A Comprehensive Analysis of Neurocognition in Young Psychosis Patients with Current Cannabis Use

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By

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Declaration of originality

To the best of my knowledge, this thesis contains no copy or paraphrase of work published by another person, accept where duly acknowledged in the text. This thesis contains no material which has been presented for a degree at the University of Sydney or any other University. Details of contents are on the next page.

Sophia Bogaty

Papers Associated with this Thesis

Peer-Reviewed Papers

The following papers form the basis of this thesis:

1. Bogaty, S.E.R., Lee, R.S.C., Hickie, I.B., Hermens, D.F. Meta-analysis of neurocognition in young psychosis patients with current cannabis use. *Journal of Psychiatric Research*; 2018: 99: 22-32.

    - This paper formed the basis for Chapter 2 of this thesis.

2. Bogaty, S.E.R., Crouse, J.J., Hickie, I.B., Hermens, D.F. The neuropsychological profiles of young psychosis patients with and without cannabis use. *Cognitive Neuropsychiatry*; [under review].

    - This paper formed the basis for Chapter 3 of this thesis.

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List of common abbreviations

BDNF – Brain-derived neurotrophic factor
CB1 – Cannabinoid receptor 1
COMT – Catechol-O-methyltransferase
CSF – Cerebral spinal fluid
FEP – First episode psychosis
NGF – Nerve growth factor
PFC – Prefrontal cortex
THC – Tetrahydrocannabinol

Abstract

The aim of this thesis is to examine the neuropsychological profiles of psychosis patients, with and without current cannabis use. Specifically, to determine how age may moderate the effects of cannabis use on neurocognition. In normal populations, cannabis use, whether previous or current, has been shown to provoke deficiencies across a range of cognitive domains, specifically verbal memory, executive functioning, working memory, and psychomotor functions. However, patients diagnosed with a psychotic disorder, in particular, non-affective psychosis (i.e. schizophrenia-spectrum disorder), who have a history of, but no longer engage in, cannabis use, demonstrate cognition that is seemingly superior to their peers who have no history of cannabis use at all. While studies generally report that drug-naïve schizophrenia-spectrum patients demonstrate a range of cognitive deficiencies compared to the general population, patients with a history of cannabis use, in some cases, exhibit neurocognition similar to control subjects. There are three predominate theories that address the unique findings of this clinical group. Initially, comorbid psychosis patients were thought to display social cognition that was better than their drug-naïve counterparts as explanation for the abilities required to source and obtain the drug. However comorbid patients tend to display poorer premorbid functioning initially, which is often an argument against this theory. Alternatively, another theory suggests cannabis use instead promotes a neuroprotective effect in such patients. Previous studies have found increased concentrations of neurotrophins, specifically brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), in psychosis patients with a history of cannabis use. As neurotrophins primarily induce the development and function of neurons, this finding indicates cannabis may demonstrate neuroprotective properties in psychosis patients. However, imaging studies have demonstrated loss of brain volume in first-episode patients who use cannabis, which is inconsistent with a neuroprotective effect. Thus, the objective of the present thesis was to explore the third theory – that vulnerable individuals instead bring about their own psychotic illness through cannabis use and represent a subgroup of patients who are less cognitively compromised than patients who would develop a psychotic disorder despite cannabis use.

The studies in this thesis focus on several tests of neuropsychological functions. Interchangeably referred to as neurocognitive tests, these assessments are commonly used in clinical settings to measure functioning of particular pathways and structures in the brain. Neuropsychological tests are critical in patient diagnoses, as well as monitoring the progression of disorders. The domains covered in this thesis include general intelligence, working memory, verbal learning, attention, and executive functions, including set-shifting, processing speed, and visuospatial function. Previous studies generally conclude cognitive decline follows a first-episode of psychosis, with patients consistently underperforming across tests of visual memory, visuospatial functions, attentional set-shifting, working memory, as well as a number of executive functions. The relatively numerous cognitive deficiencies observed across psychoses patients, specifically schizophrenia-spectrum psychosis, as compared to healthy individuals, brings about the

notion of a global cognitive deficit being fundamental in a non-affective psychosis diagnosis. In the case of this thesis, neurocognitive comparisons between psychosis patients with and without current cannabis use is a central theme.

Lifetime prevalence rates of a psychotic disorder is generally 3%, while schizophrenia-spectrum disorders remain steady around 1%, with greater prevalence in developing countries and low socioeconomic areas. Male to female ratios of schizophrenia and other psychoses, although initially believed to be equal, have been shown to be relatively higher in males. Interestingly, females exhibit better recovery rates, including significant fewer remissions and better global cognitive functioning at follow-ups. However, concurrent cannabis use by patients has consistently shown to be greater in male patients, who also tend to have a younger age of illness-onset, and greater duration of untreated psychosis. The highest incidence of a first episode of psychosis is between 16 and 25 years of age, with men typically being diagnosed with a psychotic disorder as young as 18 years. The incidence of cannabis use among psychosis patients has been reported to be as high as 60% and is significantly more prevalent among this group than healthy populations. Interestingly, both psychosis- and drug use-onset seem to occur around the same time, with young people typically between the ages of 15 and 24 years experimenting with cannabis for the first time. With most previous research examining lifetime cannabis use in adult patients, typically in the more chronic stages of schizophrenia, studies instead reporting on neurocognition during this critical time of both illness- and drug use-onset are highly warranted.

Young people represent an ideal population to follow, in regard to neurocognition in psychosis. Not only is adolescence and young adulthood the typical period for both illness- and drug use-onset, but they are also a population less likely to be exposed to other critical environmental factors such as chronic use of antipsychotic medication. Most research demonstrates superior cognition in older schizophrenia patients who have a history of cannabis use, compared to drug-naïve patients. Thus, it is critical to investigate the neurocognition in patients at the time of psychosis-onset, before both cannabis cessation and medication initiation, to explore potential alternate pathways to non-affective psychosis.

The studies presented in this thesis represent the first to address neuropsychological differences in psychosis patients with and without current cannabis use exclusively in young people (i.e. between 16 and 25 years of age). These findings are subsequently implicated in contributing to the paradoxical results of adult patients with a history of cannabis use. There have been no reported investigations of neurocognition in young non-affective psychosis patients with current cannabis use, and subsequent regression models examining their relationship with adult patients. Both young and adult psychosis (i.e. non-affective) patients have routinely been reported as having global cognitive deficiencies compared to healthy controls. Contradictorily, adult patients with a history of cannabis use demonstrate superior cognition compared to their drug-naïve peers, yet very little is known about the cognition of patients during both illness- and drug-onset. In order to further explore the theory of cannabis inducing one's illness, and ultimately

displaying spared cognition, research observing patients at this critical 'window of vulnerability' is warranted.

The first study of this thesis (i.e. Chapter 2) is a meta-analysis that investigates neuropsychological data reporting on current cannabis-using psychosis patients and compared patients in studies exploring either first-episode psychosis (FEP) or specifically schizophrenia. It was hypothesized that cannabis-using psychosis patients would demonstrate significant deficits across a range of neurocognitive tests, compared to non-using patients. Additionally, age was expected to moderate cognition. Specifically, younger cannabis-using patients were expected to demonstrate superior neurocognitive performance compared to older cannabis users, older non-users, and younger non-users. As the majority of research on psychosis patients primarily involves adults, more specifically patients over the age of 25, this study also aimed to evaluate cognitive differences between younger and older patients. Regression models were subsequently executed to analyse effect of age on neurocognition results. A literature search was performed to identify studies comparing psychosis patients with and without current cannabis use. Of the 308 studies identified through database searches and secondary referencing, 14 were selected to be included in the meta-analysis. It was found that current cannabis-using patients underperformed across 6 of the 11 cognitive domains (i.e. premorbid IQ, current IQ, verbal learning, verbal working memory, motor inhibition) compared to cannabis-naïve patients. Cannabis-using patients however outperformed non-users in tests of conceptual set-shifting. Meta-regressions showed older age in cannabis-using patients was predictive of worse performance in processing speed, sustained attention, verbal memory, and better performance in verbal learning and verbal fluency. These findings parallel previous studied indicated current users demonstrate poorer neurocognition than cannabis-naïve patients. Importantly, it appears this is exacerbated with increasing age. There also appears to be significant cognitive differences between patients even at early-onset psychosis, suggesting underlying processes involved in psychosis cognition.

In the second study (i.e. Chapter 3), psychosis patients were exclusively between 16 and 25 years of age. The young patients underwent neurocognitive assessments to compare cognition between drug-naïve patients and concurrent cannabis-using patients, to further explore the above-mentioned third theory of an alternate pathway to schizophrenia. It was expected comorbid psychosis patients and cannabis-naïve patients would demonstrate no significant neurocognitive differences. Subjects were 24 cannabis-using and 79 cannabis-naïve psychosis patients. Patients, and 63 healthy controls, were administered a neurocognitive battery, indexing estimated pre-morbid intelligence, psychomotor speed, mental flexibility, verbal learning and memory, verbal fluency, sustained attention, motor and mental response, and visuospatial learning and memory. The findings indicated no significant neurocognitive differences between the two clinical psychosis groups, despite one group concurrently engaging in cannabis use. Thus suggesting underlying neurobiologyical mechanisms involved in regulating cognition in the cannabis-using psychosis group.

The elucidation achieved by this approach parallels previous research that suggest a vulnerable subgroup of patients bring about their own illness, and so are cognitively spared compared to patients who are diagnosed regardless of such external factors. The first study (i.e. Chapter 2) demonstrated worse cognitive functioning across concurrent cannabis-using patients compared to drug-naïve patients. However, meta-regression clearly displayed the cognitive results were moderated by age. This was particularly important as the majority of studies in this area focus on older, more chronic cases of psychosis or schizophrenia, and this moderation by age showed the significance in focusing on young people, particularly when both illness- and drug use-onset occur. This was further explored in the second study (i.e. Chapter 3), which demonstrated that at this critical age (i.e. between 16 and 25 years of age), current cannabis-using patients exhibited no cognitive deficiencies compared to non-users. This is particularly remarkable as it contrasts with studies of healthy cannabis-using populations, as well as older cannabis-using patients. Ultimately, previous studies reporting superior cognition in patients with a history of cannabis use, and the current thesis demonstrating no cognitive differences between patients regardless of concurrent cannabis use, taken together indicate this concept of an alternate pathway to adult schizophrenia.

Chapter 1

1. Introduction

1.1 Neurocognition in Patients with Psychosis

Over the past 20 years, cognitive deficiencies have been regarded as a core feature of psychoses disorders, particularly schizophrenia-spectrum and non-affective psychosis (Reichenberg et al., 2009). Mounting evidence has demonstrated a range of cognitive impairments from mild, almost-normal cognition, to dementia-like intuition (Kremen, Seidman, Faraone, Toomey, & Tsuang, 2000) across a range of cognitive domains. Although there is considerable heterogeneity across individuals, psychosis patients tend to most prominently exhibit cognitive deficits across domains of memory and learning, executive functions, processing speed and attention (Holmén, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2010; Reichenberg et al., 2010; Saykin, Gur, Gur, & et al., 1991; Wilk et al., 2005). There has been a recent push to realize the substantial range of cognitive deficits as viewed in schizophrenia as reflecting a global cognitive deficit, implying that cognitive impairments across domains share a neurobiological source. Deficits across tests of working memory remain fairly common in psychotic patients and imply significant disturbances in the dorsolateral prefrontal cortex (DLPFC), and its interactions with other neural structures, in psychosis (Edwards, Barch, & Braver, 2010; Lesh, Niendam, Minzenberg, & Carter, 2011).

However, despite any heterogeneity among patients, neurocognitive discourse appears to be consistent across cultural and geographic variations, as well as time. Schaefer and colleagues conclude a substantial, generalized impairment is consistently found in schizophrenia compared to controls, in studies across three decades, and several countries (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). Importantly, moderate to large effect sizes were demonstrated across all cognitive domains in first-episode psychosis (FEP), with a greater magnitude of deficit in older, more chronic patients. Previous theories have addressed schizophrenia as a neurodegenerative disorder to explain this phenomenon, as well as neurotoxicity as a consequence of the disease itself. Recent studies suggest the length of psychotic state after commencing treatment may be predictive of functional and structural decline (Andreasen, Liu, Ziebell, Vora, & Ho, 2013; Davis et al., 1998; Neeltje et al., 2007). Furthermore, relapses early on in the illness seem to be a potent predictor of neurocognitive deterioration in later years. However, a number of longitudinal studies demonstrate that schizophrenic patients instead exhibit stability in neurocognition, and in some incidences, small improvements, over time (Hoff, Svetina, Shields, Stewart, & DeLisi, 2005; Stirling et al., 2003b). A longitudinal study found that FEP patients demonstrated greatest neurocognitive change before hospitalization, and remains relatively stable afterwards (Hoff et al., 2005). Patients did not deteriorate significantly compared to controls at the 10-year follow-up period, indicating cognitive change occurs early on in the illness. In many cases, neurocognitive deficits are observed long before the presentation of clinical symptoms in patients, indicating the significance of neurocognitive functioning in understanding the pathogenesis of schizophrenia. Rund and colleagues have also concluded

that evidence is lacking for both the neurotoxicity and neurodegenerative theories of schizophrenia (Rund et al., 2016). Their mixed model analysis of a 10-yearlong sample shows neurocognitive stability in patients over time. Interestingly they also found, however, that those with stable remission in the first year had better neurocognitive trajectory in the follow-ups than patients who remained continuously psychotic after the first year. Perhaps this subgroup represents a less severely ill phenotype that responds well to treatment and has a good prognosis, including a good neurocognitive trajectory. Ultimately, research into the course of neurocognition in schizophrenia shows treatment response in the first year is a key variable, predicting the long-term course of neurocognition. Most surprisingly, patients generally display no significant cognitive deterioration compared to controls, after treatment.

It is crucial, however, to note heterogeneity across psychosis patients may be due to separate diagnostic subgroups. Both empirical and meta-analytic studies have demonstrated distinct cognitive impairment in schizophrenia-spectrum and affective-psychoses disorders. The findings typically show worse neurocognition in schizophrenia patients compared to affective psychoses, with small to moderate effect sizes (Barch, 2009; Barch & Sheffield, 2014; Bora, Yucel, & Pantelis, 2009; Bora, Yücel, & Pantelis, 2010). Meanwhile the current literature on schizophrenia and schizoaffective disorders is mixed, with some studies concluding greater cognitive deficiency in schizophrenia (Torniainen et al., 2012; Xiao, Bartel, & Brekke, 2017), and some reporting no differences between the two (Heinrichs, Ammari, McDermid Vaz, & Miles, 2008; Sözeri-Varma et al., 2011). Regardless of the larger magnitude of cognitive impairment in schizophrenia compared to affective psychoses, the current literature consistently demonstrates greater cognitive deficits in both disorders compared to controls. Reichenberg and colleagues best demonstrate this result in their recent study measuring neurocognition in patients diagnosed with schizophrenia, schizoaffective disorder, bipolar disorder, and major depressive disorder. They found that although schizophrenia patients demonstrated significantly worse cognition compared to the other three groups across all domains, all four groups had comparable neuropsychological performance profile patterns, and exhibited impairments in memory, executive functions, and attention and processing speed (Reichenberg et al., 2009). Ultimately, all psychoses (affective and non-affective) are associated with some level of cognitive impairment. This impairment may be equally severe in schizophrenia and schizoaffective disorder, and less so in patients with psychotic bipolar and psychotic major depressive disorder. However, the profile or pattern of cognitive impairment across affective psychoses is very similar to that seen in schizophrenia. This finding supports the notion of common underlying mechanisms across psychoses disorders and validates the concern to pinpoint core neurobiological structures and pathways that transcend psychosis diagnoses.

1.2 Neurocognition in Psychosis Patients with Previous Cannabis Use

Cannabis use has been shown to mediate subsequent psychotic illness in vulnerable individuals, however the relationship between substance abuse and outcome remains unclear. As many as 64% of patients with schizophrenia use cannabis (Barnes, Mutsatsa, Hutton, Watt, & Joyce, 2006), which appears to have an effect on brain functioning and

biochemistry, as well as demonstrate seemingly paradoxical positive effects on cognition in patients with schizophrenia (Arnold, Allott, Farhall, Killackey, & Cotton, 2015; Løberg, Hugdahl, & Jørgensen, 2007). Longitudinal studies have demonstrated an increased risk for schizophrenia and other psychoses after substantial cannabis use. Two large-scale Swedish studies, which followed the same cohort of approximately 50 000 military conscripts over 15 and 26 years, reported dose-dependent relationships were found between cannabis use at 18 years of age and later diagnosis of schizophrenia (Andréasson, Engström, Allebeck, & Rydberg, 1987; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002). Several other longitudinal studies have also demonstrated a strong correlation between adolescent cannabis use and subsequent psychosis in the normal population (Arseneault et al., 2002; Ferdinand et al., 2005; Fergusson, Horwood, & Swain-Campbell, 2003; Henquet et al., 2005; Stefanis et al., 2004; Tien & Anthony, 1990; van Os et al., 2002). One possible explanation for the dramatic increase of cannabis use in this patient population is reversed causality, in other words, schizophrenia patients may use cannabis as a form of self-medication, however current data does not support this hypothesis (Chambers, Krystal, & Self, 2001). The most prominent argument against reversed causality is an order-effect, essentially, that cannabis use tends to occur before a diagnosis of psychosis, rather than the other way around (Degenhardt et al., 2007; Linszen, Dingemans, & Lenior, 1994). Several studies have also shown that tetrahydrocannabinol (THC), the main psychoactive components in cannabis, increases symptoms of psychosis and cognitive impairments (D'Souza et al., 2005; Morrison et al., 2009). Similarly, cognitive impairment is often observed before the development of psychosis, as well as in close relatives, and is often observed in patients even after clinical symptoms are reduced (Bowie & Harvey, 2006).

Interestingly, schizophrenia patients who abstain from using cannabis appear to ultimately demonstrate neurocognition superior to that of patients who have never used cannabis (Burns, 2013; Cuesta, Sánchez-Torres, Lorente-Omeñaca, & Moreno-Izco, 2017; Yücel et al., 2012). As previously discussed, schizophrenia and other psychoses patients appear to exhibit deficits across several neurocognitive domains. In parallel, individuals with long-term cannabis use, who are otherwise healthy, also demonstrate severe cognitive impairments, particularly across tests of residual memory and attention, even after abstinence (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003; Yücel, Solowij, Respondek, & et al., 2008). Yucel and colleagues also reported structural brain abnormalities in these otherwise healthy, cannabis-users, contributing to their cognitive deficits (Yücel et al., 2008). Whereas, meta-analyses have shown that patients with a history of cannabis use, often before the onset of psychosis symptoms, actually perform better across many cognitive domains, particularly executive functioning, working memory, and visual functioning, than patients who do not have a history of cannabis-use (Rabin, Zakzanis, & George, 2011; Yücel et al., 2012). Interestingly, Jockers-Scherübl et al. also found that earlier onset of cannabis use (i.e. before 17 years of age) coincided with even better cognitive performance in schizophrenia patients (Jockers-Scherübl et al., 2007), although earlier initiation in healthy controls worsened cognition. This result however is not limited to chronic, or long-term schizophrenia patients. Yucel and colleagues replicated Jockers-Scherübl et al.'s finding in first-episode patients, demonstrating an earlier-onset of

cannabis use in patients is associated with superior cognition even at the first-episode of psychosis (Yücel et al., 2012). Schnell et al. have also shown that more frequent use of cannabis by patients is associated with superior cognition (Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009a). Unsurprisingly, these contradictory results have brought about a rise in research in the neurobiology and underlying mechanisms involved in comorbid psychosis patients. One of the most prominent questions that arises through these paradoxical results is the presence of alternate pathways to psychosis, through environmental, as well as inherent, means.

1.3 Alternate Pathways to Non-Affective Psychosis

Several hypotheses exist for the paradoxical superior cognition seen in patients with previous cannabis use. It has previously been suggested that cannabis-using patients demonstrate superior social skills in order to access the drug, resulting in overall superior global cognition (Potvin, Joyal, Pelletier, & Stip, 2008). However evidence for this theory remains unconvincing, with Ringen and colleagues reporting patients who use drugs have poorer premorbid functioning initially (P. A. Ringen et al., 2008). Some studies have also suggested cannabis use, prior to illness onset, instead results in a neuroprotective effect (Coulston, Perdices, & Tennant, 2007; Jockers-Scherübl et al., 2007). Significantly higher concentrations of neurotrophins have been found in schizophrenia patients with previous cannabis use, compared to patients without history of cannabis use (Jockers-Scherübl et al., 2004; Jockers-Scherübl et al., 2003). Neurotrophins, in particular nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are involved in the development and maintenance of nerve cells. Perhaps this increase is associated with an endogenous repair mechanism, in which the cannabis induces the upregulation of neurotrophins, which in turn helps preserve cognitive functioning. This is supported by other clinical studies, which show neuroprotective effects of cannabis in both normal and neurodegenerative populations (Hampson et al., 2000; Jiang et al., 2005; Ramírez, Blázquez, del Pulgar, Guzmán, & de Ceballos, 2005; Yosef & Raphael, 2005). Giuffrida et al. similarly found an inverse relationship between cerebrospinal fluid (CSF) levels of the endocannabinoid, anandamide, and psychotic symptoms in acute schizophrenia patients (Giuffrida et al., 2004). This suggests that elevated anandamide levels in acute schizophrenia may reflect a compensatory adaptation to the disease. Taken together, these studies indicate some neuroprotective quality of cannabis in schizophrenia, which is initially brought on by the drug itself.

However, the most prominent theory at present surrounds the notion that patients who present with psychosis, as well as a history of long-term cannabis use, have brought about their illness through early-onset of drug use, which otherwise would not have occurred in the absence of cannabis (Løberg & Hugdahl, 2009; Schnell et al., 2009a; Yücel et al., 2012). Simply, early cannabis use induces psychosis in less cognitively vulnerable individuals. Meanwhile, schizophrenia patients who have no history of cannabis use are likely to have greater genetic or developmental vulnerability to psychosis; thus they manifest poorer cognitive performance at psychosis onset. This is supported by evidence that patients who began using cannabis early in adolescence are at greater risk for subsequent psychosis (Arseneault et al., 2002; Yücel et al., 2012), and perhaps ultimately

superior cognition to cannabis-naïve patients (Jockers-Scherübl et al., 2007). Ruiz-Veguilla et al. also reported that comorbid patients presenting with first-episode psychosis, and who had a history of heavy cannabis use, exhibited fewer neurological soft signs than their drug-naïve counterparts (Ruiz-Veguilla et al., 2009), suggesting these comorbid patients have less neurodevelopmental impairment. Ideally, these schizophrenia patients would not present with psychosis if they avoided cannabis use altogether.

Interestingly, the residual (7 h-20 days after use) and long-term (at least 21 days since use) effects of cannabis appear to effect psychosis patients differently to otherwise healthy individuals (Broyd, van Hell, Beale, Yucel, & Solowij, 2016; Crean, Crane, & Mason, 2011; Curran et al., 2016; Ranganathan & D'Souza, 2006). In healthy individuals, acute effects (0-6 h after use) of cannabis show the greatest degree of dysfunction, with subjects demonstrating impairment across attention, decision making, impulsivity and working memory. However, both residual and long-term effects appear to largely revert to near-normal functioning, with a greater abstinence showing the most advanced improvement in cognition. In theory, cannabis-using psychosis patients would be expected to perform worse than cannabis-naïve patients across several domain functions, paralleling the results of healthy individuals. In contrast, evidence suggests patients with a history of cannabis use, who now abstain, outperform cannabis-naïve peers in several cognitive domains.

Several recent studies demonstrate superior cognition in psychosis patients mediated by a history of adolescent cannabis use. Hanna et al. reported better global cognition in schizophrenia/schizoaffective patients who had engaged in cannabis use during adolescence compared to patients with no prior drug use (Hanna, Shalvoy, et al., 2016). However, this result did not translate to patients diagnosed with bipolar psychosis, who instead revealed no cognitive differences between adolescent cannabis users, and non-users. Løberg and colleagues similarly found schizophrenia patients with a history of cannabis use outperformed patients with no history of use across cognitive domains of general intellect, executive functions, attention, working memory, and psychomotor speed (Løberg & Hugdahl, 2009; Løberg et al., 2007). In a separate longitudinal study, both comorbid psychosis patients and drug-naïve patients showed cognitive deficits at admittance to a psychosis ward, however comorbid patients demonstrated greater neurocognitive improvements three months after admittance (Løberg & Hugdahl, 2009; Løberg et al., 2007). Yucel and colleagues similarly researched cognition in a distinctly FEP group, with and without a history of cannabis use (Yücel et al., 2012). They found patients who began using cannabis earlier on (i.e. younger than 17 years of age) displayed superior cognition compared to patients with later drug-onset, which parallel the findings of Jockers-Scherübl and colleagues (Jockers-Scherübl et al., 2007). Yucel et al. defined their comorbid group as regular cannabis users (i.e. >2 grams/week, >2 years) *preceding* illness onset. With dramatic increase in global cognition so quickly after drug cessation, it calls to question the neurocognitive profile of these patients, during illness onset, and before drug cessation. Evidently, adolescence represents an especially interesting stage to observe as both illness- and drug-onset occur around this time. Unfortunately, due to the nature of this study, much of the research observing neuropsychological consequences of cannabis use on psychosis patients involves lifetime, but not current, cannabis use, and so

tend to focus on adult, but not adolescent, patients. Young patients are at critical age to observe cognitive consequences of both drug-use and psychoses disorders at illness-onset and for longitudinal studies, to further understand alternate pathways to schizophrenia.

1.4 Psychosis and Cannabis in Youth Populations

The study of schizophrenia at the first-episode phase has become more prominent for a number of reasons – perhaps most obvious is that earlier treatment leads to better outcome (Keefe, Seidman, Christensen, Hamer, & et al., 2004; Keefe et al., 2006; Keefe, Sweeney, Gu, Hamer, & et al., 2007; Wyatt, 1991). As previously discussed, much of the research on neurocognition in comorbid psychosis patients focuses on older, more chronic cases of psychosis, however rarely are adolescents or young people, when both illness and drug onset tend to occur, the subject of focus. The incidence of psychosis rapidly increases after 15 years of age, with the highest rate of a first episode occurring between the ages of 15 and 25 years (Amminger et al., 2006; Gillberg, Wahlstrom, Forsman, Hellgren, & Gillberg, 1986; Hare et al., 2010). Young people, aged 12 to 24 years, represent an important population to study psychotic disorders as such individuals represent a subgroup of patients less likely to be exposed to critical environmental factors such as chronic use of antipsychotic medication (Epstein et al., 2014). There is also evidence that the corpus callosum, part of the highest order, latest maturing network of the brain, continues to grow until the middle 20's (i.e. 25.45 years on average) (Pujol, Vendrell, Junqué, Martí-Vilalta, & Capdevila, 1993). This, as well as synaptic pruning, which also continues until the mid-20's, suggests full brain development is incomplete until around 25 years of age (Andersen, 2003). Young people are also at a great risk of substance abuse, particularly those for whom the age of onset of drug use (alcohol and cannabis, in particular) occurs prior to around 15 years of age.

However, most individuals do not develop schizophrenia after cannabis use, suggesting that a heightened risk for a development of psychosis must be related to other vulnerability factors. The relationship between cannabis use and psychosis may demonstrate a gene by environment interaction. Caspi and colleagues' longitudinal study involved following 803 individuals into adulthood and found a functional polymorphism in the catechol-*O*-methyltransferase (COMT) gene heightened the risk of adolescent cannabis use resulting in schizophreniform disorders (Caspi et al., 2005). In accordance with this, an interaction between the COMT Val allele and sensitivity for psychosis and cognitive effects of THC has been found in individuals with psychosis, as well as their relatives (Henquet et al., 2009; Henquet et al., 2006). This is further reinforced by evidence that shows different residual and long-term effects of cannabis in psychosis patients versus healthy individuals. While the residual and long-term effects of cannabis in using controls generally revert to near-normal functioning, they ultimately cognitively underperform compared to healthy cannabis-naïve individuals. On the other hand, patients with a history of cannabis (but then abstain) demonstrate superior cognition compared to their cannabis-naïve peers.

Summary and Hypothesis

Undoubtedly, previous research has indicated that a history of cannabis use in schizophrenia patients correlates with better, and in some cases, normal, neurocognition compared to their drug-naïve peers. On the other hand, concurrent drug (i.e. cannabis) use in either older schizophrenia patients or otherwise healthy individuals has shown cognitive deficiencies that transcend psychosis diagnoses. This thesis aims to investigate the theory of an alternate pathway to schizophrenia that is mediated by adolescent cannabis use. As previous research indicates that patients with a history of cannabis use (who later demonstrate better neurocognition) represent a subgroup of patients who may be cognitively spared, it is hypothesized that young people with psychosis who concurrently use cannabis will exhibit cognition no worse than young people with no history of drug use. Ideally this subgroup of patients would not have developed psychosis without the environmental trigger of cannabis, and so are not as neurologically impaired as patients who develop psychosis regardless of external factors. However, it is also hypothesized that after this specific 'window of vulnerability', patients who continue to engage in cannabis use will begin to display cognitive deficits as their drug use further progresses their illness.

Chapter 2

2. The neurocognitive profiles of psychosis patients with cannabis use.

2.1 Study 1: Meta-analysis of neurocognition in comorbid cannabis-using patients.

This study has been published in *Journal of Psychiatric Research*, 2018; 99: 22-32, Title: Meta-analysis of neurocognition in young psychosis patients with current cannabis use.

2.2 Introduction

Cannabis remains the most prevalent illicit drug used by individuals with schizophrenia-spectrum disorders (Amminger et al., 2006; Koskinen, Löhönen, Koponen, Isohanni, & Miettunen, 2010; Smucny, Stevens, & Tregellas, 2014), and current chronic use has been shown to significantly worsen positive psychotic symptoms in patients (Dubertret, Bidard, Adés, & Gorwood, 2006; Talamo et al., 2006). Counterintuitively, meta-analyses and systematic reviews suggest that cognitive functioning in chronic schizophrenia patients with a history of, but not current, cannabis use (CANN±) is superior to that of their peers who have never used cannabis (CANN-) (Løberg & Hugdahl, 2009; Yücel et al., 2012). This suggests that there may be different phenotypes among older individuals with chronic psychotic disorders. However, relatively little is known about the cognitive profiles in the context of cannabis use in younger individuals with early psychosis. Prevalence of psychoses in pre-pubertal children is relatively rare (Thomsen, 1996), although the incidence of first episode psychosis (FEP) rapidly increases after the age of 15 years (Amminger et al., 2006; Gillberg et al., 1986; Hare et al., 2010) with the highest rate of a first episode between the ages of 15 and 24 years (Amminger et al., 2006; Archie et al., 2007). Young people, aged 12–24 years, represent an important population to study psychotic disorders as such individuals represent a subgroup of patients less likely to be exposed to critical environmental factors such as chronic use of antipsychotic medication (Epstein et al., 2014). There is also evidence that the corpus callosum, the highest order, latest maturing network of the brain, continues to grow until the middle 20's (i.e. 25.45 years) (Pujol et al., 1993). This, as well as synaptic pruning, which continues until the mid-20's, suggests full brain development is incomplete until around 25 years of age (Andersen, 2003). Young people are also at a great risk of substance abuse, particularly those for whom the age of onset of drug use (alcohol and cannabis, in particular) occurs prior to around 15 years of age (Archie et al., 2007; Palmer et al., 2009; Wells et al., 2009). Archie et al. (2007) stratified FEP subjects, between 15 and 50 years, into age ranges and found that those between the ages of 18–24 years accounted for the largest faction (i.e. 45%) of patients engaged in concurrent drug use (Archie et al., 2007). It would appear both psychotic episodes and substance use during a time when the brain has not fully developed could have detrimental effects for patients in the long-term, and cognition and

symptomatology during this formidable time needs to be further investigated. Thus, in terms of evaluating the potential cognitive dissimilarities associated with and without concurrent cannabis use in psychotic disorders a focus on young individuals is highly warranted.

Crean et al.'s extensive review demonstrates the various effects of acute (i.e. 0–6 h after use), residual (7 h–20 days after use), and long-term (at least 21 days since use) effects of cannabis on neuropsychological functions in healthy populations (Broyd et al., 2016; Crean et al., 2011; Curran et al., 2016; Ranganathan & D'Souza, 2006). Acute effects of cannabis tend to show the greatest degree of dysfunction, with subjects demonstrating impairment across attention, decision making, impulsivity and working memory. Both residual and long-term effects appear to largely revert to near-normal functioning, specifically in attention, impulsivity and working memory, with a greater period of abstinence showing the most advanced improvement in cognition. Theoretically, cannabis using patients with a psychotic disorder would be expected to perform worse than their non-using counterparts across several cognitive domains, in keeping with studies in healthy individuals; whereby poorer cognitive performance in those who are either CANN+ or CANN± is most pronounced in tests of executive functioning and processing speed (Meier et al., 2012). In contrast, there is evidence that chronic schizophrenia patients who have a history of cannabis use (CANN±) outperform their CANN- peers (with schizophrenia) in general intelligence, attention, working memory, executive abilities and visuo-spatial abilities (Bugra et al., 2013; Jockers-Scherübl et al., 2007; Rabin et al., 2011; Yücel et al., 2012). Following this logic, one might assume that younger individuals with psychotic disorders (e.g. FEP) who use cannabis, but abstain later, will demonstrate improved cognitive functioning compared to their peers who never used cannabis. Given this, it is possible that the cannabis using patients' psychoses stem from an inherent gene-environment interaction partially owing to their early onset of cannabis use. Such a subgroup of patients may be diagnosed with psychosis, but may also have an atypical neurocognitive profile. This reflects Pearlson's review examining significant clinical overlap of psychoses and schizophrenia-spectrum disorders (Pearlson, 2015). Furthermore, there is evidence such as that provided by the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study, showing that there are clusters of individuals with shared biological features (known as 'bio-types') despite there being a commingling of their traditional clinical phenotype (i.e. schizophrenia or affective psychoses disorders) (Hill et al., 2013; Tamminga et al., 2014). Importantly, one of the three biotypes identified appears to be associated with higher cannabis use, better cognition, and lower percentage of affected relatives (Tamminga et al., 2017). This theory is supported by evidence, which shows that chronic schizophrenia patients with CANN± who first began using cannabis before the age of 17 years exhibit some superior cognitive functioning compared to patients with later (i.e. after 16 years of age) cannabis-use onset (Hanna, Shalvoy, et al., 2016; Jockers-Scherübl et al., 2007; Yücel et al., 2012).

Yücel et al.s' meta-analysis investigated the effect of past cannabis use, typically prior to psychosis onset, on neuropsychological performance of older adults (i.e. mean age of patients was above 27 years) with a diagnosis of schizophrenia (Yücel et al., 2012). CANN± outperformed patients with no history of use (CANN-) in tests of global cognition,

processing speed, visual memory, planning, and working memory. However, they also found that patients who currently use cannabis (CANN+) did not demonstrate superior cognitive performance across a range of measures. Although, these groups differed significantly in one cognitive domain: the CANN+ showed worse performance in tests of verbal memory. Similarly, a separate study utilized biological radioimmunoassay testing rather than drug-use questionnaires to measure current drug use in schizophrenia patients, and found no significant cognitive differences between current cannabis-using patients and their non-using counterparts (Bahorik, Newhill, & Eack, 2014). However, there are several factors that may affect cognitive results, including frequency, dosage, and time since last cannabis intake. D'Souza et al. found evidence of dose-specific effects of THC on the cognition of schizophrenia patients (D'Souza et al., 2005). They demonstrated temporarily increased learning and recall deficits after 2.5 mg or 5 mg of intravenous THC, compared to 0 mg, with patients in the 5mg group showing a pattern of worse cognitive performance compared to 2.5 mg.

On the surface, a history of moderate, (potentially regular) lifetime use of cannabis followed (importantly) by a period of abstinence in psychosis patients reveals a 'superior' cognitive profile compared to those with a psychotic disorder who never used or those who have continued to use (i.e. current use in older, more chronic stages of schizophrenia). Intriguingly, it appears that when cannabis use begins during adolescence, before the age of 17, those who later abstain (i.e. CANN±) demonstrate better neurocognitive performance than their CANN± peers who began using after 17 years. However only a handful of studies report any evidence of cognitive dysfunction in cannabis-using adolescents diagnosed with psychosis. Furthermore, cannabis use in the neurodevelopmental period of adolescence has been shown to confer a range of cognitive, social, and psychological harms (Di Forti et al., 2014; Henquet et al., 2005; Mackie et al., 2013; Meier et al., 2012; Meier, Hill, Small, & Luthar, 2015; Scholes-Balog, Hemphill, Evans-Whipp, Toumbourou, & Patton, 2016; Szoke et al., 2014; Tien & Anthony, 1990). In fact, Henquet et al. found that any cannabis use exacerbates psychotic symptoms in young people, parti- cularly in those who have a predisposition for psychosis (Henquet et al., 2005).

Given the above-mentioned findings, the aim of the current study was to systematically review the potential effects of cannabis use on cognition in adolescent and young adult patients with psychosis. From previous evidence, we expected cannabis users to show significant deficits across a range of neurocognitive tests, as compared to non-using patients. However, young cannabis-using patients were expected to demonstrate superior neurocognitive performance compared to older CANN+ and CANN-, or young CANN-.

2.3 Methods

2.3.1 Search strategy and selection criteria

Studies were identified through extensive online database searches, including PubMed, Medline, and Psycinfo. Searches included keywords involving psychosis (i.e. schizophrenia, schizophreniform, psychosis, schizoaffective, schizo*, FEP, first, episode), cannabis (i.e. cannabis, marijuana, THC, tetrahydrocannabinol), and cognition (i.e.

neuropsycho*, neurocognit*, cogniti*), and were limited to English-language articles with human participants. All articles up to October 2016 (i.e. the month the searches were conducted) were considered for analysis. A secondary search was conducted by reviewing the reference lists of relevant review and meta-analytic papers.

The inclusion criteria were: (1) diagnosis of a psychotic disorder according to DSM (i.e. Schizophrenia Spectrum and Other Psychotic Disorders) or ICD (i.e. Schizophrenia Spectrum and Other Primary Psychotic Disorders) criteria; (2) studies had to compare a psychotic (or schizophrenia spectrum disorder) cannabis-using group to an appropriate clinical control group (i.e. psychotic nonusers); (3) cannabis was the predominate substance used by patients, as stated by the authors in the methodology; (4) the assessment of traditional neuropsychological functions using valid and reliable tests, used routinely in clinical practice (Strauss, Sherman, & Spreen, 2006); and (5) sufficient statistical data were reported for transformation into effect sizes (ES), or the relevant data were available from the original researchers.

Studies were excluded if they included cases who: (1) were diagnosed with a substance/medication-induced psychotic disorder, or were intoxicated at time of testing; or (2) investigated individual components of cannabis (e.g. tetrahydrocannabinol [THC] or cannabidiol [CBD] on their own); or (3) investigated synthetic cannabis. Only studies with the largest sample were included in the instance of overlapping samples.

As shown in Fig. 1, 308 titles and abstracts were initially identified, but only 44 studies assessed both cannabis use and cognition in psychotic patients. Thirty of these studies were excluded because: (1) the patient sample had irrelevant diagnoses (Buchy et al., 2015; Hollis et al., 2008; Korver et al., 2010; van Tricht et al., 2013), (2) the study included no relevant neuropsychological tests (Bourque et al., 2013), (3) they lacked patients involved in current cannabis use (Cunha et al., 2013; de la Serna et al., 2010; DeRosse, Kaplan, Burdick, Lencz, & Malhotra, 2010; Epstein et al., 2014; Hanna, Shalvoy, et al., 2016; Jockers-Scherübl et al., 2007; Krzysztof et al., 2012; Leeson, Harrison, Ron, Barnes, & Joyce, 2012; Løberg et al., 2012; Mata et al., 2008; Moreno-Granados, Ferrín, Salcedo-Marín, & Ruiz-Veguilla, 2014; Power et al., 2015; Rentzsch et al., 2016; Schnell et al., 2009a; Sevy et al., 2007; Stirling, Lewis, Hopkins, & White, 2005a; Wobrock et al., 2007; Yücel et al., 2012), (4) cannabis was not the predominate substance abused (I. Harrison et al., 2008), and (5) there was insufficient data and we were unable to obtain data from the authors (Arnold et al., 2015; Bahorik et al., 2014; Løberg & Hugdahl, 2009; Meijer et al., 2012; Pencer & Addington, 2003; Potvin et al., 2005).

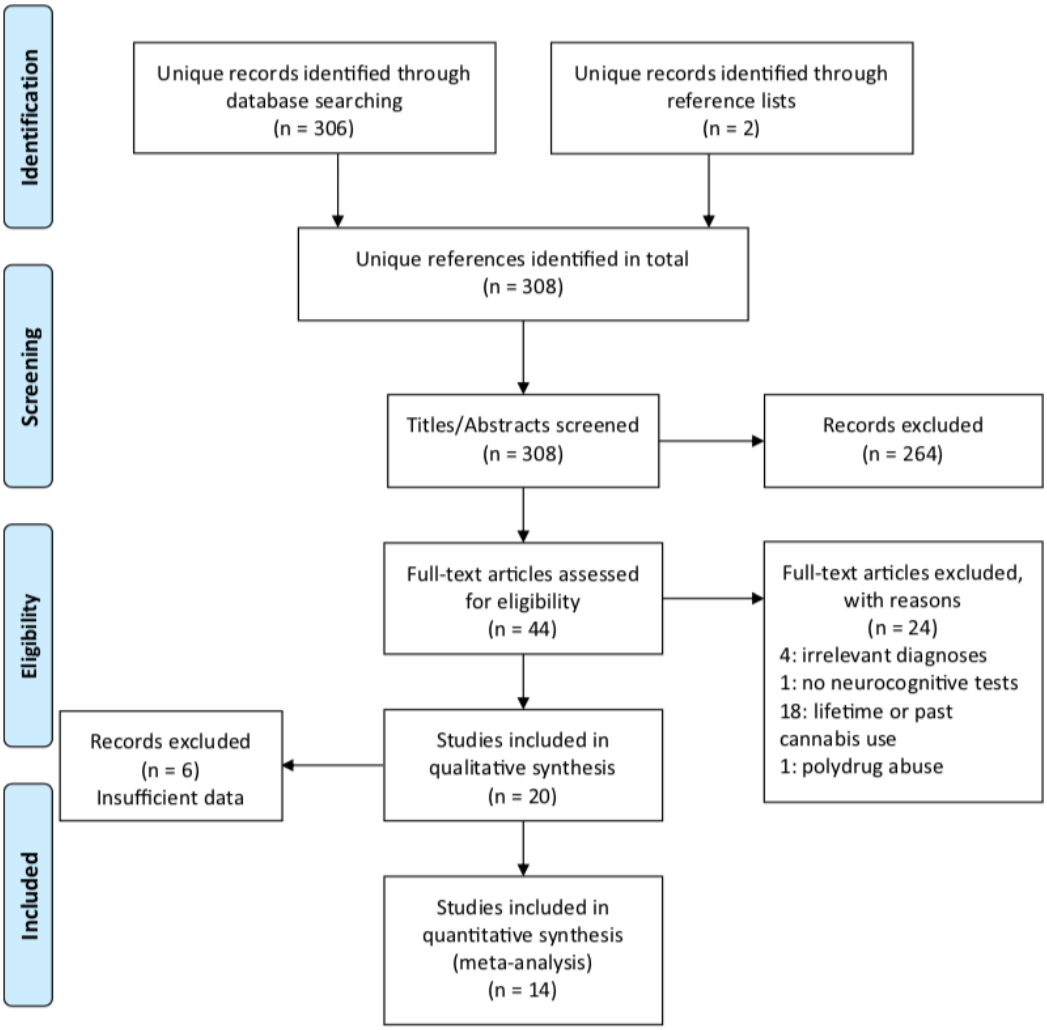

Figure 2-1: Flow chart of the studies considered and selected for review.

All studies in the meta-analysis included a psychotic patient sample who were current cannabis users, defined as at least weekly cannabis use in the past 6 months. In 4 of the 14 studies, the patients were considered a young sample (mean age is less than 25 years), while the other 10 studies comprised of adult patients (mean age is older than 24 years). Overall, our meta-analysis included 14 studies involving 1430 patients with psychosis, with (N = 529) and without (N = 901) comorbid cannabis use.

2.3.2 Meta-analytic procedure

All meta-analytic procedures were conducted using Comprehensive Meta-Analysis Version 2.0 (Borenstein, 2005). One author (S.B.) extracted patients' demographic data and cognitive test results from the articles. In cases where raw data was not available, the authors were contacted and demographic data and/or test results re- quested. Effect size (Hedges' g) was calculated for each cognitive do- main. In cases where a study used two cognitive tests for one domain, the tests were grouped together, and the average ES was calculated. A more positive ES indicated better performance for CANN+ than CANN-, and in keeping with the literature, the size of the ES was interpreted according to Hedge's g (0.2 = small; 0.5 = medium; 0.8 = large) (Hedges & Olkin, 1985; Lee, Hermens, Porter, & Redoblado-Hodge, 2012). A random effects model was used for meta-regression (i.e.

unrestricted-maximum likelihood) and subgroup analyses (i.e. method of moments), with a significance level set at $p < .10$ (Zeggini & Ioannidis, 2009). As described in Table 1, cognitive domains included were pre- morbid IQ, current IQ, processing speed, cognitive flexibility, sustained attention, verbal learning, verbal memory, verbal working memory, conceptual set-shifting, motor inhibition, and verbal fluency. In longitudinal studies, only cross-sectional neuropsychological results were used to circumvent practice effects (McCleery, Addington, & Addington, 2006; Sánchez-Torres et al., 2013; Wobrock et al., 2013). Heterogeneity between studies was tested using the Q-test, and publication bias was assessed using Egger's test (Egger, Smith, Schneider, & Minder, 1997; Higgins, Thompson, Deeks, & Altman, 2003). Subsequent tests of Rosenthal's Fail-Safe N, and Duval and Tweedie's Trim and Fill method were carried out to determine the number of studies required to establish no publication bias (Duval & Tweedie, 2000a, 2000b; Rosenthal, 1979).

Table 2-1: Cognitive domains and the corresponding neuropsychological tests included in each analysis.

Cognitive Domain	Neuropsychological test
Processing Speed	Trail Making Test-Part A; WAIS Digit Symbol-Coding; WAIS Symbol Search; CogState Matching Task; D-KEFS TMT2
Sustained Attention	Continuous Performance Task; CogState Continuous Monitoring; CANTAB Rapid Visual Information Processing
Cognitive Flexibility	Trail Making Test-Part B; D-KEFS TMT4
Working Memory (Verbal)	WAIS Digits Backward; WAIS Letter-Number Sequencing
Verbal Learning	Rey Auditory Verbal Learning Test Total; WMS Logical Memory; California Verbal Learning Test Total; TAVEC Total
Verbal Memory	Rey Auditory Verbal Learning Test Long Delay Free Recall; TAVEC Long Delay Free Recall; WMS Verbal Delayed Recall; California Verbal Learning Test Long Delay Free Recall
Conceptual Set-Shifting	Wisconsin Card Sorting Test
Verbal Fluency	Letter Fluency (F-A-S, *p*)
Motor Inhibition	Stroop Color-Word Interference; D-KEFS Color-Word Interference
Current IQ	WAIS; WASI; MWT-A; Leistungsprufsystem, scale 3
Premorbid IQ	SILS; WTAR; NART

WAIS = Wechsler Adult Intelligence Scale.
D-KEFS = Delis-Kaplan Executive Function System.
CANTAB = Cambridge Neuropsychological Test Automated Battery.
WMS = Wechsler Memory Scale.
TAVEC = Test de Aprendizaje Verbal Esapaña-Complutense (Spanish version of the California Verbal Learning Test).
TAP = Test for Attentional Performance.
WASI = Wechsler Abbreviated Scale for Intelligence.
MWT-A = Mehrfachwahl-Wortschatz Test.
SILS = Shipley-Institute of Living Scales.
NART = National Adult Reading Test.

2.3.3 Moderator analyses

Predictors of between-study variability in ES were examined using meta-regression (for continuous predictors) and subgroup analyses (Q_{bet}, for categorical predictors). The predictors were included if a sufficient number of studies had reported these variables (i.e. no more than one study missing per cognitive domain). These were grouped as either:

1) Demographic predictors included ‘age’ and ‘sex’. A number of studies have indicated the significance of age in confounding the differences between CANN+ and CANN- (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012; Potvin et al., 2008). As we are also interested in neuropsychological differences between young and adult patients, regressions for age were performed for each cognitive domain. Similarly, gender differences are well-recognized among both cannabis-users, and psychosis patients, where cannabis-users more often tend to be men (Ochoa et al., 2012; Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2003).

2) Diagnostic predictors included patient diagnosis (‘psychotic disorder’ or ‘schizophrenia-spectrum disorder’). In the present study, we classified psychosis and schizophrenia as two distinct diagnoses (A.P.A., 2013). Although psychosis is a core

symptom of schizophrenia, patients with a diagnosis of psychosis alone do not experience the full spectrum of a psychotic illness. Schizophrenia patients also display greater cognitive deficits than patients with first- episode psychosis alone (Yücel et al., 2012), the latter of which is a more heterogeneous group comprising substance use disorders and affective disorders with psychotic features.

2.4 Results

A total of 14 studies, published up to October 2016, met inclusion criteria and were incorporated into the meta-analysis (see Table 2). Six of the studies included patients diagnosed with solely psychotic disorders (Bugra et al., 2013; de la Serna et al., 2010; González-Pinto et al., 2016; Lev-Ran, Segev, Braw, & Levkovitz, 2012; McCleery et al., 2006; Núñez et al., 2016), while the remaining eight focused on patients diagnosed with narrower schizophrenia-spectrum disorders (Coulston et al., 2007; Ferraro et al., 2013; Fischer et al., 2015; Rabin, Zakzanis, Daskalakis, & George, 2013; P.A. Ringen et al., 2010; Sánchez-Torres et al., 2013; Scholes & Martin-Iverson, 2010; Wobrock et al., 2013). Four studies originated in Spain, two each from Australia, and Canada, and one each from the United Kingdom, Switzerland, Norway, the United States, Israel, and Germany. Sample sizes varied from 26 to 319. There was a total of 529 CANN+ cases, compared with a total of 901 CANN- controls. The proportion of female participants was a weighted average of 17.4% for CANN+ and 39% for CANN-. The mean age was a weighted average of 25.0 years for CANN+ and 27.9 years for CANN-. Five studies explicitly defined cannabis users as having cannabis dependence, whereas the remaining nine studies included users with any sort of cannabis use over at least the previous month.

The effect sizes and related statistics of differences in performance between CANN+ and CANN- are presented in Table 3. Effect sizes were in the small to medium range (Hedges g = 0.13–0.55), with the exception of verbal working memory (Hedges g = 0.76). Most ES suggest poorer cognitive performance in CANN+ compared to CANN-. Table 4 presents the moderator analyses for predictors of heterogeneity. A more positive ES indicates better performance in CANN+ than CANN- (see Supplementary Figures for forest plots of each cognitive domain).

Table 2-2: Summary of key characteristics of studies.

	PSY + CANN		PSY-CANN		Other Drugs	Diagnosis	Cognitive Tests Used	Key Neuropsychological Findings
	N (% female)	Mean age (years ± SD)	N (% female)	Mean age (years ± SD)				
de la Serna et al. (2010)	32 (31.3)	16.34 ± 0.16	76 (34.2)	15.16 ± 0.22		Psychosis	CPT, Letter Fluency, SCWT, TAVEC, TMT-A, TMT-B, Digit Span, LNS, WCST.	CANN+ performed better in sustained attention (CPT).
McCleery et al. (2006)	91		35		Cannabis main substance. 49 alcohol abuse, 8 polysubstance abuse.	Psychosis	CPT, Letter Fluency, NART, RAVLT, SPAN-12, TMT-A, TMT-B, Digit Symbol Coding, WCST, WMS.	CANN+ outperformed CANN- in TMT-A, CPT, RAVLT, RCFT, TMT-B, WCST, and Premorbid IQ.
González-Pinto et al. (2016)	107 (18.7)	23.0 ± 4.96	161 (40.4)	24.02 ± 6.33		Psychosis	CPT, Letter Fluency, SCWT, TMT-A, TMT-B, LNS, WAIS-III, WCST.	CANN- performed better in memory tasks.
Nunez et al. (2016)	34 (23.53)	20.65 ± 5.40	40 (55.0)	19.45 ± 7.58	All used cannabis, some occasional use of other substances (cocaine, alcohol, sedatives). Users had a higher tobacco intake than non-users.	Psychosis	CPT, SCWT, TAVEC, TMT-A, TMT-B, Digit Span, LNS, WAIS-III.	No difference between CANN+ and CANN-.
Bugra et al. (2013)	23 (30.4)	28.3 ± 8.48	24 (37.5)	33.2 ± 9.69		Psychosis	CPT, WCST, MWT-A, Leistungsprufsystem-3.	CANN+ outperformed CANN- in executive functioning (Go/No-Go).
Lev-Ran et al. (2012)	12 (8.33)	29.17 ± 4.39	16 (31.25)	27.62 ± 4.84	Substance use other than cannabis was limited to less than five occasions during lifetime. None of these occasions were during the previous year to testing.	Psychosis	RVIP	CANN- performed better in response inhibition.
Rabin et al. (2013)	18 (0.00)	31.6 ± 9.6	8 (0.00)	45.5 ± 6.5	Non-cannabis using patients had a higher tobacco intake than cannabis-users.	Schiz	CPT, CVLT, SCWT, TMT-A, TMT-B, WCST, WTAR.	No differences between CANN+ and CANN-.
Ringen et al. (2010)	23 (26.09)	27.74 ± 8.09	117 (48.72)	34.44 ± 10.21	Sporadic other substance (cocaine, amphetamine) use.	Schiz	CVLT, Color-Word Interference, Letter Fluency, NART, Digit Symbol Coding, Digit Span, WASI, WMS.	CANN+ performed better in verbal memory and cognitive flexibility. CANN- outperformed CANN+ in attention.
Sánchez-Torres et al. (2013)	12 (8.33)	37.00 ± 5.85	30 (36.67)	37.03 ± 5.17		Schiz	CPT, Letter Fluency, SCWT, TAVEC, TMT-A, TMT-B, Digit Symbol Coding, Digit Span, LNS, Symbol Search, WAIS-III, WCST.	CANN+ performed worse in working memory.
Scholes and Martin-Iverson (2010)	22 (4.5)	31.4 ± 7.5	49 (12.2)	37.8 ± 9.2	12 used other substance in the previous month (8 amphetamines, 1 narcotics, 1 benzodiazepines, 2 hallucinogens).	Schiz	SCWT, WCST, LNS.	CANN+ performed better in cognitive flexibility.
Ferraro et al. (2013)	34 (20.6)	26.2 ± 6.5	53 (42.4)	32.0 ± 8.8		Schiz	WAIS-III, Digit Symbol Coding, WTAR.	Lifetime cannabis users had higher scores in both IQ and premorbid IQ compared to patients who never used cannabis.
Wobrock et al. (2013)	85 (16.5)	23.9 ± 4.4	234 (48.5)	26.4 ± 5.6	All used cannabis (main abused substance). 14 also abused other illegal substances (mainly amphetamines, ecstasy, cocaine).	Schiz	RAVLT, TMT-A, TMT-B, Digit Symbol Coding.	No difference between CANN+ and CANN-.
Coulston et al. (2007)	18 (0.00)	25.8 ± 4.0	34 (0.00)	27.6 ± 5.9		Schiz	CogState: Continuous Monitoring, Matching Task; Color-Word Inhibition, TMT, Letter Fluency, RAVLT, SILS-V, WCST.	Dependent CANN+ were impaired in immediate memory, but above average in planning efficiency.
Fischer et al. (2015)	18 (5.6)	30.72 ± 8.17	24 (16.7)	40.75 ± 12.47		Schiz	WTAR	CANN+ reported more sensation-seeking than PSY-CANN-.

2.4.1 Current and premorbid IQ

All seven studies that incorporated tests of premorbid IQ reported poorer performance for CANN+, with the overall ES significantly in favour of CANN- (g = −0.40). Similarly, the six studies that measured current IQ also reported significant deficits in CANN+ subjects (g = −0.17). There was no significant heterogeneity in premorbid and current IQ across studies. A more equal proportion of sexes (i.e. increased female representation) was predictive of greater superiority in current IQ in CANN+ (Z = 2.03).

Table 2-3: Number of studies (k), pooled sample size (N), pooled ES (Hedge's g), homogeneity (Q, I, tau (Smucny et al., 2014)), and publication bias.

				Meta-Analysis		Heterogeneity			
	k	PSY + CANN N	PSY-CANN N	Hedges' g	95% CI	Q	*I*	tau (Smucny et al., 2014)	Egger's test (*t*)
Premorbid IQ	7	214	301	−0.40***	−0.59–−0.20	4.73	0%	0.00	1.42
Current IQ	6	268	479	−0.17*	−0.34–−0.00	5.64	11%	0.01	0.37
Processing Speed	10	672	1151	0.20	−0.05–0.44	43.35	79%	0.11	1.24
Cognitive Flexibility	8	397	618	0.19	−0.15–0.54	39.11***	82%	0.19	0.87
Sustained Attention	9	347	424	0.55	−0.11–1.62	126.70***	94%	0.94	0.55
Verbal Learning	8	427	726	−0.39†	−0.8–0.04	61.93***	89%	0.32	0.99
Verbal Memory	8	427	726	−0.13	−0.42–0.16	28.04***	75%	0.12	0.43
Working Memory (Verbal)	6	308	619	−0.76**	−1.30–−0.22	64.10***	92%	0.41	1.65
Conceptual Set-Shifting	8	323	417	0.32†	−0.05–0.68	32.86***	79%	0.20	0.47
Motor Inhibition	8	266	515	−0.19†	−0.40–0.02	11.65	34%	0.04	1.26
Verbal Fluency	6	283	453	−0.47	−1.22–0.28	89.61***	94%	0.82	0.65
Total *k*/N	14	529	901						

PSY = Psychosis. CANN = Cannabis. ES = effect size.
*p ≤ .05. **p ≤ .01. ***p ≤ .001.
†p ≤ .10.

Table 2-4: Moderator analyses to determine predictors of heterogeneity.

	Demographic factors				Diagnostic factors	
	Sex		Pooled Age		Diagnosis	
Cognitive Domain	%*k*	*Z*	%*k*	*Z*	%k	Q_{bet}
Premorbid IQ	86	0.10	86	0.21	100	0.79
Current IQ	100	2.03*	100	−0.25	100	1.82
Processing Speed	90	1.83†	90	−1.87†	100	7.22*
Cognitive Flexibility	88	1.41	88	−0.68	100	1.67
Sustained Attention	89	1.37	89	−2.61**	100	5.29*
Verbal Learning	88	−1.11	88	1.84†	100	0.08
Verbal Memory	88	0.58	88	−1.90†	100	5.30*
Working Memory (Verbal)	100	−2.28*	100	−0.80	100	0.79
Conceptual Set-Shifting	88	0.77	88	−0.81	100	0.49
Motor Inhibition	100	−1.50	100	0.14	100	0.28
Verbal Fluency	83	−1.80†	83	2.36**	100	0.93

*$p \leq .05$. **$p \leq .01$. ***$p \leq .001$.
†$p \leq .10$.

2.4.2 Processing speed

Ten studies reported tests of processing speed, demonstrating no effects between cannabis groups. A more equal sex distribution was indicative of better performance in CANN+ (Z = 1.83). Both in- creasing age and a diagnosis of schizophrenia were predictive of poorer performance in tests of processing speed for CANN+ (Z = −1.87; Q_{bet} = 7.22).

2.4.3 Cognitive flexibility

Eight studies included tests of cognitive flexibility, with only one test used in all articles (i.e. TMT-B). ES were not significant. There was a high level of heterogeneity among studies, but none of the moderators were predictive for this result.

2.4.4 Sustained attention

The nine articles that reported tests of sustained attention demonstrated non-significant ES. ES across studies were significantly heterogeneous. Both increasing age and a diagnosis of schizophrenia resulted in poorer performance for CANN+ ($Z = -2.61$; $Q_{bet} = 5.29$).

2.4.5 Verbal learning

CANN+ showed significant deficits in tests of verbal learning ($g = -0.39$). ES across studies were significantly heterogeneous. Increasing age was predictive of superior performance in tests of verbal learning for CANN+ ($Z = 1.84$).

2.4.6 Verbal memory

ES for verbal memory tests was non-significant, and heterogeneous across studies. Increasing age and diagnosis of schizophrenia were predictive of poorer performance in CANN+ ($Z = -1.90$; $Q_{bet} = 5.30$).

2.4.7 Verbal working memory

Six studies incorporated tests of (verbal) working memory, and show significant difference between cannabis groups ($g = -0.761$). ES across studies was significantly heterogeneous. A more equal sex distribution was indicative of poorer performance in CANN+ ($Z = -2.28$).

2.4.8 Conceptual set-shifting

Eight studies reported results from Wisconsin Card Sorting Test (WCST), which measures conceptual set-shifting. CANN+ performed significantly better than CANN- ($g = 0.318$), with high heterogeneity across studies. None of the moderators were predictive of this result.

2.4.9 Motor inhibition

Motor inhibition was significantly poorer in CANN+ ($g = -0.189$). Studies were not heterogeneous.

2.4.10 Verbal fluency

Tests of verbal fluency were non-significant between groups. Studies were significantly heterogeneous. Both a more equal sex distribution and decreasing age result in poorer performance for CANN+ ($Z = -1.80$; $Z = 2.36$).

2.4.11 Publication bias

Of the neuropsychological domains that differentiated CANN+ from CANN-, there was no evidence to suggest that these domains were influenced by publication bias ($p > .10$) (See Supplementary Materials for funnel plots).

2.5 Discussion

To our knowledge, this was the first meta-analysis to systematically investigate the neurocognitive profile of psychotic disorders in young people who use cannabis. As expected, never-using patients (CANN-) outperformed current cannabis-using cases (CANN+) across tests of premorbid and current IQ, verbal learning, verbal working memory, and motor inhibition. This is consistent with previous studies showing that patients with current or recent cannabis use display cognitive deficits when compared to those with a lifetime history of past cannabis use, as well as those with no history of cannabis use (Løberg & Hugdahl, 2009). Unexpectedly, CANN+ in the present study performed better than CANN- in conceptual set-shifting tasks (i.e. Wisconsin Card-Sorting Task), an outcome that contrasts with previous findings (Scholes & Martin-Iverson, 2010). However, most ES in these analyses have appeared to show a relatively small to medium degree (i.e. 0.2 to 0.5 ES range) of dysfunction in cannabis-users (Hedges & Olkin, 1985; Lee et al., 2014). This is unsurprising, as a number of epidemiological studies have instead reported non-significant to small cognitive differences between CANN+ and their non-cannabis using peers. The largest ES observed in this study was for verbal working memory, whereby CANN+ performed worse than CANN-. Yücel et al. also found that non-using patient groups performed better in verbal memory than recent users (Yücel et al., 2012). Similarly, Schoeler et al.'s meta-analysis investigating memory function in older psychosis patients (i.e. mean age of patients was above 27 years) with CANN± found users who abstained less than 10 days performed poorly in memory tasks compared to prolonged-abstinent psychosis patients. Thus, consistent with these previous meta-analyses of older adult patients (i.e. typically after the age of 25), our findings indicate that there are significant cognitive deficits in the recent cannabis-using patient groups, despite age (Schoeler, Kambeitz, Behlke, Murray, & Bhattacharyya, 2016; Yücel et al., 2012). In other words, it appears that cannabis use at any age is associated with (an overall tendency for) poorer cognitive capacity.

Thus, the findings of this study provide support for current cannabis-users with psychosis having inferior cognitive abilities. Consistent with previous papers, cannabis use was associated with a younger age and male gender (Dixon, 1999; B. Green, Young, & Kavanagh, 2005; Linszen et al., 1994; Malone, Hill, & Rubino, 2010; Mueser, Yarnold, & Bellack, 1992; H. Myles, Myles, & Large, 2016; Veen et al., 2004; Winklbaur, Ebner, Sachs, Thau, & Fischer, 2006). Several studies indicate poorer performance of CANN+ groups in immediate verbal learning, and working memory (Coulston et al., 2007; Cunha et al., 2013; de la Serna et al., 2010; González-Pinto et al., 2016; McCleery et al., 2006; Meijer et al., 2012; P.A. Ringen et al., 2010; Yücel et al., 2012). Decreased memory capability is however a well-known effect of recent cannabis use, with evidence showing any more than one cannabis joint per week was associated with poorer verbal working memory capacity in healthy individuals (Chait & Perry, 1994; Fant, Heishman, Bunker, &

Pickworth, 1998; Heishman, Huestis, Henningfield, & Cone, 1990). CANN+ also demonstrated motor inhibition deficits in the present study, supporting the notion that individuals, whether diagnosed with a psychotic disorder or otherwise healthy, perform significantly worse than non-users in tests of cognitive inhibition (Prashad & Filbey, 2017; Wrege et al., 2014). Functional magnetic resonance imaging (fMRI) has shown that individuals under the influence of delta-9-tetrahydrocannabinol (THC), the main psychoactive component in cannabis, attenuates activation in the right inferior frontal and anterior cingulate gyrus during the Go/No-Go task. Activation in these regions during the response-inhibition task is thus likely responsible for impairments in the inhibitory control of thoughts and emotions, as well as motor responses, as often viewed symptomatologically in schizophrenia (Bhattacharyya et al., 2015; Borgwardt et al., 2008).

There is evidence that CANN+ present with a higher premorbid IQ (Ferraro et al., 2013; Løberg & Hugdahl, 2009; Yücel et al., 2012), which contrasts with findings in the present study. Ferraro et al. found a significant increase in premorbid and current IQ in patients who had any lifetime experience with cannabis, but not in CANN+ (Ferraro et al., 2013). Interestingly, they also found CANN+ who engaged in their use socially tended to have higher premorbid IQ than patients who chose to use cannabis alone. Despite evidence demonstrating superior premorbid IQ in patients engaged in cannabis use, several studies have instead found no differences between CANN+ and CANN- (Bugra et al., 2013; Núñez et al., 2016; Scholes & Martin-Iverson, 2010; Waterreus, Badcock, Di Prinzio, Martin-Iverson, & Morgan, 2017). Scholes and Martin-Iverson found no significant cognitive differences between CANN+ and CANN- in older (i.e. above 24 years of age) schizophrenia patients, with the exception of CANN+ instead showing deficits in conceptual set-shifting (i.e. Wisconsin Card Sorting Task) when compared to CANN- (Scholes & Martin-Iverson, 2010). On the other hand, Jockers-Scherübl and colleagues claim there are no differences between CANN± and CANN- in conceptual set-shifting (Jockers-Scherübl et al., 2007), indicating the superior adaptive ability of CANN+ in the current study does not transcend all patient ages and varying recency of cannabis use. A recent cross-sectional study has also concluded that there are no significant differences present between CANN+ and CANN- in domains of premorbid and current IQ, attention, processing speed, and memory (Waterreus et al., 2017). Clearly several confounders influence the subsequent outcomes of neurocognitive testing in these patient groups. Unfortunately, there are very few studies available that examine the neurocognition in current cannabis-using psychosis patients. While the literature in this area is already extremely limited, there are only a handful of reports that look at cannabis' influence on young people with psychosis (i.e. under 25 years). As one of the most paramount factors in this study is the impact of patients' age, we performed meta-regressions to view the influence of age on cognitive performance.

Onset of cannabis use tends to begin during the adolescent years, with initial use on average occurring at 15 years of age (Archie et al., 2007; Palmer et al., 2009; Wells et al., 2009). This is also the age many early-onset psychosis patients, particularly males, experience their first episode. In the present study, young (i.e. below 25 years of age) CANN+ performed significantly better in processing speed, sustained attention, and verbal memory than older (i.e. above 24 years) CANN+ patients. Previous studies have suggested

that in some cases for older CANN+ patients, cumulative exposure to cannabis over several years may contribute to poorer results in cognitive tests compared to younger patients. Young patients are also more likely to have had less treatment exposure (e.g. antipsychotic medications) over their lifetimes (Bossong & Niesink, 2010; Kolb & Gibb, 2011). On the other hand, young CANN+ showed greater deficiencies in verbal learning and verbal fluency. As previously noted, cannabis effectively influences the user's memory and learning abilities. In younger patients, this would be more influential given the critical brain maturation processes occurring in the 16–25 years age period; further compounded by the early age of cannabis use onset (Bagot, Milin, & Kaminer, 2015). These results generally fall in line with Løberg and Hugdahl's reanalysis of previous data, in which CANN± outperformed CANN- in a number of cognitive domains, including learning and memory, attention and working memory, executive functions, and psychomotor speed (Løberg & Hugdahl, 2009). They also showed CANN+, who were admitted to a psychiatric emergency ward, demonstrated a significantly larger improvement in their cognitive performance only three months after admission, compared to their non-using counterparts. In fact, evidence suggests cannabis onset preceding 17 years of age leads better cognitive outcomes for CANN± later in life (i.e. within 2–10 years after cannabis abstinence) (Helle et al., 2014; Jockers-Scherübl et al., 2007; Løberg & Hugdahl, 2009; Yücel et al., 2012). One explanation regarding this paradoxical phenomenon is that the patients with such early onset of cannabis use instead triggers their own illness, and represent a subgroup of psychoses patients with high genetic loading, likely due to a specific gene poly-morphism in this cohort (Malone et al., 2010; Tost, Alam, & Meyer-Lindenberg, 2010). Caspi and colleagues conducted a longitudinal study of 800 adolescent cannabis onset users; they found that a functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderates the influence of adolescent cannabis use on developing adult psychosis (Caspi et al., 2005). However, this study has not been replicated, and the evidence on whether such polymorphisms modulate the risk for psychosis associated with exposure to cannabis is mixed with some (Caspi et al., 2005) but not other (Henquet et al., 2006; Tunbridge et al., 2015; Zammit et al., 2007) studies showing an effect. In some cases, cannabis use, combined with polymorphisms in the COMT gene appeared to not only increase the risk of schizophreniform disorder, but also results in younger age of psychosis onset (Caspi et al., 2005; Pelayo-Terán et al., 2010). On the other hand, there is also evidence of no cognitive or affective differences mediated by the COMT gene with cannabis use (Kantrowitz et al., 2009; Zammit et al., 2007). This indicates the observed gene-environment interaction may be limited to a sensitive period of brain development in adolescence.

The proportion of females in each cannabis group played a significant function in the subsequent performance of the psychoses groups. Males are three times more likely than females to be diagnosed with a psychotic disorder (Iacono & Beiser, 1992) Furthermore, several studies have found substance use by men (typically with cannabis and alcohol) well outnumber women, both in cases with and without psychotic disorders (Ochoa et al., 2012; Schepis et al., 2011). Our results parallel the underrepresentation of females in psychosis populations, as males outnumbered females in all studies, specifically in CANN+. Equal sex distributions were predictive of better performance in current IQ and

processing speed for CANN+, whereas more equal distributions implied deficiencies in verbal working memory and verbal fluency. Our findings contrast Rabin et al., who found no cognitive differences between male schizophrenia CANN+ and CANN- patients (Rabin et al., 2013). In addition to age and sex, it may be important to consider diagnostic subtypes (e.g. affective-versus schizophrenia-spectrum) as a key factor in our understanding of concurrent psychosis and cannabis use. Løberg et al. support previous hypotheses in their detailed literature review that pre-illness cannabis use confers a greater risk for affective psychosis, which appears to have a better cognitive prognosis than cannabis-using schizophrenia-spectrum patients (Bora et al., 2009; Krabbendam, Arts, van Os, & Aleman, 2005; Løberg et al., 2014; Manrique-Garcia et al., 2012). Although several studies indicate only small effect sizes between affective psychosis and schizophrenia diagnoses, schizophrenia patients consistently perform worse than affective psychosis patients in tests of crystallized knowledge, verbal skills, information processing speed, and verbal memory (Barch, 2009; Depp et al., 2007; Hill et al., 2013; Krabbendam et al., 2005; Schretlen et al., 2007). In fact we found CANN+ (affective-) outperformed CANN+ (schizophrenia-spectrum) in tests of processing speed, sustained attention and verbal memory. Schizophrenia-spectrum CANN+ showed no cognitive lead over affective- CANN+. To our knowledge, there are no present studies directly investigating cognitive differences between affective- and non-affective psychoses, however neuroimaging studies suggest atypical dopamine synthesis in the striatum may account for the induction of psychosis in a different mechanism typically seen in schizophrenia (Batalla et al., 2014; Tost et al., 2010).

Notably, the dopaminergic and cannabinoid systems in the brain develop early on in young adulthood. A number of brain regions that are implicated in psychosis and other schizophrenia-spectrum disorders, are also densely populated with cannabinoid receptors, and are as such, heavily affected by THC in cannabis (D'Souza et al., 2005). Several abnormalities of the endogenous cannabinoid system in pa- tients with schizophrenia, occurring before the use of cannabis, are apparent. These include increased levels of cannabinoids in both the frontal cortex and cerebral spinal fluids (Dean, Sundram, Bradbury, Scarr, & Copolov, 2001; Leweke, Giuffrida, Wurster, Emrich, & Piomelli, 1999). It is therefore possible that changes to this atypical endocannabinoid system, by external cannabinoids, could be involved in the pathology of psychotic disorders. The findings presented here support the notion that there are distinct cognitive profiles according to the patients' age as well as the pattern of their cannabis use. While increased cumulative exposure to cannabis may account for some of these results, it is also possible that the developing brain in young people, especially with psychosis, are more vulnerable to the effects of cannabis than a matured brain. It would be important to understand the initial effects of cannabis on the brain of a psychosis patient, specifically that of a young person, to better understand the prognostic implications of concurrent cannabis use in psychoses, and recognise how to treat young adults and adults who currently engage, and have a lifetime history, in cannabis use.

There are some limitations in our study that should be considered. First, there are a few key factors that were not investigated in this study. Frequency and dosage, which was addressed in only three of the present studies, are notable influences that impact the

effect of cannabis on patients. Nunez and colleagues demonstrated that heavy cannabis users (i.e. more than three cannabis joints per day) showed significant cognitive deficiencies in tasks of verbal learning, attention and processing speed when compared to medium users (i.e. less than three cannabis joints per day) and non-using patients (Núñez et al., 2016). Similarly, duration of cannabis use varies among the studies analysed. The findings in the present study should be taken with some caution, given the diverse range of duration of cannabis use among patients (i.e. 6 months to 2+ years). Interestingly, the majority of studies found that a higher frequency of cannabis use predicts better performance in cognition, specifically attention and working memory (Coulston et al., 2007; Schnell et al., 2009a).

Second, different methodologies across studies prove to be a limitation for reviews and meta-analyses. As the included studies all measured separate outcomes, we were unable to compare several clinical and demographic characteristics of the patient groups. Several studies have indicated the significance of general psychopathy sub-scores and symptomology on prognosis, progression and performance on cognition (Grech, van Os, Jones, Lewis, & Murray, 2005; Helle et al., 2014; Linszen et al., 1994; Meijer et al., 2012; Power et al., 2015). The magnitude of cognitive dysfunction may also be dependent on the patient's diagnosis, or sub-group of psychotic disorder (i.e. affective psychosis or schizophrenia-spectrum disorder). Schizophrenia-spectrum patients appear to be more cognitively compromised than those with affective psychosis or FEP alone (Reichenberg et al., 2009), however all psychotic disorders consistently underperform in tests of memory, executive functions, attention, and processing speed (Gooding & Tallent, 2002; Heinrichs et al., 2008; Hill, Keshavan, Thase, & Sweeney, 2004; Hill et al., 2013; Reichenberg et al., 2009; Tamminga et al., 2014). Future studies must tease out these discrete disorders in order to best represent schizophrenia-spectrum, FEP, and affective-psychosis patients, as varying heterogeneity between subgroups appears to somewhat effect cognitive outcomes of each clinical group (Van Rheenen et al., 2017; Welham, Thomis, & McGrath, 2003). Discrepancies between potential and actual performance of patients due to these confounding factors may in fact significantly alter results if not matched between patient groups. Similarly, comorbid cannabis use and psychoses patients with a family history of psychosis suggests better performance in areas of verbal memory, executive function and global cognition compared to patients without the family history of illness (González-Pinto et al., 2016), further indicating the influence of confounding factors often undisclosed to us in this study.

Third, some studies used in our analyses included patients engaging in other comorbid substance abuse, particularly alcohol and cocaine. However studies that investigated the effect of alcohol use on cognition of psychosis patients found no association (Pencer & Addington, 2003; Potvin et al., 2008; Yücel et al., 2012), instead suggesting regular alcohol use leads to greater positive symptoms. Bahorik et al. analysed the neurocognitive functioning of schizophrenia patients who currently use cocaine and/or methamphetamine and also found no associations between the drugs and cognition (Bahorik et al., 2014).

Fourth, there is evidence that some components of cannabis (e.g. cannabidiol [CBD]) might ameliorate psychotic symptoms and improve acute cognition (Morgan &

Curran, 2008). On the other hand, different strains of, as well as synthetic, cannabis, which was not taken into account in a majority of the studies analysed, may also mediate the drug's effect on cognition (Morrison et al., 2009; Radhakrishnan, Wilkinson, & D'Souza, 2014). Future studies should consider the effect of varying proportions of THC and CBD in different strains of cannabis, as well as the more neurotoxic and harming effects involved with synthetic cannabis.

Unfortunately, the literature on the neurocognitive effects of cannabis use in psychosis patients who are under the age of 25 years is exceptionally limited. Although a number of studies show evidence to suggest that older CANN± patients (i.e. above 25 years) possess a superior capability to adapt to changing environments and circumstances, which may incorporate social settings (Arnold et al., 2015; Bossong & Niesink, 2010; Joyal, Hallé, Lapierre, & Hodgins, 2003; Larsen et al., 2006; Meijer et al., 2012; Potvin et al., 2005; P. A. Ringen et al., 2008), to our knowledge there are no reports investigating the cognitive effects of lifetime cannabis use in psychosis patients who are under the age of 25 years. Similarly, despite one prevalent theory that addresses the superior social abilities of CANN+ is the social demand required to obtain illicit drugs (Bhattacharyya & McGuire, 2011; Bossong & Niesink, 2010; Burns, 2013; Løberg & Hugdahl, 2009; Yücel et al., 2012), only a limited number of studies have actually looked into any potential cognitive differences at the time of both psychosis- and cannabis-onset, as often observed in young people. In conclusion, our meta-analysis supports previous findings of cognitive deficiencies in psychosis patients who currently use cannabis. Most noteworthy is the superior performance of young patients who use cannabis, which could suggest a subgroup of psychosis patients. While prior research indicates lifetime users outperform non- using patients in several neuropsychological tests, our findings indicate young people with both an early-onset of cannabis use and FEP may represent a subgroup of patients who develop psychosis through an alternative pathway not otherwise observed in traditional psychosis patients who aren't involved in drug use. This evidence indicates distinct treatment plans for psychosis patients need to be utilized to properly care for, perhaps, differing forms of psychosis that arise through varying mechanisms. However, more research needs to be conducted into the effects of cannabis use on young psychosis patients to further investigate the cognitive changes and differences during the time of both psychosis- and cannabis-onset. This will facilitate greater understanding of the superior capabilities observed in lifetime, but not current, cannabis users, as compared to non-using psychosis patients.

Chapter 3

3. The neurocognitive profile of young psychosis patients with current cannabis use.

3.1 Study 2: The neuropsychological profiles of young psychosis patients with and without current cannabis use.

This study is under review at *Cognitive Neuropsychiatry*, Title: The neuropsychological profiles of young psychosis patients with and without current cannabis use.

3.2 Introduction

The neurocognitive and clinical profiles of patients with psychosis have been scrutinized in recent years, closely following mounting evidence of the moderating effect of history of cannabis use on expression of neurocognitive and symptomatic impairment (Frascarelli et al., 2016; González-Pinto et al., 2016; Hanna, Perez, & Ghose, 2016; Mallet, Ramoz, Le Strat, Gorwood, & Dubertret, 2017; Murray, Quigley, Quattrone, Englund, & Di Forti, 2016; Waterreus et al., 2017; Yücel et al., 2012). Much of the research observing neuropsychological consequences of cannabis use on psychosis patients involves lifetime, but not current use, and so tend to focus on adult but not adolescent patients. These studies generally conclude that patients with previous cannabis use outperform cannabis-naive patients in a number of cognitive tests, particularly in tests of working memory and executive function (Coulston et al., 2007; Jockers-Scherübl et al., 2007; Potvin et al., 2008; Schnell, Koethe, Daumann, & Gouzoulis-Mayfrank, 2009b; Stirling, Lewis, Hopkins, & White, 2005b; Wobrock et al., 2007). This peculiar outcome conflicts with studies observing cannabis-using, but otherwise healthy participants. The general consensus in healthy populations with both current and previous cannabis use is that these participants underperform in several tests of cognition compared to non-users, regardless of (long-term) abstinence (Bartholomew, Holroyd, & Heffernan, 2010; Fletcher et al., 1996; Pope & Yurgelun-Todd, 1996; Solowij, 1988).

Crean's review of acute and long-term effects of cannabis on the cognition of healthy populations revealed several cognitive impairments in abstinent cannabis-users, specifically in attention, working memory, decision-making and motor inhibition (Crean et al., 2011). Evidently, psychosis patients and participants from a healthy population demonstrate conflicting neuropsychological profiles in those who have lifetime, but not current, cannabis use. There is also evidence to suggest that psychosis patients who began using cannabis before the age of 17 (but are currently abstinent) exhibit better cognitive performance than both psychosis patients who began using after the age of 17 or never at all (Jockers-Scherübl et al., 2007; Yücel et al., 2012). Stirling and colleagues similarly found that regular cannabis use occurring before psychosis onset predicted spared cognition 10 years later (Stirling et al., 2005b). They demonstrated that although cannabis-using FEP patients were younger and exhibited more positive symptoms at baseline, these cannabis-using patients, at follow-up 10 years later, actually demonstrated equal or superior

neurocognitive profiles compared to their non-cannabis-using counterparts (Stirling et al., 2005b; Stirling et al., 2003a). These results parallel Hanna and colleagues' findings of variability in adult psychosis patients' subsequent neurocognition, as moderated by their adolescent cannabis use (Hanna, Shalvoy, et al., 2016). While neither adolescent- nor later-onset of cannabis use predicted any difference in cognition in patients with bipolar-type psychosis, patients with both adolescent-onset cannabis use and schizophrenia psychosis demonstrated superior cognition compared to other schizophrenia groups (i.e. schizophrenia with no cannabis use, and schizophrenia with later [after 18 years] onset of cannabis use). Conversely, Scholes and Martin-Iverson demonstrated that although patients with schizophrenia expectedly underperformed across all administered cognitive tests compared to healthy controls, regardless of cannabis use status, there were no significant differences between the two clinical groups (i.e. schizophrenia patients with or without current cannabis use) (Scholes & Martin-Iverson, 2010).

There appears to be emerging evidence of alternative pathophysiological pathways to schizophrenia, at least one of which is mediated by cannabis use. Several studies indicate spared cognition for patients with lifetime cannabis use after long-term abstinence, however few studies actually observe the effects of current cannabis use on patients' cognition. As expected, it appears comorbid adult psychosis patients with current cannabis use significantly underperform in a number of cognitive tests, when compared to non-using patients, demonstrating similarities between cannabis-using and non-using healthy controls. Waterreus and colleagues' study focusing on adult psychosis patients further advanced Hannah and colleagues' findings by demonstrating cognitive deficits were only present in current cannabis-using affective psychosis patients, but not in those diagnosed with non-affective psychosis (Waterreus et al., 2017). In fact, our recent meta-analysis of 1,430 participants across 14 studies (Bogaty, Lee, Hickie, & Hermens, 2018) demonstrates the potential effects of current cannabis use on patients' cognition, with a focus on the impact of age. We found that while current users present deficits in several cognitive tests compared to patients with no history of cannabis use, age moderated the effect of current cannabis use on cognition with greater impairment in most cognitive domains found for older using psychosis patients (Bogaty et al., 2018).

Despite correlation between lifetime cannabis use and subsequent (relatively) superior cognition in some psychosis patients, there is very limited research focusing on the critical period during which both illness-onset and drug-onset occurs. This suggests that there may be different phenotypes among older individuals with chronic psychotic disorders. However, relatively little is known about the cognitive profiles in the context of cannabis use in younger individuals with early psychosis. Prevalence of psychosis in pre-pubertal children is relatively rare (Thomsen, 1996), although the incidence of first episode psychosis rapidly increases after the age of 15 years, with the highest rate of a first episode between the ages of 15 and 25 years (Amminger et al., 2006; Gillberg et al., 1986; Hare et al., 2010). Young people, aged 12 to 24 years, represent an important population in which to study psychotic disorders, as such individuals represent a subgroup of patients less likely to be exposed to critical environmental factors such as chronic use of antipsychotic medication (Epstein et al., 2014). There is also evidence that the corpus callosum, the highest order and latest maturing network of the brain, continues to grow until the middle

20's (i.e. 25.45 years on average) (Pujol et al., 1993). This, as well as synaptic pruning, which also continues until the mid-20's, suggests full brain development is incomplete until around 25 years of age (Andersen, 2003). Such a graded pattern of brain maturation means that development of processes such as behavioural inhibition are deferred until later adolescence and early adulthood (Paus, 2005), placing young people at pronounced risk for substance initiation and future abuse, particularly among those with substance onset prior to ~15 years (Pitkanen, Lyyra, & Pulkkinen, 2005).

Given the above-mentioned literature, the present study aimed to determine the neurocognitive effects of current cannabis use in young psychosis patients during the critical period often-encompassing both drug- and illness-onset. Based on previous evidence, we expected no significant neurocognitive differences between cannabis-using and cannabis-naïve psychosis patients. However, it was expected both groups would underperform compared to controls.

3.3 Methods

Participants

One-hundred-and-three outpatients (aged 16-25) were recruited from one of two Sydney-based *headspace* sites, a service providing specialized assessment and early intervention for mental health problems in young people (Scott et al., 2009). Included patients were diagnosed with a primary psychotic disorder by a psychiatrist according to DSM-IV-TR criteria (A.P.A., 2013). Proportions of primary diagnoses were: first-episode psychosis (n = 36); psychotic disorder NOS (n = 24); schizophrenia (n = 23); schizophreniform disorder (n = 8); and schizoaffective disorder (n = 12). Sixty-three control subjects were recruited for comparison. Exclusion criteria were: i) neurological or physical illness known to impinge upon cognitive or neural function (e.g. epilepsy); ii) history of a sustained head injury (loss of consciousness > 30 minutes); iii) insufficient English-language ability; and iv) premorbid IQ < 70. Three patients were subsequently excluded for having an illness known to impinge upon neural function (i.e. epilepsy, cancer), and one for a traumatic head injury.

The assessment protocol was approved by the University of Sydney Human Research Ethics Committee, and written confirmed consent was collected. The healthy control group (N = 63; aged 16 to 25 years) was recruited from the community in the same metropolitan geographic area as the outpatients, and were screened for psychopathology by a research psychologist through a clinical interview.

Clinical Assessment

A self-report questionnaire was administered querying demographic, clinical and functional information. Questions collected age, gender, years of education, occupational status, personal and familial medical and psychiatric history, and medication status. A trained research psychologist conducted a structured clinical interview, the BMRI Structured Interview for Neurobiological Studies (Lee et al., 2013), to determine the nature and history of any mental health problems. All research psychologists were thoroughly trained by masters- or doctorate-level clinical psychologists or neuropsychologists. The interview included the expanded 24-item Brief Psychiatric Rating Scale (BPRS; (Ventura,

Green, Shaner, & Liberman, 1993)) and the 17-item Hamilton Depression Rating Scale (HDRS; (Hamilton, 1967)) to quantify general psychiatric and depressive symptoms at the time of assessment. Current and historical substance use was also recorded using the Alcohol, Smoking and Substance Use Involvement Screening Test, Version 2 (ASSIST-2). We focused on 'clinically-significant' substance use, which was operationalized as: daily or almost daily tobacco use, weekly or more frequent cannabis use, and weekly or more alcohol use. The Social and Occupational Functioning Assessment Scale (SOFAS; (Goldman, Skodol, & Lave, 1992)) was also used as a rating of the patient's functioning from 0 to 100, with lower scores indicating more severe impairment. Participants also completed WHO-QoL BREF (Skevington, Lotfy, & O'Connell, 2004), which measures four domains (physical; psychological; social and environment) quality of life.

Neuropsychological Assessment

Pre-morbid intelligence ('predicted IQ') was estimated on the basis of performance on the Wechsler Test of Adult Reading (WTAR; (Wechsler, 2001)) 'Psychomotor speed' was assessed using the Trail-Making Test – part A (TMT A), with 'mental flexibility' assessed by part B (TMT B; (Strauss et al., 2006)). 'Verbal learning' and 'verbal memory' were assessed by the Rey Auditory Verbal Learning Test (RAVLT; (Strauss et al., 2006)) sum of trial 1-5 (RAVLT sum) and 20-minute delayed recall (RAVLT A7), respectively. FAS letters test measured 'verbal fluency' (Patterson, 2011). Participants also completed various subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB; (Sahakian & Owen, 1992)). Specifically, 'sustained attention' was indexed by the A-prime (sensitivity to the 'target') and speed of response ('latency') measure of the Rapid Visual Processing task (RVP), 'motor and mental response' was indexed by the 5-choice Movement and Reaction Time variants of Reaction Time (RTI), 'set-shifting' was indexed by *Intra-Extra Dimensional Shift* (IED) and 'visuospatial learning and memory' was indexed by the total adjusted errors score from the Paired Associate Learning task (PAL errors).

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS; (IBM, 2012)). To control for the effects of age (and education for RAVLT performance), neuropsychological variables were converted to demographically-corrected standardised scores (z-scores) using the following established norms: TMT (Tombaugh, Rees, & McIntyre, 1998) and RAVLT (Rickert & Senior, 1998). Similarly, CANTAB z-scores, based on an internal normative database of 3000 healthy volunteers (http://www.camcog.com), were calculated for each participant. Prior to analyses, outliers with a z-score beyond ±4.0 for each neuropsychological variable were curtailed to values of +4.0 or -4.0 (depending on the direction) so that the results were not disproportionately skewed by individuals with extreme scores. We restricted the analyses to only the neuropsychological tests with less than 15% of curtailed cases. The number of cases beyond ±4.0 exceeded 10% only for PAL (14%), and IED (26%). IED was therefore removed from analyses. Differences in demographic, clinical and neuropsychological measures across the three groups were assessed using one-way analysis of variance (ANOVA). Levene's test

was used to test for homogeneity of variance, and Welch's statistic was calculated, correcting for degrees of freedom (df) and p-values, if and where this assumption was violated. The Scheffe test was used to determine post-hoc pair-wise comparisons between the three groups. Chi-square test was used to compare the ratio of females to males, smoking status, and alcohol status across groups. In any case where the two clinical groups were significantly different in demographic information or substance use (other than cannabis), a one-way ANCOVA was conducted to determine statistically significant differences between the groups on clinical and neuropsychological results, controlling for the differences in demographics or substance use.

3.4 Results

Three groups were subsequently formed: 63 controls were identified from a healthy population; 79 as patients with psychosis and no history of cannabis use; 24 as patients with comorbid psychosis and cannabis use. As shown in Table 1, there were no significant differences among the psychosis groups in terms of the distribution of sex, age, or predicted IQ. The two patient groups did, however, have significantly less years of education, and greater ratios of males to females than the control group (as is common in psychosis cohorts; (Ochoa et al., 2012). There were significant between-group differences for socio-occupational functioning (SOFAS), current depressive (HDRS) and general psychiatric (BPRS) symptoms as well as quality of life (QoL) with both psychosis groups (i.e. with or without cannabis use) exhibiting worse scores on each of these measures compared to the healthy control group. However, the clinical groups only differed from each other in BPRS negative symptoms, with cannabis-naive patients scoring lower than the comorbid cannabis-using patients ($p = 0.03$). Although the two psychosis groups did not differ in age of psychosis onset ($p = 0.98$), comorbid psychosis patients were significantly more likely to be current nicotine smokers and consume alcohol at least weekly compared to patients who did not engage in cannabis use (both $p < 0.01$). A one-way ANCOVA determined that the two psychosis groups did not differ in severity of negative symptoms when controlling for alcohol consumption ($F[1,49] = 0.24$, $p = 0.63$), or smoking status ($F[1,75] = 2.84$, $p = 0.10$).

Table 3-1: Mean scores (± standard deviation) for clinical and psychosocial variables in psychosis patients who currently use cannabis (PSY+CAN), psychosis patients who have never used cannabis (PSY-CAN) and Control groups.

	PSY+CAN	PSY-CAN	Control	Between-group test	*P*	*d*	
						+CAN vs. Con	-CAN vs. Con
Sex (f/m)[#]	4/20	26/53	41/22	22.6***	0.13	-	-
Age, years	21.6 ± 2.4	20.8 ± 2.6	21.8 ± 2.0	3.0	0.35	0.1	0.4
Education, years	11.7 ± 2.2	12.1 ± 2.0	13.9 ± 1.9	17.5***	0.66	1.1†	0.9†
Smoking Status[#]				40.1***	**0.00**	-	-
Current Smoker, n (%)	15 (62.5)	21 (26.6)	4 (6.3)	-	-	-	-
Past Smoker, n (%)	4 (16.7)	11 (13.9)	17 (27.0)	-	-	-	-
Current Alcohol Use, n (%)[#]	16 (66.7)	14 (17.7)	-	8.7**	**0.00**	-	-
Age of psychosis onset, years	17.5 ± 3.2	17.5 ± 3.9	-	0.0	0.98	-	-
Antipsychotic Use[#]				0.5	0.79	-	-
Atypicals	16	47	-	-	-	-	-
Typicals	0	0	-	-	-	-	-
No Antipsychotics	7	29	-	-	-	-	-
Missing	1	3	-	-	-	-	-
Predicted IQ	100.7 ± 9.2	99.2 ± 10.0	104.0 ± 8.6	4.4**	0.79	0.4	0.5
SOFAS	52.3 ± 9.9	55.2 ± 14.5	88.7 ± 7.2	229.9***	0.60	4.2†	2.9†
HDRS total	11.7 ± 6.9	10.6 ± 7.5	1.6 ± 2.2	68.6***	0.76	2.0†	1.6†
BPRS total	45.8 ± 9.4	41.8 ± 12.6	25.8 ± 2.5	90.7***	0.28	2.9†	1.8†
BPRS: Positive	13.5 ± 5.3	12.8 ± 5.3	7.5 ± 1.0	45.6***	0.84	1.6†	1.4†
BPRS: Negative	10.2 ± 4.1	8.4 ± 3.2	5.0 ± 0.9	50.1***	**0.03**	1.8†	1.4†
QoL: Physical	22.9 ± 4.7	23.6 ± 5.3	29.9 ± 3.9	37.1***	0.84	1.6†	1.4†
QoL: Psychol	14.8 ± 5.2	16.7 ± 4.8	23.3 ± 3.0	53.4***	0.23	2.0†	1.6†
QoL: Social	8.1 ± 3.1	9.2 ± 2.8	11.5 ± 2.3	16.8***	0.27	1.2†	0.9†
QoL: Environ	26.7 ± 6.0	27.6 ± 5.9	32.5 ± 4.1	18.6***	0.80	1.1†	1.0†

Note: Corresponding results for [#]chi-squared [df=2,166] or ANOVA [df=2,165]; *** denotes p<.001; ** denotes p<.01; * denotes p<.05]. Effect sizes (d statistic) for each pair-wise group comparison [† denote large effect sizes i.e. d>0.8].

PSY+CAN = comorbid psychosis and current cannabis use; PSY-CAN = psychosis diagnosis with no cannabis use; SOFAS = social and occupational functioning assessment scale; BPRS = brief psychiatric rating scale; HDRS = Hamilton depression rating scale; QoL = quality of life.

The neuropsychological profiles (mean z-scores) for all three groups are depicted in Figure 1, and the ANOVAs with corresponding Scheffe's post-hoc tests are summarised in Table 2. There were no significant differences between the two psychosis groups in any of the 11 cognitive tests. Both clinical groups performed significantly worse than controls in TMT-B, RVP-*A*, RAVLT sum, RAVLT-A7, and PAL. Additionally, psychosis patients without cannabis use underperformed compared to controls in TMT-A and RTI reaction time, while comorbid cannabis-using patients were significantly worse in COWAT.

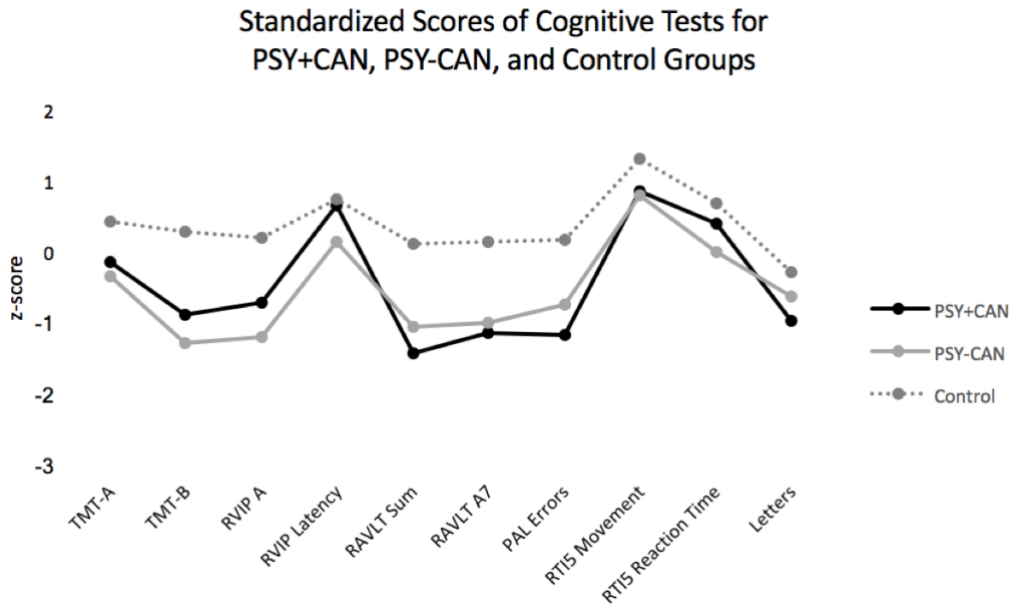

Figure 3-1: Mean scores of comorbid cannabis patients, cannabis-naive patients, and controls for each cognitive test.

Note: Scores are expressed as z-scores.

Table 3-2: Z-statistic mean scores (± standard deviation) for neuropsychological variables in PSY+CAN, PSY-CAN and Control groups.

						d	
	PSY+CAN	PSY-CAN	Control	ANOVA, *F*	*p*	+CAN vs. Con	-CAN vs. Con
TMT A	-0.1 ± 1.1	-0.3 ± 1.1	0.4 ± 0.9	9.1***	0.74	0.5	0.7*
TMT B	-0.9 ± 1.4	-1.3 ± 1.6	0.3 ± 1.0	24.8***	0.50	1.0*	1.2*
RVP A	-0.7 ± 1.2	-1.2 ± 1.4	0.2 ± 1.1	17.9***	0.36	0.8*	1.1*
RVIP Latency	0.6 ± 1.2	0.2 ± 1.6	0.7 ± 1.3	2.3	0.11	0.1	0.3
RAVLT Sum	-1.4 ± 1.4	-1.0 ± 1.4	0.1 ± 0.8	25.6***	0.41	1.3*	1.0*
RAVLT A7	-1.1 ± 1.5	-1.0 ± 1.5	0.1 ± 0.9	17.9***	0.90	1.0*	0.9*
PAL Errors	-1.2 ± 1.6	-0.7 ± 1.4	0.2 ± 0.8	14.9***	0.34	1.1*	0.8*
RTI5 Movement	0.9 ± 1.2	0.8 ± 1.2	1.3 ± 1.0	2.7	0.97	0.4	0.5
RTI5 Reaction Time	0.4 ± 0.9	0.0 ± 1.2	0.7 ± 0.7	6.3**	0.32	0.4	0.7*
Letters	-1.0 ± 0.8	-0.6 ± 0.9	-0.3 ± 0.9	5.1**	0.27	0.8*	0.3

Note: Corresponding results (F statistic) for ANOVA [df=2,162; *** denotes p<.001; ** denotes p<.01; * denotes p<.05]. Effect sizes (d statistic) for each pair-wise group comparison. '*p*' represents the *P* values for comparisons between the PSY+CAN and PSY-CAN groups. Bold values indicate comparisons that were significantly different between the PSY+CAN and the PSY-CAN groups.

TMT = Trail making test; RVIP = Rapid visual information processing; RAVLT = Rey auditory verbal learning test; PAL = Paired associate learning; RTI5 = Choice reaction time (5-choice); COWAT = Controlled oral word association test.

3.5 Discussion

The present study determined neurocognitive profiles of young (i.e. 16-25 years) psychosis patients with and without concurrent cannabis use. We found that cannabis-using and cannabis-naïve psychosis patients did not significantly differ across any of the cognitive domains. Both groups, however, performed significantly worse across a majority of cognitive tasks compared to controls. We have previously demonstrated that current cannabis-using adult patients exhibit deficits across tests of premorbid IQ, current IQ, verbal learning, verbal working memory, and motor inhibition, compared to non-using psychosis patients (Bogaty et al., 2018). However, we also observed that older age was predictive of worse performance in some cognitive measures, specifically processing speed, sustained attention, and verbal memory, with superior performance in verbal learning and verbal fluency. Based on studies involving adult psychosis patients, as well as those using healthy adult participants with current cannabis use, it would be expected that patients with comorbid cannabis use would perform worse across several cognitive domains than their non-using counterparts; however, that is not the case in the present study. On the other hand, de la Serna and colleagues found FEP patients, explicitly young adults between the ages of 9 to 17 years, who had used cannabis in the previous month outperformed non-users only in tests of Continuous Performance Task (CPT), or selective attention (de la Serna et al., 2010). There is however also evidence that suggests psychosis patients' cognition is instead mediated by their clinical diagnoses.

The present study dovetails with recent observations of no significant cognitive differences between adult patients with or without current cannabis use, or even with lifetime use (Waterreus et al., 2017). However, when taking into account clinical groupings, Waterreus and colleagues observed a significant negative relationship between current cannabis use and cognitive performance in patients with affective psychosis, but not in patients with non-affective psychosis. The diverse cognitive outcomes of psychosis patients based on distinct clinical groupings provides some support for the notion of alternative psychopathophysiological pathways to psychosis. For instance, it has been suggested that children or young people who are genetically vulnerable, and are exposed to cannabis especially at a young age, are more susceptible to a diagnosis of psychosis, and eventually schizophrenia, than if they don't engage in cannabis use (Hall & Degenhardt, 2008; Malone et al., 2010; Semple, McIntosh, & Lawrie, 2005). Therefore, while there are patients who develop psychosis regardless of external factors such as drug use (specifically cannabis) there appears to be a distinct group of psychosis patients who develop (non-affective) psychosis if they engage in cannabis use, particularly during adolescence. Previous analyses have revealed subgroups of psychoses patients based purely on their family history of illness, drug use, and neurocognitive results (Crouse, Moustafa, Bogaty, Hickie, & Hermens, 2018; Pearlson, 2015; Tamminga et al., 2014; Tamminga et al., 2017).

In one such line of inquiry, Crouse and colleagues performed a cluster analysis using patients determined to have early psychosis-spectrum illnesses (Crouse et al., 2018). They observed an appropriate clustering of patients into three discrete groups, one with near-normal cognitive performance ("Cluster 1"), one with mixed performance ("Cluster 2"), and one that was grossly impaired ("Cluster 3"). Most interesting from this study was the over representation of bipolar patients in Cluster 1, and of schizophrenia-spectrum illness

(i.e. schizophrenia, schizoaffective disorder, FEP) in Cluster 3. Although they found no significant differences in drug and alcohol use between the clusters, it is possible the substantial overrepresentation of affective psychosis in Cluster 1, and of non-affective psychosis in Cluster 3 confounded these results, as previous studies have indicated (Helle, Løberg, Gjestad, Schnakenberg Martin, & Lysaker, 2017; Løberg et al., 2014; Waterreus et al., 2017). As patients in the present study have a primary diagnosis of psychosis, rather than bipolar or an affective-psychosis diagnosis, Crouse and colleagues' results closely follow the outcomes in the present study. There appears to be considerable evidence to suggest non- affective psychosis patients demonstrate significant impairments in cognition compared to their affective psychosis peers (Crouse et al., 2018). It may be important to consider these diagnostic subtypes as a key factor in our understanding of concurrent psychosis and cannabis use. The susceptibility to non-affective psychosis in vulnerable cannabis-using individuals has been further investigated in recent years.

Current research examining associations between non-affective psychosis and early cannabis use tend to note two distinct subgroups after comparing the 'endophenotypes' of patients, specifically neurocognition, drug use, and family history of illness (Pearlson, 2015). In particular, the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study suggests an emerging biotype of psychosis centred between traditional schizophrenia and affective psychotic disorders (Hill et al., 2013; Tamminga et al., 2014; Tamminga et al., 2017). This biotype appears to be associated with higher cannabis use, better cognition, and lower percentage of affected relatives. It is plausible that Cluster 2 in Crouse et al.'s research, and this intermediate biotype discovered in the B-SNIP study, represent an alternative pathway to psychosis, in which vulnerable individuals have their psychotic illness precipitated by cannabis use. These patients would possibly have superior premorbid IQ, as well as better cognition, compared to their peers who would develop schizophrenia regardless of drug use, as the latter group may be more likely to have followed a neurodevelopmental trajectory involving aberrant cognitive development. The results in the present paper are in line with this theory, as the patients in the two clinical groups (i.e. current cannabis users, and cannabis-naive patients) demonstrate no significant differences in any neuropsychological tests. As fore mentioned, adult patients who are current cannabis users appear to underperform in cognitive tests compared to never-using patients. Thus, young patients who are current cannabis users would also be expected to underperform, however this is not the case. It appears during the early stages of illness- and drug-onset, when patients are considered adolescents or young adults (i.e. 16-25 years), their cognitive capabilities are superior to peers who will develop psychosis without cannabis use, however they may become comparable when the former group engage in protracted cannabis use. This is further supported by evidence observing the acute and residual effects of cannabis on neurocognition. Individuals demonstrate significant impairment across attention, decision making, impulsivity and working memory up to 6 hours after use. However, even residual and long-term effects of cannabis can last days, affecting most areas of cognitive functioning. Unexpectedly, longer periods of abstainence demonstrate the most advanced improvement in cognition (Crean et al., 2011).

Much of the research investigating comorbid psychosis and cannabis focuses on patients with lifetime, but not current, cannabis use, and has found superior cognitive

abilities in cannabis users rather than the cannabis-naive patients (Hanna, Shalvoy, et al., 2016; Løberg & Hugdahl, 2009; Potvin et al., 2008; Rabin et al., 2011; Yücel et al., 2012). It appears the effect of cannabis on cognition in patients with non-affective psychosis is age-related. Current cannabis use seems to influence cognition more negatively, while past drug may be a marker of a different pathway to psychosis. This is supported by previous studies that demonstrate patients with early-onset cannabis use actually demonstrate better cognitive abilities than their peers with later-onset or who are cannabis-naïve (Jockers-Scherübl et al., 2007; Yücel et al., 2012) The cannabis-using patients may constitute a sub-group with less cognitive vulnerability; cannabis use may have a more temporary influence on cognition, generating a short-term cognitive and psychotic episode. Thus, cannabis use may create transient deficits in cognition paralleling the period of acute psychosis.

As expected, cannabis users were significantly more likely to be both nicotine smokers and alcohol users (Behrendt et al., 2012; Faeh, Viswanathan, Chiolero, Warren, & Bovet, 2006; Hermens et al., 2013; Hindocha et al., 2015). While cigarette smoking is associated with concurrent cannabis dependence, there is also evidence to suggest that nicotine mediates the relationship from only cannabis use to dependence in young people (Hindocha et al., 2015). Similarly, Hermens and colleagues demonstrated young adults with early-onset illness are particularly at risk for alcohol and substance misuse (Hermens et al., 2013). Evidently, there appears to be a relationship between cannabis use with cigarette smoking and alcohol, however both the individual effects of alcohol and cigarette smoking, as well as the combined effects of all three, may confound studies looking to observe effects of cannabis use alone.

This highlights the first limitation in our study. As we were unable to quantify the quantity of cannabis, nicotine and alcohol differences in patients, we were unable to accurately determine the influence alcohol and nicotine use had on the patients. Similarly, we relied on self-report measures of drug and alcohol use. It may be beneficial to measure these external factors such as cannabis and alcohol use by objective means (e.g. radioimmunoassay) to determine more accurately a patient's drug use, as not all properties of drug use (e.g. quantity, daily sessions, frequency, age of onset) were available for all patients. Future studies should attempt to tease out these combined effects, or determine the quantity and frequency of these additional drugs to evade confounding effects, as well as attempt to complete the DFAQ-CU (Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use Inventory; (Cuttler & Spradlin, 2017)) for more accurate and consistent results across cannabis-related studies. Likewise, as previous studies have demonstrated the significance of age of cannabis-onset, it would provide advantageous to have had this information for all individuals. Unfortunately we were unable to run any analyses as this information was only available for a handful of patients. Finally, outpatients were help-seeking and may not be comparable to individuals in the community who do not seek help for various reason (e.g. lower insight).

In conclusion, these results support the notion of an alternative pathway to schizophrenia by cannabis use in vulnerable individuals. This phenomenon appears to be time-related, with older, chronic schizophrenia patients who have lifetime, but not current, cannabis use exhibiting superior cognition compared to cannabis-naive patients, yet these two subgroups demonstrate equal cognition at the time of both illness- and drug-onset.

Targeting pharmacological and cognitive remediation treatments to this individual subgroup of non-affective psychoses patients may prompt improved pathological outcomes.

Chapter 4

4. Summary, Discussion and Future Work

4.1 Summary of studies in this thesis

Study 1: Meta-analysis of neurocognition in psychosis patients with current cannabis use

This study analysed neuropsychological data from 14 studies to determine if age mediated cognitive results between patients with cannabis use, and patients with no history of cannabis use. Overall, these results indicate cognitive deficits in comorbid psychosis patients compared to cannabis-naïve patients, however this study also established a significant link between patient age and cognition in current cannabis-using patients. Analyses and meta-regressions were carried out to determine the effect sizes of results across studies. The mean age of patients ranged from 16 to 37 years of age. Compared to non-users, patients with cannabis use underperformed across tests of premorbid and current IQ, verbal learning, verbal working memory, and motor inhibition. Interestingly, the association of cannabis use and age was varied, with increasing age being predictive of worse performance in processing speed, sustained attention, verbal memory, and better performance in verbal learning and verbal fluency.

Study 2: The neuropsychological profiles of young psychosis patients with and without cannabis use

This study explored potential disparities in cognition between young (i.e. between 16 and 25 years of age) non-affective psychosis patients with and without current cannabis use. The cognitive profile of young cannabis-using psychosis patients does not appear to differentiate from young cannabis-naïve patients, despite their drug use. Subjects consisted of 24 cannabis-using and 79 cannabis-naïve patients, matched on age. Although healthy controls outperformed both psychosis groups across most cognitive measures, there were no significant differences between the two clinical groups. These results contrast the findings of cannabis-using, but otherwise healthy, individuals who display cognitive deficiencies compared to non-using counterparts. Thus, indicating underlying neuropsychological mechanisms involved in a distinct cannabis-initiated pathway.

4.2 The Overall Findings: Implications for Existing Models

The primary aim of this thesis was to investigate and compare the neurocognition of young psychosis patients who either currently use, or who have no history of using, cannabis. It was hypothesized that young patients who concurrently use cannabis would exhibit cognition equal to that of their drug-naïve peers, which was wholly supported by the results of the second study. The most consistent finding in this series of studies was that neurocognitive results appeared to be moderated by patient age. Interestingly, although comorbid adult patients demonstrated significant cognitive deficiencies across a range of domains compared to adult patients without a history of drug use, young comorbid patients

instead exhibited no cognitive differences compared to their drug-naïve peers. Specifically, in the first study (i.e. Chapter 2), comorbid patients underperformed in tests of premorbid and current IQ, verbal learning, verbal working memory, and motor inhibition. This shortfall is typically observed in comorbid older, more chronic patients, as well as otherwise healthy, cannabis-using individuals (Crean et al., 2011; Hall & Lynskey, 2016; Løberg & Hugdahl, 2009; Shrivastava, Johnston, & Tsuang, 2011). Interestingly, as Løberg and Hugdahl have shown, once cannabis-using patients cease drug use, they actually demonstrate global cognition that is superior to patients who have no history of drug use (Løberg & Hugdahl, 2009). In fact, several studies have investigated this paradoxical phenomenon, consistently reporting that patients with a history of cannabis use, but currently abstain, outperform their drug-naïve peers (Cunha et al., 2013; González-Pinto et al., 2016; Hanna, Shalvoy, et al., 2016; Helle et al., 2014; Helle et al., 2017; Waterreus et al., 2017; Yücel et al., 2012). Importantly, the first study revealed significant differences in global cognitive results was moderated by patient age, where an older age generally correlated with worse performance in comorbid psychosis patients (Bogaty et al., 2018). This finding is further emphasized in the second study, which demonstrated no significant cognitive differences between young (i.e. between 16 and 25 years of age) patients with and without concurrent cannabis use.

Cognitive deficits are recognized as a core feature of psychosis, particularly schizophrenia-spectrum disorders. These deficits often present before illness-onset (Kahn & Keefe, 2013; Woodberry, Giuliano, & Seidman, 2008) and persist after treatment of clinical symptoms (Caspi et al., 2003). The cognitive deficiencies seen across non-affective psychosis patients are extensive, demonstrating significant deficits across tests of memory, attention, motor skills, executive function, and intelligence (Bora et al., 2009; Bora et al., 2010; Bowie & Harvey, 2006; Fioravanti, Bianchi, & Cinti, 2012; O'Carroll, 2000). Cognitive impairment is considered a core feature of schizophrenia as patients normally exhibit deficits between 1 and 2 standard deviations. In fact, cognitive performance is considered more predictive of a patient's functional outcome than positive symptoms (Bowie & Harvey, 2006; M. F. Green & Harvey, 2014; Harvey, Koren, Reichenberg, & Bowie, 2006). The acute and long-term effects of cannabis in healthy populations has been well documented, with individuals typically displaying impairments across memory, learning, and working memory compared to non-users, and is more severe with younger drug-onset and heavier cannabis use (Grant et al., 2003; Schweinsburg, Brown, & Tapert, 2008). However, comorbid non-affective psychosis patients instead demonstrate counter-intuitive results, both when cannabis use has ceased (Bora et al., 2009; Coulston et al., 2007; Yücel et al., 2012), and when it is still concurrent, as seen in this thesis.

This moderation of cognition by age is of particular interest, as it dovetails previous research that suggests there is a 'window of vulnerability' for cannabis use in a subgroup of psychosis patients. Jockers-Scherübl et al. exemplified this result by showing psychosis patients who began using cannabis before the age of 17, but later abstain, exhibit better cognition than patients who have a drug-onset after 17 years (Jockers-Scherübl et al., 2007). Yücel and colleagues similarly found an early initiation of cannabis use correlated with

superior cognitive performance in first-episode psychosis patients (Yücel et al., 2012). Interestingly, more frequent or moderate use of cannabis has also been associated with improved neurocognition in patients (Schnakenberg Martin et al., 2016; Schnell et al., 2009a). A number of theories have been suggested to explain this paradoxical finding. Initially, it was thought this group of patients required superior social skills in order to gain access to an illegal drug (Potvin et al., 2008; Solowij & Michie, 2007). However, this is unsupported by evidence, which suggests patients who also engage in drug use present with poorer premorbid functioning (P. A. Ringen et al., 2008), as well as poorer premorbid academic functioning (Larsen et al., 2006). It has also been proposed that cannabis instead exhibits a neuroprotective effect, specifically when consumed prior to illness-onset. Psychosis patients with a history of cannabis use have been found to have significantly higher concentrations of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) (Jockers-Scherübl et al., 2004; Jockers-Scherübl et al., 2003). As these neurotrophins are involved in the development and maintenance of function of nerve cells, their increased presence in cannabis users who later develop schizophrenia may correspond to an endogenous repair system for impaired nerve cells. Thus cannabis may induce this repair mechanism, which in turn preserves cognitive function (Jockers-Scherübl et al., 2007). This is supported by both non-clinical and other clinical (non-psychotic) studies that demonstrate neuroprotective effects of cannabis (Hampson et al., 2000; Ramírez et al., 2005). Giuffrida et al. similarly found cerebrospinal fluid (CSF) levels of an endogenous cannabinoid, anandamide, negatively correlated with psychotic symptoms in acute untreated schizophrenia (Giuffrida et al., 2004), suggesting an endogenous compensatory adaptation within the cannabinoid system in schizophrenia. In fact, the neuroprotective properties of cannabis, as well as its compensatory effect in psychosis patients needs to be further researched to better understand the complex relationship. However, the present thesis explored this third and perhaps, most convincing concept of cannabis use by patients.

Much of the current research suggests psychosis patients who have a history of long-term cannabis use increased their risk of developing psychosis through early initiation of drug use. Ideally, this subgroup of patients would not have developed psychosis in the absence of cannabis (Løberg et al., 2014; Schnell et al., 2009a; Yücel et al., 2012). In other words, cannabis may induce psychosis in less cognitively vulnerable individuals, while non-users who develop psychosis likely have a greater genetic vulnerability to psychosis and thus manifest poorer cognitive performance at psychosis onset. This is especially supported by Yucel et al.'s and Jockers-Scherübl et al.'s findings of superior cognition in comorbid patients who have an earlier onset of cannabis use, compared to patients with later cannabis-onset or who are drug-naïve (Jockers-Scherübl et al., 2007; Yücel et al., 2012). Additionally, Arseneault and colleagues report that cannabis use before the age of 15 years significantly increases the risk of developing subsequent psychosis (Arseneault et al., 2002; Arseneault, Cannon, Witton, & Murray, 2004). Interestingly, cannabis users at first-episode have fewer neurological soft signs than non-users (Ruiz-Veguilla et al., 2009), further indicating cannabis users have less neurodevelopmental impairment. Moreover, as evidence shows that patients who engage in more moderate and frequent cannabis use actually exhibit better cognition (Núñez et al., 2016; Schnakenberg Martin et al., 2016), it

can be speculated that a greater magnitude of toxic insult is required to induce psychosis in individuals who are particularly invulnerable to psychosis. Conversely, there is data to suggest cannabis-using patients actually present with structural brain abnormalities not as severely observed in non-users. Rapp et al.'s review found that areas concentrated with cannabinoid receptors, such as the cingulate and prefrontal cortices, are particularly susceptible to injury (Rapp, Bugra, Riecher-Rössler, Tamagni, & Borgwardt, 2012). Two studies have also shown that comorbid patients tend to have reduced cortical thickness compared to non-users (Habets, Marcelis, Gronenschild, Drukker, & van Os, 2011; Rais et al., 2010). However, these studies present some important limitations, predominantly that their subjects were diagnosed with established, chronic schizophrenia, and often included comorbid alcohol and other substance use, which is likely to confound results. One way to eradicate this issue is to focus on first-episode patients, particularly young people who have less exposure to environmental effects, such as antipsychotic medications and other substance use. Interestingly, a mixed-model analysis of 10-yearlong sample shows neurocognitive stability in patients over time (Rund et al., 2016). It reported that patients with stable remission in the first year had better neurocognitive trajectory in the follow-ups than patients who remained psychostic after the first year. Patients also did not deteriorate significantly compared to controls after treatment at the 10-year follow-up period, indicating cognitive change occurs early on in the illness.

The second study in the present thesis demonstrates support for the latter theory of an alternate pathway to psychosis. While a plethora of studies report significant cognitive deficiencies in healthy individuals who use cannabis, as well as comorbid adult psychosis patients, concurrent young patients showed no cognitive differences compared to young non-users. This counter-intuitive finding indicates spared neurocognition in young users even at the first-episode. These results parallel Tamminga and colleagues' extensive research into psychoses phenotypes, particularly the Bipolar and Schizophrenia Network on Intermediate Phenotypes (B-SNIP) studies (Tamminga et al., 2014; Tamminga et al., 2017). Importantly, evidence provided by the B-SNIP study shows there are clusters of individuals with shared biological features (known as 'bio-types') despite there being a commingling of their traditional clinical phenotype (i.e. schizophrenia or affective psychoses disorders) (Hill et al., 2013; Tamminga et al., 2014). Notably, one of the three biotypes identified appears to be associated with higher cannabis use, better cognition, and lower percentage of affected relatives (Tamminga et al., 2017). Especially because age of drug use-onset appears to moderate neurocognition later in life, previous studies have suggested a 'window of vulnerability' exists in which cannabis use during a specific age frame, explicitly during adolescence, increases the risk of invulnerable young people to develop psychosis.

The main psychoactive component of cannabis, tetrahydrocannabinol (THC), has been shown to affect the endogenous cannabinoid and dopamine systems by interacting with cannabinoid receptors (Bossong & Niesink, 2010; D'Souza et al., 2005; Solowij & Michie, 2007). Kuepper et al. suggest intake of cannabis increases dopamine levels across several areas of the brain implicated in schizophrenia, including striatal and prefrontal

regions (Kuepper et al., 2010). Specifically, as THC is a cannabinoid receptor 1 (CB1) agonist, cannabis likely influence CB1 receptors on GABA and glutamate. This would influence the midbrain dopamine neurons and prefrontal cortical pyramidal cells. Thus by increasing dopamine concentration in striatal regions of the brain, THC, when repeatedly administered, decreases dopamine levels in prefrontal regions of the brain via sensitization processes resulting in expressions of a psychotic disorder (Kuepper et al., 2010). The repeated administration of THC alters the functioning of the prefrontal cortex, a region implicated in schizophrenia, by acting on dopamine signaling via activation of CB1 receptors. Interestingly, Schneider and Koch found more irreversible residual effects in prepubertal rats after chronic exposure to THC as compared to more mature rats (Schneider & Koch, 2003). Correspondingly, an earlier age of psychosis onset tends to occur in patients who have a history of cannabis use (Barnes et al., 2006; Donoghue et al., 2014; Large, Sharma, Compton, Slade, & Nielssen, 2011; H. Myles et al., 2016; N. Myles, Newall, Nielssen, & Large, 2012; Power, Dragovic, Jablensky, & Stefanis, 2013; Tosato et al., 2013), and patients who had been using high-potency cannabis everyday had the earliest onset (Di Forti et al., 2014). Evidently, cannabis use during adolescence presents with some unique consequences likely not observed in later onset of drug use. There also appears to be a stronger relationship between adolescent cannabis use and psychosis compared to adult use, supporting this neurodevelopmental hypothesis (Caspi et al., 2005; Konings, Henquet, Maharajh, Hutchinson, & Van Os, 2008). The endocannabinoid system is particularly involved in key processes of brain maturation during adolescence, and levels of endocannabinoids and cannabinoid receptors increase at this age (Schneider, 2008). Exposure to cannabis during critical neurodevelopmental stages potentially influences the endocannabinoid system and other key neurotransmitter systems. This may explain the paradoxical cognitive findings in psychosis patients with a history of cannabis use.

Several longitudinal studies, as well as meta-analyses, have indicated the existence of a gene by environment interaction in the development of psychosis in a subgroup of patients. Schizophrenia itself appears to be a highly heritable illness (Shih, Belmonte, & Zandi, 2004), however as Harrison reports, genes typically contribute no more than 50% to etiology, suggesting environmental factors considerably influence the development of schizophrenia (P. J. Harrison, 2015). Keshavan has also put forward a "multihit" theory around schizophrenia development, which suggests brain insults during the critical period of adolescence would increase the rate of subsequently developing schizophrenia (Keshavan, 1999). It's suggested early illness-onset, as seen in young people, may be the result of excessive synapse elimination, as well as dopaminergic over activity. The catechol-O-methyltransferase (COMT) enzyme in particular has been referred to as a constituent of the gene x environment model of schizophrenia. Caspi et al.'s longitudinal study found a functional polymorphism in the COMT gene moderated the influence of adolescent cannabis use on developing psychosis later on (Caspi et al., 2005). That is, carriers of the valine158 allele were more likely to display psychotic symptoms and to develop schizophrenia-spectrum illness if they used cannabis. Importantly, COMT is the prime enzyme involved in the metabolism of dopaminergic transmission in the prefrontal cortex (Tunbridge, Weinberger, & Harrison, 2006). Animal models have similarly

demonstrated the influence of the interaction between THC and the COMT gene in developing schizophrenia. Behan and colleagues found chronic THC administration in adolescent mice was modulated by COMT gene deletion in altering neurotransmitter function, and paralleled the dopaminergic and GABA-ergic functioning as seen in human patients (Behan et al., 2012). However, this specific genotype interaction should be considered carefully, as a recent study has instead found no correlation between underlying COMT genotype and cannabis use in developing psychotic symptoms (Zammit, Owen, Evans, Heron, & Lewis, 2011).

The complex relationship between cannabis use and subsequent psychosis certainly needs to be further explored. However, the general consensus of research available suggests a subgroup of psychosis patients may bring about their own illness through early onset of cannabis use. This gene-environment interaction is of particular interest as older, more chronic patients who have a history of cannabis, but currently abstain, outperform patients who have no history of cannabis use. This paradoxical finding contrasts cognitive results of healthy individuals who have a history of using cannabis, who instead demonstrate poor cognitive abilities even after stopping cannabis use. As adults, this subgroup who have a history of cannabis use exhibit spared cognition, however the research focusing on young people, specifically at the time of both illness- and drug-use onset, is extremely limited. The studies in this thesis contributed to the gap of knowledge and understanding of psychosis and drug-use clearly present in this area. Importantly, the first study (i.e. Chapter 2) determined cognitive functioning is moderated by current age of the patient. The highly variable results between younger or older patients clearly demonstrates research of cognitive abilities in young patients, rather than older patients alone, is highly warranted, particularly as this is when both illness- and cannabis-onset typically occur. Similarly, the second study (i.e. Chapter 3) exemplified spared cognition in comorbid cannabis-using patients, compared to non-using patients. This was of great significance as the individuals, who were between 16 and 25 years of age, generally had no to little exposure to additional external influences, such as other drugs and antipsychotic medication. Most compelling however, was that even as concurrent cannabis users, these patients demonstrated no cognitive deficits when compared to non-using patients. This contrasts studies of comorbid adults patients, as well as healthy cannabis-using indivduals. Therefore this thesis hopes to initiate further research into psychosis and drug use, but with a focus on the critical period when both illness- and drug use-onset typically occur.

4.3 Limitations of the studies

Neurocognitive Measures

The use of neurocognitive measures in evaluating patient performance is not without its limitations. Most predominate is the debatable validity of neurocognitive assessments. In essence, are the tests really measuring what we think they are measuring, and how well do they translate to real-world settings? While both non-computerized and computerized neurocognitive assessment tools (NCATs) exist to measure an individual's cognitive functioning, the vast majority of recent studies utilize NCATs due to their efficiency and absence of human error. With the influx of reliable NCATs accessible across

current research, more valid testing and assessments have become available that would not be achieved with simple pen and paper.

The vast amount of different types of neurocognitive assessments available is another reason for caution. While there exist different cognitive tests for adults and children, adult assessments typically exclude patients under the age of 16, and so was disregarded in this thesis. However, each cognitive domain has a number of different tests that may be used to assess it. For instance, general intelligence can be measured using any of the following: National Adult Reading Test (NART), Wechsler Adult Intelligence Scale (WAIS), or the Wechsler Test of Adult Reading (WTAR). Similarly, executive functioning may be measured via a range tests including those that assess cognitive flexibility, concept formation, and problem solving. Despite the heterogeneity available across tests for domains, there is consistency among the cognitive domains used in these studies (Committee on Psychological Testing, 2015).

Differential effects of cannabinoids

There are several cannabinoids present within cannabis, other than THC, the main psychoactive component. While THC has generally been recognised as mimicking psychotic tendencies in its users, and is responsible for producing the 'high' its users feel, cannabidiol (CBD) is another cannabinoid with a rather prominent effect on the user. Importantly, the varying quantities of cannabinoids, specifically of THC and CBD, can affect the user's disposition and ultimately, longterm effects of cannabis use.

As well as quality of cannabis, dosage and frequency of use was unable to be assessed. This was an especially critical limitation in the second study (i.e. Chapter 3). Previous research has shown that a lifetime history of moderate cannabis use, rather than heavy or minimal use, is actually predictive of improved neurocognition in patients. Unfortunately these qualities were unable to be measured and thus their influences on results assessed. Similarly, more frequent use of cannabis (i.e. daily) by patients typically resulted in superior cognitive functioning that patients who abstained or who engaged in cannabis use less often.

4.4 Future Directions

This thesis sought to explore and contribute to a gene x environment hypothesis of psychosis by early cannabis onset. Evidently, there appears to underlying processes involved within a subgroup of psychosis patients who have admittedly brought about their own illness. Unfortunately, the research reporting on patients during both illness- and drug use-onset, typically as young people (i.e. 16 – 25 years of age), is extremely limited. In order to best understand the gene x environment interaction in this subgroup, whether through cognitive measures or neuroimaging, it would be most beneficial in observing patients during this delicate period. Future studies need to focus on the differences in non-affective psychosis patients who use and abstain from cannabis during this 'window of vulnerability', especially before cannabis use ceases.

Additionally, there is a need for longitudinal studies in psychosis and drug research, in order to follow these cognitive changes over time. As shown in this thesis, cognitive functioning in comorbid patients appears to be mediated by patient age. Confounding effects of antipsychotic medications, as well as other drug use and alcohol, may be influential on cognitive results. Longitudinal studies may be able to show around what age, and why, cognitive functioning becomes more heterogenous among comorbid cannabis-using patients as they grow older. Importantly, however, it is also critical to observe how this subgroup of patients progress, both cognitively and symptomatically, should they be initiating their own illness-onset. Longitudinal studies will demonstrate psychosocial impairments likely not observed in cannabis-naive patients and also how this may fluctuate over time.

4.5 Final Comment

Evidently, cannabis use across non-affective psychosis patients presents with unique clinical consequences. The significant rate of cannabis use among schizophrenia patients similarly demonstrates cause for concern due to the neurobiological underpinnings of schizophrenia alone. Future advances in the field of neuroscience and genetics will have important implications for our understanding of this relationship, and how to best treat this particular subgroup of patients, as well as circumvent cases going forward. The interaction of vulnerability x cannabis in subsequent psychosis onset is thus critical in creating targeted interventions, and in doing so, further understanding the workings of distinct systems in the brain.

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