ADOLESCENT CANNABIS USE, PSYCHOTIC-LIKE EXPERIENCES, AND THEIR IMPACT ON BRAIN WHITE MATTER IN A SAMPLE OF DEVELOPING ADOLESCENTS

By

Nicole D. Ponto

Submitted in partial fulfillment of the requirements

for the degree of Master of Science

at

Dalhousie University

Halifax, Nova Scotia

July 2025

Dalhousie University is located in Mi'kma'ki, the ancestral and unceded territory of the Mi'kmaq. We are all Treaty people.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Background: Adolescence is characterized by a period of critical neurodevelopment particularly within brain white matter. Adolescent cannabis use, especially when started early, and used at a high potency, has been shown to increase one's risk for developing a psychotic disorder later in life 4-16x. Psychotic-like experiences (PLEs) are another factor that has been independently linked to the development of psychotic disorders. While these factors have not been examined together, preliminary studies show white matter alterations associated with both cannabis use and PLEs in adolescence, this suggests a potential neurobiological mechanism which could further explain the increased risk for psychotic disorders these individuals experience. We hypothesized that the white matter alterations seen within each factor were not independent but instead produced an interactive effect on brain white matter, further increasing one's likelihood of developing a psychotic disorder. Methods: A total sample size of 123 15–16-year-olds participated (Cannabis User = 36, Non-User = 87). Participants took part in an interview examining physical and psychological health, and previous and current substance use, they also took part in a magnetic resonance imaging (MRI) scan where both structural and diffusion sequences were acquired. White matter analysis in adolescence proves challenging due to methodological constraints, chapter 2 of this thesis aimed to address this by developing the first adolescent population specific white matter atlas. A detailed screening of physical and psychological health, and history of past and current substance use were taken. A total sample of 54 screened healthy 15–16-year-olds were included in the atlas. Chapter 3 of this thesis used the information from the interview to group participants based on the presence of a PLE (n = 24), and reported cannabis use in the last 6 months (n = 36) and examined our hypotheses using advanced neuroimaging techniques to examine white matter integrity (NODDI) and markers of neuroinflammation (DKI). Results: Results from Chapter 2 include the successful development and validation of a population specific white matter atlas, which accounts for adolescent specificity within developing white matter tracts. Chapter 3 used the aforementioned white matter atlas to examine white matter alterations within the cannabis using and PLE+ groups of adolescents. There were no significant results found when comparing white matter in healthy controls to either cannabis using or PLE+ groups. Furthermore, our hypothesis that cannabis use and PLEs would have interactive effects on white matter alterations was not supported. Exploratory analyses highlighted sex as an important predictor, and use of continuous cannabis use measures found significant differences in white matter between cannabis using and PLE+ groups. Discussion: This is the first study to examine white matter alterations and both cannabis use and PLEs in an adolescent sample. We were successful in developing and validating the first adolescent white matter atlas with a detailed history of health, and we were able to evaluate this atlas within our larger sample. While we did not find any significant differences between cannabis using and PLE+ groups, nor any interaction effects, though exploratory analyses we highlighted the need for further research into the interaction between cannabis use, PLEs, and brain white matter alterations. Interestingly we did not replicate the white matter alteration findings of either cannabis use or PLEs, but this could be due to the use of better representative measures (i.e.: MD, MK, and ODI) and a population specific validated white matter atlas. It is important that future studies build on the work highlighted in this thesis, with larger sample sizes, and continuous measures of cannabis use. Overall, the findings of this thesis offer empirical insight and a methodological foundation for future studies that may inform evidence-based screening and intervention for adolescents at risk for developing a psychotic disorder.

LIST OF ABBREVIATIONS USED

2-AG	2-arachindonoylyglycerol
3T	3 Tesla
ACC	Anterior Cingulate Cortex
AD	Axial Diffusivity
AIC	Akaike Information Criterion
AK	Axial Kurtosis
ANTs	Advanced Normalization Tools
APSS	Adolescent Psychotic-Like Symptom Screener
AUDIT	Alcohol Use Disorder Identification Test
BAI	Becks Anxiety Inventory
BDI	Becks Depression Inventory
BIC	Bayesian Information Criterion
BIDS	Brain Imaging Data Structure
BMI	Body Mass Index
CAPE	Community Assessment of Psychic Experience
CB1	Cannabinoid Receptor – 1
CC	Corpus Callosum

CHR	Clinical High Risk
CIDI	Composite International Diagnostic Interview
CJV	Coefficient of Joint Variation
CU	Cannabis Use
CUAD	Chemical Use, Abuse, and Dependence
CUD	Cannabis Use Disorder
CUDIT-R	Cannabis Use Disorder Identification Test - Revised
DICOMS	Digital Imaging and Communications in Medicine
DKI	Diffusion Kurtosis Imaging
DKT	Desikan-Killiany-Tourville
DIPY	Diffusion Imaging in Python
DTI	Diffusion Tensor Imaging
EDS	E-Cigarette Dependence scale
ECS	Endocannabinoid System
EPP	Early Phase Psychosis
FA	Fractional Anisotropy
FSPGR	Fast Spoiled Gradient Echo Sequence
FTND	Fagerstrom Nicotine Dependence scale

H1	Hypothesis 1
H2	Hypothesis 2
H3	Hypothesis 3
H4	Hypothesis 4
H5	Hypothesis 5
HD	Hausdorff Distance
HRM	Halifax Regional Municipality
IFOF	Inferior Fronto-orbital Fasciculus
ILF	Inferior Longitudinal Fasciculus
JHU	Johns Hopkins University
K-SADS	Kiddie Schedule for Affective Disorders
MD	Mean Diffusivity
MK	Mean Kurtosis
MNI	Montreal Neurological Institute
MPRAGE	Magnetization-Prepared Rapid Gradient Echo Sequence
MRI	Magnetic Resonance Imaging
MSMT-CSD	Multi-Tissue Multi-Shell Constrained Spherical Deconvolution
NICE	National Institute for Health and Care Excellence

NIFTI	Neuroimaging Informatics Technology Initiative
NODDI	Neurite Orientation Diffusion Dispersion Index
NS	Not Specified
ODI	Orientation Dispersion Index
OR	Odds Ratio
ORG	O'Donnell Research Group
PANSS	Positive and Negative Symptom Scale
PET	Positron Emission Tomography
PLEs	Psychotic-like Experiences
QC	Quality Control
RD	Radial Diffusivity
RK	Radial Kurtosis
ROI	Region of Interest
SCID	Structured Clinical Interview
SLF	Superior Longitudinal Fasciculus
SNR	Signal to Noise Ratio
T1W	T1 – Weighted
TE	Echo Time

THC	Δ9-tetrahydrocannabinol
TLFB	Timeline Follow Back
TR	Repetition Time
UF	Uncinate Fasciculus
WM	White Matter
Y-VACS	Yale-Vermont Adversity in Childhood Scale

ACKNOWLEDGEMENTS

To my supervisors, Dr. Candice Crocker and Dr. Philip Tibbo: Thank you for your continuous support, mentorship, and encouragement throughout my MSc. I am so grateful for the opportunity to learn from leaders who embody both scientific excellence and compassion. Your thoughtful feedback, patience, and dedication pushed me to grow into a more confident and capable researcher (and writer). I truly could not have asked for better support in this process.

To my committee members, Dr. Matthias Schmidt, and Dr. Sabina Abidi: Thank you for sharing your time, expertise, and insights. Your feedback challenged me to think more critically and elevated the quality of my work in meaningful ways. The smiles and thumbs up from the back of the room during committee meetings never went unnoticed and always lifted my spirits. To Dr. Frank MacMaster, thank you for serving as my external examiner and for engaging so thoughtfully with my work.

To my colleagues and friends in the lab, thank you for your enduring support, shared moments of frustration and joy, and the friendships that made this experience all the more meaningful. To my friends outside of the lab who kept me grounded through it all: your patience, laughter, and encouragement made the long days feel a little shorter. I am so lucky to have had you all by my side.

Lastly, to the participants who made this research possible – thank you for your time, your trust, and your stories. This work is truly inspired by you.

CHAPTER 1. GENERAL INTRODUCTION

1.1 PSYCHOSIS AND PSYCHOTIC DISORDERS

The global prevalence of psychotic disorders is estimated to be approximately 24 million individuals worldwide (X. Li et al., 2023). The overall pooled incidence of all psychotic disorders internationally is 26.6 per 100 000 people/year (Jongsma et al., 2019). Psychotic disorders represent a heterogenous group of mental disorders characterized by positive, negative, and cognitive symptoms. Positive symptoms are described as an addition or distortion of a person's normal functioning and include delusions, hallucinations, and disorganized speech (Carbon & Correll, 2014). While negative symptoms are characterized as reductions to a person's functioning and include blunted affect, alogia, avolition, asociality, and anhedonia (Correll & Schooler, 2020). Other symptoms often present are cognitive, which affect areas of attention, concentration, and memory (Carbon & Correll, 2014). Importantly, these symptoms are not caused by the effects of any substance, other medical condition, or mood disorder. The diagnosis of a psychotic disorder involves the work of a clinician and healthcare team. Healthcare teams may use a combination of diagnostic clinical assessments and clinical judgement to diagnose a psychotic disorder (Cohen et al., 2021; McGuire et al., 2008). Healthcare teams use various assessment tools to examine presence and severity of symptoms in an individual: for example, the structured clinical interview (SCID) and the positive and negative symptom scale (PANSS) which both aid in the characterization and identification of symptoms (First, 2015; Kay et al., 1991). Diagnostic criteria are found in validated diagnostic tools such as the DSM-5 (American Psychiatric Association, 2013) or the ICD-11(*ICD-11 for Mortality and Morbidity Statistics*, n.d.).

Psychotic disorders can present a daily challenge as they have a unique burden on the individual affected and the communities around them - areas affected can include difficulty with interpersonal relationships, job stability, social impairments, disability, and premature mortality (Jin & Mosweu, 2017; Rössler et al., 2005). Intervention services implemented globally have worked to moderate this burden with a small amount of success in obtaining any definition of recovery (Hansen et al., 2023). Remission, often defined as the presence of mild symptoms, and recovery, the presence of mild to moderate symptoms and good psychosocial function have been measured in a recent meta-analysis on first episode psychosis patients and authors report a recovery rate of 20.8% (Hansen et al., 2023). Similarly, a large scale 25-year longitudinal cohort found that 15.1% of people with psychotic disorders would experience stable remission, and 21.1% would experience a stable recovery (Tramazzo et al., 2024). Compared to the general population, individuals with a psychotic disorder are at an increased risk for premature mortality with a lifespan that is 10-15 years shorter (C. Hjorthøj et al., 2017; Oakley et al., 2018; Saha et al., 2007; Yung et al., 2021). Alongside these challenges, psychotic disorders have a significant impact on the economy. In the US, direct and indirect costs associated with psychotic disorders were estimated, with findings showing that in 2019 the economic burden of psychotic disorders was $343.2 billion, with 73% of this being associated with indirect costs (i.e.: caregiving, premature mortality, unemployment) (Kadakia et al., 2022). The rate of recovery, effect on mortality, and financial burden placed on economy have not improved over the last seventy years under routine clinical care (Fusar-Poli et al., 2017).

Psychotic disorders are increasingly understood as part of a dimensional continuum model of psychosis, in which symptoms range from transient, subclinical experiences to fully developed, chronic illness (Krabbendam et al., 2005; Van Os et al., 2000, 2009; Verdoux & Van

Os, 2002). This dimensional view emphasizes early detection and recognizes that individuals may transition through various stages of illness risk, including clinical high risk (CHR) states and early phase psychosis (EPP), before potentially developing a chronic psychotic disorder (see Figure 1). One well-established risk factor that appears to interact with these stages is cannabis use (CU). Meta-analyses have shown that individuals who use cannabis are 4-16 times more likely to develops a psychotic disorder compared to non-users, with a greater risk associated with early onset, high potency, and frequent use (Marconi et al., 2016). Cannabis has also been linked to greater persistence of psychotic-like experiences (PLEs) and earlier transition from CHR to chronic psychotic disorder (Bechtold et al., 2016; Staines et al., 2023). Integrating this understanding of psychosis as a developmental continuum which is shaped by neurobiological, environmental, and substance-related factors, provides a strong rationale for early, targeted intervention.

Imaging research on psychotic disorders and their etiology has focused on structural brain changes across the various stages of illness. Working back across the continuum model, this body of literature highlights progressive biological alterations that unfold from early risk states through to chronic disorder. Postmortem and neuroimaging research in individuals with chronic psychotic disorders have consistently shown structural and biological alterations across the brain, offering insight into the progression of illness. Postmortem studies show increased neuroinflammation, particularly elevated microglia and astrocyte activation in a large number of studies (as reviewed in Liu et al., 2022; Mallya & Deutch, 2018; Najjar & Pearlman, 2015; Trépanier et al., 2016). Previous reviews comment on the limitations of definitive conclusions about the etiology of the illness due to the large number of null results, commonality of substance use within the population, interaction of antipsychotic medications, and large presence of suicide victims in the cohorts (Liu et al., 2022; Trépanier et al., 2016). Findings of neuroinflammation in earlier stages of illness are limited due to the technical constraints of studying inflammatory and glial processes *in vivo* (Trépanier et al., 2016). Reviews do highlight multimodal examination of glial activation using histology, PET, and free water diffusion tensor imaging, and shows neuroinflammation and its association white matter pathology in schizophrenia (Liu et al., 2022; Najjar & Pearlman, 2015; Zhuo et al., 2023). Chronic schizophrenia is consistently associated with enlarged ventricles, significant grey matter volume loss, and widespread cortical thinning (Dietsche et al., 2017). These alterations are most pronounced in the frontal and temporal cortices and have been hypothesized to be a result of downstream consequences of neurodevelopmental disruption (Dietsche et al., 2017). This hypothesis is further supported by evidence linking early cortical thinning and white matter disruption to key adolescent neurodevelopmental processes such as synaptic pruning and myelination (Lebel & Deoni, 2018). As a result, neuroimaging studies have increasingly focused on earlier stages of illness to identify when and how these structural changes emerge. In individuals following a first episode of psychosis, studies report enlarged lateral ventricles ($d = 0.443$), reduced total brain volume ($d = 0.246$), and smaller grey matter volumes in the frontal ($d = -0.313$), temporal ($d = -1.093$), and prefrontal ($d = 0.400$) lobes, as well as the superior temporal gyrus (as reviewed in Gallardo-Ruiz et al., 2019; Kuo & Pogue-Geile, 2019). Early-phase psychosis (EPP) is also characterized by grey matter reductions in the thalamus and progressive cortical thinning in superior and inferior frontal regions (as reviewed in Dietsche et al., 2017). Previous white matter research in these populations is limited, diffusion tensor imaging (DTI) studies suggest reduced white matter volumes and axonal integrity even in prodromal and early stages of illness (as reviewed in Samartzis et al., 2014).

These findings support the continuum model of psychosis, in which neurobiological changes unfold progressively from subclinical vulnerability to chronic illness (Van Os et al., 2009). Early intervention efforts have targeted EPP, typically defined as the first two to five years following symptoms onset (Eaton et al., 1995; Farooq et al., 2024; Malla et al., 2005). Previous historical cohort studies have found that the early course of illness is predicative of later illness trajectories (Eaton et al., 1995; Helgason, 1990; McCreadie et al., 1992; Shepherd et al., 1989). However, not all individuals with EPP progress to chronic psychosis, with some achieving remission or functional recovery following early treatment (Hansen et al., 2023; Tramazzo et al., 2024). This variability has prompted a growing interest in pre-diagnostic stages, particularly in the identification of individuals at CHR for psychosis. CHR individuals present with subthreshold psychotic symptoms or relevant risk factors such as genetic vulnerability, functional decline, or environmental adversity and are assessed using validated screening tools to estimate conversion risk (Minichino et al., 2025). Early intervention programs tailored to CHR and EPP populations have shaped the field's emphasis on risk prediction and prevention. International and national treatment guidelines, including the 2017 Canadian Schizophrenia Treatment guidelines and the National Institute for Health and Care Excellence (NICE) guidelines, have both highlighted the need for prioritization of early intervention and treatment of this early stage of illness (Overview | Psychosis and Schizophrenia in Adults: Prevention and Management | Guidance | NICE, n.d.; Remington et al., 2017). Despite these advances, CHR tools have been limited in predictive scope – accurately identifying only a small proportion of future psychosis cases (Ajnakina et al., 2017). Although these strategies have been widely implemented, a recent meta-analysis found no strong evidence that active interventions in CHR populations significantly reduce transition rates compared to control conditions (Minichino et al., 2025), highlighting the need for more precision and scalable predictors. This has prompted a call to refine current models of risk and develop neurodevelopmentally informed approaches to prevention (Kelleher, 2023).

One such candidate for a predictor is the presence of psychotic-like experiences (PLEs) – transient, non-clinical symptoms that are relatively common in the general population and may serve as an early phenotypic marker of risk, particularly when persistent or co-occurring with other risk factors (Hinterbuchinger & Mossaheb, 2021; K. W. Lee et al., 2016; Poulton et al., 2000; Remberk, 2017). As such, PLEs offer a promising, scalable way to screen for vulnerable individuals well before the onset of diagnosable symptoms. With the social, economic, and health burdens of psychotic disorders remaining high despite existing early intervention strategies, expanding our focus to these earlier developmental and subclinical indicators is crucial for improving long-term outcomes.

1.2 PSYCHOTIC-LIKE EXPERIENCES

1.2.1 DEFINITION AND PREVALENCE

Psychotic-like experiences (PLEs) are sub-clinical hallucinations and delusions that occur in the general population and are often identified through self-report. These may include perceptual abnormalities, unusual beliefs, bizarre occurrences, and mild forms of paranoid or persecutory ideation (Cowan & Mittal, 2021). Unlike clinical symptoms observed in psychotic disorders, PLEs are often transient, non-impairing, and not distressing to the individuals who experience them. In fact, many people who report PLEs do not view them as pathological and may never seek clinical attention (Staines et al., 2022). PLEs are increasingly understood as both a normative component of child and adolescent development and, under certain conditions, a potential marker of emerging psychopathology (Hinterbuchinger & Mossaheb, 2021). PLEs are common in the general population, with studies reporting 5-6% of the general population, and 13-17% of the children and adolescent population having experienced them (Burton et al., 2024; Healy, Brannigan, et al., 2019; Kelleher, Connor, et al., 2012; Laurens et al., 2007a; Poulton et al., 2000a; Remberk, 2017; Staines et al., 2023; Van Os et al., 2009a). Although seemingly common within the child and adolescent populations, a recent meta-analysis showed that in adolescence, 5 out of 100 individuals will report a new PLE each year (Staines et al., 2023).

1.2.2 RISK AND PSYCHOPATHOLOGY

Initially, PLEs were considered direct predictors of psychotic disorders, but evidence suggests that they may also reflect risk for a range of future psychopathologies or represent normative developmental phenomena (Hinterbuchinger & Mossaheb, 2021; Murray & Jones, 2012). Adolescents who experience PLEs are 4-16 times more likely to develop a psychotic disorder (Burton et al., 2024; Cowan & Mittal, 2021; Kelleher, Connor, et al., 2012; Laurens et al., 2007b; Poulton et al., 2000b; Van Os et al., 2009a). However, PLEs are also linked to other adverse outcomes, including multimorbid psychopathology and persistent suicidal behaviour (Kelleher, Keeley, et al., 2012). For example, the co-occurrence of PLEs and suicidal ideation at ages 16-17 predicts more than a five-fold increase in future suicidal thoughts (OR = 5.53) (Kelleher et al., 2014).

One early study in the field reported that self-reported auditory hallucinations were present in adolescents with current psychiatric disorders and markers of future psychiatric disorders. (Dhossche et al., 2002). Additionally, 80% of adolescents (11-15 years old) who report PLEs will meet criteria for a non-psychotic psychiatric disorder (i.e.: anxiety disorders, behavioural disorders, affective disorders) (Kelleher, Keeley, et al., 2012). The frequency and persistence of PLEs also appear critical with higher frequency and persistence increasing the likelihood of developing a psychotic disorder in an 8-year cohort study (Dominguez et al., 2011). Therefore, while experiencing a PLE in adolescence is a risk factor for future psychotic disorders, they can also predict other psychopathology. Understanding specific PLE variables that infer this risk, such as persistence, childhood adversity, and substance use experienced during the critical developmental time period requires more attention, as there is limited literature in this area of study (Staines et al., 2022).

1.2.3 PERSISTENCE AND PREDICTIVE VALUE

Of adolescents who report PLEs each year, 35.8% of them will experience persistence beyond expected developmental transience (Staines et al., 2023). In a longitudinal cohort study, adolescents who reported PLEs at one of three measurement timepoints had a 1.5-fold increased risk of later psychosis (OR = 1.5), while those reporting PLEs at two or all three timepoints had progressively greater risk (OR = 5.0 and OR = 9.9, respectively), suggesting that persistence across timepoints, rather than isolated episodes, confers risk (Dominguez et al., 2011). Examining epidemiological frequency of PLEs in adolescents is currently not feasible due to lack of large scale homogenous reported data and only a recent use of validated scales specific for adolescents (Hinterbuchinger & Mossaheb, 2021; Kelleher et al., 2011). But, when examining the epidemiological features of PLEs in the general population, a cross-national analysis of 18 countries based on 31 261 respondents reported the prevalence of PLEs as 5.8%, with hallucinatory experiences reported in 5.2% of cases – making them four times more common than delusional experiences (1.3%) (J. J. McGrath et al., 2015). That same study found that individuals endorsing multiple types of PLEs also reported a higher frequency of experiences (J. J. McGrath et al., 2015). Some research suggests PLEs are more common in females, though findings are mixed, and some studies omit sex-based analysis entirely recruiting only males (Bechtold et al., 2016; Sullivan et al., 2020).

1.2.4 RISK FACTORS AND SUBSTANCE USE

Environmental risk factors such as trauma and victimization – especially during adolescence – have also been associated with increased PLE frequency (MacKie et al., 2011). Cannabis Use (CU) is another notable factor; weekly use (defined as >52 times per year) has been linked to increased risk of persistent PLEs in adolescence (Bechtold et al., 2016). However, while CU increases the risk of incident PLEs, it may not significantly influence their persistence over time (Staines et al., 2023). To date, the underlying mechanism driving the persistence of PLEs remain poorly understood.

1.2.5 NEUROBIOLOGICAL CORRELATES

Given the relationship between PLEs during adolescent development and the development of psychotic disorders, neuroimaging research has been employed to explore potential structural correlates. Structural brain alterations and PLEs within the general population have been investigated using a large-scale cohort (UK Biobank) and have reported reduced grey matter volumes in the caudate, putamen, accumbens, and temporal lobe, and increased volume in the amygdala (Schoorl et al., 2021). Large scale studies within the adolescent population have not been produced, but there are some preliminary studies examining adolescent populations and PLEs highlighted here.

Findings from neuroimaging studies in adolescents have shown structural grey matter changes associated with PLEs, although results vary in direction and location. Calvo et al. (2020) reported significantly reduced bilateral hippocampal volumes in adolescents with PLEs, observed at both baseline and at 2-year follow up. These reductions were not accounted for by comorbid psychopathology or early life stress but do align with neuroimaging findings in psychotic disorders (Kuo & Pogue-Geile, 2019). Jacobson et al. (2010) found increased grey matter volumes in the superior and middle temporal gyri in children (aged 11-13) with PLEs, suggesting regionally specific volumetric increases during development. Okada et al. (2018) evaluated distress on PLEs within the ABCD cohort and showed that adolescents who experienced distressing PLEs showed lower cortical and subcortical grey matter volumes compared to those who did not. However, these findings are sparse in the literature and tend to examine heterogenous regions of interest, making direct comparisons and conclusions difficult. The alterations above – specifically in the hippocampus and the temporal areas – do broadly align with neuroimaging findings in psychotic disorders (Howes et al., 2022; Kuo & Pogue-Geile, 2019).

White matter (WM) studies in adolescents with PLEs are more limited. Existing studies call for the use of higher resolution MRI scanning (e.g.: using a 3T machine instead of a 1.5T), and the prioritization of multiple shell diffusion tensor imaging (DTI) to further delineate WM tracts (Jacobson et al., 2010; O'Hanlon et al., 2015). Jacobson et al. (2010) reported reduced fractional anisotropy (FA) along the inferior fronto-occipital fasciculus, cingulum, and inferior longitudinal fasciculus. O'Hanlon et al. (2015) reported reduced FA and increased mean diffusivity (MD) in the left superior longitudinal fasciculus, uncinate fasciculus, and inferior fronto-orbital fasciculus. A more recent study examined the arcuate fasciculus in a larger (n = 77, PLE+ = 25, PLE- = 52) population-based study with adolescents aged 11-13, they reported MD and radial diffusivity (RD) being significantly lower in the PLE population (Dooley et al., 2020). Knöchel et al. (2012) reported that both clinical and subclinical presentations of psychotic symptoms were associated with lower FA values compared to healthy controls, with clinical groups showing more pronounced reductions. While these findings suggest that white matter disruptions may occur along the psychosis continuum, the interpretation of FA in adolescent populations remains challenging. FA is a non-specific metric influenced by multiple microstructural properties, including myelination, axonal density, and fiber geometry, and is particularly limited in regions with crossing fibers or ongoing developmental remodelling (Figley et al., 2022). As such, while altered FA may signal early white matter differences in adolescents with PLEs, higher specificity techniques are needed to clarify the underlying biological mechanisms. This limitation underscores the importance of employing complementary diffusion models that can more precisely characterize neurite architecture and neuroinflammatory processes during adolescent brain development.

Although research in this area is currently limited – with small sample sizes and neuroimaging limitations - results suggest differences in the superior longitudinal fasciculus, inferior fronto-occipital fasciculus, cingulum bundle, inferior longitudinal fasciculus, arcuate fasciculus, and uncinate fasciculus (Dooley et al., 2020; Jacobson et al., 2010; O'Hanlon et al., 2015).To our knowledge, no published studies have examined white matter in adolescent PLE populations with concurrent substance use.

1.2.6 ASSESSMENT AND METHODOLOGICAL CONSIDERATIONS

Within the field of PLE study, it should be noted that researchers urge caution when attempting to assess psychotic-like symptoms in children and adolescents, where gauging understanding of self-reported psychotic-like symptoms is a challenging task (Preti et al., 2012). A variety of assessment tools have been developed to establish the presence of PLEs, ranging from semi-structured clinical interviews – such as the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADs), and Composite International Diagnostic Interview (CIDI) (Healy, Gordon, et al., 2019; J. J. McGrath et al., 2015). While clinical interviews provide rich contextual information surrounding severity and persistence and greater diagnostic specificity, they are time-intensive and often impractical for large-scale or longitudinal population studies. This has prompted the widespread use of self-report measures like the Peters et al. Delusions Inventory, which is employed in general population studies (J. McGrath et al., 2010; E. R. Peters et al., 1999). Several self-report measures have also been adapted for use with adolescents, including the Community Assessment of Psychic Experience (CAPE), and the Adolescent Psychotic-Like Symptom Screener (APSS) (Kelleher et al., 2011; Mossaheb et al., 2012). A great example of validation in adolescent samples is the validation of the APSS and comparisons against a standard clinical interview (K-SADS), where the question about auditory hallucinations ("Have you ever heard voices or sounds that no one else can hear?"), reported a high positive predictive value (71.4%) and a high negative predictive value (90.4%) (Kelleher et al., 2011). Furthermore, when "yes, definitely" was reported on this self-report there was a positive predictive value of 100%, meaning that during the clinical interview it was confirmed that the adolescent had experienced at least one PLE – even if it was not an auditory hallucination specifically (Kelleher et al., 2011).

A recent meta-analysis found no significant differences in the frequency of PLEs reported across clinical interviews and self-reports suggesting a degree of converging validity (Staines et al., 2023). However, comparisons across self-report measures reveal variability in predictive accuracy based on questionnaire length, item content, and study population (Granö et al., 2016). Items probing auditory disturbances, for example, were found to be the most predictive of clinical PLEs when validated against interview-based assessments which aligned with previous findings from Kelleher et al. (2011) (Granö et al., 2016). Despite the benefits, the use of self-report is not without limitations. Another meta-analysis demonstrated that assessment type (Interview VS. Self-Report) significantly influenced odds ratio estimates in studies of PLE prevalence ($R^2 = .83$, $\beta = 6.48$, $SE = 1.43$, $p = 0.02$), indicating substantial heterogeneity in measurement outcomes (Burton et al., 2024).

Moreover, PLE assessments must account for developmental stage and cultural context, as children and adolescents may interpret and report symptoms differently from adults, and normative beliefs may vary across cultures. Another challenge lies in distinguishing between transient, benign PLEs and persistent PLEs, that may or may not be distressing and indicate elevated risk. Despite these limitations, PLE assessments – particularly self-report measures – offer scalable, non-invasive tools for early risk detection. Nevertheless, there is more work that needs to be done researching PLEs and their role as a potential early indicator of psychopathology, including psychotic disorders. One area of particular interest is the intersection between cannabis use and PLE development and persistence during adolescence, an area that remains underexplored in the literature.

1.3 ADOLESCENT CANNABIS USE

Adolescent cannabis use (CU) has been a relevant topic of research in the last decade due to increased accessibility to product, increased associations with common mental disorders in young adulthood, and evidence of structural brain changes in both adolescents and adults (Bailey et al., 2023; Batalla et al., 2013; Battistella et al., 2014; Chye et al., 2020; Degenhardt et al., 2013; Vargas et al., 2023). Contrary to popular belief, after legalization of cannabis in Canada in 2018, adolescent CU has not increased (Bailey et al., 2023; Summary of Results for the Canadian Student Tobacco, Alcohol and Drugs Survey 2018-19 - Canada.Ca, n.d.; *Summary of Results for* *the Canadian Student Tobacco, Alcohol and Drugs Survey 2021 - Canada.Ca*, n.d.). Results from the 2021-2022 Canadian Student Tobacco, Alcohol, and Drugs Survey state that students in grades 10-12 report 29% have used cannabis previously, which is unchanged from the survey results from 2018-2019 (Summary of Results for the Canadian Student Tobacco, Alcohol and Drugs Survey 2018-19 - Canada.Ca, n.d.; *Summary of Results for the Canadian Student Tobacco, Alcohol and Drugs Survey 2021 - Canada.Ca*, n.d.).

Adolescence is a critical period in neurodevelopment, marked by extensive structural and functional brain changes that shape cognitive, emotional, and behavioural outcomes. During this sensitive window, CU has been shown to negatively impact on neurodevelopmental trajectories (Chadwick, Miller, & Hurd, 2013; Crews et al., 2007). During this window, two key processes – synaptic pruning and white matter maturation – take place at a very high rate (Lubman et al., 2015). These processes are tightly regulated by genetic and environmental factors, where disruptions during this period can have profound and long-lasting effects (Chadwick, Miller, & Hurd, 2013; Crews et al., 2007; Lubman et al., 2015). The endocannabinoid system (ECS) is a key regulator of the brain maturational processes occurring during adolescence, modulating axonal guidance, neurite outgrowth, and synaptic pruning (Harkany et al., 2007). Its core components include cannabinoid receptors (CB1 and CB2) and their endogenous ligands, such as anandamide and 2-arachindonoylyglycerol (2-AG)(Flores et al., 2022). CB1 receptors are highly expressed in white matter during childhood and adolescence – particularly in the prefrontal cortex – where they are involved in regulating white matter plasticity (Flores et al., 2022). Concurrently, anandamide levels in the prefrontal cortex increase significantly, reaching approximately three times higher concentrations in late adolescence compared to early adolescence (Flores et al., 2022). Importantly, CB1 receptor density is at its highest in adolescence, and after maturation, CB1 receptors can be found densely populated in grey matter (Battistella et al., 2014; Mato et al., 2003). This developmental window is characterized by heightened ECS activity, which facilitates crucial neurodevelopmental processes but also increases vulnerability to external disruption. Given the ECS's central role in synaptic pruning and white matter maturation, its dysregulation by exogenous cannabinoids – particularly Δ9-tetrahydrocannabinol - may have distinct and potentially long-lasting effects when exposure occurs during adolescence, compared to adulthood (Lubman et al., 2015).

Δ9-tetrahydrocannabinol (THC), the psychoactive component of cannabis, has been associated with long term effects on brain structure (Chadwick, Miller, Hurd, et al., 2013). THC mimics the structure of endogenous cannabinoids, allowing it to interact with cannabinoid receptors and thus disrupt normal ECS functioning. Animal studies demonstrate that THC exposure during adolescence accelerates synaptic pruning in regions such as the prefrontal cortex (PFC), leading to premature loss of functional neural connections (Miller et al., 2018). These disruptions are thought to be mediated by THC's action on CB1 receptors located on microglia, which play a key role in activity dependent synaptic pruning (Cutando et al., 2013). Microglial activation then leads to overactive pruning of synaptic connections within the developing brain (Cutando et al., 2013; Roseborough et al., 2022). In a healthy developing brain, there is a large amount of expected neuronal pruning that occurs to eliminate excess or weak synaptic connections; but when THC interacts with the endocannabinoid system, neuronal pruning becomes aberrant (Bara et al., 2021; Miller et al., 2018). The consequences of aberrant pruning include impaired neural network efficiency and heightened vulnerability for the development of psychotic disorders (Bara et al., 2021; Hall et al., 2020; Wittchen et al., 2007).

In humans, prior research has reported that CU can enact structural changes within the brain in both grey and white matter. In grey matter, early cannabis exposure (1-2 uses before age 14) has been linked to greater gray matter volume in the bilateral medial temporal lobes, posterior cingulate, lingual gyri, and cerebellum (C. Orr et al., 2019). Heavy CU has been associated with smaller hippocampal volumes and widespread reductions in cortical volumes and surface area in parietal, frontal, and orbitofrontal regions (Ashtari et al., 2009, 2011; Chye et al., 2020). A large neuroimaging cohort study (n = 799) reported dose-dependent cortical thinning in the prefrontal cortex, along with using positron emission tomography (PET) imaging to confirm the location of CB1 receptors – in which this study reported as being densely populated in the areas of cortical thinning (Albaugh et al., 2021). Notably, sex differences may play a role in these structural alterations, as cannabis users exhibit both increased and decreased prefrontal volumes depending on sex, with enlarged prefrontal volumes linked to impaired executive function in female users (Batalla et al., 2013). White matter integrity has also been shown to be impacted by CU – but with significantly less studies examining this to date. Particularly, in the superior longitudinal fasciculus (SLF), corpus callosum (CC), and hippocampus, with earlier onset of use predicting poorer integrity in these regions (Chye et al., 2020). Consistently, reductions in fractional anisotropy in the SLF have been reported across multiple studies (Lichenstein et al., 2021; Lorenzetti et al., 2016; J. M. Orr et al., 2016). Reports of increased radial diffusivity in the SLF have also been shown in a larger sample of adolescents from within the human connectome dataset, suggesting that CU has an impact on the development of white matter tracts during adolescence (J. M. Orr et al., 2016). Additionally, tractography studies suggest that heavy CU is associated with disrupted axonal connectivity in the right fimbria of the hippocampus, splenium of the CC, and commissural fibers, with earlier initiation of regular use correlation with greater impairments (Zalesky et al., 2012). These structural and white matter changes may underlie the increased vulnerability to cognitive dysfunction and psychosis observed in cannabis users.

When considering lifetime CU, if use starts early and continues through adolescence with daily or almost daily use, research shows it can be a risk factor for the development of a psychotic disorder. This risk increases with the use of high potency THC product (Bernier et al., 2013; Chadwick, Miller, Hurd, et al., 2013). 80% of patients who use services within an early intervention program for psychosis in Canada have reported lifetime experience with CU (Ouellet-Plamondon et al., 2017). More recently it has been reported that in Canada, the proportion of incident cases of schizophrenia and cannabis use disorder have increased from 3.7% to 10.3% post legalization (Myran et al., 2025). Although CU is associated with the development of psychotic disorders, direct causality of these associations is still an active area of research. These associations are often influenced by multiple factors, including genetics, the environment, and timing and potency or THC exposure. Examining the relationship between CU and the persistence of PLEs during these critical developmental periods may give insight into these complex interactions.

1.3 CANNABIS USE AND PSYCHOTIC-LIKE EXPERIENCES

The relationship between CU and PLEs in adolescence is emerging as a focus of interest but remains methodologically and conceptually complex. Challenges arise due to the variability in expression, frequency, and developmental timing of PLEs, as well as difficulties in accurately assessing PLE presence and CU exposure in this population (Kelleher et al., 2011; Kelleher & Cannon, 2011). While a small number of studies suggest that CU may play a role in the emergence and persistence of PLEs and may interact with neurodevelopmental processes, particularly white matter development (Hides et al., 2009; MacKie et al., 2011), the literature remains limited and largely correlational. PLEs themselves exist on a continuum from benign, transient experiences to persistent distressing symptoms that may indicate elevated risk for psychotic disorders (Kelleher & Cannon, 2011). Similarly, CU varies in frequency, potency, and age of initiation, each of which may influence its impact on neurodevelopment and the expression of PLEs (Marconi et al., 2016).

Though some studies have reported dose-dependent associations and increased risk of PLEs (Marconi et al., 2016), and others have linked early CU initiation (e.g.: prior to age 16) to greater risk of persistent psychotic symptoms (Arseneault et al., 2002; Degenhardt et al., 2013; McGee et al., 2000), there is currently no consistent evidence that CU directly causes PLEs, nor a consensus on the neurobiological mechanism linking the two. Methodological challenges such as self-report bias, heterogeneity in PLE definition and assessment, and confounding variables (e.g.: concurrent substance use, socioeconomic context, underlying mental illness) make causal inference difficult in this area (Kelleher & Cannon, 2011). While the current literature points to a potential interaction between CU and PLEs during adolescence, the field is still in its early stages. As such, further research is needed to examine the biological mechanisms that occur in both CU and PLEs during this critical period of neurodevelopment.

1.4 THE INTERACTION OF BRAIN NEUROINFLAMMATION PROCESSES, CANNABIS USE, AND PSYCHOTIC-LIKE EXPERIENCES

Neuroinflammation refers to the activation of immune-related processes within the central nervous system, most notably involving microglia, astrocytes, cytokines, and chemokines (Dunn et al., 2020). Under normal conditions, particularly during development, neuroinflammatory responses play a regulatory role in brain maturation, such as glial-mediated synaptic pruning and maintenance of neural circuitry (Sancho et al., 2021). In adolescence – a period marked by extensive structural and functional brain changes – this pruning is essential for refining connections in key cognitive and emotional systems (Mordelt & de Witte, 2023). However, when neuroinflammation is chronic or dysregulated, it can become pathogenic, contributing to altered neurodevelopmental trajectories and increased risk for psychopathology (Andersen, 2022; Mallya et al., 2019). One hypothesis that ties together these processes is the glial cell hypothesis of schizophrenia, which proposes that abnormal activation of microglia and astrocytes leads to excessive synaptic pruning and disrupted brain connectivity in vulnerable individuals (Dietz et al., 2019). This model emphasizes the central role of glial cells as mediators of environmental and genetic risk factors that converge during sensitive periods of brain development.

Elevated glial responses during adolescence may result from exogenous stressors, such as substance use, which can interfere with normal pruning and white matter development, especially during critical developmental windows (Andersen, 2022). CU during adolescence, especially heavy and early-onset use, has been associated with increased neuroinflammatory activity in mouse models (Hasegawa et al., 2023; Miller et al., 2018). THC binds to CB1 receptors, influencing their activation state (Hasegawa et al., 2023). THC exposure can exacerbate glial-mediated synaptic pruning, potentially leading to over-pruning and impaired neural efficiency (Ellgren et al., 2008; Miller et al., 2018). While direct evidence in adolescent human samples is limited due to ethical constraints around invasive methodologies, animal models show that adolescent THC exposure increases microglial activation, inflammatory cytokine levels, and markers of oxidative stress (Cutando et al., 2013). This is adding to the growing body of evidence that supports the hypothesis that CU may act as a pro-inflammatory agent, altering normal neurodevelopmental processes.

The investigation into direct causes of neuroinflammation in adolescents is limited due to the intrinsic invasive methodology needed to study the neuronal and glial alterations. Postmortem studies can be used, but these would be limited in a population of healthy adolescents. Examination of synaptic pruning using animal models during neurodevelopment has suggested that microglial activation acts as an effector of excessive synaptic pruning (Mallya et al., 2019; Mallya & Deutch, 2018). Despite these results, there are limitations of histological examination in human neurodevelopment and further research using these methods are not feasible. Novel in vivo technologies have been developed to better characterize neuroinflammation without postmortem examinations, such as positron emission tomography (PET) scans and Diffusion Kurtosis Imaging (DKI). PET scans can use radiotracers specific to microglia as a measure of neuroinflammation, and in adults has shown to be highly effective. However, in a population of adolescents, medically unnecessary exposure to these radiotracers has limited research using this method. DKI uses magnetic resonance imaging (details in section 1.6) to quantify the diffusion of water in white matter. DKI indices have been shown to be markers of neuroinflammation processes but has yet to be used in a population of adolescents (Arab et al., 2018; Jensen et al., 2005; Ota et al., 2018).

Although limited research has directly examined the interactions between CU and PLEs in relation to neuroinflammation, existing evidence can be interpreted within the framework of a recent revision of the multi-hit hypothesis. This hypothesis proposes that a combination of factors including environmental stressors and genetic variants could influence positive feedback loop leading to further glial mediated pruning (Howes & Onwordi, 2023). In this model, genetic variants increase synaptic vulnerability to synaptic pruning. This stress, coupled with environmental factors, induces excessive pruning of synapses mediated by glial cells. The excessive pruning results in psychotic symptoms, cognitive impairment, and further causes stress to feed back into the system (Howes & Onwordi, 2023). Recent findings suggest that epigenetic mechanisms, particularly DNA methylation, may mediate the lasting impact of CU on neurodevelopment (Dempster et al., 2024; Wiedmann et al., 2022). Environmental exposures such as THC can alter chromatin and regulate gene expression via methylation – especially in promoter regions of genes involved in neuronal signalling and development (Wiedmann et al., 2022). In heavy cannabis users, differential DNA methylation patterns have been identified in genes related to synaptic plasticity and inflammation (Dempster et al., 2024). These changes may lead to long lasting alterations in neuroimmune function – or transient, depending on dosage, timing, and genetic background – which highlights the need for further research.

This hypothesis underscores the bidirectional nature of neuroinflammation, where CU may not act only as a 'hit' itself but also amplify an already dysregulated immune-neural feedback loop. These alterations may not be transient; some changes may persist into adulthood, contributing to increased risk for psychotic disorders. Overall, this hypothesis brings together the known processes of glial mediated synaptic pruning and allows for the examination of interactions within the positive feedback loop, for stressors such as substance use, or PLEs. This hypothesis has not yet been explored in human cannabis neuroimaging studies (Corsi-Zuelli et al., 2022; Crocker & Tibbo, 2015; Niciu & Mason, 2014).

1.5 CANNABIS USE, PSYCHOTIC-LIKE EXPERIENCES, AND BRAIN WHITE MATTER STRUCTURES

CU during adolescence has been increasingly linked to alterations in brain white matter integrity, particularly in tracts such as the superior longitudinal fasciculus (SLF), arcuate fasciculus (AF) and uncinate fasciculus (UF), and regions like the anterior cingulate cortex

(ACC). Understanding the role of these tracts and region in adolescent brain development and their relationship to CU is critical for identifying neurobiological mechanisms underlying PLEs.

The superior longitudinal fasciculus (SLF) is a major white matter tract within the brain that connects the frontal, parietal, and temporal lobes (Silva Paiva et al., 2022). It plays a crucial role in higher cognitive function, language processing, and motor function (Janelle et al., 2022). The SLF is divided into several subcomponents (SLF I, II, III), each with distinct connectivity patterns and functions (Janelle et al., 2022). A recent meta-analysis reported CU and its associations with decreased FA values in the SLF compared to non-users, indicating compromised white matter integrity (E. A. Robinson et al., 2023). In adolescents, another review reports similar decreases in FA in the SLF (Jacobus & Tapert, 2014). Alterations in the SLF have also been implicated in psychotic disorders. Research indicates that individuals with schizophrenia often exhibit reduced FA in the SLF, reflecting disrupted connectivity between key brain regions involved in cognitive and language functions (Lee et al., 2022; Podwalski et al., 2022). It has been suggested that the disruption of the maturation of the SLF could be indicative of increased amounts of PLEs in adolescents (Podwalski et al., 2022). The combined impact of CU and SLF alterations on the emergence of PLEs is an area of growing interest because of the relative similarities presented above. To our knowledge, there is currently no literature that has examined this.

The arcuate fasciculus (AF) is another white matter tract that connects Broca's area in the frontal lobe to Wernicke's area in the temporal lobe (Dick & Tremblay, 2012). It plays a critical role in language processing, verbal memory, and auditory-motor integration (Dick & Tremblay, 2012). CU has been linked to reduced FA values in the AF which could impair cognitive and linguistic functions (E. A. Robinson et al., 2023). In psychotic disorders, abnormalities in the AF have been observed, particularly in relation to auditory hallucinations (Abdul-Rahman et al., 2012; Thomas et al., 2022). Patients with schizophrenia who experience auditory verbal hallucinations often exhibit reduced FA in the AF, indicating disrupted connectivity between language processing regions (Abdul-Rahman et al., 2012; Thomas et al., 2022). This structural disconnection may underlie the misattribution of internally generated thoughts to external sources, which aligns with common auditory hallucinations. Dooley et al. (2020) suggested that reductions in FA in the AF that have been associated with auditory hallucinations and contribute to the development of PLEs – because of the large presence of auditory hallucinations.

The uncinate fasciculus (UF) is a white matter tract that connects the anterior temporal lobe to the orbitofrontal cortex and is involved in emotional regulation, semantic processing, and episodic memory (Von Der Heide et al., 2013). CU has been consistently linked to reduced FA values in the UF (E. A. Robinson et al., 2023). CU has also been shown to decrease fiber bundle length and decrease recall memory performance in users compared to controls (Levar et al., 2018). Reductions of FA in the UF have been reported in adolescents with PLEs (O'Hanlon et al., 2015). Given the UF's role in emotion regulation, disruptions in this tract may underlie the affective and perceptual disturbances associated with PLEs and early psychosis risk.

The anterior cingulate cortex (ACC) is involved in emotion regulation, decision-making, and cognitive control (Stevens et al., 2011). CU during adolescence has been associated with increased FA values in ACC structure (Lichenstein et al., 2022). In psychotic disorders, alterations in the ACC are frequently reported (Anticevic et al., 2015; Fornito et al., 2009). For example, a study by Fornito et al. (2009) found significant ACC volume reductions in patients with schizophrenia, correlating with symptom severity. Similarity, ACC volume reductions were also found in clinical high risk for psychotic disorder cohorts (Fornito et al., 2008). The combined effects of CU and ACC alterations may contribute to the emergence of PLEs. Adolescents who use cannabis may experience ACC alterations that disrupt cognitive and emotional processing – which has been shown in CHR cohorts – potentially leading to experiences characteristic of psychosis. To date there have been no studies looking at CU, PLEs, and the ACC.

Investigating these specific white matter tracts and region in vivo is only possible using advanced neuroimaging techniques. These methods allow for the integrity of the white matter and diffusion of water surrounding the axons to be examined in microstructural detail.

1.6 WHITE MATTER IN VIVO IMAGING TECHNIQUES

Neuroimaging has allowed for the advancement of research into the human brain, and with the development of new advanced techniques, researchers can see beyond basic structural differences and examine markers of inflammation and integrity of individual white matter tracts within the human brain. Diffusion tensor imaging (DTI) is a neuroimaging method used to study white matter microstructure by examining the diffusion of water molecules in brain tissue, providing broad insight into the structural integrity and organization of white matter tracts (Ranzenberger et al., 2023). Historically DTI was performed using a single b-value during acquisition, and while this approach is faster, it does not provide an accurate measure of complex tissue or adjust for confounding motion often found in adolescent neuroimaging (Pines et al., 2020). Multi-shell DTI uses multiple b-values which allows for the examination of tissue with further detail and complexity (Pines et al., 2020). DTI relies on measures of Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity (RD). FA measures the directionality of water diffusion and reflects white matter integrity – a high FA value could indicate more organized white matter bundles (Ranzenberger et al., 2023). MD represents the overall magnitude of water diffusion, with higher values potentially indicating neurodegeneration or tissue damage (Ranzenberger et al., 2023). AD measures diffusion along the primary axis of the white matter tract and is sensitive to axonal injury (Ranzenberger et al., 2023). Finally, RD measures diffusion perpendicular to the white matter tract and is associated with demyelination (Ranzenberger et al., 2023). While many neuroimaging studies utilize FA as a primary indicator of white matter integrity, it is important to recognize that relying on solely of FA can lead to misinterpretations, especially in regions with complex fiber architectures (Figley et al., 2022). FA measures the degree of directional waster diffusion, which is informative about fiber density and organization. However, in areas where multiple fiber populations intersect (e.g., crossing fibers) FA values can be significantly affected (Figley et al., 2022). This means that changes in FA might not accurately reflect alterations in white matter integrity but could instead result from the presence of these crossing fibers. Therefore, incorporating additional diffusion metrics, such as MD, which provides a more comprehensive assessment of white matter microstructure (Figley et al., 2022).

Multi-shell DTI is thought to be highly sensitive to microstructural changes in white matter, such as demyelination, axonal loss, and edema. Abnormalities in FA or MD can indicate WM pathology, however these measures alone cannot distinguish between different pathological mechanisms. This low specificity has led researchers to consider using complementary imaging techniques to obtain increased specificity (Ranzenberger et al., 2023).

Neurite orientation diffusion dispersion index (NODDI) and Diffusion Kurtosis Imaging (DKI), which utilize multi-shell DTI, have helped considerably to increase both sensitivity and specificity in neuroimaging studies and are thought to enhance research in neuroimaging (S. De Santis et al., 2014; Huang et al., 2022; Johnson et al., 2021; Timmers et al., 2016).

NODDI examines white matter microstructure in greater detail than single shell DTI, offering a more specific assessment of neurite organization and density. It enables the study of neurite orientation dispersion and microstructural complexity in regions where white matter tracts are not highly aligned such as cortical areas (Zhang et al., 2012). NODDI accounts for a Gaussian distribution of water, making it sensitive to complex microstructural changes in neurites (Zhang et al., 2012). It provides distinct measures such as orientation dispersion index (ODI) that indicate the degree of dispersion in neurite orientation. Lower ODI values are found in tightly packed, parallel bundles (e.g., corpus callosum), while higher ODI values occur in cortical and subcortical regions with multidirectional dendritic structures (Johnson et al., 2021; Wang et al., 2019; Zhang et al., 2012).

DKI examines the non-Gaussian water diffusion, which provides information on tissue microstructure that goes beyond that of DTI and NODDI. Compared to DTI, the examination of the non-Gaussian diffusion allows for a higher degree of sensitivity to subtle changes in neuroinflammation and glial responses (Cheung et al., 2009; Steven et al., 2014; Weber et al., 2015). Compared to NODDI, DKI provides broader insights into tissue integrity, particularly edema and neuronal cell loss (Arab et al., 2018; Huang et al., 2022; Jensen et al., 2005; Lanzafame et al., 2016; Ota et al., 2018). It compliments NODDI by examining different pathological processes within the mechanism(s). DKI provides distinct measures, namely Axial Kurtosis (AK), Radial Kurtosis (RK), and Mean Kurtosis (MK). AK reflects kurtosis along the primary axis of diffusion, an increased AK value has been associated with neuronal degeneration (Cheung et al., 2009; Steven et al., 2014). RK measures kurtosis along the perpendicular axes of diffusion, with an increased RK value there are associations suggesting microgliosis (Cheung et al., 2009; Steven et al., 2014). MK represents the average kurtosis across all directions and is sensitive to astrocyte/ glial inflammation, a higher MK value has been found to be linked to astrogliosis (Steven et al., 2014; Weber et al., 2015) In a recent DKI study, MK was found to improve identification of changes in white matter – compared to FA - when examining changes in white matter from CHR to healthy controls (F. Zhang et al., 2021). In adolescence, DKI has been suggested to better characterize the complex alterations that take place during neurodevelopment and allow for more specific examination of white matter development (Falangola et al., 2008; Grinberg et al., 2017). To date, there has been no published studies examining PLEs and adolescence using these neuroimaging techniques.

1.7 CURRENT GAPS IN THE LITERATURE

The current thesis aimed to address several of the gaps found in the literature. Primarily we aimed to explore the processes addressed in the multi-hit hypothesis in a human neuroimaging study. Although the process (glial mediated pruning of the prefrontal cortex) which is thought to be involved in this hypothesis is well studied in animal literature, the multi-hit hypothesis has not been explored in human cannabis neuroimaging studies (Corsi-Zuelli et al., 2022; Crocker & Tibbo, 2015; Niciu & Mason, 2014). While there has been an increase in child and adolescent neuroimaging studies in the past few years because of the presence of cohort studies - ABCD cohort, Youth Saguenay cohort, Imagen cohort, the PNC cohort, and the NCANDA cohort – these studies have yet to examine the processes mentioned above (Brown et al., 2015; Calkins et al., 2015; *IMAGEN*, n.d.; *NIMH Data Archive - Data - Study*, n.d.; Pausova et al., 2017).

The advancement of neuroimaging techniques has allowed for the use of NODDI and DKI to further characterize and examine the complex nature of white matter during adolescent neurodevelopment (Falangola et al., 2008; Grinberg et al., 2017). These methods have not yet been used to examine substance use and their effects on microglial activation and white matter structural integrity. The use of these methods will allow for a more specific characterization of white matter changes in healthy developing adolescents and potentially highlight the comparative differences in subclinical populations of adolescents with CU or PLEs.

We also aimed to address the lack of advanced white matter neuroimaging research in a population of 15–16-year-olds. Investigating a sparsely published population with neuroimaging comes with its own set of knowledge gaps. The most important being the lack of a white matter tractography atlas specific to this population. In general population adult neuroimaging studies, there are multiple atlases that can be used to describe regions of interest found in the brain. However, these atlases will not be accurate in our population of 15–16-year-olds as we know from previous literature that the structural development at 15-16 occurs rapidly and shows some significant changes compared to adults. The atlases used in other population-based studies used adult healthy controls (See chapter 2). In a recent study looking at the use of atlases in populations that are not representative of the population in question, researchers found that these atlases did not provide comprehensive detailed investigations into white matter tracts of that specific population and that there were significant differences between a population specific atlas and a general atlas (Y. Li et al., 2024). Therefore, we developed our own atlas of white matter tractography from our population of healthy 15–16-year-olds in order to fill this gap within the literature.

1.8 THE CURRENT STUDY

The current study aims to investigate how CU and PLEs relate to adolescent brain development, specifically in relation to neuroinflammatory and white matter integrity markers. Three core objectives guide this investigation: (i) to examine biological plausibility of novel neuroimaging techniques in a sample of healthy developing adolescents (ii) to evaluate the independent associations of CU and PLEs with white matter microstructure (ODI, MD) and neuroinflammation markers (MK) (iii) to assess whether CU and PLEs have additive or interactive effects on these neurobiological markers. Based on the existing literature presented, the study proposes the following hypotheses:

1. White matter integrity (ODI) will be negatively associated with markers of neuroinflammation (MK). (H1)
2. Cannabis use will be positively associated with markers of neuroinflammation and negatively associated with white matter integrity as measured by MK and ODI. (H2)
3. The presence of PLEs in adolescence will be positively associated with markers of neuroinflammation and negatively associated with white matter integrity as measured by MK, AK, RK, ODI. (H3)
4. Adolescents who use cannabis will have an increased presence of PLEs compared to those who do not. (H4)
5. Cannabis use and the presence of PLEs in adolescence will be interactive to the impact of brain white matter as seen by markers of neuroinflammation and white matter integrity (e.g.: CU-/PLE- < CU-/PLE+ == CU+/PLE- < CU+/PLE+) (H5)

By examining specific structural markers using advanced neuroimaging techniques, the neuropathological mechanism(s) which accelerate psychosis development in adolescents may be better informed. The results of this study may contribute to a better understanding of the effects of CU in adolescent brain development and expression of PLEs, potentially informing not only EPP treatment protocol but guide evidence-based education programs targeting adolescent CU and inform legislative CU policies.

CHAPTER 2. DEVELOPMENT OF POPULATION SPECIFIC WHITE MATTER ATLAS

2.1 INTRODUCTION

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that measures the diffusion of water within tissue microstructure (For more detail on DTI see section 1.6). By measuring the directionality and magnitude of diffusion, DTI provides information about white matter microstructure and integrity within the brain (Alexander et al., 2007; Ranzenberger et al., 2023). It is sensitive to pathological changes at both the cellular and microstructural level, making it a widely used tool in neurodevelopmental and psychiatric conditions (Jones et al., 2013; Lebel & Deoni, 2018). Key scalar measures derived from DTI include fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). FA reflects the degree of directional water diffusion within a specified voxel and is increased in areas of organized white matter tracts (e.g., corpus callosum) and decreased in grey matter (Alexander et al., 2007; Ranzenberger et al., 2023). However, the accuracy of, and what this metric measures, has been called into question as discussed in the general introduction (Section 1.6) and in the literature (Beaulieu, 2002; Figley et al., 2022). MD represents the average diffusivity across all directions and can increase with tissue damage or neuroinflammation (Alexander et al., 2007; Ranzenberger et al., 2023). RD captures diffusion perpendicular to axons and is often linked to demyelination, while AD reflects diffusion along axonal fibers and tends to decrease with axonal injury (Song et al., 2002). Tractography is a method used within DTI research to reconstruct white matter tracts by using the principal direction of diffusion across the brain. Various methodological approaches – deterministic, probabilistic, and global – are employed to enable subject-specific visualization and quantification of major white matter tracts without resorting to manual identification (Agarwal et al., 2023; Mori & Van Zijl, 2002). However, tractography, regardless of the methodology used has limitations, especially in clinical populations, as it is sensitive to partial volume effects, low signal to noise ratios, and anatomical variability between individuals (Maier-Hein et al., 2017; Schilling et al., 2019). These challenges can limit reproducibility and complicate cross-subject comparisons.

To address these limitations, researchers use white matter atlases, which serve as population-based references for anatomical localization and quantitative analysis of white matter. Atlases are created by spatially normalizing individual data to a common template, such as the Montreal Neurological Institute (MNI) space (Mandal et al., 2012). This normalization process enables robust group level analysis and facilitates further comparisons across studies (Hua et al., 2008). There are several methodologies that exist for anatomical white matter analysis: (i) voxel-based approaches, where researchers perform voxel-wise comparisons along a mean white matter skeleton. These approaches are efficient but lack anatomical specificity to the population being studied (Smith et al., 2006) , (ii) Region-of-Interest (ROI)-based analyses, which rely on anatomical masks and average signal within specific regions that can provide much better specificity than voxel-based approaches but can introduce bias if the ROI definitions are used differently across populations (Srivastava et al., 2016) , (iii) Tract-based or fiber clustering methods group streamlines across subjects based on shape and location, and are used in automated tractography segmentation (O'Donnell & Westin, 2007). Streamlines are computational representations of white matter trajectories, estimated by following local diffusion orientations derived from diffusion MRI (Jeurissen et al., 2019). These methods better preserve anatomical detail compared to voxel-based approaches and are increasingly being used to generate dimensional white matter atlases representative of the three-dimensional location of streamlines within the subject space (Y. Li et al., 2024; F. Zhang et al., 2018). Despite these benefits, streamline based atlases are currently limited in their methodology making comparisons across atlases difficult (F. Zhang et al., 2018). Voxel-based atlases, while providing less anatomically specificity allow for comparisons across already established atlases, and further comparisons to anatomical references (Srivastava et al., 2016). The choice of atlas, and thus the methodology to create the atlas, can impact research outcomes (Dickie et al., 2017; Tamnes et al., 2018). Atlases available can differ in spatial resolution, tract labelling schemes, and demographic specificity – all of which can influence sensitivity to group differences (Fan et al., 2016; B. D. Peters et al., 2012; Wakana et al., 2007). Most existing atlases are derived from adult samples (Mean ages range from 18-52; see Table 1), skewed sex samples (19 / 28 identified atlases either have a skewed sex sample or do not report breakdown of sex; see Table 1), or include broad age ranges (ranging from 40 gestational weeks to 52 years old; See Table 1), limiting their relevance to specific neurodevelopmental stages (Dickie et al., 2017). Furthermore, these atlases are often created without consistent psychiatric, developmental, or neurological screening and include heterogenous acquisition protocols, which complicates interpretation in pediatric populations (Dickie et al., 2017).

Adolescence represents a critical neurodevelopmental period, characterized by non-linear increases in white matter volume, maturation of synaptic connections, and changes in diffusion properties linked to myelination and axonal reorganization (Giedd et al., 2009; Morris et al., 2020). Studies have shown that white matter metrics change rapidly during this period, particularly between the ages of 13 and 17 (Lebel & Deoni, 2018; Molfese et al., 2021). As such, the application of adult derived or demographically mismatched atlases during adolescence may lead to anatomical misalignment, reduced sensitivity to developmental effects, and biased findings (Hermoye et al., 2006; Levman et al., 2017). Despite the availability of neonatal (UNC Neonatal Atlas) and adult-focused white matter atlases (e.g., JHU White Matter Atlas), there is a notable gap in the availability of high-quality, tightly age constrained white matter atlases specifically tailored for adolescents (Hua et al., 2008; Short et al., 2022) (See Table 1). Currently atlases that are publicly available assume the health of the included subjects without detailed screening for factors affecting white matter. Substance use (Hampton et al., 2019), depression (Flinkenflügel et al., 2024), anxiety (Lu et al., 2018), and childhood trauma (Corbo et al., 2016; Siehl et al., 2018) are among some of the factors that have been found to affect white matter. Previous atlases have also neglected to report race and ethnicity of the sample, which may alter white matter across global populations (Y. Li et al., 2024). An atlas developed for 15–16-year-olds, excluding confounding psychiatric or neurological factors, would address a critical need by capturing white matter architecture during a key stage of maturation, while also accounting for population level variability.

The current study aims to create a white matter voxel-based atlas derived from an extensively screened sample of 15–16-year-old participants using high resolution diffusion MRI data. The resulting atlas will provide a high-quality, age-specific, replicable representation of white matter anatomy, serving as a standardized reference for researchers studying adolescent neurodevelopment. By facilitating consistent and anatomically accurate comparisons across studies, this atlas will enhance reproducibility and advance our understanding of white matter organization during a critical developmental window.

2.2 METHODS

2.2.1 PARTICIPANTS

This study uses MRI data obtained from 54 healthy individuals (22M/30F/2 Not Specified (NS)) aged 15-16 years (M = 15.67, SD = 0.54) who were recruited from a larger community sample within the Halifax Regional Municipality (HRM) (see Chapter 3 for description of full cohort recruited). Participants were screened extensively for medical and psychiatric history, MRI contraindications, substance use, and family psychiatric risk. For the development of this atlas, we defined a healthy participant with the following characteristics: no familial history of schizophrenia or bipolar disorder, no history of severe chronic medical conditions or psychiatric diagnoses, no current or past use of psychotropic medications, no history of significant head injury, Beck's anxiety scores < 36, Beck's Depression score < 31, Adolescent Psychotic-Like Symptom Screener (APSS) score < 2, AUDIT score < 8, no history of other substance use, and no history of e-cigarette or nicotine use. These cut-offs were chosen based on previous literature showing white matter changes in cases of severe anxiety (Lu et al., 2018), clinical depression and major depressive disorder (Flinkenflügel et al., 2024), psychotic-like experiences (Bosma et al., 2023; Schoorl et al., 2021), substance use (including alcohol and nicotine) (Hampton et al., 2019). Contrary to previous literature, we did not exclude participants based on handedness, because it would limit the applicability to all sample populations (Panta et al., 2021).

2.2.2 ACQUISITION

Imaging data was acquired using a 3T GE MR750 scanner, and the following scan sequences were collected using a 32-channel head coil: T1 weighted (T1W) structural fast spoiled gradient echo sequence (FSPGR) scan (FOV= 100; Matrix = 256; Slice Thickness = 1mm; number of slices = 76; acquisition plane = Sagittal; TR = 0.006716 s; TE = 0.00294 s; Flip angle = 11; collection time = ~9 min. The diffusion protocol was as follows: Matrix = 110; Slice thickness = 2 mm; gap = 2 mm; TR = 8.5 s; TE = 0.0732 s; flip angle = 90 degrees; B-values = 1000, 2000, with eight 0 interspersed throughout the sequence; Gradient directions = 2x30). 46 participants were scanned using the 3T GE scanner and the remaining 9 participants were scanned using a 3 Tesla Siemens Vida Scanner. Moving to the Siemens scanner was a part of the ongoing renovations within the hospital, and served to replace the GE scanner. The Siemens protocol was modified and tested to determine continuity on a phantom head, as well as a 'test' head that was scanned in both scanners. The Siemens protocol was identical in practice to that of the GE scanner, but because of differences in scanner it is outlined here: FOV = 100; Matrix = 224; Slice Thickness = 1 mm; number of slices = 76; acquisition plane = sagittal; TR = 0.0023s; TE = 0.00225; Flip Angle = 8; Collection time = ~ 5 min. Diffusion sequences detailed: Matrix = 110; Slice thickness = 2 mm; gap = 2 mm; TR = 5.4 s; TE = 0.094 s; flip angle = 90 degrees; B-values = 1000, 2000, with eight 0 interspersed throughout the sequence; Gradient directions = 2x30).

2.2.3 DTI PREPROCESSING

Preprocessing of the images was performed using a custom pipeline with Diffusion Imaging in Python (DIPY) and Advanced Normalization Tools (ANTs) software library (see supplemental methods). Steps included denoising, Gibbs ringing removal, bias field correction, motion and eddy current correction (FSL EDDY), susceptibility distortion correction using field maps, and spatial normalization to T1w imaging space and MNI space. A quality control analysis was performed using MRIQC (version 25.1.0) (Esteban et al., 2017), where contrast to noise ratios (CNR), signal to noise ratio (SNR), and mean framewise displacement were reported (see Table 4). Afterwards quality control (QC) was performed manually for each subject to verify accurate preprocessing and registration. Multi-tissue multi-shell constrained spherical deconvolution (MSMT-CSD) was used to estimate fiber orientation distributions in each voxel and probabilistic tractography was used to generate streamlines with uncertainty (Cieslak et al., 2021).

2.2.4 ATLAS CREATION

The creation of the atlas was based of the tools developed in the 'whitematteranalysis' package developed by the O'Donnell Research Group (ORG) (O'Donnell et al., 2012; O'Donnell & Westin, 2007; F. Zhang et al., 2018). Generated streamlines were inspected for quality using a QC tool in 'whitematteranalysis'. The first step after QC was group registration to a common 'atlas' space – where the 54 identified healthy control participants were registered using a subject T1w space. This step ensured streamlines are in a comparable space across participants. Then participants were registered in an 'affine' space, which applies a global transformation to align one set of streamlines to another, this includes translations, rotation, scaling, and shearing, that captures whole brain alignment and orientation normalization across all participants. Lastly, a nonrigid registration is applied to capture local deformations and align streamlines – specifically in fine grained anatomical structures. Registered streamlines are then clustered using spectral clustering, based on pairwise streamline distances. Clustering was run in three distinct iterations to remove outlier fibers and refine the clusters through each iteration. All iterations were visually inspected, and quality control was reported to determine what iteration would be used within the atlas (see Figure 1a,b,c). After visual inspection, and further examination of the outliers removed, iteration 2 was chosen. Iteration 2 has gone through 3 distinct rounds of outlier removal, and represents the clusters without excess noise, spurious, or misclassified fibers (see Figure 1c).

The clustered streamlines were then further isolated by hemisphere into clusters (interhemispheric tracts i.e.: corpus callosum were separated). Then using a previously validated ORG atlas, a Hausdorff Distance (HD) – a metric that quantifies how far two sets of points are from each other – was calculated for each of the 800 clusters to identify the nearest anatomical label (Taha & Hanbury, 2015). This was performed in three separate iterations to obtain the three closest distances. Of these three results, if the difference between the outputs was less than 10, the clusters were confirmed by manual anatomical labelling. The labelled clusters were visualized in 3D Slicer (https://www.slicer.org/) via the SlicerDMRI project (https://dmri.slicer.org/) (Norton et al., 2017). Anatomical plausibility of all 800 clusters was assessed by two independent reviewers, and aberrant or false positive streamlines were manually relabeled or discarded based off reviewer consensus. A measure of maximum HD, and 95th percentile HD was taken between the proposed atlas and the ORG atlas of the streamline based labelled clusters. Labelled white matter tracts were then binarized and saved as voxel-based masks. Despite the higher anatomical specificity that streamlines can provide, a voxel-based atlas was created based off the streamline labelled clusters, this is because it enabled further comparisons between pre-established atlases, allowed for the registration of the atlas to MNI space without large processing requirements, and was more easily accessible for future use. Given the robust screening prior to the creation of the atlas, and the lack of pre-established adolescent atlases, we believe the voxel-based atlas provides adequate anatomical specificity of the adolescent population. A Dice coefficient was calculated to determine the spatial differences between adult and adolescent brain white matter (Taha & Hanbury, 2015).

2.3 RESULTS

54 participants were recruited and found to meet all inclusion criteria. The robust screening and inclusion criteria used to select the sample is reflected through the demographic and psychological characteristics (Tables 2 and 3). Demographic characteristics describe a sample population with BMI, handedness, and ethnicity all representative of the larger Halifax Regional Municipality (Table 2). Psychological characteristics highlighted scores well below cut-offs for suggested further intervention for psychotic-like experiences (Adolescent psychotic-like symptoms screener), symptoms of anxiety (Beck Anxiety Inventory), symptoms of depression (Beck Depression Inventory), symptoms of psychoticism, paranoid ideation, and phobic anxiety (Brief Symptom Inventory). Preprocessing of MRI data was successful across participants, with high visual quality observed following motion correction, distortion correction, and spatial normalization. No participants were excluded due to poor registration or artifact. Across participants, the atlas is comprised of 800 distinct white matter clusters. These clusters were matched to anatomical labels based on spatial overlap and distance comparison with the ORG atlas (as described above in Methods). 3 labelled anatomical white matter tracts were identified and labelled (See Table 5). Verification of automated tractography methods were assessed via two independent reviewers (see Table 6). Due to the probabilistic nature of the tractography method, during visual review, some clusters were removed and found to be false positives (Table 6).

To assess anatomical plausibility, the maximum HD and the 95th percentile HD were compared with the ORG atlas (See Table 7). For the arcuate fasciculus (AF) large - moderate differences were found (HD = 39.84 mm), the superior longitudinal fasciculus (SLF) reported large-moderate differences (HD = 40.89 mm), the uncinate fasciculus (UF) reported moderate differences (HD = 31.83). In the AF (HD95 = 4.3 mm), SLF (HD95 = 5.63 mm), and UF (HD95 = 3.81), the 95th percentile HD better accounts for outliers and large differences. For example, in the AF, the 95th percentile HD reports that 95% of the points within the AF tract are within 4.3 mm of the closest points. To further confirm anatomical plausibility, spatial overlap was compared between the proposed atlas and the ORG atlas using a DICE coefficient (See Table 8). The spatial overlap was reported as 0.37 in the AF, 0.35 in the SLF and 0.42 in the UF.

2.4 DISCUSSION

We developed a voxel-based white matter atlas derived from a rigorously screened, demographically specific cohort of healthy adolescents aged 15-16 years. Using high-resolution multi-shell diffusion imaging and probabilistic tractography, we created an anatomically precise atlas that captures white matter organization during a critical window of neurodevelopment. Our custom development pipeline leveraged advanced preprocessing and clustering tools, including MSMT-CSD, ANTs-based spatial normalization, and spectral clustering via the 'whitematteranalysis' tools developed by the ORG lab. The resulting atlas offers a developmentally specific, high-quality reference for use in adolescent neuroimaging. While existing white matter atlases such as JHU DTI-based white matter atlas (Hua et al., 2008; Wakana et al., 2007), and the ORG atlas (O'Donnell & Westin, 2007; F. Zhang et al., 2018) provide robust frameworks for adult populations, they are limited in specificity when examining adolescents through the critical neurodevelopmental period. Most atlases currently in use were constructed from participants ranging in age from infancy to mid-adulthood (e.g., 40 gestational weeks to 52 years) or lack detailed demographic and clinical information. The application of such atlases to adolescent data can introduce anatomical misalignment and reduce sensitivity to developmental differences (Hermoye et al., 2006; Tamnes & Agartz, 2016). By contrast, the

Adolescent White Matter (AWM) atlas includes only participants within a narrow age window (15-16 years), with strict psychiatric and substance use exclusion criteria, improving anatomical accuracy and developmental relevance.

We assessed the validity of our tractography-derived clusters using two key spatial metrics: The Hausdorff Distance (HD) and the Dice coefficient. The 95^{th} percentile HD (HD95) for tracts such as the AF, SLF, and UF ranged from 3.8 to 5.6 mm, values consistent with previous work suggesting that HD95 values <5 mm represent moderate to good alignment in tractography segmentation (Schilling et al., 2021). The larger HD95 in the SLF can be explained by the developmental differences expected in the tract – which runs from the temporal and parietal lobes to the dorsal and medial frontal cortex. White matter development follows a distinct pathway and the frontal lobe during this critical development period undergoes large amounts of dendritic pruning and myelination (Arain et al., 2013). Therefore, the larger difference seen in the SLF has biological relevance and further emphasizes the importance of population specific reference. Dice coefficients for these same tracts (AF, SLF, UF) ranged from 0.35 to 0.42, aligning with expected values for inter-protocol comparisons in probabilistic tractography (Schilling et al., 2019, 2021; Taha & Hanbury, 2015). Spatial comparisons, while less specific than HD, provide another perspective of biological relevance. The values represent masks where there is moderate overlap with the adult population reference, however, because anatomically, these tracts have been verified using manual inspection and HD measures, the spatial difference can be attributed to developmental differences.

Strengths of the proposed atlas include the use of multi-shell diffusion imaging and probabilistic tractography, both of which improve sensitivity to complex fiber configurations (Jeurissen et al., 2019; Yendiki et al., 2011). Tract segmentation was further refined using spectral clustering across subjects in a normalized space, ensuring reproducibility and anatomical precision (S. Zhang & Arfanakis, 2018). Visual QC was performed at multiple steps, and anatomical labeling was confirmed using HD to the high quality and independently verified ORG atlas followed by manual verification by two independent reviewers. This multi-level validation pipeline enhances confidence in the anatomical accuracy and biological relevance of the resulting white matter tracts.

This adolescent-specific white matter atlas provides an important normative reference for studies examining brain maturation, early risk markers for psychiatric or neurological disorders, and the impact of environmental or psychosocial exposures on white matter. Adolescence is characterized by non-linear changes in white matter microstructure, including increases in myelination and axonal organization (Arain et al., 2013; Giedd et al., 2009; Lebel & Deoni, 2018; Molfese et al., 2021). Use of age-appropriate atlases can improve sensitivity to developmental effects and help avoid false positive or anatomical misregistration (Hermoye et al., 2006; Levman et al., 2017). The robustly screened sample allows for heightened sensitivity to potential environmental and psychosocial effects on white matter in a population where these changes are currently understudied (Gray & Squeglia, 2017; Tuvel et al., 2023). Moreover, the availability of a tightly age-bounded, demographically screened template improves cross study harmonization and facilitates longitudinal analyses during a period of heightened neurodevelopmental plasticity.

Despite its strengths, the proposed atlas in limited by current tractography methods, which may influence the construction of the tracts (Schilling et al., 2019, 2020; Yendiki et al., 2011). Based off current literature, probabilistic tractography and deterministic tractography are the strongest options that both have different strengths and challenges (Schilling et al., 2019, 2021). In the future, the use of more recently developed methods may provide different results. While there were efforts made to harmonize data across scanner platforms – registering all subjects into a common space separate from 'scanner' space – the use of two different scanners (GE and SIEMENS) introduces a potential source of variability despite phantom and test-retest validations (Fortin et al., 2017). Future directions include expanding the sample to improve demographic representativeness (both of sex, and ethnicity), generating sex-specific templates, and further adapting the atlas to be in a commonly used space (e.g.: MNI space) as opposed to an atlas specific space. This would allow for ease of access and reduce the amount of preprocessing time required.

This atlas has immediate applications in studies examining white matter development, adolescent mental health, and early risk markers for psychiatric and neurological illness. Its integration with tract-based statistics, and voxel wise morphometry tolls can improve anatomical specificity and reproducibility of findings in adolescence. The atlas supports anatomically accurate and developmentally sensitive research into adolescent brain organization and pathology, offering a valuable tool for future investigations in clinical and developmental neuroscience.

2.5 TABLES

Table 1

Overview Of Available White Matter Atlases

Study	Atlas Methodology	Scanner and Processing Information	Tracts	Atlas Population	Screening methods used	Screening for Psychological or substance use measures
Hua et al. (2008)	Voxel-Based	Diffusion MRI; 1.5T single-shell DWI; Multi-ROI Tractography	20 deep WM tracts	28 healthy (29 ± 7.9 years, 11F/17M)	Healthy volunteers (no neurological disorders)	No
Hagler et al. (2009)	Voxel-Based	Diffusion MRI; 1.5T multi-shell DWI; Deterministic Tractography	23 deep WM tracts	21 healthy (21-52 years, 11F/10M) & 21 temporal lobe epilepsy patients (21-54 years)	Healthy controls with no history of neurological or serious psychiatric conditions	No
Bazin et al. (2011)	Voxel-Based	Diffusion MRI; Scanner information not given; Deterministic Tractography	39 deep WM tracts	Not given	Healthy controls (no neurological disorders)	No
Thiebaut de Schotten et al. (2011)	Voxel-Based	Diffusion MRI; 1.5T single-shell DWI; Multi-ROI. Tractography	30 deep WM tracts	40 healthy (18-22 years, 20F/20M)	screened for right-handed, no neurological illness	No
Yendiki et al. (2011)	Voxel-Based	Diffusion MRI; 1.5T single-shell DWI; Deterministic Tractography	18 deep WM tracts	33 healthy (42 ± 10 years, 14F/19M) & 34 schizophrenia patients (37 ± 10 years, 9F/25M)	Healthy controls with no history of neurological or serious psychiatric conditions	No
Suarez et al. (2012)	Voxel-Based	Diffusion MRI; 3T single-shell DWI; Stochastic Streamline Tractography	11 deep WM tracts	20 healthy controls (17.8 ± 1.1 years, 10F/10M)	Not reported	No

Ros et al. (2013)	Voxel-Based	Diffusion MRI; 3T single-shell DWI; Multi-ROI Tractography	16 deep WM tracts	15 healthy controls (sex and age not reported)	Not reported	No
Van Baarsen et. (2016)	Voxel-Based	Diffusion MRI; 3T multi-shell DWI; Probabilistic Tractography	6 cerebellar tracts	90 healthy controls (22-35 years and sex not reported)	Healthy controls with no neurological disorders	No
Akazawa et al. (2015)	Voxel-Based	Diffusion MRI; 3T single-shell DWI; Deterministic Tractography	24 deep WM tracts	11 term-born neonates (within 3 days of life, 7F/4M)	Infants were healthy term births	No
Tang et al. (2018)	Voxel-Based	Diffusion MRI (“HCP-style” connectome imaging); 3 T multi-shell DWI; Deterministic Tractography	23 deep WM tracts	20 healthy controls (age not reported, 10F/10M)	Healthy controls with no neurological disorders	No
Spencer et al. (2022)	Voxel-Based	Diffusion MRI; 3T multi-shell DWI; Deterministic tractography	13 deep WM tracts	28 healthy controls (6-8 years and sex not reported)	Healthy controls with no neurological disorders	No
Short et al. (2022)	Tract-Based	Diffusion MRI; 3T multi-shell DWI; Probabilistic tractography	Not given	144 healthy controls (scan performed at 41.88 $\pm$ 1.83 gestational weeks, 68M/76F) & 395 healthy controls (13.03 $\pm$ 0.95 months and 25.05 $\pm$ 1.07 months, 95M/75F)	Not born prematurely and considered typically developing	No
Maddah et al. (2005)	Tract-Based	Diffusion MRI; 3T single-shell DWI; stochastic tractography	Not given	1 healthy control (age or sex not reported)	Not reported	No
O’Donnell and Westin (2007)	Tract-Based	Diffusion MRI; 1.5T single-shell DWI; Deterministic Tractography	19 deep WM tracts	10 healthy controls (age or sex not reported)	Healthy controls – no abnormalities reported	No

Ziyin et al. (2009)	Tract-Based	Diffusion MRI; 1.5T single-shell DWI; Probabilistic Tractography	5 deep WM tracts	15 healthy controls (age or sex not reported)	Not reported	No
Guevara et al. (2012)	Tract-Based	Diffusion MRI; 1.5T single-shell DWI; Deterministic Tractography	36 deep WM tracts, plus 94 superficial fiber parcels	12 healthy controls (age or sex not reported)	Healthy controls with no neurological disorders	No
Jin et al. (2015)	Tract-Based	Diffusion MRI; 4T single-shell DWI; Streamline and probabilistic tractography	17 deep WM tracts	5 healthy controls (23.2 ± 2.1 years and sex not reported)	Healthy controls (twins) with no major medical or psychiatric illness	Evaluation to exclude any pathology known to affect brain structure
Tunc et al. (2014)	Tract-Based	Diffusion MRI; 3T single-shell DWI; Probabilistic Tractography	11 deep WM tracts	2 healthy controls (age not reported. 2F)	Not reported	No
Yoo et al. (2015)	Tract-Based	Diffusion MRI; 1.5T single shell DWI; Deterministic Tractography	14 deep WM tracts	12 healthy controls (32.8 ± 5.5,12M)	Healthy controls with no neurological disorders	No
Labra et al. (2017)	Tract-Based	Diffusion MRI; 3T single shell DWI; Deterministic Tractography	26 deep WM tracts	4 healthy controls (age and sex not reported)	Not reported	No
Guevara et al. (2017)	Tract-Based	Diffusion MRI; 3T single-shell DWI; Deterministic Tractography	100 superficial fiber parcels	79 healthy controls (23.6 ± 5.2 years, 32F/47M)	Healthy controls with no neurological disorders	No
Roman et al. (2017)	Tract-Based	Diffusion MRI; 3T single-shell DWI; Deterministic Tractography	93 superficial fiber parcels	74 healthy controls (23.6 ± 5.2 years, 31F/43M)	Healthy controls with no neurological disorders	No
O'Donnell et al. (2017)	Tract-Based	Diffusion MRI; 3T multi-shell DWI (single shell b = 3000 used);	10 deep WM tracts	10 healthy controls (age or sex not reported)	Healthy controls with no brain lesions	No

		Deterministic Tractography				
Yeh et al. (2018)	Tract-Based	Diffusion MRI; 3T multi-shell DWI; Deterministic Tractography	66 deep WM tracts, plus set of U-fibers	842 healthy controls (22-36 years, 470F/372M)	Healthy controls rigorously screened HCP cohort	Yes, but did not use as a tool to screen for healthy controls
Zhang et al. (2018)	Tract-Based	Diffusion MRI; 3T 6 single-shell DWI datasets and 2 multi-shell DWI datasets; Deterministic Tractography	58 deep WM tracts, plus 198 superficial fibers	100 healthy controls (22-36 years, 56F/46M)	Healthy controls with no neurological disorders or clinical conditions	No
Maffei et al. (2021)	Tract-Based	Diffusion MRI; 3T single-shell DWI; Manual Tractography	42 deep WM tracts	16 healthy controls (age and sex not reported)	Not given	No
Radwan et al. (2022)	Tract-Based	Diffusion MRI; 3T multi-shell DWI; Manual Tractography	68 deep WM tracts	20 healthy controls (age not reported, 10M/10F)	Not given	No
Zhang et al. (2024)	Tract-Based	Diffusion MRI; 3T multi-shell DWI; Deterministic Tractography	42 deep WM tracts	60 healthy controls (age and sex not reported)	Not given	No

Note: This table was created by completing a general review of the literature. Atlases may have been missed in the process.

Table 2

Demographic Characteristics of Recruited Sample by Biological Sex

Characteristic	Total Sample	Males	Females	Not Specified
	N = 56	*N = 24*	*N = 30*	*N = 2*
Age[a]	15.67 (0.54)	15.54 (0.51)	15.77 (0.57)	16.00 (0.00)
Body Mass Index (BMI)[a]	23.10 (4.74)	22.88 (5.41)	23.12 (5.10)	25.46 (5.41)
Handedness (R/L/A)	46/4/6	18/3/3	26/1/3	2/0/0
Ethnicity (%)				
European Origins	34 (61%)	12 (50%)	20 (68%)	2 (100%)
Indigenous	2 (4%)	1 (4%)	1 (3%)	0 (0%)
South Asian	4 (7%)	3 (13%)	1 (3%)	0 (0%)
Chinese	3 (5%)	2 (8%)	1 (3%)	0 (0%)
Black	3 (5%)	3 (13%)	0 (0%)	0 (0%)
Latin American	1 (2%)	0 (0%)	1 (3%)	0 (0%)
Arab	1 (2%)	0 (0%)	1 (3%)	0 (0%)
Southeast Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)
West Asian	2 (4%)	0 (0%)	2 (7%)	0 (0%)
Multiracial	6 (11%)	3 (13%)	3 (10%)	0 (0%)

Note: [a] *Mean (SD), Handedness* obtained using the Edinburgh Handedness Inventory (Right / Left / Ambidextrous). Ethnicity was recorded based on self-report.

Table 3

Psychological Characteristics of Recruited Sample by Biological Sex

Characteristic	Total Sample	Males	Females	Not Specified
	N = 56	*N = 24*	*N = 30*	*N = 2*
APSS Score[a]	0.50 (0 – 1.5)	0.50 (0 – 1.5)	0.50 (0 – 1.5)	0 (0 – 1)
BAI[a]	13.5 (0 – 35)	9.5 (0 – 35)	16 (3 – 33)	27 (20 – 34)
BDI[a]	6 (0 – 20)	6 (0 – 20)	7.5 (0 – 17)	4 (3 – 5)
Y-VACS[a]	5 (0 – 22)	5.0 (0 – 16)	5.5 (0 – 22)	6.5 (5 – 8)
Brief Symptom Inventory				
Psychoticism [b]	0.37 (0.52)	0.36 (0.52)	0.37 (0.54)	0.60 (0.57)
Paranoid Ideation [b]	0.46 (0.48)	0.48 (57)	0.45 (0.43)	0.40 (0)
Phobic Anxiety [b]	0.25 (0.33)	0.23 (0.25)	0.29 (0.40)	0.67 (0.47)

Note: [a] Median (Range), [b] Mean (SD), APSS = Adolescent Psychotic-Like Symptom Screener, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, Y-VACS = Yale-Vermont Adversity in Childhood Scale.

Table 4

Quality Control Measures Reported in Sample (n = 54)

Quality Control Measure	Reported Metric Mean (SD)
CNR	2.02 (0.27)
SNR (total)	4.73 (0.48)
SNR (White Matter)	7.51 (1.04)
CJV	0.56 (0.04)
Framewise Displacement	2.94 (1.68)

Note. CNR = Contrast to noise ratio, SNR = Signal to noise ratio, CJV = coefficient of joint variation

Table 5

Adolescent White Matter Atlas (AWM) Tract Outputs

Characteristic	Number of Identified Clusters
Arcuate Fasciculus	16
Superior Longitudinal Fasciculus	35
Uncinate Fasciculus	7

Note. Identified clusters were labelled using automated labelled methods developed by the ORG lab. Labelled clusters were then visually confirmed using two reviewers to assign an anatomically plausible label.

Table 6

Anatomical Plausibility for Arcuate Fasciculus

Cluster	Assigned Automated Label	Reviewer 1 Visual Inspection	Reviewer 2 Visual Inspection	Consensus	Label assigned to Cluster
Cluster 00677	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00687	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00706	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00716	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00723	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00725	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00731	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00734	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00748	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus
Cluster 00769	Arcuate Fasciculus	Include	Include	Include	Arcuate Fasciculus

Cluster 00703	Arcuate Fasciculus	Exclude	Exclude	Exclude and Reassign Label	False Positive
Cluster 00265	Arcuate Fasciculus	Exclude	Exclude	Exclude and Reassign Label	Superior Longitudinal Fasciculus III
Cluster 00679	Arcuate Fasciculus	Exclude	Exclude	Exclude and Reassign Label	Superior Longitudinal Fasciculus III
Cluster 00744	Arcuate Fasciculus	Exclude	Exclude	Exclude and Reassign Label	Superior Longitudinal Fasciculus III
Cluster 00753	Arcuate Fasciculus	Exclude	Exclude	Exclude and Reassign Label	Superior Longitudinal Fasciculus III
Cluster 00774	Arcuate Fasciculus	Exclude	Exclude	Exclude and Reassign Label	Superior Longitudinal Fasciculus III

Table 7

Hausdorff Distance between AWM Atlas and ORG Atlas

Identified White Matter Tract	Max Hausdorff Distance	95th Percentile Hausdorff Distance
	As Compared to ORG Atlas	
Arcuate Fasciculus	39.84	4.17
Superior Longitudinal Fasciculus	40.89	5.63
Uncinate Fasciculus	31.83	3.81

Note. ORG Atlas (F. Zhang et al., 2018)

Table 8

Dice Coefficients of AWM Atlas compared to ORG Atlas

Identified White Matter Tract	Dice Coefficient
	As Compared to ORG Atlas
Arcuate Fasciculus	0.37
Superior Longitudinal Fasciculus	0.35
Uncinate Fasciculus	0.42

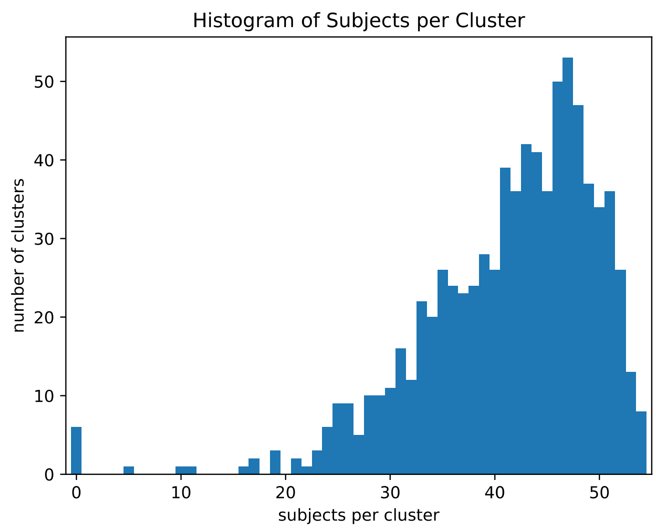
Note. Dice Coefficients compare spatial differences. ORG atlas (F. Zhang et al., 2018)

2.6 FIGURES

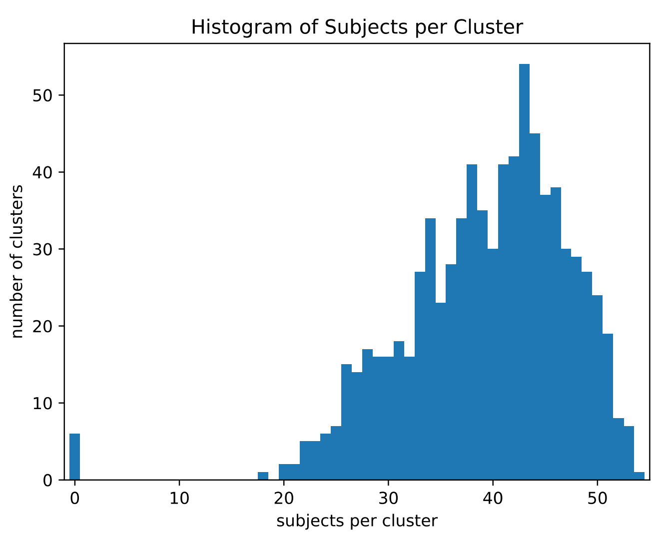
Figure 1

Quality Control Histograms of Spectral Clustering Iterations

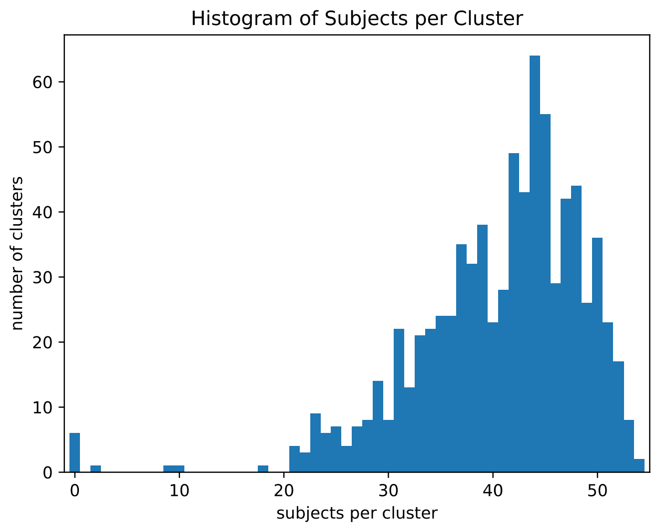
a)



b)



c)



Note: a) Iteration 0, b) Iteration 1, c) Iteration 2. Histograms display the number of participants streamlines represented in each cluster. Outliers were removed after each iteration. Iteration 2 was chosen due to larger amounts of participant streamlines being present in 40% of all identified clusters – as per methods outlined in (O'Donnell & Westin, 2007).

CHAPTER 3. DIFFUSION TENSOR IMAGING STUDY

3.1 INTRODUCTION

Psychotic-like experiences (PLEs) are subclinical phenomena that often emerge in adolescence and may precede the onset of psychotic disorders (Kelleher et al., 2010; Remberk, 2017; Van Os et al., 2009). In the general population, the prevalence of PLEs is estimated to be 5-6%, however in adolescence these rates are higher with studies reporting prevalence rates in the range of 13-17% (Healy, Brannigan, et al., 2019; Kelleher, Connor, et al., 2012; Laurens et al., 2007; Poulton et al., 2000; Remberk, 2017; Staines et al., 2023; Van Os et al., 2009). Adolescents who experience PLEs are 4-16x more likely to develop a psychotic disorder (Cowan & Mittal, 2021; Kelleher, Connor, et al., 2012; Laurens et al., 2007; Poulton et al., 2000; Van Os et al., 2009) with increased persistence of PLEs found to further increase this risk (e.g.: upwards of OR = 9.9 if multiple PLEs are reported across longitudinal timepoints) (Dominguez et al., 2011).

Recent research has suggested that cannabis use (CU) may contribute to the incidence and persistence of PLEs within adolescence and the general population (Bechtold et al., 2016; Hides et al., 2009; Mackie et al., 2011; Staines et al., 2023). Although not specific to PLEs, epidemiological studies have consistently demonstrated a strong link between early CU and elevated risk for later psychotic symptoms. Notably, adolescents who initiate cannabis use before age 16 are more likely to develop persistent psychotic symptoms in adulthood compared to adolescents who do not use cannabis (Arseneault et al., 2002; Degenhardt et al., 2013; McGee et al., 2000).

The association between PLEs and CU goes beyond the transition to psychotic disorders as studies have also reported that there are similar structural brain changes seen in both independent outcomes. Research on white matter in adolescents with PLEs remains limited, but neuroimaging studies have identified structural alterations within specific white matter tracts. Early work by Jacobson et al. (2010) found reduced fractional anisotropy (FA) in the inferior fronto-occipital fasciculus, cingulum bundle, and inferior longitudinal fasciculus among youth endorsing PLEs. Similarly, O'Hanlon et al. (2015) reported lower FA and higher mean diffusivity (MD) indicating a loss of tissue density, structure, or integrity in the left superior longitudinal fasciculus, uncinate fasciculus, and inferior fronto-occipital fasciculus in adolescents with persistent PLEs. More recent population-based research using a larger sample of adolescents aged 11-13 found significantly reduced MD and radial diffusivity (RD) in the arcuate fasciculus among those with PLEs (Dooley et al., 2020). These tract specific differences appear to extend beyond subclinical populations. For example, Knöchel et al. (2012) observed white matter disruption across patients with schizophrenia and their unaffected relatives, with lower FA values in the corticospinal tracts, commissural fibers, thalamic projections, and in the cingulum bundle in clinical cases, followed by subclinical individuals, and then healthy controls. This gradient supports the notion that white matter changes may represent a biological vulnerability marker along the psychosis continuum. Although preliminary, these findings suggest that alterations in frontotemporal and interhemispheric tracts including the SLF, AF, IFOF, cingulum, UF and ILF, may underlie risk for both clinical and subclinical psychotic phenomena in adolescence. However, studies to date, have been limited by small samples and reliance on conventional diffusion tensor imaging (DTI) metrics (Jacobson et al., 2010; O'Hanlon et al., 2015). Furthermore, no published research to our knowledge has examined white matter integrity in adolescence with PLEs who also report CU, a critical gap in the literature, given the overlapping neural basis and converging risk profiles.

Adolescence represents a critical window of neurodevelopment, characterized by rapid synaptic pruning, axonal myelination, and structural reorganization of white matter tracts (Chadwick, Miller, & Hurd, 2013; Crews et al., 2007; Lubman et al., 2015). These maturational processes are tightly regulated by both genetic and environmental factors, and disruption during this sensitive period may result in long lasting neurobiological consequences (Konrad et al., 2013). Notably, regions within the frontal lobe – including the SLF, AF, and ACC – continue to mature through adolescence and are frequently implicated in psychosis spectrum disorders (Kuo & Pogue-Geile, 2019; J. Lee et al., 2022; Podwalski et al., 2022; Samartzis et al., 2014). The endocannabinoid system (ECS) plays a central role in this maturational process. Its components – including CB1 and CB2 receptors and endogenous ligands such as anandamide – modulate neurodevelopmental processes like axonal guidance, myelination, and synaptic pruning (Flores et al., 2022; Harkany et al., 2007). CB1 receptors are densely expressed in white matter during adolescence, particularly in the prefrontal cortex, and anandamide levels are markedly elevated during late adolescence compared to earlier developmental stages (Flores et al., 2022). This period of heightened ECS activity facilitates healthy neural maturation but also increases vulnerability to disruption by exogenous cannabinoids such as Δ9-tetrahydrocannabinol (THC) (Miller et al., 2019). THC mimics the structure of endogenous cannabinoids and interacts with CB1 receptors, altering synaptic pruning and glial signalling (Caballero & Tseng, 2012). In animal models, adolescent THC exposure has been shown to accelerate microglia-mediated pruning, leading to premature or excessive synaptic elimination in key brain regions such as the prefrontal cortex (Cutando et al., 2013; Miller et al., 2019; Roseborough et al., 2022). These alterations impair neural network efficiency and have been linked to increased vulnerability to psychosis (Hall et al., 2020; Wittchen et al., 2007). While these mechanisms remain largely unexplored in vivo in human adolescents, they provide a plausible explanation for the white matter abnormalities observed in CU youth.

One proposed mechanism behind the white matter abnormalities observed in CU, is neuroinflammation. Neuroinflammatory processes, particularly those mediated by microglia and astrocytes, are central to synaptic pruning and white matter maturation (Andersen, 2022). Dysregulated microglia, whether triggered by exogenous cannabinoids like THC or other environmental stressors, can disrupt these processes, leading to white matter alterations (Chadwick, Miller, & Hurd, 2013; Ellgren et al., 2008). These white matter changes have also been implicated in youth with PLEs, populations with early phase psychosis (See Chapter 1, Section 1.4 for more detail). By investigating neuroinflammation, we can aim to clarify its role as a potential biological mechanism underlying the convergence of CU, PLEs, and white matter integrity, offering insight into why certain adolescents may be more vulnerable to emerging psychopathology.

Direct assessment of neuroinflammation in humans– such as through positron emission tomography (PET) imaging – is limited due to cost and radiation exposure. However, emerging advanced diffusion tensor imaging techniques now allow for the non-invasive investigation of glial-related white matter processes. Neurite Orientation Diffusion Dispersion Index (NODDI) and Diffusion Kurtosis Imaging (DKI) captures both microstructural integrity and markers of inflammation (Jensen et al., 2005; Jensen & Helpern, 2010; H. Zhang et al., 2012). Metrics such as orientation dispersion index (ODI) reflect axonal organization, while mean diffusivity (MD) indicates generalized diffusion (Ranzenberger et al., 2023; H. Zhang et al., 2012). Mean Kurtosis

(MK), Radial Kurtosis (RK), and Axial Kurtosis (AK) offer novel, indirect markers of microstructural complexity and neuroinflammation, and may be particularly sensitive to glial alterations (Arab et al., 2018; Cheung et al., 2009; Steven et al., 2014; Weber et al., 2015). DKI uses non-gaussian diffusion of water molecules to report the amount of 'restriction' within each voxel (Jensen et al., 2005). In biological tissues water diffusion is often hindered or restricted by complex cellular environments which have been shown to be representative of active glial cells, accumulation of cytokines, and disruption of extracellular space due to immune activity (Arab et al., 2018; Jensen et al., 2005; Ota et al., 2018; Steven et al., 2014; Weber et al., 2015). Therefore, MK and other DKI markers are not direct measures of neuroinflammation but instead provide an indirect marker of inflammatory processes through detailed examination of water diffusion.

Despite overlapping risk trajectories for psychosis, no study to date has directly examined the neurobiological mechanisms underlying this risk in adolescence with co-occurring CU and PLEs. Investigating these mechanisms is essential for understanding the early neural changes that may confer vulnerability to psychosis, and may inform the development of targeted, evidence-based prevention and intervention strategies. In a sample of 15–16-year-olds, this study aims (i) to examine whether CU is associated with increased prevalence of PLEs (ii) to evaluate the independent associations of CU and PLEs with white matter microstructure (ODI, MD) and neuroinflammation markers (MK) (iii) to assess whether CU and PLEs have additive or interactive effects on these neurobiological markers. We hypothesize:

1. White matter integrity (ODI) will be negatively associated with markers of neuroinflammation (MK). (H1)
2. Cannabis use will be positively associated with markers of neuroinflammation and negatively associated with white matter integrity as measured by MK and ODI. (H2)

3. The presence of PLEs in adolescence will be positively associated with markers of neuroinflammation and negatively associated with white matter integrity as measured by MK, AK, RK, ODI. (H3)
4. Adolescents who use cannabis will have an increased presence of PLEs compared to those who do not. (H4)
5. Cannabis use and the presence of PLEs in adolescence will be interactive to the impact of brain white matter as seen by markers of neuroinflammation and white matter integrity (e.g.: CU-/PLE- < CU-/PLE+ == CU+/PLE- < CU+/PLE+) (H5) (See Figure 1)

By leveraging tract-specific diffusion measures and a developmentally specific white matter atlas (Chapter 2), this study offers a novel lens through which to examine the neurobiological mechanisms linking CU and subclinical psychotic phenomena during adolescence. Findings may enhance early risk stratification for psychosis and inform evidence-based prevention efforts in adolescents vulnerable to cannabis-associated neurodevelopmental disruption.

3.2 METHODS

3.2.1 SAMPLE AND PROCEDURES

Participants consisted of a community sample of 123 adolescents aged 15-16-years old from the Halifax Regional Municipality (HRM) who were recruited from September 2022 to March 2025. Adolescents were recruited through convenience sampling using community postering, social media, and word of mouth. To be eligible to participate, adolescents between the ages of 15-16 had to be able to read and speak English. Participants were not required to have a history of CU, or have PLEs, group inclusion was determined naturalistically and resulted in 4 groups: PLE+/Cannabis Users, PLE-/Cannabis Users, PLE-/Non-Cannabis Users, Healthy

Controls (i.e. no PLE or cannabis use). Participants were excluded if they met any of the following criterion: presence of a known progressive brain disease, previous significant head injuries or seizures, neurological and psychiatric diagnoses (past or present), regular use of stimulants or medication that acts on the central nervous system (e.g. ADHD medications, common antidepressants), having a first degree relative with schizophrenia or bipolar disorder, and having contraindications to a magnetic resonance image (MRI), which included any type of metal in the body that cannot be removed (e.g. braces, permanent metal, pacemaker). After the individual was screened in, and consent was obtained they were enrolled in the study. All recruitment and study procedures were approved by the NSHA REB (#1027507).

3.2.2 CANNABIS USE HISTORY

Current and previous CU was quantified with the Timeline Follow Back (TLFB) (S. M. Robinson et al., 2014; Sobell & Sobell, 1992), and the Cannabis Use Disorder Identification Test – Revised (CUDIT-R) (Adamson et al., 2010). The TLFB is a commonly used calendar method that looks at detailed CU, and records the frequency of CU, amount, potency, social context (e.g.: alone vs in a social setting), strain, method of ingestion (e.g.: inhaled, consumed, absorbed etc..), method of administration (e.g.: joint, bong, vaporizer, edible, etc..), and time of day consumed looking back 30 days (S. M. Robinson et al., 2014). The TLFB shows high reports of agreement with biological measures of CU measured in urine, with a meta-analysis reporting this agreement to be between 87.3% and 90.9% (C. R. Hjorthøj et al., 2012). In adolescent populations, the TLFB has been validated in a cohort of unhoused youth (aged 12-17) where the average reported use was 6-8 days/month with an ICC ranging from 0.39-0.62 (Azrin et al., 2001). The CUDIT-R is comprised of eight items designed for participants to complete and focuses on the last 6 months of CU; it serves as a screening tool for cannabis use disorder (CUD)

(Adamson et al., 2010). The CUDIT-R cover domains related to cannabis consumption, cannabis abuse/problems, dependence, and psychological features, yielding scores within the range of 0 to 32. Scores from 0 to 7 suggest non-hazardous CU, 8 to 11 indicate hazardous CU, and a score of 12 or higher implies potential cannabis use disorder (CUD), warranting further intervention. As per Adamson et al. (2010), this assessment demonstrates high sensitivity (91%) and specificity (90%). The CUDIT-R has been well validated in young adult populations and used in youth and adolescent populations within the literature (Luquiens et al., 2021; Schultz et al., 2019). Participants were classified as CU+ if they had reported cannabis use in the last six months on the CUDIT-R.

3.2.3 ADDITIONAL SUBSTANCE USE HISTORY

Alcohol use was quantified using the Alcohol Use Disorders Identification Test (AUDIT) which is scored from 0 to 40, a score greater than 8 reflects potential for hazardous or harmful alcohol use (Saunders et al., 1993). Previous studies have reported in adolescent populations good reliability and test-retest correlations (Cronbach's alpha = 0.83, intra-class correlation = 0.81) (R. Santis et al., 2009). History of other concurrent substance use was collected using the chemical use, abuse, and dependence scale (CUAD) (McGovern & Morrison, 1992). This semi-structured interview included quantification of use of alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, PCP, sedatives and hypnotics. The Fagerstrom Nicotine Dependence Scale (FTND) (Heatherton et al., 1991) quantified nicotine dependence and is scored out of 10, and scores of 4 or less indicating low to moderate dependence, and scores over 5 indicate significant dependence (Heatherton et al., 1991). A previous validation study in adolescent populations have shown that the FTND is able to differentiate between established smokers and those who smoke less regularly and is limited in its ability to differentiate between experimental verses non-daily smokers (Cronbach's alpha = 0.75) (Nonnemaker & Homsi, 2007). To characterize e-cigarette use, the four item e-cigarette dependence scale (EDS) (Morean, Krishnan-Sarin, & S. O'Malley, 2018; Morean, Krishnan-Sarin, Sussman, et al., 2018) was used, this scale consists of 4 questions all scored from 0-4, to obtain a total score the mean of all questions is taken. In adolescent populations the EDS has shown good validation (Cronbach's alpha = 0.91) (Morean, Krishnan-Sarin, & S. O'Malley, 2018).

3.2.4 PSYCHOTIC-LIKE EXPERIENCES AND PSYCHOLOGICAL

The Adolescent Psychotic-Like Symptom Screener (APSS) was used to characterize the presence of PLEs (Kelleher et al., 2009). This self-report questionnaire consists of 7 items, and evaluates the presence (never, sometimes, often, nearly always) of psychotic experiences across various domains: perceptual disturbances (e.g., auditory and visual hallucinations), and unusual thoughts (e.g., grandiosity, persecutory ideation, passivity phenomena) (Kelleher et al., 2009). The APSS is scored out of 7 with never = 0, sometimes = 0.5, and often / nearly always =1. Specifically tailored for assessing PLEs in school-age children (ages 11-13), the APSS exhibits a sensitivity of 70% and specificity of 82.6% when compared to the outcomes of the 2- to 4-hour K-SADS interview (the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime Version) (Kelleher et al., 2009). The APSS does not allow for the characterization of severity of PLEs or an estimation of persistence, but it does with a high level of specificity, confirm the presence of a PLE. Although some recent evidence has emerged surrounding persistence of PLEs, a recent review examining both PLEs and CU in adolescence and the general population has reported that CU has not been found to be a significant factor for the persistence of PLEs, but it has been found to be significant towards the incidence of PLEs

(Staines et al., 2023). In accordance with the validation study (Kelleher et al., 2011), in this study if participants scored ≥ 2 than they were classified as having a PLE (PLE+).

Other psychological measures collected were the Beck Anxiety Inventory (Beck et al., 1988) and Beck Depression Inventory (Beck et al., 1996) and the Yale-Vermont Adversity in Childhood Scale (Hudziak & Kaufman, 2014). Becks Anxiety Inventory scores that exceed 36 indicate cause for potential concern, Becks Depression Inventory scores that exceed 20 indicate moderate to extreme clinical depression, the Y-VACS is a summed scale out of 50, where the higher the score, the more severe and prevalent adverse experiences were reported in the participants lifetime. This scale has been validated in children and adolescents with a high level so reliability (Cronbach's alpha = 0.95) (Hudziak & Kaufman, 2014).

3.2.5 MRI ACQUISITION AND PREPROCESSING

123 participants were recruited, but two participants were unable to complete the MRI, leaving 121 participants that took part in an MRI at the Nova Scotia Health Imaging suite. A 3T MR750 GE scanner with a 32-channel phased-array head coil was used with the following protocol on 103 participants: T1W structural fast spoiled gradient echo sequence (FSPGR) scan (FOV= 100; Matrix = 256; Slice Thickness = 1 mm; number of slices = 76; acquisition plane =. Sagittal; TR = 0.006716 s; TE = 0.00294 s; Flip angle = 11; collection time = ~9 min. Diffusion sequences including NODDI and DKI (Matrix = 110; Slice thickness = 2 mm; gap = 2 mm; TR = 8.5 s; TE = 0.0732 s; flip angle = 90 degrees; B-values = 1000, 2000. 0; Gradient directions = 2x30. The remaining 19 participants were scanned using a 3T Siemens Vida scanner with a 32-channel phase array head coil. The protocol was adapted for the new scanner and was tested to determine continuity via a phantom head, and a 'test' head who was scanned using both scanners. Moving from the GE scanner to the Siemens scanner was part of ongoing renovations

on the study site. The protocol followed was identical in practice to that of the GE scanner, but because of small differences the revised protocol is outlined as follows: T1W magnetization-prepared rapid gradient echo (MPRAGE) scan: FOV = 100; Matrix = 224; Slice Thickness = 1 mm; number of slices = 76; acquisition plane = sagittal; TR = 0.0023 s; TE = 0.00225; Flip Angle = 8; Collection time = ~ 5 min. Diffusion sequences collected including detailed examination of white matter microstructure in neurite orientation diffusion and dispersion index (NODDI) and diffusion kurtosis imaging (DKI) (Matrix = 110; Slice thickness = 2 mm; gap = 2 mm; TR = 5.4 s; TE = 0.094 s; flip angle = 90 degrees; B-values = 1000, 2000, with eight 0 interspersed throughout the sequence; Gradient directions = 2x30). Data harmonization was performed during image processing to account for variability in the different scanners during analysis.

3.2.6 IMAGE PROCESSING

Structural and diffusion weighted MRI data were processed using a combination of established neuroimaging pipelines optimized for data quality, anatomical precision, and multimodal integration. First raw digital imaging and communications in medicine (DICOMS) were converted into a neuroimaging informatics technology initiative (NIfTI) format using “dcm2niix” (X. Li et al., 2016) and then organized into a standardized Brain Imaging Data Structure (BIDS) (Clark et al., 2016) directory to ensure reproducibility and interoperability across tools.

For structural data, MRI quality control (MRIQC) (Esteban et al., 2017) was employed to perform automated quality control of T1 weighted images, flagging scans with excessive motion or artifacts, and reporting common quality control metrics (e.g.: contrast-to-noise ratio, signal-to-noise ratio, coefficient of joint variation). This was done for each image, and then again with the entire group to determine if there were any outliers or excessive motion (Figure 1). This was followed by preprocessing with fMRIPrep (Esteban et al., 2019, 2020), a robust and widely validated pipeline that integrates FreeSurfer (a program that specializes in cortical parcellation) (Desikan et al., 2006) and Advanced Normalization Tools (ANTs) (Avants et al., 2011) for bias field correction, skull stripping, tissue segmentation, and cortical parcellation. Structural scans were registered to the MNI152NLin2009cAsym 1mm template using nonlinear transformations. fMRIPrep is consistently rated among the most reliable and reproducible structural pipelines for neuroimaging datasets (Esteban et al., 2019; Notter et al., 2023).

Diffusion MRI preprocessing was conducted using QSIPrep (Cieslak et al., 2021), a BIDS-compatible platform that offers end-to-end preprocessing and reconstruction for multi-shell diffusion data. This included head motion correction, susceptibility distortion correction, eddy current correction (using FSL's EDDY), bias field correction, denoising, and registration to both the subject's T1 image and the MNI152NLin2009cAsym 2 mm space. QSIPrep is considered a gold standard pipeline for harmonized diffusion preprocessing across datasets, especially for studies involving advanced modelling techniques such as NODDI and DKI (Cieslak et al., 2021). Diffusion modelling was performed using QSIRecon's module within QSIPrep, which outputs key microstructural metrics. The accelerated microstructure imaging via convex optimization (AMICO) NODDI (Daducci et al., 2015) workflow was used to compute the orientation dispersion index (ODI) and mean diffusivity (MD), while the diffusion imaging in Python (DIPY) DKI (Henriques et al., 2021) workflow produced the kurtosis-based measure, mean kurtosis (MK). These advanced metrics provide sensitive markers of axonal density, myelination, and glial related complexity (Jensen et al., 2005; Jensen & Helpern, 2010; H. Zhang et al., 2012). Tractography was performed using automated fiber quantification in Python

(PyAFQ) (Yeatman et al., 2012) workflow and probabilistic tractography which has been reliability reproduced in multiple datasets (Kruper et al., 2021) (For more information on tractography, see Chapter 2).

Regions of interest (ROIs) were selected a priori based on their relevance to psychosis risk and white matter development (See Chapter 1.5). The anterior cingulate cortex (ACC) in both hemispheres was extracted using the Desikan-Killiany-Tourville (DKT) atlas (Desikan et al., 2006), allowing for standardized cortical parcellation of the grey matter region. In contrast, white matter tracts including the superior longitudinal fasciculus (SLF), arcuate fasciculus (AF), and uncinate fasciculus (UF) were extracted using a custom population specific white matter atlas developed from the current sample using tractography clustering and resulting in a voxel-based mask (see Chapter 2 for details). This atlas enabled anatomically specific extraction of DKI and NODDI metrics, addressing limitations of adult atlases in adolescent populations. In normative neurodevelopment, grey matter volume peaks during early adolescence (ages 9-12 years) and because of the age of the sample (15-16 years), a standard structural grey matter atlas will allow for an accurate measure of the ACC (Giedd et al., 1996; Huttenlocher & Dabholkar, 1997; Wilke et al., 2003). Once metrics were extracted from ROIs, data was harmonized using ‘NeuroCombat’ (Fortin et al., 2017; Richter et al., 2022), correcting for scanner-related variance while preserving biological variability. This harmonization method has demonstrated flexibility and robust application (Tassi et al., 2024). The use of integrated pipelines such as fMRIPrep and QSIPrep ensures reproducibility, harmonization across modalities, and compatibility with cutting edge diffusion models, all of which are essential for detecting subtle white matter alterations in neurodevelopmental populations.

3.2.7 STATISTICAL ANALYSES

All statistical analyses were conducted using R and RStudio (R Core Team, 2024; Posit team, 2025). Descriptive statistics were examined for all demographic, substance use, psychological, and neuroimaging measures. Outliers, normality, and missingness were assessed prior to modelling. If collected data did not meet model assumptions variables were transformed or categorized as needed to support interpretability. It was identified that self-reported CU had large amounts of variance when examining the means and standard deviations (See Table 1), linear models require standardized distributions to properly account for variance, so to account for this variability continuous TLFB self-reported data was not used to categorize participants. Instead past 6-month CU was chosen, this also showed non-normal distributions and sparse high-end values (See Table 1), to account for this in the analysis the continuous measure was operationalized as a binary variable (CUDIT-R: yes/no). Although a continuous variable, the presence of PLEs was also assessed dichotomously (score of 2 or above on the APSS: yes/no) based on the validation of the APSS.

Independent linear models were used to test each hypothesis to maintain clarity of interpretation and reduce the risk of overfitting given the group sizes and multiple predictors of interest. Modelling each hypothesis separately allowed us to check assumptions specific to the predictors and outcomes under consideration. This was important because the statistical assumptions relevant to one hypothesis did not necessarily apply to another (e.g. H2 compared to H3, where H2 had large amounts of variance in self-reported CU and H3 examined the presence of PLEs). By structuring the analyses independently, a single model framework did not have to be applied across multiple hypotheses, which could have obscured assumption violations or led to misinterpretation of effects. This approach also minimized collinearity across predictors and ensured that effect estimates reflected relationships directly relevant to the theoretical framework of each hypothesis, while preserving transparency in reporting and reproducibility.

3.2.7.1 Hypothesis 1: Association between Markers of Neuroinflammation and White Matter Integrity.

To test whether markers of neuroinflammation (MK) are negatively associated with white matter integrity (ODI, MD) (H1), linear regression models where used. This allowed for the assessment of ROIs (AF, SLF, UF, and ACC bilaterally). These analyses serve as a validation step, examining the baseline relationship between markers of neuroinflammation and white matter integrity in healthy developing adolescents. To assess the impact of CU and PLEs on white matter integrity and markers of neuroinflammation (H2, H3), general linear models were conducted using diffusion metrics (ODI, MD, and MK) as separate outcomes. CU (H2) and PLEs (H3) were independent predictors. These models were applied across the pre-selected ROIs (AF, SLF, UF, and ACC). To examine whether adolescents who use cannabis report PLEs more often than those who do not (H4), a logistic regression will be fitted using CU (CUDIT-R: yes/no) and PLEs (APSS: yes/no). To examine interactive and additive effects of CU and PLEs, general linear models were conducted using hypothesis driven groups (See Table 2) CU-/PLE- (Healthy controls), CU+/PLE-, CU-/PLE+, CU+/PLE+ (See Figure 1). These models were applied across the pre-selected ROIs (AF, SLF, UF, and ACC). In addition to the hypotheses driven analyses, a series of exploratory analyses would be conducted examining any identified predictors based off covariates (age, sex, handedness, and alcohol use). CUDIT-R scores will also replace CU (CUDIT-R: yes/no) in models to examine a continuous dimensional measure of CU. This exploratory analysis is planned because CU and psychosis research often exhibits large amounts of variance within the population and when modelled, does not meet normality assumptions (Greenwood et al., 2019). By examining a more continuous dimensional measure of CU, this exploratory analysis will further inform future methodology surrounding a population with large variance in CU. These models would then be compared to hypotheses driven models to examine model fit using AIC and BIC to explore whether this model better explains the variance seen within the population. All exploratory models are to be interpreted with caution and are strictly intended to inform future hypothesis-driven research.

Covariates were selected based on prior research demonstrating their relevance to white matter development in adolescence and their potential to confound associations between CU, PLEs, and neuroimaging outcomes. All models controlled for age, sex, alcohol use, and handedness (Brière et al., 2011; Kodiweera et al., 2016; Kopec et al., 2018; Spechler et al., 2019; Thayer et al., 2017). All p-values are two-tailed, and statistical significance was defined as $p < 0.05$ unless otherwise stated.

3.3 RESULTS

3.3.1 DESCRIPTIVES

A total of 123 adolescents aged 15-16 years were enrolled in the study. Two participants were excluded from the neuroimaging analysis (one due to excessive artifact, one due to failure to complete MRI scan), resulting in a final sample of 121 participants with complete neuroimaging data. Participant demographics, psychological measures, and substance use characteristics are summarized in Tables 1, 3, and 4. The full sample was 57% female, with a mean age of 15.74 years (SD = 0.60). Ethnic and socioeconomic backgrounds reflect the diversity of the Halifax Regional Municipality (*Focus on Geography Series, 2021 Census - Halifax (Census Subdivision)*, n.d.).

Participants were categorized into four groups based on CU (CUDIT-R: yes/no) and the presence of PLEs (APSS: yes/no): healthy controls (n = 72), PLE+/CU- (n = 15), PLE-/CU+ (n=27), PLE+/CU+ (n=9) (see Table 1, 3, and 4). There were no significant differences between the groups for sex, age, BMI, or handedness. APSS scores showed significant differences across all groups ($p < 0.001$) and post hoc Tukey HSD further highlighted significant differences between PLE+/CU- and healthy controls ($p < 0.001$), PLE+/CU+ compared to healthy controls ($p <0.001$), PLE+/CU- to PLE-/CU+ ($p>0.001$), and no significant differences were found between PLE+/CU- and PLE+/CU+ groups (See Table 5). Beck anxiety scores showed significant differences ($p <0.001$) and post hoc Tukey HSD further highlighted significant differences between PLE+/CU- and healthy controls ($p < 0.001$), PLE+/CU+ compared to healthy controls ($p <0.001$), PLE+/CU- to PLE-/CU+ ($p < 0.001$), and no significant differences were found between PLE+/CU- and PLE+/CU+ groups (See Table 6). Beck depression scores showed significant differences ($p <0.001$) and post hoc Tukey HSD further highlighted significant differences between PLE+/CU- and healthy controls ($p < 0.001$), PLE+/CU+ compared to healthy controls ($p <0.05$), PLE+/CU- to PLE-/CU+ ($p<0.05$), and no significant differences were found between PLE+/CU- and PLE+/CU+ groups (See Table 7).

All MRI scans were visually inspected and underwent automated quality control using MRIQC (See Table 8). One scan was excluded due to excessive artifact caused by metal appliance. No other scans were excluded for anatomical abnormalities or reconstruction failure. The mean and standard deviations for each imaging metric and analysis grouping in Table 9.

3.3.2 HYPOTHESIS DRIVEN ANALYSIS

In H1 we examined whether markers of neuroinflammation (as measured by MK) were associated with reduced white matter integrity (ODI) across the AF, SLF, and UF, and MD across the ACC in healthy developing adolescents (n = 72). Linear regression models were fitted separately for each tract of interest (AF, SLF, UF for ODI; ACC for MD), adjusting for age, sex, handedness, and alcohol use. Model comparisons using AIC and BIC showed that including MK and demographic covariates improved model fit for the left SLF, right AF, and left UF (See Table 10)

Significant negative associations between MK and ODI were observed in five out of six tracts, indicating that increased neuroinflammation was associated with reduced white matter integrity. The strongest effects were found in the left AF (β = -0.198, SE = 0.038, 95% CI [–0.27, –0.12], $p < 0.001$), followed by the right AF (β = –0.098, SE = 0.028, 95% CI [–0.15, –0.04], $p < 0.001$), left SLF (β = –0.147, SE = 0.031, 95% CI [–0.21, –0.08], $p < 0.001$), left UF (β = –0.170, SE = 0.042, 95% CI [–0.25, –0.08], $p < 0.001$), and right UF (β = –0.101, SE = 0.036, 95% CI [–0.17, –0.02], $p = 0.01$). The right SLF association did not reach statistical significance (β = –0.053, SE = 0.027, 95% CI [–0.10, –0.001], $p = 0.06$) (see Table 11).

Given the structural composition to the ACC (primarily a grey matter structure), MK was examined in relationship to MD rather than ODI. No significant associations were found in either hemisphere within the ACC (left ACC: β = –0.000001, SE = 0.00001, 95% CI [–0.0003, –0.0002], $p = 0.92$; right ACC: β = –0.00002, SE = 0.00009, 95% CI [–0.0002, –0.0001], $p = 0.82$)). Scatterplots of the residualized MK-ODI relationships for each tract are shown in Figure 2, 3, 4.

H2 and H3 evaluated whether CU or the presence of PLEs were associated with markers of neuroinflammation (MK) and white matter integrity (ODI, MD) within the AF, SLF, UF, and ACC bilaterally. General linear models were fitted separately for each tract of interest, and either CU (H2) or the presence of PLEs (H3), adjusting for age, sex, handedness, and alcohol use.

The H2 models showed no significant associations between CU (CUDIT-R, yes/no) and markers of neuroinflammation (MK) or white matter integrity (ODI, MD) in any of the bilateral ROIs (AF, SLF, UF, and ACC). All p-values were well above the threshold for significance. However, sex emerged as a significant predictor of differences in the brain within CU models across the AF (Left; ODI, $p < 0.001$, MK, $p = 0.02$; Right; ODI, $p < 0.001$) SLF (Left; ODI, $p < 0.001$, MD, $p = 0.02$, MK, $p < 0.001$; Right; ODI, $p < 0.001$, MD, $p = 0.04$, MK, $p = 0.01$), and UF (Left; ODI, $p = 0.02$) (see Table 12).

As with H2, H3 PLE models showed no significant associations between PLEs (APSS: yes/no) and markers of neuroinflammation (MK) or white matter integrity (ODI, MD) in any of the bilateral ROIs (AF, SLF, UF, and ACC). All models returned non-significant results for PLEs across all tracts.

Consistent with CU models (H2), sex was a significant predictor of differences in the brain, mirroring the patterns observed in the CU models (H2). Differences were seen in the AF (Left; ODI, $p < 0.001$, MK, $p = 0.02$; Right; ODI, $p < 0.001$), SLF (Left; ODI, $p < 0.001$, MD, $p = 0.02$, MK, $p < 0.001$; Right; ODI, $p < 0.001$, MD, $p = 0.04$), and UF (Left; ODI, $p = 0.02$) (see Table 13).

H4 examined whether adolescents who use cannabis would experience PLEs more compared to those who do not. A logistic regression model was fitted using CU (CUDIT-R: yes/no) and the presence of PLEs (APSS: yes/no) adjusting for age, sex, handedness, and alcohol use. The logistic regression model predicting presence of PLEs (yes/no) from CU (yes/no) while covarying for age, sex, handedness, and alcohol use revealed no statistically significant predictors. CU was not significantly associated with odds of PLEs (OR = 1.02, 95% CI [0.31, 3.02], $p = 0.97$).

H5 examined additive or interactive effects of both CU and PLEs on white matter integrity (ODI, MD) and markers of neuroinflammation (MK) in the SLF, AF, UF, and ACC bilaterally. General linear models were fitted using CU (CUDIT-R: yes/no), and presence of PLEs (APSS: yes/no). Two distinct linear models were estimated across bilateral tracts and regions of interest (AF, SLF, UF, ACC). The first model used the four-level categorical grouping variable (See Table 2) and examined additive effects of CU and PLEs, and the second tested an interaction effect with CU (CUDIT-R: yes/no) and presence of PLEs (APSS: yes/no). All models included age, sex, handedness, and alcohol use as covariates. Model comparisons were made using AIC and BIC to evaluate relative fit. Across all 24 interaction models, no significant main or interaction effects were found for CU, PLEs, or the CUxPLE interaction. Mean p-values for these terms ranged from 0.5 to 0.9. However, sex continued to show significant associations with ODI within the AF (left, $\beta = -0.01$, $p <0.001$; right, $\beta = -0.007$, $p <0.001$), SLF (left, $\beta = -0.009$, $p<0.001$; right, $\beta = -0.006$, $p < 0.001$), and UF (left, $\beta = -0.004$, $p = 0.025$; right, $\beta = -0.002$, $p = 0.147$) (See Table 14). Age, handedness, and alcohol use were not significantly associated with any outcome across models.

Interaction models best fit ODI in the AF and SLF, while additive models better fit MD and MK in the ACC and UF (see Table 15).

3.3.3 EXPLORATORY ANALYSIS: DIMENSIONAL MEASURE OF CANNABIS USE

An exploratory analysis using continuous CUDIT-R scores (as opposed to dichotomous CUDIT-R: yes/no) was conducted to re-explore H2, H4, and H5. Model fit was assessed using AIC and BIC comparing original hypothesized models and exploratory models.

The continuous model for H2 examined whether CUDIT-R scores were associated with markers of neuroinflammation (MK) and white matter integrity (ODI, MD) within the bilateral AF, SLF, UF, and ACC. General linear models were fitted for each tract of interest and covaried for age, sex, handedness, and alcohol use. The model showed no statistically significant associations. Although not statistically significant, the association between CUDIT-R scores and MD in the right ACC ($\beta = -0.000001$, SE = 0.0000008, 95% CI [–.000003, 0.0000002], p = 0.07) may suggest a subtle trend towards reduced white matter integrity with increasing CU. Furthermore, the continuous H2 model showed better fit across all ROIs than the binary model (See Table 16).

The continuous model for H4 examined whether increasing CUDIT-R scores explained which adolescents would experience PLEs (APSS: yes/no). No significant associations were found between CUDIT-R scores and PLEs (APSS: yes/no) (OR= 1.05, 95% CI [0.98, 1.13], p= 0.16). Model comparison showed that the H4 continuous model was a better fit compared to the hypothesized H4 model (See Table 17)

The continuous model for H5 examined whether CUDIT-R scores and PLEs (APSS: yes/no) were interactive predictors of white matter integrity (ODI, MD) and markers of neuroinflammation (MK). General linear models covaried for age, sex, handedness, and alcohol use. The models showed that MD in the left SLF was negatively associated with the presence of PLEs ($\beta = -0.000007$, SE = 0.000003, 95% CI [-0.00001, -0.0000003], p = 0.04). This model explained 12% of the variance observed ($R^2 = 0.119$, Adj. $R^2 = 0.056$, AIC = -2084.3, BIC = -2056.4). In the UF, higher CUDIT-R scores were associated with lower MK (left, $\beta = -0.001$, SE = 0.006, 95% CI [-0.002, 0.0002], p = 0.095; right, $\beta = -0.0008$, SE= 0.0007, 95% CI [-0.002, 0.0006], $p = 0.244$). This model explained 7.4% of the variance ($R^2 = 0.074$, Adj. $R^2 = 0.008$, AIC = -461.2, BIC = -433.2).

Across models, sex remained a significant predictor of lower MD ($\beta = -0.00002$, SE = -0.000008, 95% CI [-0.00004, -0.000007], $p = 0.005$). Additionally, alcohol use was significantly associated with increased MK ($\beta = 0.001$, SE = 0.0009, 95% CI [0.0001, 0.004], $p = 0.034$).

3.3.4 EXPLORATORY ANALYSIS: SEX-STRATIFIED MODELS

In previous models, sex was identified as a significant predictor. To further investigate sex-specific patterns, linear models were conducted using sex-stratified models: a female subsample ($n = 69$), and a male subsample ($n = 50$). H2, H3, H4, and H5 were conducted on the sex-stratified samples. All models controlled for age, alcohol use, and handedness.

3.3.4.1 FEMALE SUBSAMPLE

The female H2 model showed no significant associations between CU (CUDIT-R: yes/no), markers of neuroinflammation (MK) and white matter integrity (ODI, MD). The female H3 model showed statistically significant associations with PLEs and markers of neuroinflammation (MK) in the UF (right: $\beta = -0.02$, SE = 0.01, 95% CI [-0.05, -0.001], $p = 0.03$). There were also significant associations with PLEs and white matter integrity (ODI) in the UF (right: $\beta = 0.006$, SE = 0.003, 95% CI [0.0002, 0.01], $p = 0.04$). H4 models showed no significant associations. H5 models showed no significant interactions between CU and PLEs and markers of neuroinflammation and white matter integrity. However, in the categorical additive models, cannabis using females showed significantly higher MD within the UF compared to healthy controls (left, $\beta = 0.00003$, SE = 0.00001, 95% CI [0.000001, 0.00005], p

=0.040). PLE+ females showed marginal elevation in MD within the UF compared to healthy controls (left, β = 0.00003, SE = 0.00001, 95% CI [-0.0000002, 0.00006] p = 0.067).

PLE+ groups (PLE+/CU- and PLE+/CU+) showed decreases in MK compared to healthy controls within the UF, though not significant (β = -0.023, SE = 0.01, 95% CI [-0.05, 0.05], p = 0.11). Alcohol use and age were found to be a significant predictor of MK in the UF (left, β = 0.002, SE = 0.0009, 95% CI [0.00009, 0.004], p = 0.041; right, β = 0.002, SE = 0.001, 95% CI [0.0003, 0.004], p = 0.02; Age – right: β = 0.02, SE = 0.007, 95% CI [0.001, 0.03], p = 0.02).

3.3.4.2 MALE SUBSAMPLE

The male H2 model showed significant associations between CU and the SLF. Markers of neuroinflammation (MK) and CU showed negative associations within the left SLF (β = -0.04, SE = 0.02, 95% CI [-0.07, 0.0001], p = 0.05). White matter integrity (ODI) and CU in the SLF also showed statistically significant associations (left: β = 0.01, SE = 0.005, 95% CI [0.002, 0.02], p = 0.01; right: β = 0.01, SE = 0.005, 95% CI [0.002, 0.02], p = 0.03).

The male H3 models showed statistically significant associations with PLEs and markers of neuroinflammation (MK) within the AF (left: β = 0.03, SE = 0.01, 95% CI [0.005, 0.06], p = 0.02; right: β = 0.04, SE = 0.02, 95% CI [0-0.0006, 0.07], p = 0.05), SLF (left: β = 0.03, SE = 0.02, 95% CI [0.005, 0.07], p = 0.02; right: β = 0.04, SE = 0.02, 95% CI [0.0002, 0.09], p = 0.04), and the UF (left: β = 0.04, SE = 0.01, 95% CI [0.02, 0.07], p = 0.002; right: β = 0.04, SE = 0.02, 95% CI [0.003, 0.07], p = 0.03). H4 models showed no significant associations.

H5 models showed no significant interactions between CU and PLEs and markers of neuroinflammation and white matter integrity. However, there was significant additive associations in the SLF for cannabis-using males, and associations in the UF for males with

PLEs and males with CU and PLEs. In the SLF, cannabis using males showed significantly higher ODI compared to healthy controls (left, $\beta = 0.0014$, SE = 0.006, 95% CI [0.002, 0.0025], $p = 0.03$; right, $\beta = 0.012$, SE = 0.006, 95% CI [-0.075, -0.002], $p = 0.04$). In the UF, PLE+ males showed significantly higher MK than healthy controls (left, $\beta = 0.034$, SE = 0.015, 95% CI [0.004, 0.064], $p = 0.03$) and CU+/PLE+ males showed marginal increases in MK (left, $\beta = 0.049$, SE =0.027, 95% CI [-0.006, 0.104], $p = 0.08$; right, $\beta = 0.066$, SE = 0.034, 95% CI [-0.003, 0.134], $p = 0.06$).

3.4 DISCUSSION

This study examined the independent and combined effects of CU and PLEs on adolescent white matter microstructure and markers of neuroinflammation using tract-specific diffusion metrics (ODI, MD, and MK). Leveraging advanced diffusion MRI and a population specific adolescent white matter atlas, we sought to clarify whether CU and PLEs are associated with alterations in neuroinflammatory and microstructural pathways during a sensitive neurodevelopmental period.

3.4.1 HYPOTHESIS 1: MARKERS OF NEUROINFLAMMATION AND WHITE MATTER INTEGRITY

Findings show H1 to be supported, demonstrating a robust relationship between markers of neuroinflammation (MK) and white matter integrity (ODI, MD) in healthy developing adolescents. Increased MK was negatively associated with ODI in the left AF, bilateral SLF, and UF (Figures 2-4). These findings align with prior work suggesting that microglia-mediated pruning and glial signalling during adolescence is occurring during this critical period of development – which we would expect to see based on hypothetical and animal models (Andersen, 2022; Chadwick, Miller, & Hurd, 2013). The absence of effects in the ACC further supports that glial related alterations may be tract specific, particularly in association pathways rich in cannabinoid density and does not occur in grey matter regions (Flores et al., 2022).

3.4.2 HYPOTHESIS 2: CU EFFECTS ON WHITE MATTER INTEGRITY AND MARKERS OF NEUROINFLAMMATION

Based on findings from this study, H2 was found to not be supported. Regardless of CU, there were no significant associations between markers of neuroinflammation and white matter integrity in any of the bilateral ROIs. However, a consistent significant finding across nearly all models was the role of biological sex as a predictor.

These null findings within the H2 CU models may reflect several key factors. First the group sizes were skewed – even though they did reflect a representative community sample - with small CU+/PLE- (n = 27), CU-/PLE+ (n = 15), and CU+/PLE+ (n = 9) subgroups compared to healthy controls (n = 72 – 70 with usable MRI data). In total the sample had 36 cannabis users, and within this group, there was large amounts of variance in the frequency of use, potency, amount, and social context. This variance and small size limited statistical power and increased the risk of type II errors. Secondly, due to large variance within use frequency and amount, CU was operationalized as a dichotomous measure, CU (CUDIT-R: yes/no), which could be masking the unique variability in CU patterns. Literature supports that earlier onset of CU does reflect changes in structural gray matter with as little as 1-2 uses prior to the age of 12 (C. Orr et al., 2019). However, adolescent CU is known to be highly heterogenous (Greenwood et al., 2019; Imtiaz et al., 2024; Patrick et al., 2018), and lacking information surrounding age of onset, and frequency and severity of CU may have provided the information needed to better investigate this hypothesis. Collectively these factors may have diluted group-level effects despite known neurobiological vulnerabilities. Despite preliminary null results, this hypothesis warrants further investigation into the relationship between CU and markers of neuroinflammation (MK) and white matter integrity (ODI, MD) in this population including the role of biological sex.

3.4.3 HYPOTHESIS 3: PLES EFFECTS ON WHITE MATTER INTEGRITY AND MARKERS OF NEUROINFLAMMATION

The results of this study did not support H3. The presence of PLEs did not associate with changes in markers of neuroinflammation or white matter integrity. Similar to H2, sex emerged as a significant predictor of associations within models, and these associations seemed to mirror those within H2.

The null findings directly contradict the findings of preliminary neuroimaging studies examining PLEs and their associations with white matter within the AF (Dooley et al., 2020), SLF, and UF (O'Hanlon et al., 2015). This could be due to a variety of reasons. The first being that this was the first study to our knowledge, to use more advanced neuroimaging techniques that examined white matter microstructure in significantly more detail than DTI and FA have previously been able to provide (Falangola et al., 2008; Grinberg et al., 2017; F. Zhang et al., 2021). We were able to account for the vast complexities and potential confounding factors that occur within neurodevelopment which is shown through results of H1 (e.g., normative developmental synaptic pruning) (Flores et al., 2022; Grinberg et al., 2017; Lebel & Deoni, 2018). Though we did have a community representative sample of PLEs (n = 24), compared to our larger sample (n = 123), both preliminary studies had larger samples of PLEs (n = 28 (O'Hanlon et al., 2015), and n = 52 (Dooley et al., 2020)). It is possible that the differences seen in those studies are a result of a younger population. Both preliminary studies have younger sample sizes with ages ranging from 11-16, so it is entirely possible that the results presented here represent a detailed examination with neurodevelopment considered using DKI and

NODDI. Regardless, the findings from this study warrant more research into this hypothesis using neuroimaging techniques such as NODDI and DKI to provide a clearer picture of the effects of PLEs on white matter integrity and neuroinflammation.

3.4.4 HYPOTHESIS 4: CU AND PLES

The findings presented in this study do not support H4. There was no evidence to support the hypothesis that adolescents who use cannabis are more likely to experience a PLE compared to those who do not. This hypothesis was based on prior literature, specifically a study examining CU and incidence of PLEs within an adolescent population (aged 13-18) (Bechtold et al., 2016). This study focused on a large population of males (n = 1009), and was able to follow participants for several years, and it found that for each year that adolescent males engage in cannabis use their odds of experiencing subclinical paranoia or hallucinations rose by 133% and 92% (Bechtold et al., 2016). The present study does have several methodological differences, cross-sectional design, the examination of both sexes, involvement of neuroimaging, but we did not find any evidence to support the findings reported in the prior study (Bechtold et al., 2016). This could be due to a variety of factors including a large effect in the male sex, as the current study had a larger sample of females (n = 42) compared to males (n = 28). The current study also had a significantly tighter age range (15-16) as opposed to 13 – 18 years old and lacked longitudinal data to follow-up with participants. The current study does have an interesting range of CU, with large reports of variance (See Table 1) on the reported amounts and frequency, which was not reported within the Bechtold study. It is important to note that male and female neurodevelopmental pathways take place along different timelines, with females often showing signs of development ahead of males (Flores et al., 2022; Konrad et al., 2013; Lebel & Deoni, 2018). It is entirely possible that by limiting the current studies age range to 15-16 years old, we will be able to easily examine adolescent incidence of PLEs in males but have missed the 'critical window' within the female population. Overall, the current study and this hypothesis add to the current body of literature and emphasizes the importance of inclusion of both sexes. These null results warrant further investigation into CU and PLEs specifically in female populations with larger age ranges.

3.4.5 HYPOTHESIS 5: INTERACTION MODELS OF CU AND PLES AND THEIR EFFECTS ON WHITE MATTER INTEGRITY AND MARKERS OF NEUROINFLAMMATION

The findings presented in this study do not support H5. This hypothesis posited that the potential effects of CU and PLE interact to enact larger changes compared to just the effects of CU or PLEs on white matter integrity and markers of neuroinflammation. Although models showed that no effects had significant associations with changes in white matter integrity and markers of neuroinflammation, model comparisons indicated a better fit for interaction models in capturing white matter variance for ODI in the SLF and AF (ΔAIC = 4.2 – 9.0). Showing that interactions between CU and PLEs may better explain changes in detailed white matter integrity. However, in markers of neuroinflammation (MK) and broad white matter integrity (MD), categorical grouping additive models showed better fit, especially in the ACC and UF. These results suggest that modelling the interaction between CU and PLEs may help detect more subtle white matter differences, especially in tracts involved in executive and language function (Levar et al., 2018; Stevens et al., 2011; Von Der Heide et al., 2013) and modelling independent and additive effects may better explain grey matter and deeper cortical structures. Nevertheless, the overall absence of significant interaction effects likely reflects a combination of insufficient power, group heterogeneity, and potentially the need for dimensional measures of CU and PLEs to capture effects in an already complex environment. Importantly, sex continued to be a significant covariate in nearly all models, reinforcing the need for sex-stratified approaches. To our knowledge, this is the first study to examine markers of neuroinflammation and white matter integrity within an adolescent population that both uses cannabis and has experienced a PLE. Despite null results, this hypothesis warrants further research to address the current study limitations, and to further examine the potential biological mechanism behind PLEs and CU.

3.4.6 EXPLORATORY CONTINUOUS MODELS

An exploratory analysis was performed using continuous CUDIT-R scores which are indicative of problematic cannabis use, to account for the large amounts of variance seen in the recruited sample. CUDIT-R scores do not solely rely on frequency of use or quantity (like the TLFB in grams / day) (Sobell & Sobell, 1992), but instead focuses on the predetermined disordered use, which posits there is non-problematic CU, questionable CU, and problematic CU, and of those, a cannabis use disorder can be determined (Adamson et al., 2010). By using this measure, as opposed to a measure of frequency or quantity, the unique use patterns of adolescence can better represent the population (Patrick et al., 2018). When re-examining H2, there was no significant associations, but evaluation of model fit showed that the CUDIT-R total scores better represented the model compared to a dichotomous use measure. Using the continuous measure in H4 resulted in similar findings, with no significant differences reported, however, the model was shown to be a better fit compared to the original hypothesized model. Re-examining H5 with the continuous measure showed significant differences in white matter integrity (MD) within the left SLF when PLEs were present in the sample. Markers of neuroinflammation (MK) in the UF were also significantly associated with more problematic CU. In all models' sex was identified as a significant predictor of lower white matter integrity measures (MD), and alcohol use was significantly associated with increased markers of neuroinflammation (MK). While these findings are exploratory and cannot be interpreted with the same rigor as hypothesis driven analyses, the findings of these analyses can influence and guide further research methodologies within the field. The variance in CU was significant in our sample, and to better account for this, continuous measures that account for more than just frequency or amount can better represent use patterns and changes within the population. CU in adolescence is typically difficult to model statistically, due to this variance (Greenwood et al., 2019) so exploring different measures could drive further research into effects of CU on brain white matter and the underlying biological mechanisms. These findings also serve as an indicator that these hypotheses need further investigation to fully examine the proposed research aims.

3.4.7 SEX-STRATIFIED MODELS

Based on findings within the current study, that sex significantly predicted outcomes in both CU and PLEs, a sex-stratified examination of posited hypotheses was conducted. H2, stratified by sex showed no significant differences in white matter integrity or markers of neuroinflammation with CU in females, but showed a significant association between CU and the SLF. In males' markers of neuroinflammation were negatively associated with CU in the left SLF, and white matter integrity was positively associated with CU in the bilateral SLF. This exploratory finding builds on the discussion above from the preliminary CU neuroimaging studies from C. Orr et al. (2019) and J. M. Orr et al. (2016) where even with low amounts of reported CU, there were differences within the white and grey matter structures. It does bring in the question of why biological sex is a significant factor, to which the current literature cannot yet answer. Sex-specific CU initiation and patterns has been proposed (Spechler et al., 2019), but the field still needs significant amounts of research to prove these hypotheses. This finding should not be interpreted as a concrete result, instead it should be used to guide further research into these observed differences to examine the potential differences in effects and underlying biological mechanisms. H3 when stratified by sex, showed significant differences in the female subsample. There were negative associations between PLEs and markers of neuroinflammation within the UF, and positive associations between PLEs and white matter integrity. In the male subsample, positive associations between PLEs and markers of neuroinflammation were observed in the AF, SLF, and UF bilaterally, but unlike the female subsample there was not association with white matter integrity in any ROI. The opposing associations are indicative of opposite underlying mechanisms warranting the further investigation of sex-stratified models. When H4 models were stratified, there was no significant associations between CU and PLEs, further suggesting the need for a continuous or more detailed measure of CU.

H5 models stratified by sex revealed a distinct relationship with CU and PLEs. In the female subsample cannabis using females showed higher measures of white matter integrity compared to healthy controls within the UF, and PLE+ females showed a similar association of higher measures of white matter integrity within the UF. Markers of neuroinflammation in the UF were found to show decreases in PLE+/CU- and PLE+/CU+ groups, although they were not statistically significant. Both alcohol use and age were found to be significant predictors of markers of neuroinflammation in the UF. To contrast, in the male subsample, markers of neuroinflammation within the UF were found to have positive associations with PLE+/ CU- and PLE+/CU+ males, opposite of the observed in females. In the male subsample, white matter integrity was also observed to have positive associations with cannabis using males in the SLF, which was not observed in the female subsample. These exploratory findings suggests that CU and PLEs may disrupt different neurobiological pathways in males, with preliminary observations suggesting CU may be affecting microstructure and PLEs may impact glial processes. This warrants further research into the biological mechanisms underlying these changes. These sex differences may reflect sex-specific developmental windows, differential expression of cannabinoid receptors, sex-specific variability in CU or PLEs, or unique variability to comorbid exposures such as trauma, other substance use, or psychiatric symptoms (Adjorlolo et al., 2024; Kodiweera et al., 2016; Kopec et al., 2018; Spechler et al., 2019).

3.4.8 INTEPRETIVE CONSIDERATIONS AND LIMITATIONS

Although the findings of the hypothesized study yielded largely null findings, these results should not be interpreted as evidence against the hypothesized effects of CU and PLEs on white matter microstructure or neuroinflammatory markers in adolescence. This study utilized the presence of a PLE in adolescents to determine the analysis groupings, but future studies should consider measures that examine persistence or severity, which could better capture the unique differences within the population.

Each of the imaging metrics used in this study captures a distinct biological feature of white matter microstructure. MD reflects the average mobility of water molecules in tissue and is sensitive to global tissue density; in adolescence, declining MD is generally interpreted as an index of increasing white matter integrity and myelination (Ranzenberger et al., 2023). MK, derived from DKI quantifies non-Gaussian water diffusion, offering highly sensitive interpretations of tissue complexity and microstructural heterogeneity (Steven et al., 2014). In developmental contexts, higher MK has been associated with more complex, mature microstructure – suggesting ongoing myelination, axonal packing, and glial proliferation (Cheung et al., 2009; Jensen & Helpern, 2010; Tabesh et al., 2011; Weber et al., 2015). ODI reflects the dispersion of neurites (axons and dendrites); increased ODI in adolescence may reflect pruning or the refinement of white matter (Johnson et al., 2021; Wang et al., 2019; H. Zhang et al., 2012). It is important to note the complexity of adolescent populations compared to adults. Adolescents, particularly in this sample aged 15-16 years, are undergoing a period of critical development in which we would expect a large amount of axonal reorganization, myelination, synaptic pruning, and neuroinflammation (Flores et al., 2022; Harkany et al., 2007; Konrad et al., 2013; Lebel & Deoni, 2018). This study utilizes healthy developing adolescents who were screened through robust protocols (see Chapter 3.1 for screening protocols) to compare across CU and PLE groups. It also examines highly sensitive imaging metrics as opposed to more commonly referenced FA, which has been shown to yield misleading interpretations in areas of fiber crossing, an important and consistent characteristic feature of adolescent white matter development (Figley et al., 2022; Grinberg et al., 2017; Lebel & Deoni, 2018).

While the hypotheses examined provided null results, the absence of significant effects does not invalidate the theoretical model, or research aims proposed previously (See 3.1). Rather, it underscores the complexity of studying CU and PLEs in adolescence, a period marked by significant interindividual variability in both brain maturation and substance exposure (Batalla et al., 2013; Chadwick, Miller, Hurd, et al., 2013; Dominguez et al., 2011; Shi et al., 2015; Tu et al., 2008). Moreover, exploratory analyses revealed important covariates that accounted for a modest proportion of variance in neuroimaging outcomes, indicating potential confounds that warrant careful control in future designs. These findings also support the need for dimensional, rather than categorical, assessment of CU. Binary definitions used (e.g.: yes/no in past 6 months) likely obscured meaningful differences in exposure patterns, including cumulative use, age of onset, frequency, and THC potency, all of which are known to influence white matter structure in older and clinical samples (Batalla et al., 2013; Battistella et al., 2014; C. Orr et al., 2019; Zalesky et al., 2012). Dimensional measures such as CUDIT-R scores offer a more detailed picture of use severity and duration and should be emphasized in future studies.

The current study is not without limitations, the community recruited sample (n = 123) although large for a neuroimaging study, showed large amounts of variance when it came to their reported substance use. This limited the types of statistical analyses that could be performed, and further limited the measures examined. The recruited sample was large, but due to the high variance in substance use, variables such as cannabis use, were dichotomized. It is also possible that CU and PLE effects on white matter may only emerge with measures of severity, persistence, or in conjunction with other risk factors such as trauma or mood dysregulation, which were not fully captured in this sample. It is also entirely possible that due to variance in neurodevelopmental patterns in adolescence and lack of further neuroimaging studies in this area, increased sample sizes may be required to detect significant differences between groups.

Despite its limitations, this study offers several strengths. It applies a high-resolution, age-specific white matter atlas representative of this developmental stage. The present study also followed hypotheses guided by literature, including H1 which improved upon the current literature of adolescent neurodevelopment in a large sample of healthy controls to confirm assumptions about the biophysical models used in DKI and NODDI imaging (DiPiero et al., 2022). The combination of categorical, dimensional, and interaction models also provides a robust framework for testing complex developmental hypotheses, which will benefit larger longitudinal datasets. While the cross-sectional design precludes causal inferences, this preliminary dataset provides foundational analyses for designing future cross-sectional and longitudinal studies aimed at disentangling the temporal relationships between CU, neuroinflammation, white matter maturation, and the emergence and persistence of PLEs.

In summary, this study represents a critical step forward in the application of biologically relevant neuroimaging metrics to adolescent substance use research. It provides both empirical insight and a methodological blueprint for future investigations, underscoring the need for detailed assessments and developmental sensitivity in emerging fields of research.

3.4.9 CLINCIAL IMPLICATIONS

Although CU and PLEs did not robustly alter white matter in this sample, the observed effects of markers of neuroinflammation and sex, highlight potential biomarkers of vulnerability. The findings from H2, H3, and H5 describe the importance of balanced sex samples, and exploratory analyses direct future research to further investigate the underlying mechanisms behind the significance of sex as a predictor for both PLEs and CU. While null findings in the hypotheses do not directly allow for the conclusions of our research aims, the findings presented in the current study will direct future research, aimed at identifying the underlying biological mechanisms behind psychosis and psychotic disorders.

3.5 TABLES

Table 1

Substance Use Characteristics of Recruited Sample by Analysis Grouping

Characteristic	CU-/PLE-		PLE-/CU+		PLE+/CU-		PLE+/CU+	
	n	M (SD)	*n*	M (SD)	*n*	M (SD)	*n*	M (SD)
Cannabis Use								
TLFB g/month***	0	0	15	25.5 (45.8)	0	0	6	103.6 (119.7)
CUDIT-R Total** Score	0	0	27	8.04 (6.24)	0	0	9	14.44 (8.60)
Reported Lifetime Use	5		27		1		9	
Alcohol Use								
AUDIT Total Score***	29	1.22 (3.52)	25	5.19 (4.26)	11	2.00 (1.96)	9	7.78 (3.80)
Nicotine Use								
FND (Y/N)	1/71		4/23		0/15		3/6	
EDS (Y/N)	5/67		13/14		2/13		4/5	
Other Substances (Y/N)								
Cocaine	1/71		2/25		0/15		2/7	
Hallucinogens	2/70		5/22		0/15		4/5	
Opioids	0/72		2/25		0/15		1/8	
Sedative / Hypnotics Anxiolytics	1/71		1/26		0/15		3/6	

*Note. N = 123 (Males n = 50, Females n = 71, Not specified n = 2). Participants were on average 15.75 years old (SD = 0.60). TLFB = Timeline follow back, represents cannabis use in the past 30 days. CUDIT-R = Cannabis use disorder identification rest – revised, represents cannabis use in the last 6 months. Lifetime use was accounted for if the participant had ever used cannabis. AUDIT = Alcohol use disorder identification test, represents history of alcohol use. FND = Fagerstrom test for nicotine dependance, represents current cigarette use, EDS = E-cigarette dependance scale for adolescent use, represents reported e-cigarette use. History of use with other substances were obtained using the chemical use /abuse / dependance scale (CUAD). * p < 0.05, ** p < 0.01, *** p <0.001*

Table 2

Categorical Grouping of Recruited Sample

	No History of Cannabis Use	Self-Reported Cannabis Use
No PLEs	72	27
Presence of PLEs	15	9

Note. Psychotic-Like Experiences (PLEs) characterized using the adolescent psychotic-symptom screener (APSS), and the presence of a PLE was indicative of a score greater than 2. Self-reported cannabis use was characterized using the cannabis use disorder identification test (CUDIT-R) where participants indicated whether they had used cannabis use in the last 6-months.

Table 3

Demographic Characteristics of Recruited Sample by Analysis Grouping

Characteristic	CU-/PLE-	PLE-/CU+	PLE+/CU-	PLE+/CU+
	N = 72	*N = 27*	*N = 15*	*N = 9*
Sex (M/F/U)	28/42/2	14/13/0	6/9/0	2/7/0
Age[a]	15.65 (0.56)	15.89 (0.64)	15.80 (0.68)	15.89 (0.60)
Body Mass Index (BMI)[a]	23.15 (4.45)	22.41 (3.99)	23.64 (6.23)	21.13 (1.70)
Handedness (R/L/A)	61/5/6	24/0/3	12/2/1	8/1/0

Note: [a] Mean (SD), Handedness obtained using the Edinburgh Handedness Inventory (Right / Left / Ambidextrous). No significant differences between groups were observed.

Table 4

Psychological Characteristics of Recruited Sample by Analysis Grouping

Characteristic	CU-/PLE-	PLE-/CU+	PLE+/CU-	PLE+/CU+
	N = 72	*N = 27*	*N = 15*	*N = 9*
APSS Score[a] ***	0.50 (0 – 1.5)	0.5 (0 – 1.5)	3.0 (1 – 6.5)	2.5 (1 – 5.5)
Beck Anxiety Inventory[a] ***	16 (0 – 44)	18 (3 – 43)	34 (17 – 59)	35 (12 –43)
Beck Depression Inventory[a] ***	7 (0 – 47)	10 (1 – 44)	17 (7 – 49)	16 (7 – 44)
Y-VACS[a] ***	5 (0 – 29)	8 (1 – 28)	11 (5 – 29)	14 (6 – 28)

*Note: [a] Median (Range), [b] Mean (SD), APSS = Adolescent Psychotic-Like Symptom Screener, Y-VACS = Yale-Vermont Adversity in Childhood Scale. * p < 0.05, ** p < 0.01, *** p <0.001.*

Table 5

Post Hoc Tukey HSD – APSS Score

Group	PLE-/CU-	PLE-/CU+	PLE+/CU-	PLE+/CU+
PLE-/CU-	X	0.97	>0.001	>0.001
PLE-/CU+	0.97	X	>0.001	>0.001
PLE+/CU-	>0.001	>0.001	X	0.93
PLE+/CU+	>0.001	>0.001	0.93	X

Note. Completed Post Hoc using Tukey HSD. APSS = Adolescent psychotic-like symptom screener. P-Values reported.

Table 6

Post Hoc Tukey HSD – Beck Anxiety Inventory Score

Group	PLE-/CU-	PLE-/CU+	PLE+/CU-	PLE+/CU+
PLE-/CU-	X	0.25	>0.001	0.001
PLE-/CU+	0.25	X	>0.001	0.09
PLE+/CU-	>0.001	>0.001	X	0.83
PLE+/CU+	0.001	0.09	0.83	X

Note. Completed Post Hoc using Tukey HSD. P-Values reported.

Table 7

Post Hoc Tukey HSD – Beck Depression Inventory Score

Group	PLE-/CU-	PLE-/CU+	PLE+/CU-	PLE+/CU+
PLE-/CU-	X	0.27	>0.001	0.01
PLE-/CU+	0.27	X	0.03	0.29
PLE+/CU-	>0.001	0.03	X	0.95
PLE+/CU+	0.01	0.29	0.95	X

Note. Completed Post Hoc using Tukey HSD. P-Values reported.

Table 8

Quality Control Measures Reported in Sample (n = 121)

Quality Control Measure	Reported Metric
CNR	1.74 (0.25)
SNR (total)	4.93 (0.69)
SNR (White Matter)	7.88 (1.05)
CJV	0.55 (0.04)

Note. Derived from MRIQC.

Table 9

Demographic Characteristics of Recruited Sample by Analysis Grouping

Characteristic	CU-/PLE-	PLE-/CU+	PLE+/CU-	PLE+/CU+
	N = 70	*N = 27*	*N = 15*	*N = 9*
		ACC		
MD	0.001 / 0.00098 (0.00005/0.00004)	0.001 / 0.00097 (0.00006/ 0.00005)	0.001/0.00098 (0.0001/0.00005)	0.001/ 0.00097 (0.00008/0.00004)
		AF		
MD	0.0009/0.0009 (0.00003 / 0.00003)	0.0009 / 0.0009 (0.00003/0.00003)	0.0009/ 0.0009 (0.00006/0.00004)	0.0009 / 0.0009 (0.00003/0.00003)
MK	0.77/0.78 (0.04/0.05)	0.78/0.79 (0.04 / 0.04)	0.77 / 0.79 (0.07/ 0.7)	0.78 /0.79 (0.5/0.4)
ODI	0.35 / 0.35 (0.01/0.01)	0.35/0.35 (0.01/0.01)	0.35/0.35 (0.02/0.01)	0.36/0.35 (0.015/0.007)
		SLF		
MD	0.001/0.001 (0.00004 / 0.00003)	0.001/0.001 (0.00004/0.00004)	0.001/0.001 (0.00008/0.00006)	0.001/0.001 (0.00003/0.00003)
MK	0.77 / 0.74 (0.04 / 0.05)	0.78 / 0.75 (0.05/0.04)	0.77/0.76 (0.07/0.07)	0.78 / 0.75 (0.04 / 0.04)
ODI	0.36/0.36 (0.01/0.01)	0.36 / 0.36 (0.01/0.01)	0.36/0.36 (0.02/0.02)	0.36/0.37 (0.01/0.006)
		UF		

MD	0.001 / 0.001 (0.00004/0.00004)	0.001/0.001 (0.00005/0.00004)	0.001/0.001 (0.00004/0.00006)	0.001/0.001 (0.00003/0.00003)
MK	0.66 / 0.64 (0.03/ 0.04)	0.70 / 0.70 (0.04/0.04)	0.70/0.60 (0.04/0.05)	0.070/0.070 (0.03/0.03)
ODI	0.34/0.34 (0.01/0.01)	0.34/0.34 (0.01 / 0.01)	0.34 / 0.35 (0.01/0.01)	0.34/0.34 (0.01/0.01)

Note. Left Hemisphere / Right Hemisphere Mean (SD) for each analysis grouping. AF = Arcuate Fasciculus, SLF = Superior Longitudinal Fasciculus, UF = Uncinate Fasciculus, ACC = Anterior Cingulate Cortex

Table 10

H1 Summary of Model Fit

Model	ΔAIC	ΔBIC
Left SLF	27.06	15.82
Right AF	17.42	6.18
Left UF	13.11	1.87

Note. Model fit assessed to examine covariates and examination of mean kurtosis within white matter integrity measure (ODI). These models favor the Full model over the base model.

Table 11

H1 Multi-Model Linear Regression Outputs.

Tract	Hemisphere	Estimate	Standard Error	95 % CI	P-Value
AF	Left	-0.198	0.038	[-0.27, -0.12]	$p < 0.001$
AF	Right	-0.098	0.028	[-0.15, -0.04]	$p < 0.001$
SLF	Left	-0.147	0.031	[-0.21, -0.08]	$p < 0.001$
SLF	Right	-0.053	0.027	[-0.10, 0.001]	$p = 0.0567$
UF	Left	-0.170	0.042	[-0.01, -0.08]	$p < 0.001$
UF	Right	-0.101	0.036	[-0.17, -0.02]	$p = 0.00714$
ACC	Left	-0.00001	0.0001	[-0.0003, -0.0002]	$p = 0.92$
ACC	Right	-0.00002	0.00009	[-0.0002, -0.0001]	$p = 0.81$

Note. AF = Arcuate Fasciculus, SLF = Superior Longitudinal Fasciculus, UF = Uncinate Fasciculus, ACC = Anterior Cingulate Cortex

Table 12

H2 Summary of Significant Sex Effects Across White Matter Tracts

Tract	Hemisphere	Metric	Estimate (β)	Std. Error	P-Value	95% CI
AF	Left	ODI	-0.010	0.002	< .001	[-0.015, -0.005]
AF	Left	MK	0.01	0.007	0.02	[0.002, 0.031]
AF	Right	ODI	-0.007	0.0003	< .001	[-0.011, -0.003]
SLF	Left	ODI	-0.009	0.002	< .001	[-0.01, -0.004]
SLF	Left	MD	-0.00002	0.000007	0.019	[-.00003, -.000003]
SLF	Left	MK	0.03	0.008	< .001	[0.012, 0.045]
SLF	Right	ODI	-0.007	0.001	< .001	[-0.01, -0.002]
SLF	Right	MD	-0.00001	0.000007	0.04	[-.00002, -.0000008]
SLF	Right	MK	0.02	0.008	0.01	[0.004, 0.038]
UF	Left	ODI	-0.004	0.002	0.02	[-0.009, -0.0008]

Note. This table summarizes covariate effects of sex, based off the models from hypothesis 2. AF = Arcuate Fasciculus, SLF = Superior Longitudinal Fasciculus, UF = Uncinate Fasciculus, ACC = Anterior Cingulate Cortex These linear models examined binary CU in bilateral AF, SLF, and UF. Covariates included age, sex, alcohol use, and handedness.

Table 13

H3 Summary of Significant Sex Effects Across White Matter Tracts

Tract	Hemisphere	Metric	Estimate (β)	Std. Error	P-Value	95% CI
AF	Left	ODI	-0.010	0.002	< .001	[-0.015, -0.005]
AF	Left	MK	0.01	0.007	0.02	[0.002, 0.031]
AF	Right	ODI	-0.007	0.0003	< .001	[-0.011, -0.003]
SLF	Left	ODI	-0.009	0.002	< .001	[-0.01, -0.004]
SLF	Left	MD	-0.00002	0.000007	0.019	[-.00003, -.000003]
SLF	Left	MK	0.03	0.008	< .001	[0.012, 0.045]
SLF	Right	ODI	-0.007	0.001	< .001	[-0.01, -0.002]
SLF	Right	MD	-0.00001	0.000007	0.04	[-.00002, -.0000008]
SLF	Right	MK	0.02	0.008	0.01	[0.004, 0.038]
UF	Left	ODI	-0.004	0.002	0.02	[-0.009, -0.0008]

Note. This table summarizes covariate effects of sex, based off the models from hypothesis 3. AF = Arcuate Fasciculus, SLF = Superior Longitudinal Fasciculus, UF = Uncinate Fasciculus, ACC = Anterior Cingulate Cortex. These linear models examined the presence of PLEs in bilateral AF, SLF, and UF. Covariates included age, sex, alcohol use, and handedness.

Table 14

H5 Summary of Significant Sex Effects Across White Matter Tracts in Categorical Model

Tract	Hemisphere	Metric	Estimate (β)	Std. Error	P-Value	95% CI
AF	Left	ODI	-0.010	0.002	< .001	[-0.015, -0.005]
AF	Right	ODI	-0.007	0.002	< .001	[-0.011, -0.003]
SLF	Left	ODI	-0.009	0.002	< .001	[-0.014, -0.005]
SLF	Right	ODI	-0.007	0.002	0.001	[-0.011, -0.003]
UF	Left	ODI	-0.005	0.002	0.025	[-0.009, -0.001]
UF	Right	ODI	-0.002	0.001	0.147	[-0.006, 0.001]

Note. This table summarizes covariate effects of sex, based off the categorical models from hypothesis 5. AF = Arcuate Fasciculus, SLF = Superior Longitudinal Fasciculus, UF = Uncinate Fasciculus, ACC = Anterior Cingulate Cortex. These linear models examined ODI in bilateral AF, SLF, and UF across the four categorical groups. Covariates included age, sex, alcohol use, and handedness.

Table 15

H5 Summary of Model Fit

Model	Hemisphere	ΔAIC	ΔBIC
Measure	ODI		
SLF	Left	8.61	-2.57
SLF	Right	4.19	-6.99
AF	Left	9.00	-2.19
AF	Right	6.76	-4.42
Measure	MK		
UF	Left	-2.98	14.16
UF	Right	-4.81	-15.99
Measure	MD		
ACC	Left	-6.10	-15.94
ACC	Right	-6.46	-17.65

Note. Comparing the categorical additive model to the interaction model.

Table 16

Exploratory Continuous H2 Summary of Model Fit

Model	Degrees of Freedom	AIC	BIC
Cannabis Use (yes/no)	7	-2068.562	-2048.991
Cannabis Use (CUDIT-R total score)	7	-2071.358	-2051.787

Note. Model fit assessed for MD in the right hemisphere ACC.

Table 17

Exploratory Continuous H4 Summary of Model Fit

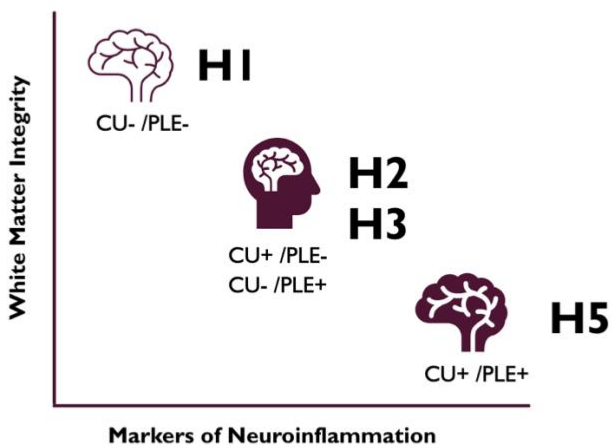
Model	Degrees of Freedom	AIC	BIC
Cannabis Use (yes/no)	6	128.38	145.25
Cannabis Use (CUDIT-R total score)	6	126.47	143.34

Note. Model fit assessed for MD in the right hemisphere ACC.

3.6 FIGURES

Figure 1

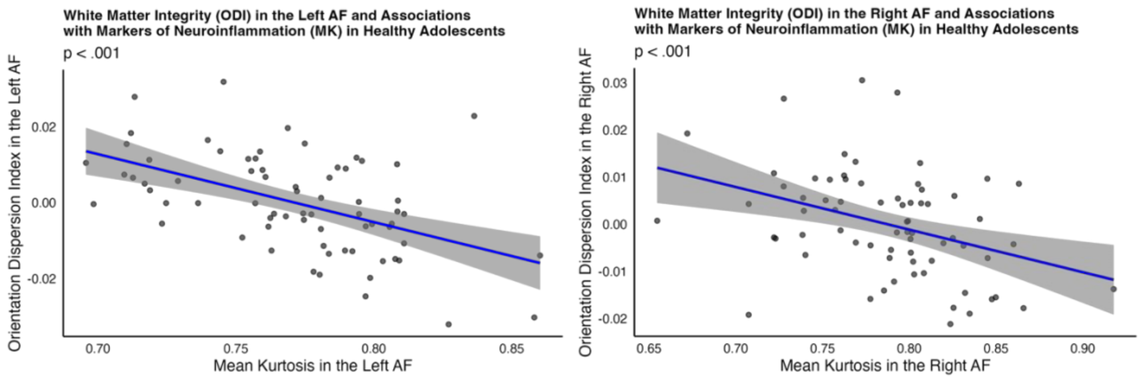
Visual Representation of Hypotheses



Note. CU = Cannabis Use, PLE = Psychotic-Like Experience, White matter integrity as measured by orientation dispersion index and mean diffusivity, and markers of neuroinflammation as measured by mean kurtosis.

Figure 2

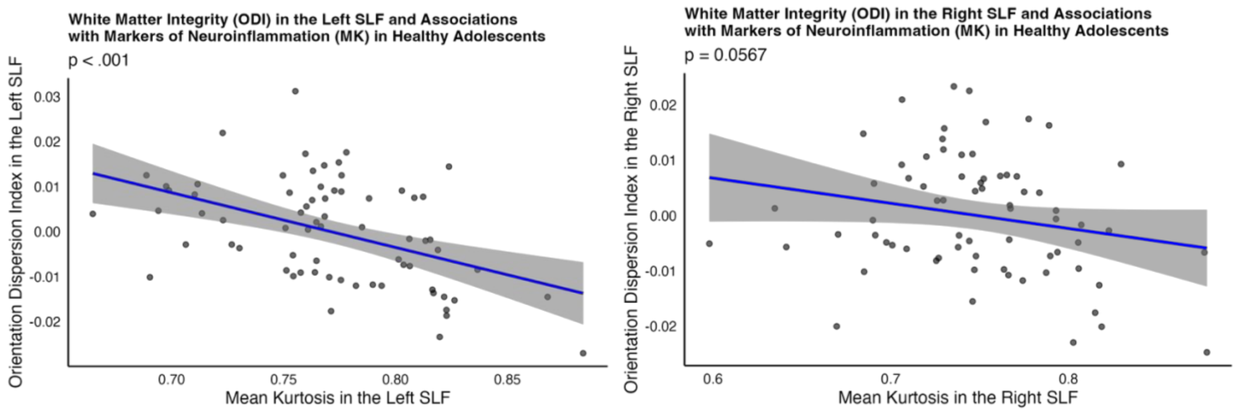
White Matter Integrity (ODI) in the Arcuate Fasciculus is negatively associated with Markers of Neuroinflammation (MK)



Note. *WM integrity values were residualized for age, sex, and alcohol use. Each point represents a participant from the healthy adolescent group. A linear regression line with 95% confidence interval is shown. P-values reflect the association between marker of neuroinflammation (MK) and white matter integrity (ODI) in the indicated tract and hemisphere, controlling for covariates.*

Figure 3

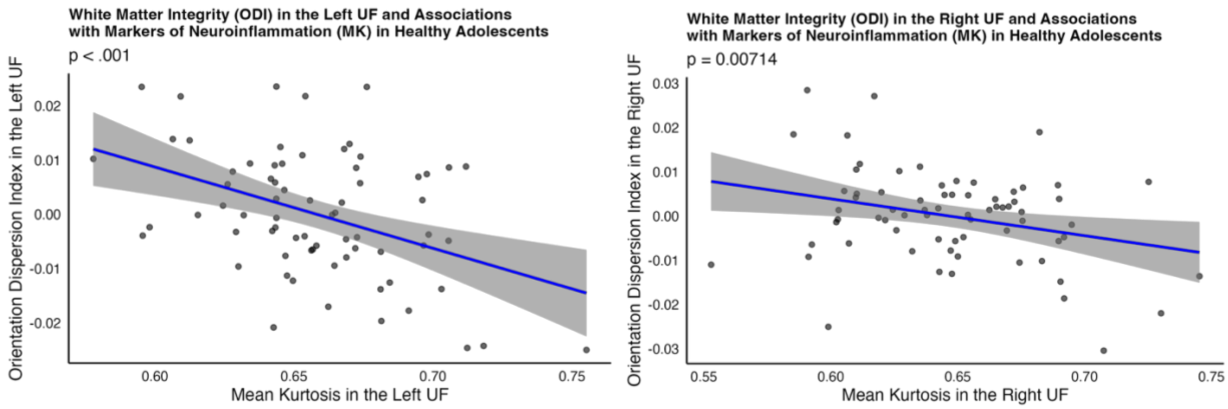
White Matter Integrity (ODI) in the Superior Longitudinal Fasciculus is negatively associated with Markers of Neuroinflammation (MK)



Note. *WM integrity values were residualized for age, sex, and alcohol use. Each point represents a participant from the healthy adolescent group. A linear regression line with 95% confidence interval is shown. P-values reflect the association between marker of neuroinflammation (MK) and white matter integrity (ODI) in the indicated tract and hemisphere, controlling for covariates.*

Figure 4

White Matter Integrity (ODI) in the Uncinate Fasciculus is negatively associated with Markers of Neuroinflammation (MK)



Note. WM integrity values were residualized for age, sex, and alcohol use. Each point represents a participant from the healthy adolescent group. A linear regression line with 95% confidence interval is shown. P-values reflect the association between marker of neuroinflammation (MK) and white matter integrity (ODI) in the indicated tract and hemisphere, controlling for covariates.

CHAPTER 4. GENERAL DISCUSSION

4.1 OVERVIEW OF THESIS

This thesis investigated the neurobiological impact of CU and PLEs on adolescent brain white matter, with a specific focus on white matter integrity and markers of neuroinflammation. Motivated by evidence independently linking CU and PLEs to increased risk for psychotic disorders, and the growing concern over adolescent cannabis exposure, this project aimed to explore potential biological mechanisms underlying this risk. Specifically, we hypothesized that

1. White matter integrity (ODI) will be negatively associated with markers of neuroinflammation (MK). (H1)
2. Cannabis use will be positively associated with markers of neuroinflammation and negatively associated with white matter integrity as measured by MK and ODI. (H2)
3. The presence of PLEs in adolescence will be positively associated with markers of neuroinflammation and negatively associated with white matter integrity as measured by MK, AK, RK, ODI. (H3)
4. Adolescents who use cannabis will have an increased presence of PLEs compared to those who do not. (H4)
5. Cannabis use and the presence of PLEs in adolescence will be interactive to the impact of brain white matter as seen by markers of neuroinflammation and white matter integrity (e.g.: CU-/PLE- < CU-/PLE+ == CU+/PLE- < CU+/PLE+) (H5)

To address these hypotheses, we used advanced neuroimaging techniques and developed an adolescent specific white matter atlas to improve biological specificity. Our sample consisted of 123 adolescents aged 15-16 years, categorized into four groups based on the presence/absence of

CU and PLEs (e.g.: PLE-/CU-, PLE+/CU-, PLE-/CU+, PLE+/CU+). Regions of interest were selected based on previous literature – bilateral AF, SLF, UF, and ACC – and their associations with psychosis and CU.

4.2 INTEGRATED SUMMARY OF FINDINGS

4.2.1 SUMMARY: DEVELOPMENT OF WHITE MATTER ATLAS

Chapter 2 aimed to develop and validate an anatomically reflective population specific white matter atlas to be used in diffusion white matter analysis. This chapter was motivated by the limitations of existing atlases, which are largely derived from adult or demographically broad samples (See Chapter 2). Given the rapid, non-linear changes in white matter structure during adolescence – including myelination, synaptic pruning, and tract reorganization (Lebel & Deoni, 2018) – existing atlases may lead to anatomical misalignment and reduced sensitivity to changes in white matter (Tamnes et al., 2018). To address this gap, we created an age specific and anatomically validated white matter atlas, with a large and robust screening protocol for psychiatric and other health conditions, substance use, and medication history, using high quality MRI multi-shell diffusion protocols, for a large sample (n=54) of 15–16-year-old adolescents. Using high resolution multi-shell diffusion imaging and probabilistic tractography, we created an anatomically precise atlas that captures white matter organization during a critical period of neurodevelopment. Our development pipeline leveraged advanced preprocessing and clustering tools-including MSMT-CSD, ANTs-based spatial normalization, and spectral clustering via the ORG lab's 'whitematteranalysis' software – to ensure anatomical accuracy, developmental specificity, and reproducibility.

Unlike existing atlases derived from broad or adult populations, the proposed atlas (PHAWM) includes participants in a tightly age constrained window with rigorous screening for psychiatric, substance use, and neurological conditions. Validation of proposed tracts using Hausdorff Distance (HD) and Dice coefficients confirmed biologically meaningful spatial differences from adult templates in white matter tracts AF, SLF, and UF. HD95 values ranged from 3.8 to 5.6 mm, while dice coefficients indicated moderate alignment between 0.35 and 0.42 with accepted standards for probabilistic tractography comparisons – underscoring developmental divergence, not methodological error. The PHAWM atlas addresses critical limitations in neuroimaging research and offers a high-quality reference for examining white matter maturation and vulnerability during adolescence. Its integration into our later analysis provided anatomical precision needed to detect subtle associations between white matter microstructure and neuroinflammation. Findings from Chapter 2 confirmed the anatomical validity of the PHAWM atlas.

4.2.2 SUMMARY: CHAPTER 3

Chapter 3 aimed to address the five proposed hypotheses, using findings to evaluate independent associations of CU and PLEs within white matter microstructure and markers of neuroinflammation, and assess whether CU and PLEs have additive or interactive effects on these neurobiological markers. Motivated by theories of adolescent neurodevelopment, psychosis risk, and endocannabinoid system disruption, the chapter examined how CU and PLEs may influence white matter integrity and neuroinflammation. H1 explored whether markers of neuroinflammation (MK) was negatively associated with white matter integrity (ODI and MD) in healthy developing adolescents. Results supported the hypothesis: higher MK was significantly associated with reduced ODI in five of six tracts – bilateral AF, Left SLF, bilateral UF –

indicating that the neuroinflammatory processes indicative of healthy neurodevelopment could be measured to a high degree of specificity. No significant associations were found within the ACC. H2 and H3 examined independent associations between CU and PLEs and white matter integrity and neuroinflammation. No significant differences were found when comparing groups to healthy controls. However, sex emerged as a robust predictor across nearly all ODI models, with males generally showing lower ODI values, suggesting sex-dependant neurodevelopmental trajectories. These null group results are interpreted cautiously due to skewed and small subgroup sizes and limitations in the binary measures of CU and PLEs. H4 aimed to examine CU and how it would increase the odds of someone reporting a PLE. This hypothesis was not support, contrary to previous research (Staines et al., 2023). H5 tested whether CU and PLEs were interactive or additive in the effects on markers of neuroinflammation and white matter integrity. Neither model showed statistically significant results. However, interaction models showed better model fit for ODI in the SLF and AF, providing some insight for future investigations. Exploratory analyses using continuous measures (CUDIT-R total scores) provided a more nuanced insight. Higher CU severity was associated with lower MK in the UF. Alcohol use emerged as a significant covariate in MK models, particularly in the UF. Sex stratified analyses revealed distinct patterns: among males, CU was associated with increased ODI in the SLF, and PLEs were associated with elevated MK in the UF. Among females, CU was linked to increased MD in the UF, and alcohol use was found to be a stronger predictor of MK than CU or PLEs. In sum, findings from chapter 3 confirm the hypothesis that MK is negatively associated with ODI, which further confirms the use of sensitive markers of neuroinflammation and white matter integrity. Findings from this study found null results for H2, H3, H4, and H5, however, these hypotheses should be further examined based on later performed exploratory analyses. While no robust group-level effects were observed for H2, H3, H4, or H5, continuous and sex stratified exploratory models revealed preliminary patterns suggestive of sex-dependant and tract specific influences. These findings support a shift toward dimensional, longitudinal, and sex informed designs in future research on adolescent neurodevelopment and psychopathology risk and warrant further research before these hypotheses are rejected.

4.3 INTERPRETATION IN THE CONTEXT OF THE LITERATURE

Our results support the notion that neuroinflammatory processes underlie normative pruning, consistent with microglia mediated models of adolescent reorganization (Roseborough et al., 2022). The observed inverse relationship between MK and ODI are in line with recent work suggesting that reductions in MK may signal increased glial activity and synaptic refinement (Arab et al., 2018; Goryawala et al., 2018; Grinberg et al., 2017; Lanzafame et al., 2016; Ota et al., 2018; H. Zhang et al., 2023). Contrary to expectations, group comparisons did not reveal differences in microstructure associated with CU or PLEs. Examining these factors in adolescent white matter is novel in the literature, but based on other preliminary works, may be explained by methodological differences (e.g.: atlas specificity, metric sensitivity), the cross-sectional nature of our study, or the transient and overlapping nature of CU and PLEs during adolescence. Importantly continuous models revealed subtle associations that were not evident in binary groupings which further reinforces the importance of dimensional approaches.

The role of the ECS in modulating adolescent white matter development has been shown in animal models to exhibit sex-specific developmental patterns (Kopec et al., 2018) and may result in differential CB1 receptor expression and hormonal influence contributing to observed sex specific interactions with CU and PLEs. Although these exploratory analyses need to be interpreted with caution and serve as a future direction for research to examine sex stratified models in white matter neurodevelopment.

4.4 METHODOLOGICAL STRENGTHS AND LIMITATIONS

This thesis has several strengths and methodological considerations. The development and validation of an adolescent-specific white matter atlas addressed a key limitation in adolescent white matter research by improving registration accuracy, specificity, and anatomical relevance. Due to the complexity of adolescent neurodevelopment – even seen in healthy developing adolescents – having a specific and anatomically representative atlas of white matter helped to ensure validity in analyses. This atlas will also serve to further address these limitations by being openly available, with the intention that it can be used for intra-study comparisons. The multimodal diffusion approach used within the study provided sensitive metrics of microstructural complexity and neuroinflammation, offering insight into glial involvement and their potential mechanisms, examining potential biological mechanisms behind psychosis risk. The null results should be interpreted with caution and should warrant the further investigation into CU and PLEs and their potential interactions. This study highlights the need for further research in the field using continuous dimensional measures of CU and large longitudinal samples.

Limitations include the cross-sectional design which precludes causal inference. Due to the complex nature of psychosis development and risk, there is also the potential for confounding variables that could not or were not accounted for in analyses. The sample size was skewed in its groupings (i.e.: 72 PLE-/CU- and 9 PLE+/CU+) which led to continuous variables such as CU and PLEs to be dichotomized using binary cut-offs to better meet model assumptions, which may have missed or not fully explained variance in the population.

4.5 THEORETICAL AND CLINICAL IMPLICATIONS

Our findings contribute to a growing body of work suggesting that white matter integrity and neuroinflammatory processes are intricately linked during adolescence. DKI and NODDI offer promising non-invasive tools for examining neurodevelopmental trajectories, particularly in non-clinical populations. The associations between MK and ODI point to a biologically plausible mechanism (through glial mediated pruning) that could potentially serve as a marker of vulnerability to psychosis and psychotic disorders. Clinically, this research highlights the need for early monitoring of youth with high CU or PLE burden, particularly in the context of emerging sex differences.

4.6 FINAL CONCLUSIONS

This thesis offers novel insight into the neurobiological underpinnings of CU and PLEs during adolescence. The successful development and internal validation of an age specific white matter atlas (AWM) represents a critical advance in adolescent neuroimaging and will enhance future research into white matter maturation during this sensitive developmental period. The use of the AWM atlas along with neuroimaging modalities (DKI and NODDI) provides a level of specificity in adolescent white matter previously only available in post-mortem examinations, clinical populations (through positron emission tomography) and animal models. The significant finding of associations of MK inversely with ODI confirms the notion that glial mediated processes of healthy neurodevelopment can be measured using proxies such as MK in adolescents – which will allow for further investigation into the neurobiological mechanisms surrounding psychosis development. The null results highlight the complex and potentially subtle interactions between CU and PLEs and their effects on white matter integrity and neuroinflammation. The detailed exploratory analyses call attention to the subtle but potentially important changes occurring in adolescents who experience PLEs and those who use cannabis, and emphasize the need for larger, longitudinal samples alongside dimensional modelling approaches to explain the large variance seen in adolescent neurodevelopment, CU, and PLEs. This work contributes to a growing body of literature emphasizing early identification of neurobiological vulnerabilities linked to psychosis. Unwinding the biological interactions that contribute to white matter disruptions in CU and PLE-affected adolescents can aid in designing preventative strategies and identifying early biomarkers. Ultimately, the findings of this thesis offer both empirical insight and a methodological foundation for future longitudinal studies that may inform evidence-based screening and intervention efforts in adolescent mental health.

REFERENCES

Abdul-Rahman, M. F., Qiu, A., Woon, P. S., Kuswanto, C., Collinson, S. L., & Sim, K. (2012). Arcuate Fasciculus Abnormalities and Their Relationship with Psychotic Symptoms in Schizophrenia. *PLOS ONE*, *7*(1), e29315. https://doi.org/10.1371/JOURNAL.PONE.0029315

Adamson, S. J., Kay-Lambkin, F. J., Baker, A. L., Lewin, T. J., Thornton, L., Kelly, B. J., & Sellman, J. D. (2010). An improved brief measure of cannabis misuse: the Cannabis Use Disorders Identification Test-Revised (CUDIT-R). *Drug and Alcohol Dependence*, *110*(1–2), 137–143. https://doi.org/10.1016/J.DRUGALCDEP.2010.02.017

Adjorlolo, S., Awortwe, V., Anum, A., Huang, K. Y., & Mamah, D. (2024). Psychotic-like experiences and adverse life events in young people. Does gender matter? *Child and Adolescent Mental Health*, *29*(2), 154–160. https://doi.org/10.1111/CAMH.12674

Agarwal, S., Al Khalifah, H., Zaca, D., & Pillai, J. J. (2023). fMRI and DTI: Review of Complementary Techniques. *Functional Neuroradiology: Principles and Clinical Applications*, 1025–1060. https://doi.org/10.1007/978-3-031-10909-6_44/FIGURES/37

Ajnakina, O., Morgan, C., Gayer-Anderson, C., Oduola, S., Bourque, F., Bramley, S., Williamson, J., MacCabe, J. H., Dazzan, P., Murray, R. M., & David, A. S. (2017). Only a small proportion of patients with first episode psychosis come via prodromal services: A retrospective survey of a large UK mental health programme. *BMC Psychiatry*, *17*(1), 1–9. https://doi.org/10.1186/S12888-017-1468-Y/TABLES/2

Albaugh, M. D., Ottino-Gonzalez, J., Sidwell, A., Lepage, C., Juliano, A., Owens, M. M., Chaarani, B., Spechler, P., Fontaine, N., Rioux, P., Lewis, L., Jeon, S., Evans, A., D'Souza, D., Radhakrishnan, R., Banaschewski, T., Bokde, A. L. W., Quinlan, E. B., Conrod, P., … Garavan, H. (2021). Association of Cannabis Use During Adolescence With Neurodevelopment. *JAMA Psychiatry*, *78*(9), 1. https://doi.org/10.1001/JAMAPSYCHIATRY.2021.1258

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, *4*(3), 316. https://doi.org/10.1016/J.NURT.2007.05.011

American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. https://doi.org/10.1176/APPI.BOOKS.9780890425596

Andersen, S. L. (2022). Neuroinflammation, Early-Life Adversity, and Brain Development. *Harvard Review of Psychiatry*, *30*(1), 24–39. https://doi.org/10.1097/HRP.0000000000000325

Anticevic, A., Savic, A., Repovs, G., Yang, G., McKay, D. R., Sprooten, E., Knowles, E. E., Krystal, J. H., Pearlson, G. D., & Glahn, D. C. (2015). Ventral Anterior Cingulate Connectivity Distinguished Nonpsychotic Bipolar Illness From Psychotic Bipolar Disorder and Schizophrenia. *Schizophrenia Bulletin*, *41*(1), 133–143. https://doi.org/10.1093/schbul/sbu051

Arab, A., Wojna-Pelczar, A., Khairnar, A., Szabó, N., & Ruda-Kucerova, J. (2018a). Principles of diffusion kurtosis imaging and its role in early diagnosis of neurodegenerative disorders. *Brain Research Bulletin*, *139*, 91–98. https://doi.org/10.1016/J.BRAINRESBULL.2018.01.015

Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric Disease and Treatment*, *9*, 449. https://doi.org/10.2147/NDT.S39776

Arseneault, L., Cannon, M., Poulton, R., Murray, R., Caspi, A., & Moffitt, T. E. (2002). Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ*, *325*(7374), 1212–1213. https://doi.org/10.1136/BMJ.325.7374.1212

Ashtari, M., Avants, B., Cyckowski, L., Cervellione, K. L., Roofeh, D., Cook, P., Gee, J., Sevy, S., & Kumra, S. (2011). Medial temporal structures and memory functions in adolescents with heavy cannabis use. *Journal of Psychiatric Research*, *45*(8), 1055–1066. https://doi.org/10.1016/J.JPSYCHIRES.2011.01.004

Ashtari, M., Cervellione, K., Cottone, J., Ardekani, B. A., & Kumra, S. (2009). Diffusion abnormalities in adolescents and young adults with a history of heavy cannabis use. *Journal of Psychiatric Research*, *43*(3), 189–204. https://doi.org/10.1016/J.JPSYCHIRES.2008.12.002

Avants, B. B., Tustison, N. J., Song, G., Cook, P. A., Klein, A., & Gee, J. C. (2011). A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, *54*(3), 2033–2044. https://doi.org/10.1016/J.NEUROIMAGE.2010.09.025,

Azrin, N. H., Donohue, B., Teichner, G. A., Crum, T., Howell, J., & DeCato, L. A. (2001). A Controlled Evaluation and Description of Individual-Cognitive Problem Solving and Family-Behavior Therapies in Dually-Diagnosed Conduct-Disordered and Substance-Dependent Youth. *Journal of Child and Adolescent Substance Abuse*, *11*(1), 1–43. https://doi.org/10.1300/J029V11N01_01

Bailey, J. A., Tiberio, S. S., Kerr, D. C. R., Epstein, M., Henry, K. L., & Capaldi, D. M. (2023). Effects of Cannabis Legalization on Adolescent Cannabis Use Across 3 Studies. *American Journal of Preventive Medicine*, *64*(3), 361–367. https://doi.org/10.1016/J.AMEPRE.2022.09.019

Bara, A., Ferland, J. M. N., Rompala, G., Szutorisz, H., & Hurd, Y. L. (2021). Cannabis and synaptic reprogramming of the developing brain. *Nature Reviews Neuroscience*, *22*(7), 423–438. https://doi.org/10.1038/S41583-021-00465-5;SUBJMETA=1695,1696,2571,2584,378,631;KWRD=EPIGENETICS+AND+PLASTICITY,NEURONAL+DEVELOPMENT

Batalla, A., Bhattacharyya, S., Yücel, M., Fusar-Poli, P., Crippa, J. A., Nogué, S., Torrens, M., Pujol, J., Farré, M., & Martin-Santos, R. (2013). Structural and Functional Imaging Studies in Chronic Cannabis Users: A Systematic Review of Adolescent and Adult Findings. *PLOS ONE*, *8*(2), e55821. https://doi.org/10.1371/JOURNAL.PONE.0055821

Battistella, G., Fornari, E., Annoni, J. M., Chtioui, H., Dao, K., Fabritius, M., Favrat, B., Mall, J. F., Maeder, P., & Giroud, C. (2014). Long-Term Effects of Cannabis on Brain Structure. *Neuropsychopharmacology 2014 39:9*, *39*(9), 2041–2048. https://doi.org/10.1038/npp.2014.67

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - A technical review. *NMR in Biomedicine*, *15*(7–8), 435–455. https://doi.org/10.1002/NBM.782;CSUBTYPE:STRING:SPECIAL;PAGE:STRING:ARTICLE/CHAPTER

Bechtold, J., Hipwell, A., Lewis, D. A., Loeber, R., & Pardini, D. (2016). Concurrent and Sustained Cumulative Effects of Adolescent Marijuana Use on Subclinical Psychotic Symptoms. *The American Journal of Psychiatry*, *173*(8), 781–789. https://doi.org/10.1176/APPI.AJP.2016.15070878

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: psychometric properties. *Journal of Consulting and Clinical Psychology*, *56*(6), 893–897. https://doi.org/10.1037//0022-006X.56.6.893

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *BDI-II: Beck depression inventory*. Pearson.

Bernier, D., Cookey, J., McAllindon, D., Bartha, R., Hanstock, C. C., Newman, A. J., Stewart, S. H., & Tibbo, P. G. (2013). Multimodal neuroimaging of frontal white matter microstructure in early phase schizophrenia: The impact of early adolescent cannabis use. *BMC Psychiatry*, *13*. https://doi.org/10.1186/1471-244X-13-264

Bosma, M. J., Cox, S. R., Ziermans, T., Buchanan, C. R., Shen, X., Tucker-Drob, E. M., Adams, M. J., Whalley, H. C., & Lawrie, S. M. (2023). White matter, cognition and psychotic-like experiences in UK Biobank. *Psychological Medicine*, *53*(6), 2370–2379. https://doi.org/10.1017/S0033291721004244,

Brière, F. N., Fallu, J. S., Descheneaux, A., & Janosz, M. (2011). Predictors and consequences of simultaneous alcohol and cannabis use in adolescents. *Addictive Behaviors*, *36*(7), 785–788. https://doi.org/10.1016/J.ADDBEH.2011.02.012

Brown, S. A., Brumback, T., Tomlinson, K., Cummins, K., Thompson, W. K., Nagel, B. J., De Bellis, M. D., Hooper, S. R., Clark, D. B., Chung, T., Hasler, B. P., Colrain, I. M., Baker, F. C., Prouty, D., Pfefferbaum, A., Sullivan, E. V., Pohl, K. M., Rohlfing, T., Nichols, B. N., … Tapert, S. F. (2015). The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA): A Multisite Study of Adolescent Development and Substance Use. *Journal of Studies on Alcohol and Drugs*, *76*(6), 895. https://doi.org/10.15288/JSAD.2015.76.895

Burton, I. J., Tibbo, P. G., Ponto, N., & Crocker, C. E. (2024). Heterogeneity in assessing the risk of developing a psychotic disorder given a previous subclinical psychotic-like experience in children and adolescents: A systematic review and meta-analysis. *Psychiatry Research*, *342*. https://doi.org/10.1016/J.PSYCHRES.2024.116207

Caballero, A., & Tseng, K. Y. (2012). Association of cannabis use during adolescence, prefrontal CB1 receptor signaling, and schizophrenia. *Front Pharmacol*, *3*, 101. https://doi.org/10.3389/fphar.2012.00101

Calkins, M. E., Merikangas, K. R., Moore, T. M., Burstein, M., Behr, M. A., Satterthwaite, T. D., Ruparel, K., Wolf, D. H., Roalf, D. R., Mentch, F. D., Qiu, H., Chiavacci, R., Connolly, J. J., Sleiman, P. M. A., Gur, R. C., Hakonarson, H., & Gur, R. E. (2015). The Philadelphia Neurodevelopmental Cohort: constructing a deep phenotyping collaborative. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *56*(12), 1356–1369. https://doi.org/10.1111/JCPP.12416

Calvo, A., Roddy, D. W., Coughlan, H., Kelleher, I., Healy, C., Harley, M., Clarke, M., Leemans, A., Frodl, T., O'Hanlon, E., & Cannon, M. (2020). Reduced hippocampal volume in adolescents with psychotic experiences: A longitudinal population-based study. *PLOS ONE*, *15*(6), e0233670. https://doi.org/10.1371/JOURNAL.PONE.0233670

Carbon, M., & Correll, C. U. (2014). Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectrums*, *19*(S1), 35–53. https://doi.org/10.1017/S1092852914000601

Chadwick, B., Miller, M. L., Hurd, Y. L., Hemby, S. E., & Forest, W. (2013). Cannabis Use during Adolescent Development: Susceptibility to Psychiatric Illness. *Frontiers in Psychiatry*, *4*, 57619. https://doi.org/10.3389/FPSYT.2013.00129

Cheung, M. M., Hui, E. S., Chan, K. C., Helpern, J. A., Qi, L., & Wu, E. X. (2009). Does diffusion kurtosis imaging lead to better neural tissue characterization? A rodent brain maturation study. *NeuroImage*, *45*(2), 386–392. https://doi.org/10.1016/J.NEUROIMAGE.2008.12.018

Chye, Y., Christensen, E., & Yücel, M. (2020). Cannabis Use in Adolescence: A Review of Neuroimaging Findings. *Journal of Dual Diagnosis*, *16*(1), 83–105. https://doi.org/10.1080/15504263.2019.1636171

Cieslak, M., Cook, P. A., He, X., Yeh, F. C., Dhollander, T., Adebimpe, A., Aguirre, G. K., Bassett, D. S., Betzel, R. F., Bourque, J., Cabral, L. M., Davatzikos, C., Detre, J. A., Earl, E., Elliott, M. A., Fadnavis, S., Fair, D. A., Foran, W., Fotiadis, P., … Satterthwaite, T. D. (2021). QSIPrep: an integrative platform for preprocessing and reconstructing diffusion MRI data. *Nature Methods*, *18*(7), 775–778. https://doi.org/10.1038/S41592-021-01185-5

Clark, D., Gorgolewski, K. J., & Craddock, R. C. (2016). Integrating the Brain Imaging Data Structure (BIDS) standard into C-PAC. *GigaScience*, *5*(suppl_1). https://doi.org/10.1186/S13742-016-0147-0-C

Cohen, B. M., Öngür, D., & Babb, S. M. (2021). Alternative Diagnostic Models of the Psychotic Disorders: Evidence-Based Choices. *Psychotherapy and Psychosomatics*, *90*(6), 373–385. https://doi.org/10.1159/000517027

Corbo, V., Amick, M. A., Milberg, W. P., McGlinchey, R. E., & Salat, D. H. (2016). Early life trauma is associated with altered white matter integrity and affective control. *Journal of Psychiatric Research*, *79*, 70–77. https://doi.org/10.1016/J.JPSYCHIRES.2016.05.001

Correll, C. U., & Schooler, N. R. (2020). Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatric Disease and Treatment*, *16*, 519. https://doi.org/10.2147/NDT.S225643

Corsi-Zuelli, F., Marques, L., da Roza, D. L., Loureiro, C. M., Shuhama, R., Di Forti, M. D., Menezes, P. R., Louzada-Junior, P., & Del-Ben, C. M. (2022). The independent and combined effects of cannabis use and systemic inflammation during the early stages of psychosis: exploring the two-hit hypothesis. *Psychological Medicine*, *52*(16), 3874–3884. https://doi.org/10.1017/S0033291721000726

Cowan, H. R., & Mittal, V. A. (2021). Three types of psychotic-like experiences in youth at clinical high risk for psychosis. *European Archives of Psychiatry and Clinical Neuroscience*, *271*(4), 733–744. https://doi.org/10.1007/S00406-020-01143-W/TABLES/5

Crews, F., He, J., & Hodge, C. (2007). Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol Biochem Behav*, *86*(2), 189–199. https://doi.org/10.1016/j.pbb.2006.12.001

Crocker, C., & Tibbo, P. (2015). Cannabis and the maturing brain: Role in psychosis development. *Clinical Pharmacology & Therapeutics*, *97*(6), 545–547. https://doi.org/10.1002/cpt.102

Cutando, L., Busquets-Garcia, A., Puighermanal, E., Gomis-González, M., Delgado-García, J. M., Gruart, A., Maldonado, R., & Ozaita, A. (2013). Microglial activation underlies cerebellar deficits produced by repeated cannabis exposure. *The Journal of Clinical Investigation*, *123*(7), 2816–2831. https://doi.org/10.1172/JCI67569

Daducci, A., Canales-Rodríguez, E. J., Zhang, H., Dyrby, T. B., Alexander, D. C., & Thiran, J. P. (2015). Accelerated Microstructure Imaging via Convex Optimization (AMICO) from diffusion MRI data. *NeuroImage*, *105*, 32–44. https://doi.org/10.1016/j.neuroimage.2014.10.026

De Santis, S., Drakesmith, M., Bells, S., Assaf, Y., & Jones, D. K. (2014). Why diffusion tensor MRI does well only some of the time: variance and covariance of white matter tissue microstructure attributes in the living human brain. *NeuroImage*, *89*(100), 35–44. https://doi.org/10.1016/J.NEUROIMAGE.2013.12.003

Degenhardt, L., Coffey, C., Romaniuk, H., Swift, W., Carlin, J. B., Hall, W. D., & Patton, G. C. (2013). The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. *Addiction*, *108*(1), 124–133. https://doi.org/10.1111/J.1360-0443.2012.04015.X

Dempster, E. L., Wong, C. C. Y., Burrage, J., Hannon, E., Quattrone, D., Trotta, G., Rodriguez, V., Alameda, L., Spinazzola, E., Tripoli, G., Austin-Zimmerman, I., Li, Z., Gayer-Anderson, C., Freeman, T. P., Johnson, E. C., Jongsma, H. E., Stilo, S., La Cascia, C., Ferraro, L., … Di Forti, M. (2024). Methylomic signature of current cannabis use in two first-episode psychosis cohorts. *Molecular Psychiatry 2024 30:4*, *30*(4), 1277–1286. https://doi.org/10.1038/s41380-024-02689-0

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., Hyman, B. T., Albert, M. S., & Killiany, R. J. (2006). *An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest*. https://doi.org/10.1016/j.neuroimage.2006.01.021

Dhossche, D., Ferdinand, R., Van Der Ende, J., Hofstra, M. B., & Verhulst, F. (2002). Diagnostic outcome of self-reported hallucinations in a community sample of adolescents. *Psychological Medicine*, *32*(4), 619–627. https://doi.org/10.1017/S003329170200555X

Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: consensus and controversy in the connectional anatomy of language. *Brain*, *135*(12), 3529–3550. https://doi.org/10.1093/BRAIN/AWS222

Dickie, D. A., Shenkin, S. D., Anblagan, D., Lee, J., Cabez, M. B., Rodriguez, D., Boardman, J. P., Waldman, A., Job, D. E., & Wardlaw, J. M. (2017). Whole brain magnetic resonance image atlases: A systematic review of existing atlases and caveats for use in population imaging. *Frontiers in Neuroinformatics*, *11*, 226915. https://doi.org/10.3389/FNINF.2017.00001/BIBTEX

Dietsche, B., Kircher, T., & Falkenberg, I. (2017). Structural brain changes in schizophrenia at different stages of the illness: A selective review of longitudinal magnetic resonance imaging studies. *Australian and New Zealand Journal of Psychiatry*, *51*(5), 500–508. https://doi.org/10.1177/0004867417699473/ASSET/IMAGES/LARGE/10.1177_00048674 17699473-FIG1.JPEG

Dietz, A. G., Goldman, S. A., & Nedergaard, M. (2019). Glial cells in schizophrenia: A unified hypothesis. *The Lancet. Psychiatry*, *7*(3), 272. https://doi.org/10.1016/S2215-0366(19)30302-5

DiPiero, M., Rodrigues, P. G., Gromala, A., & Dean, D. C. (2022). Applications of advanced diffusion MRI in early brain development: a comprehensive review. *Brain Structure and Function 2022 228:2*, *228*(2), 367–392. https://doi.org/10.1007/S00429-022-02605-8

Dominguez, M. D. G., Wichers, M., Lieb, R., Wittchen, H. U., & Van Os, J. (2011). Evidence that onset of clinical psychosis is an outcome of progressively more persistent subclinical psychotic experiences: an 8-year cohort study. *Schizophrenia Bulletin*, *37*(1), 84–93. https://doi.org/10.1093/SCHBUL/SBP022

Dooley, N., O'Hanlon, E., Healy, C., Adair, A., McCandless, C., Coppinger, D., Kelleher, I., Clarke, M., Leemans, A., Frodl, T., & Cannon, M. (2020). Psychotic experiences in childhood are associated with increased structural integrity of the left arcuate fasciculus - A population-based case-control study. *Schizophrenia Research*, *215*, 378–384. https://doi.org/10.1016/J.SCHRES.2019.08.022

Dunn, G. A., Loftis, J. M., & Sullivan, E. L. (2020). Neuroinflammation in psychiatric disorders: An introductory primer. *Pharmacology, Biochemistry, and Behavior*, *196*, 172981. https://doi.org/10.1016/J.PBB.2020.172981

Eaton, W. W., Thara, R., Federman, B., Melton, B., & Liang, K. yee. (1995). Structure and Course of Positive and Negative Symptoms in Schizophrenia. *Archives of General Psychiatry*, *52*(2), 127–134. https://doi.org/10.1001/ARCHPSYC.1995.03950140045005

Ellgren, M., Artmann, A., Tkalych, O., Gupta, A., Hansen, H. S., Hansen, S. H., Devi, L. A., & Hurd, Y. L. (2008). Dynamic changes of the endogenous cannabinoid and opioid mesocorticolimbic systems during adolescence: THC effects. *Eur Neuropsychopharmacol*, *18*(11), 826–834. https://doi.org/10.1016/j.euroneuro.2008.06.009

Esteban, O., Birman, D., Schaer, M., Koyejo, O. O., Poldrack, R. A., & Gorgolewski, K. J. (2017). MRIQC: Advancing the automatic prediction of image quality in MRI from unseen sites. *PLOS ONE*, *12*(9), e0184661. https://doi.org/10.1371/journal.pone.0184661

Esteban, O., Ciric, R., Finc, K., Blair, R. W., Markiewicz, C. J., Moodie, C. A., Kent, J. D., Goncalves, M., DuPre, E., Gomez, D. E. P., Ye, Z., Salo, T., Valabregue, R., Amlien, I. K., Liem, F., Jacoby, N., Stojić, H., Cieslak, M., Urchs, S., … Gorgolewski, K. J. (2020). Analysis of task-based functional MRI data preprocessed with fMRIPrep. *Nature Protocols 2020 15:7*, *15*(7), 2186–2202. https://doi.org/10.1038/s41596-020-0327-3

Esteban, O., Markiewicz, C. J., Blair, R. W., Moodie, C. A., Isik, A. I., Erramuzpe, A., Kent, J. D., Goncalves, M., DuPre, E., Snyder, M., Oya, H., Ghosh, S. S., Wright, J., Durnez, J., Poldrack, R. A., & Gorgolewski, K. J. (2019). fMRIPrep: a robust preprocessing pipeline for functional MRI. *Nature Methods*, *16*(1), 111–116. https://doi.org/10.1038/s41592-018-0235-4

Falangola, M. F., Jensen, J. H., Babb, J. S., Hu, C., Castellanos, F. X., Di Martino, A., Ferris, S. H., & Helpern, J. A. (2008). Age-related non-Gaussian diffusion patterns in the prefrontal brain. *Journal of Magnetic Resonance Imaging*, *28*(6), 1345–1350. https://doi.org/10.1002/JMRI.21604,

Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., Yang, Z., Chu, C., Xie, S., Laird, A. R., Fox, P. T., Eickhoff, S. B., Yu, C., & Jiang, T. (2016). The Human Brainnetome Atlas: A New Brain Atlas Based on Connectional Architecture. *Cerebral Cortex*, *26*(8), 3508–3526. https://doi.org/10.1093/CERCOR/BHW157

Farooq, S., Fonseka, N., Ali, M. W., Milner, A., Hamid, S., Sheikh, S., Khan, M. F., Azeemi, M. M. U. H., Ariyadasa, G., Khan, A. J., & Ayub, M. (2024). Early Intervention in Psychosis and Management of First Episode Psychosis in Low- and Lower-Middle-Income Countries: A Systematic Review. *Schizophrenia Bulletin*, *50*(3), 521–532. https://doi.org/10.1093/SCHBUL/SBAE025

Figley, C. R., Uddin, M. N., Wong, K., Kornelsen, J., Puig, J., & Figley, T. D. (2022). Potential Pitfalls of Using Fractional Anisotropy, Axial Diffusivity, and Radial Diffusivity as Biomarkers of Cerebral White Matter Microstructure. *Frontiers in Neuroscience*, *15*, 799576. https://doi.org/10.3389/FNINS.2021.799576/BIBTEX

First, M. B. (2015). Structured Clinical Interview for the DSM (SCID). *The Encyclopedia of Clinical Psychology*, 1–6. https://doi.org/10.1002/9781118625392.WBECP351

Flinkenflügel, K., Meinert, S., Hirtsiefer, C., Grotegerd, D., Gruber, M., Goltermann, J., Winter, N. R., Stein, F., Brosch, K., Leehr, E. J., Böhnlein, J., Dohm, K., Bauer, J., Redlich, R., Hahn, T., Repple, J., Opel, N., Nitsch, R., Jamalabadi, H., … Dannlowski, U. (2024). Associations between white matter microstructure and cognitive decline in major depressive disorder versus controls in Germany: a prospective case-control cohort study. *The Lancet Psychiatry*, *11*(11), 899–909. https://doi.org/10.1016/S2215-0366(24)00291-8

Flores, C., Tseng, K. Y., Delevich, K., Reynolds, L. M., & Naneix, F. (2022). The role of dopamine and endocannabinoid systems in prefrontal cortex development: Adolescence as a critical period. *Frontiers in Neural Circuits*, *16*, 939235. https://doi.org/10.3389/FNCIR.2022.939235

Focus on Geography Series, 2021 Census - Halifax (Census subdivision). (n.d.). Retrieved May 31, 2025, from https://www12.statcan.gc.ca/census-recensement/2021/as-sa/fogs-spg/page.cfm?lang=e&topic=10&dguid=2021A00051209034

Fornito, A., Yücel, M., Dean, B., Wood, S. J., & Pantelis, C. (2009). Anatomical Abnormalities of the Anterior Cingulate Cortex in Schizophrenia: Bridging the Gap Between Neuroimaging and Neuropathology. *Schizophrenia Bulletin*, *35*(5), 973–993. https://doi.org/10.1093/SCHBUL/SBN025

Fornito, A., Yung, A. R., Wood, S. J., Phillips, L. J., Nelson, B., Cotton, S., Velakoulis, D., McGorry, P. D., Pantelis, C., & Yücel, M. (2008). Anatomic Abnormalities of the Anterior Cingulate Cortex Before Psychosis Onset: An MRI Study of Ultra-High-Risk Individuals. *Biological Psychiatry*, *64*(9), 758–765. https://doi.org/10.1016/J.BIOPSYCH.2008.05.032

Fortin, J. P., Parker, D., Tunç, B., Watanabe, T., Elliott, M. A., Ruparel, K., Roalf, D. R., Satterthwaite, T. D., Gur, R. C., Gur, R. E., Schultz, R. T., Verma, R., & Shinohara, R. T. (2017). Harmonization of multi-site diffusion tensor imaging data. *NeuroImage*, *161*, 149–170. https://doi.org/10.1016/J.NEUROIMAGE.2017.08.047

Fusar-Poli, P., McGorry, P. D., & Kane, J. M. (2017). Improving outcomes of first-episode psychosis: an overview. *World Psychiatry*, *16*(3), 251–265. https://doi.org/10.1002/WPS.20446

Gallardo-Ruiz, R., Crespo-Facorro, B., Setién-Suero, E., & Tordesillas-Gutierrez, D. (2019). Long-Term Grey Matter Changes in First Episode Psychosis: A Systematic Review. *Psychiatry Investigation*, *16*(5), 336. https://doi.org/10.30773/PI.2019.02.10.1

Giedd, J. N., Lalonde, F. M., Celano, M. J., White, S. L., Wallace, G. L., Lee, N. R., & Lenroot, R. K. (2009). Anatomical Brain Magnetic Resonance Imaging of Typically Developing Children and Adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *48*(5), 465. https://doi.org/10.1097/CHI.0B013E31819F2715

Giedd, J. N., Snell, J. W., Lange, N., Rajapakse, J. C., Casey, B. J., Kozuch, P. L., Vaituzis, A. C., Vauss, Y. C., Hamburger, S. D., Kaysen, D., & Rapoport, J. L. (1996). Quantitative Magnetic Resonance Imaging of Human Brain Development: Ages 4–18. *Cerebral Cortex*, *6*(4), 551–559. https://doi.org/10.1093/CERCOR/6.4.551

Goryawala, M. Z., Heros, D. O., Komotar, R. J., Sheriff, S., Saraf-Lavi, E., & Maudsley, A. A. (2018). Value of diffusion kurtosis imaging in assessing low-grade gliomas. *Journal of Magnetic Resonance Imaging*, *48*(6), 1551–1558. https://doi.org/10.1002/jmri.26012

Granö, N., Kallionpää, S., Karjalainen, M., Roine, M., Ranta, K., & Heinimaa, M. (2016). Discrepancy between self-reported and interviewed psychosis risk symptoms: auditory distortions are the most reliably reported symptom by self-report. *Early Intervention in Psychiatry*, *10*(2), 129–136. https://doi.org/10.1111/EIP.12154

Gray, K. M., & Squeglia, L. M. (2017). Research Review: What Have We Learned About Adolescent Substance Use? *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *59*(6), 618. https://doi.org/10.1111/JCPP.12783

Greenwood, C. J., Youssef, G. J., Betts, K. S., Letcher, P., Mcintosh, J., Spry, E., Hutchinson, D. M., Macdonald, J. A., Hagg, L. J., Sanson, A., Toumbourou, J. W., & Olsson, C. A. (2019). A comparison of longitudinal modelling approaches: Alcohol and cannabis use from adolescence to young adulthood. *Drug and Alcohol Dependence*, *201*, 58–64. https://doi.org/10.1016/J.DRUGALCDEP.2019.05.001

Grinberg, F., Maximov, I. I., Farrher, E., Neuner, I., Amort, L., Thönneßen, H., Oberwelland, E., Konrad, K., & Jon Shah, N. (2017). Diffusion kurtosis metrics as biomarkers of microstructural development: A comparative study of a group of children and a group of adults. *NeuroImage*, *144*, 12–22. https://doi.org/10.1016/J.NEUROIMAGE.2016.08.033

Hall, W., Leung, J., & Lynskey, M. (2020). The Effects of Cannabis Use on the Development of Adolescents and Young Adults. *Annual Review of Developmental Psychology*, *2*(Volume 2, 2020), 461–483. https://doi.org/10.1146/ANNUREV-DEVPSYCH-040320-084904

Hampton, W. H., Hanik, I. M., & Olson, I. R. (2019). Substance Abuse and White Matter: Findings, Limitations, and Future of Diffusion Tensor Imaging Research. *Drug and Alcohol Dependence*, *197*, 288. https://doi.org/10.1016/J.DRUGALCDEP.2019.02.005

Hansen, H. G., Speyer, H., Starzer, M., Albert, N., Hjorthøj, C., Eplov, L. F., & Nordentoft, M. (2023). Clinical Recovery Among Individuals With a First-Episode Schizophrenia an Updated Systematic Review and Meta-Analysis. *Schizophrenia Bulletin*, *49*(2), 297–308. https://doi.org/10.1093/SCHBUL/SBAC103

Harkany, T., Guzmán, M., Galve-Roperh, I., Berghuis, P., Devi, L. A., & Mackie, K. (2007). The emerging functions of endocannabinoid signaling during CNS development. *Trends in Pharmacological Sciences*, *28*(2), 83–92. https://doi.org/10.1016/J.TIPS.2006.12.004

Hasegawa, Y., Kim, J., Ursini, G., Jouroukhin, Y., Zhu, X., Miyahara, Y., Xiong, F., Madireddy, S., Obayashi, M., Lutz, B., Sawa, A., Brown, S. P., Pletnikov, M. V., & Kamiya, A. (2023). Microglial cannabinoid receptor type 1 mediates social memory deficits in mice produced by adolescent THC exposure and 16p11.2 duplication. *Nature Communications 2023 14:1*, *14*(1), 1–19. https://doi.org/10.1038/s41467-023-42276-5

Hatton, S. N., Lagopoulos, J., Hermens, D. F., Hickie, I. B., Scott, E., & Bennett, M. R. (2014). White matter tractography in early psychosis: clinical and neurocognitive associations. *J Psychiatry Neurosci*, *39*(6), 417. https://doi.org/10.1503/jpn.130280

Healy, C., Brannigan, R., Dooley, N., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). Childhood and adolescent psychotic experiences and risk of mental disorder: a systematic review and meta-analysis. *Psychological Medicine*, *49*(10), 1589–1599. https://doi.org/10.1017/S0033291719000485

Healy, C., Gordon, A. A., Coughlan, H., Clarke, M., Kelleher, I., & Cannon, M. (2019). Do childhood psychotic experiences improve the prediction of adolescent psychopathology? A longitudinal population-based study. *Early Intervention in Psychiatry*, *13*(5), 1245–1251. https://doi.org/10.1111/EIP.12762

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. (1991). The Fagerström Test for Nicotine Dependence: a revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*, *86*(9), 1119–1127. https://doi.org/10.1111/J.1360-0443.1991.TB01879.X

Helgason, L. (1990). Twenty years' follow-up of first psychiatric presentation for schizophrenia: what could have been prevented? *Acta Psychiatrica Scandinavica*, *81*(3), 231–235. https://doi.org/10.1111/J.1600-0447.1990.TB06486.X

Henriques, R. N., Correia, M. M., Marrale, M., Huber, E., Kruper, J., Koudoro, S., Yeatman, J. D., Garyfallidis, E., & Rokem, A. (2021). Diffusional Kurtosis Imaging in the Diffusion Imaging in Python Project. *Frontiers in Human Neuroscience*, *15*. https://doi.org/10.3389/FNHUM.2021.675433,

Hermoye, L., Saint-Martin, C., Cosnard, G., Lee, S. K., Kim, J., Nassogne, M. C., Menten, R., Clapuyt, P., Donohue, P. K., Hua, K., Wakana, S., Jiang, H., Van Zijl, P. C. M., & Mori, S. (2006). Pediatric diffusion tensor imaging: normal database and observation of the white matter maturation in early childhood. *NeuroImage*, *29*(2), 493–504. https://doi.org/10.1016/J.NEUROIMAGE.2005.08.017

Hides, L., Lubman, D. I., Buckby, J., Yuen, H. P., Cosgrave, E., Baker, K., & Yung, A. R. (2009). The association between early cannabis use and psychotic-like experiences in a community adolescent sample. *Schizophrenia Research*, *112*(1–3), 130–135. https://doi.org/10.1016/J.SCHRES.2009.04.001

Hinterbuchinger, B., & Mossaheb, N. (2021). Psychotic-Like Experiences: A Challenge in Definition and Assessment. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/FPSYT.2021.582392,

Hjorthøj, C. R., Hjorthøj, A. R., & Nordentoft, M. (2012). Validity of Timeline Follow-Back for self-reported use of cannabis and other illicit substances--systematic review and meta-analysis. *Addictive Behaviors*, *37*(3), 225–233. https://doi.org/10.1016/J.ADDBEH.2011.11.025

Hjorthøj, C., Stürup, A. E., McGrath, J. J., & Nordentoft, M. (2017). Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *The Lancet Psychiatry*, *4*(4), 295–301. https://doi.org/10.1016/S2215-0366(17)30078-0

Howes, O. D., Cummings, C., Chapman, G. E., & Shatalina, E. (2022). Neuroimaging in schizophrenia: an overview of findings and their implications for synaptic changes. *Neuropsychopharmacology 2022 48:1*, *48*(1), 151–167. https://doi.org/10.1038/s41386-022-01426-x

Howes, O. D., & Onwordi, E. C. (2023). The synaptic hypothesis of schizophrenia version III: a master mechanism. *Molecular Psychiatry 2023 28:5*, *28*(5), 1843–1856. https://doi.org/10.1038/s41380-023-02043-w

Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D. S., Calabresi, P. A., Pekar, J. J., van Zijl, P. C. M., & Mori, S. (2008). Tract probability maps in stereotaxic spaces: Analyses of white matter anatomy and tract-specific quantification. *NeuroImage*, *39*(1), 336–347. https://doi.org/10.1016/J.NEUROIMAGE.2007.07.053

Huang, S., Huang, C., Li, M., Zhang, H., & Liu, J. (2022). White Matter Abnormalities and Cognitive Deficit After Mild Traumatic Brain Injury: Comparing DTI, DKI, and NODDI. *Frontiers in Neurology*, *13*, 803066. https://doi.org/10.3389/FNEUR.2022.803066/BIBTEX

Hudziak, J. J. &, & Kaufman, J. (2014). *Yale-Vermont Adversity in Childhood Scale (Y-VACS)*.

Huttenlocher, P. R., & Dabholkar, A. S. (1997). Regional differences in synaptogenesis in human cerebral cortex. *Journal of Comparative Neurology*, *387*(2), 167–178. https://doi.org/10.1002/(SICI)1096-9861(19971020)387:2<167::AID-CNE1>3.0.CO;2-Z

ICD-11 for Mortality and Morbidity Statistics. (n.d.). Retrieved January 10, 2025, from https://icd.who.int/browse/2024-01/mms/en

IMAGEN. (n.d.). Retrieved April 7, 2025, from https://www.imagen-project.org/

Imtiaz, S., Nigatu, Y. T., Sanches, M., Ali, F., Boak, A., Douglas, L., Hamilton, H. A., Rehm, J., Rueda, S., Schwartz, R. M., Wells, S., & Elton-Marshall, T. (2024). Effects of cannabis legalisation on patterns of cannabis consumption among adolescents in Ontario, Canada (2001–2019). *Drug and Alcohol Review*, *43*(3), 764–774. https://doi.org/10.1111/DAR.13786;JOURNAL:JOURNAL:14653362B;REQUESTEDJOURNAL:JOURNAL:14653362;WGROUP:STRING:PUBLICATION

Jacobson, S., Kelleher, I., Harley, M., Murtagh, A., Clarke, M., Blanchard, M., Connolly, C., O'Hanlon, E., Garavan, H., & Cannon, M. (2010). Structural and functional brain correlates of subclinical psychotic symptoms in 11–13 year old schoolchildren. *NeuroImage*, *49*(2), 1875–1885. https://doi.org/10.1016/J.NEUROIMAGE.2009.09.015

Jacobus, J., & Tapert, S. F. (2014). Effects of Cannabis on the Adolescent Brain. *Current Pharmaceutical Design*, *20*(13), 2186. https://doi.org/10.2174/13816128113199990426

Janelle, F., Iorio-Morin, C., D'amour, S., & Fortin, D. (2022). Superior Longitudinal Fasciculus: A Review of the Anatomical Descriptions With Functional Correlates. *Frontiers in Neurology*, *13*. https://doi.org/10.3389/FNEUR.2022.794618

Jensen, J. H., & Helpern, J. A. (2010). MRI quantification of non-Gaussian water diffusion by kurtosis analysis. *NMR in Biomedicine*, *23*(7), 698–710. https://doi.org/10.1002/NBM.1518

Jensen, J. H., Helpern, J. A., Ramani, A., Lu, H., & Kaczynski, K. (2005). Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. *Magnetic Resonance in Medicine*, *53*(6), 1432–1440. https://doi.org/10.1002/MRM.20508

Jeurissen, B., Descoteaux, M., Mori, S., & Leemans, A. (2019). Diffusion MRI fiber tractography of the brain. *NMR in Biomedicine*, *32*(4). https://doi.org/10.1002/NBM.3785,

Jin, H., & Mosweu, I. (2017). The Societal Cost of Schizophrenia: A Systematic Review. *PharmacoEconomics*, *35*(1), 25–42. https://doi.org/10.1007/S40273-016-0444-6/TABLES/7

Johnson, D., Ricciardi, A., Brownlee, W., Kanber, B., Prados, F., Collorone, S., Kaden, E., Toosy, A., Alexander, D. C., Gandini Wheeler-Kingshott, C. A. M., Ciccarelli, O., & Grussu, F. (2021). Comparison of Neurite Orientation Dispersion and Density Imaging and Two-Compartment Spherical Mean Technique Parameter Maps in Multiple Sclerosis. *Frontiers in Neurology*, *12*, 662855. https://doi.org/10.3389/FNEUR.2021.662855/BIBTEX

Jones, D. K., Knösche, T. R., & Turner, R. (2013). Comments and Controversies White matter integrity, fiber count, and other fallacies: The do's and don'ts of diffusion MRI. *NeuroImage*, *73*, 239–254. https://doi.org/10.1016/j.neuroimage.2012.06.081

Jongsma, H. E., Turner, C., Kirkbride, J. B., & Jones, P. B. (2019). International incidence of psychotic disorders, 2002–17: a systematic review and meta-analysis. *The Lancet Public Health*, *4*(5), e229–e244. https://doi.org/10.1016/S2468-2667(19)30056-8

Kadakia, A., Catillon, M., Fan, Q., Williams, G. R., Marden, J. R., Anderson, A., Kirson, N., & Dembek, C. (2022). The Economic Burden of Schizophrenia in the United States. *The Journal of Clinical Psychiatry*, *83*(6). https://doi.org/10.4088/JCP.22M14458

Kay, S. R., Opler, L. A., Spitzer, R. L., Williams, J. B. W., Fiszbein, A., & Gorelick, A. (1991). SCID-PANSS: Two-tier diagnostic system for psychotic disorders. *Comprehensive Psychiatry*, *32*(4), 355–361. https://doi.org/10.1016/0010-440X(91)90085-Q

Kelleher, I. (2023). Psychosis prediction 2.0: why child and adolescent mental health services should be a key focus for schizophrenia and bipolar disorder prevention research. *The British Journal of Psychiatry*, *222*(5), 185–187. https://doi.org/10.1192/BJP.2022.193

Kelleher, I., & Cannon, M. (2011). Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. *Psychological Medicine*, *41*(1), 1–6. https://doi.org/10.1017/S0033291710001005

Kelleher, I., Connor, D., Clarke, M. C., Devlin, N., Harley, M., & Cannon, M. (2012). Prevalence of psychotic symptoms in childhood and adolescence: a systematic review and meta-analysis of population-based studies. *Psychological Medicine*, *42*(9), 1857–1863. https://doi.org/10.1017/S0033291711002960

Kelleher, I., Devlin, N., Wigman, J. T. W., Kehoe, A., Murtagh, A., Fitzpatrick, C., & Cannon, M. (2014). Psychotic experiences in a mental health clinic sample: implications for suicidality, multimorbidity and functioning. *Psychological Medicine*, *44*(8), 1615–1624. https://doi.org/10.1017/S0033291713002122

Kelleher, I., Harley, M., Murtagh, A., & Cannon, M. (2009). Are Screening Instruments Valid for Psychotic-Like Experiences? A Validation Study of Screening Questions for Psychotic-Like Experiences Using In-Depth Clinical Interview. *Schizophrenia Bulletin*, *37*(2), 362. https://doi.org/10.1093/SCHBUL/SBP057

Kelleher, I., Harley, M., Murtagh, A., & Cannon, M. (2011). Are screening instruments valid for psychotic-like experiences? A validation study of screening questions for psychotic-like experiences using in-depth clinical interview. *Schizophrenia Bulletin*, *37*(2), 362–369. https://doi.org/10.1093/schbul/sbp057

Kelleher, I., Jenner, J. A., & Cannon, M. (2010). Psychotic symptoms in the general population - an evolutionary perspective. *The British Journal of Psychiatry : The Journal of Mental Science*, *197*(3), 167–169. https://doi.org/10.1192/BJP.BP.109.076018

Kelleher, I., Keeley, H., Corcoran, P., Lynch, F., Fitzpatrick, C., Devlin, N., Molloy, C., Roddy, S., Clarke, M. C., Harley, M., Arseneault, L., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., & Cannon, M. (2012). Clinicopathological significance of psychotic experiences in non-psychotic young people: evidence from four population-based studies. *The British Journal of Psychiatry : The Journal of Mental Science*, *201*(1), 26–32. https://doi.org/10.1192/BJP.BP.111.101543

Knöchel, C., O'Dwyer, L., Alves, G., Reinke, B., Magerkurth, J., Rotarska-Jagiela, A., Prvulovic, D., Hampel, H., Linden, D. E. J., & Oertel-Knöchel, V. (2012). Association between white matter fiber integrity and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives. *Schizophrenia Research*, *140*(1–3), 129–135. https://doi.org/10.1016/J.SCHRES.2012.06.001

Kodiweera, C., Alexander, A. L., Harezlak, J., McAllister, T. W., & Wu, Y. C. (2016). Age effects and sex differences in human brain white matter of young to middle-aged adults: A DTI, NODDI, and q-space study. *NeuroImage*, *128*, 180–192. https://doi.org/10.1016/j.neuroimage.2015.12.033

Konrad, K., Firk, C., & Uhlhaas, P. J. (2013). Brain Development During Adolescence: Neuroscientific Insights Into This Developmental Period. *Deutsches Ärzteblatt International*, *110*(25), 425. https://doi.org/10.3238/ARZTEBL.2013.0425

Kopec, A. M., Smith, C. J., Ayre, N. R., Sweat, S. C., & Bilbo, S. D. (2018). Microglial dopamine receptor elimination defines sex-specific nucleus accumbens development and social behavior in adolescent rats. *Nature Communications*, *9*(1). https://doi.org/10.1038/s41467-018-06118-z

Krabbendam, L., Myin-Germeys, I., Bak, M., & Van Os, J. (2005). Explaining transitions over the hypothesized psychosis continuum. *The Australian and New Zealand Journal of Psychiatry*, *39*(3), 180–186. https://doi.org/10.1080/J.1440-1614.2005.01541.X

Kruper, J., Yeatman, J. D., Richie-Halford, A., Bloom, D., Grotheer, M., Caffarra, S., Kiar, G., Karipidis, I. I., Roy, E., Chandio, B. Q., Garyfallidis, E., & Rokem, A. (2021). Evaluating the Reliability of Human Brain White Matter Tractometry. *Aperture Neuro*, *1*(1). https://doi.org/10.52294/E6198273-B8E3-4B63-BABB-6E6B0DA10669

Kuo, S. S., & Pogue-Geile, M. F. (2019). Variation in fourteen brain structure volumes in schizophrenia: A comprehensive meta-analysis of 246 studies. *Neuroscience and Biobehavioral Reviews*, *98*, 85–94. https://doi.org/10.1016/J.NEUBIOREV.2018.12.030

Lanzafame, S., Giannelli, M., Garaci, F., Floris, R., Duggento, A., Guerrisi, M., & Toschi, N. (2016). Differences in Gaussian diffusion tensor imaging and non-Gaussian diffusion kurtosis imaging model-based estimates of diffusion tensor invariants in the human brain. *Medical Physics*, *43*(5), 2464–2475. https://doi.org/10.1118/1.4946819

Laurens, K. R., Hodgins, S., Maughan, B., Murray, R. M., Rutter, M. L., & Taylor, E. A. (2007). Community screening for psychotic-like experiences and other putative antecedents of schizophrenia in children aged 9-12 years. *Schizophrenia Research*, *90*(1–3), 130–146. https://doi.org/10.1016/J.SCHRES.2006.11.006

Lebel, C., & Deoni, S. (2018). The development of brain white matter microstructure. *NeuroImage*, *182*, 207–218. https://doi.org/10.1016/J.NEUROIMAGE.2017.12.097

Lee, J., Oh, J. S., Park, C. Il, Bang, M., Sung, G., Jung, S., & Lee, S. H. (2022). White matter microstructure of superior longitudinal fasciculus II is associated with intelligence and treatment response of negative symptoms in patients with schizophrenia. *Schizophrenia 2022 8:1*, *8*(1), 1–9. https://doi.org/10.1038/s41537-022-00253-9

Lee, K. W., Chan, K. W., Chang, W. C., Lee, E. H. M., Hui, C. L. M., & Chen, E. Y. H. (2016). A systematic review on definitions and assessments of psychotic-like experiences. *Early Intervention in Psychiatry*, *10*(1), 3–16. https://doi.org/10.1111/EIP.12228

Levar, N., Francis, A. N., Smith, M. J., Ho, W. C., & Gilman, J. M. (2018). Verbal Memory Performance and Reduced Cortical Thickness of Brain Regions Along the Uncinate Fasciculus in Young Adult Cannabis Users. *Cannabis and Cannabinoid Research*, *3*(1), 56–65. https://doi.org/10.1089/CAN.2017.0030/ASSET/IMAGES/LARGE/FIGURE3.JPEG

Levman, J., MacDonald, P., Lim, A. R., Forgeron, C., & Takahashi, E. (2017). A pediatric structural MRI analysis of healthy brain development from newborns to young adults. *Human Brain Mapping*, *38*(12), 5931–5942. https://doi.org/10.1002/HBM.23799

Li, X., Morgan, P. S., Ashburner, J., Smith, J., & Rorden, C. (2016). The first step for neuroimaging data analysis: DICOM to NIfTI conversion. *Journal of Neuroscience Methods*, *264*, 47–56. https://doi.org/10.1016/J.JNEUMETH.2016.03.001

Li, X., Wei, N., Song, J., Liu, J., Yuan, J., Song, R., Liu, L., Mei, L., Yan, S., Wu, Y., Pan, R., Yi, W., Jin, X., Li, Y., Liang, Y., Sun, X., Cheng, J., & Su, H. (2023). The global burden of schizophrenia and the impact of urbanization during 1990-2019: An analysis of the global burden of disease study 2019. *Environmental Research*, *232*. https://doi.org/10.1016/J.ENVRES.2023.116305

Li, Y., Zhang, W., Wu, Y., Yin, L., Zhu, C., Chen, Y., Cetin-Karayumak, S., Cho, K. I. K., Zekelman, L. R., Rushmore, J., Rathi, Y., Makris, N., O'Donnell, L. J., & Zhang, F. (2024). A diffusion MRI tractography atlas for concurrent white matter mapping across Eastern and Western populations. *Scientific Data 2024 11:1*, *11*(1), 1–14. https://doi.org/10.1038/s41597-024-03624-2

Lichenstein, S. D., Manco, N., Cope, L. M., Egbo, L., Garrison, K. A., Hardee, J., Hillmer, A. T., Reeder, K., Stern, E. F., Worhunsky, P., & Yip, S. W. (2021). Systematic review of structural and functional neuroimaging studies of cannabis use in adolescence and emerging adulthood: evidence from 90 studies and 9441 participants. *Neuropsychopharmacology 2021 47:5*, *47*(5), 1000–1028. https://doi.org/10.1038/s41386-021-01226-9

Lichenstein, S. D., Shaw, D. S., & Forbes, E. E. (2022). Cannabis, connectivity, and coming of age: Associations between cannabis use and anterior cingulate cortex connectivity during the transition to adulthood. *Frontiers in Human Neuroscience*, *16*, 951204. https://doi.org/10.3389/FNHUM.2022.951204/FULL

Liu, S. H., Du, Y., Chen, L., & Cheng, Y. (2022). Glial Cell Abnormalities in Major Psychiatric Diseases: A Systematic Review of Postmortem Brain Studies. *Molecular Neurobiology*, *59*(3), 1665–1692. https://doi.org/10.1007/S12035-021-02672-8, Lorenzetti, V., Alonso-Lana, S., Youssef, G., Verdejo-Garcia, A., Suo, C., Cousijn, J., Takagi, M., Yücel, M., & Solowij, N. (2016). Adolescent Cannabis Use: What is the Evidence for Functional Brain Alteration? *Current Pharmaceutical Design*, *22*(42), 6353–6365. https://doi.org/10.2174/1381612822666160805155922/CITE/REFWORKS

Lu, M., Yang, C., Chu, T., & Wu, S. (2018). Cerebral White Matter Changes in Young Healthy Individuals With High Trait Anxiety: A Tract-Based Spatial Statistics Study. *Frontiers in Neurology*, *9*(AUG), 704. https://doi.org/10.3389/FNEUR.2018.00704

Lubman, D. I., Cheetham, A., & Yücel, M. (2015). Cannabis and adolescent brain development. *Pharmacology & Therapeutics*, *148*, 1–16. https://doi.org/10.1016/J.PHARMTHERA.2014.11.009

Luquiens, A., Berger-Viergat, A., Larrieu, A., Artigaud, L., Fener, C., Adamson, S., Laprévote, V., & Rolland, B. (2021). Validation of the French version of the Cannabis Use Disorder Identification Test—Revised and comparison with the Cannabis Abuse Screening Test for screening cannabis use disorder in a psychiatric sample. *Drug and Alcohol Review*, *40*(7), 1334–1339. https://doi.org/10.1111/DAR.13298,

MacKie, C. J., Castellanos-Ryan, N., & Conrod, P. J. (2011). Developmental trajectories of psychotic-like experiences across adolescence: impact of victimization and substance use. *Psychological Medicine*, *41*(1), 47–58. https://doi.org/10.1017/S0033291710000449

Mackie, C. J., Castellanos-Ryan, N., & Conrod, P. J. (2011). Developmental trajectories of psychotic-like experiences across adolescence: impact of victimization and substance use. *Psychological Medicine*, *41*(1), 47–58. https://doi.org/10.1017/S0033291710000449

Maier-Hein, K. H., Neher, P. F., Houde, J. C., Côté, M. A., Garyfallidis, E., Zhong, J., Chamberland, M., Yeh, F. C., Lin, Y. C., Ji, Q., Reddick, W. E., Glass, J. O., Chen, D. Q., Feng, Y., Gao, C., Wu, Y., Ma, J., Renjie, H., Li, Q., … Descoteaux, M. (2017). The challenge of mapping the human connectome based on diffusion tractography. *Nature Communications 2017 8:1*, *8*(1), 1–13. https://doi.org/10.1038/s41467-017-01285-x

Malla, A. K., Norman, R. M. G., & Joober, R. (2005). First-Episode Psychosis, Early Intervention, and Outcome: What Have We Learned? *Http://Dx.Doi.Org/10.1177/070674370505001402*, *50*(14), 881–891. https://doi.org/10.1177/070674370505001402

Mallya, A. P., & Deutch, A. Y. (2018). (Micro)glia as effectors of cortical volume loss in schizophrenia. *Schizophrenia Bulletin*, *44*(5), 948–957. https://doi.org/10.1093/SCHBUL/SBY088,

Mallya, A. P., Wang, H. D., Lee, H. N. R., & Deutch, A. Y. (2019). Microglial Pruning of Synapses in the Prefrontal Cortex during Adolescence. *Cerebral Cortex*, *29*(4), 1634–1643. https://doi.org/10.1093/CERCOR/BHY061,

Mamah, D., Chen, S., Shimony, J. S., & Harms, M. P. (2024). Tract-based analyses of white matter in schizophrenia, bipolar disorder, aging, and dementia using high spatial and directional resolution diffusion imaging: a pilot study. *Frontiers in Psychiatry*, *15*, 1240502. https://doi.org/10.3389/fpsyt.2024.1240502

Mandal, P. K., Mahajan, R., & Dinov, I. D. (2012). Structural Brain Atlases: Design, Rationale, and Applications in Normal and Pathological Cohorts. *Journal of Alzheimer's Disease : JAD*, *31*(0 3), S169. https://doi.org/10.3233/JAD-2012-120412

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull*, *42*(5), 1262–1269. https://doi.org/10.1093/schbul/sbw003

Mato, S., Del Olmo, E., & Pazos, A. (2003). Ontogenetic development of cannabinoid receptor expression and signal transduction functionality in the human brain. *The European Journal of Neuroscience*, *17*(9), 1747–1754. https://doi.org/10.1046/J.1460-9568.2003.02599.X

McCreadie, R. G., Wiles, D. H., Livingston, M. G., Watt, J. A. G., Greene, J. G., Kershaw, P. W., Todd, N. A., Scott, A. M., Crocket, G. T., Mahmood, Z., Loudon, J., Dyer, J. A. T., Philip, A. E., & Batchelor, D. (1992). The Scottish First Episode Schizophrenia Study: VIII. Five-Year Follow-Up: Clinical and Psychosocial Findings. *The British Journal of Psychiatry*, *161*(4), 496–500. https://doi.org/10.1192/BJP.161.4.496

McGee, R., Williams, S., Poulton, R., & Moffitt, T. (2000). A longitudinal study of cannabis use and mental health from adolescence to early adulthood. *Addiction*, *95*(4), 491–503. https://doi.org/10.1046/J.1360-0443.2000.9544912.X

McGovern, M. P., & Morrison, D. H. (1992). The chemical use, abuse, and dependence scale (CUAD): Rationale, reliability, and validity. *Journal of Substance Abuse Treatment*, *9*(1), 27–38. https://doi.org/10.1016/0740-5472(92)90007-B

McGrath, J. J., Saha, S., Al-Hamzawi, A., Alonso, J., Bromet, E. J., Bruffaerts, R., Caldas-De-Almeida, J. M., Chiu, W. T., De Jonge, P., Fayyad, J., Florescu, S., Gureje, O., Haro, J. M., Hu, C., Kovess-Masfety, V., Lepine, J. P., Lim, C. C. W., Mora, M. E. M., Navarro-Mateu, F., … Kessler, R. C. (2015). Psychotic Experiences in the General Population: A Cross-National Analysis Based on 31 261 Respondents From 18 Countries. *JAMA Psychiatry*, *72*(7), 697–705. https://doi.org/10.1001/JAMAPSYCHIATRY.2015.0575

McGrath, J., Welham, J., Scott, J., Varghese, D., Degenhardt, L., Hayatbakhsh, M. R., Alati, R., Williams, G. M., Bor, W., & Najman, J. M. (2010). Association Between Cannabis Use and Psychosis-Related Outcomes Using Sibling Pair Analysis in a Cohort of Young Adults. *Archives of General Psychiatry*, *67*(5), 440–447. https://doi.org/10.1001/ARCHGENPSYCHIATRY.2010.6

McGuire, P., Howes, O. D., Stone, J., & Fusar-Poli, P. (2008). Functional neuroimaging in schizophrenia: diagnosis and drug discovery. *Trends in Pharmacological Sciences*, *29*(2), 91–98. https://doi.org/10.1016/J.TIPS.2007.11.005/ASSET/2B7D005F-EAB2-412B-88C2-73568AA362E0/MAIN.ASSETS/GR2.SML

Miller, M. L., Chadwick, B., Dickstein, D. L., Purushothaman, I., Egervari, G., Rahman, T., Tessereau, C., Hof, P. R., Roussos, P., Shen, L., Baxter, M. G., & Hurd, Y. L. (2018). Adolescent exposure to Δ9-tetrahydrocannabinol alters the transcriptional trajectory and dendritic architecture of prefrontal pyramidal neurons. *Molecular Psychiatry 2018 24:4*, *24*(4), 588–600. https://doi.org/10.1038/s41380-018-0243-x

Miller, M. L., Chadwick, B., Dickstein, D. L., Purushothaman, I., Egervari, G., Rahman, T., Tessereau, C., Hof, P. R., Roussos, P., Shen, L., Baxter, M. G., & Hurd, Y. L. (2019). Adolescent exposure to Δ 9 -tetrahydrocannabinol alters the transcriptional trajectory and dendritic architecture of prefrontal pyramidal neurons. *Molecular Psychiatry*, *24*(4), 588–600. https://doi.org/10.1038/s41380-018-0243-x

Minichino, A., Davies, C., Karpenko, O., Christodoulou, N., Ramalho, R., Nandha, S., Damiani, S., Provenzani, U., Esposito, C. M., Mensi, M. M., Borgatti, R., Stefana, A., McGuire, P., & Fusar-Poli, P. (2025). Preventing psychosis in people at clinical high risk: an updated meta-analysis by the World Psychiatric Association Preventive Psychiatry section. *Molecular Psychiatry 2025*, 1–10. https://doi.org/10.1038/s41380-025-02902-8

Molfese, P. J., Glen, D., Mesite, L., Cox, R. W., Hoeft, F., Frost, S. J., Mencl, W. E., Pugh, K. R., & Bandettini, P. A. (2021). The Haskins pediatric atlas: a magnetic-resonance-imaging-based pediatric template and atlas. *Pediatric Radiology*, *51*(4), 628–639. https://doi.org/10.1007/S00247-020-04875-Y/TABLES/3

Mordelt, A., & de Witte, L. D. (2023). Microglia-mediated synaptic pruning as a key deficit in neurodevelopmental disorders: Hype or hope? *Current Opinion in Neurobiology*, *79*, 102674. https://doi.org/10.1016/J.CONB.2022.102674

Morean, M. E., Krishnan-Sarin, S., & S. O'Malley, S. (2018). Assessing nicotine dependence in adolescent E-cigarette users: The 4-item Patient-Reported Outcomes Measurement Information System (PROMIS) Nicotine Dependence Item Bank for electronic cigarettes. *Drug and Alcohol Dependence*, *188*, 60–63. https://doi.org/10.1016/J.DRUGALCDEP.2018.03.029

Morean, M. E., Krishnan-Sarin, S., Sussman, S., Foulds, J., Fishbein, H., Grana, R., & O'Malley, S. S. (2018). Psychometric Evaluation of the E-cigarette Dependence Scale. *Nicotine & Tobacco Research*, *21*(11), 1556. https://doi.org/10.1093/NTR/NTX271

Mori, S., & Van Zijl, P. C. M. (2002). Fiber tracking: principles and strategies – a technical review. *NMR in Biomedicine*, *15*(7–8), 468–480. https://doi.org/10.1002/NBM.781

Morris, S. R., Holmes, R. D., Dvorak, A. V., Liu, H., Yoo, Y., Vavasour, I. M., Mazabel, S., Mädler, B., Kolind, S. H., Li, D. K. B., Siegel, L., Beaulieu, C., MacKay, A. L., & Laule, C. (2020). Brain Myelin Water Fraction and Diffusion Tensor Imaging Atlases for 9-10 Year-Old Children. *Journal of Neuroimaging*, *30*(2), 150–160. https://doi.org/10.1111/JON.12689

Mossaheb, N., Becker, J., Schaefer, M. R., Klier, C. M., Schloegelhofer, M., Papageorgiou, K., & Amminger, G. P. (2012). The Community Assessment of Psychic Experience (CAPE) questionnaire as a screening-instrument in the detection of individuals at ultra-high risk for psychosis. *Schizophrenia Research*, *141*(2–3), 210–214. https://doi.org/10.1016/J.SCHRES.2012.08.008

Murray, G. K., & Jones, P. B. (2012). Psychotic symptoms in young people without psychotic illness: mechanisms and meaning. *The British Journal of Psychiatry : The Journal of Mental Science*, *201*(1), 4–6. https://doi.org/10.1192/BJP.BP.111.107789

Myran, D. T., Pugliese, M., Harrison, L. D., Solmi, M., Anderson, K. K., Fiedorowicz, J. G., Finkelstein, Y., Manuel, D., Taljaard, M., Webber, C., & Tanuseputro, P. (2025). Changes in Incident Schizophrenia Diagnoses Associated With Cannabis Use Disorder After Cannabis Legalization. *JAMA Network Open*, *8*(2), e2457868. https://doi.org/10.1001/JAMANETWORKOPEN.2024.57868,

Najjar, S., & Pearlman, D. M. (2015). Neuroinflammation and white matter pathology in schizophrenia: Systematic review. *Schizophrenia Research*, *161*(1), 102–112. https://doi.org/10.1016/j.schres.2014.04.041

Niciu, M. J., & Mason, G. F. (2014). Neuroimaging in Alcohol and Drug Dependence. *Current Behavioral Neuroscience Reports*, *1*(1), 45–54. https://doi.org/10.1007/S40473-013-0005-7/FIGURES/1

NIMH Data Archive - Data - Study. (n.d.). Retrieved April 7, 2025, from https://nda.nih.gov/study.html?id=2313

Nonnemaker, J. M., & Homsi, G. (2007). Measurement properties of the Fagerström Test for nicotine dependence adapted for use in an adolescent sample. *Addictive Behaviors*, *32*(1), 181–186. https://doi.org/10.1016/j.addbeh.2006.03.028

Norton, I., Essayed, W. I., Zhang, F., Pujol, S., Yarmarkovich, A., Golby, A. J., Kindlmann, G., Wasserman, D., Estepar, R. S. J., Rathi, Y., Pieper, S., Kikinis, R., Johnson, H. J., Westin, C. F., & O'Donnell, L. J. (2017). SlicerDMRI: Open source diffusion MRI software for brain cancer research. *Cancer Research*, *77*(21), e101–e103. https://doi.org/10.1158/0008-5472.CAN-17-0332/SUPPLEMENTARY-VIDEO-S2

Notter, M. P., Herholz, P., Da Costa, S., Gulban, O. F., Isik, A. I., Gaglianese, A., & Murray, M. M. (2023). fMRIflows: A Consortium of Fully Automatic Univariate and Multivariate fMRI Processing Pipelines. *Brain Topography*, *36*(2), 172–191. https://doi.org/10.1007/S10548-022-00935-8/FIGURES/12

Oakley, P., Kisely, S., Baxter, A., Harris, M., Desoe, J., Dziouba, A., & Siskind, D. (2018). Increased mortality among people with schizophrenia and other non-affective psychotic disorders in the community: A systematic review and meta-analysis. *Journal of Psychiatric Research*, *102*, 245–253. https://doi.org/10.1016/J.JPSYCHIRES.2018.04.019

O'Donnell, L. J., Wells, W. M., Golby, A. J., & Westin, C. F. (2012). Unbiased groupwise registration of white matter tractography. *Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, *7512 LNCS*(Pt 3), 123–130. https://doi.org/10.1007/978-3-642-33454-2_16,

O'Donnell, L. J., & Westin, C. F. (2007). Automatic tractography segmentation using a high-dimensional white matter atlas. *IEEE Transactions on Medical Imaging*, *26*(11), 1562–1575. https://doi.org/10.1109/TMI.2007.906785

O'Hanlon, E., Leemans, A., Kelleher, I., Clarke, M. C., Roddy, S., Coughlan, H., Harley, M., Amico, F., Hoscheit, M. J., Tiedt, L., Tabish, J., McGettigan, A., Frodl, T., & Cannon, M. (2015). White Matter Differences Among Adolescents Reporting Psychotic Experiences: A Population-Based Diffusion Magnetic Resonance Imaging Study. *JAMA Psychiatry*, *72*(7), 668–677. https://doi.org/10.1001/JAMAPSYCHIATRY.2015.0137

Okada, N., Yahata, N., Koshiyama, D., Morita, K., Sawada, K., Kanata, S., Fujikawa, S., Sugimoto, N., Toriyama, R., Masaoka, M., Koike, S., Araki, T., Kano, Y., Endo, K., Yamasaki, S., Ando, S., Nishida, A., Hiraiwa-Hasegawa, M., & Kasai, K. (2018). Abnormal asymmetries in subcortical brain volume in early adolescents with subclinical psychotic experiences. *Translational Psychiatry 2018 8:1*, *8*(1), 1–11. https://doi.org/10.1038/s41398-018-0312-6

Orr, C., Spechler, P., Cao, Z., Albaugh, M., Chaarani, B., Mackey, S., D'Souza, D., Allgaier, N., Banaschewski, T., Bokde, A. L. W., Bromberg, U., Büchel, C., Quinlan, E. B., Conrod, P., Desrivières, S., Flor, H., Frouin, V., Gowland, P., Heinz, A., … Garavan, H. (2019). Grey Matter Volume Differences Associated with Extremely Low Levels of Cannabis Use in Adolescence. *Journal of Neuroscience*, *39*(10), 1817–1827. https://doi.org/10.1523/JNEUROSCI.3375-17.2018

Orr, J. M., Paschall, C. J., & Banich, M. T. (2016). Recreational marijuana use impacts white matter integrity and subcortical (but not cortical) morphometry. *NeuroImage. Clinical*, *12*, 47–56. https://doi.org/10.1016/J.NICL.2016.06.006

Ota, M., Noda, T., Sato, N., Hidese, S., Teraishi, T., Setoyama, S., Sone, D., Matsuda, H., & Kunugi, H. (2018). The use of diffusional kurtosis imaging and neurite orientation dispersion and density imaging of the brain in major depressive disorder. *Journal of Psychiatric Research*, *98*, 22–29. https://doi.org/10.1016/J.JPSYCHIRES.2017.12.011

Ouellet-Plamondon, C., Abdel-Baki, A., Salvat, E., & Potvin, S. (2017). Specific impact of stimulant, alcohol and cannabis use disorders on first-episode psychosis: 2-year functional and symptomatic outcomes. *Psychological Medicine*, *47*(14), 2461–2471. https://doi.org/10.1017/S0033291717000976

Overview | Psychosis and schizophrenia in adults: prevention and management | Guidance | NICE. (n.d.).

Panta, S. R., Anderson, N. E., Maurer, J. M., Harenski, K. A., Nyalakanti, P. K., Calhoun, V. D., & Kiehl, K. A. (2021). Classifying handedness with MRI. *Neuroimage: Reports*, *1*(4), 100057. https://doi.org/10.1016/j.ynirp.2021.100057

Patrick, M. E., Kloska, D. D., Terry-McElrath, Y. M., Lee, C. M., O'Malley, P. M., & Johnston, L. D. (2018). Patterns of simultaneous and concurrent alcohol and marijuana use among adolescents. *The American Journal of Drug and Alcohol Abuse*, *44*(4), 441–451. https://doi.org/10.1080/00952990.2017.1402335

Pausova, Z., Paus, T., Abrahamowicz, M., Bernard, M., Gaudet, D., Leonard, G., Peron, M., Pike, G. B., Richer, L., Seguin, J. R., & Veillette, S. (2017). Cohort Profile: The Saguenay Youth Study (SYS). *International Journal of Epidemiology*, *46*(2). https://doi.org/10.1093/IJE/DYW023

Peters, B. D., Szeszko, P. R., Radua, J., Ikuta, T., Gruner, P., Derosse, P., Zhang, J. P., Giorgio, A., Qiu, D., Tapert, S. F., Brauer, J., Asato, M. R., Khong, P. L., James, A. C., Gallego, J. A., & Malhotra, A. K. (2012). White Matter Development in Adolescence: Diffusion Tensor Imaging and Meta-Analytic Results. *Schizophrenia Bulletin*, *38*(6), 1308–1317. https://doi.org/10.1093/SCHBUL/SBS054

Peters, E. R., Joseph, S. A., & Garety, P. A. (1999). Measurement of delusional ideation in the normal population: introducing the PDI (Peters et al. Delusions Inventory). *Schizophrenia Bulletin*, *25*(3), 553–576. https://doi.org/10.1093/OXFORDJOURNALS.SCHBUL.A033401

Pines, A. R., Cieslak, M., Larsen, B., Baum, G. L., Cook, P. A., Adebimpe, A., Dávila, D. G., Elliott, M. A., Jirsaraie, R., Murtha, K., Oathes, D. J., Piiwaa, K., Rosen, A. F. G., Rush, S., Shinohara, R. T., Bassett, D. S., Roalf, D. R., & Satterthwaite, T. D. (2020). Leveraging multi-shell diffusion for studies of brain development in youth and young adulthood. *Developmental Cognitive Neuroscience*, *43*, 100788. https://doi.org/10.1016/J.DCN.2020.100788

Podwalski, P., Tyburski, E., Szczygieł, K., Rudkowski, K., Waszczuk, K., Andrusewicz, W., Kucharska-Mazur, J., Michalczyk, A., Mak, M., Cyranka, K., Misiak, B., Sagan, L., & Samochowiec, J. (2022). Psychopathology and Integrity of the Superior Longitudinal Fasciculus in Deficit and Nondeficit Schizophrenia. *Brain Sciences*, *12*(2). https://doi.org/10.3390/BRAINSCI12020267

Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000). Children's Self-Reported Psychotic Symptoms and Adult Schizophreniform Disorder. *Archives of General Psychiatry*, *57*(11), 1053. https://doi.org/10.1001/archpsyc.57.11.1053

Preti, A., Cella, M., & Raballo, A. (2012). Letter to the Editor: All that shines is not psychosis: a cautionary note on the assessment of psychotic symptoms in childhood and adolescence. *Psychological Medicine*, *42*(8), 1787–1788. https://doi.org/10.1017/S0033291712001249

Ranzenberger, L. R., Das, J. M., & Snyder, T. (2023). Diffusion Tensor Imaging. *Surgery of Spinal Cord Tumors Based on Anatomy: An Approach Based on Anatomic Compartmentalization*, 147–151. https://doi.org/10.1007/978-981-15-7771-0_16

Remberk, B. (2017). Clinical significance of psychotic-like experiences in children and adolescents. *Psychiatria Polska*, *51*(2), 271–282. https://doi.org/10.12740/PP/63894

Remington, G., Addington, D., Honer, W., Ismail, Z., Raedler, T., & Teehan, M. (2017). Guidelines for the Pharmacotherapy of Schizophrenia in Adults. *Https://Doi.Org/10.1177/0706743717720448*, *62*(9), 604–616. https://doi.org/10.1177/0706743717720448

Richter, S., Winzeck, S., Correia, M. M., Kornaropoulos, E. N., Manktelow, A., Outtrim, J., Chatfield, D., Posti, J. P., Tenovuo, O., Williams, G. B., Menon, D. K., & Newcombe, V. F. J. (2022). Validation of cross-sectional and longitudinal ComBat harmonization methods for magnetic resonance imaging data on a travelling subject cohort. *Neuroimage. Reports*, *2*(4). https://doi.org/10.1016/J.YNIRP.2022.100136

Robinson, E. A., Gleeson, J., Arun, A. H., Clemente, A., Gaillard, A., Rossetti, M. G., Brambilla, P., Bellani, M., Crisanti, C., Curran, H. V., & Lorenzetti, V. (2023). Measuring white matter microstructure in 1,457 cannabis users and 1,441 controls: A systematic review of diffusion-weighted MRI studies. *Frontiers in Neuroimaging*, *2*. https://doi.org/10.3389/FNIMG.2023.1129587

Robinson, S. M., Sobell, L. C., Sobell, M. B., & Leo, G. I. (2014). Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychology of Addictive Behaviors : Journal of the Society of Psychologists in Addictive Behaviors*, *28*(1), 154–162. https://doi.org/10.1037/A0030992

Roseborough, A. D., Jaremek, V. M., & Whitehead, S. N. (2022). Editorial Focus: White matter-associated microglia (WAMs) represent an important link between aging, white matter disease and microglial activity. *GeroScience*, *44*(1), 63–65. https://doi.org/10.1007/S11357-021-00435-W

Rössler, W., Joachim Salize, H., Van Os, J., & Riecher-Rössler, A. (2005). Size of burden of schizophrenia and psychotic disorders. *European Neuropsychopharmacology*, *15*(4), 399–409. https://doi.org/10.1016/J.EURONEURO.2005.04.009

Saha, S., Chant, D., & McGrath, J. (2007). A Systematic Review of Mortality in Schizophrenia: Is the Differential Mortality Gap Worsening Over Time? *Archives of General Psychiatry*, *64*(10), 1123–1131. https://doi.org/10.1001/ARCHPSYC.64.10.1123

Samartzis, L., Dima, D., Fusar-Poli, P., & Kyriakopoulos, M. (2014). White Matter Alterations in Early Stages of Schizophrenia: A Systematic Review of Diffusion Tensor Imaging Studies. *Journal of Neuroimaging*, *24*(2), 101–110. https://doi.org/10.1111/J.1552-6569.2012.00779.X

Sancho, L., Contreras, M., & Allen, N. J. (2021). Glia as sculptors of synaptic plasticity. *Neuroscience Research*, *167*, 17–29. https://doi.org/10.1016/J.NEURES.2020.11.005

Santis, R., Garmendia, M. L., Acuña, G., Alvarado, M. E., & Arteaga, O. (2009). The Alcohol Use Disorders Identification Test (AUDIT) as a screening instrument for adolescents. *Drug and Alcohol Dependence*, *103*(3), 155–158. https://doi.org/10.1016/J.DRUGALCDEP.2009.01.017

Saunders, J. B., AASLAND, O. G., BABOR, T. F., DE LA FUENTE, J. R., & GRANT, M. (1993). Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption-II. *Addiction*, *88*(6), 791–804. https://doi.org/10.1111/J.1360-0443.1993.TB02093.X, Schilling, K. G., Nath, V., Hansen, C., Parvathaneni, P., Blaber, J., Gao, Y., Neher, P., Aydogan, D. B., Shi, Y., Ocampo-Pineda, M., Schiavi, S., Daducci, A., Girard, G., Barakovic, M., Rafael-Patino, J., Romascano, D., Rensonnet, G., Pizzolato, M., Bates, A., … Landman, B. A. (2019). Limits to anatomical accuracy of diffusion tractography using modern approaches. *NeuroImage*, *185*, 1–11. https://doi.org/10.1016/J.NEUROIMAGE.2018.10.029

Schilling, K. G., Petit, L., Rheault, F., Remedios, S., Pierpaoli, C., Anderson, A. W., Landman, B. A., & Descoteaux, M. (2020). Brain connections derived from diffusion MRI tractography can be highly anatomically accurate—if we know where white matter pathways start, where they end, and where they do not go. *Brain Structure and Function*, *225*(8), 2387–2402. https://doi.org/10.1007/S00429-020-02129-Z/FIGURES/6

Schilling, K. G., Rheault, F., Petit, L., Hansen, C. B., Nath, V., Yeh, F. C., Girard, G., Barakovic, M., Rafael-Patino, J., Yu, T., Fischi-Gomez, E., Pizzolato, M., Ocampo-Pineda, M., Schiavi, S., Canales-Rodríguez, E. J., Daducci, A., Granziera, C., Innocenti, G., Thiran, J. P., … Descoteaux, M. (2021). Tractography dissection variability: What happens when 42 groups dissect 14 white matter bundles on the same dataset? *NeuroImage*, *243*, 118502. https://doi.org/10.1016/J.NEUROIMAGE.2021.118502

Schoorl, J., Barbu, M. C., Shen, X., Harris, M. R., Adams, M. J., Whalley, H. C., & Lawrie, S. M. (2021). Grey and white matter associations of psychotic-like experiences in a general population sample (UK Biobank). *Translational Psychiatry 2021 11:1*, *11*(1), 1–11. https://doi.org/10.1038/s41398-020-01131-7

Schultz, N. R., Bassett, D. T., Messina, B. G., & Correia, C. J. (2019). Evaluation of the psychometric properties of the cannabis use disorders identification test - revised among college students. *Addictive Behaviors*, *95*, 11–15. https://doi.org/10.1016/j.addbeh.2019.02.016

Shepherd, M., Watt, D., Falloon, I., & Smeeton, N. (1989). The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. *Psychological Medicine Monograph Supplement*, *15*, 1–46. https://doi.org/10.1017/S026418010000059X

Shi, Y., Lenzi, M., & An, R. (2015). Cannabis Liberalization and Adolescent Cannabis Use: A Cross-National Study in 38 Countries. *PLOS ONE*, *10*(11), e0143562. https://doi.org/10.1371/JOURNAL.PONE.0143562

Short, S. J., Jang, D. K., Steiner, R. J., Stephens, R. L., Girault, J. B., Styner, M., & Gilmore, J. H. (2022). Diffusion Tensor Based White Matter Tract Atlases for Pediatric Populations. *Frontiers in Neuroscience*, *16*, 806268. https://doi.org/10.3389/FNINS.2022.806268/BIBTEX

Siehl, S., King, J. A., Burgess, N., Flor, H., & Nees, F. (2018). Structural white matter changes in adults and children with posttraumatic stress disorder: A systematic review and meta-analysis. *NeuroImage : Clinical*, *19*, 581. https://doi.org/10.1016/J.NICL.2018.05.013

Silva Paiva, W., Cabeen, R. P., Caruyer, E., Fortin DavidFortin, D., Janelle, F., Iorio-Morin, C., & Fortin, D. (2022). Superior Longitudinal Fasciculus: A Review of the Anatomical Descriptions With Functional Correlates. *Frontiers in Neurology*, *13*, 794618. https://doi.org/10.3389/FNEUR.2022.794618

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., Watkins, K. E., Ciccarelli, O., Cader, M. Z., Matthews, P. M., & Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage*, *31*(4), 1487–1505. https://doi.org/10.1016/J.NEUROIMAGE.2006.02.024

Sobell, L. C., & Sobell, M. B. (1992). Timeline Follow-Back. *Measuring Alcohol Consumption*, 41–72. https://doi.org/10.1007/978-1-4612-0357-5_3

Song, S. K., Sun, S. W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination Revealed through MRI as Increased Radial (but Unchanged Axial) Diffusion of Water. *NeuroImage*, *17*(3), 1429–1436. https://doi.org/10.1006/NIMG.2002.1267

Spechler, P. A., Allgaier, N., Chaarani, B., Whelan, R., Watts, R., Orr, C., Albaugh, M. D., D'Alberto, N., Higgins, S. T., Hudson, K. E., Mackey, S., Potter, A., Banaschewski, T., Bokde, A. L. W., Bromberg, U., Büchel, C., Cattrell, A., Conrod, P. J., Desrivières, S., … Tahmasebi, A. (2019). The initiation of cannabis use in adolescence is predicted by sex-specific psychosocial and neurobiological features. *European Journal of Neuroscience*, *50*(3), 2346–2356. https://doi.org/10.1111/EJN.13989

Srivastava, S., Bhatia, M. S., Bhargava, S. K., Kumari, R., & Chandra, S. (2016). A Diffusion Tensor Imaging Study Using a Voxel-Based Analysis, Region-of-Interest Method to Analyze White Matter Abnormalities in First-Episode, Treatment-Naïve Major Depressive Disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *28*(2), 131–137. https://doi.org/10.1176/APPI.NEUROPSYCH.15050120

Staines, L., Healy, C., Coughlan, H., Clarke, M., Kelleher, I., Cotter, D., & Cannon, M. (2022). Psychotic experiences in the general population, a review; definition, risk factors, outcomes and interventions. *Psychological Medicine*, *52*(15), 3297. https://doi.org/10.1017/S0033291722002550

Staines, L., Healy, C., Murphy, F., Byrne, J., Murphy, J., Kelleher, I., Cotter, D., & Cannon, M. (2023). Incidence and Persistence of Psychotic Experiences in the General Population: Systematic Review and Meta-Analysis. *Schizophrenia Bulletin*, *49*(4), 1007–1021. https://doi.org/10.1093/SCHBUL/SBAD056

Steven, A. J., Zhuo, J., & Melhem, E. R. (2014). Diffusion kurtosis imaging: an emerging technique for evaluating the microstructural environment of the brain. *AJR. American Journal of Roentgenology*, *202*(1). https://doi.org/10.2214/AJR.13.11365

Stevens, F. L., Hurley, R. A., & Taber, K. H. (2011). Anterior cingulate cortex: Unique role in cognition and emotion. *Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(2), 121–125. https://doi.org/10.1176/JNP.23.2.JNP121/ASSET/IMAGES/LARGE/JNP0021103200003.C.JPEG

Sullivan, S. A., Kounali, D., Cannon, M., David, A. S., Fletcher, P. C., Holmans, P., Jones, H., Jones, P. B., Linden, D. E. J., Lewis, G., Owen, M. J., O'Donovan, M., Rammos, A., Thompson, A., Wolke, D., Heron, J., & Zammit, S. (2020). A Population-Based Cohort Study Examining the Incidence and Impact of Psychotic Experiences From Childhood to Adulthood, and Prediction of Psychotic Disorder. *The American Journal of Psychiatry*, *177*(4), 308–317. https://doi.org/10.1176/APPI.AJP.2019.19060654

Summary of results for the Canadian Student Tobacco, Alcohol and Drugs Survey 2018-19 - Canada.ca. (n.d.). Retrieved January 18, 2025, from https://www.canada.ca/en/health-canada/services/canadian-student-tobacco-alcohol-drugs-survey/2018-2019-summary.html

Summary of results for the Canadian Student Tobacco, Alcohol and Drugs Survey 2021 - Canada.ca. (n.d.). Retrieved January 26, 2025, from https://www.canada.ca/en/health-canada/services/canadian-student-tobacco-alcohol-drugs-survey/2021-2022-summary.html

Tabesh, A., Jensen, J. H., Ardekani, B. A., & Helpern, J. A. (2011). Estimation of tensors and tensor-derived measures in diffusional kurtosis imaging. *Magnetic Resonance in Medicine*, *65*(3), 823–836. https://doi.org/10.1002/mrm.22655

Taha, A. A., & Hanbury, A. (2015). Metrics for evaluating 3D medical image segmentation: Analysis, selection, and tool. *BMC Medical Imaging*, *15*(1), 1–28. https://doi.org/10.1186/S12880-015-0068-X/TABLES/5

Tamnes, C. K., & Agartz, I. (2016). White Matter Microstructure in Early-Onset Schizophrenia: A Systematic Review of Diffusion Tensor Imaging Studies. *Journal of the American Academy of Child & Adolescent Psychiatry*, *55*(4), 269–279. https://doi.org/10.1016/J.JAAC.2016.01.004

Tamnes, C. K., Roalf, D. R., Goddings, A. L., & Lebel, C. (2018). Diffusion MRI of white matter microstructure development in childhood and adolescence: Methods, challenges and progress. *Developmental Cognitive Neuroscience*, *33*, 161–175. https://doi.org/10.1016/J.DCN.2017.12.002

Tassi, E., Bianchi, A. M., Calesella, F., Vai, B., Bellani, M., Nenadić, I., Piras, F., Benedetti, F., Brambilla, P., & Maggioni, E. (2024). Assessment of ComBat Harmonization Performance on Structural Magnetic Resonance Imaging Measurements. *Human Brain Mapping*, *45*(18), e70085. https://doi.org/10.1002/HBM.70085

Thayer, R. E., York., Williams, S., Karoly, H. C., Sabbineni, A., Ewing, S. F., Bryan, A. D., & Hutchison, K. E. (2017). Structural neuroimaging correlates of alcohol and cannabis use in adolescents and adults. *Addiction*, *112*(12), 2144–2154. https://doi.org/10.1111/ADD.13923

Thomas, F., Gallea, C., Moulier, V., Bouaziz, N., Valero-Cabré, A., & Januel, D. (2022). Local alterations of left arcuate fasciculus and transcallosal white matter microstructure in schizophrenia patients with medication-resistant auditory verbal hallucinations: A pilot study. *Neuroscience*, *507*, 1–13. https://doi.org/10.1016/j.neuroscience.2022.10.027

Timmers, I., Roebroeck, A., Bastiani, M., Jansma, B., Rubio-Gozalbo, E., & Zhang, H. (2016). Assessing Microstructural Substrates of White Matter Abnormalities: A Comparative Study Using DTI and NODDI. *PloS One*, *11*(12). https://doi.org/10.1371/JOURNAL.PONE.0167884

Tramazzo, S., Lian, W., Ajnakina, O., Carlson, G., Bromet, E., Kotov, R., & Jonas, K. (2024). Long-Term Course of Remission and Recovery in Psychotic Disorders. *The American Journal of Psychiatry*, *181*(6), 532–540. https://doi.org/10.1176/APPI.AJP.20230189/SUPPL_FILE/APPI.AJP.20230189.DS001.PDF

Trépanier, M. O., Hopperton, K. E., Mizrahi, R., Mechawar, N., & Bazinet, R. P. (2016). Postmortem evidence of cerebral inflammation in schizophrenia: a systematic review. *Molecular Psychiatry 2016 21:8*, *21*(8), 1009–1026. https://doi.org/10.1038/mp.2016.90

Tu, A. W., Ratner, P. A., & Johnson, J. L. (2008). Gender Differences in the Correlates of Adolescents' Cannabis Use. *Substance Use & Misuse*, *43*(10), 1438–1463. https://doi.org/10.1080/10826080802238140

Tuvel, A. L., Winiger, E. A., & Ross, J. M. (2023). A Review of the Effects of Adolescent Cannabis Use on Physical Health. *Child and Adolescent Psychiatric Clinics of North America*, *32*(1), 85–105. https://doi.org/10.1016/j.chc.2022.07.005

Van Os, J., Hanssen, M., Bijl, R. V., & Ravelli, A. (2000). Strauss (1969) revisited: A psychosis continuum in the general population? *Schizophrenia Research*, *45*(1–2), 11–20. https://doi.org/10.1016/S0920-9964(99)00224-8

Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine*, *39*(2), 179–195. https://doi.org/10.1017/S0033291708003814

Vargas, G., Shrier, L. A., Chadi, N., & Harris, S. K. (2023). High-Potency Cannabis Use in Adolescence. *The Journal of Pediatrics*, *252*, 191-197.e1. https://doi.org/10.1016/J.JPEDS.2022.07.034

Verdoux, H., & Van Os, J. (2002). Psychotic symptoms in non-clinical populations and the continuum of psychosis. *Schizophrenia Research*, *54*(1–2), 59–65. https://doi.org/10.1016/S0920-9964(01)00352-8

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain*, *136*(6), 1692–1707. https://doi.org/10.1093/BRAIN/AWT094

Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., Hua, K., Zhang, J., Jiang, H., Dubey, P., Blitz, A., van Zijl, P., & Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, *36*(3), 630–644. https://doi.org/10.1016/J.NEUROIMAGE.2007.02.049

Wang, N., Zhang, J., Cofer, G., Qi, Y., Anderson, R. J., White, L. E., & Allan Johnson, G. (2019). Neurite orientation dispersion and density imaging of mouse brain microstructure. *Brain Structure & Function*, *224*(5), 1797–1813. https://doi.org/10.1007/S00429-019-01877-X

Weber, R. A., Hui, E. S., Jensen, J. H., Nie, X., Falangola, M. F., Helpern, J. A., & Adkins, D. L. (2015). Diffusional kurtosis and diffusion tensor imaging reveal different time-sensitive stroke-induced microstructural changes. *Stroke*, *46*(2), 545–550. https://doi.org/10.1161/STROKEAHA.114.006782

Wiedmann, M., Kuitunen-Paul, S., Basedow, L. A., Wolff, M., DiDonato, N., Franzen, J., Wagner, W., Roessner, V., & Golub, Y. (2022). DNA methylation changes associated with cannabis use and verbal learning performance in adolescents: an exploratory whole genome methylation study. *Translational Psychiatry 2022 12:1*, *12*(1), 1–10. https://doi.org/10.1038/s41398-022-02025-6

Wilke, M., Schmithorst, V. J., & Holland, S. K. (2003). Normative pediatric brain data for spatial normalization and segmentation differs from standard adult data. *Magnetic Resonance in Medicine*, *50*(4), 749–757. https://doi.org/10.1002/MRM.10606;WGROUP:STRING:PUBLICATION

Wittchen, H. U., Fröhlich, C., Behrendt, S., Günther, A., Rehm, J., Zimmermann, P., Lieb, R., & Perkonigg, A. (2007). Cannabis use and cannabis use disorders and their relationship to mental disorders: A 10-year prospective-longitudinal community study in adolescents. *Drug and Alcohol Dependence*, *88*(SUPPL.1), S60–S70. https://doi.org/10.1016/J.DRUGALCDEP.2006.12.013

Yeatman, J. D., Dougherty, R. F., Myall, N. J., Wandell, B. A., & Feldman, H. M. (2012). Tract Profiles of White Matter Properties: Automating Fiber-Tract Quantification. *PLOS ONE*, *7*(11), e49790. https://doi.org/10.1371/JOURNAL.PONE.0049790

Yendiki, A., Panneck, P., Srinivasan, P., Stevens, A., Zöllei, L., Augustinack, J., Wang, R., Salat, D., Ehrlich, S., Behrens, T., Jbabdi, S., Gollub, R., Fischl, B., Hilgetag, C., & Tittgemeyer, M. (2011). *Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy*. https://doi.org/10.3389/fninf.2011.00023

Yung, N. C. L., Wong, C. S. M., Chan, J. K. N., Chen, E. Y. H., & Chang, W. C. (2021). Excess Mortality and Life-Years Lost in People With Schizophrenia and Other Non-affective Psychoses: An 11-Year Population-Based Cohort Study. *Schizophrenia Bulletin*, *47*(2), 474–484. https://doi.org/10.1093/SCHBUL/SBAA137

Zalesky, A., Solowij, N., Yücel, M., Lubman, D. I., Takagi, M., Harding, I. H., Lorenzetti, V., Wang, R., Searle, K., Pantelis, C., & Seal, M. (2012). Effect of long-term cannabis use on axonal fibre connectivity. *Brain*, *135*(7), 2245–2255. https://doi.org/10.1093/brain/aws136

Zhang, F., Cho, K. I. K., Tang, Y., Zhang, T., Kelly, S., Biase, M. Di, Xu, L., Li, H., Matcheri, K., Whitfield-Gabrieli, S., Niznikiewicz, M., Stone, W. S., Wang, J., Shenton, M. E., & Pasternak, O. (2021). MK-Curve improves sensitivity to identify white matter alterations in clinical high risk for psychosis. *NeuroImage*, *226*, 117564. https://doi.org/10.1016/J.NEUROIMAGE.2020.117564

Zhang, F., Wu, Y., Norton, I., Rigolo, L., Rathi, Y., Makris, N., & O'Donnell, L. J. (2018). An anatomically curated fiber clustering white matter atlas for consistent white matter tract parcellation across the lifespan. *NeuroImage*, *179*, 429–447. https://doi.org/10.1016/J.NEUROIMAGE.2018.06.027

Zhang, H., Schneider, T., Wheeler-Kingshott, C. A., & Alexander, D. C. (2012). NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain. *NeuroImage*, *61*(4), 1000–1016. https://doi.org/10.1016/J.NEUROIMAGE.2012.03.072

Zhang, H., Wang, Z., Chan, K. H., Shea, Y. F., Lee, C. Y., Chiu, P. K. C., Cao, P., & Mak, H. K. F. (2023). The use of Diffusion Kurtosis Imaging for the Differential Diagnosis of Alzheimer's Disease Spectrum. *Brain Sciences*, *13*(4). https://doi.org/10.3390/brainsci13040595

Zhang, S., & Arfanakis, K. (2018). Evaluation of standardized and study-specific diffusion tensor imaging templates of the adult human brain: Template characteristics, spatial normalization accuracy, and detection of small inter-group FA differences. *NeuroImage*, *172*, 40–50. https://doi.org/10.1016/J.NEUROIMAGE.2018.01.046

Zhuo, C., Tian, H., Song, X., Jiang, D., Chen, G., Cai, Z., Ping, J., Cheng, L., Zhou, C., & Chen, C. (2023). Microglia and cognitive impairment in schizophrenia: translating scientific progress into novel therapeutic interventions. *Schizophrenia*, *9*(1). https://doi.org/10.1038/S41537-023-00370-Z,