unpleasant affect did not account for this relationship. Further, when evaluating a more clinically relevant psychosis construct, potential higher/lower risk for psychosis (i.e., D-APPS status), several statistically significant mediators emerged. Specifically, the relationship between cannabis and D-APPS status was mediated by negative psychotic symptoms, aggression symptoms, using cannabis alone, and using cannabis to cope with negative affect. Similarly, the relationship between increased cannabis use and decreased likelihood of being at high-D-APPS status was mediated by a higher endorsement of using cannabis to feel better around others (i.e. social motives), suggesting that social motives are more common in cannabis users who are not at risk for psychosis. Similar to the model with APPS, this model held when controlling for family history of excessive alcohol/substance use and amphetamine use. Only depression symptoms did not mediate the relationship between cannabis use and D-APPS status. This study supports previous investigations indicating that there are factors that impact
the cannabis-psychosis relationship, such as confounding alcohol/substance use (Auther et al., 2015; Gage, Matthew, & Zammit, 2015) or childhood experiences (Gage et al., 2015), as well as mediators (e.g., symptoms of generalized anxiety) (Reeves et al., 2014). The current study extends prior studies by including a wide range of individual and contextual variables related to both psychosis and cannabis.

Aggression and negative symptoms were the only variables that emerged as significant mediators in the APPS model. Further, these variables were the only ones that mediated the relationship between cannabis and both psychosis variables: APPS and D-APPS status. Research has explored the connection between aggressive behaviors and cannabis use (Liu, Lynne-Landsman, Petras, Masyn, & Ialongo, 2013; Testa & Brown, 2015), and aggression is common in first-episode psychosis patients (Dean et al., 2007; Huber et al., 2012). Further, the aggression/psychosis relationship is measurable in nonclinical populations: there is an association between risk of psychotic-like experiences and peer victimization, with higher rates of psychotic-like experiences endorsed by perpetrators of bullying (Kelleher et al., 2008; Nishida et al., 2008), and psychosis proneness (a latent variable consisting of three dimensions of psychosis) is associated with increases in aggressive behavior (Fanning et al., 2011). However, no other study has examined whether negative and aggression symptoms account for the cannabis-psychosis relationship. Persistent antisocial behavior, impaired functioning, and aggressive behavior are some of the hallmark features of conduct disorder, a diagnosis marked by externalizing behaviors (Loeber, Burke, Lahey, Winters, & Zera, 2000). Few studies have examined the relationship between conduct disorder symptoms, cannabis use, and psychosis (Malcolm et al., 2011; Mueser et al., 1997, 1999). However, results suggest
that among young adults with recent-onset psychosis, conduct disorder symptoms may increase the likelihood of early cannabis use, which in turn may increase likelihood of transition to psychosis (Malcolm et al., 2011). As related to the present findings, aggression symptoms may be considered a proxy for externalizing behaviors, in which case it may not be aggression itself, but conduct problems that are related to cannabis use and APPS. Indeed, conduct disorder may increase risk for both cannabis use (Moffitt, Caspi, Rutter, & Silva, 2001) and adult schizophreniform disorder (Kim-Cohen et al., 2003), and although conduct disorder has been controlled for in previous studies (Caspi et al., 2005), it has never been formally tested as a mediator or moderator of this relationship (Keller, 2014). Externalizing behaviors are often cited as a potential confounder to the cannabis-psychosis association, but are rarely accounted for in models. Thus, the current study and previous findings (Malcolm et al., 2011) point to a critical role for externalizing behaviors, which may be an important target for treatment and a potential clue for future gene-environmental interactions studies (i.e., targeting genes associated with conduct problems).

Evidence from psychosis populations indicates that cannabis use is typically associated with fewer or no differences in negative symptoms (Addington & Addington, 2007; Baeza et al., 2009; Compton et al., 2007; Grech et al., 2005; Stirling et al., 2005), yet in the general population cannabis use is related to increases in subthreshold negative symptoms (Schubart et al., 2011; Stefanis et al., 2004). The present results support the latter findings, as negative symptoms were positively related to both cannabis use and APPS/potential higher risk for psychosis. Taking into consideration that using cannabis to cope with unpleasant affect was related to increased cannabis use in this sample, it is
possible that negative symptoms precipitate and contribute to cannabis use. In support of this, deficits in hedonic functioning may promote cannabis use in individuals with schizophrenia spectrum disorders (Cassidy, Lepage, & Malla, 2014). However, other studies have failed to find that negative symptoms, such as anhedonia, lead to increased odds of cannabis use disorders among individuals with psychosis (Liraud & Verdoux, 2000). These discrepant findings may highlight an important distinction between frequency of cannabis use and cannabis abuse/dependence, and it is possible that negative symptoms are related to the increased cannabis use, rather than problematic use. However, future studies are necessary to parse apart specific negative symptoms that may be contributing to this relationship. An important consideration is that negative psychotic symptoms were conceptualized as a mediator in the present study, due to its independent associations with psychosis and cannabis use. Yet, it is critical to note that there was a stronger bivariate correlation between negative symptoms and APPS, than between cannabis use and APPS (see Appendix A), and negative symptoms accounted for nearly 50% of the variance in APPS, leaving a small amount of variance to be explained by the other mediators. To determine whether negative symptoms impacted the overall model due to this strong association, supplemental analyses were conducted without negative psychotic symptoms as a mediator, and mediation results persisted (see Appendix F).

Numerous significant mediators emerged in the model examining a psychosis outcome that is potentially more clinically relevant, based on the number of distressing positive psychotic symptoms endorsed. In addition to negative and aggression symptoms, being less likely to use cannabis with peers, and using cannabis to cope with unpleasant affect explained the relationship between cannabis and high-D-APPS status. It is
interesting to note that although both reasons for use (i.e., social motives and coping with unpleasant affect) were related to increased cannabis use, frequently using cannabis to cope with unpleasant symptoms was related to higher likelihood of high-D-APPS status, whereas using cannabis for social motives was associated with decreased likelihood of high-D-APPS status. This supports previous findings that using cannabis for social reasons is more developmentally normative and associated with better outcomes, including reduced likelihood of being at potential higher risk for psychosis. These results may point to an important indicator of potential risk for psychosis, and it may be clinically useful to evaluate reasons for using cannabis in young adults who may be at risk for psychosis. Additionally, the present findings suggest that using cannabis alone was related to frequency of use, APPS, and D-APPS status, and further, that it mediated the relationship between cannabis use frequency and D-APPS status. Individuals at potential higher risk for psychosis were more likely to use cannabis alone than those at lower risk, and individuals who typically use alone were more likely to use cannabis more frequently in the past three months. Whether a young adult uses substances alone or with peers may be a key indicator of problematic substance use and frequency of use (Tucker et al., 2014), and although there is a high level of individual variation in cannabis-using characteristics among healthy young adults (Shrier, Walls, Rhoads, & Blood, 2013), research suggests that a preponderance of adolescent drug use takes place with others (Kandel, Kessler, & Margulies, 1978; Newcomb & Bentler, 1989; Tucker et al., 2014). Among individuals with a psychotic disorder, they may be more likely to use alone than those without psychosis (Saddichha et al., 2010), and this was echoed by a later study examining individuals at clinical high risk for psychosis (Buchy et al., 2015),
suggesting that this could be a key characteristic of cannabis users who may be at risk for psychosis. It has been largely unknown whether these findings apply to young adults with APPS and/or who may be at higher risk for psychosis. Thus, the present findings suggest that the context of cannabis use is an important consideration when evaluating the cannabis-psychosis relationship, and that even in non-clinical, undergraduate populations, those who may be at higher risk for psychosis are more likely to use cannabis by themselves.

Few studies have examined motivations for cannabis use in non-clinical populations with variations in APPS, and only one study has done so in individuals at clinical high risk for psychosis (Gill et al., 2013). Some research evaluated reasons for use within psychosis populations (Green et al., 2004; Kolliakou et al., 2015; Pencer & Addington, 2008; Saddichha et al., 2010; Spencer et al., 2002), but whether these motivations for use explained the association between cannabis use and psychosis was previously unknown. In line with previous research, our findings suggested that the most frequently reported reasons for using cannabis were for enhancement and for social motives in this undergraduate sample (Gill et al., 2013). However, being less likely to use for social motives (e.g., to make social gatherings more enjoyable/improve sociability) and more likely to use to cope with unpleasant affect (e.g., managing a variety of undesirable symptoms like restlessness, anxiety, depression, boredom, etc.) were the only RUS variables related to both cannabis and psychosis outcomes, and found to be significant mediators of the cannabis/D-APPS status association. Thus, in line with previous research, individuals who may be at higher risk for psychosis are typically using cannabis to feel better (Gill et al., 2013), and they are less likely to be using because of
social reasons, unlike their same-aged cannabis-using peers. In non-psychotic populations, peer influences substantially contribute to and exacerbate substance use behaviors in healthy young adults. Indeed, the strongest proximal influence on substance use behaviors in adolescents may be the role that peers play in influencing initiation of drug use (Steinberg, Fletcher, & Darling, 1994). For cannabis use, in particular, the influence of peers may outweigh that of selection (i.e., the propensity for substance-using young adults to seek out friendships with like-minded individuals) (Kandel, 1973; Kandel, 1978; Pearson, Steglich, & Snijders, 2006), and healthy adolescents may be more likely to initiate cannabis use if their friends use, they believe their friends are using, and/or they share beliefs with their friends that promote cannabis use and are counter to adult standards (Kandel et al., 1978). Although there are robust findings that using cannabis with peers/using cannabis due to peer influences is critical in the non-psychosis literature, our results suggest that these characteristics are related to lower risk for psychosis. Future studies should utilize a longitudinal approach and/or ecological momentary assessment to determine whether these motivations to use are related to actual cannabis use. This is particularly important as previous studies have indicated that motivations for using cannabis are incongruent with its reported effects (Addington & Duchak, 1997; Green et al., 2004; Swendsen et al., 2011). A similar disconnect in the present study may be that some individuals reported using cannabis to improve social situations, but in reality are using largely in isolation.

There are several important differences between the current findings and previous research. First, despite the finding that increases in cannabis use were related to frequently using cannabis to cope with unpleasant affect, symptoms of generalized
anxiety and social anxiety were not related to cannabis use in this sample, and symptoms of depression did not emerge as a significant mediator in either of the models. This result contrasts with findings demonstrating that cannabis use is associated with both social anxiety (Buckner, Heimberg, Schneier, et al., 2012; Najolia et al., 2012), and major depression (Anglin et al., 2012), and that symptoms of generalized anxiety mediate the relationship between cannabis use and APPS (Reeves et al., 2014). It is unclear if the lack of association between cannabis use and anxiety can be explained by our measurement of cannabis consumption (frequency of use in past three months), whereas other studies utilized cannabis use disorders (Buckner, Heimberg, Schneier, et al., 2012). Indeed, social anxiety may be more strongly related to cannabis dependence, rather than abuse (Buckner, Heimberg, Schneier, et al., 2012), suggesting that only at high severity of use (including problematic use) is cannabis associated with social anxiety. In regards to the contrasting results from our earlier work in which generalized anxiety symptoms accounted for the cannabis-psychosis relationship, the present sample included a higher percentage of individuals using cannabis in the past three months (approximately 48% compared to 38%), although levels of anxiety and depression symptoms were almost identical (Reeves et al., 2014). It is possible that the current sample represented a wider range of cannabis users, with more diffuse mood and anxiety symptoms, or, although speculative, cannabis users in this sample may have been adequately self-medicating for symptoms of anxiety and depression. This latter possibility is supported by our findings that participants endorsed using cannabis to alleviate negative affect. Second, social functioning was not related to cannabis use in the present sample and was therefore not included as a potential mediator of the cannabis-psychosis association. As our sample
consisted of undergraduate students with relatively good social functioning, this finding is not a surprise. However, individuals at potential higher risk for psychosis (high-D-APPS status) had lower social functioning compared to those at presumed lower risk for psychosis, supporting previous findings from the clinical high risk literature (Cannon et al., 2008). Further, there were other indicators from our results suggesting that social functioning in the cannabis-using participants at high-D-APPS may differ from other cannabis users, given that they were more likely to use cannabis alone and less likely to use cannabis for social purposes. Within the clinical high risk literature, cannabis users may have better social functioning than their non-cannabis using counterparts (Auther et al., 2012), although some find that this is isolated to early adolescence, and not late adolescence (Compton et al., 2011). For individuals with a psychotic disorder, cannabis is sometimes associated with worse psychosocial functioning (Caspari, 1999), but substance-users have also been found to have better social functioning (Salyers & Mueser, 2001). Thus, the findings on social functioning, psychosis, and cannabis are mixed, which may be related to the population (i.e., psychosis, clinical high risk, or general population) or measurement of social functioning (e.g., Global Assessment of Functioning versus SFS).

Limitations/strengths

Several limitations are noted. First, our sample included a smaller percentage of males (approximately 24%). There are typically gender differences in cannabis use, with evidence pointing to women using cannabis for longer periods of time per episode of use compared to males (Shrier et al., 2013), and trends indicating that males use cannabis more frequently than females (Johnston, O’Malley, Bachman, Schulenberg, & Miech,
2015), the latter of which was the case in our sample. However, gender did not appear to be related to either psychosis outcome in our sample and was thus not explored as a potential confounder. In addition, many studies examining cannabis use and psychosis outcomes utilize male-only samples (e.g., Andreasson, Engstrom, Allebeck, & Rydberg, 1987; Manrique-Garcia et al., 2012; Rössler et al., 2011; Zammit et al., 2002), and although it is optimal to have equal representation of males and females, this study does expand previous findings by including a largely female sample. Second, in order to balance (1) the objective of the research, with (2) maintaining some level of consistency with other studies examining the cannabis-psychosis relationship, and (3) collecting accurate data, the average frequency of cannabis use was assessed in the present study, rather than other metrics of cannabis use. Nonetheless, future studies should evaluate varying indicators of cannabis use, such as the amount of consumption (although this may be prone to recall bias) or include method of consumption (e.g., pipe, vaporizer, tincture, edible, etc.). The data collected and conclusions made will vary based on whether an investigator is focused on the prevalence of cannabis use, rather than the amount used or the frequency of use (Burns, Caulkins, Everingham, & Kilmer, 2013). Third, our D-APPS status is exploratory and we do not have data indicating whether individuals considered high-D-APPS status transitioned to a psychotic disorder. However, this group is very clearly exhibiting more severe symptomatology, not only based on a higher number of distressing-APPS endorsed, but by their affective symptomatology, and the percentage that either sought or received psychiatric treatment in the past month (32%) compared to 7% of the low-D-APPS group. This provides collateral support that individuals at high-D-APPS characterize a clinically meaningful
group that is potentially at increased risk for a range of psychiatric disorders, including psychosis. Finally, although our study included individuals who are at an age when psychosis begins to develop, and employed a powerful multiple mediation model, the nature of the present study was cross-sectional, and thus mediation cannot be demonstrated in a causal manner. For instance, the data do not indicate that cannabis, the significant mediating individual and contextual factors, and psychosis outcomes are related in a temporal manner. The critical point that the present study underscores is that prior to even attributing causality in the cannabis-psychosis relationship, there are meaningful clinical characteristics and context that need to be assessed and included in analyses (i.e., reasons for using cannabis, negative and aggression symptoms, context of cannabis use).

Strengths of the study include (1) its demographically and racially diverse nonclinical sample, (2) the dimensional measurement of clinical features using well-validated questionnaires, and (3) the application of path analysis to test mediation of important variables linked to substance use and psychosis. Our sample included participants from a large institution (approximately 30,000 undergraduate students) that encapsulates a wide range of socioeconomic and demographic backgrounds. Despite this study drawing from a college population, the age of the participants is approximately when psychosis tends to emerge, and extends previous studies that only include help-seeking individuals. Moreover, there is evidence to suggest extensive similarities and some shared mechanisms between clinical and non-clinical psychosis (Kelleher & Cannon, 2011), and there are similar rates of cannabis use between college students and their non-college peers (Johnston, O’Malley, Bachman, & Schulenberg, 2009). In terms
of the dimensional approach to symptoms employed by the present study, Rössler and colleagues (2011) outline some of the methodological advantages of measuring subclinical symptoms compared to clinical psychotic disorders, which includes being able to use larger sample sizes to allow for improved statistical modeling opportunities, less interference with antipsychotic medications, and potentially fewer comorbid disorders which may result in fewer biased effects. We may also be able to better understand the early stages of psychiatric disorders and improve pathogenetic models by studying psychopathology at levels below clinical significance (Rössler et al., 2011). By only considering the clinical end of the psychosis spectrum, we may be undermining the contribution of subthreshold symptoms to the liability of psychotic disorders; thus, studying APPS in non-clinical samples may offer new insights into risk factors for psychosis. Further, other studies employed diagnostic over dimensional approaches to clinical symptoms (e.g., Anglin et al., 2012; Fergusson, Horwood, & Swain-Campbell, 2003), whereas individuals with increases in APPS may experience more attenuated affective symptoms that have a higher chance of being captured with a dimensional approach. Lastly, the current study design examined a variety of clinical and contextual characteristics in a mediational role, contrasting to prior studies that controlled for such variables to minimize variance.

Notwithstanding its limitations, the current study brings forth several factors that may explain the relationship between not only cannabis use and psychotic symptoms, but also cannabis and potential higher risk for psychosis. Residual confounding and bias have been proposed as issues that may be distorting the association between cannabis and psychosis, thus resulting in a major limitation in interpreting this relationship (Auther et
al., 2015; Gage, Zammit, & Hickman, 2013; Macleod et al., 2004). With an abundance of studies espousing a causational link between cannabis and psychosis, the legalization of cannabis for both recreational and medical uses in an increasing number of states, as well as reviews that demand cautiousness in interpreting this relationship and propose they are related to due shared vulnerability (Ksir & Hart, 2016), further understanding is critical. Studies that report upon significant associations between cannabis and psychosis, but fail to include negative symptoms, aggression symptoms, context of use, and reasons for using cannabis in analyses may be obscuring important findings. The current study offers new insight into this relationship and utilizes a nonclinical sample, which may ultimately assist in our understanding of associations earlier in development.
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### APPENDIX A

**INTER-CORRELATIONS OF MAIN STUDY MEASURES**

<table>
<thead>
<tr>
<th></th>
<th>M(SD)</th>
<th>Median</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. APPS(^1)</td>
<td>9.9 (7.7)</td>
<td>8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Negative psychotic symptoms</td>
<td>7.7 (4.9)</td>
<td>7.0</td>
<td>.71**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Cannabis use</td>
<td>1.6 (2.5)</td>
<td>1.6</td>
<td>.11**</td>
<td>.10**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Social anxiety symptoms</td>
<td>14.7 (.0)</td>
<td>11.0</td>
<td>.50**</td>
<td>.59**</td>
<td>-.02</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Generalized anxiety symptoms</td>
<td>12.7 (4.9)</td>
<td>12.0</td>
<td>.57**</td>
<td>.57**</td>
<td>.04</td>
<td>.50**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Depression symptoms</td>
<td>7.8 (5.1)</td>
<td>7.0</td>
<td>.54**</td>
<td>.66**</td>
<td>.07*</td>
<td>.51**</td>
<td>.67**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Aggression symptoms</td>
<td>6.3 (4.7)</td>
<td>6.0</td>
<td>.33**</td>
<td>.32**</td>
<td>.20**</td>
<td>.20**</td>
<td>.26**</td>
<td>.29**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Social functioning</td>
<td>141.7 (19.6)</td>
<td>142.0</td>
<td>-.16**</td>
<td>-.27**</td>
<td>.04</td>
<td>-.26**</td>
<td>-.19**</td>
<td>-.25**</td>
<td>-.09*</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Use cannabis for enhancement</td>
<td>1.8 (1.4)</td>
<td>1.7</td>
<td>.11*</td>
<td>.09*</td>
<td>.66**</td>
<td>.05</td>
<td>.09*</td>
<td>.09*</td>
<td>.16**</td>
<td>.06</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Use cannabis for social motives</td>
<td>1.2 (1.2)</td>
<td>0.8</td>
<td>.15**</td>
<td>.12*</td>
<td>.57**</td>
<td>.10*</td>
<td>.12**</td>
<td>.10*</td>
<td>.11*</td>
<td>.04</td>
<td>.72**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Use cannabis for coping with unpleasant affect</td>
<td>.8 (.8)</td>
<td>0.6</td>
<td>.22**</td>
<td>.20**</td>
<td>.69**</td>
<td>.13**</td>
<td>.24**</td>
<td>.24**</td>
<td>.21**</td>
<td>.03</td>
<td>.77**</td>
<td>.66**</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Use cannabis for conformity and acceptance</td>
<td>.3 (.5)</td>
<td>0.0</td>
<td>.14**</td>
<td>.21**</td>
<td>.07</td>
<td>.27**</td>
<td>.18**</td>
<td>.18**</td>
<td>.09*</td>
<td>-.04</td>
<td>.22**</td>
<td>.50**</td>
<td>.31**</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>13. Use cannabis for relief of positive symptoms and side effects</td>
<td>.1 (.3)</td>
<td>0.0</td>
<td>.17**</td>
<td>.16**</td>
<td>.08*</td>
<td>.14**</td>
<td>.19**</td>
<td>.21**</td>
<td>.10*</td>
<td>-.06</td>
<td>.25**</td>
<td>.30**</td>
<td>.47**</td>
<td>.31**</td>
<td>--</td>
</tr>
</tbody>
</table>

\(^1\) APPS descriptive data derived from raw score; log-transformed APPS variable used to calculate correlations; Spearman rank-order correlations were utilized because not all variables were normally distributed

* Indicates correlation is significant at \( p < .05 \) level; ** Indicates correlation is significant at \( p < .001 \) level
APPENDIX B

PEER INFLUENCE MEASURES

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male M(SD)</th>
<th>Female M(SD)</th>
<th>Overall M(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPI</td>
<td>3.1393 (0.32357)</td>
<td>3.1595 (0.4765)</td>
<td>3.256 (0.455)</td>
</tr>
<tr>
<td>Stoplight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peer influence(^1)</td>
<td>-0.0007 (.12706)</td>
<td>-0.0076 (0.12246)</td>
<td>-0.0061 (0.123)</td>
</tr>
</tbody>
</table>

Note: M, mean; SD, standard deviation; RPI, Resistance to Peer Influence Scale.

\(^1\)Peer influence was calculated by subtracting the overall risk score of the alone round from the peer round for each participant.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Male M(SD)</th>
<th>Female M(SD)</th>
<th>Overall M(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Round: Peer</td>
<td>0.2486 (0.11488)</td>
<td>0.2805 (0.13278)</td>
<td>0.2736 (0.12938)</td>
</tr>
<tr>
<td>First Round: Alone</td>
<td>0.265 (0.13803)</td>
<td>0.2917 (0.15871)</td>
<td>0.2736 (0.12938)</td>
</tr>
<tr>
<td>Overall First Round</td>
<td>0.2801 (.14307)</td>
<td>0.2864 (0.14686)</td>
<td>0.2573 (0.12696)</td>
</tr>
<tr>
<td>Second Round: Peer</td>
<td>0.2184 (0.16326)</td>
<td>0.2159 (0.17085)</td>
<td>0.2165 (0.16868)</td>
</tr>
<tr>
<td>Second Round: Alone</td>
<td>0.195 (0.11286)</td>
<td>0.1809 (0.14448)</td>
<td>0.1839 (0.138)</td>
</tr>
<tr>
<td>Overall Second Round</td>
<td>0.2075 (0.14132)</td>
<td>0.1994 (0.1596)</td>
<td>0.2012 (0.15561)</td>
</tr>
<tr>
<td>Overall Peer</td>
<td>0.2325 (0.14238)</td>
<td>0.2463 (0.15714)</td>
<td>0.2433 (0.15392)</td>
</tr>
<tr>
<td>Overall Alone</td>
<td>0.2323 (0.13069)</td>
<td>0.2396 (0.16163)</td>
<td>0.238 (0.15526)</td>
</tr>
</tbody>
</table>

Note: means and SD's reflect risk taking scores

No significant differences between sex, age group, or by receipt of incentive
## APPENDIX D

SAMPLE LATENT CLASS ANALYSIS FOR DIFFERENT CLASS SOLUTIONS

<table>
<thead>
<tr>
<th>Class</th>
<th>LL</th>
<th>AIC</th>
<th>BIC</th>
<th>SSBIC</th>
<th>VLMR p-value</th>
<th>BLRT p-value</th>
<th>Entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Class</td>
<td>-21609</td>
<td>43247</td>
<td>43247</td>
<td>43272</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>2 Class</td>
<td>-20870</td>
<td>41788</td>
<td>41904</td>
<td>41828</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>0.871</td>
</tr>
<tr>
<td>3 Class</td>
<td>-20634</td>
<td>41335</td>
<td>41495</td>
<td>41390</td>
<td>.003</td>
<td>&lt;.001</td>
<td>0.897</td>
</tr>
<tr>
<td>4 Class</td>
<td>-20455</td>
<td>40994</td>
<td>41198</td>
<td>41064</td>
<td>.006</td>
<td>&lt;.001</td>
<td>0.92</td>
</tr>
<tr>
<td>5 Class</td>
<td>-20295</td>
<td>40691</td>
<td>40939</td>
<td>40777</td>
<td>.006</td>
<td>&lt;.001</td>
<td>0.866</td>
</tr>
<tr>
<td>6 Class</td>
<td>-20169</td>
<td>40459</td>
<td>40750</td>
<td>40559</td>
<td>.038</td>
<td>&lt;.001</td>
<td>0.876</td>
</tr>
<tr>
<td>7 Class</td>
<td>-20088</td>
<td>40314</td>
<td>40649</td>
<td>40430</td>
<td>.032</td>
<td>&lt;.001</td>
<td>0.886</td>
</tr>
</tbody>
</table>

Note: This sample model included eight variables: negative psychotic symptoms, social phobia symptoms, depressive symptoms, generalized anxiety symptoms, anger symptoms, cannabis use frequency, context of cannabis use, social functioning. LL, loglikelihood; AIC, Akaike information criterion; BIC, Bayesian information criterion; SSBIC, sample-size adjusted Bayesian information criterion; VLMR, Vuong-Lo-Mendell-Rubin likelihood ratio test for k - 1(H0) vs. k Classes; BLRT, bootstrapped likelihood ratio test.
APPENDIX E

SAMPLE LATENT CLASS ANALYSIS FOR FIVE CLASS SOLUTION
### SUMMARY OF INDIRECT EFFECTS FROM TWO MEDIATIONAL MODELS WITHOUT NEGATIVE SYMPTOMS

<table>
<thead>
<tr>
<th>Model and Mediators</th>
<th>Estimate (SE)</th>
<th>95% CI (LL, UL)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cannabis &amp; APPS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coping with unpleasant affect</td>
<td>-.004 (.007)</td>
<td>-.019, .007</td>
</tr>
<tr>
<td>Social motive reasons</td>
<td>.007 (.005)</td>
<td>-.002, .019</td>
</tr>
<tr>
<td>Enhancement reasons</td>
<td>.002 (.005)</td>
<td>-.012, .008</td>
</tr>
<tr>
<td>Context of cannabis use</td>
<td>.009 (.005)</td>
<td>.000, .020</td>
</tr>
<tr>
<td>Aggressive symptoms</td>
<td>.004 (.001)*</td>
<td>.002, .007*</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>.004 (.002)</td>
<td>-.001, .008</td>
</tr>
<tr>
<td><strong>Cannabis &amp; D-APPS Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coping with unpleasant affect</td>
<td>1.085 (.361)*</td>
<td>.417, 1.692*</td>
</tr>
<tr>
<td>Social motive reasons</td>
<td>-.725 (.296)*</td>
<td>-1.205, -.060*</td>
</tr>
<tr>
<td>Context of cannabis use</td>
<td>-.576 (.258)*</td>
<td>-.869, -.252*</td>
</tr>
<tr>
<td>Aggressive symptoms</td>
<td>.167 (.058)*</td>
<td>.067, .310*</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>.128 (.088)</td>
<td>-.034, .302</td>
</tr>
</tbody>
</table>

Note: Unstandardized indirect effects and standard error (SE) are reported, and based on 500 bootstrapped samples; *Indicates significant indirect effect based on 95% bias-corrected bootstrapped confidence interval (CI)