The impact of cannabis and methamphetamine use on clinical and functional aspects of outcome in First-Episode Schizophrenia Spectrum Disorders: A longitudinal study

by

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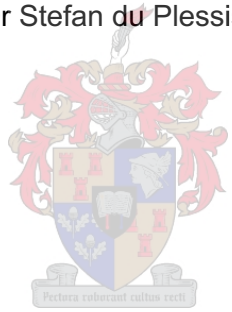

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DECLARATION

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ABSTRACT

Schizophrenia spectrum disorders, which includes schizophrenia, schizophreniform, and schizoaffective disorders, are severe and disabling disorders characterised by a range of symptoms that include psychosis, apathy and withdrawal, mood changes, and cognitive impairment. The illness, hereafter referred to as schizophrenia spectrum disorders or SSD, often starts to manifest during adolescence or early adulthood, and may have a lifelong persistence. This negative impact already conferred by schizophrenia spectrum disorders is further exacerbated by a high rate of comorbid substance use. Despite the high rate of comorbid substance abuse in schizophrenia spectrum disorders in South Africa, this population has remained under-researched in our setting. Specifically, cannabis and methamphetamine are the two most commonly used illicit substances in the Western Cape. Although there is literature on the role of cannabis and methamphetamine use in the context of SSD, a number of questions as yet remain unanswered. Addressing such questions is necessary, especially in the South African context as resources for mental health are limited. The primary objective of this study was to investigate the impact of cannabis and methamphetamine use on baseline symptom severity and brain structure, and on clinical outcomes over 24 months of treatment with a long-acting injectable antipsychotic in patients with a schizophrenia spectrum disorder. Based on the nature of our cohort, as well as recent developments in the literature, we focussed specifically on the effects of cannabis and methamphetamines, as the two most commonly used illicit substances in our region, and because of the availability of good data on these substances. We hypothesised that firstly, cannabis use is associated with poor psychopathology outcomes and higher relapse rates in first-episode schizophrenia spectrum disorder patients for whom treatment adherence is assured (objective I); cannabis and methamphetamine have independent, and dose- and time-dependent effects on cognitive functioning in first-episode schizophrenia spectrum disorder patients (objective II); cannabis use is associated with pre-treatment hippocampal volume reductions in first-episode schizophrenia spectrum disorder patients compared to matched

controls (objective III); First-episode schizophrenia spectrum disorder patients who use cannabis are at increased risk for treatment-emergent metabolic syndrome changes (objective IV).

Regarding the selection of brain structural regions, we chose the hippocampal subfields, based on the recent development of software to accurately measure the subfields, together with an emerging literature on the relevance of the hippocampus in substance abuse. Specifically, this project investigated differences between First-Episode Schizophrenia Spectrum Disorder patients with and without cannabis and/or methamphetamine use in terms of relapse rates, psychopathology, functionality and quality of life, cognitive function, body mass and metabolic changes, and pre-treatment hippocampal volumes.

This sample consisted of 126 patients with a schizophrenia spectrum disorder and 100 healthy controls who were similar in age, sex, and educational attainment. Each sub-study reported on in the present dissertation included a subset of the larger sample based upon the inclusion and exclusion criteria specified for each sub-study.

First, regarding treatment response, we found little evidence for an effect of cannabis use on clinical improvement over 24 months in first-episode schizophrenia spectrum disorder patients. That being said, relapse events were more common in cannabis users compared to their non-using counterparts. Our findings point to an important role for non-adherence in previously reported poorer treatment outcomes in cannabis users, and a direct effect for cannabis in reducing the relapse threshold. Second, we found that methamphetamine use, but not cannabis use, was associated with poorer cognitive performance over the treatment period. Third, we found differential illness-specific associations with cannabis use and hippocampal subfield volumes, specifically increased subiculum volumes in cannabis using first-episode SSD patients. And lastly, compared to non-users, first-episode SSD patients who used cannabis gained less weight and showed less deterioration of lipid profiles during the treatment period.

Both cannabis and methamphetamine influence outcome over the first two years of treatment in first-episode schizophrenia spectrum disorders. Some of our findings were contrary to our

expectations and these have become the foundation for future projects. In conclusion, our study highlights the benefits of the use of long-acting injectable antipsychotics for first-episode schizophrenia spectrum disorders, perhaps particularly in individuals who are currently using substances.

OPSOMMING

Skisofrenie-spektrumafwykings, wat skisofrenie, skisofrenieform, en skiso-affektiewe afwykings insluit, is ernstige afwykings wat gekenmerk word deur 'n reeks simptome gekenmerk word. Die simptome sluit psigose, apatie en onttrekking, gemoedsveranderings en kognitiewe inkorting in. Die siekte, hierna verwys as skisofrenie-spektrumversteurings, begin dikwels tydens adolessensie of vroeë volwassenheid manifesteer. Dit kan lewenslank duur. Hierdie negatiewe impak wat reeds deur skisofrenie-spektrumversteurings verleen word, word verder deur die gebruik van dwelms vererger. Ten spyte van die hoë voorkoms van dwelmmisbruik in die skisofrenie-spektrumversteurings populasie in Suid Afrika, is daar ’n gebrek aan omvattende navorsing rakende hierdie hoë risiko populasie. Dagga en tik is die mees gebruikte dwelms in die Wes-Kaap provinsie. Alhoewel daar literatuur oor die rol van gebruik van dagga en tik in die konteks van skisofrenie bestaan, bly 'n aantal vrae nog onbeantwoord. Dit is nodig om hierdie vrae aan te spreek, veral in die Suid-Afrikaanse konteks, waar daar ’n tekort aan voldoende geestesgesondheidsorg hulpbronne is.

Die primêre doel van hierdie studie was om die impak van die gebruik van dagga en tik op die basislyn simptoom erns en breinstruktuur te ondersoek. Verder fokus die studie op die kliniese uitkomste gedurende 24 maande van behandeling met 'n langwerkende inspuitbare antipsigotiese medikasie by pasiënte met 'n skisofrenie-spektrumversteuring. Op grond van die aard van ons steekproef-groep, die onlangse ontwikkeling in die literatuur, die hoë streeksverbruik, en beskikbaarheid van goeie dat, het ons spesifiek op die gevolge van dagga en tik gefokus. Eerstens het ons veronderstel dat die gebruik van dagga verband hou met swakker psigopatologie-uitkomste en hoër terugvalsgetalle by pasiënte met eerste-episode skisofrenie-spektrumversteuring vir wie die behandeling verseker word deur gebruik van langwerkende inspuitbare antipsigotiese medikasie (objektiewe I); dat dagga en tik onafhanklik, en dosis- en tydafhanklike effekte op kognitiewe funksionering by pasiënte met eerste-episode-spektrumversteuring het (doelstelling II); dat die gebruik van dagga geassosieer word met die vermindering van hippokampus-onderafdelings volume in pasiënte

met eerste-episode skisofrenie spektrumversteuring in vergelyking met kontroles (doelstelling III); en dat pasiënte met die eerste-episode van ’n skisofrenie-spektrumafwyking wat terselfde tyd dagga gebruik, 'n groter risiko vir die verandering van metaboliese sindroom binne die eerste jaar van die behandelingsperiode loop (doelstelling IV).

Wat die keuse van breinstruktuurstreke betref, het ons die hippokampus-onderafdelings gekies. Die keuse is op die onlangse ontwikkeling van sagteware om die onderafdelings akkuraat te meet, tesame met opkomende literatuur oor die relevansie van die hippokampus in dwelmmisbruik gebaseer. Hierdie projek het spesifiek die verskille tussen pasiënte met die eerste-episode skisofrenie spektrumversteuring met en sonder dagga en/of tik gebruik in terme van terugvalstempo, psigopatologie, funksionaliteit en lewensgehalte, kognitiewe funksie, liggaamsmassa en metaboliese veranderinge, en hippokampus volumes by basislyn assessering ondersoek.

Die steekproef het uit 126 pasiënte met 'n skisofrenie-spektrumversteuring en 100 gesonde kontrolegroep wat soortgelyk was in terme van ouderdom, geslag en opvoedkundige prestasie bestaan. Elke substudie waaroor daar in die huidige proefskrif verslag gelwer word, bevat 'n deelversameling van die groter steekproef op grond van die insluiting- en uitsluitingskriteria wat vir elke substudie gespesifiseer is.

Eerstens, met betrekking tot die reaksie op die behandeling, het ons min bewyse vir die effek van die gebruik van dagga op kliniese verbetering gedurende 24 maande by pasiënte met eerste-episode skisofrenie gevind. Dit gesê, terugvalgebeurtenisse was meer gereeld by daggagebruikers in vergelyking met hul eweknieë wat nie dagga gebruik nie. Ons bevindinge dui op 'n belangrike rol vir nie-gebruik van antipsigotiese medikasie in voorheen gerapporteerde swakker behandelingsuitkomste by daggagebruikers, en 'n direkte effek vir dagga om die terugvaldrempel te verminder in skisofrenie-spektrumversteuring. Tweedens het ons gevind dat tikgebruik, maar nie daggagebruik nie, met 'n swakker kognitiewe prestasie gedurende die behandelingsperiode geassosieer word. Derdens het ons differensiële

siektespesifieke assosiasies met die gebruik van dagga en hippokampus-onderafdelings volumes gevind. Daar was spesifiek verhoogde subikulum volumes in eerste-episode pasiënte wat terselfdertyd dagga gebruik het. Laastens, in vergelyking met nie-gebruikers, het pasiënte met eerste episodes wat dagga gebruik minder gewig opgetel en minder verswakking van lipiedprofiele gedurende die behandelingsperiode getoon.

Beide dagga en tik beïnvloed die uitkoms gedurende die eerste twee jaar van behandeling by eerste-episode skisofrenie-spektrumafwykings. Sommige van ons bevindinge was die teenoorgestelde van ons verwagtinge en dit het die basis vir toekomstige projekte geword. Ter afsluiting beklemtoon ons studie die voordele van die gebruik van langwerkende inspuitbare antipsigotika vir eerste-episode skisofrenie-spektrumafwykings, miskien veral by individue wat tans dwelmmiddels gebruik.

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CHAPTER I

INTRODUCTION

1.1. Background

This chapter provides the background and rationale for the doctoral studies described in this dissertation, focusing on the associations of cannabis and methamphetamine use on treatment outcome in first-episode schizophrenia spectrum disorders (SSD). The aims and objectives as well as research hypotheses are also outlined, and the role as well as research contributions of the doctoral candidate within the broader scope of the parent project are described. The overall structure and presentation of the doctoral thesis presented for examination is also provided.

1.2. Healthcare impact of schizophrenia spectrum disorders

Schizophrenia spectrum disorders are severe and disabling disorders characterised by a range of symptoms that include psychosis, apathy and withdrawal, mood changes, and cognitive impairment (Asmal, et al., 2014; Olivier et al., 2015). SSDs often start to manifest during adolescence or early adulthood, and may have a lifelong persistence (Asmal, et al., 2014). The negative health impact of SSD is further exacerbated by recurrent relapses and rehospitalisation in chronic patients (Emsley, Chiliza, & Asmal, 2013).

The global prevalence rate of SSD is estimated to be ~0.28% (95% uncertainty interval [UI]: 0.24–0.31) (Charlson et al., 2018). According to one systematic review, global prevalence rose from 13.1 (95% UI: 11.6–14.8) million cases in 1990 to 20.9 (95% UI: 18.5–23.4) million cases in 2016 (Charlson et al., 2018). SSD is thought to contribute to 13.4 (95% UI: 9.9–16.7) million years of life lived with disability as a reflection of its disease burden (Charlson et al., 2018). Several important socio-political issues, including homelessness and limited access to medical care, are believed to contribute to variations in disease prevalence and associated health burden in developed compared to developing countries (Ayano et al., 2019) with higher rates of adversity associated with higher prevalence rates of SSD. Indeed, the adverse effect of the illness on social and occupational functioning confers an emotional and economic

burden on affected individuals, their families, and society (Chong et al., 2016; Addo et al., 2018).

This negative impact already conferred by SSD is further exacerbated by the use of illicit substances (Winklbaur et al., 2006). A high rate of comorbid substance use in SSD is observed globally (Grant, et al., 2011; Bahorik, Newhill, Eack, & Queen, 2014; Dharmawardene & Menkes, 2015; Myles, Myles, & Large, 2015) as well as in South Africa (Paruk, Burns & Caplan, 2013). In South Africa, the illicit use of cannabis ("dagga") and methamphetamine ("tik") is especially prevalent, particularly in the Western Cape (Dada et al., 2021). Plüddemann et al., (2013) conducted a study to determine the demographic profile of methamphetamine related admissions to major psychiatric services in Cape Town and found that 41% of the patients admitted presented with substance-induced psychotic disorder and 31% with schizophrenia. Moreover, Temmingh and colleagues (2020) found a high prevalence and wide distribution of SUDs in patients with psychotic disorders, similar to reports from high income countries. Specifically, in a total sample of 248 participants, they found 55.6% of participants had any SUD, 34.3% had cannabis use disorders, 30.6% alcohol use disorders, 27.4% methamphetamine use disorders, 10.4% methaqualone use disorders and 4.8% had other SUDs (Temmingh et al., 2020). Another study focused on first-episode schizophrenia and found that 56% of their adolescent sample reported lifetime cannabis use (Paruk et al., 2015). This is particularly relevant, given that cannabis is regarded as the most commonly used illicit substance in the world (Di Forti, et al., 2015), and especially given the move towards more widespread legalisation of cannabis which may result in more widespread use through increased availability and accessibility.

1.3. Substance use as a risk factor for schizophrenia spectrum disorders

The exact role of cannabis and other illicit substances in the development of schizophrenia spectrum disorders remains unclear. This echoes ongoing uncertainties concerning the

phenomenological nature of SSDs and substance-induced psychosis as overlapping or discrete clinical entities (e.g. Green & Glausier, 2016).

It is known that SSD has heterogeneous aetiologies. On the one hand, some researchers have proposed that the use of illicit substances such as cannabis use has an equivalent effect on the development of schizophrenia and its ultimate presentation compared to other risk factors (Håkansson & Johansson, 2015; Green & Glausier, 2016). Others however argue that there are sufficient differences between SSD and cannabis-induced psychosis to support their classification as discrete clinical entities (Dragogna, et al., 2014; Morales-Muñoz, et al., 2014). Similar to cannabis, both similarities and differences in clinical presentation as well as brain morphological and functional changes have been described for methamphetamine-induced psychosis and SSD (Aoki, et al., 2013; Ezzatpanah, Shariat, & Tehrani-Doost, 2014; Ghaffari-Nejad, et al., 2014; Harro, 2015; Okada, et al., 2015).

It is therefore still unclear whether cannabis and methamphetamine are independent risk factors for SSD as distinct from substance-induced psychosis (Callaghan, et al., 2012; Rognli, Berge, Håkansson, & Bramness, 2015). Their use might however constitute an important predictor of disease onset in high-risk individuals. For example, the association between cannabis as well as methamphetamine use and SSD risk might be more pronounced in certain individuals, e.g. those with a genetic predisposition (Bramness, et al., 2012; Ikeda, et al., 2013; Fischer, et al., 2014; Li, et al., 2014; Colizzi, et al., 2015). Other factors including the age of onset of use might be important. For example, it is possible that cannabis use during adolescence could have a more pronounced effect on SSD risk, mediated by its adverse impact on brain maturation (Epstein & Kumra, 2015; French, et al., 2015).

One possible mechanism underscoring the role of cannabis use in particular on SSD risk lies in its effects on functioning of the endocannabinoid signalling system (ECS) as part of a cannabinoid pathway to psychosis (Løberg et al., 2014; Suárez-Pinilla, et al., 2015). This

notion is supported in part by differences in endocannabinoid levels reported for patients compared to controls, which might in turn be related to other risk mechanisms including chronic stress implicated in SSD (Appiah-Kusi, et al., 2015; Gonzáles-Blanch, et al., 2015; Mizrahi, 2015). In particular, there is interest in the risk-associated effects of delta-9-tetrahydrocannabinol (THC) as the main psychoactive cannabinoid present in most strains of cannabis. Moreover, there is evidence to suggest that high levels of THC in potent cannabis strains is associated with elevated risk for SSD, with the frequency and duration of use also playing a role (Parakh & Basu, 2013; Lorenzetti et al., 2016).

In contrast, cannabidiol (CBD) appears to oppose the effects of THC (Bhattacharyya et al., 2010; Niesink & van Laar, 2013). This observation underscores its possible antipsychotic properties, which are of ongoing interest as a possible treatment option for SSD with relatively few side-effects (Manseau, 2015; Pedrazzi, et al., 2015). CBD also appears to have anti-inflammatory and neuroprotective properties (Gomes, et al., 2015) which might help explain its proposed role in the prevention and perhaps even treatment of cognitive impairment in SSD (Morales-Muñoz, et al., 2015). However, a number of studies have found no support for the antipsychotic effect of CBD (McLoughlin, et al., 2014; Pushpa-Rajah, et al., 2014) nor for an additive effect on cognitive function (Power, et al., 2015).

1.4. Cannabis and methamphetamine use and treatment outcomes in schizophrenia spectrum disorders

There is ongoing interest in the role of cannabis as a risk factor for SSD. However, cannabis use might also affect the onset, clinical presentation, and eventual outcome of SSD in affected patients (Fischer et al., 2014; Volk, et al., 2014; Van der Meer & Velthorst, 2015). For example, several studies have shown that cannabis use is associated with an earlier age of onset (Di Forti et al., 2014). The use of cannabis in SSD is most often associated with a more complicated course of illness, characterised by more severe psychopathology (Ringen et al., 2016), poor adherence to medication (Miller et al., 2009; Colizzi et al., 2016; Schoeler et al.,

2017a), higher risk of relapse (Malla et al., 2008; Schoeler et al., 2017b; Schoeler, et al., 2016), and poorer levels of functioning (Abdel-Baki et al., 2017; van der Meer et al., 2015).

It remains unclear whether poorer outcomes are a direct effect of cannabis use (Wisdom et al., 2011; Glasner-Edwards and Mooney, 2014; Foglia et al., 2017; Suetani et al., 2017), or whether non-adherence to treatment (Zammit et al., 2008; Colizzi et al., 2016; Schoeler et al., 2017b) might better account for this effect. The comorbid use of methamphetamine is also associated with poor outcomes in some studies (Bernacer, et al., 2013; Chen, et al., 2015) (McKetin, Lubman, Baker, Dawe, & Ali, 2013), but not all (Medhus, Mordal, Holm, Mørland, &Bramness, 2013; Orikabe, et al., 2011) and could also be a factor in the poorer outcomes associated with cannabis use in SSD (Wisdom et al., 2011; Glasner-Edwards and Mooney, 2014; Foglia et al., 2017; Suetani et al., 2017).

Several studies have also found that cannabis use is associated with cognitive deficits (Scott et al., 2018; Burggren et al., 2019; Duperrouzel et al., 2020) also evident in SSD (Olivier et al., 2015; Kuo and Eack, 2020) as a predictor of poor functional outcomes (Halverson et al., 2019; Silberstein and Harvey, 2019; Zizolfi et al., 2019; Zhu et al., 2020). Others however either suggest an association between cannabis use and better cognitive functioning in schizophrenia specifically (Yücel et al., 2012) or no difference in cognition between users and non-users when other illicit substances are also considered (Sánchez-Gutiérrez et al., 2020). Methamphetamine in particular is associated with poor cognitive functioning (McCann et al., 2007; Ezzatpanah et al., 2014; Chen et al., 2015; Fassbender et al., 2015; Khalkhali et al., 2018; Potvin et al., 2018; Guerin et al., 2019). First-episode SSD patients who continue to use methamphetamine are at risk for cognitive impairment (e.g. Bahorik et al., 2014) as well as re-hospitalization over the course of treatment (Lin, Huang, Wu, & Chen, 2014).

The association of both cannabis use and SSD with poor cognition might be underpinned by similar brain morphological changes. A region of particular interest is the hippocampus as this

structure plays an integral part in cognitive functioning including working memory, known to be affected in both SSD (Osborne et al., 2017; Ott Vintergaard et al., 2019) and cannabis use disorder (Kutlu & Gould, 2016). However, in patients with SSD, the effects of cannabis use on hippocampus structure are less clear-cut. Some studies report larger (Kumra et al., 2012), others smaller (Bangalore et al., 2008; Solowij et al., 2013), and others still no difference (Wobrock et al., 2009; James et al., 2011) in hippocampal volumes between SSD patients who use cannabis and their non-using counterparts.

These inconsistencies could be accounted for in part by differences in illness severity, chronicity, and medication use across prior studies (Haukvik et al., 2018). Cannabis use might also have a more pronounced or differential effect on specific hippocampal subfields as opposed to the structure as a whole. For example, volumetric changes in the cornus ammonis 1 (CA1), 3 (CA3), and 4 (CA4) as well as the molecular layer and the granular cell layers of the dentate gyrus (Li et al 2018), the subicular complex (Beale et al 2018), and the fimbria (Mandelbaum & de la Monte, 2017) have been associated with cannabis use in the general population with less known about the case in SSD.

In the case of methamphetamine use, Du and colleagues (2015) reported a gender difference in how methamphetamine affects hippocampal volume in abstinent methamphetamine users with a significant difference observed between male and female controls but not between male and female patients. In a rat model of methamphetamine binge use, Garcia-Cabrerizo, Bis-Humbert and Garcia-Fuster (2018) found that a history of methamphetamine administration was associated with enduring hippocampal cell damage by decreasing cell survival and mature-BDNF, which in turn is associated with neuronal survival, growth and differentiation.

Lastly, SSD is associated with an increased risk of cardiometabolic comorbidities associated with poor functioning and decreased quality of life (Correll et al., 2017). SSD patients are at increased risk for cardiovascular disease, due, for example to poor diet, genetic factors,

inflammation, and antipsychotic use (Saha et al., 2007; Emul and Kalelioglu, 2015; Tek et al., 2016). In addition, in SSD, cannabis use has been associated with lower body mass index, smaller waist circumference, lower diastolic blood pressure, and more severe psychotic symptoms than non-users at baseline (Bruins et al., 2016) as well as a reduced risk for individual metabolic syndrome constituent criteria (Waterreus et al., 2016).

Concerningly, following overdose and accidents, the leading cause of death in methamphetamine users is cardiovascular disease (Kevil et al., 2019). This can be ascribed to significant effects of methamphetamine on vasoconstriction, pulmonary hypertension, atherosclerotic plaque formation, cardiac arrhythmias, and cardiomyopathy even among relatively young adults (Kevil et al., 2019; Darke, Duflou & Kaye, 2017). Moreover, Zhang and colleagues (2017) found a negative association between methamphetamine dependence and total cholesterol as well as BMI. More specifically, they found significant decreases of total cholesterol, total triglycerides, glucose, and BMI in methamphetamine-dependent patients compared to controls (Zhang et al., 2017). They also reported that daily use of methamphetamine was associated with total cholesterol, whereas the duration of methamphetamine use was independently related to BMI (Zhang et al., 2017). In another study, Zhang and colleagues (2018) found significantly decreased fasting blood glucose in female methamphetamine abusers who had been abstinent for 30 days while in treatment for substance use.

1.5. Problem Statement and Rationale

Several challenges remain in elucidating the associations of cannabis and methamphetamine use on treatment outcome in first-episode SSD. Earlier studies were often cross-sectional in nature, or failed to include a suitable control group for comparison. In the case of prospective studies, their diagnostic composition and follow-up periods differ, and clinical assessments as well as treatment are often not standardized. Illness stage and the use of different medications are also important considerations. The examination of ongoing cannabis use is also often

limited to self-report rather than in combination with toxicological assessment. The timing and duration of use is also often not considered. Longitudinal studies also differ in their assessment of important treatment outcomes across different clinical domains. The inclusion of standardized treatment outcomes, such as remission and relapse, is also inconsistent. In particular, earlier studies often fail to use a standardized approach for controlling medication adherence.

In summary, the high rate of comorbid cannabis and methamphetamine use in first-episode SSD patients in South Africa signals the need for research that explores the broader consequences of cannabis and methamphetamine use on mental health. Inconsistencies across prior first-episode studies in terms of treatment exposure, methods for controlling adherence, as well as standardization of clinical outcomes, and consideration of comorbid substance use (Grech et al., 2005), emphasize the need for well-designed prospective research on cannabis and methamphetamine associations with treatment outcome in SSD.

1.6. Aims and Objectives

The overarching aim of the present doctoral research was to explore the associations of cannabis and methamphetamine use on pre-treatment symptom severity and brain structure, and on treatment effects, including psychopathology, functionality, cognition and emergent metabolic syndrome risk factors, in adult individuals with first-episode SSD over 24 months of treatment with a long-acting injectable antipsychotic.

The specific research objectives were as follows:

1) To examine the associations of cannabis use with psychopathology improvement and relapse rates in patients with SSD treated with a long-acting injectable antipsychotic over 24 months

2) To examine the differential associations of cannabis use compared to methamphetamine use on cognitive performance in patients with SSD treated with a long-acting injectable antipsychotic over 24 months
3) To examine the associations of cannabis use with pre-treatment brain structural differences, specifically hippocampal volumes in patients with SSD at baseline assessment
4) To examine the associations of cannabis use with metabolic syndrome risk factors in patients with SSD treated with a long-acting injectable antipsychotic over 24 months

1.7. Hypotheses

The corresponding research hypotheses were as follows:

- Cannabis use is associated with poor psychopathology outcomes and higher relapse rates in first-episode schizophrenia spectrum disorder patients for whom treatment adherence is assured (objective I)
- Cannabis and methamphetamine have independent, and dose- and time-dependent associations with cognitive functioning in first-episode schizophrenia spectrum disorder patients (objective II)
- Cannabis use is associated with pre-treatment hippocampal volume reductions in first-episode schizophrenia spectrum disorder patients compared to matched controls (objective III)
- First-episode schizophrenia spectrum disorder patients who use cannabis are at increased risk for treatment-emergent metabolic syndrome changes (objective IV)

1.8. Structure of Dissertation

The present doctoral dissertation consists of individual sub-studies presented as individual chapters corresponding to each objective of interest.

Chapter Two describes the examination of cannabis use on clinical outcomes in first-episode schizophrenia patients over 24 months of treatment (sub-study I). This first-author manuscript was published in Psychiatry Research.

Chapter Three describes the examination of substance use and its association with cognition over 24 months of treatment in first-episode schizophrenia (sub-study II). This first-author manuscript was submitted to the journal Early Intervention in Psychiatry and is under revision as of August 2021.

Chapter Four describes the associations of cannabis use with hippocampal subfield volumes in first-episode schizophrenia patients compared to matched controls (sub-study III). This first-author manuscript was published in Schizophrenia Research.

Chapter Five describes the associations of cannabis use with body mass, fasting glucose and lipids during the first 12 months of treatment in first-episode schizophrenia spectrum disorder patients (sub-study IV). This first-author manuscript was published in Schizophrenia Research.

Chapter Six synthesizes the four individual studies and discusses the implications of these findings.

Chapter Seven provides the conclusions drawn from the doctoral studies as a whole and elaborates on next steps and future directions based on these conclusions.

1.9. Research contributions of the doctoral candidate

The specific contributions of the doctoral candidate to the research described in this dissertation included:

- Formulation of research questions and analysis plans across all sub-studies (I-IV)

- Performing statistical analyses using SPSS and R software (sub-studies I-III) in part with assistance from a qualified biostatistician (sub-study IV)
- Conducting clinical and neurocognitive assessments (sub-studies I, II and IV)
- Overseeing magnetic resonance imaging (MRI) acquisitions (sub-study III)
- Neuroimaging pre- and post-processing (sub-study III)
- Drafted initial manuscripts for submission, managed co-author inputs, submitted manuscripts for review, and addressed reviewer comments for four first-author publications (sub-studies I - IV)

The corresponding research skills acquired by the doctoral candidate included:

- Synthesizing distinct sub-studies as part of a coherent research study at the doctoral level
- Data management and associated administrative tasks (project management)
- Academic writing and manuscript development
- Statistical methods and techniques including mixed models important in prospective research
- Neuroimaging pre- and post-processing utilizing new software to generate novel spreadsheet-level data for future studies

REFERENCES

Abdel-Baki, A., Ouellet-Plamondon, C., Salvat, É., Grar, K., Potvin, S., 2017. Symptomatic and functional outcomes of substance use disorder persistence 2 years after admission to a first-episode psychosis program. *Psychiatry Res.* 247, 113–119. https://doi.org/10.1016/j.psychres.2016.11.007

Addo R, Agyemang SA, Tozan Y, Nonvignon J (2018) Economic burden of caregiving for persons with severe mental illness in sub-Saharan Africa: A systematic review. *PLoS ONE* 13(8): e0199830. https://doi.org/10.1371/journal.pone.0199830

Aoki, Y., Orikabe, L., Takayanagi, Y., Yahata, N., Mozue, Y., Sudo, Y., Ishii, T., Itokawa, M., Suzuki, M., Kurachi, M., Okazaki, Y., Kasai, K., & Yamasue, H. 2013. Volume reductions in frontopolar and left perisylvian cortices in methamphetamine induced psychosis. *Schizophr Res*, 147(2-3):355-61. doi: 10.1016/j.schres.2013.04.029.

Appiah-Kusi, E., Leyden, E., Parmar, S., Mondelli, V., McGuire, P., & Bhattacharyya, S. 2015. Abnormalities in neuroendocrine stress response in psychosis: the role of endocannabinoids. *Psychol Med*, 15:1-19.

Asmal, L., Mall, S., Emsley, R., Chiliza, B., & Swartz, L. 2014 Towards a treatment model for family therapy for schizophrenia in an urban African setting: Results from a qualitative study. *Int J Soc Psychiatry*, 60(4): 315-320. doi: 10.1177/0020764013488569

Ayano, G., Tesfaw, G., Shumet, S., 2019. The prevalence of schizophrenia and other psychotic disorders among homeless people: A systematic review and meta-analysis. *BMC Psychiatry* 19, 1–14. https://doi.org/10.1186/s12888-019-2361-7

Bahorik, A.L., Newhill, C.E., Eack, S.M., 2014. Neurocognitive functioning of individuals with Schizophrenia: Using and not using drugs. *Schizophr. Bull*. https://doi.org/10.1093/schbul/sbt099

Bangalore, S.S., Prasad, K.M.R., Montrose, D.M., Goradia, D.D., Diwadkar, V.A., Keshavan, M.S., 2008. Cannabis use and brain structural alterations in first episode schizophrenia - A region of interest, voxel based morphometric study. *Schizophr. Res*. https://doi.org/10.1016/j.schres.2007.11.029

Beale, C., Broyd, S. J., Chye, Y., Suo, C., Schira, M., Galettis, P., et al. 2018. Prolonged Cannabidiol Treatment Effects on Hippocampal Subfield Volumes in Current Cannabis Users. *Cannabis and Cannabinoid Research*, 3(1), 94–107. http://doi.org/10.1089/can.2017.0047

Bernacer, J., Corlett, P. R., Ramachandra, P., McFarlane, B., Turner, D. C., Clark, L., Robbins, T. W., Fletcher, P. C., & Murray, G. K. 2013. Methamphetamine-induced disruption of frontostriatal reward learning signals: relation to psychotic symptoms. *Am J Psychiatry,* 170(11):1326-34. doi: 10.1176/appi.ajp.2013.12070978.

Bhattacharyya, S., Morrison, P. D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., O' Carroll, C. M., Seal, M., Allen, P., Mehta, M. A., Stone, J. M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R. M., Zuardi, A. W., Crippa, J. A., Atakan, Z., & McGuire, P. K. (2010). Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology*, *35*(3), 764–774. https://doi.org/10.1038/npp.2009.184

Bramness, J. G., Gundersen, Ø. H., Guterstam, J., Rognli, E. B., Konstenius, M., Løberg, E. M., Medhus, S., Tanum, L., & Franck, J. 2012. Amphetamine-induced psychosis-a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry*, 5;12-221. doi: 10.1186/1471-244X-12-221.

Bruins, J., Pijnenborg, M.G., Bartels-Velthuis, A.A., Visser, E., van den Heuvel, E.R., Bruggeman, R. and Jorg, F., 2016. Cannabis use in people with severe mental illness: The association with physical and mental health--a cohort study. A Pharmacotherapy Monitoring and Outcome Survey study. J Psychopharmacol. 30, 354-362.

Burggren, A.C., Shirazi, A., Ginder, N., London, E.D., 2019. Cannabis effects on brain structure, function, and cognition: considerations for medical uses of cannabis and its

derivatives. *Am J Drug Alcohol Abus*. 45, 563–579. https://doi.org/10.1016/j.physbeh.2017.03.040

Callaghan, R. C., Cunningham, J. K., Allebeck, P., Arenovich, T., Sajeev, G., Remington, G., Boileau, I., & Kish, S. J. 2012. Methamphetamine use and schizophrenia: a population-based cohort study in California. *Am J Psychiatry,* 169(4):389-96. doi: 10.1176/appi.ajp.2011.10070937.

Charlson, F.J., Ferrari, A.J., Santomauro, D.F., Diminic, S., Stockings, E., Scott, J.G., McGrath, J.J., Whiteford, H.A., 2018. Global epidemiology and burden of schizophrenia: Findings from the global burden of disease study 2016. *Schizophr. Bull*. 44, 1195–1203. https://doi.org/10.1093/schbul/sby058

Chen, C. K., Lin, S. K., Chen, Y. C., Huang, M. C., Chen, T. T., Ree, S. C., & Wang, L. J. 2015. Persistence of psychotic symptoms as an indicator of cognitive impairment in methamphetamine users. *Drug Alcohol Depend,* 1;148:158-64. doi: 10.1016/j.drugalcdep.2014.12.035.

Chong, H. Y., Teoh, S. L., Wu, D. B., Kotirum, S., Chiou, C. F., & Chaiyakunapruk, N. (2016). Global economic burden of schizophrenia: a systematic review. *Neuropsychiatric disease and treatment*, *12*, 357–373. https://doi.org/10.2147/NDT.S96649

Colizzi, M., Carra, E., Fraietta, S., Lally, J., Quattrone, D., Bonaccorso, S., Mondelli, V., Ajnakina, O., Dazzan, P., Trotta, A., Sideli, L., Kolliakou, A., Gaughran, F., Khondoker, M., David, A.S., Murray, R.M., MacCabe, J.H., Di Forti, M., 2016. Substance use, medication adherence and outcome one year following a first episode of psychosis. *Schizophr. Res*. 170, 311–317. https://doi.org/10.1016/j.schres.2015.11.016

Correll, C.U., Ng-Mak, D.S., Stafkey-Mailey, D., Farrelly, E., Rajagopalan, K. and Loebel, A., 2017. Cardiometabolic comorbidities, readmission, and costs in schizophrenia and bipolar disorder: a real-world analysis. Ann Gen Psychiatry. 16, 9.

Dada, S., Harker Burnhams, N., Erasmus, J., Lucas, W., Parry, C., Pretorius, S., Weimann, R., TB HIV Care, Anova Health Institute, University of Pretoria COSUP, Foundation for Provessional Development, NACOSA, & Tintswalo Home Based Care. (2021). Monitoring alcohol, tobacco, and other drug use trends in South Africa July 1996 – June 2020 Phase 48. Research Brief, 23(2). Doi: https://www.samrc.ac.za/sites/default/files/attachments/2021-06-15/SACENDU%20Brief_Phase%2048.pdf

Darke, S., Duflou, J., & Kaye, S. (2017). Prevalence and nature of cardiovascular disease in methamphetamine-related death: A national study. *Drug and Alcohol Dependence*, *179*, 174–179. https://doi.org/10.1016/j.drugalcdep.2017.07.001

Dharmawardene, V., & Menkes, D. B. 2015. Substance use disorders in New Zealand adults with severe mental illness: descriptive study of an acute inpatient population. *Australas Psychiatry*, 23(3):236-40. doi: 10.1177/1039856215586147.

Di Forti, M., Sallis, H., Allegri, F.,Trotta, A., Ferraro, L., Stilo, S.A., Marconi, A., La Cascia, C., Marques, T. R., Pariante, C., Dazzan, P., Mondelli, V., Paparelli, A., Kolliakou, A., Prata, D., Gaughran, F., David, A. S., Morgan, C., Stahl, D., Khondoker, M., MacCabe, J. H., & Murray, R. M. (2014). Daily use, especially of high-potency

cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophrenia Bulletin*, 40(6), 1509-1517. doi: 10.1093/schbul/sbt181

Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., Bianconi, F., et al. 2015. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. *The Lancet Psychiatry*, *2*(3), 233-238. Elsevier Ltd.

Dragogna, F., Mauri, M. C., Marotta, G., Armao, F. T., Brambilla, P., & Altamura, A. C. 2014. Brain metabolism in substance-induced psychosis and schizophrenia: a preliminary PET study. *Neuropsychobiology,* 70(4):195-202. doi: 10.1159/000366485.

Du, J., Quan, M., Zhuang, W., Zhong, N., Jiang, H., Kennedy, D. N., … Zhao, M. (2015). Hippocampal volume reduction in female but not male recent abstinent methamphetamine users. *Behavioural Brain Research*, *289*, 78–83. https://doi.org/10.1016/j.bbr.2015.04.033

Duperrouzel, J. C., Granja, K., Pacheco-Colón, I.,& Gonzalez, R. 2020. Adverse Effects of Cannabis Use on Neurocognitive Functioning: A Systematic Review of Meta- Analytic Studies, *Journal of Dual Diagnosis,* 16(1), 43-57, DOI: 10.1080/15504263.2019.1626030

Emsley, R., Chiliza, B., & Asmal, L. 2013. The evidence for illness progression after relapse in schizophrenia. *Schizophrenia Research*, 148(1-3):117-21. doi: 10.1016/j.schres.2013.05.016

Emul, M., Kalelioglu, T., 2015. Etiology of cardiovascular disease in patients with schizophrenia: current perspectives. Neuropsychiatr. Dis. Treat. 11, 2493–2503

Epstein, K. A, & Kumra, S. 2015. Altered cortical maturation in adolescent cannabis users with and without schizophrenia. *Schizophr Res,* 162(1-3):143-52. doi: 10.1016/j.schres.2014.11.029.

Ezzatpanah, Z., Shariat, S.V., Tehrani-doost, M., 2014. Cognitive functions in methamphetamine induced psychosis compared to schizophrenia and normal subjects. *Iran. J. Psychiatry* 9, 152–157.

Fassbender, C., Lesh, T.A., Ursu, S., Salo, R., 2015. Reaction Time Variability and Related Brain Activity in Methamphetamine Psychosis. *Biol. Psychiatry* 77, 465–474. https://doi.org/10.1016/j.biopsych.2014.07.028

Fischer, A. S., Whitfield-Gabrieli, S., Roth, R. M., Brunette, M. F., & Green, A. I. 2014. Impaired functional connectivity of brain reward circuitry in patients with schizophrenia and cannabis use disorder: Effects of cannabis and THC. *Schizophr Res,* 158(1-3):176-82. doi: 10.1016/j.schres.2014.04.033.

Fischer, B. A., McMahon, R. P., Kelly, D. L., Wehring, H. J., Meyer, W. A., Feldman, S., Carpenter, W. T., & Gorelick, D. A. 2015. Risk-taking in schizophrenia and controls with and without cannabis dependence. *Schizophr Res,* 161(2-3):471-7. doi: 10.1016/j.schres.2014.11.009.

Foglia, E., Schoeler, T., Klamerus, E., Morgan, K., Bhattacharyya, S., 2017. Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis. *Psychol. Med.* 47, 1691–1705. https://doi.org/10.1017/S0033291717000046

French, L., Gray, C., Leonard, G., Perron, M., Pike, G. B., Richer, L., Séguin, J. R., Veillette, S., Evans, C. J., Artiges, E., Banaschewski, T., Bokde, A. W., Bromberg, U., Bruehl, R., Buchel, C., Cattrell, A., Conrod, P. J., Flor, H., Frouin, V., Gallinat, J., Garavan, H., Gowland, P., Heinz, A., Lemaitre, H., Martinot, J. L., Nees, F., Orfanos, D. P., Pangelinan, M. M., Poustka, L., Rietschel, M., Smolka, M. N., Walter, H., Whelan, R., Timpson, N. J., Schumann, G., Smith, G. D., Pausova, Z., & Paus, T. 2015. Early Cannabis Use, Polygenic Risk Score for Schizophrenia and Brain Maturation in Adolescence. *JAMA Psychiatry,* Aug 26. doi: 10.1001/jamapsychiatry.2015.1131.

García-Cabrerizo, R., Bis-Humbert, C., & García-Fuster, M. J. (2018). Methamphetamine binge administration during late adolescence induced enduring hippocampal cell damage following prolonged withdrawal in rats. *NeuroToxicology*, *66*, 1–9. https://doi.org/10.1016/j.neuro.2018.02.016

Ghaffari-Nejad, A., Ziaadini, H., Saffari-Zadeha, S., Kheradmand, A., & Pouya, F. 2014. A study of the phenomenology of psychosis induced by methamphetamine: a preliminary research. *Addict Health*, 6(3-4):105-111.

Glasner-Edwards, S., Mooney, L.J., 2014. Methamphetamine psychosis: Epidemiology and management. *CNS Drugs.* https://doi.org/10.1007/s40263-014-0209-8

Gomes, F. V., Llorente, R., Del Bel, E. A., Viveros, M. P., López-Gallardo, M., & Guimarães, F. S. 2015. Decreased glial reactivity could be involved in the antipsychotic-like effect of cannabidiol. *Schizophr Res,* 164(1-3):155-63. doi: 10.1016/j.schres.2015.01.015.

González-Blanch, C., Gleeson, J. F., Cotton, S. M., Crisp, K., McGorry, P. D., & Alvarez-Jimenez, M. 2015. Longitudinal relationship between expressed emotion and cannabis misuse in young people with first-episode psychosis. *Eur Psychiatry,* 30(1):20-5. doi: 10.1016/j.eurpsy.2014.07.002.

Grant, K. M., LeVan, T. D., Wells, S. M., Li, M., Stoltenberg, S. F., Gendelman, H. E., Carlo, G., & Bevins, R. A. 2012. Methamphetamine-associated psychosis. *J Neuroimmune Pharmacol*, 7(1):113-39. doi: 10.1007/s11481-011-9288-1.

Grech, A., Van Os, J., Jones, P.B., Lewis, S.W., Murray, R.M., 2005. Cannabis use and outcome of recent onset psychosis. *Eur. Psychiatry* 20, 349–353. https://doi.org/10.1016/j.eurpsy.2004.09.013

Green, I. W., & Glausier, J. R. 2015. Different Paths to Core Pathology: The Equifinal Model of the Schizophrenia Syndrome. *Schizophr Bull*, Sep 20. pii: sbv136. [Epub ahead of print] PubMed PMID: 26392629.

Guerin, A.A., Bonomo, Y., Lawrence, A.J., Baune, B.T., Nestler, E.J., Rossell, S.L., Kim, J.H., 2019. Cognition and Related Neural Findings on Methamphetamine Use Disorder: Insights and Treatment Implications From Schizophrenia Research. *Front. Psychiatry* 10. https://doi.org/10.3389/fpsyt.2019.00880

Håkansson, A., & Johansson, B. A. 2015. Atypical course in severe catatonic schizophrenia in a cannabis-dependent male adolescent: a case report. *J Med Case Rep,* 21;9(1):200. doi: 10.1186/s13256-015-0678-5.

Halverson, T. F., Orleans-Pobee, M., Merritt, C., Sheeran, P., Fett, A. K., & Penn, D. L. 2019. Pathways to functional outcomes in schizophrenia spectrum disorders: Meta-analysis of social cognitive and neurocognitive predictors. *Neuroscience &Biobehavioral Reviews,* 105, 212-219. doi:10.1016/j.neubiorev.2019.07.020

Harro, J. (2015). Neuropsychiatric Adverse Effects of Amphetamine and Methamphetamine. *Int Rev Neurobiol,* 120:179-204. doi: 10.1016/bs.irn.2015.02.004.

Haukvik, U.K., Tamnes, C.K., Söderman, E., Agartz, I., 2018. Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: A systematic review and meta-analysis. J. *Psychiatr. Res.* 104, 217–226. https://doi.org/10.1016/j.jpsychires.2018.08.012

Ikeda, M., Okahisa, Y., Aleksic, B., Won, M., Kondo, N., Naruse, N., Aoyama-Uehara, K., Sora, I., Iyo, M., Hashimoto, R., Kawamura, Y., Nishida, N., Miyagawa, T., Takeda, M., Sasaki, T., Tokunaga, K., Ozaki, N., Ujike, H., & Iwata, N. 2013. Evidence for shared genetic risk between methamphetamine-induced psychosis and schizophrenia. *Neuropsychopharmacology,* 38(10):1864-70. doi: 10.1038/npp.2013.94.

James, A., Hough, M., James, S., Winmill, L., Burge, L., Nijhawan, S., et al. 2011. Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS). *Schizophrenia Research,* 128(1-3), 91–97. http://doi.org/10.1016/j.schres.2011.02.014

Kevil, C. G., Goeders, N. E., Woolard, M. D., Bhuiyan, M. S., Dominic, P., Kolluru, G. K., … Orr, A. W. (2019, September 1). Methamphetamine Use and Cardiovascular Disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*. NLM (Medline). https://doi.org/10.1161/ATVBAHA.119.312461

Khalkhali, M., Golshahi, M., Hasandokht, T., Kafie, M., Zare, R., 2018. Cognitive Functioning in Schizophrenia, Methamphetamine-induced Psychotic Disorder, and Healthy People: A Comparative Study. *Adv. Biomed. Res.* 7, 123–129. https://doi.org/10.4103/abr.abr

Kumra, S., Robinson, P., Tambyraja, R., Jensen, D., Schimunek, C., Houri, A., Reis, T., Lim, K., 2012. Parietal lobe volume deficits in adolescents with schizophrenia and adolescents with cannabis use disorders. *J. Am. Acad. Child Adolesc. Psychiatry*. https://doi.org/10.1016/j.jaac.2011.11.001

Kuo, S.S., Eack, S.M., 2020. Meta-Analysis of Cognitive Performance in Neurodevelopmental Disorders during Adulthood: Comparisons between Autism Spectrum Disorder and Schizophrenia on the Wechsler Adult Intelligence Scales. *Front. Psychiatry* 11, 1–16. https://doi.org/10.3389/fpsyt.2020.00187

Kutlu, M.G., Gould, T.J., 2016. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: Contributions to development and maintenance of addiction. *Learn. Mem*. 23, 515–533. https://doi.org/10.1101/lm.042192.116

Li, H., Lu, Q., Xiao, E., Li, Q., He, Z., & Mei, X. (2014). Methamphetamine enhances the development of schizophrenia in first-degree relatives of patients with schizophrenia. *Can J Psychiatry,* 59(2):107-13.

Li, W., Li, K., Guan, P., Chen, Y., Xiao, Y., Lui, S., et al. 2018. Volume alteration of hippocampal subfields in first-episode antipsychotic-naïve schizophrenia patients before and after acute antipsychotic treatment. *NeuroImage: Clinica;,* 20, 169–176. http://doi.org/10.1016/j.nicl.2018.07.008

Lin, C. H., Huang, Y. H., Wu, H. C., & Chen, C. C. (2014). Differences between patients with schizophrenia with and without co-occurring methamphetamine use disorders in a Taiwanese public psychiatric hospital. *J Nerv Ment Dis,* 202(11):802-6. doi: 10.1097/NMD.0000000000000197.

Løberg, E.M., Helle, S., Nygard, M., Berle, J. øystein, Kroken, R.A., Johnsen, E., 2014. The cannabis pathway to non-affective psychosis may reflect less neurobiological vulnerability. *Front. Psychiatry* 5, 1–13. https://doi.org/10.3389/fpsyt.2014.00159

Lorenzetti, V., Solowij, N., Yücel, M., 2016. The role of cannabinoids in neuroanatomic alterations in cannabis users. *Biol. Psychiatry*. https://doi.org/10.1016/j.biopsych.2015.11.013

Malla, A., Norman, R., Bechard-Evans, L., Schmitz, N., Manchanda, R., Cassidy, C., 2008. Factors influencing relapse during a 2-year follow-up of first-episode psychosis in a specialized early intervention service. *Psychol. Med*. 38, 1585–1593. https://doi.org/10.1017/S0033291707002656

Mandelbaum, D.E., de la Monte, S.M., 2017. Adverse Structural and Functional Effects of Marijuana on the Brain: Evidence Reviewed. *Pediatr. Neurol.* 66, 12–20. https://doi.org/10.1016/j.pediatrneurol.2016.09.004

Manseau, M. W., & Goff, D. C. 2015. Cannabinoids and Schizophrenia: Risks and Therapeutic Potential. *Neurotherapeutics.* PubMed PMID:26311150.

McCann UD, Kuwabara H, Kumar A, et al. 2007. Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. *Synapse,* 62(2), 91-100. doi:10.1002/syn.20471McKetin, R., Lubman, D. I., Najman, J. M., Dawe, S., Butterworth, P., & Baker, A. L. 2014. Does methamphetamine use increase violent behaviour? Evidence from a prospective longitudinal study. *Addiction,* 109(5):798-806. doi: 10.1111/add.12474.

McLoughlin, B. C., Pushpa-Rajah, J. A., Gillies, D., Rathbone, J., Variend, H., Kalakouti, E., & Kyprianou, K. 2014. Cannabis and schizophrenia. *Cochrane Database Syst Rev*, 14;10:CD004837. doi: 10.1002/14651858.CD004837.pub3.

Medhus, S., Mordal, J., Holm, B., Mørland, J., & Bramness, J. G. 2013. A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. *Psychiatry Res,* 30;206(1):17-21. doi: 10.1016/j.psychres.2012.09.023.

Miller, R., Ream, G., McCormack, J., Gunduz-Bruce, H., Sevy, S., Robinson, D., 2009. A prospective study of cannabis use as a risk factor for non-adherence and treatment dropout in first-episode schizophrenia. *Schizophr. Res.* 113, 138–144. doi:/10.1016/j.schres.2009.04.018

Mizrahi, R. (2015). Social Stress and Psychosis Risk: Common Neurochemical Substrates? *Neuropsychopharmacology*. doi: 10.1038/npp.2015.274.

Morales-Muñoz, I., Jurado-Barba, R., Ponce, G., Martínez-Gras, I., Jiménez-Arriero, M. Á., Moratti, S., & Rubio, G. 2014. Characterizing cannabis-induced psychosis: a study with prepulse inhibition of the startle reflex. *Psychiatry Res,* 15;220(1-2):535-40. doi: 10.1016/j.psychres.2014.08.010.

Morales-Muñoz, I., Jurado-Barba, R., Caballero, M., Rodríguez-Jiménez, R., Jiménez-Arriero, M. Á., Fernández-Guinea, S., & Rubio, G. 2015. Cannabis abuse effects on prepulse inhibition in patients with first episode psychosis in schizophrenia. *J Neuropsychiatry Clin Neurosci,* 27(1):48-53. doi: 10.1176/appi.neuropsych.12120398.

Myles, H., Myles, N., & Large, M. 2015. Cannabis use in first episode psychosis: Meta-analysis of prevalence, and the time course of initiation and continued use. *Aust N Z J Psychiatry,* Aug 18. pii: 0004867415599846.

Niesink, R. J., & van Laar, M. W. (2013). Does Cannabidiol Protect Against Adverse Psychological Effects of THC?. *Frontiers in psychiatry*, *4*, 130. https://doi.org/10.3389/fpsyt.2013.00130

Okada, N., Takahashi, K., Nishimura, Y., Koike, S., Ishii-Takahashi, A., Sakakibara, E., Satomura, Y., Kinoshita, A., Takizawa, R., Kawasaki, S., Nakakita, M., Ohtani, T., Okazaki, Y., & Kasai, K. 2015. Characterizing prefrontal cortical activity during inhibition task in methamphetamine-associated psychosis versus schizophrenia: a multi-channel near-infrared spectroscopy study. *Addict Biol,* Jan 26. doi: 10.1111/adb.12224.

Olivier, M.R., Killian, S., Chiliza, B., Asmal, L., Schoeman, R., Oosthuizen, P.P., Kidd, M., Emsley, R., 2015. Cognitive performance during the first year of treatment in first-episode schizophrenia: A case-control study. *Psychol. Med*. 45, 2873–2883. https://doi.org/10.1017/S0033291715000860

Orikabe, L., Yamasue, H., Inoue, H., Takayanagi, Y., Mozue, Y., Sudo, Y., Ishii, T., Itokawa, M., Suzuki, M., Kurachi, M., Okazaki, Y., & Kasai, K. 2011. Reduced amygdala and hippocampal volumes in patients with methamphetamine psychosis. *Schizophr Res,* 132(2-3):183-9. doi: 10.1016/j.schres.2011.07.006.

Osborne, A.L., Solowij, N., Weston-Green, K., 2017. A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia. *Neurosci. Biobehav*. Rev. 72, 310–324. https://doi.org/10.1016/j.neubiorev.2016.11.012

Ott Vintergaard, C., Bergstrom Johnson, C., Macoveanu, J., Miskowiak, K., 2019. Structural changes in the hippocampus as a biomarker for cognitive improvements in neuropsychiatric disorders: A systematic review. *Eur. Neuropsychopharmacol.* 1–11. https://doi.org/10.1016/j.euroneuro.2019.01.105

Parakh, P., Basu, D., 2013. Cannabis and psychosis: Have we found the missing links? *Asian J. Psychiatr.* 6, 281–287. https://doi.org/10.1016/j.ajp.2013.03.012

Paruk, S., Jhazbhay, K., Singh, K., Sartorius, B., & Burns, J. K. 2015. Clinical correlates of first episode early onset psychosis in KwaZulu-Natal, South Africa. *J Child Adolesc Ment Health,* 27(2):103-11. doi: 10.2989/17280583.2015.1080710.

Pedrazzi, J. F., Issy, A. C., Gomes, F. V., Guimarães, F. S., & Del-Bel, E. A. Cannabidiol effects in the prepulse inhibition disruption induced by amphetamine. *Psychopharmacology (Berl),* 232(16):3057-65. doi: 10.1007/s00213-015-3945-7.

Plüddemann, A., Dada, S., Parry, C. D., Kader, R., Parker, J. S., Temmingh, H., van Heerden, S., de Clercq, C., & Lewis, I. 2013. Monitoring the prevalence of methamphetamine-related presentations at psychiatric hospitals in Cape Town,

South Africa. *Afr J Psychiatry (Johannesbg),* 16(1):45-9. doi: http://dx.doi.org/10.4314/ajpsy.v16i1.8.

Potvin, S., Pelletier, J., Grot, S., Hébert, C., Barr, A., Lecomte, T., 2018. Cognitive deficits in individuals with methamphetamine use disorder: A meta-analysis. *Addict. Behav*. 80, 154–160. https://doi.org/10.1016/j.addbeh.2018.01.021

Power, B. D., Dragovic, M., Badcock, J. C., Morgan, V. A., Castle, D., Jablensky, A., & Stefanis, N. C. 2015. No additive effect of cannabis on cognition in schizophrenia. *Schizophr Res,* Jul 30. pii: S0920-9964(15)00356-4. doi: 10.1016/j.schres.2015.06.026.

Pushpa-Rajah, et al., 2014 Pushpa-Rajah, J. A., McLoughlin, B. C., Gillies, D., Rathbone, J., Variend, H., Kalakouti, E., & Kyprianou, K. 2014. Cannabis and schizophrenia. *Schizophr Bull,* 41(2):336-7. doi: 10.1093/schbul/sbu168.

Ringen, P.A., Nesvåg, R., Helle, S., Lagerberg, T. V., Lange, E.H., Loberg, E.M., Agartz, I., Andreassen, O.A., Melle, I., 2016. Premorbid cannabis use is associated with more symptoms and poorer functioning in schizophrenia spectrum disorder. *Psychol. Med*. 1–10. https://doi.org/10.1017/S0033291716001999

Rognli, E. B., Berge, J., Håkansson, A., & Bramness, J. G. 2015. Long-term risk factors for substance-induced and primary psychosis after release from prison. A longitudinal study of substance users. *Schizophr Res,* Sep 8. pii: S0920-9964(15)00461-2. doi: 10.1016/j.schres.2015.08.032

Saha, S., Chant, D., McGrath, J., 2007. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? Arch. Gen. Psychiatry 64 (10), 1123–1131

Sánchez-Gutiérrez, T., Fernandez-Castilla, B., Barbeito, S., González-Pinto, A., Becerra-García, J.A., Calvo, A., 2020. Cannabis use and nonuse in patients with first-episode psychosis: A systematic review and meta-analysis of studies comparing neurocognitive functioning. *Eur. Psychiatry* 63. https://doi.org/10.1192/j.eurpsy.2019.9

Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Camuri, G., Altamura, A.C., Murray, R., Bhattacharyya, S., 2016. Continued versus discontinued cannabis use in patients with psychosis: A systematic review and meta-analysis. The *Lancet Psychiatry* 3, 215–225. https://doi.org/10.1016/S2215-0366(15)00363-6

Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Murray, R., Bhattacharyya, S., 2017a. Effect of continued cannabis use on medication adherence in the first two years following onset of psychosis. *Psychiatry Res*. 255, 36–41. https://doi.org/10.1016/j.psychres.2017.05.009

Schoeler, T., Petros, N., Di Forti, M., et al. 2017b. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. The Lancet Psychiatry, 4, 627–633. https://doi.org/10.1016/s2215-0366(17)30233-x

Scott, J.C., Slomiak, S.T., Jones, J.D., Rosen, A.F.G., Moore, T.M., Gur, R.C., 2018. Association of Cannabis With Cognitive Functioning in Adolescents and Young

Adults A Systematic Review and Meta-analysis. *JAMA Psychiatry* 75, 585–595. https://doi.org/10.1001/jamapsychiatry.2018.0335

Silberstein, J., Harvey, P.D., 2019. Cognition, social cognition, and Self-assessment in schizophrenia: Prediction of different elements of everyday functional outcomes. *CNS Spectr*. 24, 88–93. https://doi.org/10.1017/S1092852918001414

Solowij, N., Walterfang, M., Lubman, D.I., Whittle, S., Lorenzetti, V., Styner, M., Velakoulis, D., Pantelis, C., Yücel, M., 2013. Alteration to hippocampal shape in cannabis users with and without schizophrenia. *Schizophr*. Res. 143, 179–184. https://doi.org/10.1016/j.schres.2012.10.040

Suetani, S., Reddan, J., Anderson, C., 2017. Methamphetamine and psychiatry: A story of the colourless substance of abuse. *Australas. Psychiatry* 25, 254–256. https://doi.org/10.1177/1039856217695702

Tek, C., Kucukgoncu, S., Guloksuz, S., Woods, S.W., Srihari, V.H., Annamalai, A., 2016. Antipsychotic-induced weight gain in first-episode psychosis patients: a meta-analysis of differential effects of antipsychotic medications. Early. Interv. Psychiatry 10 (3), 193–202.

Temmingh, H. S., Mall, S., Howells, F. M., Sibeko, G., & Stein, D. J. (2020). The prevalence and clinical correlates of substance use disorders in patients with psychotic disorders from an upper-middle-income country. *South African Journal of Psychiatry*, *26*, 1–9. https://doi.org/10.4102/sajpsychiatry.v26i0.1473

van der Meer, F.J., Velthorst, E., Genetic Risk and Outcome in Psychosis (G.R.O.U.P), 2015. Course of cannabis use and clinical outcome in patients with non-affective psychosis: A 3-year follow-up study. *Psychol. Med*. 45, 1977–1988. https://doi.org/10.1017/S0033291714003092

Volk, D. W., Eggan, S. M., Horti, A. G., Wong, D. F., & Lewis, D. A. 2014. Reciprocal alterations in cortical cannabinoid receptor 1 binding relative to protein immunoreactivity and transcript levels in schizophrenia. *Schizophr Res,* 159(1):124-9. doi: 10.1016/j.schres.2014.07.017

Waterreus, A., Di P.P., Watts, G.F., Castle, D., Galletly, C. and Morgan, V.A., 2016. Metabolic syndrome in people with a psychotic illness: is cannabis protective? Psychol Med. 46, 1651-1662.

Winklbaur, B., Ebner, N., Sachs, G., Thau, K., & Fischer, G. (2006). Substance abuse in patients with schizophrenia. Dialogues in clinical neuroscience, 8(1), 37–43. https://doi.org/10.31887/DCNS.2006.8.1/bwinklbaur.

Wisdom, J.P., Manuel, J.I., Drake, R.E., 2011. Substance use disorder among people with first-episode psychosis: a systematic review of course and treatment. *Psychiatr. Serv*. 62, 1007–1012.

Wobrock, T., Sittinger, H., Behrendt, B., D'Amelio, R., Falkai, P., 2009. Comorbid substance abuse and brain morphology in recent-onset psychosis. *Eur. Arch. Psychiatry Clin*. Neurosci. https://doi.org/10.1007/s00406-008-0831-x

Yücel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Conus, P., Takagi, M.J., Fornito, A., Wood, S.J., McGorry, P.D., Pantelis, C., 2012. The impact

of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophr. Bull*. 38, 316–330. https://doi.org/10.1093/schbul/sbq079

Zammit, S., Moore, T.H.M., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., Lewis, G., 2008. Effects of cannabis use on outcomes of psychotic disorders: systematic review. *Br. J. Psychiatry* 193, 357–363. https://doi.org/10.1192/bjp.bp.107.046375

Zhang, M., Lv, D., Zhou, W., Ji, L., Zhou, B., Chen, H., … He, J. (2017). The levels of triglyceride and total cholesterol in methamphetamine dependence. *Medicine (United States)*, *96*(16). https://doi.org/10.1097/MD.0000000000006631

Zhang, Y., Shu, G., Bai, Y., Chao, J., Chen, X., & Yao, H. (2018). Effect of methamphetamine on the fasting blood glucose in methamphetamine abusers. *Metabolic Brain Disease*, *33*(5), 1585–1597. https://doi.org/10.1007/s11011-018-0265-8

Zhu X, Fan H, Fan F, et al. 2020. Improving social functioning in community-dwelling patients with schizophrenia: a randomized controlled computer cognitive remediation therapy trial with six months follow-up. *Psychiatry Res.*, 2020;287:112913. doi:10.1016/j.psychres..112913

Zizolfi, D., Poloni, N., Caselli, I., Ielmini, M., Lucca, G., Diurni, M., Cavallini, G., Callegari, C., 2019. Resilience and recovery style: A retrospective study on associations among personal resources, symptoms, neurocognition, quality of life and psychosocial functioning in psychotic patients. *Psychol. Res. Behav. Manag*. 12, 385–395. https://doi.org/10.2147/prbm.s205424

CHAPTER II

CANNABIS USE AND CLINICAL OUTCOME IN PEOPLE WITH FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS OVER 24 MONTHS OF TREATMENT

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Cannabis use and clinical outcome in people with first-episode schizophrenia spectrum disorders over 24 months of treatment

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ABSTRACT

Cannabis use is associated with an unfavourable course of illness in schizophrenia, although several factors may confound this association. In this longitudinal study, we explored the influence of cannabis use on baseline symptom severity and treatment outcomes in 98 patients with first-episode schizophrenia spectrum disorders treated with a long acting injectable antipsychotic over 24 months. Using mixed models for repeated measures, we compared visit-wise changes in psychopathology, social and occupational functioning and quality of life between recent/current cannabis users (n=45) and non-users (n=53). There were no significant group by time interactions for any of our outcomes, and with the exception of poorer functionality in cannabis users at baseline, no significant differences in these domains at baseline or month 24. Also, remission rates were similar. However, more cannabis users met our operationally defined relapse criteria compared to non-users, and more frequent cannabis use over the course of treatment, as assessed by positive urine toxicology testing, predicted relapse. Our results suggest that cannabis users do not have poorer treatment response than non-users in terms of symptom reduction over the 24 months of treatment. However, dose-related risk of relapse remains with ongoing cannabis use, possibly by directly reducing the threshold for psychotic breakthrough.

1. Introduction

Cannabis use in schizophrenia and other psychotic disorders is associated with more severe symptomatology (Ringen et al., 2016; Quattrone et al., 2018) and poorer overall outcome (Large, et al., 2014). Particularly, ongoing cannabis use after the onset of psychosis is associated with a more complicated course of illness, poor adherence to medication (Miller et al., 2009; Colizzi et al., 2016; Schoeler et al., 2017a), more severe psychopathology, and lower levels of functioning (van der Meer, et al., 2015; Abdel-Baki et al., 2017). Additionally, an association between cannabis use and risk of relapse is well documented (Malla et al., 2008; Schoeler et al., 2016a; Schoeler et al., 2017b), and a dose-response relationship is suggested by the finding that continued use of cannabis after the onset of psychosis has been reported as a direct risk modifier for relapse in a study comparing periods of use with non-use over 2 years (Schoeler et al., 2016b). However, the poorer outcome in cannabis users may, at least in part, be explained by other factors such as alcohol or other illicit substance use, and most importantly, by non-adherence to treatment (Zammit et al., 2008; Colizzi et al., 2016). Studies have consistently found an increased risk of non-adherence to antipsychotic medication in cannabis users compared to non-users (Foglia et al., 2017), and non-adherence is in turn a major determinant of poorer outcome in multiple domains (Haddad et al., 2014). Therefore, at least part of the association between cannabis use and poor outcome may be attributable to non-adherence. Indeed, a prospective analysis of longitudinal data from a first-episode psychosis sample found that medication non-adherence mediated the effect of continued cannabis use on relapse, although a considerable proportion of the risk remained unexplained (Schoeler et al., 2017b).

Many of the studies to date did not assess the role of factors that could potentially confound the association between cannabis use and treatment outcome. Analyses were often performed on retrospectively collected data (e.g. Schoeler et al., 2017b) or from studies conducted in naturalistic settings (e.g. Schoeler et al., 2016b). Details of cannabis use mostly relied on self-report or clinician-rated measures rather than objective measures (Large et al., 2014), and used dichotomous rather

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than continuous measures to assess cannabis use patterns (Foglia et al., 2017). Few assessed clinical outcomes in multiple domains with standardised instruments, and proxy measures were often employed for important outcomes such as hospital admission as an indicator of relapse (Schoeler et al., 2016b). Furthermore, the confounding effects of alcohol and other illicit substance use were not always taken into account (Grech et al., 2005; Foti et al., 2010). This may be important, as the use of substances such as methamphetamine is also associated with poor treatment outcomes in patients with a psychotic disorder (Wisdom et al., 2011; Glasner-Edwards and Mooney, 2014; Suetani et al., 2017).

To address some of these uncertainties, we conducted an analysis of data from a prospective, longitudinal study in which patients with a first episode of a schizophrenia spectrum disorder were treated for 24 months according to a standardised protocol, with a long-acting injectable antipsychotic. Regular, comprehensive clinical assessments enabled us to assess the treatment outcome in multiple domains over time, and the outcomes of relapse and remission were operationally defined. Also, repeated urine screening for cannabis allowed objective assessment of frequency of cannabis use over the treatment period. The aim of the present study was to investigate the influence of cannabis use on illness severity and treatment outcomes in patients with first-episode schizophrenia spectrum disorders, when treatment adherence was assured. We hypothesized that cannabis users would experience more severe symptoms and a poorer outcome in the domains of psychopathology, functionality and quality of life, and have lower remission and higher relapse rates. We also hypothesised that the effects of cannabis would be most apparent in those with more frequent positive urine cannabis tests during the study.

2. Methods

2.1. Study design and ethical approval

The over-arching aim of this study was to investigate factors affecting the treatment outcome over the first two years of treatment. Ethics approval for this prospective, longitudinal, single-site cohort study was obtained from the Health Research Ethics Committee (HREC) at the Faculty of Medicine and Health Sciences, Stellenbosch University (S17/03/047). Patients and/or their legal guardians provided written, informed consent.

2.2. Selection of study participants

Patients were recruited during their first admissions to psychiatric hospitals and community clinics within a well-defined catchment area in Cape Town and surrounding districts in the Western Cape Province of South Africa. Inclusion criteria were: in- or outpatients, 16 to 45 years of age, meeting the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) (First et al., 1994) criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder. Patients were excluded if they had a lifetime exposure to antipsychotics of more than four weeks, were previously treated with a long-acting injectable antipsychotic, had a serious or unstable medical condition, intellectual disability, or a current diagnosis of substance abuse or dependence, or substance induced psychotic disorder (DSM IV). Each participant underwent a thorough physical examination.

2.3. Clinical assessments

Diagnosis was confirmed with the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Duration of untreated psychosis (DUP) was estimated from the onset of continuous positive symptoms (>1 week duration) to initiation of study treatment, expressed in weeks. Psychopathology was assessed by physicians using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Rater training was conducted and inter-rater reliability testing was performed periodically for the PANSS (intra-class correlation 0.7 or higher). PANSS factor-analysis derived positive, negative and disorganised domains were calculated as previously described (Emsley et al., 2003). We also assessed depressive symptoms using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington and Addington, 1993); overall level of functioning using the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994); and patient-rated quality of life using the global item score of The World Health Organisation WHOQOL-BREF Quality of Life Scale (WHO, 1998). Remission status was determined according to the Remission in Schizophrenia Working Group (RSWG) consensus criteria (Andreasen et al., 2005), and relapse was operationally defined as a 25% increase in PANSS total scores from the previous visit, a greater than 10 point increase if the total score was less than 40, or a score of “much worse” or “very much worse” on the Clinical Global Impressions (CGI) scale (Csernansky et al., 2002).

2.4. Study treatment

The treatment protocol consisted of a seven day lead-in period of oral flupenthixol 1 to 3mg per day, followed by long-acting flupenthixol decanoate injections every 2 weeks for 24 months, starting with 10 mg 2-weekly, with 6-weekly increments of 10 mg if necessary, to a maximum of 30 mg 2 weekly. Additional oral flupenthixol tablets were allowed for acute exacerbation of psychotic symptoms between visits. Permitted concomitant medication included medication for general medical conditions, lorazepam for sedation, orphenadrine or biperiden for extra-pyramidal symptoms and propranolol for akathisia. However, no benzodiazepines, propranolol or anticholinergics were permitted in the twelve hours prior to assessment. Other antipsychotics, mood stabilizers and psychostimulants were prohibited.

To assess the total cumulative antipsychotic dose received by each patient we summed the number and dose of each flupenthixol injection plus each dose of oral flupenthixol received. The flupenthixol injection dose was converted to flupenthixol milligram equivalents, according to consensus-derived guidelines for dose equivalencies (Gardner et al. 2010).

2.5. Substance use determination

We determined substance use status by patient and carer report, and with repeated urine toxicology testing for cannabis and methamphetamine (the most frequently used illicit substances in our catchment area) at baseline and at months 3, 6, 12, 18 and 24. Participants were grouped as cannabis users if they or their carers reported cannabis use within the three months prior to the study, or if they tested positive for cannabis on any occasion. Furthermore, to investigate the effect of persistent use during the study, we created a discrete variable according to the number of positive urine tests. Non-users would therefore have a score of zero, while users would score ranging between one and six, based on the number of urine positive screens over the 24 months of treatment.

2.6. Statistical analysis

Our analysis sample comprised the intent to treat population (i.e. all entered patients who had at least a baseline assessment, including urine toxicology screen). Statistical analyses were performed using the SPSS v26 and R v3.5.2 software packages. Categorical data were compared between cannabis users and non-users using a Chi-squared test, while normally distributed numerical data were compared between the two groups using a student’s t-test. Mann-Whitney U non-parametric tests were used for non-normally distributed variables.

PANSS total scores were considered our primary outcome measure; secondary measures included factor-analysis derived PANSS domain scores (positive, negative and disorganized symptoms), depressive symptoms (CDSS), social and occupational functioning (SOFAS), and

patient-rated global quality of life (single item on the WHOQOL-BREF scale). To assess the changes in symptom severity over time at the fixed assessment points we compared visit-wise differences and changes over time were compared between cannabis users and non-users using mixed models for repeated measures (MMRM), controlling for age, sex, and methamphetamine use as covariates. Time-points were 0, 6, 12 and 24 months. We applied Bonferroni correction for multiple comparisons (*alpha*= 0.05/6 = 0.008). As additional outcome measures, rates of remission and relapse were compared between the two study groups (observed cases analysis). Finally, to assess the impact of ongoing cannabis use during the study, we constructed logistic regression models to explore whether the frequency of positive testing for cannabis use independently predicted relapse.

3. Results

3.1. Baseline characteristics of study participants

Of 234 patients who were assessed for eligibility 108 did not meet the study criteria or refused to consent to participate. Of these, 11 met substance abuse criteria and 15 were diagnosed as having a substance-induced psychotic disorder. Compared to the study participants, those excluded were older (26.32±7.89 vs. 24.07±6.59, p=0.02), more likely to be female (n=51, 45% vs. n=33, 26.2%, p=0.002) and more likely to have used other illicit substances during the past three months (n=29, 52.7% vs. n=25, 35.2%, p=0.049), although cannabis use was similar (n=45, 45.9% vs. n=34, 56.7%, p=0.2) as was years of schooling (9.72 ± 2.16 vs. 9.0 ± 2.55, p=0.62). Thus, 126 participants initially entered into the study, of whom 98 had baseline assessments including urine toxicology screening, and were included in our analysis. At baseline, 36 were admitted to hospital, whereas 9 were admitted to hospital over the course of the two years of treatment. The average length of admission was 8.82 weeks with a minimum of 1 day and a maximum of 19 weeks. Of the 98 entered, 70 completed the study. Reasons for dropout (*n*=28) were consent withdrawal (n=12), lost to follow-up (*n*=5), poor efficacy (*n*=3), relocation (*n*=3), medication side-effects (*n*=2), and other (*n*=3). Of those who dropped out, 15 were cannabis users and 13 were non-users.

The socio-demographic and clinical characteristics of cannabis users (*n*=45; 46%) versus non-users (*n*=53; 54%) were compared, as shown in Table 1. Cannabis users were significantly younger (*p*=0.004) as well as more likely to be male (*p*=0.001), and to test positive for methamphetamine use (*p*<0.001) compared to non-users. Patterns of alcohol use were similar between the groups (*p*=0.5). The duration of untreated psychosis was similar between cannabis users and non-users. Documented treatment adherence was high in the study, and did not differ between the cannabis users and non-users. Cannabis users were prescribed a slightly higher modal dose of antipsychotic medication compared to non-users (*p*=0.04), although there was no difference in cumulative exposure to antipsychotic medication over the 24 months of treatment (*p*=0.1). The number of weeks spent in the study also did not differ between the two groups (*p*=0.2).

3.2. Influence of cannabis use on clinical outcome measures over 24 months

Results of the MMRM analyses investigating the changes in clinical outcome measures between cannabis users and non-users over the course of the study are provided in Table 2. For the primary outcome measure (PANSS total scores), the group (cannabis users versus non-users) by time interaction effect was not significant (*F*=0.448, p=0.7) (Fig. 1), and there were no group differences at either baseline or month 24. There was a significant fixed effect for age (*p*=0.004), but not for gender (*p*=0.5), or methamphetamine use (*p*=0.07). Similarly, for the secondary outcome measures of positive, negative, disorganised and depressive symptoms and quality of life, there were no significant group by time interactions and no significant differences at either baseline or month 24. We did, however, find significantly poorer social and occupational functioning in cannabis users versus non-users at baseline (*p*=0.008) and at uncorrected significance level at month 24 (*p*=0.02), despite similar rates of improvement over 24 months of treatment (*F*=0.374, *p*=0.8).

Table 1
Demographic, clinical and treatment characteristics of the cannabis users* compared to the non-users.

Patient Characteristic	CannabisUsersn=45	Cannabis Non-Usersn=53	Unadjusted p-value
Age in years, mean (SD)	22.1 (4.15)	25.9 (1.03)	0.004
Sex, Males (%)	40 (88.8%)	32 (60.4%)	0.001
Highest grade of school completed, mean (SD)	9.4 (1.7)	10.4 (2.1)	0.03
Ethnicity, n (%)			0.4
Mixed Ancestry	37 (82.2%)	38 (71.7%)	
African	5 (11.1%)	8 (15.1%)	
White	3 (6.6%)	7 (13.2%)	
Diagnosis, n (%)			0.6
Schizophrenia	30 (66.6%)	36 (67.9%)	
Schizophreniform	15 (33.3%)	16 (30.2%)	
Schizoaffective	-	1 (1.8%)	
Duration of untreated psychosis in weeks, mean (SD)	35.3 (51.1)	34.1 (39.1)	0.90
Number of positive cannabis tests, mean (SD)	2.93 (1.96)		
Number of positive methamphetamine tests, n (%)	28 (62.2%)	4 (7.5%)	p<0.001
Alcohol, n (%)			0.3
History of excessive alcohol use	6 (13.3%)	3 (5.7%)	
Occasional alcohol use	32 (71.1%)	32 (60.4%)	
Duration of study treatment in weeks, mean (SD)	82.9 (29.4)	88.46 (28.8)	0.2
Modal flupenthixol decanoate dose, mg IM/2 weeks, mean (SD)	12.9 (3.9)	11.2 (3.2)	0.04
Cumulative antipsychotic dose, mg flupenthixol equivalents, mean (SD)	1989.11 (853.71)	1723.45 (731.63)	0.1
Treatment adherence, % (SD) of prescribed injections received	97.4% (3.7)	98.5% (4.5)	0.2

* Cannabis users were those with a history of use in the 3 months prior to the study or who had a positive urine cannabis test at any time-point during the study.

3.3. Influence of cannabis use on remission and relapse rates over 24 months

The rates of remission were similar between the cannabis using (*n*=34; 75.6%) and non-using (*n*=44; 83%) patients (*p*=0.361). However, a greater proportion of cannabis users (*n*=10; 22.2%) compared to non-users (*n*=4, 7.5%) relapsed during this time (*p*=0.039). Also, our logistic regression model (*R2*=0.95, *F*(4,93)=2.439, *p*=0.05) indicated that the frequency of positive cannabis urine toxicology screens significantly predicted relapse (ß=0.47, *t*=2.273, *p*=0.03), adjusting for age (*p*=0.7), sex (*p*=0.02), and methamphetamine use (*p*=0.8).

4. Discussion

This is the first study to investigate the association between cannabis use and treatment outcome in psychosis when antipsychotic adherence was objectively accounted for, and antipsychotic exposure accurately quantified. We also addressed other potential confounding factors that

Table 2
MMRM derived baseline and month 24 least squares means and 95% confidence intervals and group by time interactions for the outcome measures for the cannabis users* vs. non-users.

	Baseline			Month 24			
	CannabisUsing	CannabisNon-Using	p**	CannabisUsing	CannabisNon-Using	p**	p***
PANSS Total, mean(CI)	95.5 (91.5 – 99.7)	95.6 (91.6 – 99.6)	0.976	45.7 (40.7 – 50.7)	44.9 (40.5 – 49.3)	0.811	0.72
PANSS Positive Factor, mean(CI)	17.17 (16.24 – 18.11)	17.56 (16.65 – 18.46)	0.567	5.77 (4.61 – 6.94)	5.05 (4.04 – 6.06)	0.365	0.32
PANSS Negative Factor, mean(CI)	20.27 (18.72 – 21.8)	20.07 (18.54 – 21.6)	0.857	9.72 (7.91 – 11.5)	10.53 (8.89 – 12.2)	0.526	0.79
PANSS Disorganised Factor, mean(CI)	12.57 (11.81- 13.33)	11.79 (11.05 – 12.54)	0.157	6.35 (5.46 – 7.24)	5.56 (4.75 – 6.36)	0.204	0.87
SOFAS, mean(CI)	40.1 (36.7 – 43.4)	46.6 (43.3 – 49.9)	0.008	62.0 (58.0 – 66.0)	68.4 (64.8 – 72.0)	0.022	0.77
CDSS, mean(CI)	3.27 (2.3 – 4.23)	4.22 (3.29 – 5.15)	0.168	1.07 (-0.1 – 2.25)	1.10 (0.08 – 2.13)	0.969	0.24
WHOQoL, Patient-Rated overall QoL, mean(CI)	3.06 (2.65 – 3.47)	3.01 (2.59 – 3.43)	0.855	3.40 (2.91 – 3.89)	3.60 (3.16 – 4.05)	0.539	0.51

*Cannabis users were those with a history of use in the 3 months prior to the study or who had a positive urine cannabis test at any time-point during the study.
** = Fishers least significant difference test comparing recent/current cannabis users vs non-users at baseline and month 24 respectively
*** = P-values for the group (cannabis users vs non-users) by time interaction effect over the 24 months of treatment
PANSS = Positive and Negative Syndrome Scale
SOFAS = Social and Occupational Functioning Assessment Scale
CDSS = Calgary Depression Scale for Schizophrenia
WHOQoL = The World Health Organisation WHOQOL-BREF Quality of Life Scale.

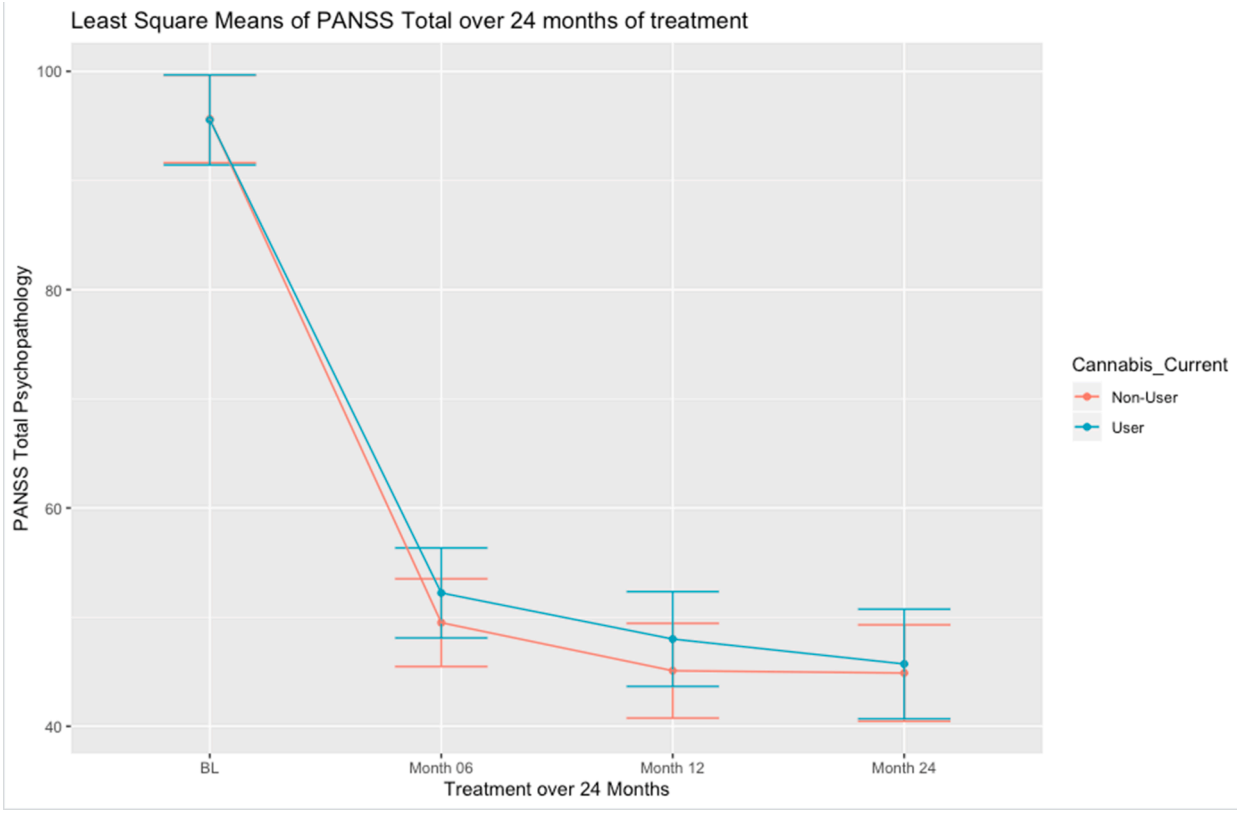

Fig. 1. Least Square Means of PANSS Total over 24 months of treatment.

limit interpretation of many previous studies, including illness chronicity, effects of previous treatment, and other substance use. Our findings suggest that different mechanisms may account for the effects of cannabis on symptom reduction and on relapse risk during antipsychotic treatment. In contrast to several previous studies (Harrison et al., 2008; Baeza et al., 2009; Foti et al., 2010; Kuepper et al., 2011; van der Meer et al., 2015), we found little evidence of an association between cannabis use and greater illness severity prior to treatment or blunted symptom reduction with treatment, although our sample size may not have been sufficient to detect more subtle effects. While the slightly higher mean modal antipsychotic dose prescribed to the cannabis users could indicate some degree of reduced response, we found no group differences in any of the outcome trajectories over time, and with the exception of social and occupational functioning, no differences between the groups at baseline or month 24. Social and occupational functioning was significantly poorer at baseline in cannabis users compared to non-users but the lack of a significant group x time effect in the MMRM indicated a similar improvement trajectory over the treatment period. Also, remission rates were similar between the groups. These findings therefore suggest that, on the one hand, baseline symptom severity and treatment response in terms of symptom reduction are not adversely affected by cannabis use when antipsychotic adherence is assured, and point to an important mediating role for antipsychotic non-adherence in the previously reported association between cannabis use and poorer treatment outcomes in psychosis in terms of symptom reduction, depression and psychosocial functioning (Seddon et al.,

2016).

On the other hand, the one important aspect of outcome that did differ between cannabis users and non-users was that of risk of relapse, with relapse events occurring more than twice as frequently in cannabis users. This is in keeping with the findings of systematic reviews of longitudinal studies of consistent links between cannabis use and relapse (Zammit et al., 2008). Furthermore, our finding that more frequent positive cannabis urine testing predicted relapse suggests a dose-risk effect, and that continued use, rather than an enduring effect of past use, is the critical factor (Schoeler et al., 2016a; Schoeler et al., 2016b). While some did not find a relationship between cannabis dose and risk of relapse (Barrowclough et al 2013; Barrowclough et al 2014), others did. Schoeler et al. (2017b) found a greater risk of relapse during periods of cannabis use vs. no use, and path analysis of their data indicated an effect of cannabis use on subsequent risk of relapse rather than an effect of relapse on subsequent cannabis use. In another study the same group reported that patients who continued to use high-potency cannabis after the onset of psychosis were at greatest risk of relapse and of experiencing more frequent and earlier relapses than those who did not continue cannabis use (Schoeler et al., 2017a), and in a further study they reported that continued cannabis use predicted poor outcome, including increased risk of relapse (Schoeler et al., 2016c).

Previous studies have emphasised the role of non-adherence in mediating increased relapse risk in cannabis using individuals with psychosis, given the association between cannabis use and non-adherence and the finding that discontinuation of antipsychotic treatment is the greatest risk of relapse by far (Foglia et al., 2017). In a systematic review that included 15 observational studies, Foglia and colleagues (2017) reported an increased odds ratio of non-adherence of 2.5 for cannabis use at baseline, increasing to 5.79 for ongoing cannabis use. Schoeler and colleagues (2017b) estimated that between 20% and 36% of the adverse effects of cannabis use on outcome might be mediated through its effects on medication adherence. However, these studies relied on retrospective case notes and patient report for assessing adherence and none used objective measures (Foglia et al., 2017). As such, they were not able to address whether cannabis use directly or indirectly affects relapse rates. It has nevertheless been suggested that the cannabis use may directly increase the risk of relapse by reducing the effectiveness of antipsychotics (Schoeler et al., 2017b). Our results indicate that, with assured treatment adherence, cannabis use increases the risk of relapse, but without other evidence of a poorer treatment response in terms of symptom reduction. Therefore, our findings suggest that cannabis use directly reduces the threshold for psychotic breakthrough without blunting the symptom reduction effects of antipsychotic treatment. A possible role for delta-9-tetrahydrocannabiniol (THC), the main psychoactive ingredient in cannabis, should be considered, given its psychotogenic propensity and its demonstrated effects on the dopamine system (Bloomfield et al., 2017). Indeed, rat studies report that chronic treatment with THC gives rise to supersensitivity of D2/3 signalling, that is fully reversible following drug discontinuation (Tournier et al., 2016) – consistent with our observed dose-risk effect.

The present study has several strengths. First, restricting our sample to first-episode patients who were minimally treated at baseline reduced the confounding effects of illness chronicity and prior treatment. Second, repeated toxicology screening provided an objective measure of cannabis use over time. Additionally, our ability to adjust for methamphetamine use was important, given its frequency of use in our catchment area and its reported association with poorer treatment outcome (Wisdom et al., 2011; Glasner-Edwards and Mooney, 2014; Suetani et al., 2017). Third, comprehensive clinical assessments at multiple time-points with standard instruments allowed us to assess the treatment changes longitudinally, and in multiple outcome domains. Fourth, determining relapse according to operationally defined criteria avoided the inaccuracies of proxy measures such as hospitalisation. Finally, providing treatment according to a standard protocol avoided possible differential effects of multiple antipsychotics on outcome, and the use of a depot formulation allowed us to objectively assess adherence and to quantify antipsychotic exposure with precision.

There are also study limitations that should be considered. First, considering the relatively small sample size, we conducted a post-hoc power analysis and found that our study was sufficiently powered to detect a small effect size of between 0.1 and 0.15. Our finding of no group differences between cannabis users and non-users in terms of PANSS total psychopathology scores is therefore fairly clear cut. However, it should be noted that, for a single site study, the sample is relatively large. Further, the disadvantages of a limited sample size should be balanced against the advantages of a single site, prospective, longitudinal study in which pre-specified outcome domains were assessed by raters who underwent regular training and inter-rater reliability testing. Second, we were not able to address questions regarding the type and precise frequency of cannabis use, as this information was not captured. We were also not able to compare baseline cannabis users who became abstinent during the study with those who continued use, as only seven fell into the former category. This might be important, as evidence suggests that stopping cannabis use is associated with better outcomes, perhaps even than those who had never used cannabis (Schoeler et al., 2016a). Also, we categorised patients according to current or recent (past 3 months) of cannabis use. It is possible that some of those classified as non-users could have had enduring effects from cannabis use in the past. However, we were able to assess the effect of frequency of positive cannabis urine testing on relapse, as an indication of continuous use. Third, our results cannot necessarily be generalised to patients receiving antipsychotic medications other than flupenthixol. Fourth, by excluding patients with substance abuse or dependence, or substance induced psychotic disorder, our sample excluded those patients with the most severe effects of substance use. Fifth, we did not have complete data on tobacco use in our patients, which could reduce levels of antipsychotic medication by CYP1A2 induction (e.g. Carvalho Henriques et al., 2020; Lesche et al., 2020). Sixth, as with the majority of longitudinal studies in in patients with psychotic disorders, the relatively high attrition rate is a limiting factor. Finally, the longer-term effects of cannabis beyond the first two years of treatment were not assessed.

5. Conclusions

In conclusion, we found that cannabis use increases the risk of relapse but does not obviously blunt the treatment response when medication adherence is assured in schizophrenia spectrum disorders. Although a higher rate of relapse events occurred in cannabis users the overall response trajectory was similar, indicating that those who experienced relapses subsequently responded to treatment and the overall trajectory did not differ between users and non-users. However, given the potentially grave consequences of illness recurrence (Emsley et al., 2013), prioritising relapse prevention may be particularly important in patients with schizophrenia spectrum disorders who continue to use cannabis. In addition to psychosocial interventions aimed at improving adherence, long-acting antipsychotics may be an effective option for patients with psychosis and comorbid substance use requiring maintenance antipsychotic treatment. Future studies should further explore the role of mediating factors relating to cannabis use as well as other factors such as tobacco smoking, alcohol use, and type of antipsychotic medication prescribed in the association between cannabis use and relapse.

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Declaration of Competing Interest

FS, SdP, LA, SK, LP, and HKL have no conflict of interest to declare. RE has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck. RM has received honoraria for lectures supported by Janssen, Lundbeck, Otsuka and Sunovian. MDF has received honoraria for lectures supported by Lundbeck and Janssen in 2016.

References

Abdel-Baki, A., Ouellet-Plamondon, C., Salvat, É., Grar, K., Potvin, S., 2017. Symptomatic and functional outcomes of substance use disorder persistence 2 years after admission to a first-episode psychosis program. Psychiatry Res. 247, 113–119. https://doi.org/10.1016/j.psychres.2016.11.007.

Addington, D., Addington, J., 1993. Assessing depression in schizophrenia: the calgary depression scale. Br. J. Psychiatry 163, S39–S44.

Association, American Psychiatric, 1994. Diagnostic and Statistical Manual of Mental Dis- orders fourth ed. (Washington, D.C.).

Andreasen, NC, Carpenter Jr, WT, Kane, JM, Lasser, RA, Marder, SR, Weinberger, DR., 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. Am. J. Psychiatry 162 (3), 441–449. Mar.

Baeza, I., Graell, M., Moreno, D., et al., 2009. Cannabis use in children and adolescents with first episode psychosis: influence on psychopathology and short-term outcome (CAFEPS study). Schizophr. Res. 113, 129–137. https://doi.org/10.1016/j.schres.2009.04.005.

Barrowclough, C, Emsley, R, Eisner, E, Beardmore, R, Wykes, T., 2013. Does change in cannabis use in established psychosis affect clinical outcome? Schizophr. Bull. 39 (2), 339–348.

Barrowclough, C., Gregg, L., Lobban, F., Bucci, S., Emsley, R., 2014. The impact of cannabis use on clinical outcomes in recent onset psychosis. Schizophr. Bull. 41, 382–390. https://doi.org/10.1093/schbul/sbu095.

Bloomfield, MAP., Ashok, AH., Volkow, ND., Oliver, D., 2017. Europe PMC funders group the effects of Δ9-tetrahydrocannabinol on the dopamine system. Nature 539 (7629), 369–377. https://doi.org/10.1038/nature20153.

Carvalho Henriques, B., Yang, E.H., Lapetina, D., Carr, M.S., Yavorskyy, V., Hague, J., Aitchison, K.J., 2020. How can drug metabolism and transporter genetics inform psychotropic prescribing? Front. Gen. 11, 491895 https://doi.org/10.3389/fgene.2020.491895.

Colizzi, M., Carra, E., Fraietta, S., et al., 2016. Substance use, medication adherence and outcome one year following a first episode of psychosis. Schizophr. Res. 170, 311–317. https://doi.org/10.1016/j.schres.2015.11.016.

Csernansky, J.G., Mahmoud, R., Brenner, R., Group, RUS., 2002. A comparison of riseridone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl. J. Med. 346 (1), 16–22.

Emsley, R., Rabinowitz, J., Torreman, M., et al., 2003. The factor structure for the positive and negative syndrome scale (PANSS) in recent-onset psychosis. Schizophr. Res. 61 (1), 47–57. https://doi.org/10.1016/S0920-9964(02)00302-X.

Emsley, R., Chiliza, B., Asmal, L., Harvey, B.H., 2013. The nature of relapse in schizophrenia. BMC Psychiatry 13, 50. https://doi.org/10.1186/1471-244X-13-50.

First, MB., Spitzer, RLGM., Williams, LBW., 1994. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition (SCID-P).

Foglia, E., Schoeler, T., Klamerus, E., Morgan, K., Bhattacharyya, S., 2017. Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis. Psychol. Med. 47, 1691–1705. https://doi.org/10.1017/S0033291717000046.

Foti, DJ., Kotov, R., Guey, LT., Bromet, EJ., 2010. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. AM J. Psychiatry 167, 987–993.

Gardner, DM., Murphy, AL., O'Donnell, H., Centorrino, F., Baldessarini, RJ, 2010. International consensus study of antipsychotic dosing. Am. J. Psychiatry 167, 686–693.

Glasner-Edwards, S., Mooney, L.J., 2014. Methamphetamine psychosis: epidemiology and management. CNS Drugs. https://doi.org/10.1007/s40263-014-0209-8.

Grech, A., Van Os, J., Jones, PB., Lewis, SW., Murray, RM., 2005. Cannabis use and outcome of recent onset psychosis. Eur. Psychiatry 20, 349–353. https://doi.org/10.1016/j.eurpsy.2004.09.013.

Haddad, P.M., Brain, C., Scott, J., 2014. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. Patient Related Outcome Measures 5, 43–62. https://doi.org/10.2147/PROM.S42735.

Harrison, I., Joyce, EM., Mutsatsa, SH., et al., 2008. Naturalistic follow-up of co-morbid substance use in schizophrenia: the West London first-episode study. Psychol. Med. 38, 79–88. https://doi.org/10.1017/S0033291707000797.

Kay, SR., Fizbein, A., Opler, LA., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–267.

Kuepper, R., van Os, J., Lieb, R., Wittchen, HU., Hofler, M., Henquet, C., 2011. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. BMJ 342, 1–8. https://doi.org/10.1136/bmj.d738.

Large, M., Mullin, K., Gupta, P., Harris, A., Nielssen, O., 2014. Systematic meta-analysis of outcomes associated with psychosis and co-morbid substance use. Aust. N. Z. J. Psychiatry 48 (5), 418–4432. https://doi.org/10.1177/0004867414525838.

Lesche, D, Mostafa, S, Everall, I, Pantelis, C, Bousman, CA., 2020. Impact of CYP1A2, CYP2C19, and CYP2D6 genotype- and phenoconversion-predicted enzyme activity on clozapine exposure and symptom severity. Pharmacogenom. J. 20 (2), 192–201. https://doi.org/10.1038/s41397-019-0108-y. AprEpub 2019 Oct 15. PMID: 31616047.

Malla, A., Norman, R., Bechard-Evans, L., Schmitz, N., Manchanda, R., Cassidy, C., 2008. Factors influencing relapse during a 2-year follow-up of first-episode psychosis in a specialized early intervention service. Psychol. Med. 38, 1585–1593. https://doi.org/10.1017/S0033291707002656.

Miller, R., Ream, G., McCormack, J., Gunduz-Bruce, H., Sevy, S., Robinson, D., 2009. A prospective study of cannabis use as a risk factor for non-adherence and treatment dropout in first-episode schizophrenia. Schizophr. Res. 113, 138–144. https://doi.org/10.1016/j.schres.2009.04.018.

Quattrone, D., Gayer-Anderson, C., Ferraro, L., et al., 2018. First episode psychotic patients with a history of frequent cannabis use express more positive symptoms at illness onset than those who never used cannabis. Schizophr. Bull. (Suppl 1), S158–S159. https://doi.org/10.1093/schbul/sby016.386.

Ringen, P.A., Nesvåg, R., Helle, S., et al., 2016. Premorbid cannabis use is associated with more symptoms and poorer functioning in schizophrenia spectrum disorder. Psychol. Med. 1–10. https://doi.org/10.1017/S0033291716001999.

Seddon, J.L., Birchwood, M., Copello, A., Everard, L., Jones, P.B., Fowler, D., Amos, T., Freemantle, N., Sharma, V., Marshall, M., Singh, S.P., 2016. Cannabis use is associated with increased psychotic symptoms and poorer psychosocial functioning in first-episode psychosis: a report from the UK national EDEN study. Schizophr. Bull. 42 (3), 619–625. https://doi.org/10.1093/schbul/sbv154.

Schoeler, T., Monk, A., Sami, M.B., Klamerus, E., Foglia, E., Brown, R., Bhattacharyya, S., 2016a. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. Lancet Psychiatry 3 (3), 215–225. https://doi.org/10.1016/S2215-0366(15)00363-6.

Schoeler, T., Petros, N., Forti, M.D., Pingault, J.B., Klamerus, E., Brown, E., Bhattacharyya, S., 2016c. Association between continued cannabis use and risk of relapse in first-episode psychosis a quasi-experimental investigation within an observational study. JAMA Psychiatry 73 (11), 1173–1179. https://doi.org/10.1001/jamapsychiatry.2016.2427.

Schoeler, T., Petros, N., Di Forti, M., et al., 2016b. Effects of continuation, frequency, and type of cannabis use on relapse in the first 2 years after onset of psychosis: an observational study. Lancet Psychiatry 3, 947–953. https://doi.org/10.1016/s2215-0366(16)30188-2.

Schoeler, T., Petros, N., Di Forti, M., et al., 2017a. Effect of continued cannabis use on medication adherence in the first two years following onset of psychosis. Psychiatry Res. 255, 36–41. https://doi.org/10.1016/j.psychres.2017.05.009.

Schoeler, T., Petros, N., Di Forti, M., et al., 2017b. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. Lancet Psychiatry 4, 627–633. https://doi.org/10.1016/s2215-0366(17)30233-x.

Suetani, S., Reddan, J., Anderson, C., 2017. Methamphetamine and psychiatry: a story of the colourless substance of abuse. Australas. Psychiatry 25 (3), 254–256. https://doi.org/10.1177/1039856217695702.

Tournier, BB, Tsartsalis, S, Dimiziani, A, Millet, P, Ginovart, N., 2016. Time-dependent effects of repeated THC treatment on dopamine D2/3 receptor-mediated signalling in midbrain and striatum. Behav. Brain Res. 311, 322–329. https://doi.org/10.1016/j.bbr.2016.05.045.

van der Meer, F.J., Velthorst, E., Genetic Risk and Outcome in Psychosis (G.R.O.U.P), 2015. Course of cannabis use and clinical outcome in patients with non-affective psychosis: a 3-year follow-up study. Psychol. Med. 45, 1977–1988. https://doi.org/10.1017/S0033291714003092.

WHO, 1998. Development of the world health organization WHOQOL-BREF quality of life assessment. Psychol. Med. 28 (3), 551–558.

Wisdom, JP., Manuel, JI., Drake, R.E., 2011. Substance use disorder among people with first-episode psychosis: a systematic review of course and treatment. Psychiatr. Serv. 62 (9), 1007–1012.

Zammit, S., Moore, THM., Lingford-Hughes, A., et al., 2008. Effects of cannabis use on outcomes of psychotic disorders: systematic review. Br. J. Psychiatry 193, 357–363. https://doi.org/10.1192/bjp.bp.107.046375.

CHAPTER III

THE ASSOCIATIONS OF CANNABIS AND METHAMPHETAMINE USE WITH COGNITIVE PERFORMANCE OVER THE FIRST TWO YEARS OF TREATMENT IN FIRST-EPISODE SCHIZOPHRENIA SPECTRUM DISORDERS

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The associations of cannabis and methamphetamine use with cognitive performance over the first two years of treatment in schizophrenia spectrum disorders

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1. Introduction

Deficits in cognitive functioning are one of the core features of schizophrenia (Dickinson et al., 2020; McCleery et al., 2014) and are associated with poorer functional outcomes (Mohamed et al., 2008; Halverson et al., 2019; Silberstein & Harvey, 2019; Zizolfi et al., 2019; Zhu et al., 2020), treatment non-adherence (Haddad et al., 2014) and a greater risk of relapse (Chen et al., 2005). While cognitive deficits are considered intrinsic to the illness itself (Dickinson et al., 2008), the use of illicit substances likely plays a contributory role. Indeed, cannabis (Burggren et al., 2019; Duperrouzel et al., 2020; Scott et al., 2018) and methamphetamine (Potvin et al., 2018) use are both associated with cognitive impairments in the general population.

Similarly, in patients with psychosis, methamphetamine use has been associated with cognitive impairment (Chen et al., 2015; Fassbender etal., 2015). In contrast, the effects of cannabis use on cognition in patients with psychosis are less clear-cut. In a meta-analysis of studies conducted in patients with schizophrenia, the authors reported moderately superior cognitive performance in cannabis users compared to non-users (Rabin et al., 2011). In a

subsequent meta-analysis, Yucel and colleagues (2012) also reported moderately better cognition in schizophrenia patients who used cannabis. However, a more recent meta-analysis by Sanchez-Gutierrez and colleagues (2020) found no difference in cognitive performance between patients with a first-episode of psychosis who used cannabis when compared to their non-using counterparts.

Of note is that the Yucel and colleagues (2012) meta-analysis did not exclude poly-substance use, whereas both Rabin and colleagues (2011) and Sanchez-Gutierrez and colleagues (2020) excluded studies with poly-substance use. This is important, as the majority of cannabis users also use other illicit substances (National Academies of Sciences, 2017). Of particular interest is methamphetamine, given its often long-lasting adverse effects on short-term memory, executive functioning, and manual dexterity (McCann et al., 2008). Interpretation of studies to date is limited by the different approaches used to estimate the history and frequency of use (Sánchez-Gutiérrez et al., 2020; Yucel et al 2012), their cross-sectional design (Sánchez-Gutiérrez et al., 2020), and heterogeneity in terms of treatment (Sánchez-Gutiérrez et al., 2020).

The aim of this study was to investigate the effects of cannabis and methamphetamine use on cognitive performance in first-episode schizophrenia spectrum disorder patients over the first two years of treatment. The overall treatment outcome in this cohort has been previously described (Phahladira et al., 2020). Our primary objective was to assess the independent effects of cannabis and methamphetamine use on the cognitive performance trajectories over 24 months of treatment in first-episode patients. In addition, we considered the effects of cannabis and methamphetamine on pre-treatment (baseline) and post-treatment (endpoint) cognitive performance. We hypothesised that methamphetamine use would be associated with a frequency-of-positive-urine-test-response poorer overall cognitive performance, whereas cannabis use would have no discernible effects, or be associated with better overall cognitive performance in patients but not in controls.

1. Methods

1.1. Study design and ethical approval

This prospective, longitudinal, single-site cohort study aimed to investigate factors affecting the treatment outcome over the first two years of treatment in schizophrenia spectrum disorder. In this analysis we focused on the associations between cannabis and methamphetamine use and cognitive performance over the treatment period. Ethical approval was obtained from the Health Research Ethics Committee (HREC) at the Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa (S17/03/047). Patients and/or their legal guardians provided written, informed consent.

1.2. *Selection of study participants*

Patients were recruited during first admissions to psychiatric hospitals and community clinics within a well-defined catchment area in Cape Town and surrounding districts in the Western Cape Province of South Africa. Inclusion criteria were: in- or out-patients, 16 to 45 years of age, meeting the Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, text revision (DSM-IV-TR) (American Psychiatric Association, 1994) criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder. Patients were excluded if they had a lifetime exposure to antipsychotics exceeding four weeks, previous treatment with a long-acting injectable antipsychotic, a serious or unstable medical condition, or were intellectually disabled. The control group was recruited from the same catchment area, with similar socioeconomic status as the patients. Controls were excluded if they had a first-degree relative with a psychotic disorder or if they had a DSM-IV-TR axis I or II disorder as determined by the SCID-Non-Patient Edition interviews. Controls were matched for age, sex and ethnicity. Each participant underwent a thorough physical examination. We also excluded participants with an educational level of lower than grade seven or who were not fluent in English or Afrikaans. Lastly, both patients and controls were excluded if their substance use met the diagnostic threshold for abuse or dependence, or if they were judged to have an acute substance-

induced psychotic disorder (DSM-IV-TR). Controls therefore did not have a psychiatric or medical disorder but were not excluded on the basis of their substance use.

1.3. Measures

1.3.1. Clinical Assessments

Investigators were psychiatrists or trainee psychiatrists who had undergone extensive training in the study instruments. Diagnosis was made according to consensus of the research team which included psychiatrists and psychologists. The patients were assessed with the Structured Clinical Interview for DSM-IV (SCID; First et al. 1994) to confirm diagnosis, the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) to assess psychopathology, the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994) to assess overall functioning, and the Calgary Depression Scale for Schizophrenia (CDSS) (Addington and Addington, 1993) for depressive symptoms. Duration of untreated psychosis was estimated from the onset of continuous positive symptoms (>1 week duration) to initiation of study treatment.

1.3.2. Antipsychotic Treatment

The treatment protocol consisted of a seven-day lead-in period of oral flupenthixol 1-3mg/day, followed by long-acting flupenthixol decanoate injections every two weeks for 24 months, starting with 10-mg two-weekly, with six-weekly increments of 10-mg if necessary, to a maximum of 30-mg two-weekly. Additional oral flupenthixol tablets were allowed for acute exacerbation of psychotic symptoms between visits. Permitted concomitant medication included medication for general medical conditions, lorazepam, orphenadrine or biperiden, and propranolol. Other antipsychotics, mood stabilizers and psychostimulants were not permitted. No benzodiazepines, propranolol or anticholinergics were permitted in the twelve hours prior to assessments.

1.3.3. Substance Use

At the time when the study was conducted, both cannabis and methamphetamine were considered illicit substances in South Africa. Currently, legislation is underway to relax the status of recreational cannabis use. Urine toxicology testing (Beckman DXC enzyme immunoassay) for cannabis, methamphetamine, and methaqualone, the most frequently used illicit substances in the Western Cape (Dada et al., 2021). Methaqualone was not reported on due to the small number of positive tests in our sample. The laboratory cut-offs for cannabinoids (specifically for THC) positive > 50 ng/ml; methamphetamine positive > 500 ng/ml, and for methaqualone positive > 300 ng/ml. Screening was performed at baseline, and again at months 3, 6, 12, 18 and 24 in the patients. We created discrete variables for the frequency of positive urine toxicology testing for both cannabis and methamphetamine for the patients. Non-users would therefore have a score of zero, while users would score ranging between one and six. Controls were screened at their baseline assessment only. The study did not include a formal program for people who use substances. However, those with persistent substance use were provided with focussed psychoeducation and offered other psychosocial interventions in line with standard care.

1.3.4. Cognitive Assessment

Cognitive function was assessed by means of the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery (MCCB), developed specifically to measure cognitive functioning and its changes during treatment in schizophrenia. The MCCB measures seven cognitive domains and a composite score. The seven domains are: speed of processing; attention/vigilance; working memory; verbal learning; visual learning; reasoning and problem solving; and social cognition (Nuechterlein et al. 2008). The MCCB was administered at baseline, month 6, month 12, and month 24. For the baseline assessment, a window period of up to two weeks was permitted and for those who took longer to stabilise sufficiently, the baseline assessment was omitted. Randomized alternate forms were used on repeat assessments for visual learning, verbal learning and the

Neuropsychological Assessment Battery mazes (Stern & White, 2003). Age- and sex-corrected norms were used according to the guidelines outlined in the MCCB manual (Nuechterlein& Green, 2006). To ensure cultural sensitivity, we used the international scoring program of Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Branch 4) (Hellemann et al., 2017). We have previously used the MCCB and found it to be reliable for assessing cognitive functioning in our study population (Olivier et al., 2015).

1.4. Statistical analysis

Our sample comprised a modified intent-to-treat population, i.e. all entered patients who had at least one cognitive assessment, as well as a urine toxicology screen. Statistical analyses were performed using the SPSS v27 and R v3.5.2 software packages. Mann-Whitney U non-parametric tests was used for education. Chi-squared tests were used for our categorical variables like sex and substance use and t-tests for continuous variables like age. We constructed three sets of linear mixed-effect models for repeated measures (MMRM) to assess visit-wise changes in MCCB composite scores over the 24-month study period. For all three sets, visit was entered as a fixed effect, patient ID as a random effect, and education as a covariate. Then, in the first model, we compared patients and controls with visit-wise MCCB Composite scores with group (patients vs controls) as a fixed effect. Cannabis and methamphetamine use status were entered as categorical fixed effects. The second MMRM model, in the patients only, visit-wise MCCB Composite score was the dependent variable, with the number of positive urine tests entered as a discrete, fixed effect, for cannabis and methamphetamine independently. For the third set, we conducted secondary MMRM analyses for each of the seven MCCB domains, with the number of positive urine tests as a discrete, fixed effect, for cannabis and methamphetamine independently. These secondary analyses were purely exploratory, and we did not correct for multiple comparisons. To evaluate the pre-treatment effects, we utilised a linear regression model with baseline MCCB composite score, cannabis or methamphetamine use status (self-report within the past three months or positive urine toxicology at baseline) and educational level as covariate. To evaluate the end-of-study

effects, we again utilised a similar linear regression model with endpoint (calculated using last observation carried forward) MCCB composite score. To investigate this effect in controls only, we utilised a linear regression model with baseline MCCB composite score, cannabis or methamphetamine use status (self-report within the past three months or positive urine toxicology at baseline) and educational level as covariate. Lastly, a MMRM model with PANSS total score was constructed with cannabis and methamphetamine frequencies, controlling for age, sex, and education in order to assess the overall clinical profile of patients.

2. Results

2.1. Sample characteristics

Of 126 patients initially entered into the study, 81 completed at least one MCCB assessment and urine toxicology screen, and were included in the analysis (Table 1). At baseline, 36 were admitted to hospital, whereas 9 were admitted to hospital over the course of the two years of treatment. The average length of admission was 8.82 weeks with a minimum of 1 day and a maximum of 19 weeks. Compared to controls, patients were younger at the onset of substance use, and used both cannabis (p=0.001) and methamphetamine (p=0.01) more frequently than controls. The control group comprised 100 matched, healthy individuals with at least one MCCB assessment and toxicology screen. The numbers of patients and controls at each timepoint were, respectively, 54 and 91 at baseline, 72 and 73 at month 6, 57 and 54 at month 12, and 41 and 33 at month 24.

Table 1. Demographic, substance use and baseline clinical characteristics of the study sample.

	Patients n=81	Controls n=100	p
Age in years, mean (SD)	23.78 (6.01)	25.69 (7.28)	0.085
Sex Males, n (%)	58 (71.6%)	63 (63%)	0.221
*Education, mean (SD)	9.90 (2.1)	10.48 (1.52)	0.123
Ethnicity, n (%)			0.732
Mixed Ancestry	62 (76.5%)	77 (77%)	
African	11 (13.6%)	16 (16%)	
White	8 (9.9%)	7 (7%)	
**Current tobacco use, n (%)	38 (59.3%)	49 (76.6%)	0.037
Cannabis Use:			
Ever Used n (%)	43 (53.1%)	42 (42%)	0.137
Used in the past 3 months, n (%)	17 (20.9%)	26 (26%)	0.052
At least 1 positive test, n (%)	36 (44.4%)	42 (42%)***	0.741
Age at first use, mean (SD)	15.88 (2.55)	17.97 (3.59)	0.009
Daily Use, n (%)	29 (35.8%)	13 (13%)	0.001
Weekly Use, n (%)	1 (%)	3 (3%)	
Occasional Use, n (%)	6 (%)	23 (%)	
Methamphetamine Use:			
Ever used, n (%)	23 (32.1%)	16 (16%)	0.635
Used in the past 3 months, n (%)	15 (18.5%)	19 (19%)	0.934
At least 1 positive test, n (%)	26 (32.1%)	16 (16%)***	0.011
Age at first use, mean (SD)	17.55 (2.92)	20.71 (5.08)	0.013
Daily Use, n (%)	22 (27.2%)	6 (6%)	0.006
Weekly Use, n (%)	1(1.2%)	6 (6%)	
Occasional Use, n (%)	3 (3.7%)	5 (5%)	
****Lifetime History of Excessive Alcohol Use, n (%)	6 (7.4%)	6 (6%)	0.645
DUP in weeks, mean (SD)	30.62 (33.4)	-	-
PANSS Total, mean (SD)	95.3 (16.7)	-	-
CDSS, mean (SD)	3.83 (4.4)	-	-
SOFAS, mean (SD)	44.6 (11.9)	-	-

*Education = highest grade of school completed
** Tobacco data available for 64 patients and 64 controls only
***Controls only underwent one urine toxicology test
****Defined as a lifetime history of binge drinking or heavy drinking considered excessive by the participant, or having resulted in health problems
DUP= Duration of untreated psychosis
PANSS = Positive and Negative Syndrome Scale
CDSS = Calgary Depression Scale for Schizophrenia
SOFAS = Social and Occupational Functioning Scale

2.2. Cognitive performance in patients and controls over 24 months

At baseline, MCCB composite scores were 16.54 ± 13.16 for patients with substance use in the past 3 months and 23.37 ± 12.87 for patients without substance use in the past 3 months, and 27.4 ± 12.47 for controls with substance use in the past 3 months and 32.67 ± 14.9 without substance use in the past 3 months. MMRM analysis of the MCCB composite score over 24 months revealed a significant group by time interaction effect ($F(3,298)=6.987$; $p=0.0001$) (Figure 1). Least square means with 95% confidence intervals are provided in Table 2, indicating persistently poorer cognitive performance in patients compared to controls. Fisher's LSD post-hoc tests indicated significant improvements for the patients from baseline to month 6 ($p<0.0001$), with no further improvements from month 6 to 12 ($p=0.9$) nor month 12 to 24 ($p=0.4$). For the controls, there were significant improvements in MCCB composite scores from baseline to month 6 ($p<0.001$) and from month 6 to 12 ($p=0.02$) but not from 12 to 24 ($p=0.2$). We found a significant fixed effect for methamphetamine ($F(1,166)=4.141$; $p=0.043$), but not for cannabis ($F(2,166)=0.812$; $p=0.368$) use.

Thus, the cognitive performance was poorer in the patients than the controls throughout, and this was associated with methamphetamine, but not cannabis use.

Figure 1: Least square means of MCCB Composite scores over 24 months for the patients and controls

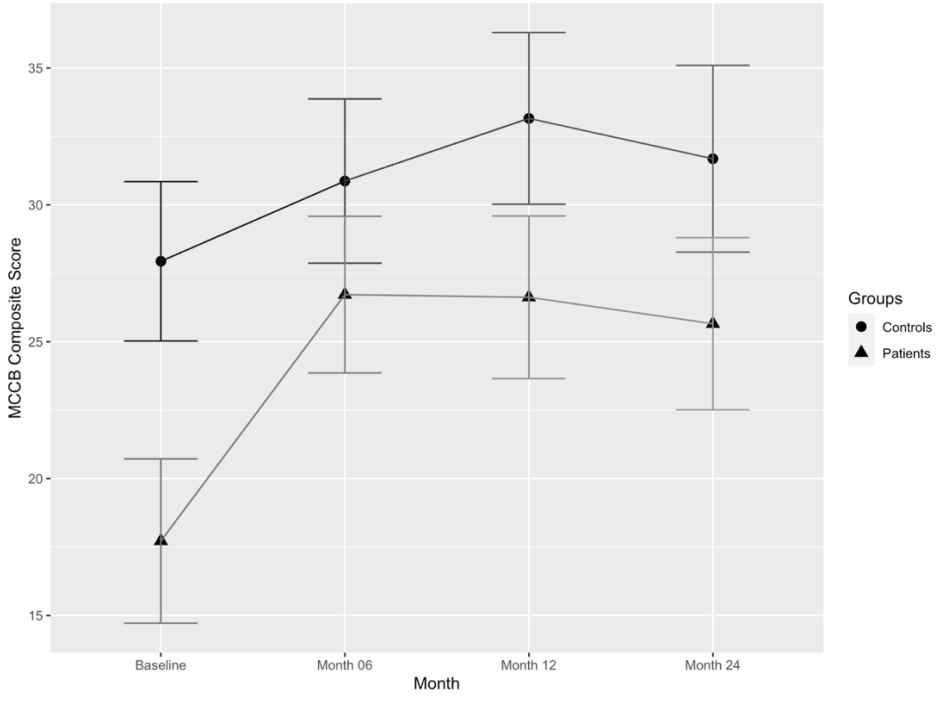

Table 2: Least Square Means of MCCB Composite scores comparing patients and controls over 24 months

Visit	Patients		Controls		
	Mean (CI)	p* (Visit)	Mean (CI)	p* (Visit)	p** (Group)
Baseline	17.7 (14.7 - 20.7)		27.9 (25.0 - 30.8)		p<0.0001
Month 6	26.7 (23.9 - 29.6)	p<0.0001	30.9 (27.9 - 33.9)	0.0009	0.0351
Month 12	26.6 (23.7 - 29.6)	0.9227	33.2 (30.0 - 36.3)	0.0238	0.0016
Month 24	25.7 (22.5 - 28.8)	0.4031	31.7 (28.3 - 35.1)	0.2318	0.0070

*p (Visit) is the p-value for the difference from the previous visit

**p (Group) is the p-value for the difference between patients and controls at that visit

2.3. Effects of number of positive tests for cannabis and methamphetamine use on cognitive performance in the patients over 24 months of treatment

For the 36 (44.4%) patients testing positive for cannabis the mean (SD) number of positive tests was 3.56 (1.56), and for the 26 (32.1%) patients testing positive for methamphetamine, the mean (SD) number of positive tests was 2.14 (1.06). The MMRM analysis of the MCCB composite score changes over 24 months in patients revealed a significant fixed effect for methamphetamine ($F(1,49)=9.09$; $p=0.004$), but not for cannabis ($F(1,49)=0.287$; $p=0.6$) use. More frequent positive testing for methamphetamine was associated with poorer cognitive performance as determined by post-hoc partial correlation analyses. The results for the secondary MMRM models for the seven MCCB domains are provided in Table 3. We found a significant effect (uncorrected) for methamphetamine use for the domains of Attention and Vigilance, Verbal and Visual Learning and Social Cognition, and no significant effects for cannabis on any of the domains.

In summary, these analyses identified a frequency of positive urine test-related association between methamphetamine use and poorer cognitive performance globally as well as on

several cognitive domains, and no significant associations between cannabis use and cognition.

Table 3: Fixed effects for the number of positive tests for cannabis and methamphetamine, from the MMRM of MCCB Composite and Domain scores over 24 months in patients

MCCB Domain	**Cannabis Frequency of positive urine test**	**Methamphetamine Frequency of positive urine test**
MCCB Composite	F=0.287 p=0.6	F=9.093 p=0.004
Speed of Processing	F=3.722 p=0.06	F=0.583 p=0.4
Attention / Vigilance	F=2.772 p=0.1	F=4.151 p=0.05
Working Memory	F=2.736 p=0.1	F=0.798 p=0.4
Verbal Learning	F=0.047 p=0.8	F=3.939 p=0.05
Visual Learning	F=1.018 p=0.3	F=6.646 p=0.01
Reasoning & Problem Solving	F=0.697 p=0.4	F=0.678 p=0.4
Social Cognition	F=0.0246 p=0.9	F=5.095 p=0.03

2.4. Pre- and post-treatment effects of cannabis and methamphetamine on cognitive performance in the patients

At baseline (n=66), our linear regression model (R^2=0.1.85, F(3,65)=4.691, p=0.005) indicated that neither methamphetamine (ß=-.236, t=-1.591, p=0.117) nor cannabis (ß=-.050, t=-.325,p=0.746) use predicted MCCB composite score, adjusting for education (p=0.002). At endpoint (n=64), our linear regression model (R^2=0.293, F(3,59)=8.148, p<0.001) indicated that frequency of positive urine tests for methamphetamine (ß=-.276, t=-2.049, p=0.045) but not cannabis (ß=0.025, t=0.191, p=0.849) predicted MCCB composite score, adjusting for education (p=0.001).

In summary, a frequency of positive urine test-related association was found in the patients between methamphetamine use, but not cannabis use, and the global cognitive performance at the end of the treatment period.

2.5. Effects of cannabis and methamphetamine use on cognitive performance at baseline in the control group

Additional demographic and substance use characteristics of the control sample are provided in Table 4. At baseline (n=91), our linear regression model (R^2=0.407, F(3,87)=19.89, p<0.001) indicated that methamphetamine (ß=-.187, t=-2.054, p=0.04) but not cannabis (ß=-.013, t=-.140,p=0.889) use predicted MCCB composite score, adjusting for education (p<0.001).

Thus, although we did not have longitudinal urine toxicology testing data in our controls, the finding that methamphetamine use at baseline was associated with a poorer global cognitive performance, suggests that the association is not illness specific.

Table 4. Additional demographic and substance use characteristics of the control sample.

	Cannabis Users n=42	Cannabis Non-Users n=58	p
Age in years, mean (SD)	23.4 (6.16)	27.3 (7.62)	0.004
Sex Males, n (%)	37 (88%)	26 (44.8%)	p<0.001
*Education, mean (SD)	10.24 (1.43)	10.66 (1.57)	0.1
Ethnicity, n (%)			0.2
Mixed Ancestry	32 (76.2%)	45 (77.6%)	
African	5 (11.9%)	11 (19%)	
White	5 (11.9%)	2 (3.4%)	
**Current tobacco use, n (%)	22 (52.4%)	27 (46.6%)	0.03
Methamphetamine Use, n (%)	9 (21.4%)	7 (12%)	0.9
Occasional Alcohol Use, n (%)	32 (76.2%)	38 (65.5%)	0.07

*Education = highest grade of school completed
** Tobacco data available for 64 of the 100 control participants only

2.6. Clinical profile of patients over 24 months of treatment

The PANSS total score MMRM revealed highly significant improvements over time (F=407.5, p<0.001), with a non-significant effect for both cannabis (F=2.313, p=0.1) and methamphetamine frequency of use (F=0.815, p=02), controlling for age (F=7.755, p=0.007), sex (F=1.050, p=0.3), and education (F=3.394, p=0.07).

These findings suggest that the observed associations between methamphetamine use and cognitive performance occurred in the context of good overall clinical response that was not affected by substance-use status.

3. Discussion

As far as we are aware, this is the first study to assess the independent effects of cannabis and methamphetamine use on cognition in patients with schizophrenia spectrum disorders in a longitudinal design. Our main finding was that of a frequency of positive urine test-related (i.e. number of positive tests) negative effect for methamphetamine use, and no significant effect for cannabis use, on cognitive performance over the two-year treatment period in the patient group. The finding that methamphetamine use was associated with poorer cognitive performance in both our control and patient groups suggests that the association is being driven by the substance use and is independent of illness status. Moreover, these findings are similar to what has been found in general population samples of methamphetamine users. A meta-analysis of people with methamphetamine use disorder (not specifically with psychosis) reported moderate cognitive deficits across most cognitive domains compared to healthy controls (Potvin et al., 2018). Our finding is also consistent with reports of cognitive impairments in methamphetamine users with chronic psychosis (Wearne & Cornish 2018). While these findings suggest that methamphetamine use impairs cognitive functioning, both in psychotic and non-psychotic individuals, the possibility of reverse-causation also needs to be considered – i.e. people with poorer cognitive function may be more likely to use methamphetamine. Our secondary analysis suggests that the poorer cognition observed in methamphetamine users extends across several cognitive domains (attention/vigilance,

verbal learning and visual learning), including social cognition. Potvin et al (2018) also reported an association with social cognition in a meta-analysis of subjects with methamphetamine use disorder. The finding has important clinical implications, given that impaired social cognition is a prominent feature of schizophrenia (Javed & Charles, 2018), and is associated with poor functional outcomes (Han & Jun, 2020; Halverson et al., 2019).

There are several possible explanations for our failure to demonstrate a significant association between cannabis use and cognition in our sample. One possibility is that cannabis use is not associated with cognitive impairments, or that our sample was too small to detect subtle differences. Indeed, while recent meta-analyses of healthy population studies suggest that, compared to non-users, regular cannabis-users display poorer cognitive functioning across many cognitive domains, the effect sizes were only small to moderate (Duperrouzel et al., 2020; Scott et al., 2018). Furthermore, a review of longitudinal studies reported that while cannabis use was associated with cognitive decline, the associations were modest, were present only for the heaviest cannabis users, and were not clear-cut after controlling for potential confounding factors (Gonzalez et al., 2017).

There is evidence to suggest that the association between cannabis use and cognition may be different in schizophrenia than it is in healthy individuals. Several studies found that cannabis users with schizophrenia had better cognitive performance than non-users with schizophrenia (Loberg & Hugdahl 2009; Yucel et al., 2010). It has been proposed that the better cognition in cannabis users could reflect a beneficial effect for cannabinoids on the cognitive impairments in schizophrenia (Coulston et al., 2007). Alternatively, this may represent a subset of patients with schizophrenia whose cannabis use was sufficient to precipitate the illness in the absence of other risk factors associated with neurodevelopmental compromise, including cognitive impairments (Loberg & Hugdahl 2009; Yucel et al., 2010). Citing reports of an earlier age of illness onset and fewer neurological soft signs in cannabis users with schizophrenia, it has been suggested that this group may represent an alternative

pathway to psychosis (Loberg & Hugdahl 2009). However, our results do not support this proposal. Rather, our finding of no significant effect on cognition for cannabis use is consistent with the most recent meta-analysis, reporting no differences in cognitive functioning between cannabis users and non-users in first-episode psychosis samples (Sanchez-Gutierrez et al, 2019). While cannabis users had a slightly earlier age of illness onset (21.86⊥4.51) compared to non-users (24.25⊥6.57), the difference was not statistically significant (p=0.07). Also, according to a post-hoc analysis, we did find an association between earlier age of illness onset and cognitive performance in our cannabis using patients (F=27.895; p=0.0001), but in the opposite direction – i.e. a younger age of illness onset was associated with poorer cognitive performance.

Finally, the combined effects of multiple substances on cognition need to be considered. Most cannabis users also use other illicit substances (National Academies of Sciences, 2017), and in our patients 64% of those using cannabis also used methamphetamine. Thus, a positive association between cognition and cannabis use in our sample could have been negated by the negative effect of methamphetamine use.

The cognitive impairments in our patients at baseline improved significantly over the first 6 months of treatment, although there were no subsequent gains after that, and scores remained lower than the controls throughout. While the significant improvements observed in the controls indicate a practice effect (Goldberg et al., 2010), the significant group x time effect indicates treatment-related improvements in the patients over and above the practice effect. To what extent the initial improvement in cognition is secondary to improvements in psychosis, or to a direct cognitive enhancing effect of antipsychotic treatment is not known. There is some evidence to suggest that antipsychotics partially improve cognitive function, although they may also worsen cognition via their adverse metabolic effects (MacKenzie et al., 2018). However,

the cognitive performance in our patients remained stable over time, with no evidence of deterioration over the course of the study.

Several study limitations need to be acknowledged. Firstly, the difficulty in differentiating between substance-induced psychotic disorders and schizophrenia spectrum disorders. While acute substance-induced psychotic disorders are relatively easy to identify on the basis of their transient nature, there is controversy as to whether persistent substance-induced psychotic disorders represent distinct entities, or whether they are primary psychotic disorders precipitated by, or coexisting with, substance use. High rates of transition from a diagnosis of substance-induced psychosis to that of schizophrenia are reported, and this is particularly the case with cannabis and methamphetamine use (Murrie et al., 2020). A detailed discussion on the topic is beyond the scope of this article. For recent reviews of methamphetamine and psychosis see e.g. Wearne & Cornish (2018) and for cannabis and psychosis see e.g. Pearson & Berry (2019). A second study limitation is the modest sample size. This constrained the analyses and limited our ability to detect small effect sizes. This is particularly applicable to our secondary analyses of MCCB cognitive domains, the findings of which should be considered preliminary. Third, although thorough substance use histories were taken as part of the general intake assessments, we did not further quantify cannabis and other illicit substance use frequency, exact frequency of use or type, nor cannabinoid composition of cannabis. Nevertheless, this is one of few studies using repeated urinalysis to provide objective measurement and an estimate of frequency of use of cannabis and methamphetamine during the study. Fourth, baseline cognitive assessments were conducted when the patients were still acutely ill and this may have affected their performance. Fifth, the MCCB scores for participants were low compared with North American norms. This may in part be explained by educational and cultural differences, and although fluency in English or Afrikaans (the dominant language in our study population) was a requirement for inclusion, not all patients were tested in their first language. Sixth, we did not have self-reported substance use data at the time of cognitive assessment to assess their acute intoxication

effects on cognitive performance. However, we do have urine toxicology test results for each of the timepoints for the patient group. Therefore, to address whether a positive test was associated with cognitive performance at the time of assessment we conducted a post-hoc MMRM analysis entering both cannabis and methamphetamine test status at the time of cognitive testing as time-dependent predictors. In this model, we saw no effect for either cannabis (F=0.416; p=0.5) or methamphetamine on the visit-wise composite cognitive performance (F= 0.007; p=0.9). Seventh, a number of patients were inpatients at the time of baseline assessment (n=26) and it is possible that the hospital environment may have influenced our findings, although the mean duration of hospitalization was brief (8.82 weeks). Eighth, attrition was considerable. Lastly, our study sample is representative of the ethnic distribution of our catchment area in the Cape Town metropole and Western Cape province and is not generalizable to the rest of South Africa or other populations. That being said, this study has important strengths. The participants are well-characterised, with regular, repeated assessments over a period of 24 months. Selecting first-episode, minimally treated patients reduced the risk of confounding effects of illness chronicity and previous treatment. Using a single antipsychotic avoided possible differential treatment effects and the long-acting formulation provided assured medication delivery and avoided confounding effects of non-adherence. Also, inclusion of case controls allowed us to compare the cognitive performance in our patients with that of population-matched norms.

4. Conclusion

This study identifies methamphetamine use, but not cannabis use, as a risk factor for cognitive impairments in schizophrenia spectrum disorders. Future studies should aim at further exploring the direction of causality, and better understanding its frequency of positive urine test-dependent effects on cognition by careful assessment of lifetime exposure to methamphetamine in addition to its frequency of use and frequency of positive urine test. Mediating effects of other risk factors should also be investigated. Our findings highlight the

need to build monitoring of illicit substance use into treatment protocols, and suggest that targeting the cessation of methamphetamine use is a priority.

REFERENCES

Allen DN, Strauss GP, Barchard KA, Vertinski M, Carpenter WT, Buchanan RW. (2013). Differences in developmental changes in academic and social premorbid adjustment between males and females with schizophrenia. *Schizophr Res*, 146:132–137. doi: 10.1016/j.schres.2013.01.032

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. (Washington, D.C.).

Aso, E.; Fernández-Dueñas, V.; López-Cano, M.; Taura, J.; Watanabe, M.; Ferrer, I.; Luján, R.; Ciruela, F.Adenosine A2A-Cannabinoid CB1 Receptor Heteromers in the Hippocampus: Cannabidiol BluntsΔ9-Tetrahydrocannabinol-Induced Cognitive Impairment. *Mol. Neurobiol.*2019.

Bogaty, S. E. R., Lee, R. S. C., Hickie, I. B., & Hermens, D. F. (2018). Meta-analysis of neurocognition in young psychosis patients with current cannabis use. *Journal of Psychiatric Research,* 99, 22–32. https://doi.org/10.1016/j.jpsychires.2018.01.010

Buchanan, R.W., Heinrichs, D.W., 1989. The Neurological Evaluation Scale (NES): a structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry Res.* 27, 335–350

Burggren, A. C., Shirazi, A., Ginder, N., & London, E. D. (2019). Cannabis effects on brain structure, function, and cognition: considerations for medical uses of cannabis and its derivatives. *Am J Drug Alcohol Abuse,* 45(6), 563–579. https://doi.org/10.1016/j.physbeh.2017.03.040

Castner, S. A., Vosler, P. S., and Goldman-Rakic, P. S. (2005). Amphetamine sensitization impairs cognition and reduces dopamine turnover in primate prefrontal cortex. *Biol. Psychiatry* 57, 743–751. doi: 10.1016/j.biopsych.2004. 12.019

Chen, E. Y., Hui, C. L., Dunn, E. L., Miao, M. Y, Yeung, W. S, Wong, C. K., Chan, W. F., &Tang, W. N. (2005). A prospective 3-yearlongitudinal study of cognitive predictors of relapse infirst-episode schizophrenic patients.*Schizophrenia Research,* 77,99–104

Chen, C. K., Lin, S. K., Chen, Y. C., Huang, M. C., Chen, T. T., Ree, S. C., & Wang, L. J. (2015). Persistence of psychotic symptoms as an indicator of cognitive impairment in methamphetamine users. *Drug and Alcohol Dependence,* 148, 158-164. doi: https://doi.org/10.1016/j.drugalcdep.2014.12.035

Coulston C. M., Perdices, M., & Tennant, C. C. (2007). The neuropsychological correlates of cannabis use in schizophrenia: Lifetime abuse/dependence, frequency of use, and recency of use. *Schizophrenia Research*, 96, (1–3), Pages 169-184, doi: https://doi.org/10.1016/j.schres.2007.08.006.

Dada, S., Harker Burnhams, N., Erasmus, J., Lucas, W., Parry, C., Pretorius, S., Weimann, R., TB HIV Care, Anova Health Institute, University of Pretoria COSUP, Foundation for Provessional Development, NACOSA, & Tintswalo Home Based Care. (2021).

Monitoring alcohol, tobacco, and other drug use trends in South Africa July 1996 – June 2020 Phase 48. Research Brief, 23(2). Doi: https://www.samrc.ac.za/sites/default/files/attachments/2021-06-15/SACENDU%20Brief_Phase%2048.pdf

D'Souza, D.C., Abi-Saab, W.M., Madonick, S., Forselius-Bielen, K., Doersch, A., Braley, G.,Gueorguieva, R., Cooper, T.B., Krystal, J.H., 2005. Delta-9-tetrahydrocannabinoleffects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol.Psychiatry,* 57, 594–608.

Dickinson, D., Ragland, J. D., Gold, J. M., & Gur, R. C. (2008). General and Specific Cognitive Deficits in Schizophrenia: Goliath Defeats David? *Biological Psychiatry,* 64(9), 823–827. https://doi.org/10.1016/j.biopsych.2008.04.005

Dickonson, D., Zaidman, S. R., Giangrande, E. J., Eisenberg, D. P., Gregory, M. D., & Berman, K. F. (2019). Distinct polygenic score profiles in schizophrenia subgroups with different trajectories of cognitive development. *The American Journal of Psychiatry*. doi: https://doi.org/10.1176/appi.ajp.2019.19050527

Duperrouzel, J. C., Granja, K., Pacheco-Colón, I.,& Gonzalez, R. (2020) Adverse Effects of Cannabis Use on Neurocognitive Functioning: A Systematic Review of Meta- Analytic Studies, *Journal of Dual Diagnosis,* 16(1), 43-57, DOI: 10.1080/15504263.2019.1626030

Fassbender, C., Lesh, T. A., Ursu, S., & Salo, R. (2015). Reaction Time Variability and Related Brain Activity in Methamphetamine Psychosis. *Biological Psychiatry,* 77(5), 465–474. https://doi.org/10.1016/j.biopsych.2014.07.028

First, M.B., Spitzer, R.L.G.M.,Williams, L.B.W., 1994. *Structured Clinical Interview for DSM- IV Axis I Disorders, Patient Edition (SCID-P). 2nd ed.* NewYork State Psychiatric Institute, Biometrics Research, New York.

Goldberg, T. E., Keefe, R. S. E., Goldman, R. S., Robinson, D. G., & Harvey, P. D. (2010). Circumstances under which practice does not make perfect: A review of the practice effect literature in schizophrenia and its relevance to clinical treatment studies. *Neuropsychopharmacology,* 35(5), 1053–1062. https://doi.org/10.1038/npp.2009.211

Gonzalez R, Pacheco-Colón I, Duperrouzel JC, Hawes SW. (2017). Does Cannabis Use Cause Declines in Neuropsychological Functioning? A Review of Longitudinal Studies. J Int *Neuropsychol Soc.* 2017 Oct;23(9-10):893-902. doi: 10.1017/S1355617717000789.

Haddad, P. M., Brain, C., & Scott, J. (2014). *Nonadherence With Antipsychotic Medication*. Dovepress, 43–62.

Halverson, T. F., Orleans-Pobee, M., Merritt, C., Sheeran, P., Fett, A. K., & Penn, D. L. (2019). Pathways to functional outcomes in schizophrenia spectrum disorders: Meta-analysis of social cognitive and neurocognitive predictors. *Neuroscience &Biobehavioral Reviews,* 105, 212-219. Doi: https://doi.org/10.1016/j.neubiorev.2019.07.020

Han, M.& Jun, S.S. Effects of Psychotic Symptoms and Social Cognition on Job Retention in Patients with Schizophrenia in Korea. *Int. J. Environ. Res. Public Health,* 2020, 17, 2628

Hellemann, G., Green, M., Kern, R., Sitarenios, G., & Nuechterlein, K. (2017). Developing an

international scoring system for a consensus-based social cognition measure: MSCEIT-managing emotions. *Psychological Medicine*, 47(14), 2494-2501. doi:10.1017/S0033291717001052

Løberg, E.M., Hugdahl, K., 2009. Cannabis use and cognition in schizophrenia. *Front. Hum. Neurosci.* 3, 1–8. https://doi.org/10.3389/neuro.09.053.2009

Luján, M.Á.; Castro-Zavala, A.; Alegre-Zurano, L.; Valverde, O. Repeated Cannabidiol treatment reducescocaine intake and modulates neural proliferation and CB1R expression in the mouse hippocampus. *Neuropharmacology*, 2018,143, 163–175.

Javed, A., & Charles, A. (2018). The importance of social cognition in improving functional outcomes in schizophrenia. *Frontiers in Psychiatry,* 9(APR), 1–14. https://doi.org/10.3389/fpsyt.2018.00157

MacKenzie, N. E., Kowalchuk, C., Agarwal, S. M., Costa-Dookhan, K. A., Caravaggio, F., Gerretsen, P., … Hahn, M. K. (2018). Antipsychotics, Metabolic Adverse Effects, and Cognitive Function in Schizophrenia. *Frontiers in Psychiatry,* 9(December), 1–12. https://doi.org/10.3389/fpsyt.2018.00622

McCann UD, Kuwabara H, Kumar A, et al. (2008). Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. *Synapse,* 62(2), 91-100. doi:10.1002/syn.20471

McCleery, A., Ventura, J., Kern, R. S., Subotnik, K. L., Gretchen-Doorly, D., Green, M. F., … Nuechterlein, K. H. (2014). Functioning in first-episode schizophrenia: MATRICS Consensus Cognitive Battery (MCCB) profile of impairment. *Schizophrenia Research,* 157(0), 33–39. https://doi.org/10.1016/j.schres.2014.04.039.

Mohamed, S., Rosenheck, R., Swartz, M., Stroup, S., Lieberman, J. A., & Keefe, R. S. E. (2008). Relationship of cognition and psychopathology to functional impairment in schizophrenia. *American Journal of Psychiatry*. https://doi.org/10.1176/appi.ajp.2008.07111713

Muly, E. C., Szigeti, K., and Goldman-Rakic, P. S. (1998). D1 receptor in interneu- rons of macaque prefrontal cortex: distribution and subcellular localization. *J. Neurosci.* 18, 10553–10565.

Murrie, B., Lappin, J., Large, M., & Sara, G. (2020). Transition of Substance-Induced, Brief, and Atypical Psychoses to Schizophrenia: A Systematic Review and Meta-analysis. *Schizophrenia Bulletin,* 46(3), 505–516. https://doi.org/10.1093/schbul/sbz102

Nagai, T., and Yamada, K. (2010). Molecular mechanism for methamphetamine-induced memory impairment. *Nihon ArukoruYakubutsuIgakkaizasshi* 45, 81–91.

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; *Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* Washington (DC): National Academies Press (US); 2017 Jan 12. 14, Cannabis Use and the Abuse of Other Substances.Available from: https://www.ncbi.nlm.nih.gov/books/NBK425760/

Olivier, M. R., Killian, S., Chiliza, B., Asmal, L., Schoeman, R., Oosthuizen, P. P., … Emsley, R. (2015). Cognitive performance during the first year of treatment in first-episode

schizophrenia: A case-control study. *Psychological Medicine,* 45(13), 2873–2883. https://doi.org/10.1017/S0033291715000860

Pearson, N. T., & Berry, J. H. (2019). Cannabis and Psychosis Through the Lens of DSM-5. *International Journal of Environmental Research and Public Health,* 16(4149), 1–14. https://doi.org/10.3390/ijerph16214149

Phahladira, L., Luckhoff, H. K., Asmal, L., Kilian, S., Scheffler, F., du Plessis, S., Chiliza, B., & Emsley, R. (2020). Early recovery in the first 24 months of treatment in first-episode schizophrenia-spectrum disorders. *Npj Schizophrenia*, *6*(1). https://doi.org/10.1038/s41537-019-0091-y

Potvin, S., Pelletier, J., Grot, S., Hébert, C., Barr, A., & Lecomte, T. (2018). Cognitive deficits in individuals with methamphetamine use disorder: A meta-analysis. *Addictive Behaviors,* 80(September 2017), 154–160. https://doi.org/10.1016/j.addbeh.2018.01.021

Rabin, R. A., Zakzanis, K. K., & George, T. P. (2011). The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis. *Schizophrenia Research,* 128(1–3), 111–116. https://doi.org/10.1016/j.schres.2011.02.017

Sánchez-Gutiérrez, T., Fernandez-Castilla, B., Barbeito, S., González-Pinto, A., Becerra-García, J. A., & Calvo, A. (2020). Cannabis use and nonuse in patients with first-episode psychosis: A systematic review and meta-analysis of studies comparing neurocognitive functioning. *European Psychiatry,* 63(1). https://doi.org/10.1192/j.eurpsy.2019.9

Sanders, R.D., Keshavan, M.S., Forman, S.D., Pieri, J.N., McLaughlin, N., Allen, D.N., van Kammen, D.P., Goldstein, G., 2000. Factor structure ofneurologic examination abnormalities in unmedicated schizophrenia. *Psychiatry Res.* 95, 237–243.

Schroder, N., O'Dell, S. J., andMarshall, J. F. (2003). Neurotoxic methamphetamine regimen severely impairs recognition memory in rats. *Synapse* 49, 89–96. doi: 10.1002/syn.10210

Scott, J. C., Slomiak, S. T., Jones, J. D., Rosen, A. F. G., Moore, T. M., & Gur, R. C. (2018). Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults A Systematic Review and Meta-analysis. *JAMA Psychiatry,* 75(6), 585–595. https://doi.org/10.1001/jamapsychiatry.2018.0335

Setién-Suero, E., Neergaard, K., Ramírez-Bonilla, M., Correa-Ghisays, P., Fañanás, L., Crespo-Facorro, B., & Ayesa-Arriola, R. (2017). Cannabis use in male and female first episode of non-affective psychosis patients: Long-term clinical, neuropsychological and functional differences. *PLoS ONE,* 12(8), 1–17. https://doi.org/10.1371/journal.pone.0183613

Silber, B. Y., Croft, R. J., Papafotiou, K., and Stough, C. (2006). The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology* 187, 154–169. doi: 10.1007/s00213-006-0410-7

Silberstein, J., & Harvey, P. D. (2019). Cognition, social cognition, and Self-assessment in schizophrenia: Prediction of different elements of everyday functional outcomes. *CNS Spectrums,* 24(1), 88–93. https://doi.org/10.1017/S1092852918001414

Solowij, N.; Broyd, S.J.; Beale, C.; Prick, J.A.; Greenwood, L.; van Hell, H. Therapeutic effects of prolongedcannabidiol treatment on psychological symptoms and cognitive

function in regular cannabis users:A pragmatic open-label clinical trial. *Cannabis Cannabinoid Res*., 2018(3) 21–34

Yücel, M., Bora, E., Lubman, D. I., Solowij, N., Brewer, W. J., Cotton, S. M., … Pantelis, C. (2012). The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophrenia Bulletin,* 38(2), 316–330. https://doi.org/10.1093/schbul/sbq079

Zhu X, Fan H, Fan F, et al. Improving social functioning in community-dwelling patients with schizophrenia: a randomized controlled computer cognitive remediation therapy trial with six months follow-up. *Psychiatry Res.*, 2020;287:112913. doi:10.1016/j.psychres.2020.112913

Zizolfi, D., Poloni, N., Caselli, I., Ielmini, M., Lucca, G., Diurni, M., … Callegari, C. (2019). Resilience and recovery style: A retrospective study on associations among personal resources, symptoms, neurocognition, quality of life and psychosocial functioning in psychotic patients. *Psychology Research and Behavior Management,* 12, 385–395. https://doi.org/10.2147/prbm.s205424

CHAPTER IV

CANNABIS USE AND HIPPOCAMPAL SUBFIELD VOLUMES IN MALES WITH A FIRST EPISODE OF A SCHIZOPHRENIA SPECTRUM DISORDER AND HEALTHY CONTROLS

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Cannabis use and hippocampal subfield volumes in males with a first episode of a schizophrenia spectrum disorder and healthy controls

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ABSTRACT

Background: Both schizophrenia and cannabis use are associated with structural brain changes. The hippocampus is a region of particular interest due to its role in memory and select cognitive functions, impairment of which is a core feature of schizophrenia and has also been observed in substance abuse. This study aimed to explore the effects of recent/current cannabis use on hippocampal subfield volumes in male patients with first-episode schizophrenia spectrum disorders and matched controls.

Methods: This cross-sectional, case-control study included 63 patients and 58 controls scanned on 3T MRI scanners, with hippocampal segmentation performed using recently validated Freesurfer v6.0 software. Cannabis use status was determined by self and carer report together with urine toxicology screening, and patients were categorised as recent/current users or non-users. We used multivariate analysis of covariance (MANCOVA) with age, scan sequence, scan quality, and total intracranial volume as covariates, with subsequent analysis of variance (ANOVA) to test the effects of diagnosis and cannabis use status on individual hippocampal subfields.

Results: We found a group (patient/control) by cannabis use interaction effect in the subiculum, with decreased volumes observed in the cannabis non-using patients compared to the cannabis using patients, and decreased volumes in the cannabis using controls compared to the cannabis non-using controls.

Conclusion: The increased subiculum volume in cannabis using patients compared to cannabis non-using patients raises important questions regarding the pathophysiology of schizophrenia and the role of cannabis use therein.

1. Introduction

The high prevalence of cannabis use among schizophrenia spectrum disorder patients is well-documented (Malchow et al., 2013a), particularly among males (van Dijk et al., 2012). In patients with schizophrenia, cannabis use is associated with earlier disease onset (Donoghue et al., 2014; Novick et al., 2016), greater severity of psychopathology (Abdel-Baki et al., 2017), and poorer treatment outcomes (Crocker and Tibbo, 2018). Importantly, cannabis use in the general population (Schlaepfer et al., 2006) as well as in schizophrenia (van Haren et al., 2013) is associated with brain structural differences. However, the influence of cannabis use on brain structure in schizophrenia remains unclear. While some studies have reported that grey matter volume reductions are more pronounced in patients with schizophrenia who use cannabis (Rais et al., 2008), others have reported larger volumes of certain subcortical regions including the putamen (Koenders et al., 2015) in cannabis users compared to their non-using counterparts. In contrast, others still have failed to find an association between cannabis use and subcortical brain volumes in either schizophrenia (James et al., 2011; Wobrock et al., 2009) or otherwise healthy controls (Gillespie et al., 2018).

A region of particular interest when considering the effects of cannabis use on the brain in schizophrenia is the hippocampus. This structure plays an integral part in cognitive functioning including working memory, known to be affected in both schizophrenia (Osborne et al., 2017; Ott Vintergaard et al., 2019) and cannabis use disorder (Kutlu and Gould, 2016). Indeed, the hippocampus is rich in cannabinoid receptors (Hill et al., 2009), and exogenous intake of tetrahydrocannabinol (THC) and cannabidiol (CBD) is known to affect functioning of the endocannabinoid system (Bhattacharyya et al., 2009; Aguilar et al., 2016). Post-mortem studies further support the involvement of cannabinoid receptor density in the hippocampus as a determinant of morphological differences evident between users and non-users (Villares, 2007; Szűcs et al., 2016). Importantly, both schizophrenia (Wobrock et al., 2009; Malchow et al., 2013b; Arnold et al., 2014; Ho et al., 2017; Brambilla et al., 2018; Haukvik et al., 2018) and cannabis use in the general population (Demirakca et al., 2011; Pagliaccio et al., 2015; Yücel et al., 2015; Koenders et al., 2016; Lorenzetti et al., 2018; Gilman et al., 2018) have been associated with hippocampal volume reductions, although some studies have failed to replicate these findings

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(Jager et al., 2007; Welch et al., 2011; Cousijn et al., 2012; Koenders et al., 2017). In patients with schizophrenia, the effects of cannabis use on hippocampus structure are less clear-cut, with some studies reporting larger (Kumra et al., 2012), others smaller (Bangalore et al., 2008; Solowij et al., 2013), and others still no difference (Wobrock et al., 2009; James et al., 2011) in volumes between patients who use cannabis and their non-using counterparts. Therefore, the interrelationships between schizophrenia, cannabis use and hippocampus structure remain incompletely understood and warrant further inquiry.

Inconsistencies in existing findings may be ascribed to failure to consider important confounders, including illness severity, chronicity, and medication use, when exploring the influence of cannabis use on hippocampal volumes in schizophrenia patients (Haukvik et al., 2018). Importantly, discrepancies in the literature may also be ascribed to cannabis exerting a detrimental effect on specific hippocampal subfields, rather than the structure as a whole. Indeed, several prior studies have shown that cannabis use in the general population is associated with volumetric changes in certain hippocampal subfields, for example in the CA1, 3, and 4 as well as the molecular layer and the granular cell layers of the dentate gyrus (Li et al., 2018), the subicular complex (Beale et al., 2018), and the fimbria (Mandelbaum and de la Monte, 2016) but not others. There is therefore a need to explore the effects of cannabis use on specific hippocampal subfield volumes, in both patients with schizophrenia and healthy controls. In particular, the use of a first-episode sample would be considered advantageous, as this would exclude confounding effects of illness chronicity and long-term antipsychotic medication, which could have affected results in prior studies.

In response to this knowledge gap, the aim of the present cross-sectional study was to investigate the association between cannabis use and hippocampal subfield volumes in minimally treated male patients with a first episode of a schizophrenia spectrum disorder (FES) and matched healthy controls. This study furthermore addresses some of the previously reported confounds by excluding polysubstance users as well as accounting for additional medication use effects. Firstly, we hypothesised that, compared to healthy controls, FES patients would have smaller hippocampal volumes. Secondly, we hypothesised that, in both patients and controls, cannabis users would have smaller hippocampal subfield volumes than non-users.

2. Materials and methods

2.1. Study design and ethical approval

This is a single-site, cross-sectional, case-control study. Ethics approval was obtained from the Human Research Ethics Committee (HREC) of Stellenbosch University (SU) Faculty of Medicine and Health Sciences (S17/03/047).

2.2. Selection of study participants

Participants were recruited to our Schizophrenia Research Unit between 2007 and 2017 from first-admissions to psychiatric hospitals and community clinics within our catchment areas in Cape Town. Patients and/or their legal guardians provided written, informed consent. Eligible participants were in- or outpatients, aged 16 to 45 years, meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) (First et al., 1994) criteria for a schizophrenia spectrum disorder, including schizophreniform disorder, schizophrenia or schizoaffective disorder. Patients were excluded if they had, during their lifetime, been exposed to >4 weeks of antipsychotic medication, been treated with a long-acting injectable antipsychotic, had a serious or unstable medical condition, intellectual disability, or substance-induced psychosis. Medication for general medical conditions, lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms and propranolol for akathisia were permitted concomitant medications. In the 12 h prior to assessment, no benzodiazepines, propranolol or anticholinergics were permitted. Oher antipsychotics, mood stabilizers and psychostimulants were not permitted.

For this study, we selected males only due to the low rate of substance use among the females in our sample. The healthy control group consisted of neighbourhood contacts of the families of patients recruited by means of advertisements that were placed in community centres in the same catchment area as described above. Controls were excluded if they had a first-degree relative with a psychotic disorder or if they had a DSM-IV axis I or II disorder as determined by the SCID-Non-Patient Edition interviews. Controls were matched for age, ethnicity, and level of education. Furthermore, each participant was carefully screened with a thorough physical examination and review of history, ECG, urine toxicology screen and structured assessment of symptoms to verify that inclusion criteria were met.

2.3. Clinical assessments

Diagnosis was assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDSS) (Addington and Addington, 1993). We also used the Clinical Global Impression (CGI) scale for severity of illness (Guy, 1976), and the Social and Occupational Functioning Assessment Scale (SOFAS) (American Psychiatric Association, 1994) to asses overall functionality.

Registered psychiatrists undertook diagnostic and clinical assessments, and inter-rater reliability testing was conducted periodically for the PANSS (intraclass correlation 0.7 or higher). Duration of untreated psychosis (DUP) was estimated from the onset of continuous positive psychotic symptoms to initiation of adequate treatment, defined as the start of structured treatment with antipsychotic medication.

2.4. Cannabis use assessments

Substance use was determined by patient and carer report and urine toxicology screening for the most commonly used substances in our population, i.e. cannabis, methamphetamine, benzodiazepines, and methaqualone. We excluded participants who tested positive for any of the substances other than cannabis, as this may have confounded the results. Participants were classified as cannabis users on the basis of either self-report of use in the past three months or positive urine toxicology screening at baseline, or at any subsequent toxicology screening during follow up treatment. Those who reported no use in the three months prior to the study and tested negative for cannabis with toxicology screening were classified as cannabis non-users, even if they had a lifetime history of cannabis use.

2.5. MRI acquisition

T1-weighted high-resolution data was acquired for 52 patients and 47 controls on a research-dedicated 3T Siemens Allegra MRI brain scanner (Erlangen, Germany) at the Combined Universities Brain Imaging Centre (CUBIC) with a MPRAGE sequence (2080 ms repetition time; 4.88 ms echo time, Field of view: 230 mm, 176 slices, 0.9 mm × 0.9 mm × 1 mm voxel size). An additional 11 patients and 8 controls were scanned on the same scanner using an updated T1 ME-MPRAGE weighted structural sequence (TR = 2530 ms; TE1 = 1.53 ms TE2 = 3.21, ms, TE3 = 4.89 ms, TE4 = 6.57 ms, flip-angle: 7 degrees,FoV: 256 mm, 128 slices, 1 isotropic voxel size). A further 11 patients and 13 controls were scanned with a 3T Siemens Skyra full-body scanner (Erlangen, Germany) using a T1 ME-MPRAGE weighted structural sequence (TR = 2530 ms; TE1 = 1.63 ms TE2 = 3.47 ms, TE3 = 5.31 ms, TE4 = 7.15 ms, flip-angle: 7 degrees, FoV: 280 mm, 128 slices, 1 isotropic voxel size). All scans were

screened for intracranial pathology by a radiologist and inspected for motion artefacts and overall quality by trained research assistants.

2.6. MRI processing

Scans were processed and analysed using FreeSurfer stable release version 6.0. (http://surfer.nmr.mgh.harvard.edu/) which has been reported to be reliable across scanners from the same manufacturer (Han et al., 2006). Details of these procedures have been previously described (Dale et al., 1999). Briefly, slices were resampled to a three- dimensional image with 1 mm isotropic voxels followed by non-uniform intensity normalisation. Images were registered to the Montreal Neurological Institute (MNI) space. A second normalisation step was performed with a different algorithm in which control points were automatically identified and normalised to a standard intensity value. Next, an automated skull-strip procedure was performed. Global brain anatomy was then delineated into cortical and subcortical labels. Reconstructions were performed with custom batching scripts, on the Centre for High Performance Computing, Rosebank, Cape Town, Sun Intel Lengau cluster (http://www.chpc.ac.za/). All data were visually inspected for errors in Talairach transformation, skull-stripping, final segmentations, as well as the within-subject registrations. Detailed quality assessment was conducted according to the ENIGMA consortium QC protocol (www.enigma.ini.usc.edu), which consisted of visual inspections of the cortical and subcortical segmentation sets for each individual. Any errors in processing were corrected manually and re-inspected. Scans that did not meet the threshold for reasonable quality or could not be processed successfully were excluded from all analyses. Furthermore, we checked for systematic differences over time in scan image quality by correlating our quality assessment scores with scan age (i.e. current date minus date of MRI scan) which was non-significant ($p = 0.617$), suggesting that time does not correlate with image quality in our dataset. Of the 171 male participants who underwent MRI scanning, 50 were excluded due to poor scan quality, intracranial pathology, excessive motion artefacts, or missing data. The final sample ($n = 121$) consisted of 63 patients and 58 controls.

FreeSurfer processing generated subfield volume variables (see for e.g. Iglesias et al., 2015) which were imported into SPSS version 26 (SPSS Inc.) for statistical analyses. All hippocampal subfield volume measures were inspected for deviations from normality assumption. A scan quality metric (acceptable or good, as a categorical variable) was included in the main model to account for the variation in scan quality over the period of acquisition. We therefore included a total of 24 hippocampal subfields as dependent variables with age, estimated total intracranial volume, scan quality, and scanner sequence included as covariates.

2.7. Statistical analysis

The characteristics of the patient and control groups, as well as cannabis using and non-using patients, were compared using independent samples Mann-Whitney U nonparametric tests and independent samples *t*-test for non-normally and normally distributed continuous variables respectively. As the subfield volumes are highly correlated, we used multivariate analysis of covariance (MANCOVA) with age, scan sequence, scan quality, and estimated total intracranial volume as covariates to investigate a potential interaction effect between diagnosis and cannabis use. Following a significant interaction effect, post hoc analysis of variance (ANOVA) would be utilised to examine the effects of diagnosis and cannabis use status on individual hippocampal subfields. We used Bonferroni correction for multiple comparisons with an adjusted significance level of $p < 0.006$ in the post hoc analyses. Lastly, partial correlational analyses were used to explore the relationship between cannabis use and non-use, differences in hippocampal subfield volumes, and select clinical parameters in the total group of patients.

3. Results

3.1. Characteristics of study sample

There were no significant differences between patients and controls regarding age, education, ethnicity and urine cannabis test status (Table 1). Patients and controls also did not differ in terms of current tobacco use, BMI (as a proxy for nutritional status) alcohol use, or age when first used cannabis. However, a significantly higher proportion of cannabis using patients used cannabis daily, compared to control cannabis users ($p = 0.002$). The clinical characteristics of cannabis using compared to non-using patients are presented in Table 2. Cannabis using patients were significantly younger ($p = 0.005$) and scored significantly lower on the SOFAS ($p = 0.03$) compared to non-using patients. For the patients who had received antipsychotics prior to study entry, there were no differences for cannabis users and non-users respectively, in the number of days on antipsychotic medication (6.2 ± 8.5 days vs. 4.2 ± 7.6 days) nor in total dose of antipsychotic medication (1152.5 ± 1030.7 mg vs. 1642.7 ± 1617.1 mg Chlorpromazine equivalence).

3.2. Effects of cannabis use and diagnosis on hippocampal subfield volumes

MANCOVA revealed a significant interaction between group (patient/control) and cannabis use ($F(24,90) = 2.301$, $p = 0.003$) adjusting for age ($F = 0.628$, $p = 0.9$), scanner sequence ($F = 6.081$, $p < 0.001$), scan quality ($F = 1.104$, $p = 0.4$), and estimated total intracranial volume ($F = 5.608$, $p < 0.001$) as covariates. Post hoc ANOVA analyses are provided in Table 3 and revealed a significant group by cannabis use interaction for the left and right subiculum, of which only the left subiculum survived Bonferroni correction for multiple comparisons at $p = 0.002$ based on 24 comparisons. Fig. 1 illustrates the interaction effect wherein cannabis non-using patients had decreased subiculum volumes compared to cannabis using patients, while cannabis using controls had decreased subiculum volumes compared to cannabis non-using controls. Fig. 2 illustrates the volume comparisons for all of

Table 1
Demographic characteristics of study sample.

	Patients n = 63	Controls n = 58	p
Age in years, mean (SD)	24.6 (6.7)	24.03 (7.1)	0.7
Education, mean (SD)[a]	9.9 (2.09)	10.31 (1.6)	0.5
BMI, mean (SD)	21.8 (3.67)	22.8 (4.9)	0.5
Tobacco current, n (%)	29 (46%)	27 (46.6%)	0.9
Alcohol use, n (%)	36 (57%)	47 (81%)	0.1
Alcohol use occasional	29 (46%)	44 (69.8%)	
Alcohol dependence	1 (1.6%)	0	
Alcohol abuse	6 (9.5%)	3 (5.2%)	
Ethnicity, n (%)			0.5
Mixed ancestry	47 (74.6%)	45 (77.6%)	
African	11 (17.5%)	7 (12.1%)	
White	4 (6.4%)	6 (10.3)	
Asian	1 (1.6%)		
Recent/current cannabis use, n (%)	18 (28.6%)	16 (27.6%)	0.9
Lifetime history of cannabis use, n (%)	37 (58.8%)	29 (50%)	0.3
Age when first used cannabis, mean (SD)	15.8 (2.8)	17.4 (2.96)	0.6
Frequency of most use, n (%)[b]			0.002
Daily use	23 (36.5%)	6 (10.3%)	
4/week	1 (1.6%)	0	
3/week	2 (3.2%)	1 (1.7%)	
Weekly	2 (3.2%)	1 (1.7%)	
2-Weekly	0	1 (1.7%)	
Occasional	1 (1.6%)	9 (15.5%)	
Once	1 (1.6%)	5 (8.6%)	
Reported no use but tested positive, n (%)	7 (11.1%)	6 (10.3%)	

[a] Education = highest grade of school completed.
[b] Frequency reported for the time when cannabis was used actively, or frequency at time of most use.

Table 2
Comparison of clinical characteristics between cannabis using and non-using patients with schizophrenia spectrum disorders.

	Cannabis using n = 18	Cannabis non-using n = 45	p
Age in years, mean(SD)	21.2 (4.03)	25.9 (7.1)	0.002
Diagnosis, n(%)			0.1
Schizophrenia, n(%)	12 (19%)	38 (60%)	
Schizophreniform, n(%)	6 (10%)	7 (11%)	
DUP weeks, mean(SD)	52.03 (79.1)	39.87 (44.02)	0.09
Treatment naïve, n(%)	9 (50%)	30 (66.6%)	0.2
Total days of AP use, mean(SD)	6.2 (8.5)	4.2 (7.6)	0.4
Total dose of AP in mg, mean(SD)[a]	1152.5 (1030.8)	1642.7 (1617.1)	0.4
PANSS Total, mean(SD)	90.6 (16.99)	89.7 (17.6)	0.9
PANSS Positive Total, mean(SD)	22.7 (4.6)	23.8 (5.1)	0.4
PANSS Negative Total, mean(SD)	27.3 (5.7)	23.8 (7.3)	0.08
PANSS General Total, mean(SD)	40.6 (10.3)	42.09 (8.7)	0.6
CGI Severity of Illness, mean(SD)	4.8 (0.9)	4.7 (0.8)	0.7
SOFAS, mean(SD)	41.1 (9.95)	48.04 (11.4)	0.03
CDSS, mean(SD)	2.6 (2.97)	2.4 (2.8)	0.8

[a] Chlorpromazine equivalent dose; DUP = duration of untreated psychosis in weeks; AP = antipsychotic medication; PANSS = Positive and Negative Syndrome Scale; CGI = Clinical Global Impressions; SOFAS = Social and Occupational Functioning Assessment Scale; CDSS = Calgary Depression Scale for Schizophrenia.

the subfields between patient and control cannabis users and non-users. Although we also found a significant diagnosis by cannabis use effect in other subfields, these did not survive Bonferroni correction.

Additionally, we conducted a partial correlation analysis to assess the effect of frequency of cannabis use on hippocampal subfield volumes in the total group of 121 participants. We found that frequency of cannabis use correlated positively with left CA 3 ($r = 0.282$, $p = 0.043$) when controlling for group (patient versus control) but not with any of the other subfield volumes.

To further explore the relationships between hippocampal subfield volumes and cannabis use, we conducted partial correlational analyses in the total patient group (n = 63) for the hippocampal subfields and the PANSS Total score, Positive, Negative, and General subscale scores as well as the SOFAS and CDSS scores, controlling for age and cannabis use (Table 4). There were significant negative correlations between both the left ($r^2 = -0.262$; $p = 0.043$) and right ($r^2 = -0.280$; $p = 0.030$) subiculum and the PANSS Negative subscale. In addition, there were significant correlations between the PANSS Negative subscale and the right ($r^2 = -0.287$; $p = 0.026$) presubiculum, the left ($r^2 = -0.256$; $p = 0.048$) and right ($r^2 = -0.261$; $p = 0.044$) HATA, left ($r^2 = 0.260$; $p = 0.045$) fissure, right ($r^2 = -0.264$; $p = 0.042$) GCMLDG, and right ($r^2 = -0.272$; $p = 0.036$) molecular layer. The left ($r^2 = 0.263$; $p = 0.042$) CA 3 and right ($r^2 = -0.369$; $p = 0.004$) fimbria correlated with the PANSS General subscale, whereas the right ($r^2 = -0.285$; $p = 0.027$) parasubiculum, right ($r^2 = -0.284$; $p = 0.028$) HATA, and left ($r^2 = -0.368$; $p = 0.004$) fissure correlated with the SOFAS.

Lastly, in order to determine whether our findings were specific to the hippocampal structures, or whether they were part of a more generalised whole brain effect, we conducted an ANOVA with total grey matter volume, adjusting for age, scanner sequence, and total intracranial volume. A significant group (patient/control) by cannabis use interaction effect was indeed observed ($F(1,97) = 4.208$, $p = 0.04$). We also ran an ANOVA with subcortical volume, adjusting for age, scanner sequence, and total intracranial volume, and again found a significant interaction effect for group by cannabis use ($F(1, 97) = 4.105$, $p = 0.05$) neither of which survived correction for multiple comparisons.

4. Discussion

In this study, we examined the effect of cannabis use on hippocampal subfield volumes in male patients with a first episode of a schizophrenia spectrum disorder and matched healthy controls. Most importantly, we found that cannabis use has differential effects on hippocampal subfield volumes in patients with schizophrenia spectrum disorder versus healthy controls. More specifically, our post hoc analyses indicated that this interaction was observable in a number of subfields, namely the left CA 4, left and right presubiculum, left parasubiculum, right fimbria, left and right HATA, left GCMLDG, and the left and right molecular layer, although our strongest finding was in the subiculum, which remained significant after Bonferroni correction. We also found some suggestion of a dose effect for cannabis frequency of use on hippocampal volumes, although this was not

Table 3
Comparison of hippocampal subfield volumes between cannabis using and non-using patients and controls.

Subfield	SZ using	SZ non-using	HC using	HC non-using	F	η^2	p[a]
Left subiculum	436.545778 (47.6018429)	412.902778 (44.3141132)	396.356375 (42.0099841)	446.928595 (48.7024037)	14.596	0.114	p < 0.001
Right subiculum	434.231278 (45.7217642)	413.349756 (47.6796896)	405.391312 (49.7404226)	446.916071 (51.8874138)	9.204	0.075	0.003
Left CA 1	616.200056 (77.6242830)	612.283244 (77.5874863)	618.759625 (61.3585841)	647.020143 (74.3533835)	0.435	0.004	0.511
Right CA 1	646.720444 (68.1199121)	642.995844 (83.5532046)	622.024938 (63.1960528)	675.111548 (77.7045902)	2.208	0.019	0.140
Left CA 3	208.749889 (35.2483436)	204.489578 (26.9421217)	204.022875 (22.2787964)	218.091690 (27.6810956)	1.575	0.014	0.212
Right CA 3	236.632722 (44.3641146)	228.167756 (31.6244740)	218.118562 (27.9985800)	233.395810 (32.4850603)	2.441	0.021	0.121
Left CA 4	252.550667 (35.1986060)	248.023644 (25.1149022)	238.389750 (24.1733097)	261.018643 (25.7502191)	5.015	0.042	0.027
Right CA 4	271.692111 (46.3104370)	263.389667 (30.0168702)	252.179312 (30.9220844)	272.082976 (33.1679917)	3.721	0.032	0.056
Left presubiculum	302.829000 (40.0552327)	283.352756 (39.0262062)	287.505188 (31.5793864)	310.327500 (36.0466502)	6.142	0.052	0.015
Right presubiculum	293.745833 (31.1752965)	272.821956 (35.3990386)	284.765000 (34.9224284)	302.216762 (38.5385566)	6.343	0.053	0.013
Left parasubiculum	61.593672 (9.1178731)	54.436676 (10.3561038)	58.653719 (10.6541189)	62.020995 (9.6745701)	4.579	0.039	0.035
Right parasubiculum	61.128133 (8.9229681)	55.564429 (9.0331270)	56.843888 (10.1267424)	60.621343 (11.0551164)	3.526	0.030	0.063
Left fimbria	87.244883 (17.6646356)	80.082849 (19.9419939)	73.500219 (21.4474416)	84.114376 (18.1743360)	3.827	0.033	0.053
Right fimbria	77.314900 (16.4630466)	75.774707 (20.6736335)	61.780275 (14.7587192)	83.253817 (22.2147334)	7.401	0.061	0.008
Left HATA	64.261400 (9.6778744)	59.818811 (9.6298836)	60.792550 (6.8876663)	64.813762 (8.6882474)	4.199	0.036	0.043
Right HATA	67.836500 (11.2605704)	63.259136 (9.4260503)	60.104319 (7.5394879)	68.079807 (10.8540152)	8.523	0.070	0.004
Left hippocampal tail	534.582000 (61.4170255)	520.497089 (80.1219420)	515.111937 (48.3351332)	548.834476 (65.6124377)	2.209	0.019	0.140
Right hippocampal tail	567.404556 (82.9536099)	551.444778 (70.9722666)	574.955000 (67.8245803)	597.144357 (78.7446187)	1.476	0.013	0.227
Left fissure	151.439722 (23.8953600)	154.012469 (34.0036234)	166.819456 (39.5665273)	157.178779 (28.3498300)	1.528	0.013	0.219
Right fissure	154.145889 (22.8399615)	150.334111 (26.9540951)	152.568513 (31.9619591)	155.891269 (34.4450055)	0.351	0.003	0.555
Left GCMLDG	295.557833 (37.0224386)	288.947089 (29.5136216)	279.583188 (29.4153608)	305.559071 (29.0331410)	6.149	0.052	0.015
Right GCMLDG	312.906167 (49.1042510)	305.137267 (34.1233007)	293.648438 (33.5692568)	315.898310 (38.0599147)	3.376	0.029	0.069
Left molecular layer HP	558.049889 (56.4043035)	547.987489 (59.0711071)	543.607625 (49.0224496)	587.969214 (54.9829523)	4.513	0.038	0.036
Right molecular layer HP	581.721278 (62.8092840)	568.991378 (65.1304574)	555.073938 (54.4289854)	602.266952 (61.0582581)	4.836	0.041	0.030

HATA = hippocampal-amygdaloid transition area.
GCMLDG = granule cell layer of the dentate gyrus.
[a] Values not corrected for multiple comparisons.

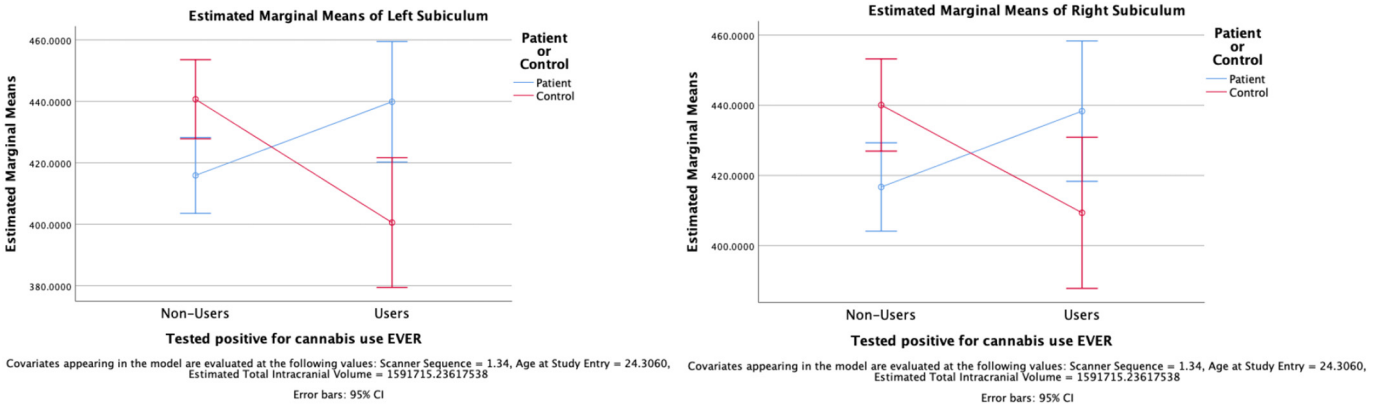

Fig. 1. The cannabis use by diagnosis interaction effect in the left and right subiculum.

significant at the corrected alpha level. The similar pattern that we observed for total grey matter volumes and subcortical grey matter volumes was not significant at adjusted levels, suggesting that cannabis has more pronounced effects on the hippocampus than other brain areas. This may have important clinical implications for patients with schizophrenia and related disorders. The significant correlations that we found between the hippocampal volumes and the PANSS subscale scores are in accordance with previous reports (Kühn et al., 2012; Brambilla et al., 2018; Mamah et al., 2016), particularly with the PANSS negative subscale (Kawano et al., 2015). This suggests that cannabis use may be associated with more severe psychopathology in schizophrenia, and that its effects on hippocampal structures may mediate this.

Our results in the cannabis non-using patients are consistent with previous studies reporting reduced hippocampal volumes in schizophrenia and other psychotic disorders compared with controls (Wobrock et al., 2009; Malchow et al., 2013b; Arnold et al., 2014; Brambilla et al., 2018). Moreover, the reduced subiculum volumes in cannabis using compared to cannabis non-using controls are also consistent with previous findings in general population samples with and without cannabis use (Demirakca et al., 2011; Pagliaccio et al., 2015; Yücel et al., 2015; Koenders et al., 2016; Gilman et al., 2018; Lorenzetti et al., 2018). However, our finding of increased subiculum volumes in cannabis using patients compared to cannabis non-using patients was somewhat unexpected, given the previously reported finding of greater grey matter volume reductions and ventricular enlargements in schizophrenia patients who use cannabis compared to non-users (Rais et al., 2008). On the other hand, our findings of increased subiculum volumes in cannabis using patients are consistent with previous reports of increases in other subcortical structure volumes such as the putamen in patients with schizophrenia who use cannabis compared to non-users (Koenders et al., 2015).

While it is difficult to relate structural imaging measures to underlying cellular and molecular events, the increased volumes may reflect structural plasticity which could involve remodelling of neuronal processes rather than neurogenesis, or a potentially compensatory increase in the number of non-neuronal cells (Zatorre et al., 2013). The larger subiculum volumes in cannabis using patients could reflect exacerbation of underlying hippocampal dysfunction in schizophrenia. One possible mechanism is that of inflammation. There is accumulating evidence that neuroinflammation plays a role in schizophrenia (Kahn and Sommer, 2014), particularly in the acute phase of the illness (Pasternak et al., 2016). Hippocampal subfields are differentially affected by pro-inflammatory factors (Raz et al., 2015). Cannabis use may aggravate this inflammatory response. Cannabis use has differential effects on inflammation, depending on the relative concentration of its two main compounds. THC has pro-inflammatory effects, while CBD has anti-inflammatory effects (Radhakrishnan et al., 2017). Therefore, neuroinflammation could explain increased volumes in the early stage of the illness, as this is associated with increased local blood

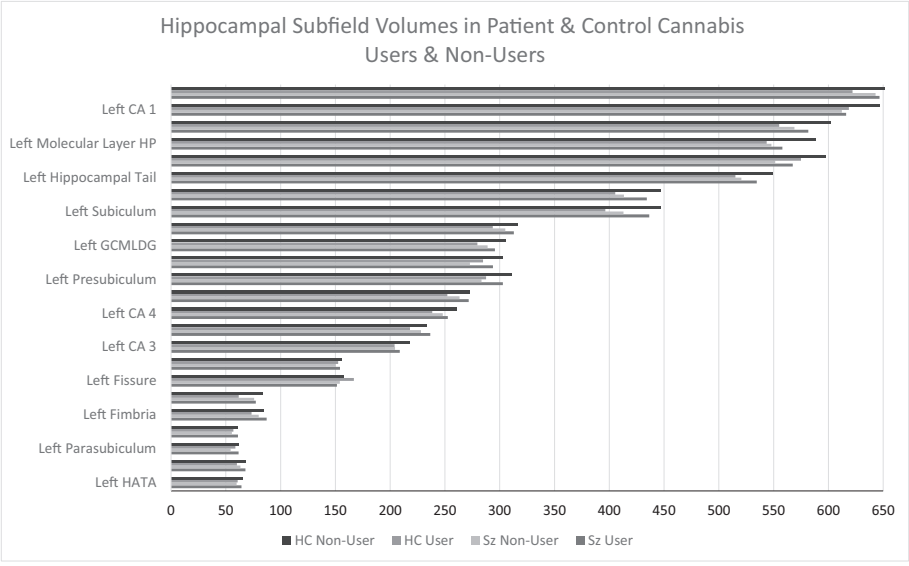

Fig. 2. Hippocampal subfield volumes in patient and control cannabis users and non-users.

Table 4
Partial correlations between clinical parameters and hippocampal subfield volumes in the total patient group.

Subfield[a]	PANSS Positive	PANSS Negative	PANSS General	CGI Severity	SOFAS	CDSS
LH subiculum	$r^2 = -0.212$; $p = 0.105$	$r^2 = -0.262$; $p = \mathbf{0.043}^{**}$	$r^2 = -0.036$; $p = 0.785$	$r^2 = -0.163$; $p = 0.214$	$r^2 = -0.022$; $p = 0.870$	$r^2 = 0.090$; $p = 0.496$
RH subiculum	$r^2 = -0.221$; $p = 0.090$	$r^2 = -0.280$; $p = \mathbf{0.030}^{**}$	$r^2 = 0.043$; $p = 0.745$	$r^2 = -0.175$; $p = 0.181$	$r^2 = -0.069$; $p = 0.601$	$r^2 = 0.101$; $p = 0.442$
LH CA 1	$r^2 = 0.008$; $p = 0.951$	$r^2 = -0.173$; $p = 0.187$	$r^2 = 0.121$; $p = 0.356$	$r^2 = -0.036$; $p = 0.784$	$r^2 = -0.179$; $p = 0.170$	$r^2 = -0.005$; $p = 0.969$
RH CA 1	$r^2 = -0.128$; $p = 0.329$	$r^2 = -0.183$; $p = 0.162$	$r^2 = 0.047$; $p = 0.724$	$r^2 = -0.081$; $p = 0.539$	$r^2 = -0.122$; $p = 0.353$	$r^2 = 0.043$; $p = 0.741$
LH CA 3	$r^2 = -0.039$; $p = 0.765$	$r^2 = -0.033$; $p = 0.802$	$r^2 = 0.263$; $p = \mathbf{0.042}^{**}$	$r^2 = -0.103$; $p = 0.433$	$r^2 = -0.039$; $p = 0.765$	$r^2 = 0.035$; $p = 0.792$
RH CA 3	$r^2 = -0.074$; $p = 0.572$	$r^2 = -0.187$; $p = 0.152$	$r^2 = 0.213$; $p = 0.102$	$r^2 = -0.141$; $p = 0.282$	$r^2 = -0.054$; $p = 0.684$	$r^2 = 0.145$; $p = 0.268$
LH CA 4	$r^2 = -0.038$; $p = 0.775$	$r^2 = -0.131$; $p = 0.317$	$r^2 = 0.154$; $p = 0.241$	$r^2 = -0.130$; $p = 0.321$	$r^2 = -0.030$; $p = 0.819$	$r^2 = 0.033$; $p = 0.802$
RH CA 4	$r^2 = -0.084$; $p = 0.525$	$r^2 = -0.223$; $p = 0.086$	$r^2 = 0.192$; $p = 0.142$	$r^2 = -0.141$; $p = 0.281$	$r^2 = -0.042$; $p = 0.752$	$r^2 = 0.107$; $p = 0.415$
LH presubiculum	$r^2 = -0.117$; $p = 0.375$	$r^2 = -0.237$; $p = 0.068$	$r^2 = -0.082$; $p = 0.535$	$r^2 = -0.001$; $p = 0.995$	$r^2 = -0.148$; $p = 0.258$	$r^2 = 0.118$; $p = 0.367$
RH presubiculum	$r^2 = -0.172$; $p = 0.189$	$r^2 = -0.287$; $p = \mathbf{0.026}^{**}$	$r^2 = 0.039$; $p = 0.765$	$r^2 = -0.110$; $p = 0.401$	$r^2 = -0.058$; $p = 0.661$	$r^2 = 0.164$; $p = 0.210$
LH parasubiculum	$r^2 = 0.015$; $p = 0.912$	$r^2 = -0.084$; $p = 0.524$	$r^2 = 0.006$; $p = 0.964$	$r^2 = 0.009$; $p = 0.943$	$r^2 = -0.219$; $p = 0.093$	$r^2 = 0.074$; $p = 0.576$
RH parasubiculum	$r^2 = 0.176$; $p = 0.178$	$r^2 = -0.044$; $p = 0.737$	$r^2 = 0.143$; $p = 0.275$	$r^2 = 0.188$; $p = 0.150$	$r^2 = -0.285$; $p = \mathbf{0.027}^{**}$	$r^2 = 0.094$; $p = 0.476$
LH fimbria	$r^2 = -0.048$; $p = 0.716$	$r^2 = -0.157$; $p = 0.231$	$r^2 = -0.094$; $p = 0.477$	$r^2 = 0.122$; $p = 0.351$	$r^2 = -0.136$; $p = 0.299$	$r^2 = 0.058$; $p = 0.659$
RH fimbria	$r^2 = -0.077$; $p = 0.557$	$r^2 = -0.201$; $p = 0.123$	$r^2 = -0.369$; $p = \mathbf{0.004}^{**}$	$r^2 = 0.074$; $p = 0.574$	$r^2 = -0.093$; $p = 0.482$	$r^2 = -0.110$; $p = 0.403$
LH HATA	$r^2 = 0.062$; $p = 0.636$	$r^2 = -0.256$; $p = \mathbf{0.048}^{**}$	$r^2 = -0.061$; $p = 0.642$	$r^2 = 0.012$; $p = 0.929$	$r^2 = -0.182$; $p = 0.164$	$r^2 = 0.110$; $p = 0.404$
RH HATA	$r^2 = 0.156$; $p = 0.233$	$r^2 = -0.261$; $p = \mathbf{0.044}^{**}$	$r^2 = -0.095$; $p = 0.469$	$r^2 = 0.121$; $p = 0.359$	$r^2 = -0.284$; $p = \mathbf{0.028}^{**}$	$r^2 = 0.050$; $p = 0.705$
LH hippocampal tail	$r^2 = -0.122$; $p = 0.353$	$r^2 = -0.125$; $p = 0.340$	$r^2 = -0.106$; $p = 0.419$	$r^2 = -0.161$; $p = 0.218$	$r^2 = 0.057$; $p = 0.663$	$r^2 = -0.077$; $p = 0.559$
RH hippocampal tail	$r^2 = 0.005$; $p = 0.970$	$r^2 = -0.155$; $p = 0.237$	$r^2 = 0.175$; $p = 0.180$	$r^2 = -0.005$; $p = 0.969$	$r^2 = -0.133$; $p = 0.310$	$r^2 = -0.092$; $p = 0.482$
LH fissure	$r^2 = 0.110$; $p = 0.404$	$r^2 = 0.260$; $p = \mathbf{0.045}^{**}$	$r^2 = 0.197$; $p = 0.132$	$r^2 = 0.194$; $p = 0.138$	$r^2 = -0.368$; $p = \mathbf{0.004}^{**}$	$r^2 = -0.081$; $p = 0.539$
RH fissure	$r^2 = 0.018$; $p = 0.889$	$r^2 = 0.214$; $p = 0.101$	$r^2 = 0.233$; $p = 0.073$	$r^2 = -0.077$; $p = 0.559$	$r^2 = -0.158$; $p = 0.227$	$r^2 = -0.019$; $p = 0.883$
LH GCMLDG	$r^2 = -0.035$; $p = 0.788$	$r^2 = -0.182$; $p = 0.164$	$r^2 = 0.124$; $p = 0.344$	$r^2 = -0.085$; $p = 0.521$	$r^2 = -0.092$; $p = 0.485$	$r^2 = 0.051$; $p = 0.700$
RH GCMLDG	$r^2 = -0.103$; $p = 0.434$	$r^2 = -0.264$; $p = \mathbf{0.042}^{**}$	$r^2 = 0.159$; $p = 0.224$	$r^2 = -0.134$; $p = 0.309$	$r^2 = -0.067$; $p = 0.611$	$r^2 = 0.101$; $p = 0.441$
LH molecular layer HP	$r^2 = -0.115$; $p = 0.380$	$r^2 = -0.229$; $p = 0.078$	$r^2 = 0.091$; $p = 0.491$	$r^2 = -0.104$; $p = 0.430$	$r^2 = -0.088$; $p = 0.506$	$r^2 = 0.045$; $p = 0.731$
RH molecular layer HP	$r^2 = -0.165$; $p = 0.208$	$r^2 = -0.272$; $p = \mathbf{0.036}^{**}$	$r^2 = 0.073$; $p = 0.581$	$r^2 = -0.156$; $p = 0.235$	$r^2 = -0.059$; $p = 0.655$	$r^2 = 0.078$; $p = 0.556$

LH & RH = left and right hemisphere.
HATA = hippocampal-amygdaloid transition area.
GCMLDG = granule cells of the dentate gyrus.
[a] Values not corrected for multiple comparison.
** Values significant at unadjusted p-value of $p < 0.05$.

flow and vascular permeability, cytokine production, activation of microglia and infiltration of mobile cells of the immune system (Graeber et al., 2011). In the longer term, chronic inflammation may however be associated with volume reductions, as activated microglia produce neurotoxic substances, including free radicals and proinflammatory cytokines, which may damage neuronal and glial cells (Kahn and Sommer, 2014). This notion is consistent with findings reported by Rais et al. (2008) who demonstrated more pronounced grey matter volume reductions and greater ventricular increases in cannabis users with schizophrenia over five years.

While we found a significant Bonferroni corrected difference in the subiculum, uncorrected significance was also observed in the left CA 4, left and right presubiculum, left parasubiculum, right fimbria, left and right HATA, left GCMLDG, and the left and right molecular layer. Our findings may therefore relate predominantly, but not exclusively, to the subiculum. The subiculum is a major output structure of the hippocampus, receiving primary projection from CA1 and projecting out to a number of cortical and subcortical targets (O'Mara, 2005; O'Mara et al., 2001). Mammalian animal studies implicate the subiculum in the inhibition of the hypothalamic-pituitary-adrenal (HPA) axis, suggesting that it plays a key role in limiting HPA axis response to stress (O'Mara, 2005). Another proposed key function of the subiculum is processing of information regarding space, movement, and memory (O'Mara, 2005). More recent publications suggest that the entorhinal cortex layer five plays a crucial role in memory formation; specifically with recall, memory updating, and retrieval-driven instinctive fear responses (Roy et al., 2017).

Furthermore, the ventral subiculum has been implicated in fear responses, stress, anxiety, and generation of motivated behaviour, particularly in reward response (O'Mara et al., 2009). Reward processing is known to be affected in both schizophrenia (Deserno et al., 2016; Segarra et al., 2016) and in cannabis use (Lawn et al., 2016; Volkow et al., 2017). Indeed, the subiculum may provide important clues regarding the link between psychosis and cannabis use. The

ventral subiculum is an important component in the neurobiology of psychotic symptoms in schizophrenia, as it plays a key role in regulating the firing of dopamine neurons, and adjusting the responsivity of the dopamine system according to environmental cues and the needs of the organism. It has been proposed that this function may be disrupted in schizophrenia, with resultant overdrive of the dopamine system (Grace, 2010). Cannabis use also impacts the dopamine system. THC, the main psychoactive ingredient of cannabis, increases dopamine release and neuron activity in the short term, while long-term use is associated with blunting of the dopamine system (Bloomfield et al., 2016).

Our study has several important limitations that restrict the generalisability of our findings. First, this study focused on cannabis use only, as it is the most common substance of illicit use in our population (Dada et al., 2018). Resultantly, we could not address the effects of polysubstance use in our sample. Secondly, we only included male participants, as there were too few cannabis positive females in either our patient 3(3.9%) or control 3(3.9%) groups. Thirdly, tobacco smoking has been reported to affect hippocampal volume (El Marroun et al., 2016), as has alcohol abuse (Mole et al., 2016). We did not consider tobacco smoking status in the primary analysis because all of the cannabis users were also tobacco smokers; however, the distribution of smokers and non-smokers was equal between patients and controls. Similarly, the role of alcohol consumption was not considered in the present study. The distribution of alcohol use was similar between patients and controls ($p = 0.1$, Table 1) and only a small number of the cannabis using patients ($n = 5$; 7.9%) and the cannabis using controls ($n = 2$; 3.4%) did not use alcohol. We did however conduct a partial correlation analysis with alcohol use ever and hippocampal subfield volumes, controlling for group (patient or control), and found no significant correlations between any of the subfield volumes and alcohol use ($p > 0.05$). It is therefore unlikely that alcohol use was the driver of our results.

Importantly, our ability to assess a dose effect for cannabis use on hippocampal volumes is limited by the small subgroup numbers, and the lack of detailed information on duration of use and potency of cannabis. Cannabis use during adolescence is associated with earlier onset of a FES (Casadio et al., 2011; Myles et al., 2016) as well as a deleterious effect on brain volumes (Epstein and Kumra, 2015; Alpár et al., 2016). Higher levels of exposure are also associated with smaller hippocampal volumes (Yücel et al., 2008; Cousijn et al., 2012; Yücel et al., 2015; Lorenzetti et al., 2016; Lorenzetti et al., 2018). Finally, our categorisation of cannabis users into recent/current and non-users meant that we were unable to assess any enduring effects of previous cannabis use.

The strength of our study lies in the well-characterised nature of the sample. Selection of first-episode patients who were treatment-naïve or minimally treated addressed the confounding effects of illness chronicity and medication status on hippocampal subfield volumes in cannabis using compared to non-using patients. Also, inclusion of healthy controls from the same catchment area allowed us to assess the illness specific effects of cannabis use. Finally, urine toxicology screening for cannabis and other substances, together with patient- and carer- report provided both objective and subjective measures of our primary predictor variable. This is important, given the potential risk of bias associated with self-report only (Wilcox et al., 2013; Clark et al., 2016). Furthermore, our data regarding frequency of use, age when first used, as well as the concordance of self and carer-report and urine toxicology screening provide adequate history of use for the purposes of this manuscript.

5. Conclusions

Our finding of differences in hippocampal subfield volumes in cannabis using and non-using patients and controls highlight the importance of considering the impact of cannabis use in both patient and control populations. Specifically, the broad inclusion definition of cannabis use employed by this study highlights the fact that even occasional and discontinued use potentially has an impact on the hippocampal structure. Furthermore, the increased subiculum volume in cannabis using patients compared to cannabis non-using patients as well as the clinical correlates with subfield volumes raises important questions regarding the pathophysiology of schizophrenia and the role of cannabis use therein. Further research is needed to explore the potential mediating effects of cannabis use on hippocampal structure in the pathophysiology and treatment outcome of FES patients. Future studies should also investigate the effects of frequency, potency and composition of cannabis, as well as moderating genetic and other environmental effects such as alcohol and tobacco use, on hippocampal subfields in first episode schizophrenia. Lastly, future longitudinal studies should also look at changes in hippocampal subfield volumes over time, how these are impacted by cannabis use, and how they relate to psychopathology and clinical outcome.

Role of the funding source

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CRediT authorship contribution statement

RE, LP, and LA were responsible for the conception and design of the larger study. FS and SdP were responsible for the MRI processing, quality control and extraction of MRI related variables. FS, SK, SdP and HKL were responsible for collection, extraction and coding of demographic and clinical data included in the study. FS provided the analysis and together with RE drafted the manuscript. All authors provided intellectual contribution, critical comments, and approved the final manuscript.

Declaration of competing interest

FS, SdP, LA, SK, LP, and HKL have no conflict of interest to declare. RE has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck.

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References

Abdel-Baki, A., Ouellet-Plamondon, C., Salvat, E., Grar, K., Potvin, S., 2017. Symptomatic and functional outcomes of substance use disorder persistence 2 years after admission to a first-episode psychosis program. Psychiatry Res. 247, 113–119.

Addington, D., Addington, J., 1993. Assessing depression in schizophrenia: the Calgary depression scale. Br. J. Psychiatry 163, S39–S44.

Aguilar, D.D., Giuffrida, A., Lodge, D.J., 2016. THC and endocannabinoids differentially regulate neuronal activity in the prefrontal cortex and hippocampus in the subchronic PCP model of schizophrenia. Journal of Psychopharmacology (Oxford, England) 30 (2), 169–181. https://doi.org/10.1177/0269881115612239.

Alpár, A., Di Marzo, V., Harkany, T., 2016. At the tip of an iceberg: prenatal marijuana and its possible relation to neuropsychiatric outcome in the offspring. Biol. Psychiatry 79 (7), e33–e45. https://doi.org/10.1016/j.biopsych.2015.09.009.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. (Washington D.C).

Arnold, S.J.M., Ivleva, E.I., Gopal, T.A., Reddy, A.P., Jeon-Slaughter, H., Sacco, C.B., et al., 2014. Hippocampal volume is reduced in schizophrenia and schizoaffective disorder but not in psychotic bipolar I disorder demonstrated by both manual tracing and automated parcellation (FreeSurfer). Schizophr. Bull. 41 (1), 233–249. https://doi.org/10.1093/schbul/sbu009.

Bangalore, S.S., Prasad, K.M.R., Montrose, D.M., Goradia, D.D., Diwadkar, V.A., Keshavan, M.S., 2008. Cannabis use and brain structural alterations in first episode schizophrenia—a region of interest, voxel based morphometric study. Schizophr. Res. 99 (1–3), 1–6. https://doi.org/10.1016/j.schres.2007.11.029.

Beale, C., Broyd, S.J., Chye, Y., Suo, C., Schira, M., Galettis, P., et al., 2018. Prolonged cannabidiol treatment effects on hippocampal subfield volumes in current cannabis users. Cannabis and Cannabinoid Research 3 (1), 94–107. https://doi.org/10.1089/can.2017.0047.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martín-Santos, R., Borgwardt, S., Winton-Brown, T., et al., 2009. Opposite effects of Δ-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35 (3), 764–774. https://doi.org/10.1038/npp.2009.184.

Bloomfield, M.A.P., Ashok, A.H., Volkow, N.D., Howes, O.D., 2016. The effects of Δ9-tetrahydrocannabinol on the dopamine system. Nat. Publ. Group 539 (7629), 369–377. https://doi.org/10.1038/nature20153.

Brambilla, P., Perlini, C., Rajagopalan, P., Saharan, P., Rambaldelli, G., Bellani, M., et al., 2018. Schizophrenia severity, social functioning and hippocampal neuroanatomy: three-dimensional mapping study. Br. J. Psychiatry 202 (01), 50–55. https://doi.org/10.1192/bjp.bp.111.105700.

Casadio, P., Fernandes, C., Murray, R.M., Di Forti, M., 2011. Cannabis use in young people: the risk for schizophrenia. Neurosci. Biobehav. Rev. 35 (8), 1779–1787. https://doi.org/10.1016/j.neubiorev.2011.04.007.

Clark, C.B., Zyambo, C.M., Li, Y., Cropsey, K.L., 2016. The impact of non-concordant self-report of substance use in clinical trials research. Addict. Behav. 58, 74–79. https://doi.org/10.1016/j.addbeh.2016.02.023.

Cousijn, J., Wiers, R.W., Ridderinkhof, K.R., van den Brink, W., Veltman, D.J., Goudriaan, A.E., 2012. Grey matter alterations associated with cannabis use: results of a VBM study in heavy cannabis users and healthy controls. NeuroImage 59 (4), 3845–3851. https://doi.org/10.1016/j.neuroimage.2011.09.046.

Crocker, C.E., Tibbo, P.G., 2018. The interaction of gender and cannabis in early phase psychosis. Schizophr. Res. 194 (C), 18–25. https://doi.org/10.1016/j.schres.2017.04.046.

Dada, S., Harker Burnhams, N., Erasmus, J., Parry, C., Bhana, A., TB HIV Care. (2018). South African Community Epidemiology Network on Drug Use. SA Medical Research Council (pp. 1–3). Retrieved from http://www.samrc.ac.za/sites/default/files/attachments/2018-07-26/SACENDUupdateJun2018.pdf

Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage 9, 179–194.

Demirakca, T., Sartorius, A., Ende, G., Meyer, N., Welzel, H., Skopp, G., et al., 2011. Diminished gray matter in the hippocampus of cannabis users: possible protective effects of cannabidiol. Drug Alcohol Depend. 114 (2–3), 242–245. https://doi.org/10.1016/j.drugalcdep.2010.09.020.

Deserno, L., Schlagenhauf, F., Heinz, A., 2016. Striatal dopamine, reward, and decision making in schizophrenia. Dialogues Clin. Neurosci. 18 (1), 77–89.

Donoghue, K., Doody, G.A., Murray, R.M., Jones, P.B., Morgan, C., Dazzan, P., et al., 2014. Cannabis use, gender and age of onset of schizophrenia: data from the ÆSOP study. Psychiatry Res. 215 (3), 528–532. https://doi.org/10.1016/j.psychres.2013.12.038.

Epstein, K.A., Kumra, S., 2015. Altered cortical maturation in adolescent cannabis users with and without schizophrenia. Schizophr. Res. 162 (1–3), 143–152. https://doi.org/10.1016/j.schres.2014.11.029.

First, M.B., Spitzer, R.L.G.M., Williams, L.B.W., 1994. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient ed (SCID-P). New York State Psychiatric Institute, Biometrics Research, New York.

Gillespie, N.A., Neale, M.C., Bates, T.C., Eyler, L.T., Fennema-Notestine, C., Vassileva, J., et al., 2018. Testing associations between cannabis use and subcortical volumes in two large population-based samples. Addiction 113 (9), 1661–1672. https://doi.org/10.1111/add.14252.

Gilman, J., Ulysse, C., Schoenfeld, D., Evins, A.E., 2018. S260. An updated report of associations between cannabis use and brain structure. Biological Psychiatry 83 (Supplement), S449. https://doi.org/10.1016/j.biopsych.2018.02.1152.

Grace, A.A., 2010. Dopamine system dysregulation by the ventral subiculum as the common pathophysiological basis for schizophrenia psychosis, psychostimulant abuse, and stress. Neurotox. Res. 18 (3–4), 367–376. https://doi.org/10.1007/s12640-010-9154-6.

Graeber, M.B., Li, W., Rodriguez, M.L., 2011. Role of microglia in CNS inflammation. FEBS Lett. 585 (23), 3798–3805. https://doi.org/10.1016/j.febslet.2011.08.033.

Guy W. ECDEU Assessment Manual for Psychopharmacology. ADM 76–338 ed. Rockville, Md: US Department of Health, Education and Welfare. 1976, 217–22.

Han, X., Jovicich, J., Salat, D., van der Kouwe, A., Quinn, B., Czanner, S., Busa, E., Pacheco, J., Albert, M., Killiany, R., Maguire, P., Rosas, D., Makris, N., Dale, A., Dickerson, B., Fischl, B., 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 32, 180–194.

Haukvik, U.K., Tamnes, C.K., Söderman, E., Agartz, I., 2018. Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: a systematic review and meta-analysis. J. Psychiatr. Res. 104, 217–226. https://doi.org/10.1016/j.jpsychires.2018.08.012.

Hill, M.N., Hunter, R.G., McEwen, B.S., 2009. Chronic stress differentially regulates cannabinoid CB1 receptor binding in distinct hippocampal subfields. Eur. J. Pharmacol. 614 (1–3), 66–69. https://doi.org/10.1016/j.ejphar.2009.04.048.

Ho, N.F., Holt, D.J., Cheung, M., Iglesias, J.E., Goh, A., Wang, M., et al., 2017. Progressive decline in hippocampal CA1 volume in individuals at ultra-high-risk for psychosis who do not remit: findings from the longitudinal youth at risk study. Nat. Publ. Group 42 (6), 1361–1370. https://doi.org/10.1038/npp.2017.5.

Iglesias, J.E., Augustinack, J.C., Nguyen, K., Player, C.M., Player, A., Wright, M., et al., 2015. A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: application to adaptive segmentation of in vivo MRI. NeuroImage 115 (C), 117–137. https://doi.org/10.1016/j.neuroimage.2015.04.042.

Jager, G., van Hell, H.H., De Win, M.M.L., Kahn, R.S., van den Brink, W., Van Ree, J.M., Ramsey, N.F., 2007. Effects of frequent cannabis use on hippocampal activity during an associative memory task. Eur. Neuropsychopharmacol. 17 (4), 289–297. https://doi.org/10.1016/j.euroneuro.2006.10.003.

James, A., Hough, M., James, S., Winmill, L., Burge, L., Nijhawan, S., et al., 2011. Greater white and grey matter changes associated with early cannabis use in adolescent-onset schizophrenia (AOS). Schizophr. Res. 128 (1–3), 91–97. https://doi.org/10.1016/j.schres.2011.02.014.

Kahn, R.S., Sommer, I.E., 2014. The neurobiology and treatment of first-episode schizophrenia. Mol. Psychiatry 20 (1), 84–97. https://doi.org/10.1038/mp.2014.66.

Kawano, M., Sawada, K., Shimodera, S., Ogawa, Y., Kariya, S., Lang, D.J., et al., 2015. Hippocampal subfield volumes in first episode and chronic schizophrenia. PLoS One 10 (2), e0117785–14. https://doi.org/10.1371/journal.pone.0117785.

Kay, S.R., Fizbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale (PANSS) for Schizophrenia. 13th ed. pp. 261–267.

Koenders, L., Machielsen, M.W.J., van der Meer, F.J., van Gasselt, A.C.M., Meijer, C.J., van den Brink, W., et al., 2015. Brain volume in male patients with recent onset schizophrenia with and without cannabis use disorders. J. Psychiatry Neurosci. 40 (3), 197–206. https://doi.org/10.1503/jpn.140081.

Koenders, L., Cousijn, J., Vingerhoets, W.A.M., van den Brink, W., Wiers, R.W., Meijer, C.J., et al., 2016. Grey matter changes associated with heavy cannabis use: a longitudinal sMRI study. PLoS One 11 (5), e0152482–13. https://doi.org/10.1371/journal.pone.0152482.

Koenders, L., Lorenzetti, V., De Haan, L., Suo, C., Vingerhoets, W., van den Brink, W., et al., 2017. Longitudinal study of hippocampal volumes in heavy cannabis users. J. Psychopharmacol. 31 (8), 1027–1034. https://doi.org/10.1177/0269881117718380.

Kühn, S., Musso, F., Mobascher, A., Warbrick, T., Winterer, G., Gallinat, J., 2012. Hippocampal subfields predict positive symptoms in schizophrenia: First evidence from brain morphometry. Transl. Psychiatry 2 (6), e127–2. https://doi.org/10.1038/tp.2012.51.

Kumra, S., Robinson, P., Tambyraja, R., Jensen, D., Schimunek, C., Houri, A., et al., 2012. Parietal lobe volume deficits in adolescents with schizophrenia and adolescents with cannabis use disorders. J. Am. Acad. Child Adolesc. Psychiatry 51 (2), 171–180. https://doi.org/10.1016/j.jaac.2011.11.001.

Kutlu, M.G., Gould, T.J., 2016. Effects of drugs of abuse on hippocampal plasticity and hippocampus-dependent learning and memory: contributions to development and maintenance of addiction. Learn. Mem. 23 (10), 515–533. https://doi.org/10.1101/lm.042192.116.

Lawn, W., Freeman, T.P., Pope, R.A., Joye, A., Harvey, L., Hindocha, C., et al., 2016. Acute and chronic effects of cannabinoids on effort-related decision-making and reward learning: an evaluation of the cannabis "amotivational" hypotheses. Psychopharmacology 233 (19–20), 1–16. https://doi.org/10.1007/s00213-016-4383-x.

Li, W., Li, K., Guan, P., Chen, Y., Xiao, Y., Lui, S., et al., 2018. Volume alteration of hippocampal subfields in first-episode antipsychotic-naïve schizophrenia patients before and after acute antipsychotic treatment. NeuroImage: Clinica 20, 169–176. https://doi.org/10.1016/j.nicl.2018.07.008.

Lorenzetti, V., Solowij, N., Yücel, M., 2016. The role of cannabinoids in neuroanatomic alterations in cannabis users. Biol. Psychiatry 79 (7), e17–e31. https://doi.org/10.1016/j.biopsych.2015.11.013.

Lorenzetti, V., Solowij, N., Whittle, S., Fornito, A., Lubman, D.I., Pantelis, C., Yücel, M., 2018. Gross morphological brain changes with chronic, heavy cannabis use. Br. J. Psychiatry 206 (01), 77–78. https://doi.org/10.1192/bjp.bp.114.151407.

Malchow, B., Hasan, A., Fusar-Poli, P., Schmitt, A., Falkai, P., Wobrock, T., 2013a. Cannabis abuse and brain morphology in schizophrenia: a review of the available evidence. Eur. Arch. Psychiatry Clin. Neurosci. 263 (1), 3–13. https://doi.org/10.1007/s00406-012-0346-3.

Malchow, B., Hasan, A., Schneider-Axmann, T., Jatzko, A., Gruber, O., Schmitt, A., et al., 2013b. Effects of cannabis and familial loading on subcortical brain volumes in first-episode schizophrenia. Eur. Arch. Psychiatry Clin. Neurosci. 263 (S2), 155–168. https://doi.org/10.1007/s00406-013-0451-y.

Mamah, D., Alpert, K.I., Barch, D.M., Csernansky, J.G., Wang, L., 2016. Subcortical neuromorphometry in schizophrenia spectrum and bipolar disorders. NeuroImage: Clinical 11, 276–286. https://doi.org/10.1016/j.nicl.2016.02.011.

Mandelbaum, D.E., de la Monte, S.M., 2016. Adverse structural and functional effects of marijuana on the brain: evidence reviewed. Pediatr. Neurol. 66, 1–26. https://doi.org/10.1016/j.pediatrneurol.2016.09.004.

El Marroun, H., Tiemeier, H., Franken, I.H.A., Jaddoe, V.W.V., van der Lugt, A., Verhulst, F.C., et al., 2016. Prenatal cannabis and tobacco exposure in relation to brain morphology—a prospective neuroimaging study in young children. Biol. Psychiatry 79 (12), 971–979. https://doi.org/10.1016/j.biopsych.2015.08.024.

Mole, T.B., Mak, E., Chien, Y., Voon, V., 2016. Dissociated accumbens and hippocampal structural abnormalities across obesity and alcohol dependence. The International Journal of Neuropsychopharmacology 19 (9), pyw039–8. https://doi.org/10.1093/ijnp/pyw039.

Myles, H., Myles, N., Large, M., 2016. Cannabis use in first episode psychosis: meta-analysis of prevalence, and the time course of initiation and continued use. The Australian and New Zealand Journal of Psychiatry 50 (3), 208–219. https://doi.org/10.1177/0004867415599846.

Novick, D., Montgomery, W., Treuer, T., Moneta, M.V., Haro, J.M., 2016. Sex differences in the course of schizophrenia across diverse regions of the world. Neuropsychiatr. Dis. Treat. 12, 2927–2939. https://doi.org/10.2147/NDT.S101151.

O'Mara, S.M., 2005. The subiculum: what it does, what it might do, and what neuroanatomy has yet to tell us. J. Anat. 207, 271–282.

O'Mara, S.M., Commins, S., Anderson, M., Gigg, J., 2001. The subiculum: a review of form, physiology and function. Prog. Neurobiol. 64, 129–155.

O'Mara, S.M., Sanchez-Vives, M.V., Brotons-Mas, J.R., O'Hare, E., 2009. Roles for the subiculum in spatial information processing, memory, motivation and the temporal control of behaviour. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 33 (5), 782–790. https://doi.org/10.1016/j.pnpbp.2009.03.040.

Osborne, A.L., Solowij, N., Weston-Green, K., 2017. A systematic review of cannabidiol on cognitive function: relevance to schizophrenia. Neuroscience and Behavioural Reviews 72, 310–324. https://doi.org/10.1016/j.neubiorev.2016.11.012.

Ott Vintergaard, C., Bergstrom Johnson, C., Macoveanu, J., Miskowiak, K., 2019. Structural changes in the hippocampus as a biomarker for cognitive improvements in neuropsychiatric disorders: a systematic review. Eur. Neuropsychopharmacol., 1–11 https://doi.org/10.1016/j.euroneuro.2019.01.105.

Pagliaccio, D., Barch, D.M., Bogdan, R., Wood, P.K., Lynskey, M.T., Heath, A.C., Agrawal, A., 2015. Shared predisposition in the association between cannabis use and subcortical brain structure. JAMA Psychiatry 72 (10), 994–998. https://doi.org/10.1001/jamapsychiatry.2015.1054.

Pasternak, O., Kubicki, M., Shenton, M.E., 2016. In vivo imaging of neuroinflammation in schizophrenia. Schizophr. Res. 173 (3), 200–212. https://doi.org/10.1016/j.schres.2015.05.034.

Radhakrishnan, R., Kaser, M., Guloksuz, S., 2017. The link between the immune system, environment, and psychosis. Schizophr. Bull. 43 (4), 693–697. https://doi.org/10.1093/schbul/sbx057.

Rais, M., Cahn, W., van Haren, N.E., Schnack, H.G., Caspers, E., Hulshoff Pol, H.E., Kahn, R.S., 2008. Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. Am. J. Psychiatry 165, 490–496.

Raz, N., Daugherty, A.M., Bender, A.R., Dahle, C.L., Land, S., 2015. Volume of the hippocampal subfields in healthy adults: differential associations with age and a pro-inflammatory genetic variant. Brain Struct. Funct. 220 (5), 2663–2674. https://doi.org/10.1007/s00429-014-0817-6.

Roy, D.S., Kitamura, T., Okuyama, T., Ogawa, S.K., Sun, C., Obata, Y., et al., 2017. Distinct neural circuits for the formation and retrieval of episodic memories. Cell 170 (5), 1–33. https://doi.org/10.1016/j.cell.2017.07.013.

Schlaepfer, T.E., Lancaster, E., Heidbreder, R., Strain, E.C., Kosel, M., Fisch, H.-U., Pearlson, G.D., 2006. Decreased frontal white-matter volume in chronic substance abuse. Int. J. Neuropsychopharmacol. 9 (02), 147. https://doi.org/10.1017/S1461145705005705.

Segarra, N., Metastasio, A., Ziauddeen, H., Spencer, J., Reinders, N.R., Dudas, R.B., et al., 2016. Abnormal frontostriatal activity during unexpected reward receipt in depression and schizophrenia: relationship to anhedonia. Neuropsychopharmacology 41 (8), 2001–2010. https://doi.org/10.1038/npp.2015.370.

Solowij, N., Walterfang, M., Lubman, D.I., Whittle, S., Lorenzetti, V., Styner, M., et al., 2013. Alteration to hippocampal shape in cannabis users with and without schizophrenia. Schizophr. Res. 143 (1), 179–184. https://doi.org/10.1016/j.schres.2012.10.040.

Szűcs, E., Dvorácskó, S., Tömböly, C., Büki, A., Kékesi, G., Horváth, G., Benyhe, S., 2016. Decreased CB receptor binding and cannabinoid signaling in three brain regions of a rat model of schizophrenia. Neurosci. Lett. 633, 87–93. https://doi.org/10.1016/j.neulet.2016.09.020.

van Dijk, D., Koeter, M.W.J., Hijman, R., Kahn, R.S., van den Brink, W., 2012. Effect of cannabis use on the course of schizophrenia in male patients: a prospective cohort study. Schizophr. Res. 137 (1–3), 50–57. https://doi.org/10.1016/j.schres.2012.01.016.

van Haren, N.E., Cahn, W., Pol, H.E.H., Kahn, R.S., 2013. Confounders of excessive brain volume loss in schizophrenia. Neurosci. Biobehav. Rev. 37 (10), 2418–2423. https://doi.org/10.1016/j.neubiorev.2012.09.006.

Villares, J., 2007. Chronic use of marijuana decreases cannabinoid receptor binding and mRNA expression in the human brain. Neuroscience 145 (1), 323–334. https://doi.org/10.1016/j.neuroscience.2006.11.012.

Volkow, N.D., Hampson, A.J., Baler, R.D., 2017. Don't worry, be happy: endocannabinoids and cannabis at the intersection of stress and reward. Annu. Rev. Pharmacol. Toxicol. 57 (1), 285–308. https://doi.org/10.1146/annurev-pharmtox-010716-104615.

Welch, K.A., Stanfield, A.C., McIntosh, A.M., Whalley, H.C., Job, D.E., Moorhead, T.W., et al., 2011. Impact of cannabis use on thalamic volume in people at familial high risk of schizophrenia. Br. J. Psychiatry 199 (5), 386–390. https://doi.org/10.1192/bjp.bp.110.090175.

Wilcox, C.E., Bogenschutz, M.P., Nakazawa, M., Woody, G., 2013. Concordance between self-report and urine drug screen data in adolescent opioid dependent clinical trial participants. Addict. Behav. 38 (10), 2568–2574. https://doi.org/10.1016/j.addbeh.2013.05.015.

Wobrock, T., Sittinger, H., Behrendt, B., D'Amelio, R., Falkai, P., 2009. Comorbid substance abuse and brain morphology in recent-onset psychosis. European Archives of Psychiatry & Clinical Neuroscience 259 (1), 28–36. https://doi.org/10.1007/s00406-008-0831-x.

Yücel, M., Solowij, N., Respondek, C., Whittle, S., Fornito, A., Pantelis, C., Lubman, D.I., 2008. Regional brain abnormalities associated with long-term heavy cannabis use. Arch. Gen. Psychiatry 65 (6), 694–701. https://doi.org/10.1001/archpsyc.65.6.694.

Yücel, M., Lorenzetti, V., Suo, C., Zalesky, A., Fornito, A., Takagi, M.J., et al., 2015. Hippocampal harms, protection and recovery following regular cannabis use. Transl. Psychiatry 6 (1), e710–e717. https://doi.org/10.1038/tp.2015.201.

Zatorre, R.J., Fields, R.D., Johansen-Berg, H., 2013. Plasticity in gray and white: neuroimaging changes in brain structure during learning. Nat. Neurosci. 15 (4), 528–536. https://doi.org/10.1038/nn.3045.

CHAPTER V

EFFECTS OF CANNABIS USE ON BODY MASS, FASTING GLUCOSE AND LIPIDS DURING THE FIRST 12 MONTHS OF TREATMENT IN SCHIZOPHRENIA SPECTRUM DISORDERS

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Effects of cannabis use on body mass, fasting glucose and lipids during the first 12 months of treatment in schizophrenia spectrum disorders

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ABSTRACT

While acute cannabis use stimulates appetite, general population studies suggest that chronic use is associated with reduced risk of obesity and other cardiometabolic risk factors. In this study we investigated changes in body mass index (BMI), fasting blood glucose and lipids, and rates of metabolic syndrome risk factors in cannabis users vs. non-users in 109 minimally treated patients with first-episode schizophrenia, schizophreniform or schizo-affective disorder who were treated according to a standardized treatment regime with depot antipsychotic medication over 12 months. Participants underwent repeated urine toxicology tests for cannabis and those testing positive at any time during the study ($n = 40$), were compared with those who tested negative at all time points ($n = 69$). There was a significant group*time interaction effect ($p = 0.002$) with the cannabis negative group showing a greater increase in BMI than the cannabis positive group, after adjusting for age, sex, methamphetamine use and modal dose of antipsychotic. There were no group*time interaction effects for fasting blood glucose or lipids. Post hoc tests indicated significant increases in fasting blood glucose and triglycerides and a decrease in high-density lipoprotein cholesterol for the cannabis negative group, with no significant changes in the cannabis positive group. Rates of metabolic syndrome did not differ significantly between groups, although more cannabis negative patients had elevated waist-circumference at endpoint ($p = 0.003$). It may be that chronic cannabis use directly suppresses appetite, thereby preventing weight gain in users. However, other indirect effects such as dietary neglect and smoking may be contributory and could explain our findings.

1. Introduction

Acute cannabis use stimulates appetite and increases food intake (Kirkham, 2009), and as such has been proposed as a treatment for weight-loss in persons with cancer and HIV infection (Sansone and Sansone, 2014). On the other hand, there is emerging evidence that chronic cannabis use is associated with lower body mass and fewer cardiometabolic risk factors in general population samples, at least in adults (Penner et al., 2013;Le Strat and Le Foll, 2011;Hayatbakhsh et al., 2010;Smit and Crespo, 2001;Ngueta et al., 2015;Thompson and Hay, 2015;Vidot et al., 2016). The situation may be different in adolescents, where an association was reported between cannabis use and increased body mass index (BMI) in two studies (Huang et al., 2013;Ross et al., 2016), in younger girls only in another (Farhat et al., 2010), while no association was found in two other studies (Jin et al., 2017;Rodondi et al., 2006).

A link between cannabis use, body mass and cardiometabolic risk factors is of particular interest in individuals with schizophrenia, given both the high rates of cannabis use (Green et al., 2005) and the increased risk of cardiometabolic comorbidities (Correll et al., 2017) associated with this illness. Two known studies have addressed this possible link. In the first, the association between cannabis use and changes in metabolic syndrome risk factors over 9 to 24 months of treatment was investigated using data obtained from a treatment monitoring and outcome survey in a Dutch cohort with severe mental illness ($N = 3169$). Patients were chronically ill (mean illness duration 14.4 [10.7] yrs) and three-quarters were on antipsychotic medication prior to the study. Cannabis users (determined by patient interview) had lower BMI, smaller waist circumference, lower diastolic blood pressure, and more severe psychotic symptoms than non-users at baseline. Patients who stopped using cannabis after the first assessment had a greater increase in BMI, waist circumference, diastolic blood pressure and triglyceride concentrations than both the ongoing users and non-users. The

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authors concluded that extra attention should be paid to the monitoring and treatment of metabolic measures in patients who discontinue their cannabis use (Bruins et al., 2016). In the second study, an analysis of data derived from an Australian psychosis survey reported that, in adults with psychotic illness ($N = 1825$), frequent cannabis use was associated with reduced risk for individual metabolic syndrome criteria (increased waist circumference, elevated blood pressure, triglycerides and glucose and low HDL) (Waterreus et al., 2016).

In the present study, we compared longitudinal changes in BMI and metabolic measures in patients with schizophrenia spectrum disorder who tested positive versus those who tested negative for cannabis, during the first 12 months of treatment. By selecting patients who were previously never treated or minimally treated, and with a first-episode of illness, we were able to minimise the effects of previous treatment and disease chronicity. Furthermore, we treated the patients with a long-acting injectable antipsychotic, thereby removing a confounding effect of non-adherence and at the same time allowing accurate estimation of treatment dose and duration.

2. Methods

This was a single-site cohort study. We obtained approval from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences. The study was conducted in accordance with the International Conference on Harmonization (1996) guidelines on good clinical practice (GCP) and was registered at the South African National Clinical Trials Register (DOH-27-0710-1957), URL: www.sanctr.gov.za/SAClinicalTrials/tabid/169/ Default.aspx.

2.1. Participants

We recruited patients from first-admissions to psychiatric hospitals and community clinics within the Cape Town region between April 2007 and March 2011. The patients and/or their legal guardians provided written, informed consent. Eligible participants were men and women, in- or out- patients, aged 16 to 45 years, meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (APA, 1994) diagnostic criteria for schizophreniform disorder, schizophrenia or schizo-affective disorder. Patients were excluded if they had, during their lifetime, been exposed to >4 weeks of antipsychotic medication, been treated with a long-acting injectable antipsychotic, had a serious or unstable medical condition, intellectual disability or if the psychotic episode was considered to be related to acute substance intoxication.

2.2. Assessments

A physical examination was conducted at the start and completion of the study. For the body mass and waist circumference measurements, patients removed all surplus clothing including shoes and socks. They were weighed on a regularly calibrated electronic scale. Waist circumference was measured between the lowest rib and the iliac crest with patients standing upright and breathing normally. BMI was calculated as the weight in kilograms divided by the square of height in meters. Metabolic assessments comprised fasting glucose, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides and total cholesterol. Patients fasted for at least 8 h overnight and rested for 10 min prior to venepuncture. We recorded BMI and metabolic assessments at baseline and months 3, 6 and 12. Systolic and diastolic blood pressure were recorded at baseline and endpoint. Patients were categorised as meeting the metabolic syndrome criteria, adapted from the Adult Treatment Panel (ATP III-A) as proposed by the American Heart Association (Alberti et al., 2009). These criteria comprise elevated blood pressure (systolic >130 mmHg and/or diastolic >85 mmHg, or antihypertensive drug treatment), elevated triglycerides (≥1.7 mmol/l or drug treatment for elevated triglycerides), lowered HDL (≤1 mmol/l for men, ≤1.3 mmol/l for women or drug treatment for reduced HDL), elevated fasting glucose (≥5.5 mmol/l or drug treatment for elevated glucose), and central obesity as measured by waist circumference according to population-specific definitions. We made two adaptations to these criteria. First, we used a waist circumference cut-off for central obesity of ≥90 cm for men and ≥80 cm for women, as recommended by Matsha et al. (Matsha et al., 2013) based on a study conducted in a similar population, in our catchment area. Second, we used a threshold score of ≥6.1 mmol/l for defining impaired fasting glucose, as recommended by the World Health Organisation (World Health Organisation, 2006). Metabolic syndrome was defined as abnormal values for any three of the five criteria. We assessed psychosis symptom severity with the Positive and Negative Syndrome Scale (Kay et al., 1987). Alcohol use was assessed using a self-report questionnaire based on the CAGE criteria (Ewing, 1984). Urine toxicology screening for cannabis and methamphetamine was conducted at 9 time-points over the 12 months of treatment (screening, weeks 0 and 2 and months 1, 2, 3, 6, 9 and 12). Patients were grouped as cannabis positive if any of the post-screening tests were positive and as cannabis negative if all of the post-screening tests were negative.

2.3. Treatment

We treated the patients according to a fixed protocol, with a long-acting injectable antipsychotic, flupenthixol decanoate. Flupenthixol is a high potency thioxanthene, whose receptor binding profile of D1-5 dopamine, 5-HT2, H1 histamine and alpha-1 adrenergic-antagonism is not dissimilar to several second generation antipsychotics (de Wit, 2010). It has been associated with significant increases in BMI, waist circumference and triglycerides, and a decrease in HDL in patients with first-episode schizophrenia (Chiliza et al., 2015). Flupenthixol decanoate is widely available and remains a popular choice of psychiatrists for treating psychosis (Shen et al., 2012). There was a one week lead-in period with oral flupenthixol 1 to 3 mg/day followed by long acting flupenthixol decanoate injections every two weeks for the duration of the study. The starting dose was 10 mg 2-weekly. Additional oral flupenthixol was prescribed at the discretion of the investigator. Permitted concomitant treatment included lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms, propranolol for akathisia and medication for general medical conditions. Medications not permitted included other antipsychotics, mood stabilizers and psychostimulants.

2.4. Statistical analyses

All participants with a baseline and at least one post-baseline measure were included in the analyses. For baseline demographic and clinical group comparisons, we used independent samples *t*-tests for continuous variables and chi-square test for categorical variables. Linear mixed effect models for continuous repeated measures (MMRM) were constructed to assess the changes in BMI and metabolic measures over time. The model included fixed terms of age, sex, modal flupenthixol dose, methamphetamine positive test, group (cannabis users vs cannabis non-users), time, and the interaction terms "gender*time" and "group*time". Where data were not normally distributed, the data were log transformed. All tests were 2-tailed, with a significance level of 0.05. Within analyses Fisher's Least Significant Difference (LSD) tests were used for post-hoc multiple comparisons.

3. Results

Of 126 participants entered into the study, 109 had at least one post-baseline assessment and were included in the analysis. Forty (37%) tested positive for cannabis at least once after screening, and 69 (63%) tested negative for cannabis at all post-screening assessments. Table 1 provides the baseline demographic, clinical and laboratory details for

Table 1
Demographic, clinical and laboratory characteristics of the cannabis positive and cannabis negative groups with first-episode schizophrenia spectrum disorders.

	Cannabis positive $n = 40$ (37%)	Cannabis negative $n = 69$ (63%)	p
Age in years, mean(SD)	22.03(4.31)	25.19(7.20)	0.01
Men, n(%)	35(88%)	44(69%)	0.007
Ethnicity, n(%)			0.46
Mixed ancestry	33(82%)	51(74%)	
Black	5(13%)	10(14%)	
White	2(5%)	8(12%)	
DUP in weeks, mean(SD)	36.35(53.69)	30.53(35.53)	0.49
Diagnosis, n(%)			0.6
Schizophrenia	26	48	
Schizophreniform	14	20	
Schizoaffective	0	1	
PANSS total score, mean(SD)	94.48(17.59)	95.96(15.83)	0.65
Methamphetamine positive, n(%)	21(53%)	12(17%)	0.0001
Alcohol abuse	1(3%)	3(4%)	0.6
Blood pressure (mmHg), mean(SD)			
Systolic	121.25(12.65)	121.57(14.28)	0.9
Diastolic	78.0(9.85)	80.31(10.39)	0.25
BMI (kg/m^2), mean(SD)	21.18(3.68)	22.09(3.97)	0.24
Glucose (mmol/l), mean(SD)	4.66(0.52)	4.84(0.78)	0.17
HDL (mmol/l), mean(SD)	1.10(0.49)	1.21(0.58)	0.29
LDL (mmol/l), mean(SD)	2.63(0.92)	2.72(0.91)	0.60
Triglycerides (mmol/l), mean(SD)	0.89(0.49)	0.88(0.53)	0.95
Cholesterol (mmol/l), mean(SD)	3.99(1.20)	4.36(1.00)	0.09
Waist circumference (cm), mean(SD)	75.45(11.64)	78.18(9.76)	0.26
Duration of study treatment in weeks, mean(SD)	43.35(9.04)	40.38(12.53)	0.19
Modal flupenthixol dose, mean(SD)	12.88(4.06)	11.45(3.75)	0.07

DUP = duration of untreated psychosis; PANSS = Positive and Negative Syndrome Scale; BP = blood pressure; BMI = body mass index; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol.

the two groups. The cannabis positive group was significantly younger and included more men and more methamphetamine users, but the groups did not differ in terms of BMI and metabolic measures. There were also no significant group differences regarding the mean modal flupenthixol dose and the duration of study treatment.

Fig. 1 shows the least squares mean BMI by MMRM over the 12 month treatment period for the cannabis positive and cannabis negative groups. There was a significant group*time effect ($F(3, 271) = 5.21$, $p = 0.001$) with the cannabis negative group showing a greater increase in BMI. There were no significant effects for age ($p = 0.2$), sex ($p = 0.9$), modal flupenthixol dose ($p = 0.5$), methamphetamine-positive test ($p = 0.09$) and no significant gender*time interaction ($p = 0.2$). Additional MMRM analyses indicated that there were no group*time effects for fasting blood glucose ($F(3,273) = 0.98$, $p = 0.4$), HDL ($F(3, 273) = 0.56$, $p = 0.6$), LDL ($F(3, 273) = 0.61$, $p = 0.6$), total cholesterol ($F(3, 273) = 0.62$, $p = 0.6$) and triglycerides ($F(3, 273) = 0.25$, $p = 0.9$). However, post hoc LSD tests (Table 2) indicated significant baseline to month 12 increase in fasting blood glucose ($p = 0.004$), decrease in HDL ($p = 0.0001$) and increase in triglycerides in the cannabis negative group ($p = 0.0005$), with no significant changes in the cannabis positive group.

The numbers (%) of patients from the two groups meeting individual and full criteria for the metabolic syndrome are provided in Table 3. The only significant group difference was that more cannabis negative patients ($n = 25$ [36%]) than cannabis positive patients ($n = 4$ [10%]) had elevated waist circumference values at endpoint ($p = 0.003$).

4. Discussion

The present study is, as far as we are aware, the first to investigate longitudinally the relationship between cannabis use and body mass and metabolic measures in a first-episode schizophrenia cohort, and the first in a relatively antipsychotic naïve group. Obesity and its accompanying cardiometabolic complications are very common in schizophrenia, with multiple factors potentially contributing to this increased risk, including sedentary lifestyle (Brown et al., 1999) and poor diet (Strassnig et al., 2003). Most importantly, antipsychotics are major contributors, via their adipogenic and dysmetabolic effects (Gohlke et al., 2012). Young people with limited exposure to antipsychotic medication are particularly susceptible to these effects (Alvarez-Jimenez et al., 2008), so that studying this population provides a good opportunity to investigate underlying mechanisms (Correll et al., 2011).

The most important finding in this study was that patients with schizophrenia who tested positive for cannabis during their first year of treatment gained significantly less weight than those who tested negative for cannabis. This finding was not explained by differences in sex, age, comorbid methamphetamine or alcohol use, treatment dose or duration. In addition, because patients received long acting injectable antipsychotic treatment, we were able to rule out the possibility that nonadherence among cannabis users could account for lack of weight gain.

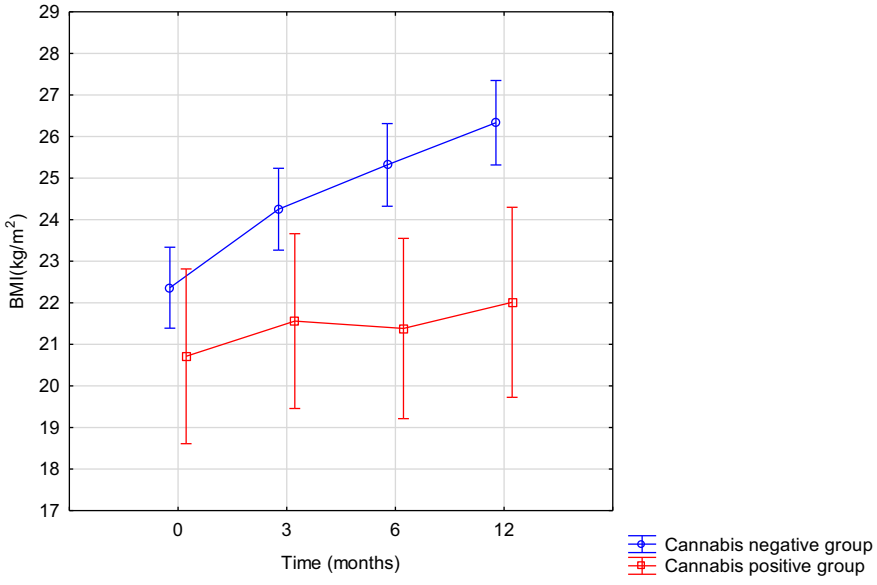

Fig. 1. Least squares means BMI by mixed model repeated measures over the 12 month treatment period for the cannabis positive and cannabis negative groups.

Table 2
Changes from baseline to month 12 for BMI and metabolic measures for the cannabis positive and cannabis negative groups.

	Cannabis negative		Cannabis positive	
	Change mean (CI)	p^a	Change mean (CI)	p^a
BMI (kg/m^2)	3.97 (3.37, 4.56)	0.0001	1.3 (0.15, 2.75)	0.08
Glucose (mmol/l)	0.39 (0.12, 0.66)	0.005	0.05 (−0.7, 0.6)	0.9
HDL (mmol/l)	−0.22 (−0.33, −0.11)	0.0001	−0.16 (−0.43, 0.1)	0.2
LDL (mmol/l)	0.07 (−0.1, 0.24)	0.4	−0.14 (−0.71, 0.43)	0.5
Triglycerides (mmol/l)	0.31 (0.13, 0.48)	0.0005	0.17 (−0.25, 0.58)	0.4
Cholesterol (mmol/l)	−0.05 (−0.26, 0.15)	0.6	−0.13 (−0.77, 0.51)	0.5
Waist circumference (cm)	8.47 (4.36,12,58)	0.0001	3.2 (−2.69, 9.1)	0.3

BMI = body mass index; HDL = high density lipoprotein cholesterol; LDL = low density lipoprotein cholesterol.
[a] LSD tests.

Our findings are consistent with reports of reduced prevalence of obesity in cannabis users in general adult population samples (Penner et al., 2013;Le Strat and Le Foll, 2011;Hayatbakhsh et al., 2010;Smit and Crespo, 2001;Ngueta et al., 2015;Thompson and Hay, 2015). Our findings are also consistent with the reports of lower BMI in severely mentally ill patients who use cannabis (Bruins et al., 2016). Furthermore, while there were no significant group*time effects for any of the metabolic measures, the post-hoc tests suggested deteriorating profiles in the cannabis negative group insofar as blood glucose and triglyceride levels increased and HDL levels decreased, while the cannabis positive group showed no significant changes. Finally, although there were no significant differences in rates of metabolic syndrome, more of the cannabis negative group had elevated waist circumference at endpoint. These results are consistent with the report of fewer metabolic syndrome risk factors in psychotic patients who used cannabis (Waterreus et al., 2016).

There are several possible explanations for our findings. First, it may be that cannabis users neglect their diet. Indeed, cannabis use is associated with poor dietary intake among first episode psychosis samples (Hahn et al., 2014). This may be particularly relevant in socio-economically disadvantaged communities such as the one from which our participants were recruited where healthy food options are less accessible.

Second, the effects of other substances may be important as many individuals who use cannabis use other substances as well (Jones et al., 2017). In this regard, methamphetamine and tobacco smoking may be important, given their appetite-suppressant effects (Heal et al., 2013;Chiolero et al., 2008). Indeed, methamphetamine use is very common in the Cape Town area (Watt et al., 2014). In addition, alcohol consumption is associated with reduced body-mass (Dumesnil et al., 2013). We did not find an effect for methamphetamine use and only a few of our patients reported abusing alcohol. However, we were unable to rule out a role for tobacco smoking as we did not have reliable data. Tobacco smoking has been reported to modify the association between cannabis use and adiposity in young men (Dube et al., 2015), although studies failed to find an effect for tobacco smoking in the relationship between cannabis use and body mass in the general population (Le Strat and Le Foll, 2011), as well as in psychiatric populations (Waterreus et al., 2016;Bruins et al., 2016).

Third, it may be that, as reported by Bruins et al. (Bruins et al., 2016), patients who discontinued cannabis use after the initiation of treatment had low baseline BMI and subsequently a greater increase in BMI. We assessed this possibility post-hoc by comparing the patients who reported cannabis use in the 3 months prior to the study but tested negative throughout the study ($n = 8$) with those who tested positive for cannabis during the study ($n = 40$). There were no differences in baseline BMI (21.2[3.8] vs 21.2 [3.68]) or endpoint BMI (20.9 [3.0] vs. 22.7 [4.8]) respectively, between these groups.

Another possible factor is genetic susceptibility, which may mediate the effect of cannabis use on BMI and metabolic syndrome risk. For example, the AKT1 risk allele increases the risk of psychosis in cannabis users, and carriers are also at greater risk of developing metabolic syndrome (Di Forti et al., 2012). However, another study found that AKT1 does not appear to mediate the effect of cannabis on BMI (Liemburg et al., 2016).

Finally, the possibility that cannabis use reduces food intake by appetite suppression should be considered. Such an association is consistent with studies reporting reduced weight gain in diet-induced obese rats fed a cannabis extract (Levendal et al., 2012;Cluny et al., 2015), and animal and human studies indicating that endocannabinoids, acting via cannabinoid (CB)[1] receptors, help to regulate energy balance by modulating hypothalamic circuits controlling food intake and energy expenditure, thereby influencing glucose uptake, lipoprotein lipase activity, lipogenesis and adipogenesis (Vettor and Pagano, 2009). However, the association between cannabis use and body weight is complex and may be influenced by neuroadaptive changes, insofar as it has been reported that CB[1] receptor downregulation and desensitisation in cortical brain regions occurs in chronic cannabis users (Hirvonen et al., 2012). Another possibility is that the cannabinoids obtained from *Cannabis sativa* interact with CB[1] and CB[2] receptors in different ways. For example, tetrahydrocannabinol (THC), the principal psycho-active constituent of cannabis, is a CB[1] and CB[2] receptor partial agonist, and cannabidiol, despite its low affinity for the CB[1] receptors, has indirect effects against CB[1] agonists via inverse agonism (Thomas et al., 2007). Therefore, depending on both the cannabinoid composition and the dose of the cannabis used, the overall effect may be either orexigenic or anorexigenic.

Strengths of this study include the well-characterised sample of first-episode patients with minimal exposure to previous antipsychotic treatment, the longitudinal nature of the study, the frequent toxicology screening tests, repeated assessments of BMI and metabolic measures and the standardized, assured antipsychotic treatment. There are a number of study limitations. First, we did not assess the frequency or type of cannabis used, nor the effect of lifetime duration of cannabis use. The latter may be important, given the finding that each year increase in marijuana use was significantly associated with increased risk of metabolic syndrome and hypertension (Yankey et al., 2016). Thus, we could not evaluate any dose-related differences or

Table 3
Number (%) of patients meeting individual and full metabolic syndrome criteria[a] at baseline and at endpoint.

	Baseline		Endpoint	
	Cannabis+	Cannabis−	Cannabis+	Cannabis−
Elevated WC (males ≥90 cm females ≥80 cm)	3 (8%)	10 (14%)	4 (10%)	25 (36%)*
Elevated triglycerides (≥1.7 mmol/l)	5(13%)	3 (4%)	7 (18%)	11 (16%)
Reduced HDL (males <1.0 mmol/l females <1.3 mmol/l)	24 (60%)	38 (55%)	27 (68%)	44 (64%)
Elevated BP (≥130 &/or ≥85 mmHg)	17 (43%)	31 (45%)	18 (45%)	31 (45%)
Elevated glucose (≥6.1 mmol/l)	1 (3%)	3 (4%)	1 (3%)	3 (4%)
Metabolic syndrome full criteria (meeting at least 3 criteria)	3 (8%)	8 (12%)	7 (18%)	14 (20%)

WC = waist circumference; HDL = high density lipoprotein cholesterol; BP = blood pressure.
[a] Metabolic syndrome criteria adapted from the Adult Treatment Panel (ATP III-A) criteria proposed by the American Heart Association (Alberti et al., 2009).
* Chi-square $p = 0.003$ for difference between cannabis positive and cannabis negative endpoint WC.

cannabinoid composition variation which may have contributed to differential effects. Second, the potential confounding effects of lifestyle, diet and tobacco smoking were not assessed. However, in the Bruins et al. study (Bruins et al., 2016), the association between metabolic risk and cannabis use remained significant after correcting for both baseline tobacco use and changes in tobacco use. Third, our findings with flupenthixol decanoate may not necessarily be generalisable to other antipsychotics. On the other hand, most antipsychotics are associated with weight gain (Leucht et al., 2013) and flupenthixol is no exception (Chiliza et al., 2015). The sample was also relatively small. Thus, while it was sufficiently powered to detect changes in BMI between the groups it may not have been able to detect smaller scale changes in lipid and glucose levels. Finally, longer term effects of cannabis beyond the first year of treatment were not assessed.

In conclusion, patients with schizophrenia spectrum disorders using cannabis gained less weight than those not using cannabis during the first year of antipsychotic treatment. Future longitudinal studies should assess possible differential effects of dose and composition of cannabis and a possible role for genetic susceptibility, as well as confounding effects of lifestyle, diet and comorbid substance use, in larger samples and over a longer follow-up period. Given the concerns regarding its deleterious effects on mental health (Murray et al., 2016) and medical health (National Academies of Science, 2017), cannabis is unlikely to be suitable as a means of preventing weight gain associated with antipsychotic treatment. However, determining the mechanisms by which cannabis reduces weight gain may offer insight into developing suitable, safe adjuncts to antipsychotic treatment to address the cardiometabolic risk associated with schizophrenia.

Conflict of interest

MK, SK, SdP, FS, LA, LP have no conflict of interest to declare. RM has received honoraria for lectures supported by Janssen, Lundbeck, Otsuka and Sunovian. MDF has received honoraria for lectures supported by Lundbeck and Janssen in 2016. SS has received speaker's honoraria and travel sponsorship from Lundbeck, Servier, Cipla, Sanofi, and Dr. Reddy's. BC has received honoraria from Cipla, Lundbeck, and Sanofi for speaking at educational meetings. RE has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck.

Contributors

All authors contributed to and have approved the final manuscript.

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References

Alberti, K.G., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I.., Donato, K.A., Fruchart, J. C., James, W.P., Loria, C.M., Smith Jr., S.C., 2009. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; world heart federation; international atherosclerosis society; and International Association for the Study of obesity. Circulation 120, 1640–1645.

Alvarez-Jimenez, M., Gonzalez-Blanch, C., Crespo-Facorro, B., Hetrick, S., Rodriguez-Sanchez, J.M., Perez-Iglesias, R., Vazquez-Barquero, J.L., 2008. Antipsychotic-induced weight gain in chronic and first-episode psychotic disorders: a systematic critical reappraisal. CNS Drugs 22, 547–562.

APA, 1994. Diagnostic and Statistical Manual of Mental Disorders. 4th edn. American Psychiatric Association, Washington: DC.

Brown, S., Birtwistle, J., Roe, L., Thompson, C., 1999. The unhealthy lifestyle of people with schizophrenia. Psychol. Med. 29, 697–701.

Bruins, J., Pijnenborg, M.G., Bartels-Velthuis, A.A., Visser, E., van den Heuvel, E.R., Bruggeman, R., Jorg, F., 2016. Cannabis use in people with severe mental illness: the association with physical and mental health–a cohort study. A pharmacotherapy monitoring and outcome survey study. J. Psychopharmacol. 30, 354–362.

Chiliza, B., Asmal, L., Oosthuizen, P., van Niekerk, E., Erasmus, R., Kidd, M., Malhotra, A., Emsley, R., 2015. Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic. Eur. Psychiatry 30, 277–283.

Chiolero, A., Faeh, D., Paccaud, F., Cornuz, J., 2008. Consequences of smoking for body weight, body fat distribution, and insulin resistance. Am. J. Clin. Nutr. 87, 801–809.

Cluny, N.L., Keenan, C.M., Reimer, R.A., Le Foll, B., Sharkey, K.A., 2015. Prevention of diet-induced obesity effects on body weight and gut microbiota in mice treated chronically with Delta9-tetrahydrocannabinol. PLoS One 10, e0144270.

Correll, C.U., Lencz, T., Malhotra, A.K., 2011. Antipsychotic drugs and obesity. Trends Mol. Med. 17, 97–107.

Correll, C.U., Ng-Mak, D.S., Stafkey-Mailey, D., Farrelly, E., Rajagopalan, K., Loebel, A., 2017. Cardiometabolic comorbidities, readmission, and costs in schizophrenia and bipolar disorder: a real-world analysis. Ann. General Psychiatry 16, 9.

de Wit, H., 2010. Flupenthixol. In: Stolerman, I.P. (Ed.), Encyclopedia of Psychopharmacology. Springer, Berlin, pp. 538–539.

Di Forti, M., Iyegbe, C., Sallis, H., Kolliakou, A., Falcone, M.A., Paparelli, A., Sirianni, M., La Cascia, C., Stilo, S.A., Marques, T.R., Handley, R., Mondelli, V., Dazzan, P., Pariante, C., David, A.S., Morgan, C., Powell, J., Murray, R.M., 2012. Confirmation that the AKT1 (rs2494732) genotype influences the risk of psychosis in cannabis users. Biol. Psychiatry 72, 811–816.

Dube, E., O'Loughlin, J., Karp, I., Jutras-Aswad, D., 2015. Cigarette smoking may modify the association between cannabis use and adiposity in males. Pharmacol. Biochem. Behav. 135, 121–127.

Dumesnil, C., Dauchet, L., Ruidavets, J.B., Bingham, A., Arveiler, D., Ferrieres, J., Ducimetiere, P., Haas, B., Bongard, V., Wagner, A., Amouyel, P., Dallongeville, J., 2013. Alcohol consumption patterns and body weight. Ann. Nutr. Metab. 62, 91–97.

Ewing, J.A., 1984. Detecting alcoholism. The CAGE questionnaire. JAMA 252, 1905–1907.

Farhat, T., Iannotti, R.J., Simons-Morton, B.G., 2010. Overweight, obesity, youth, and health-risk behaviors. Am. J. Prev. Med. 38, 258–267.

Gohlke, J.M., Dhurandhar, E.J., Correll, C.U., Morrato, E.H., Newcomer, J.W., Remington, G., Nasrallah, H.A., Crystal, S., Nicol, G., Allison, D.B., 2012. Recent advances in understanding and mitigating adipogenic and metabolic effects of antipsychotic drugs. Front. Psych. 3, 62.

Green, B., Young, R., Kavanagh, D., 2005. Cannabis use and misuse prevalence among people with psychosis. Br. J. Psychiatry 187, 306–313.

Hahn, L.A., Galletly, C.A., Foley, D.L., Mackinnon, A., Watts, G.F., Castle, D.J., Waterreus, A., Morgan, V.A., 2014. Inadequate fruit and vegetable intake in people with psychosis. Aust. N. Z. J. Psychiatry 48, 1025–1035.

Hayatbakhsh, M.R., O'Callaghan, M.J., Mamun, A.A., Williams, G.M., Clavarino, A., Najman, J.M., 2010. Cannabis use and obesity and young adults. Am. J. Drug Alcohol Abuse 36, 350–356.

Heal, D.J., Smith, S.L., Gosden, J., Nutt, D.J., 2013. Amphetamine, past and present–a pharmacological and clinical perspective. J. Psychopharmacol. 27, 479–496.

Hirvonen, J., Goodwin, R.S., Li, C.T., Terry, G.E., Zoghbi, S.S., Morse, C., Pike, V.W., Volkow, N.D., Huestis, M.A., Innis, R.B., 2012. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. Mol. Psychiatry 17, 642–649.

Huang, D.Y., Lanza, H.I., Anglin, M.D., 2013. Association between adolescent substance use and obesity in young adulthood: a group-based dual trajectory analysis. Addict. Behav. 38, 2653–2660.

Jin, L.Z., Rangan, A., Mehlsen, J., Andersen, L.B., Larsen, S.C., Heitmann, B.L., 2017. Association between use of cannabis in adolescence and weight change into midlife. PLoS One 12, e0168897.

Jones, J.D., Calkins, M.E., Scott, J.C., Bach, E.C., Gur, R.E., 2017. Cannabis use, polysubstance use, and psychosis spectrum symptoms in a community-based sample of U.S. youth. J. Adolesc. Health 60 (6), 653–659.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.

Kirkham, T.C., 2009. Cannabinoids and appetite: food craving and food pleasure 208. Int. Rev. Psychiatry 21, 163–171.

Le Strat, Y., Le Foll, B., 2011. Obesity and cannabis use: results from 2 representative national surveys. Am. J. Epidemiol. 174, 929–933.

Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R.R., Geddes, J.R., Kissling, W., Stapf, M.P., Lassig, B., Salanti, G., Davis, J.M., 2013. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 382, 951–962.

Levendal, R.A., Schumann, D., Donath, M., Frost, C.L., 2012. Cannabis exposure associated with weight reduction and beta-cell protection in an obese rat model. Phytomedicine 19, 575–582.

Liemburg, E.J., Bruins, J., van Beveren, N., Islam, M.A., Alizadeh, B.Z., 2016. Cannabis and a lower BMI in psychosis: what is the role of AKT1? Schizophr. Res. 176, 95–99.

Matsha, T.E., Hassan, M.S., Hon, G.M., Soita, D.J., Kengne, A.P., Erasmus, R.T., 2013. Derivation and validation of a waist circumference optimal cutoff for diagnosing metabolic syndrome in a South African mixed ancestry population. Int. J. Cardiol. 168, 2954–2955.

Murray, R.M., Quigley, H., Quattrone, D., Englund, A., Di Forti, M., 2016. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. World Psychiatry 15, 195–204.

National Academies of Science, 2017. E.a.M. The Health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. National Academies Press (US), Washington (DC) (1-12).

Ngueta, G., Belanger, R.E., Laouan-Sidi, E.A., Lucas, M., 2015. Cannabis use in relation to obesity and insulin resistance in the Inuit population. Obesity (Silver Spring) 23, 290–295.

Penner, E.A., Buettner, H., Mittleman, M.A., 2013. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. Am. J. Med. 126, 583–589.
Rodondi, N., Pletcher, M.J., Liu, K., Hulley, S.B., Sidney, S., 2006. Marijuana use, diet, body mass index, and cardiovascular risk factors (from the CARDIA study). Am. J. Cardiol. 98, 478–484.
Ross, J.M., Graziano, P., Pacheco-Colon, I., Coxe, S., Gonzalez, R., 2016. Decision-making does not moderate the association between cannabis use and body mass index among adolescent cannabis users. J. Int. Neuropsychol. Soc. 22, 944–949.
Sansone, R.A., Sansone, L.A., 2014. Marijuana and body weight. Innov. Clin. Neurosci. 11, 50–54.
Shen, X., Xia, J., Adams, C.E., 2012. Flupenthixol versus placebo for schizophrenia. Cochrane Database Syst. Rev. 11, CD009777.
Smit, E., Crespo, C.J., 2001. Dietary intake and nutritional status of US adult marijuana users: results from the third National Health and nutrition examination survey. Public Health Nutr. 4, 781–786.
Strassnig, M., Brar, J.S., Ganguli, R., 2003. Nutritional assessment of patients with schizophrenia: a preliminary study. Schizophr. Bull. 29, 393–397.
Thomas, A., Baillie, G.L., Phillips, A.M., Razdan, R.K., Ross, R.A., Pertwee, R.G., 2007. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br. J. Pharmacol. 150, 613–623.
Thompson, C.A., Hay, J.W., 2015. Estimating the association between metabolic risk factors and marijuana use in U.S. adults using data from the continuous National Health and Nutrition Examination Survey. Ann. Epidemiol. 25, 486–491.
Vettor, R., Pagano, C., 2009. The role of the endocannabinoid system in lipogenesis and fatty acid metabolism. Best Pract. Res. Clin. Endocrinol. Metab. 23, 51–63.
Vidot, D.C., Prado, G., Hlaing, W.M., Florez, H.J., Arheart, K.L., Messiah, S.E., 2016. Metabolic syndrome among marijuana users in the United States: an analysis of national health and nutrition examination survey data. Am. J. Med. 129, 173–179.
Waterreus, A., Di Prinzio, P., Watts, G.F., Castle, D., Galletly, C., Morgan, V.A., 2016. Metabolic syndrome in people with a psychotic illness: is cannabis protective? Psychol. Med. 46, 1651–1662.
Watt, M.H., Meade, C.S., Kimani, S., MacFarlane, J.C., Choi, K.W., Skinner, D., Pieterse, D., Kalichman, S.C., Sikkema, K.J., 2014. The impact of methamphetamine ("tik") on a peri-urban community in cape town, South Africa. Int. J. Drug Policy 25, 219–225.
World Health Organisation, 2006. Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia. Report of a WHO/IDF Consultation. World Health Organisation, Geneva, WHO Document Production Services.
Yankey, B.N., Strasser, S., Okosun, I.S., 2016. A cross-sectional analysis of the association between marijuana and cigarette smoking with metabolic syndrome among adults in the United States. Diabetes Metab. Syndr. 10, S89–S95.

CHAPTER VI

DISCUSSION

6.1. Introduction

The present chapter summarises the results of the series of studies that were conducted, and highlights the contribution of our work to the extant literature. Lastly, we discuss the primary mechanism of action and conclude by considering the implications for future research projects.

6.2. The effect of cannabis and methamphetamine use on clinical, social, and functional aspects of outcome in first-episode schizophrenia spectrum disorders

The overarching aim of the present doctoral study was to explore the effects of cannabis and methamphetamine use on selected outcomes of interest in first-episode schizophrenia spectrum disorders over 24 months of assured antipsychotic treatment. The outcomes of interest selected for the doctoral studies were psychopathology, functionality, quality of life, cognitive performance, and brain morphology (specifically, hippocampal subfields) and body mass, blood glucose and lipid profile. While a plethora of studies exist that address the question of the effect of cannabis and methamphetamine use on these selected outcomes of interest, we were able to address a number of confounding factors that make interpretation of the previously reported findings equivocal rather than clear-cut.

Previously reported studies were often cross-sectional in nature, or failed to include a suitable control group for comparison. Their diagnostic composition, illness stage, and follow-up periods also differed. Furthermore, clinical assessments as well as treatment were mostly not standardized, and the use of different antipsychotic medications were also important limitations in these prospective studies. In the case of longitudinal studies, assessment of important treatment outcomes across different clinical domains and the inclusion of standardized treatment outcomes including remission and relapse was also inconsistent. In particular, earlier studies often failed to use a standardized approach for assessing medication adherence. Lastly, the examination of ongoing cannabis and methamphetamine use was also often limited to self-report rather than in combination with toxicological assessment.

The well-characterised nature of our sample therefore addressed a number of these confounds. More specifically, sub-studies I, II, and IV utilised a longitudinal design with repeated clinical assessments with validated instruments and the standardised treatment protocol with a single antipsychotic addressed the potential confounding effects of efficacy and tolerability differences associated with different medications. An important strength of our study was the use of a long acting injectable formulation which enabled precise delivery of the prescribed antipsychotic dose and accurate assessment of treatment adherence. Unfortunately, sub-study III was restricted to a cross-sectional analysis due to high rate of missing or unusable follow-up MRI scans. This was further complicated by the high rate of comorbid methamphetamine use, or alternatively an insufficient number of participants who used only methamphetamine. However, these shortcomings were balanced by the inclusion of a suitable control group.

6.2.1. Symptom trajectory over 24 months of treatment in patients with and without cannabis and methamphetamine use

To our knowledge, at the date of submission, sub-study I was the first study to investigate the association between cannabis and methamphetamine use and treatment outcome in schizophrenia spectrum disorder when antipsychotic adherence was objectively accounted for, and antipsychotic exposure accurately quantified. We hypothesised that cannabis and methamphetamine use would be associated with poorer psychopathology outcomes and higher relapse rates. In contrast to several previous studies (Harrison et al., 2008; Baeza et al., 2009; Foti et al., 2010; Kuepper et al., 2011; van der Meer et al., 2015), we found little evidence of an association between cannabis use and greater illness severity or poorer treatment outcome in terms of symptom reduction. However, relapse events occurred more than twice as frequently in cannabis users compared to non-users. This is in keeping with the findings of systematic reviews of longitudinal studies of consistent links between cannabis use and relapse (Zammit et al., 2008).

These findings therefore suggest that symptom severity and treatment response are not adversely affected by cannabis use when antipsychotic adherence is assured, and point to an important mediating role for antipsychotic non-adherence in the previously reported association between cannabis use and poorer treatment outcomes in schizophrenia spectrum disorder (Zammit et al., 2008; Foglia et al., 2017). Moreover, our finding that more frequent positive cannabis urine testing predicted relapse suggests a dose-risk effect, and that continued use, rather than an enduring effect of past use, is the critical factor (Schoeler et al., 2017a; Schoeler et al., 2017b).

6.2.2. The associations of cannabis and methamphetamine use with cognitive performance in first-episode schizophrenia spectrum disorders over 24 months of treatment

As far as we are aware, sub-study II is the first study to assess the independent effects of cannabis and methamphetamine use on cognition in patients with schizophrenia spectrum disorders in a longitudinal design. We hypothesised that cannabis and methamphetamine would exert independent dose and time related effects on cognitive performance. Our main finding was that of a dose-related (i.e. number of positive tests) negative effect for methamphetamine use, but no significant effect for cannabis use, on cognitive performance over the 24 month treatment period. The finding that methamphetamine use was associated with poorer cognitive performance in our patients with schizophrenia spectrum disorders is similar to what has been found in general population samples of methamphetamine users. A meta-analysis of people with methamphetamine use disorder (not specifically with psychosis) reported moderate cognitive deficits across most cognitive domains compared to healthy controls (Potvin et al., 2018). Our finding is also consistent with reports of cognitive impairments in methamphetamine users with chronic psychosis (Wearne & Cornish 2018).

Our study sample was carefully characterised. Psychiatrists performed the initial evaluations and the diagnosis was confirmed by a panel of study psychiatrists. Follow-up clinical assessments monitored the diagnostic consistency over time. A critical factor in our studies, and particularly in sub-study II, was the exclusion of patients with substance-induced psychotic disorders, substance dependence or substance-withdrawal disorders. The diagnostic interface between substance-induced psychosis and schizophrenia spectrum disorders is not clear cut, and whether these are separate disorders or not remains controversial (Dragogna, et al., 2014; Green & Glausier, 2015; Håkansson & Johansson, 2015; Morales-Muñoz, et al., 2014). Therefore, our findings need to be interpreted with this in mind and cannot be generalised to individuals with more severe substance use disorders. In other words, our sample represents those individuals considered to have a primary diagnosis of a schizophrenia spectrum disorder, of whom a substantial proportion used cannabis and/or methamphetamine, but without meeting criteria for dependence, withdrawal or substance-induced psychosis.

6.2.3. Cannabis use and pre-treatment brain morphological concomitants in first-episode schizophrenia spectrum disorders

In sub-study III, our finding of differences in hippocampal subfield volumes in cannabis using and non-using patients and controls highlighted the importance of considering the impact of cannabis use in both patient and control populations. This is necessary in order to identify differential effects of substance use on brain morphology in patients versus healthy individuals. We hypothesised that cannabis use would be associated with brain structural differences compared to controls. While our finding of reduced subiculum volumes in cannabis using compared to cannabis non-using controls was consistent with previous findings in general population samples with and without cannabis use (Demirakca et al 2011; Pagliaccio et al 2015; Yücel et al 2015; Koenders et al 2016; Gilman et al 2018; Lorenzetti et al 2018), our finding of increased subiculum volumes in cannabis using patients compared to cannabis non-using patients was somewhat unexpected, given the previously reported finding of greater

grey matter volume reductions and ventricular enlargements in schizophrenia patients who use cannabis compared to non-users (Rais et al 2008). However, increases in other subcortical structure volumes such as the putamen has previously been reported in patients with schizophrenia who use cannabis compared to non-users (Koenders et al 2015).

Our finding of an illness-specific differential effect on the hippocampal structure raises important questions regarding the pathophysiology of schizophrenia spectrum disorders and the role of cannabis use therein. We recommended that future research should also investigate the effects of frequency, potency and composition of cannabis, as well as moderating genetic and other environmental effects such as alcohol and tobacco use, on hippocampal subfields in first episode schizophrenia spectrum disorders over an extended follow-up period.

6.2.4. The associations of cannabis and methamphetamine use and body mass, blood glucose and lipid profiles in first-episode schizophrenia spectrum disorders over 12 months of treatment

At the time of publication, sub-study IV was the first to investigate the relationship between cannabis use and measures of metabolic syndrome in a cohort of minimally treated or antipsychotic naïve first-episode schizophrenia patients longitudinally. Based on reports of increased appetite and weight gain associated with cannabis use (Kirkham, 2009) we hypothesized that cannabis use would be associated with an increased risk for treatment-emergent metabolic syndrome changes. Rather, we found that patients with schizophrenia who used cannabis during their first year of treatment gained significantly less weight compared to non-users, and the non-cannabis using patients showed significantly more deterioration of their metabolic profiles. Our findings are consistent with reports of a reduced prevalence of obesity in cannabis users in general adult population samples (Hayatbakhsh et al., 2010; Le Strat and Le Foll, 2011; Ngueta et al., 2015; Penner et al., 2013; Smit and Crespo, 2001; Thompson and Hay, 2015), as well as with the reports of a lower BMI in severely

mentally ill patients who use cannabis (Bruins et al., 2016). Although there were no significant differences in rates of metabolic syndrome, more of the non-using patients had elevated waist circumference at endpoint, consistent with the report of fewer metabolic syndrome risk factors in psychotic patients who used cannabis (Waterreus et al., 2016).

While the effects of cannabis use on cardiometabolic risk factors appeared to be somewhat beneficial, cannabis is unlikely to be suitable as a means of preventing weight gain associated with antipsychotic treatment, similarly to other recreational substances such as methamphetamine, tobacco and alcohol, given the concerns regarding its recognized detrimental effects on mental (Murray et al., 2016) and general (National Academies of Science, 2017) health. However, the research into the potential therapeutic benefits associated with cannabidiol (CBD) is promising and it is recommended that future research consider investigating its effect on cardiometabolic risk factors as a potential means of offsetting the increased risk for cardiometabolic ill-health associated with prolonged antipsychotic medication exposure (Brown et al., 1999; Gohlke et al., 2012; Strassnig et al., 2003).

6.3. Effects of cannabis use on dopamine metabolism in schizophrenia spectrum disorders

The interaction between dopamine and endocannabinoid signalling represents a possible mechanistic link between cannabis use and its effects on treatment outcome in first-episode schizophrenia. Aberrant dopaminergic neurotransmission is implicated as a core feature of schizophrenia spectrum disorders and an important treatment target (Brisch et al., 2014; Kesby et al., 2018). The exogenous cannabinoids delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are thought to have opposing effects on dopamine signalling (Bloomfield et al., 2017; Bloomfield et al., 2019). THC is the main psychoactive compound in cannabis and a potent CB1 receptor agonist which has region-specific effects on different parts of the brain depending on cannabinoid receptor density (Bloomfield et al., 2017). CBD on the other

hand is an indirect CB1 agonist thought to counteract the effects of THC in the brain (Coulston et al., 2011; Osborne et al., 2017; Sami and Bhattacharyya, 2018). The opposing effects of THC and CBD on cannabinoid signalling further affect its complex interactions with central dopamine signalling and metabolism (see for e.g. Thomas et al., 2007; Baik 2013; Meiser et al., 2013).

6.4. Effects of cannabis and methamphetamine use on dopamine metabolism in schizophrenia spectrum disorders

Methamphetamine had a significant effect on cognition in first-episode schizophrenia, although it was difficult to disentangle the comorbid role of cannabis use in our sample (Chapter III). The inverted U-shaped dose-effect curve for methamphetamine describes better short-term cognitive functioning at low doses due to moderate dopamine receptor (D1) activation (Silber et al., 2006). In contrast, higher doses of methamphetamine activate D1 receptors to such an extent that prefrontal cortical signals are excessively inhibited (Muly et al., 1998) resulting in impaired cognitive function (Schroder et al., 2003). The timing of exposure to substance use in our sample could have influenced our results. In particular, age of onset of use is important, since cannabis use during adolescence might have long-term effects on dopamine metabolism and risk for addiction (Bloomfield, 2017). Future studies would do well to examine patterns of comorbid substance use over time in terms of age of onset of use, dosage, frequencies of use, and pharmacological profiles.

6.3. Conclusions

The findings emerging from the doctoral studies described in this dissertation suggest that ongoing cannabis and methamphetamine use has differential effects on symptom expression and brain morphology, as well as on specific domains of outcome during the early years of treatment in first-episode schizophrenia spectrum disorder patients. The sub-studies that we chose were highly selective, and we did not attempt to address all aspects of cannabis and methamphetamine use and schizophrenia spectrum disorders. We chose this approach based

on what we considered were the most important research questions that our unique dataset could best address. The majority of the sub-studies focused on cannabis use while controlling for methamphetamine use in order to highlight the stronger association of cannabis use with the outcomes of interest in each study. A strong association of methamphetamine was identified in sub-study II and appropriately addressed in the published manuscript.

While the doctoral sub-studies reported in this dissertation addressed a number of important potentially confounding factors, more questions were raised regarding the mechanism of action. Each of the doctoral sub-studies considered the interplay between the endocannabinoid signalling system (ECS), dopamine receptor activity, and the intake of exogenous cannabinoids such as cannabidiol (CBD) and tetrahydrocannabinol (THC). A number of projects are currently under development to further investigate the differential effects for THC and CBD. These are discussed in more detail in the concluding chapter.

REFERENCES

Baeza, I., Graell, M., Moreno, D., et al. 2009. Cannabis use in children and adolescents with first episode psychosis: Influence on psychopathology and short-term outcome (CAFEPS study). *Schizophrenia Research,* 113, 129–137. https://doi.org/10.1016/j.schres.2009.04.005

Baik J. H. 2013. Dopamine signaling in reward-related behaviors. *Frontiers in neural circuits*, *7*, 152. https://doi.org/10.3389/fncir.2013.00152

Bloomfield, M.A.P., Ashok, A.H., Volkow, N.D., Oliver, D., 2017. The effects of Δ9-tetrahydrocannabinol on the dopamine system. Nature 539, 369–377. https://doi.org/10.1038/nature20153.

Bloomfield, M.A.P., Hindocha, C., Green, S.F., Wall, M.B., Lees, R., Petrilli, K., Costello, H., Ogunbiyi, M.O., Bossong, M.G., Freeman, T.P., 2019. The neuropsychopharmacology of cannabis: A review of human imaging studies. Pharmacol. Ther. 195, 132–161. https://doi.org/10.1016/j.pharmthera.2018.10.006

Brisch, R., Saniotis, A., Wolf, R., Bielau, H., Bernstein, H.G., Steiner, J., Bogerts, B., Braun, K., Kumaratilake, J., Henneberg, M., Gos, T., 2014. The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: Old fashioned, but still in vogue. Front. Psychiatry 5, 1–11. https://doi.org/10.3389/fpsyt.2014.00047

Brown, S., Birtwistle, J., Roe, L. and Thompson, C., 1999. The unhealthy lifestyle of people with schizophrenia. *Psychol Med.* 29, 697-701.

Bruins, J., Pijnenborg, M.G., Bartels-Velthuis, A.A., Visser, E., van den Heuvel, E.R., Bruggeman, R. and Jorg, F., 2016. Cannabis use in people with severe mental illness: The association with physical and mental health--a cohort study. A Pharmacotherapy Monitoring and Outcome Survey study. *J Psychopharmacol.* 30, 354-362.

Coulston, C.M., Perdices, M., Henderson, A.F., Malhi, G.S., 2011. Cannabinoids for the Treatment of Schizophrenia? A Balanced Neurochemical Framework for Both Adverse and Therapeutic Effects of Cannabis Use. Schizophr. Res. Treatment 2011, 1–9. https://doi.org/10.1155/2011/501726

Demirakca, T., Sartorius, A., Ende, G., Meyer, N., Welzel, H., Skopp, G., et al. 2011. Diminished gray matter in the hippocampus of cannabis users: Possible protective effects of cannabidiol. *Drug and Alcohol Dependence*, 114(2-3), 242–245. http://doi.org/10.1016/j.drugalcdep.2010.09.020

Foglia, E., Schoeler, T., Klamerus, E., Morgan, K., Bhattacharyya, S., 2017. Cannabis use and adherence to antipsychotic medication: a systematic review and meta-analysis. *Psychol. Med.* 47, 1691–1705. https://doi.org/10.1017/S0033291717000046

Foti, DJ., Kotov, R., Guey, LT., & Bromet, EJ. 2010. Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization. *AM J Psychiatry,* 167, 987–993.

Gilman, J., Ulysse, C., Schoenfeld, D., & Evins, A. E. 2018. S260. An Updated Report of Associations Between Cannabis Use and Brain Structure. *Biological Psychiatry,* 83(Supplement), S449. http://doi.org/10.1016/j.biopsych.2018.02.1152

Gohlke, J.M., Dhurandhar, E.J., Correll, C.U., Morrato, E.H., Newcomer, J.W., Remington, G., Nasrallah, H.A., Crystal, S., Nicol, G. and Allison, D.B., 2012. Recent advances in understanding and mitigating adipogenic and metabolic effects of antipsychotic drugs. *Front Psychiatry.* 3, 62.

Green, I. W., & Glausier, J. R. 2015. Different Paths to Core Pathology: The Equifinal Model of the Schizophrenia Syndrome. *Schizophr Bull*, Sep 20. pii: sbv136. [Epub ahead of print] PubMed PMID: 26392629.

Harrison, I., Joyce, EM., Mutsatsa, SH., et al. 2008. Naturalistic follow-up of co-morbid substance use in schizophrenia: The West London first-episode study. *Psychological Medicine,* 38, 79–88. https://doi.org/10.1017/S0033291707000797

Hayatbakhsh, M.R., O'Callaghan, M.J., Mamun, A.A., Williams, G.M., Clavarino, A. and Najman, J.M., 2010. Cannabis use and obesity and young adults. *Am J Drug Alcohol Abuse.* 36, 350-356.

Kesby, J.P., Eyles, D.W., McGrath, J.J., Scott, J.G., 2018. Dopamine, psychosis and schizophrenia: The widening gap between basic and clinical neuroscience. Transl. Psychiatry 8. https://doi.org/10.1038/s41398-017-0071-9

Kirkham, T.C., 2009. Cannabinoids and appetite: food craving and food pleasure. Int Rev Psychiatry. 21, 163-171.

Koenders, L., Machielsen, M. W. J., van der Meer, F. J., van Gasselt, A. C. M., Meijer, C. J., van den Brink, W., et al. 2015. Brain volume in male patients with recent onset schizophrenia with and without cannabis use disorders. *Journal of Psychiatry & Neuroscience*, 40(3), 197–206. http://doi.org/10.1503/jpn.140081

Koenders, L., Cousijn, J., Vingerhoets, W. A. M., van den Brink, W., Wiers, R. W., Meijer, C. J., et al. 2016. Grey Matter Changes Associated with Heavy Cannabis Use: A Longitudinal sMRI Study. *Plos One,* 11(5), e0152482–13. http://doi.org/10.1371/journal.pone.0152482

Kuepper, R., van Os, J., Lieb, R., Wittchen, HU., Hofler, M., & Henquet, C. 2011. Continued cannabis use and risk of incidence and persistence of psychotic symptoms: 10 year follow-up cohort study. *BMJ,* 342, 1–8. https://doi.org/10.1136/bmj.d738

Le Strat, Y. and Le Foll, B., 2011. Obesity and cannabis use: results from 2 representative national surveys. *Am J Epidemiol.* 174, 929-933.

Lorenzetti, V., Solowij, N., Whittle, S., Fornito, A., Lubman, D. I., Pantelis, C., & Yücel, M. 2018. Gross morphological brain changes with chronic, heavy cannabis use. The *British Journal of Psychiatry,* 206(01), 77–78. http://doi.org/10.1192/bjp.bp.114.151407

Meiser, J., Weindl, D., & Hiller, K. 2013. Complexity of dopamine metabolism. *Cell communication and signaling : CCS*, *11*(1), 34. https://doi.org/10.1186/1478-811X-11-34

Muly, E. C., Szigeti, K., and Goldman-Rakic, P. S. 1998. D1 receptor in interneu- rons of macaque prefrontal cortex: distribution and subcellular localization. *J. Neurosci.* 18, 10553–10565.

Murray, R.M., Quigley, H., Quattrone, D., Englund, A. and Di Forti, M., 2016. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry.* 15, 195-204.

National Academies of Science, E.a.M. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, *Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda.* 1-12-2017. Washington (DC), National Academies Press (US).

Ngueta, G., Belanger, R.E., Laouan-Sidi, E.A. and Lucas, M., 2015. Cannabis use in relation to obesity and insulin resistance in the Inuit population. *Obesity* (Silver Spring). 23, 290-295.

Osborne, A.L., Solowij, N., Weston-Green, K., 2017. A systematic review of the effect of cannabidiol on cognitive function: Relevance to schizophrenia. Neurosci. Biobehav. Rev. 72, 310–324. https://doi.org/10.1016/j.neubiorev.2016.11.012

Pagliaccio, D., Barch, D. M., Bogdan, R., Wood, P. K., Lynskey, M. T., Heath, A. C., & Agrawal, A. 2015. Shared Predisposition in the Association Between Cannabis Use and Subcortical Brain Structure. *JAMA Psychiatry,* 72(10), 994–8. http://doi.org/10.1001/jamapsychiatry.2015.1054

Penner, E.A., Buettner, H. and Mittleman, M.A., 2013. The impact of marijuana use on glucose, insulin, and insulin resistance among US adults. *Am J Med.* 126, 583-589.

Potvin, S., Pelletier, J., Grot, S., Hébert, C., Barr, A., Lecomte, T., 2018. Cognitive deficits in individuals with methamphetamine use disorder: A meta-analysis. *Addict. Behav*. 80, 154–160. https://doi.org/10.1016/j.addbeh.2018.01.021

Rais, M., Cahn, W., Van Haren, N., Schnack, H., Caspers, E., Pol, H.H., Kahn, R., 2008. Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. *Am. J. Psychiatry* 165, 490–496. https://doi.org/10.1176/appi.ajp.2007.07071110

Sami, M.B., Bhattacharyya, S., 2018. Are cannabis-using and non-using patients different groups? Towards understanding the neurobiology of cannabis use in psychotic disorders. J. Psychopharmacol. 32, 825–849. https://doi.org/10.1177/0269881118760662

Schoeler, T., Petros, N., Di Forti, M., Klamerus, E., Foglia, E., Murray, R., Bhattacharyya, S., 2017a. Effect of continued cannabis use on medication adherence in the first two years following onset of psychosis. *Psychiatry Res*. 255, 36–41. https://doi.org/10.1016/j.psychres.2017.05.009

Schoeler, T., Petros, N., Di Forti, M., et al. 2017b. Poor medication adherence and risk of relapse associated with continued cannabis use in patients with first-episode psychosis: a prospective analysis. *The Lancet Psychiatry*, 4, 627–633. https://doi.org/10.1016/s2215-0366(17)30233-x

Schroder, N., O'Dell, S. J., andMarshall, J. F. (2003). Neurotoxic methamphetamine regimen severely impairs recognition memory in rats. *Synapse* 49, 89–96. doi: 10.1002/syn.10210

Silber, B. Y., Croft, R. J., Papafotiou, K., and Stough, C. (2006). The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology* 187, 154–169. doi: 10.1007/s00213-006-0410-7

Smit, E. and Crespo, C.J., 2001. Dietary intake and nutritional status of US adult marijuana users: results from the Third National Health and Nutrition Examination Survey. *Public Health Nutr.* 4, 781-786.

Strassnig, M., Brar, J.S. and Ganguli, R., 2003. Nutritional assessment of patients with schizophrenia: a preliminary study. *Schizophr Bull.* 29, 393-397.

Thomas MJ, Kalivas PW, Shaham Y. 2008. Neuroplasticity in the mesolimbic dopamine system and cocaine addiction. Br J Pharmacol. 2008 May;154(2):327-42. doi: 10.1038/bjp.2008.77.

Thompson, C.A. and Hay, J.W., 2015. Estimating the association between metabolic risk factors and marijuana use in U.S. adults using data from the continuous National Health and Nutrition Examination Survey. *Ann Epidemiol.* 25, 486-491.

van der Meer, F.J., Velthorst, E., Genetic Risk and Outcome in Psychosis (G.R.O.U.P), 2015. Course of cannabis use and clinical outcome in patients with non-affective psychosis: A 3-year follow-up study. *Psychol. Med*. 45, 1977–1988. https://doi.org/10.1017/S0033291714003092

Waterreus, A., Di P.P., Watts, G.F., Castle, D., Galletly, C. and Morgan, V.A., 2016. Metabolic syndrome in people with a psychotic illness: is cannabis protective? *Psychol Med.* 46, 1651-1662.

Wearne, T.A., Cornish, J.L., 2018. A comparison of methamphetamine-induced psychosis and schizophrenia: A review of positive, negative, and cognitive symptomatology. *Front. Psychiatry* 9, 1–21. https://doi.org/10.3389/fpsyt.2018.00491

Yücel, M., Bora, E., Lubman, D.I., Solowij, N., Brewer, W.J., Cotton, S.M., Conus, P., Takagi, M.J., Fornito, A., Wood, S.J., McGorry, P.D., Pantelis, C., 2012. The impact of cannabis use on cognitive functioning in patients with schizophrenia: A meta-analysis of existing findings and new data in a first-episode sample. *Schizophr. Bull*. 38, 316–330. https://doi.org/10.1093/schbul/sbq079

Zammit, S., Moore, T.H.M., Lingford-Hughes, A., Barnes, T.R.E., Jones, P.B., Burke, M., Lewis, G., 2008. Effects of cannabis use on outcomes of psychotic disorders: systematic review. *Br. J. Psychiatry* 193, 357–363. https://doi.org/10.1192/bjp.bp.107.046375

CHAPTER VII

CONCLUSIONS

7.1. Introduction

The present chapter provides a synthesis of the overall insights gathered as a result of the doctoral studies described in this dissertation. A summary and synthesis of the research findings along with the strengths and limitations of the study, followed by a reflection on the study aims and objectives as outlined in the introductory chapter are provided. Finally, recommendations for future research studies including those in current development are discussed, and an overall conclusion provided.

7.2. Summary of our research findings

The uniqueness of our study design and the selected choice of research objectives allowed us to make several notable contributions to the extant literature. First, we found limited evidence for an effect of cannabis use on clinical improvement over 24 months in first-episode schizophrenia spectrum disorder patients. That being said, relapse events were more common in cannabis users compared to their non-using counterparts (Chapter II). Second, despite improvements in cognition over the course of assured treatment, overall impairment relative to controls remained over 24 months of treatment with a stronger negative association of methamphetamine in particular (Chapter III). Third, we found differential illness-specific associations with cannabis use with hippocampal subfield volumes, specifically with increased subiculum volume in male cannabis using first-episode schizophrenia spectrum disorder patients compared to controls (Chapter IV). First-episode schizophrenia spectrum disorder patients who used cannabis also gained less weight over 12 months of assured treatment exposure compared to their non-using counterparts (Chapter V).

7.3. Strengths and limitations

Although the findings from each of the manuscripts were clear-cut, a number of study limitations need to be taken into account to temper their interpretation. The main limitation faced by the doctoral studies was the nature of the substance use data available for analysis. We were not able to address the type and frequency of cannabis and methamphetamine used,

as this information was not captured. Tobacco smoking and alcohol consumption was also not quantified in detail. The doctoral study was a sub-study of a larger parent project in which information regarding substance use was captured primarily in the SCID, a non-validated structured alcohol use questionnaire, and clinical interviews with patients and caregivers. All of the data that was available was utilised to give as clear a description of participants' use of tobacco, alcohol, cannabis and methamphetamine use as possible. Nevertheless, utilising both urine toxicology screening, together with patient- and carer-based report, provided both objective and subjective measures of our primary predictor variable.

Despite a moderately large sample size overall, subgroup sizes with all valid data points present resulted in somewhat smaller participant numbers per group. This was particularly evident in the neuroimaging component of the study. Utilising mixed models for repeated measures (MMRM) in the longitudinal assessments was particularly advantageous as this statistical model accounts for missing values and allows for the inclusion of a larger number of data points per analysis.

Finally, our results cannot necessarily be generalised to other populations, or indeed treatment with antipsychotic medications other than flupenthixol decanoate. The longer-term effects of cannabis and methamphetamine use beyond the first two years of treatment were also not assessed. However, the study's core strength lies in the well-characterised nature of our sample and the systematic, repeated assessments administered over a period of 24 months. Selection of first-episode schizophrenia spectrum disorder patients with minimal prior treatment exposure addressed the confounding effects of illness chronicity and medication status on outcome measures of interest. In addition, the inclusion of healthy controls from the same catchment area allowed us to assess the illness-specific effects of cannabis and methamphetamine use on neurocognitive, neurobiological, and metabolic outcomes.

7.4. Reflection on study aims and objectives

The overarching aim of the present doctoral research was to explore the effects of cannabis and methamphetamine use on pre-treatment symptom severity and brain structure, and on treatment effects on psychopathology, functionality, cognition and emergent metabolic syndrome risk factors, in individuals with first-episode schizophrenia spectrum disorders.

This aim was divided into four distinct objectives which were as follows:

5) To examine the associations of cannabis use with psychopathology improvement and relapse rates in patients with SSD treated with a long-acting injectable antipsychotic over 24 months (Chapter Two)
6) To examine the differential associations of cannabis use compared to methamphetamine use on cognitive performance in patients with SSD treated with a long-acting injectable antipsychotic over 24 months (Chapter Three)
7) To examine the associations of cannabis use with pre-treatment brain structural differences, specifically hippocampal volumes in patients with SSD at baseline assessment (Chapter Four)
8) To examine the associations of cannabis use with metabolic syndrome risk factors in patients with SSD treated with a long-acting injectable antipsychotic over 24 months (Chapter Five)

The aims and objectives as set out at the beginning of the study were achieved and meaningful contributions to the extant body of literature made. Each of these objectives were reported as separate but related studies, and were submitted for peer-review as independent manuscripts to scientific journals. Moreover, each manuscript addressed a specific research question that was developed by carefully considering the strengths and limitations of the core study as outlined above. At the date of submission of this dissertation three of the four manuscripts have been published and the fourth is currently under revision. The purpose of the present dissertation was to better understand the associations of cannabis and methamphetamine use

with the clinical expression and treatment response in people with schizophrenia spectrum disorders from our local community. In addition, the study has provided our research team with an opportunity to develop our skills in the field and to define priority areas for future research. Our results will be of interest to policymakers and clinicians and will hopefully translate into improved care. For example, the prescription of a long-acting injectable as the preferred treatment for first-episode schizophrenia spectrum disorder patients who are currently using cannabis and/or methamphetamine may be particularly important.

7.5. Future research

The doctoral studies described in this dissertation unearthed a number of avenues for future research. These include the need for projects examining detailed lifetime exposure to cannabis and methamphetamine, as well as the effects of other substances. Future studies would also do well to use standardized clinical questionnaires to capture detailed information on substance use. This would include the age of onset, frequency, and duration of cannabis use, as well as other substances. Also, longer-term studies are required to establish the enduring associations of substance use and outcome in schizophrenia spectrum disorders. There is also a need for more information on the cannabinoid profiles of different cannabis strains and their associations with illness expression and outcome in schizophrenia spectrum disorders.

In keeping with the above research needs, a number of projects emanating from the present doctoral studies are in development:

- The research potential in our setting is unique, given the high prevalence of comorbid substance use. This was exemplified in our sample, where cannabis users often also used methamphetamine. Our research team thus plans to use structural neuroimaging to examine the associations of both substances with changes in brain structural connectivity and white matter microstructure over the course of treatment. While a

substantial literature exists on cannabis use and the brain in schizophrenia spectrum disorder, few studies have investigated the effects of methamphetamine use.

- There is a need for better treatment options to address comorbid substance use in schizophrenia spectrum disorders. The doctoral candidate has secured ethics approval and funding to conduct pilot research to be conducted at an addiction treatment facility in the Western Cape. The research aim is to examine the association between stress and craving using virtual reality as a promising treatment option to support substance use cessation in a community-based health setting. This could assist teaching of effective coping strategies in order to decrease rates of relapse in high-risk individuals.
- In addition to emerging technologies, several cost-effective pharmacological options might help improve treatment outcomes in first-episode schizophrenia spectrum disorder patients who use substances. In this context, a proof-of-concept randomized placebo-controlled trial is being developed with the aim of comparing the effectiveness and tolerability of cannabidiol (CBD) supplementation to antipsychotic treatment and its effects on relapse-prevention in schizophrenia spectrum disorders. Other outcomes of interest will include the effects of CBD on the temporal evolution of metabolic syndrome risk factors over time.

7.6. Conclusion

In conclusion, the findings emerging from the doctoral studies described in this dissertation identify several important associations between the two most commonly used illicit substances in our community and brain morphology and symptom expression of schizophrenia spectrum disorders pre-treatment and during the early years of treatment. The effects of cannabis use in particular on clinical outcomes appear to be subtle, but might have important implications for treatment. More well designed research studies on the effects of methamphetamine are urgently needed.