PSYCHOTIC-LIKE EXPERIENCES IN CHILDREN AND ADOLESCENTS: CLINICAL AND NEUROBIOLOGICAL INSIGHTS INTO RISK FOR PSYCHOTIC DISORDERS

by

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Abstract

This thesis examines psychotic-like experiences (PLEs) in children and adolescents, focusing on its assessment and neurobiological underpinnings to improve psychosis risk identification. The Chapter 2 systematic review and meta-analysis revealed that 17.3% of children and adolescents experience PLEs and are at a greater risk of developing psychosis in adulthood (OR = 3.80). Interview-based assessments identified individuals at greater risk than self-reports. The Chapter 4 population-based neuroimaging study using proton magnetic resonance spectroscopy found reduced myoinositol in the left hippocampus of adolescents with PLEs, but not in the prefrontal cortex nor in cannabis users. While no significant association was found between PLEs and cannabis use status, past-month cannabis exposure was positively associated with PLE severity and externalizing psychopathology. These findings highlight a role of hippocampal neuroinflammatory alterations in subclinical psychosis risk.

Keywords. Adolescent cannabis use, extended psychosis spectrum, population-based, proton magnetic resonance spectroscopy, psychosis, psychotic-like experiences, risk identification, schizophrenia, subclinical psychotic symptoms, youth mental health

List of Abbreviations & Symbols Used

APSS	Adolescent Psychotic-Like Symptom Screener
ASWS	Adolescent Sleep Wake Scale
β	Beta, regression coefficient
CB1R	Cannabinoid receptor Type 1
CB2R	Cannabinoid receptor Type 2
CCPRT	Canadian Cannabis and Psychosis Research Team
CSF	Cerebrospinal fluid
CU(+/-)	Cannabis use status (user/non-user)
CUAD	Chemical Use/Abuse/Dependence Scale
CU1(+/-)	Cannabis users, past 1-month use (yes/no)
DALYs	Daily adjusted life-years
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECC	Eddy-current correction
FAS	Family Affluence Scale
FDR	False discovery rate
FEP	First episode psychosis
FWHM	Full width at half maximum
GM	Grey matter
HIP	Hippocampus
HRM	Halifax Regional Municipality
I^2	Proportion of variability explained by heterogeneity
LCModel	Linear Combination of Model Spectra
MRS	Magnetic resonance spectroscopy
NSHA	Nova Scotia Health Authority
PFC	Prefrontal cortex
PLEs	Psychotic-like experiences
PLE+/-	Positive for PLEs / negative for PLEs
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

REB	Research Ethics Board
ROBINS-E	Risk Of Bias In Non-Randomized Studies – of Exposure
SD	Standard deviation
SE	Standard error
SDQ	Strengths and Difficulties Questionnaire
SDQ-Em	SDQ - Emotional Difficulties subscale
SDQ-Ext	SDQ - Externalizing Difficulties subscale
SDQ-Int	SDQ - Internalizing Difficulties subscale
SNR	Signal-to-noise ratio
TE	Echo time
THC	Tetrahydrocannabinol
THCe	Exposure to THC (g)
TLFB	Timeline Follow Back
T1-w	T1-weighted
UHR	Ultra high-risk
VOI	Voxel of interest
WM	White matter
y	Years

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Chapter 1: Introduction

1.1. The Extended Psychosis Spectrum

Psychosis, a profound disturbance in perception and interpretation of reality, manifests through a spectrum of symptoms classified into positive, negative, and cognitive dimensions (Jeong et al., 2022; Carbon et al., 2014). Positive symptoms are a great detriment to patient well-being (Rabinowitz et al., 2013), which present as an excess or distortion of normal neuropsychological processes including hallucinations, delusions, and disorganized thinking (Heckers et al., 2016). Hallucinations are described as sensory experiences occurring in the absence of external stimuli (NeuRA, 2022), most commonly of auditory type (Dudley et al., 2018; Oorschot et al., 2012; Olfson et al., 2002). Delusions, on the other hand, are firmly held false beliefs that are out of character from an individual's background (e.g., educational, sociocultural, religious) and persist despite all evidence (Rituanno et al., 2022; Sims, 2007). The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., text rev.; *DSM–5-TR*; American Psychiatric Association, 2022) identifies common themes of delusions, including persecution, grandiosity, and those of somatic nature. Disorganized thinking is a third type of positive symptom, including tangential or incoherent associations that impair communication, often evident through speech patterns (Lieberman et al., 2018; DSM-5-TR; APA, 2022). While positive symptoms reflect an excess of normal processes, negative symptoms present as reduced emotional expression (e.g., blunted affect, alogia), motivation (e.g., avolition, asociality) and pleasure (e.g., anhedonia) (Blanchard & Cohen, 2006). Alternatively, cognitive symptoms present as deficits in up to 7 domains: working memory, attention, visual learning/memory, verbal learning/memory, problem solving, social cognition, and processing speed (Green et al., 2004). These symptoms can significantly disrupt daily life, making it challenging for individuals to maintain relationships, employment, and personal care (GBD 2019 Mental Disorders Collaborators, 2022; Harvey et al., 2012).

Psychotic disorders, including schizophrenia, schizoaffective disorder, schizophreniform disorder, delusional disorder, and brief psychotic disorder, are characterized by varying combinations of these symptoms and timeline of symptom

expression (DSM-5-TR; APA, 2022). The median lifetime prevalence of psychotic disorders in a recent meta-analysis was found to be 7.49 per 1000 (Moreno-Küstner et al., 2018), with schizophrenia, the most common psychotic disorder, suggested to represent between 28–50% of diagnoses (Chang et al., 2017; Perala et al., 2007; Jongsma et al., 2019). Not only is schizophrenia responsible for the greatest burden of disability among psychotic disorders (McGrath et al., 2004; Calabrese & Khalili, 2024), but among all mental health disorders (GBD 2019 Mental Disorders Collaborators 2022). Disability adjusted life-years (DALYs), the sum of years lived with the disability and years of life lost, is significant for schizophrenia, accounting for 191 of the 1566 per 100,000 DALYs attributable to mental health disorders (GBD 2019 Mental Disorders Collaborators 2022). The loss of opportunity and productivity experienced by both the patient and caregiver is considered to be an economic burden that is equal to, if not greater than, $20 billion in direct annual medical costs worldwide (Tajima-Pozo et al., 2015).

Historically, schizophrenia had been conceptualized as a distinct disease with specific pathophysiological mechanisms presumed to be conserved across patients (Carpenter et al., 2013; van Os et al., 2002). However, this traditional perspective was challenged by the substantial heterogeneity observed among patients. Variations in symptom types, genetic risk factors, and response to antipsychotics highlighted the limitations of viewing schizophrenia as a single, uniform entity (Carpenter et al., 2013). The focus on early identification of illness also raised the awareness of a psychosis prodrome, a state characterized to occur prior to onset of symptoms meeting criteria for diagnosis (Beiser et al., 1993; Carpenter et al., 2013). This state can be characterized by a variety of mood and functional problems, in addition to attenuated/subclinical psychotic symptoms (Yung 1996). Intervening during this prodromal period may delay the onset of a psychotic disorder in those on such a trajectory (Mei et al., 2021). However, ‘prodrome’ implies that disease-specific processes have already begun, whereas most people who report such symptoms do not develop a psychotic disorder (Fusar-Poli et al., 2016). Termed the “prevention paradox” (Rose et al., 1981; van Os et al., 2017), this concept was poorly equipped to distinguish individuals on a psychosis-prone trajectory and limits efficient intervention (van Os & Kapur, 2009).

The concept of the extended psychosis spectrum better navigates these limitations by recognizing a phenotypic subclinical extension of psychosis whereby individuals are not all presumed to be on a trajectory towards clinical status (van Os et al., 2002; van Os, 2009; van Os et al., 2012; van Os et al., 2017; Staines et al., 2022). Subclinical status is instead believed to reflect some degree of psychosis vulnerability capable of being modified by psychotogenic risk factors. These genetic, epigenetic, and environmental factors accumulate and interact to increase the risk for psychosis, and identification of individuals with subclinical symptoms believed to be on a psychosis-prone trajectory can be done through the assessment of these risk factors (van Os et al., 2017; Staines et al., 2022).

Risk status in the extended psychosis spectrum can be further defined based on the individual's age, presence of genetic risk factors, and the frequency, distress, and duration of subclinical psychotic symptoms. The highest degree of subclinical risk is often termed the ultra-high-risk (UHR) state, where subclinical psychotic symptoms meet specific criteria for distress, frequency, and duration, and are experienced during the developmental window where the onset of psychosis is most likely (ages 15-25) (Nelson et al., 2011). Identified via interview, these criteria allow for a further subclassification of risk status based on the presence of attenuated positive symptoms (APS: multiple weekly subthreshold positive symptoms for between 1 week and 5 years), brief limited intermittent psychotic symptoms (BLIPS: transient episode of threshold psychotic symptoms lasting less than a week), and symptoms of genetic risk and deterioration (GRD: genetic high-risk with significant functional deterioration in the past year) (McGlashan et al., 2014; Nelson et al., 2011; Fusar-Poli et al., 2016; Andreou et al., 2023). UHR status exists in 2% of the population, with about one quarter to one third ultimately developing a psychotic disorder (Simon et al., 2011; Cannon et al., 2011; Man-Iam-Fook et al., 2017; Yung et al., 2007; Salazar de Pablo et al., 2021; Bang et al., 2019). Clinical high-risk (CHR) is a term that is often used interchangeably with UHR but may alternatively specify only those with at least subthreshold psychotic symptoms (i.e., excluding GRD) (Kiburi et al., 2021; Hasmi et al., 2021; Woods et al., 2014; Stowkowy & Addington, 2013), or specify any UHR category including a fourth for cognitive disturbances (Fusar-Poli et al., 2013; Schultze-Lutter et al., 2014; Andreou et al., 2023).

Cognitive-behavioural therapy and other psychosocial interventions in UHR/CHR has demonstrated the ability to reduce symptoms and delay psychosis onset, thereby reducing the burden on both the individual and healthcare services (Mei et al., 2021).

At a lower level of risk for psychosis development are those individuals experiencing psychotic-like experiences (PLEs). There is much less consensus on the criteria to define PLEs, with 41 different criteria having been used across studies (Lee et al., 2016). The age at which PLEs are experienced appears to influence psychosis risk, as only children and adolescents with PLEs are at a significantly increased risk for psychosis compared to PLEs experienced in adulthood (Kaymaz et al., 2012), however, children and adolescents experience PLEs at a higher prevalence (8–17%) than adults (5-6%), (van Os, 2009; Kelleher et al., 2012; Maijer et al., 2018; Solmi et al., 2022). Further discussion of PLEs and psychosis risk can be found in section 1.2 and in Chapter 2.

One obstacle that has arisen in psychosis spectrum research involves the use of terminology to describe subclinical manifestations of psychosis. Terms such as "psychotic-like experiences" (PLEs), "subclinical psychotic symptoms," and "prodromal symptoms" are often used interchangeably (Kiburi et al., 2021; Lee et al., 2016), despite representing overlapping but distinct concepts. For instance, PLEs are more widespread and generally less clinically severe, often measured using tools like the Youth Self Report (YSR) or the Adolescent Psychotic-Like Symptom Screener (APSS) (Lee et al., 2016; Remberk et al., 2017). In contrast, "subclinical psychotic symptoms" often encompass more clinically significant manifestations identified in UHR and CHR statuses. The term “psychotic experiences” is a fairly liberal expression, often referring to any form of subclinical psychotic manifestation (Kiburi et al., 2021). However, application of these terms in various contexts has made it especially difficult to integrate findings across studies in meta-analyses (Kiburi et al., 2021; Healy et al., 2019; Matheson 2023; Lee et al., 2016). This heterogeneity reflects broader challenges in psychosis research and clinical practice, complicating the development of standardized assessment and intervention strategies. For the purposes of this thesis, PLEs have been defined as subclinical psychotic experiences that do not fit the criteria for UHR/CHR status nor cause psychiatric help-seeking behaviour.

1.2. Psychotic-Like Experiences (PLEs) in Children and Adolescents

Interest in child and adolescent PLEs stems from their widespread prevalence and association with poorer mental health and particularly psychotic outcomes (Staines et al., 2022; Healy et al., 2019; Kaymaz et al., 2012). As PLEs are at one of the earliest points in the psychosis continuum, studying child and adolescent PLEs longitudinally has the potential to reveal early pathophysiological mechanisms in the psychosis spectrum, highlighting individuals with varying degrees of psychosis proneness who could benefit most from intervention strategies. Understanding how risk factors interact in this population can also provide novel targets for intervention in the disordered population. These approaches align with the goal of identifying and altering psychosis-prone trajectories to prevent the onset of clinical psychosis and improve long-term outcomes.

1.2.1. Epidemiological and Clinical Review

The prevalence of PLEs in children and adolescents varies widely across studies, reflecting differences in definitions, assessment tools, and sample characteristics. Meta-analyses report a median prevalence of 8-17% in the child and adolescent population (Kelleher et al., 2012a; Maijer et al., 2018; Healy et al., 2019), but individual studies show a much broader range. For instance, Dennissoff and colleagues (2022) reported a prevalence of 30.5% for PLEs in adolescents aged 15-16 years in a northern Finland birth cohort (Denissoff et al., 2022). Further, a self-report assessment of PLEs including distress among 9–10-year-olds identified a prevalence of 43% (Karcher et al., 2018). On the contrary, a YSR-based assessment of 11–18-year-olds only found that 5% endorsed a hallucinatory experience (Dhossche et al., 2002).

Longitudinal studies indicate that PLEs in childhood and adolescence can predict the development of clinical psychosis (Healy et al., 2019; Kaymaz et al., 2012; Poulton et al., 2000; Dominguez et al., 2011; Welham et al., 2009; Bechtold et al., 2016; Zammit et al., 2013; Cedorlof et al., 2017; Denissoff et al., 2022). Adolescents with PLEs have a significantly higher risk of developing schizophrenia-spectrum disorders in adulthood, with the most recently meta-analytical odds ratio (OR) of 3.96 and approximately 5% of adolescents who experienced PLEs developing a psychotic disorder (Healy et al., 2019). To a lesser degree, non-psychotic psychiatric disorders have also been implicated as an

outcome of adolescent PLEs (Dhossche et al., 2002; Cedorlof et al., 2017), though only substance use disorders (SUDs) were identified in the previously mentioned meta-analysis (Healy et al., 2019).

The persistence of PLEs, and the outcomes of persistent PLEs, has been an area of study. Persistent PLEs are reported in 9–46% of adolescents (Dominguez et al., 2011; Mackie et al., 2011; Hafeez et al., 2020; Staines et al., 2023), dependant on the follow-up period and study design. A pooled prevalence of PLE persistence was calculated to be 31% across studies (Staines et al., 2023). Furthermore, Mackie and colleagues (2011) used growth mixture modelling to identify three trajectories of PLEs following four 6-month assessments of adolescents (mean age at baseline: 14.7y): increasing (7%), persistent (9%), and low/stable (84%) PLE trajectories. The increasing trajectory in this study was found to be associated with cannabis, cocaine, and other drug use at subsequent timepoints, and those on the persistent trajectory scored consistently high on depression and anxiety ratings (Mackie et al., 2011). Longitudinal studies have shown that persistent PLEs are also a strong predictor of transition to psychosis, with higher rates of conversion observed in individuals with persisting symptoms (Dominguez et al., 2011; Kaymaz et al., 2012). In addition to persistence, high levels of distress associated with PLEs can affect various outcomes. For example, Kelleher et al. (2012) found that adolescents who reported distressing PLEs were more likely to seek help and receive clinical intervention, a finding replicated in a recent study by Karcher and colleagues (2022). Furthermore, the incorporation of distress into PLE assessments can improve its predictive value for psychosis in adulthood (Sullivan et al., 2020), suggesting that distress is a factor in the progression from subclinical to clinical psychosis (Kelleher et al., 2012).

PLEs can also impact social, academic, and emotional functioning. Adolescents with PLEs often experience difficulties in school, impaired social relationships, and increased rates of anxiety and depression (Armando et al., 2010; Yung et al., 2009; Knight et al., 2020; Calkins et al., 2017; Yamasaki et al., 2018). These functional impairments could potentially create a feedback loop, where the stress and challenges associated with PLEs exacerbate the symptoms and vice versa, increasing the likelihood of persistent and distressing PLEs.

1.2.2. Risk Factors

The development and persistence of PLEs are thought to be influenced by a complex interplay of genetic, neurobiological, and environmental factors. Genetic predisposition plays a significant role, with a family history of psychotic disorders being a strong risk factor for PLEs. Twin studies have shown that heritability estimates for PLEs range from 9% to 59% (Zavos et al., 2014; Taylor et al., 2022). Exposure to childhood adversity, including physical and emotional abuse, neglect, and bullying, has also been consistently associated with an increased risk of PLEs (Abajobir et al., 2017; Boyda et al., 2018; Mackie et al., 2011; Catone et al., 2017; Strauss et al., 2018; Fisher et al., 2013a; Kelleher et al., 2013). For instance, Kelleher et al. (2013) found that children who experienced trauma were three times more likely to report PLEs compared to those who did not. Urban living is another significant risk factor, with higher rates of PLEs observed in individuals residing in urban areas compared to rural settings (Saxena et al., 2022; Bouter et al., 2023; Beyer et al., 2024; Linscott et al., 2013; van Os, 2009). This urban-rural difference may be due to increased environmental stressors, social isolation, and reduced social cohesion in urban areas (Staines et al., 2022). Substance use is another well-documented risk factor; substance-using youth are about twice as likely to report PLEs than their non-using peers, with individual relationships existing for use of cannabis, alcohol, tobacco, amphetamines, and cocaine (Matheson et al., 2023).

The interaction between genetic vulnerability and environmental stressors is thought to contribute to the onset and persistence of PLEs. The stress-vulnerability model posits that individuals with a genetic predisposition for psychosis are more susceptible to environmental stressors, which can trigger or exacerbate PLEs (Wied & Jansen, 2002; Park et al., 2022; Mayo et al., 2017). This model underscores the importance of considering both genetic and environmental factors in understanding and addressing PLEs in children and adolescents.

1.2.3. Assessment Tools

Assessing PLEs in children and adolescents involves a variety of tools, each with unique methodologies and criteria. Some commonly used tools include the Adolescent Psychotic-Like Symptom Screener (APSS), Community Assessment of Psychic Experiences (CAPE), Youth Self Report (YSR), Psychosis-Like Symptoms Interview

(PLIKSi), the Prodromal Questionnaire (PROD-screen), and the Symptom Checklist-90-Revised (SCL-90-R). While these assessments aim to identify similar phenomena related to subclinical psychotic experiences, they differ in their focus, structure, and criteria for inclusion. This results in significant heterogeneity between studies that have been highlighted in previous meta-analyses (Kaymaz et al., 2012; Lee et al., 2016; Kaymaz et al., 2012; Staines et al., 2023). Below are descriptors and foci of the commonly used assessment scales, highlighting the differences on PLE assessment methodology.

Adolescent Psychotic-Like Symptom Screener (APSS). The APSS is designed to identify psychotic-like symptoms in adolescents through self-report (Kelleher et al., 2011a). It includes items that assess the frequency and distress associated with hallucinations, delusions, and other unusual experiences. For example, the question "Have you ever heard voices or sounds that no one else can hear?" can be rated as "no" (0 points), "maybe" (0.5 points), or "yes, definitely" (1 point), with a score of 2+ from 7 items designating positive for PLE risk status. The APSS is particularly useful for large-scale epidemiological studies due to its brevity and ease of administration. However, its reliance on self-report may lead to overreporting or underreporting of symptoms, depending on the individual's insight and willingness to disclose experiences (Kelleher et al., 2011b).

Community Assessment of Psychic Experiences (CAPE). The CAPE is another self-report tool that assesses the frequency and distress of psychotic-like experiences in the general population (Stefanis et al., 2002; Mossaheb et al., 2012). It includes 42 items representing three subscales: positive symptoms, negative symptoms, and depressive symptoms (Stefanis et al., 2002). The presence of these symptoms is reported using responses of "no" (1 point), "sometimes" (2 points), "often" (3 points), and "nearly always" (4 points). The CAPE is comprehensive in capturing a wide range of psychotic and mood-related symptoms, making it suitable for in-depth research on the content of psychotic experiences. Although designed to assess UHR status, the CAPE can also be used for assessing PLEs (Konings et al., 2012; Schubart et al., 2011; Hides 2009; Konings et al., 2008). However, a lack of validation for assessing PLEs leave studies including various items with differing criteria for PLE risk status. Additionally, its length

can be a drawback in time-limited settings, and like the APSS, it depends on the participant's ability to accurately report their experiences.

Prodromal Questionnaire (PROD-screen). The PROD-screen is a self-report tool sharing similarities with the APSS and YSR. While it has been validated for specific use in the extended psychosis spectrum (Heinimaa et al., 2003), a various inclusion of items and score cut-offs have allowed for diverse identifications of at-risk individuals (Granö et al., 2016; Heinimaa et al., 2003; Denissoff et al., 2022; Ellman et al., 2020).

Psychosis-Like Symptoms Interview (PLIKSi). The PLIKSi is a structured interview designed to assess psychotic-like symptoms in children and adolescents (Zammit et al., 2013). It includes 11 questions about various hallucinations and delusions experienced since age 12 and allows for the incorporation of clinical insight to permit a thorough assessment of PLEs. Clinicians rate each experience as “not present”, “suspected”, or “definite”, with any definite experience indicating PLE risk status. The PLIKSi is advantageous due to its structured format and the ability to probe for additional information, but it requires trained interviewers and can be time-consuming to administer.

Symptom Checklist-90-Revised (SCL-90-R). The SCL-90-R is a widely used self-report inventory designed to screen for a broad range of psychological problems and symptoms of psychopathology (Derogatis, 1977). It includes items that assess various dimensions, including paranoid ideation and psychoticism, which can capture psychotic-like experiences. The SCL-90-R is comprehensive and easy to administer, making it suitable for both clinical and research settings. However, a lack of validation in the extended psychosis spectrum has allowed for dissimilar criteria for PLE status in the literature (Dominguez et al., 2011; Muller et al., 2010; Bakhshaie et al., 2011). And like other self-report tools, it relies on the individual's ability and willingness to accurately report their symptoms, which can introduce bias.

Youth Self Report (YSR). The YSR is part of the Achenbach System of Empirically Based Assessment (ASEBA) and is a widely used tool for assessing a broad range of emotional and behavioral problems in children and adolescents (Achenbach & Rescorla, 2001). Many versions exist with variously included yes/no items of auditory

hallucinations, visual hallucinations, thought problems, paranoia, and unusual behaviours. With only one positive report sufficient to indicate PLE status, these various versions provide heterogenous contributions to PLE research.

Of note, a significant challenge in the assessment of PLEs is the inconsistent criteria across these tools to identify and define PLE presence. For example, studies using the YSR may refer to thought problems as indicative of PLEs (Lacasa et al., 2015; de Jong et al., 2022) or may only include hallucinations (Dhossche et al., 2002; Wehlam et al., 2009; Oorschot et al., 2012). Alternatively, studies using the APSS may focus on positive symptoms (Bourque et al., 2017; Dolphin et al., 2015; Kelleher et al., 2011b), while those using the CAPE focus on both positive and negative symptoms (Schubart et al., 2011; Pignon et al., 2022; Brañas et al., 2016). Furthermore, while one self-report may be sufficient to confidently identify PLE status (Dhossche et al., 2002; Welham et al., 2009; de Jong et al., 2022; Zammit et al., 2013), other instances require a greater endorsement of experiences (Denissoff et al., 2022; Bourque et al., 2017; Dolphin et al., 2015; Kelleher et al., 2011). The heterogeneity in terminology and assessment criteria underscores the need for standardized and comprehensive tools that can accurately capture the spectrum of subclinical psychotic experiences. Such standardization could better facilitate cross-study comparisons and meta-analyses, ultimately improving our understanding of PLEs and their role in psychosis risk.

1.3. Neurobiology of Psychosis Risk

The neurobiology of psychosis risk encompasses an interplay of genetic, biochemical, and environmental factors. Understanding the underlying mechanisms that contribute to the onset and progression of psychotic disorders is important for identifying markers of psychotic risk status and targets for intervention. This thesis will focus on three key areas of brain research in this area, including the glutamate hypothesis, the dopamine hypothesis, and the impact of neuroinflammation as it relates to psychosis. Of note to begin this discussion, there is a notable lack of neurobiological assessments in participants reporting PLEs.

1.3.1. Glutamate Hypothesis

The glutamate hypothesis suggests that abnormalities in glutamatergic neurotransmission play a significant role in the pathophysiology of psychotic disorders. This hypothesis centres around the hypofunctioning of the N-methyl-d-aspartate (NMDA) glutamate receptor in the prefrontal cortex (PFC), leading to increased prefrontal glutamate release and disruption of the excitatory/inhibitory (E/I) balance (Uno & Coyle, 2019; Goff & Coyle, 2001; Merrit et al., 2013; Lieberman et al., 2018). The role of NDMA receptor dysfunction originates from research of ketamine and other NMDA receptor antagonists, which can induce positive, cognitive, and negative symptoms resembling psychosis in healthy volunteers (Krystal et al., 1994; Vollenweider et al., 1997; Holcomb 2001; Xu et al., 2015; Abdalla et al., 2018) and exacerbate symptoms in schizophrenia patients (Lahti et al., 1995; Lahti et al., 2001; Moghaddam et al., 2012). NMDA receptor dysfunction not only allows for the extracellular glutamate to remain in synapses for longer, but its high concentration on parvalbumin-expressing (PV+) interneurons, neurons responsible for the GABAergic modulation of excitability of pyramidal neurons, permit prefrontal disinhibition and an overall net increase in excitability (Schobel et al., 2013; Uno & Condyle, 2019). This creates a positive feedback loop where prefrontal hyperactivity results in the further production and release of glutamate that is unable to initiate NMDA receptor-mediated compensatory feedback, further disrupting E/I balance and exacerbating excitotoxicity. This increase in prefrontal excitatory output due to NMDA receptor dysfunction is also associated with glutamatergic abnormalities in other brain regions, including the thalamus, basal ganglia, and hippocampus (Lieberman et al., 2018; Schobel et al., 2013; Gruter et al., 2015; Uno & Condyle, 2019; Merrit et al., 2013).

In high-risk individuals for psychosis, the findings reported in in *vivo* brain glutamate studies are mixed. A recent meta-analysis reported significant elevations in Glx (glutamate + glutamine) concentrations in the medial PFC (mPFC), with a trend towards significance in the basal ganglia (Romeo et al., 2020), suggesting a hyperglutamatergic state that might precede the onset of psychosis. However, not all individual studies find significant differences in Glx concentrations between UHR individuals and healthy controls in the mPFC (Yoo et al., 2009; Purdon et al., 2008; Keshavan et al., 1997;

Menchivok et al., 2016; Natsubori et al., 2014; Egerton et al., 2014; Uhl et al., 2011; Buyn et al., 2009). This meta-analysis also found that excluding those with familial risk erased the significant finding in the mPFC (Romeo et al., 2020), which may suggest diverse mechanisms of glutamatergic psychosis vulnerability.

Mixed findings are also reported in FEP patients. A recent meta-analysis identified increased glutamatergic signalling in the basal ganglia, but no changes in prefrontal regions (Nakahara et al., 2021). However, this meta-analysis did find decreased GABAergic function in the midcingulate cortex, still implicating disrupted E/I balance in regions within the PFC (Nakahara et al., 2021). On the study level, mixed reports exist for the anterior cingulate cortex (ACC): some suggest an increase in glutamatergic transmission (Theberge et al., 2002; Theberge et al., 2007; Egerton et al., 2012; Smensy et al., 2015) or no change (Blasi et al., 2004; Uhl et al., 2011; Tibbo et al., 2013; Natsubori et al., 2014). This may reflect heterogeneity in study design, particularly in regard to the precise location analyzed within the ACC (Dempster et al., 2015; Egerton et al., 2012).Interestingly, glutamate transmission in the ACC has been reported to correlate with cognitive symptoms (Demptster et al., 2015), negative symptoms, global functioning, and non-remission (Egerton et al., 2012), which may relate to glutamate function in the context of metabolic changes (Tibbo et al., 2013).

In chronic schizophrenia, the glutamatergic signal appears to shift from an increased glutamate state to a normal or decreased state over time, particularly in the mPFC and hippocampus (Natsubori et al., 2014; Ohrmann et al., 2005; Marsman et al., 2011). This may reflect neuroadaptive changes or neurodegenerative processes influenced by prolonged illness and chronic antipsychotic treatment. Natsubori et al. (2014) found reduced frontal Glx levels in patients with chronic schizophrenia, which were associated with cognitive deficits and negative symptoms such as anhedonia and social withdrawal. This may also reflect changes in energy metabolism that has reached a more chronic state, because while glutamate concentrations are significantly lower and likely driving decreased Glx findings, glutamine concentrations are elevated, suggesting abnormal glutamate cycling (Marsman et al., 2011; Petroff, 2007).

1.3.2. Dopamine Hypothesis

The dopamine hypothesis posits that hyperactivity of dopaminergic transmission, particularly in the striatum, is a core feature of schizophrenia. This hypothesis suggests that increased dopamine synthesis and release contribute to the positive symptoms of schizophrenia, such as hallucinations and delusions (Howes et al., 2022). Meta-analyses have consistently found elevated markers of dopamine functioning in the striatum of patients with schizophrenia (Brugger et al., 2020; Howes et al., 2012; McCutcheon et al., 2018). This arises from hyperactivity in the PFC which regulates mesostriatal dopamine neurons (Howes et al., 2022). Specifically, the increased excitatory output from the PFC as a result of perturbed glutamate functioning allows for a disinhibition of dopaminergic neurons in the striatum, a model having been demonstrated in both animals (Pycock et al., 1980a; Pycock et al., 1980b) and in humans (Quiroz et al., 2016; Androver et al., 2020). This increase in dopamine synthesis capacity has also been shown to correlate with the severity of positive psychotic symptoms (Jauhar et al., 2017; Jauhar et al., 2019). Further highlighting the functional impact of this hyperdopaminergic state, all currently licenced antipsychotics have a role in blocking or acting as partial agonists on the various dopamine receptors (Kaar et al., 2020; Howes et al., 2022).

In UHR individuals, neuroimaging studies report alterations in dopamine synthesis capacity. PET scans show increased striatal dopamine synthesis, which may subsequently predispose individuals to psychosis development (Howes et al., 2011a; Howes et al., 2009; Rogdaki et al., 2021; Mizrahi et al., 2012; McCutcheon et al., 2021; Howes et al., 2020). The largest increase in dopamine synthesis is observed among striatal subregions that are the most innervated by frontal projections, correlating with symptom severity in this UHR population (Howes et al., 2020; Howes et al., 2012). Indeed, this is complimented with finding of abnormal prefrontal activation during cognitive tasks associated with presynaptic dopaminergic capacity (Fusar-Poli et al., 2011). These hyperdopaminergic states early in the psychosis continuum suggest a pre-psychotic neurochemical environment that increases the risk of transitioning to clinical psychosis.

In FEP patients, neuroimaging studies show very similar findings of relatively equal or increased dopamine changes to the UHR state (Howes et al., 2022; Meyer-

Lindenberg et al., 2005; Kegeles et al., 2010). Like the UHR state, markedly increased dopamine synthesis and release in the striatum has been found to correlates with the severity of positive symptoms (Kegeles et al., 2010). Additionally, reduced D1 receptor availability in the prefrontal cortex has been implicated in the cognitive deficits and negative symptoms observed in FEP (Abi-Dargham et al., 2002). fMRI studies in FEP patients show hyperactivation in the striatum and hypoactivation in the prefrontal cortex during executive function tasks, which correlate with striatal dopamine activity (Minzenberg et al., 2009). Structural MRI studies also demonstrate progressive gray matter loss in the prefrontal and temporal regions, which correlates with the duration and severity of psychosis (Borgwardt et al., 2008).

In chronic schizophrenia, neuroimaging findings reflect both persistent and adaptive changes in the dopaminergic system. PET findings suggest reduced dopamine receptor availability and decreased dopamine synthesis capacity in chronic patients compared to FEP patients, indicating neuroadaptive changes over the course of the illness (Howes et al., 2012). Specifically, Howes et al. (2012) found a reduction in D2/3 receptor availability and lower dopamine synthesis capacity in the associative striatum, suggesting a downregulation of dopamine synthesis as a response to chronic dopaminergic overstimulation. Structural MRI studies show widespread reductions in cortical thickness and gray matter volume, particularly in the prefrontal cortex (Vita et al., 2012), which correlate with striatal dopamine function (D'Ambrosio et al., 2021). fMRI research also reveals altered connectivity patterns within the default mode network and executive control network, highlighting persistent dysregulation in brain regions associated with dopaminergic activity (Anticevic et al., 2015).

1.3.3. Role of the Hippocampus

In addition to the PFC and striatal regions mentioned previously in this discussion the hippocampus has also been implicated in psychosis development. Research has connected glutamate dysfunction with significantly altered basal metabolism in this region, leading to atrophy and structural and functional changes (Lieberman et al., 2018). In a longitudinal analysis of UHR subjects, Lieberman and colleagues (2018) found no difference in hippocampal volumes at baseline, but conversion to clinical psychosis was associated with a lower baseline hippocampal volume, particularly in the CA1 and

subiculum subfields. This volume effect was most prominent in the anterior left hippocampus (Lieberman et al., 2018). Also assessing local blood flow as a measure of basal metabolism, they found that an increase in blood flow in the CA1 region preceded the structural alterations at the following visit, suggesting a hypermetabolic state as responsible (Lieberman et al., 2018).

Exploring sources for this hypermetabolism, authors followed this study with a post-mortem analysis of gene expression of patients with schizophrenia and found decreased activity of the enzyme glutamate dehydrogenase 1 (GLUD1), responsible for the degradation of glutamate, in the CA1 region, but not in a nearby region nor in controls (Lieberman et al., 2018). Examining whether a hyperglutamatergic state may be responsible for affected CA1 metabolism, they then followed this with a study in mice using fMRI to measure blood flow and an implanted glutamate sensor. Administration of ketamine was able to produce the same pattern of CA1-biased increased blood flow and could be prevented with pretreatment of a metabotropic glutamate receptor agonist that prevents glutamate release, directly implicating extracellular glutamate in this hypermetabolic state (Lieberman et al., 2018). Furthermore, they found that repeated surges of ketamine over time to cause a dose-dependent increase in basal metabolism, followed by a decrease in volume, again, most strongly biased to the CA1 subregion (Lieberman et al., 2018). This mechanism was also found to correlate with the loss of detectable PV+ interneurons, suggesting that dysfunction in these interneurons and the resulting hyperexcitability may be responsible for this increase in basal hippocampal metabolism (Lieberman et al., 2018).

This elevated hippocampal extracellular glutamate, particularly in the CA1 subregion, is thought to lead to a dysfunction in PV+ interneurons, allowing for regional increases in basal metabolism, which mediates hippocampal volume loss and subsequent functional deficit. The authors propose that persistence of this dysregulated hippocampal glutamate may also influence the PFC (Lieberman et al., 2018), responsible for the accelerated loss of prefrontal grey matter (Brugger et al., 2017; Schnack et al., 2016; Haijma et al., 2013; Olabi et al., 2011; Brans et al., 2008; Dietsche et al., 2017), lower density of frontal synapses (Berdenis et al., 2020), reduced dendritic branching (Selemon et al., 1999), and reduced gyrification in the ACC of patients with schizophrenia

(Zakharova et al., 2021; Yucel et al., 2002). What is unknown, however, is the source of this dysregulated glutamate in the hippocampus.

1.3.4. Role of Neuroinflammation

Neuroinflammation is increasingly recognized as a potential contributing factor in the pathophysiology of psychotic disorders, interfacing at critical points of these aforementioned processes (de Bartolomeis et al., 2022). Astrocytes, a glial cell type in the CNS involved in pro-inflammatory cytokine release and glutamate metabolism, show signs of dysfunction in schizophrenia (Tarasov et al., 2020; Lieberman et al., 2018). For example, patients with schizophrenia express reduced hippocampal GLUD1 concentrations, an enzyme highly concentrated on astrocytes (Lieberman et al., 2018). Astrocytes have been shown to control the activity of NMDA receptors, suggesting its dysregulation in psychotic disorders may arise from inflammatory processes (Tarasov et al., 2020).

Microglia, the resident immune cells of the CNS responsible for primary immune defence, become activated in response to brain inflammation and play a role in synaptic pruning (Paolicelli et al., 2011). Studies have found that activated microglia can excessively prune synapses in the DLPFC and ACC, potentially leading to the observed E/I imbalance and contributing to cognitive deficits (Müller et al., 2015; Beadle et al., 2012; Volk et al., 2015; Hensch et al., 2005). Microglial-mediated pruning involves the recruitment of major histocompatibility complex (MHC) proteins that tag synapses for glial cell engulfment (Sekar et al., 2016; Paolicelli et al., 2011), with animal studies having shown that manipulating the complement cascade and availability of its proteins cause aberrant glial-mediated pruning and behavioural deficits in the cortex of mice (Gaisler-Salomon et al., 2009; Hammelrath et al., 2016). Genetic variations in the complement protein C4A, involved in the tagging of these synapses, have also been implicated as a risk factor for psychotic disorders (Lewis et al., 2005; Howes & Shatalina, 2022; Lee et al., 2014). Furthermore, exposure to stress during adolescence has been implicated in glial-mediated pruning in the PFC and hippocampus, further implicating a role of neuroinflammatory processes in the pathophysiology of psychotic disorders (Hayashi et al., 1998; Leuddid et al., 2008; Bueno-Fernandez et al., 2021; Ota et al., 2014; Milior et al., 2016; Wohleb et al., 2018; Musazzi et al., 2015; Miller et al.,

2019). Moreover, interleukin-6 (IL-6), a pro-inflammatory cytokine involved in astrocytic and microglial activity, is found to be elevated in the CSF of patients with schizophrenia (Ganguli et al., 1994; Garver et al., 2003), FEP (Corsi-Zuelli et al., 2022), and a marker of conversion to psychosis among UHR subjects (Misiak et al., 2021; Zhang et al., 2022). Together, the activation of microglia and astrocytes, along with elevated levels of pro-inflammatory cytokines, indicate neuroinflammation processes being involved in the psychosis spectrum, and may be a significant source of the dysregulated hippocampal and prefrontal glutamate function that subsequently affects striatal dopamine function. Environmental exposures such as childhood stress, trauma, and early substance use are associated with chronic changes in neuroinflammatory balance (Danese et al., 2011; Chiang et al., 2022; Doggui et al., 2021; Okafor et al., 2020), which may mediate the increased risk for psychosis with these exposures. Another more recent area of research in this area is the role of cannabis, another environmental exposure that may be related to neuroinflammatory processes and psychosis risk.

1.4. Adolescent Cannabis Use

Cannabis use among adolescents has been steadily rising, with variations in prevalence rates across different regions and demographic groups (Shi et al., 2015). According to the Monitoring the Future study, approximately 29% of 12th graders and 18% of 10^{th} graders in the United States reported using cannabis in the past year, highlighting a significant proportion of the adolescent population engaged in cannabis use (Miech et al., 2023). The European School Survey Project on Alcohol and Other Drugs (ESPAD) reported that 16% of 15-16-year-old students in Europe had used cannabis at least once in their lifetime (Leal-Lopez et al., 2020). In Canada, the 2023 Canadian Cannabis Survey indicated youth aged 16-19 were the fastest growing group of cannabis users, with 43% having reported cannabis use within the past 12 months (Canadian Cannabis Survey, 2023).

The legal status of cannabis varies widely across different regions, influencing its availability and use among adolescents. In some areas, the legalization of cannabis for medical or recreational use has raised concerns about increased accessibility and the potential for higher rates of use among youths (Wang et al., 2017; Zvonarev et al., 2019).

For instance, the 43% of 16-19-year-olds consuming cannabis in Canada is up from 37% since its legalization in 2018 (Canadian Cannabis Survey, 2023). In US states where cannabis has been legalized, there has been an observed increase in cannabis use among adolescents, although this trend is not uniform across all states (Cerdá et al., 2017). Public health policies aimed at reducing adolescent cannabis use include age restrictions, public education campaigns, and the regulation of marketing and sales. Prevention and intervention programs, such as school-based education and family interventions, have shown to significantly reduce cannabis use among adolescents, thus mitigating its potential harms (Momanyi et al., 2024). With the rates of cannabis use in this population, it becomes important for us to have an understanding of the outcomes associated with its use in this developmental time period.

1.4.1. Neurobiological Relevance

Adolescent cannabis use is of particular concern due to its impact on the developing brain. The adolescent brain undergoes extensive remodeling, including synaptic pruning and myelination, which are essential for efficient neural communication (Patel et al., 2021). Cannabis interacts with the endocannabinoid system, which plays a key role in regulating these developmental processes (Onaivi et al., 2009; Sherif et al., 2016; Blest-Hopley et al., 2020a). The primary psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), binds to cannabinoid receptors in the brain and influences neurotransmitter release and neuronal connectivity (Volkow et al., 2016; Blest-Hopley et al., 2020a). THC exerts its effects in the CNS by binding to the cannabinoid receptors CB1R and CB2R (Di Marzo et al., 2015). CB1R is mainly located on neuronal cells in regions such as the PFC (Chiu et al., 2010) and hippocampus (Jappy et al., 2016; Bloomfield et al., 2016) and inhibit neurotransmitter release upon activation (Mackie, 2006). Alternatively, CB2Rs in the brain are concentrated on glial cells, typically only present where active neuroinflammation is taking place, and function as inhibitors of the immune response (Bie et al., 2018; Miller & Stella, 2009; Guindon & Hohmann, 2009; Ehrhart et al., 2005; Buckley et al., 2000). Disruption of the endocannabinoid system by THC during critical periods of brain development has been directly shown to alter the neurodevelopmental trajectory, which include long-term changes in prefrontal and hippocampal expression of cannabinoid receptors and dysregulated prefrontal dendritic

branching, synaptic pruning, and expression of glutamate receptor subunits (Miller et al., 2019; Poulia et al., 2019; Rubino et al., 2015; Weed et al., 2016).

Neuroimaging studies have provided insights into the structural and functional brain alterations associated with adolescent cannabis use. Structural MRI studies have shown that regular cannabis use during adolescence is associated with reduced gray matter volume in the prefrontal cortex, (Orihuel et al., 2023; Hirjak et al., 2021; Koenders et al., 2016; Churchwell et al., 2010). Reduced cortical thickness in this region has also been reported, suggesting that cannabis use may interfere with normal cortical maturation (Lopez-Larson et al., 2011; Levar et al., 2018). Additionally, changes in white matter integrity, as indicated by altered fractional anisotropy in diffusion tensor imaging (DTI) studies, have been observed in adolescent cannabis users, implicating disruptions in neural connectivity (Zalesky et al., 2012). fMRI has revealed altered brain activity patterns in cannabis-using adolescents during cognitive tasks, with cannabis users exhibiting increased activation in the prefrontal cortex and decreased activation in the hippocampus during memory tasks, suggesting compensatory mechanisms in response to cannabis-induced deficits (Jager et al., 2010). These alterations in brain function are consistent with the cognitive impairments reported in adolescent cannabis users, including deficits in memory, attention, and executive function (Meier et al., 2015).

Beyond structural and functional brain changes, cannabis use during adolescence has been linked to alterations in neurotransmitter systems. The endocannabinoid system modulates the release of various neurotransmitters, including a dampening effect on NMDA glutamate receptors (Rodriguez-Muñoz et al., 2016), plasticity of cortical control over midbrain dopamine function (Covey et al., 2018), and negative feedback of GABAergic transmission (James & Bondugji, 2021). Chronic exposure to THC can lead to dysregulation of these neurotransmitter systems, including reduced measures of glutamate activity in the PFC, striatum, and frontal white matter (Rigucci et al., 2018; Silveri et al., 2011; Muetzel et al., 2013; Prescot et al., 2011; Watts et al., 2020), reduced striatal dopamine availability (van de Giessen et al., 2017), potentiated response to mesolimbic dopamine (Cadoni et al., 2013), and reduced GABA synthesis (Renard et al., 2018).

Furthermore, cannabis use during adolescence has been associated with altered indices of neuroinflammation. Studies have reported that chronic cannabis use can lead to decreased levels of pro-inflammatory (Bayazit et al., 2017; Lima 2021; Henshaw et al., 2021; Moretti et al., 2015) and anti-inflammatory (Zamberletti et al., 2015) cytokines in the brain. However, it appears these effects differ when isolating certain psychoactive components of cannabis. It appears an anti-inflammatory effect on cytokines is most strongly produced by cannabidiol (CBD), the second most common cannabinoid in cannabis that exerts opposing effects to THC at CB1 and CB2 receptors (Atakan, 2012; Henshaw et al., 2021; Peng et al., 2022). Alternatively, THC demonstrates a biphasic effect on pro-inflammatory cytokines, whereby low doses can inhibit (Berdyshev et al., 1997), and high doses can stimulate its production (Berdyshev et al., 1997; Srivastava et al., 1998; Cutando et al., 2013; Zamberletti et al., 2015; Moretti et al., 2015). Anti-inflammatory cytokines are also modulated by THC, whereby chronic exposure during adolescence has been shown to increase the long-term production of IL-10 in the PFC, hippocampus, and hypothalamus (Moretti et al., 2015; Zamberletti et al., 2015). The aberrant prefrontal synaptic pruning as a result of chronic adolescent THC exposure in rats also suggests a mechanism of THC-induced microglial involvement (Miller et al., 2019). Neuroinflammation has been implicated in various neuropsychiatric disorders including depression, addiction, and autism, in addition to psychotic disorders, suggesting that cannabis-mediated neuroinflammatory processes could have broad implications for mental health (Hong 2016; Rubino et al., 2011; Stark et al., 2021).

The neurobiological relevance of adolescent cannabis use extends to its potential to interact with genetic predispositions. For example, polymorphisms in the gene encoding the cannabinoid receptor 1 (CB1R) have been associated with differential effects of cannabis on brain structure and function (Ho et al., 2011; Onaivi et al., 2009). Ho et al. (2011) demonstrated that specific CB1R gene polymorphisms are linked to greater brain atrophy and cognitive deficits in individuals with CUD. This study showed that carriers of certain CB1R variants experienced more significant white matter loss and impairments in cognitive functions, such as memory and executive function, compared to non-carriers. Alternatively, Ketcherside et al. (2017) revealed that variations in the CB1R gene can affect the density and function of cannabinoid receptors in the brain. This modulation can

influence how cannabis impacts cognitive processes and emotional regulation. For example, individuals with certain CB1R polymorphisms may exhibit heightened sensitivity to the anxiogenic and psychotomimetic effects of cannabis, increasing their risk for developing anxiety disorders and psychosis (Onaivi et al., 2009; Domschlke et al., 2008). In addition to CB1R gene polymorphisms, variations in genes related to the dopamine system, such as the catechol-O-methyltransferase (COMT) gene, also play a crucial role. Adolescents with the Val158Met polymorphism in the COMT gene, which affects dopamine metabolism, are more susceptible to the psychotomimetic effects of cannabis, including paranoia and hallucinations (Caspi et al., 2005). Understanding these neurobiological interactions may be important for identifying individuals who may be at higher risk for adverse outcomes related to cannabis use.

1.4.2. Clinical Relevance

The health consequences of cannabis use during adolescence are multifaceted and may have lasting impacts on both physical and mental health. Regarding physical health, long-term cannabis use has been associated with respiratory problems, such as chronic bronchitis, due to the inhalation of smoke (Taylor, 2002). The combustion of cannabis releases toxic chemicals including tar, ammonia, hydrogen cyanide, and polycyclic aromatic hydrocarbons (PAHs) such as benz[a]pyrene, among other known carcinogens (Tashkin et al., 2002). These substances can irritate the respiratory system, leading to chronic cough, phlegm production, wheezing, and impaired lung function (Tetrault et al., 2007). Furthermore, studies have indicated that cannabis smoke contains many of the same harmful components as tobacco smoke, potentially increasing the risk of respiratory infections and chronic obstructive pulmonary disease (COPD) (Moore et al., 2005). Additionally, cannabis use may negatively affect cardiovascular health, increasing heart rate and potentially contributing to an increased risk of heart attack in individuals with pre-existing heart conditions (Mittleman et al., 2001).

Cognitive effects of adolescent cannabis use are also apparent. Longitudinal studies show that frequent cannabis users may suffer significant declines in IQ and memory function that persist into adulthood even after cessation of use (Meier et al., 2012; Volkow et al., 2014). These cognitive deficits can impair academic and occupational performance, compounding the adverse effects on educational attainment and career

prospects. For example, Meier et al. (2012) found that persistent cannabis use from adolescence into adulthood was associated with an average decline of 8 IQ points, which could not be fully regained even after stopping cannabis use. Studies have also demonstrated that adolescent cannabis use impairs attention, executive function, and spatial working memory, which are critical for academic success and daily functioning (Crean et al., 2011; Becker et al., 2015; Camchong et al., 2017; Sweeny et al., 2017; Fried et al., 2002; Fried et al., 2005; Meier et al., 2012; Tait et al., 2011; McKetin et al., 2016; Morin et al., 2019). Adolescents who use cannabis regularly are also more likely to experience difficulties with learning and information processing (Lisdahl et al., 2013; Scott et al., 2018; Jaeger, 2018). Moreover, Silins et al. (2014) reported that heavy adolescent cannabis users were significantly less likely to graduate from high school and obtain a degree compared to non-users.

The mental health effects of adolescent cannabis use are especially concerning. There is strong evidence to suggest that cannabis use can exacerbate symptoms of anxiety and depression, and potentially contribute to the development of mood disorders (Silins et al., 2014; Gobbi et al., 2019; Page et al., 2019; Solmi et al., 2022; Lowe et al., 2019). Adolescents who use cannabis are more likely to experience depressive symptoms, suicidal ideation, and attempts compared to their non-using peers (Gobbi et al., 2019). Persistent cannabis use is also associated with an increased risk of developing substance use disorders, including cannabis use disorder (CUD) (Kosty et al., 2017). Adolescents with CUD face challenges in controlling their use, experiencing withdrawal symptoms and increased tolerance, which can significantly impair their daily functioning and quality of life (Simpson, 2016). Moreover, the early onset of cannabis use is correlated with a higher likelihood of using other illicit drugs and engaging in other risky behaviors, which can further exacerbate mental health issues and lead to a cycle of substance dependence and psychological distress (Fergusson & Horwood, 2000). Importantly, cannabis use during adolescence has been linked to an increased risk of developing psychotic disorders, such as schizophrenia, especially in individuals with a genetic predisposition or family history of psychosis (Arseneault et al., 2004; Ho et al., 2011; Martinez-Gras et al., 2006; Di Forti et al., 2019; Leroy et al., 2001).

1.4.3. Implications in the Psychosis Spectrum

The relationship between adolescent cannabis use and psychosis is well-documented, with a significant body of research indicating that cannabis use can exacerbate the risk of developing schizophrenia (Large et al., 2011; Kiburi et al., 2021; Marconi et al., 2016; Matheson et al., 2023). The evidence suggests that cannabis use, particularly during the vulnerable developmental period of adolescence, may interact with genetic and environmental risk factors, increasing the likelihood of psychosis onset and influencing its trajectory (Kiburi et al., 2021; Malone et al., 2010; Keshavan et al., 2014; Crocker et al., 2017; Abush et al., 2018).

Studies commonly show that cannabis use is associated with an earlier onset of schizophrenia. A meta-analysis found that cannabis users developed schizophrenia approximately 2.7 years earlier than non-users (Large et al., 2011). In relation to first-episode psychosis (FEP), cannabis use typically precedes onset, occurring prior to FEP in 94% of patients, whereas for only 1%, cannabis use begins after onset (Kline et al., 2022). Sustained cannabis use among FEP subjects in remission is also linked to subsequent relapse (Levi et al., 2023). These findings suggest that cannabis may accelerate the pathology of psychosis in vulnerable individuals. Furthermore, the risk appears dose-dependent, with higher frequency and potency of cannabis use correlating with a greater risk of developing psychosis (Marconi et al., 2016; Di Forti et al., 2019).

Clinical findings in the UHR and CHR populations also implicate a relationship, although are not as robust in the clinical population. For example, one longitudinal study followed UHR subjects for 2 years after presentation, finding that cannabis use disorder (CUD) was not associated with development of psychosis (Brucato et al., 2017). A similarly structured 2-year follow-up of UHR subjects however found that sustained cannabis use after presentation, but not lifetime use, significantly increased the risk of psychosis development (Valmaggia et al., 2014). While vastly different prevalences for lifetime cannabis use between these two studies likely contributed to these findings (17% vs. 74%), these findings also suggest that cannabis use may exacerbate vulnerabilities in those already on a trajectory towards psychosis, resulting in the acceleration of psychosis onset.

An effect of adolescent cannabis use in PLEs has also been reported. Research indicates that adolescent cannabis use can increase the frequency and distress of PLEs, potentially elevating the risk of progression to more severe psychotic symptoms (Miettunen et al., 2008; van Gastel et al., 2013; Bourque et al., 2017; Hides et al., 2009; Stefanis et al., 2004; Mackie et al., 2011). A recent cohort analysis found that cannabis use at 15- and 16-years approximately doubles the risk of psychotic disorders compared to PLEs alone (Denissoff et al., 2022). This relationship may be mediated by similar neurobiological mechanisms as those implicated in clinical psychosis: disruptions in the endocannabinoid system (Morris et al., 2022; Rubino et al., 2014; Miller et al., 2019), alterations in dopaminergic (Bloomfield et al., 2014; Henquet et al., 2008) and glutamatergic neurotransmission (Rigucci et al., 2017), and neurodevelopmental perturbations (Miller et al., 2019; Rubino et al., 2014; Malone et al., 2010). Moreover, neuroinflammation is emerging as a critical factor in this context and may play a role in the cannabis related exacerbation of PLEs and their potential progression to clinical psychosis (Miller et al., 2019; Moretti et al., 2015; Corsi-Zuelli et al., 2022).

Among the implicated mechanisms underlying the link between cannabis use and psychosis include the dopaminergic system, glutamatergic system, and mechanisms of neuroinflammation. Cannabis has been shown to increase dopaminergic capacity in the striatum and mesolimbic projections in a dose-dependent effect (Bloomfield et al., 2014), which may contribute to the mechanisms of negative feedback seen with psychotic disorders. This interaction may explain why individuals with a genetic predisposition to dopaminergic dysregulation are more susceptible to the psychotogenic effects of cannabis (Henquet et al., 2008). Glutamate levels are also significantly lower in the PFC of cannabis-using FEP patients, but not in non-using FEP patients (Rigucci et al., 2017), nor in the general FEP population (Bissonnette et al., 2022), implicating a role of cannabis use in the glutamate hypothesis as well.

The biochemical links between cannabis use, psychosis, and neuroinflammation are more theoretical; however, emerging evidence continues to suggest a role. Preclinical evidence suggests ECS disruption via CB1 and CB2 chronic hyperactivity during adolescence may result in mechanisms of oxidative stress in the hippocampus, permitting alterations in hippocampal glial activity and the emergence of psychotic-like symptoms in

adulthood (Morris et al., 2022; Rubino et al., 2014). These cannabis-mediated microglial and astrocytic alterations may also be responsible for the reduced WM tract integrity (Crocker & Tibbo, 2018; Iwabuchi et al., 2015; Zhang et al., 2013) and functional connectivity (Stephan et al., 2009; Friston et al., 2016) seen with schizophrenia. A CB1R-mediated dysregulation of oligodendrocyte progenitor cells from chronic THC exposure could contribute to this mechanism (Torre et al., 2022; Moline-Holgado et al., 2002). It has also been suggested that the perturbed prefrontal pruning induced by chronic adolescent THC exposure in rats may be responsible for similar alterations in the development of schizophrenia (Miller et al., 2019). Furthermore, a recent analysis found that the onset of cannabis use before 17 years moderated the association between high markers of systemic inflammation and psychosis (Corsi-Zuelli et al., 2022). Despite these implications on neuroinflammatory processes, the precise pathways and interactions remain unclear. One neuroimaging strategy that is becoming increasing helpful in elucidating the context and degree of metabolic and neuroinflammatory changes is magnetic resonance spectroscopy (MRS).

1.5. Neuroimaging Strategies: ^{1}H Magnetic Resonance Spectroscopy (MRS)

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive imaging technique that allows for the in vivo measurement of biochemical compounds within the brain. Unlike traditional MRI, which provides detailed anatomical images, MRS focuses on the chemical composition of tissues. This technique exploits the magnetic properties of hydrogen protons to detect the concentration of various metabolites. More specifically, a strong magnetic field aligns the protons in the brain (Frangou et al., 1996; Shen et al., 2020). A radiofrequency pulse then perturbs this alignment, causing the protons to emit signals as they relax back to their equilibrium state. These signals are detected and analyzed to produce a spectrum that displays the resonance frequencies of different metabolites. The area under each peak in the spectrum corresponds to the concentration of the respective metabolite. The specific chemical shifts and peak positions for many neurometabolites are well-characterized, providing markers for various biochemical processes within the brain, including states of neuroinflammation. Commonly measured

metabolites to proxy neuroinflammatory processes include N-acetyl aspartate (NAA), N-acetyl-aspartyl glutamate (NAAG), total choline (tCho), myoinositol (mI), creatine (Cr), and phosphocreatine (PCr). Each metabolite resonates at a unique frequency, allowing for their identification and quantification.

1.5.1. Neurobiological Significance

^{1}H MRS provides critical insights into the neurobiological processes underlying brain function and pathology by measuring the concentration of specific metabolites associated with neuronal health, membrane turnover, and energy metabolism.

Total N-acetyl aspartate (tNAA). NAA is synthesized in neurons and cycles between neurons and oligodendrocytes, maintaining roles in myelin synthesis, mitochondrial energy production, and osmotic balance (Moffett et al., 2007; Moore & Galloway 2002). N-acetyl-aspartyl glutamate (NAAG), present in smaller concentrations than NAA and therefore more difficult to resolve, arises from the synthesis of NAA and glutamate and is shown to modulate glutamate transmission and astrocyte function (Baslow et al., 2000). A combined measure of NAA and NAAG (NAA+NAAG or tNAA) is thus thought to reflect a combination of neuronal health and density (Crocker et al., 2017; Paslakis et al., 2014). Reduced tNAA levels are often observed in neurodegenerative diseases and conditions involving neuronal loss or dysfunction (Moffett et al., 2007).

Total choline (tCho). Total choline reflects the combined concentrations of cytosolic (i.e., “free”) choline and cell membrane-bound phosphocholine (PC) and glycerophosphocholine (GPC). Free choline is involved in many extracellular processes including membrane synthesis, acetylcholine synthesis, and methyl group donation (Tayebati 2012). Membrane-bound choline is essential for membrane stability, signal transduction, and lipid metabolism (Tayebati et al., 2012). Thus, as a marker of cell membrane turnover and integrity, total choline concentrations are shown to be elevated in states of increased membrane turnover, such as neuroinflammatory and demyelinating conditions, and reduced in states of less cellular proliferation or membrane synthesis (Tayebati et al., 2012).

Total Creatine (tCr). Creatine and its phosphorylated form, PCr, comprise the measure total creatine (Cr+PCr or tCr). Creatine and PCr cycle high-energy phosphate groups within cells, serving as an energy reservoir and a marker of overall metabolic activity that can provide context to a possible state of neuroinflammation (Chen et al., 2023). It is involved in the storage and transfer of high-energy phosphate groups. Elevated creatine can suggest ongoing inflammation (Chang et al., 2013).

Myoinositol (mI). Myoinositol has roles in both intracellular and regional osmotic balance, energy production, membrane integrity, and signal transduction (Downes & Macphee, 1990; Chhetri et al., 2019), expressed at high concentrations in astrocytes (Brand et al., 1994). Myoinositol concentrations are therefore thought to be representative of astrocyte activity and osmoregulation (Crocker et al., 2017; Chang et al., 1998; Hattingen et al., 2008). Increased mI levels are indicative of gliosis and are often observed in neuroinflammatory conditions and psychiatric disorders (Plitman et al., 2016).

1.5.2. Findings in the Psychosis Spectrum

Numerous studies have employed ^{1}H MRS to investigate the biochemical abnormalities associated with the psychosis spectrum, allowing for a small handful of meta-analyses to have been conducted. These analyses exist for the UHR population (Romeo et al., 2020; Brugger et al., 2011; Whitehurst et al., 2020) and those with FEP and/or chronic schizophrenia (Mateos et al., 2023; Whitehurst et al., 2020; Brugger et al., 2011; Steen et al., 2005; Iwata et al., 2018; Yang et al., 2023). These studies report alterations in key metabolites that are indicative of the underlying neurobiological changes in the psychosis spectrum and highlight a potential role of neuroinflammation.

Three systematic reviews have been recently conducted among UHR subjects, each arriving to different findings. While Brugger and colleagues (2011) identified significantly reduced NAA in the thalamus, Whitehurst and authors (2020) found this reduction restricted to the hippocampus. Alternatively, Romeo and colleagues (2020) only found a trend towards reduced NAA in the temporal lobe, although also found significantly increased myoinositol in the DLPFC. Together, these findings suggest that

heterogenous metabolic alterations may already be present in the subclinical status in both cortical and subcortical structures.

Reduced NAA is one of the more consistent metabolic changes in both FEP and schizophrenia, namely in the PFC, temporal lobe, and thalamus (Mateos et al., 2023; Whitehurst et al., 2020; Brugger et al., 2011; Bissonette et al., 2022; Steen et al., 2005; Iwata et al., 2018; Yang et al., 2023). A recent meta-analysis specifically isolated this finding in the DLPFC, mPFC, frontal WM, and hippocampus in addition to the thalamus (Yang et al., 2023). These reductions in NAA, particularly in the PFC are believed to be associated with the cognitive deficits and negative symptoms characteristic of schizophrenia, such as impairments in executive function and motivation (Bertolino et al., 2000; Marenco et al., 2006). Furthermore, NAA reductions show a left hemisphere bias and are more pronounced in the more chronic schizophrenia compared to early-onset psychosis, which may suggest a progressive deterioration of neuronal health and integrity (Molina et al., 2005). Elevated choline is also reported in the basal ganglia and frontal WM of patients with schizophrenia (Yang et al., 2023), also demonstrated in FEP patients as an effect of illness that is distinct from the effect of substance use (Bernier et al., 2016). These findings suggest that diminished neuronal health and membrane instability play a role in the pathophysiology of psychotic disorders and may reflect a neural environment of ongoing inflammation.

1.5.3. Findings in Adolescent Cannabis Users

^{1}H MRS studies have also been used to investigate the impact of cannabis use on brain chemistry, although limited in number. For example, reduced NAA has been reported in the PFC (Prescot et al., 2011; Hermann et al., 2007), and reduced myoinositol in both the PFC (Prescott et al., 2011) and hippocampus (Blest-Hopley et al., 2020b) of youth-onset cannabis users compared to non-users. The reductions in NAA are believed to be linked to the cognitive deficits observed in adolescent cannabis users (Prescot et al., 2011), and in addition with reduced myoinositol, have been suggested to reflect glial-mediated mechanisms of inflammation (Blest-Hopley et al., 2020b; Prescot et al., 2011).

Neurotransmitter levels are also altered in cannabis users. Interestingly, two studies found chronic cannabis use to be associated with reduced glutamate (Prescot et al., 2011) and GABA (Subramaniam et al., 2022) concentrations in the ACC but were not able to

confirm each other's findings. However, the significant finding for glutamate was identified in a population with more cannabis exposure, which may suggest an accumulating effect on disrupting the excitatory-inhibitory balance (Page et al., 2019). The effects of THC during adolescence on inducing a pro-inflammatory state has not been significantly studied but may also affect the E/I balance through changes in the astrocytic metabolism of glutamate and microglial-mediated pruning of prefrontal synapses.

The neurometabolic changes observed in adolescent cannabis users are similar to those seen in individuals with psychotic disorders, and some of these changes are often exacerbated in cannabis users with a psychotic disorder. Specifically, both populations exhibit reductions in NAA and myoinositol, alterations in glutamate and GABA levels, and increased markers of neuroinflammation in frontal and/or hippocampal regions (Romeo et al., 2020; Whitehurst et al., 2020; Brugger et al., 2011; Iwata et al., 2018; Mateos et al., 2023; Nakahara et al., 2021; Natsubori et al., 2014; Lieberman et al., 2018; Garver et al., 2003). These findings may highlight a potential convergence of similar mechanisms by which cannabis use may precipitate or exacerbate the neurobiological vulnerabilities associated with the psychosis spectrum.

1.6. Current Gaps

1.6.1. The Impact of Comprehensive Assessment Methods

The assessment of psychotic-like experiences (PLEs) in children and adolescents has been marked by significant heterogeneity, which has obscured the clinical value of these assessments in identifying psychosis-prone trajectories and improving outcomes. Comprehensive assessment methods are needed to address this variability and enhance the predictive utility of PLEs. The wide variability in PLE prevalence estimates can be attributed to differences in assessment tools as discussed, each with their own strengths and limitations (Staines et al., 2022; Lee et al., 2016; Fisher et al., 2013b; Barragan et al., 2011). A systematic review could critically examine the predictive validity of various assessment tools, thereby identifying the most effective methods for early identification of psychosis risk.

1.6.2. The Impact of Altering Psychosis-Prone Trajectories

Identifying and altering psychosis-prone trajectories in children and adolescents is crucial for reducing the long-term burden of psychotic disorders. Research has shown that early intervention in high-risk populations can delay the onset of psychosis and improve global functioning (Morrison et al., 2004; van der Gaag et al., 2012; Mei et al., 2021). If an individual's risk status is being largely influenced by modifiable risk factors, a more preventative approach can focus on reducing encounters with these exposures. The relatively widespread use of cannabis among adolescents suggests this be an example of a potentially highly modifiable factor of risk. Studies have demonstrated that early and frequent cannabis use is associated with an increased risk and earlier development of psychotic disorders (Large et al., 2011; Kiburi et al., 2021; Marconi et al., 2016; Matheson et al., 2023). Therefore, identifying specific features of cannabis use, such as frequency, potency, age of onset, and total exposure may provide valuable insights into psychosis risk. Strategies aimed at reducing cannabis use among adolescents, particularly those with high-risk PLE profiles, could be an effective strategy for altering psychosis-prone trajectories.

Furthermore, incorporating neurobiological measures into the assessment and intervention process may provide additional insights into the mechanisms underlying psychosis risk. ^{1}H MRS, for instance, can identify metabolic changes in the brain associated with psychosis and cannabis use, with the potential to offer biomarkers of psychosis-proneness and targets for early intervention (Crocker et al., 2017). The paucity of ^{1}H MRS studies in samples of adolescents reporting PLEs and using/not using cannabis presents the opportunity to meaningfully contribute to this goal of reducing the burden of psychotic disorders on the population. Furthermore, combining these neurobiological findings with comprehensive, homogenized assessment methods can enhance the accuracy of risk identification and the effectiveness of interventions.

1.7. Thesis Rationale & Overview

This thesis aims to address critical gaps in the understanding and assessment of psychotic-like experiences (PLEs) in children and adolescents, focusing on both a systematic review and meta-analysis (Chapter 2) and an empirical primary study (Chapter

4). The rationale for this comprehensive approach is grounded in the need to enhance early identification, improve intervention strategies, and ultimately alter psychosis-prone trajectories to mitigate the burden of psychotic disorders.

Key findings from existing literature highlight the heterogeneity in the prevalence and assessment of PLEs, hampering the ability to accurately identify at-risk individuals and develop effective interventions (Kelleher et al., 2012; Fisher et al., 2013b; Lee et al., 2016). The systematic review and meta-analysis in Chapter 2 critically examines and synthesize existing evidence, seeking to provide an updated picture of the prevalence, characteristics, and prognostic quality of PLEs in children and adolescents. By identifying the most reliable features of assessment tools and highlighting the gaps in current methodologies, this review aims to contribute to standardizing PLE assessments and enhance their predictive validity.

The pathophysiological underpinnings of psychotic disorders further justify the need for early and accurate identification of PLEs. Neuroimaging studies have revealed significant biochemical changes in individuals with, or at ultra-high risk of psychosis, such as reduced NAA levels, altered myoinositol concentrations (Romeo et al., 2020; Bossong et al., 2019), and increased markers of systemic inflammation (Corsi-Zuelli et al., 2022; Garver et al., 2003; Zhang et al., 2022). These metabolic and neuroinflammatory changes that are present after functional decline but before the onset of psychosis raise the possibility of pathophysiological processes existing in the lower risk context of adolescent PLEs. The empirical study in Chapter 4 will explore these neurometabolic markers in a community-based sample of adolescents with PLEs, examining how these markers correlate. With the rationale that adolescent cannabis use may accelerate the pathophysiology of psychosis, Chapter 4 will also study how cannabis use in this sample may influence neurometabolic markers to contribute to the psychopathology of PLEs.

There is a unique benefit for a neurobiological investigation into adolescent PLEs. Adolescence is a critical period for brain development, and early interventions during this time can significantly alter developmental trajectories. Furthermore, identifying specific features of cannabis use that are associated with adolescent PLEs and its pathophysiology may provide insight to a neurobiological basis for the psychotogenic effects of adolescent

cannabis use. Additionally, assessing PLEs in the general population of non-help-seeking adolescents may provide a broader understanding of psychosis risk. Many adolescents with PLEs do not seek clinical help, yet they may still be at significant risk for developing psychotic disorders. By including these individuals in research analyses, a greater proportion of psychosis-prone individuals could be identified, and preventative/interventive strategies can be developed for a wider population. That is, this approach can help to identify at-risk individuals who might otherwise be missed and provide early support to prevent the development of clinical psychosis.

The integration of findings from the systematic review and the empirical study seeks to provide a renewed perspective to adolescent PLEs and their implications for psychosis risk. By addressing both clinical and neurobiological rationales, this thesis aims to systematically contribute to bridging the gap between research and practice.

Chapter 2. Heterogeneity in the Risk of Developing a Psychotic Disorder Given a Previous Subclinical Psychotic-Like Experience in Children & Adolescents: A Systematic Review & Meta-Analysis

This chapter is one of two research endeavours taken by Isaiah Burton in support of this thesis. Under the co-supervision of Dr. Philip Tibbo and Dr. Candice Crocker, this systematic review and meta-analysis was drafted by Isaiah, who also incorporated suggestions from his co-authors before preparing it for submission to a peer reviewed journal. This chapter was submitted to *Psychiatry Research* on April 2nd, 2024. As of August 28th, 2024, a first round of peer reviews had been completed and the journal has requested the revisions be addressed before re-submission to the journal. In this Chapter, and at the discretion of his supervisors, Isaiah has incorporated some of the requested revisions that were suitable to be addressed within the timeline of his thesis. Isaiah intends to address the remaining revisions under the guidance of his supervisors and the remaining co-author (NP).

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2.1. Abstract

Psychotic-like experiences (PLEs) are common in the general population. Child and adolescent PLEs are the most prevalent and linked with future psychopathology, particularly psychotic disorders. Significant heterogeneity in PLE assessment has obscured its clinical utility to identify psychosis-prone trajectories to improve clinical outcomes. This meta-analysis aimed to assess i) PLE prevalence in children and adolescents and ii) their relationship with subsequent psychotic disorder while exploring sources of heterogeneity. PubMed, Embase, PsycINFO, and CINAHL databases were searched in August 2023 for population-based longitudinal studies that assessed child or adolescent PLEs and early adulthood psychotic outcomes. Studies were appraised using a recognized tool for non-interventional studies. Two reviewers independently extracted data to generate a pooled sample. Six studies were included (n = 16560), showing a pooled PLE prevalence of 17.3%. Child and adolescent PLEs were associated with an increased risk of psychotic disorder in early adulthood (unadjusted OR = 3.80, 95% CI: 2.31–6.26), with a population attributable fraction of 32.6%. Significant heterogeneity in the strength of this relationship (I^2 = 70%, p = .01) was related to assessment type (self-report vs. interview) in our exploration. This review contends that interview-based PLE assessments could more accurately identify children or adolescents on a path towards psychosis and are better suited for psychotic risk identification. Further research is needed to elucidate interactions between PLEs and other psychotic risk factors.

Keywords. Non-clinical, psychosis, psychosis proneness, psychotic experience, risk identification, schizophrenia, schizoaffective disorder, subclinical psychotic symptom, youth mental health

2.2. Introduction

Subclinical psychotic symptoms have a well-documented presence in the general population (Staines et al., 2022). Known as psychotic-like experiences (PLEs), they are more common during childhood and adolescence (8–17%) than during adulthood (5–6%) (van Os et al., 2009; Kelleher et al., 2012; Maijer et al., 2018). Despite a shared overlap in risk factors with psychosis, PLEs tend to be transient and typically non-distressing, suggesting that these experiences represent a non-clinical phenotype on an extended psychosis spectrum (Kelleher and Cannon, 2011; van Os and Linscott, 2012; Staines et al., 2022).

There have been widely varying reported rates of PLE prevalence in children and adolescents from as low as 1.6% (Fisher et al., 2013b) to as high as 37.5% (Barragan et al., 2011). These primary papers have led to several previous syntheses of the literature to try and determine a consistent population prevalence rate for these experiences. Kelleher et al. (2012) reported a lifetime prevalence of 7.5% among 13–18-year-olds and 17% for 9–12-year-olds, based on five and nine different samples, respectively. This review noted a high amount of heterogeneity. A review on auditory hallucinations, the most frequently experienced PLE type (McGrath et al., 2015), noted prevalence estimates of 12.7% in children under 13 (nine samples) and 12.4% among 13–17-year-olds (13 samples) (Maijer et al., 2018). Authors also revealed significant heterogeneity in prevalence estimates that could not be explained by age at assessment. With 41 different PLE assessment tools having been identified as used in research (Lee et al., 2016), heterogeneity within its assessment poses a distinct challenge to our understanding of PLEs (Staines et al., 2022).

The higher prevalence of PLEs during childhood and adolescence has prompted investigations into their ability to improve detection of those at risk of psychosis. While a meta- analysis of longitudinal studies did not find a significant increase in the risk of psychosis from PLEs in the general population (Kaymaz et al., 2012), an analysis on children and adolescents revealed a significant fourfold increase, along with lesser associations with concurrent affective, behavioural, and depressive disorders (Healy et al., 2019). As with a common event forecasting a comparatively rare outcome, most

individuals who experience PLEs do not develop a psychotic disorder (Fisher et al., 2013b). However, nearly a quarter of those who developed a psychotic disorder had experienced a childhood or adolescent PLE (Healy et al., 2019), with only 4.1% of first episode psychosis patients having had previous contact with clinical high-risk services (Ajnakina, 2017). Together, this emphasizes the need for refined risk identification using PLEs to better aid in mitigating potential negative outcomes.

Similar to the research in PLE prevalence, existing analyses have also highlighted significant heterogeneity in assessing the prognostic value of PLEs (Kaymaz et al., 2012; Healy et al., 2019). Some exploration into the possible sources of this heterogeneity revealed no significant effect of PLE assessment type (i.e., self-report vs. interview), sample size, age at assessment, time to follow-up, and gender on heterogeneity, leaving authors to postulate additional or interaction effects (Healy et al., 2019). However, this analysis focused on the relationship between PLEs and any psychiatric disorder. Focusing on the stronger relationship between PLEs and psychotic disorders may highlight design elements that are especially sensitive to psychosis proneness and thus should be retained in future assessments. This systematic review and meta-analysis aims to enhance our understanding of the link between adolescent PLEs and subsequent psychotic disorder by updating previous reviews and exploring for sources of heterogeneity in PLE assessment. To achieve this, the objectives of this review are to (i) assess the prevalence of child and adolescent PLEs and (ii) assess the relationship between child and adolescent PLEs and a subsequent psychotic disorder with a careful exploration of heterogeneity in the assessment of PLEs and its effects on the observed relationship.

2.3. Methods

This meta-analysis followed the most recent guidelines established in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021). The protocol for this review was registered a priori in the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD42023384445). Modifications to the original protocol are described in Appendix A.

2.3.1. Inclusion and Exclusion Criteria

Sample. Only longitudinal studies with a time to follow-up of at least one year were considered. Studies must have recruited in a manner that allowed for a representative sample of the general, non-help-seeking population. This criterion was used to ensure this review assesses non-clinical experiences at baseline. Studies were included if participants were at least 11 years of age at the first assessment of PLEs and not over the age of 35 years at follow-up. Case and case-control studies were excluded from this review to maintain ecological validity for how assessments are intended to perform in the general population. Studies that recruited from clinical registries (excluding birth cohorts), and studies including genetic high-risk participants were excluded to maintain generalizability.

Exposure. Exposure for this study was defined as any documented experience of a delusion, hallucination, or disordered cognition that was not caused by substance use nor causing the individual to seek clinical care. Both self-report measures and clinician verified experiences were considered acceptable for inclusion. For purposes of this review, the exposed group was designated PLE+ and the non-exposed group was designated PLE-. Given the lack of a consensus around PLE assessment, the assessment tool used did not need to have been validated if the assessment collected information on any type of hallucination, as they are the most frequently experienced type of PLE (McGrath et al., 2015). In addition, there was no requirement for recency of the PLE in order to maximize the number of studies analyzed. Dichotomous and categorical (e.g., based on type or strength) classifications of PLEs were deemed acceptable for this review, so long as they could be dichotomized into exposed and non-exposed for meta-analysis (described in section 2.4). Studies using continuous measures without an a priori threshold were excluded. The initial assessment of PLEs was considered the baseline assessment, and it must have occurred at least 1 year before assessment of psychotic outcomes for the study to be included.

Outcome. Data must have been collected on the diagnosis of, or the receipt of care for psychosis or an affective or non-affective psychotic disorder at any follow-up

assessment to satisfy the outcome criterion. The diagnosis of a psychotic disorder was only considered an acceptable outcome if it was made by a clinician using any version of the Diagnostic and Statistical Manual (DSM) or International Classification of Diseases (ICD). No distinctions needed to be made for type of psychotic disorder to meet the inclusion criteria.

2.3.2. Review Process and Data Extraction

Study Screening. Citations from PubMed, Embase, PsycINFO, and CINAHL databases were uploaded to Covidence (covidence.org) for online screening and data extraction. Two blinded researchers (IB and NP) independently screened the studies. The first selection filter was applied to titles and abstracts, whereby studies were assessed and excluded based on the presence of exclusion criteria. The second filter was applied to remaining studies and involved a full-text review to assess all inclusion and exclusion criteria. When multiple studies reported on overlapping samples, the study with the largest sample containing exposure and outcome data (first priority) or longest time to follow-up (second priority) was selected. An exception was made for studies that assessed the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, as the study with the largest sample and longest follow up was not suitable for inclusion in this review. This was due to changes in the cohort's confidentiality policy that restricted publication of exact numbers in small outcome groups (Sullivan et al., 2020). As a result, a previous analysis on this cohort with exact exposure and outcome proportions was selected (Zammit et al., 2013). Following independent screening, disagreements were reviewed jointly by IB and NP to determine appropriate action. The reference lists from the remaining studies that were not excluded were examined for additional studies to include.

Data Extraction. Data coding involved two researchers (IB and NP) independently extracting all of the required data (outlined below). Disagreements were resolved by consensus. If consensus could not be reached, then a third reviewer (CC) was asked to extract data for comparison. Quantitative data extraction included the final sample size (the sample with all exposure and outcome data available), mean age at baseline and last follow-up, cumulative proportions of the final sample exposed at

baseline and who developed a psychotic outcome at follow-up, and the reported strength of this relationship. When outcomes were assessed at multiple timepoints, the cumulative occurrence of psychotic outcomes were taken. When data was not available in this format, authors were contacted for data in an analyzable format. This occurred for one study in this review (Welham et al., 2009), however these authors no longer had access to this data when contacted. Therefore, data for this study was extracted from an existing meta-analysis (Kaymaz et al., 2012) where it was presented in the appropriate format.

Features of PLE assessments were extracted, including assessment type (interview or self-report questionnaire), number of items, nature of items (auditory and visual hallucinations, delusions, disordered cognition), and the number of positive items to be designated full PLE status. Geographical region(s) for the source of study populations were also extracted, as this has been thought to influence how PLEs may be interpreted (Larøi et al., 2014). Each of these variables have been previously investigated or hypothesized as a source of heterogeneity (Healy et al., 2019). In addition, an evaluation of features impacting within-study bias and internal validity was conducted to produce a risk of bias table following the Risk Of Bias In Non-Randomized Studies – of Exposure (ROBINS-E) guidelines (Higgins et al., 2023).

2.3.3. Statistical Analysis

To permit meta-analysis, studies that reported a categorical assessment of PLEs were dichotomized in a manner that has been previously exercised (Healy et al., 2019). When PLEs were assessed by strength of symptoms (e.g., none, weak, strong), the highest level of exposure was designated PLE+ and all lower levels, including controls, were designated PLE-. This also helps to reduce variability in PLE threshold between assessments and to improve generalizability to the community. Alternatively, if multiple PLE types (e.g., auditory and visual) or levels of persistence (e.g., once, twice, thrice) were assessed, all were designated PLE+ in this review to ensure all participants who were considered to meet full exposure criteria were correctly allocated.

All analyses were performed using R Studio (Version 4.3.2; R Core Team, 2021) with meta: General Package for Meta-Analysis (Version 7.0.0). Prevalence of PLEs was calculated from the cumulative dichotomized exposure across all PLE assessments. A random effects model was applied to produce unadjusted ORs ($\alpha = 0.05$) for the

relationship between PLEs at baseline and psychotic disorder at the last follow-up. Unadjusted ORs were generated at both the study level and for the pooled sample and incorporated into a forest plot. A random effects model was selected to account for the substantial expected heterogeneity, which was quantified with the I^2 metric. In addition, the population attributable fraction (PAF) in the pooled sample was used to further characterize this relationship. In this context, PAF was viewed as a complementary addition to characterizing this relationship because while OR quantifies the strength of the association, PAF quantifies the prevalence of this exposure-outcome trajectory among those with a psychotic disorder. Additionally, the exploration of heterogeneity involved separate univariate regression models to assess the effects of the following study features on unadjusted OR estimates: assessment type (interview or self-report), number of PLEs assessed, threshold number of positive items for PLE status, nature of items (hallucinations only, yes or no), mean age at baseline, time to follow-up, and geographical region. Each feature explored was set as the sole independent variable in separate models. Despite its inability to assess interaction effects, univariate regression was preferred over the more exploratory multivariate regression as it is less prone to overfitting a small sample. For similar reasons, a funnel plot was not generated due to insufficient power recommended to assess publication bias (Sterne et al., 2011).

2.4. Results

Search Results. Figure 2.1 depicts the PRISMA flow diagram of the study selection process and Table 2.1 describes the included studies. Across databases, the search yielded 8676 unique studies. Title and abstract screening subsequently identified 49 full-text articles for review. Full-text review excluded studies for the following reasons: not meeting the age criterion (k = 13), no DSM- or ICD-based assessment of any psychotic disorder at follow up (k = 12), duplicate samples (k = 10), not using a community representative sample (k = 7), assessment at baseline not meeting the definition of PLEs (k = 1), and not using a longitudinal study design (k = 1). This left five studies meeting all inclusion criteria. Review of their reference lists identified one additional study for inclusion, allowing six studies (n = 16560) to be included in this review (Poulton et al., 2000; Dhossche, Ferdinand, Van Der Ende, Hofstra, & Verhulst,

2002; Welham et al., 2009; Dominguez, Wichers, Lieb, Wittchen, & van Os, 2011; Zammit et al., 2013; Denissoff et al., 2022).

Objective 1: Prevalence of PLEs. Five different assessments were used to measure PLE status across the six studies in this review, identifying a range of prevalence from 1.6–30.5% (Table 2.2). One study inquired about lifetime prevalence (1.6%, Poulton et al., 2000), two asked about past 6-month prevalence (4.5%, Zammit et al., 2013; 30.5%, Denissoff et al., 2022) and another two employed the same assessment of current PLEs (5.0%, Dhossche et al., 2002; 12.7%, Welham et al., 2009). The remaining study assessed the past two-week prevalence at three timepoints over 3.5 years, finding a cumulative prevalence of 21.8% (Dominguez et al., 2011). In the pooled community sample, PLEs had been experienced by 17.3% (2862/16560) of participants.

Objective 2: PLEs and Subsequent Psychotic Disorder. Results from each study and the pooled sample are summarized in Table 2.2. Five of the six studies reported that child and adolescent PLEs significantly predicted the development of a psychotic disorder later in adolescence or early adulthood. Among these five studies, a subsequent psychotic disorder had developed in 4.0–25.0% of participants experiencing PLEs compared with 1.2–3.5% of those who did not experience a PLE. The one study reporting insignificant findings did not document any cases of psychotic disorder in exposed individuals and noted three cases (0.41%) among those unexposed (Dhossche et al., 2002). In the pooled sample, 4.5% (130/2862) and 1.5% (206/13698) of those with and without adolescent PLEs, respectively, met criteria for a psychotic disorder in early adulthood.

The unadjusted ORs and confidence intervals for each study and the pooled sample are presented in Figure 2.2. For the five studies in which this was calculable, the unadjusted ORs ranged from 2.19 to 11.02, all of which reaching significance. The OR for one study could not be computed as it found 0/39 of those with a PLE develop a psychotic disorder compared to 3/740 of those without PLEs. The OR for the pooled sample was also statistically significant, indicating that children and adolescents with a PLE are 3.80 times more likely (95% CI: 2.31–6.26) to develop a psychotic disorder in late adolescence or early adulthood. The PAF was calculated to be 32.6%.

There was significant heterogeneity between studies that could not be explained by chance alone (I^2 = 70%, p = .01). Across the six studies, five different assessments of PLEs were employed (Table 2.1). These assessed the presence of auditory hallucinations (5/5), delusional thinking (3/5), visual hallucinations (2/5), and cognitive difficulties (1/5). Three of the five assessments were self-report, containing 1, 12, and 16 items, while the remaining two were interview-based and led by a trained professional, containing 5 and 11 items. Threshold for PLEs also varied between assessments, with criteria including one positive self-report, three positive self-reports, a top 10% self-report score, one "definite" interviewer-designated experience, and two "likely" interviewer-designated experiences. The lowest OR was observed with the Symptom Checklist-90 Revised (SCL-90-R), and the highest OR was seen with the Diagnostic Interview Schedule for Children for DSM-III (DISC-C) (Figure 2.2).

A quantitative exploration of heterogeneity revealed a significant effect of assessment type (interview or self-report) on the odds ratio estimated by each PLE assessment tool (R^2 = .83, β = 6.48, SE = 1.43, p = .02). None of the other relationships explored were significant (Table 2.3). Because one study in this review produced a null OR (Dhossche et al., 2002), it was unable to be included in this analysis.

Risk of Bias. A ROBINS-E assessment identified sources of bias within studies likely arising from assessment of exposure, assessment and controlling for known prognostic factors, and follow-up of cohorts (Figure 2.3).

2.5. Discussion

This analysis supported the common occurrence of PLEs in non-help seeking adolescents, and that those who experience them are at an increased risk of developing a psychotic disorder by emerging adulthood. This is also the first study to provide evidence for interview based PLE assessments being significantly better than self-report questionnaires at predicting psychotic outcomes, though with limited statistical power. A PLE prevalence of 17.8% amongst children and adolescents is higher than previous meta-analytical estimates of 12.4% (Maijer et al., 2018), 9.3% (Healy et al., 2019), and 7.5% (Kelleher et al., 2012) in similar populations. Baseline assessments in our sample

were typically completed during early adolescence, which compares more similarly to the 17.5% prevalence seen in 9–12-year-olds (Kelleher et al., 2012). Our estimate was also heavily influenced by the PROD-screen assessment (Denissoff et al., 2022), which identified a prevalence of 30.5% in their study and accounted for 70% of all exposed individuals in this review. Excluding this study brings the pooled prevalence down to 8.9%. This maintains the notion that PLEs are more prevalent before adulthood, with meta-analytical estimates of 5–6% in adult populations (Maijer et al., 2018; van Os et al., 2009). The higher prevalence in children and adolescents may be best understood within the framework of the extended psychosis spectrum. Given that psychotic disorders typically manifest around the age of 25 (Solmi et al., 2022), this developmental period captures a broader population, including those who may be on a trajectory toward psychosis and those for whom PLEs represent a transient, non-prodromal experience. This suggests that the elevated rates of PLEs in younger individuals reflect both a stage of heightened vulnerability and a broader distribution of subclinical psychotic phenomena.

Five of the six studies documented a significant relationship between adolescent PLEs and subsequent psychotic disorder. The other study saw none of the 39 participants who reported auditory hallucinations during adolescence develop a psychotic disorder in early adulthood. This is likely the effect of a small sample, as their prevalence of psychotic disorders (0.4%) was less than what would be expected for this age group after nine years (0.8–1.1%) (Simon et al., 2017). Across all studies, the nearly fourfold elevated risk closely matches the findings of a previous meta-analysis that reported an OR of 3.96 (Healy et al., 2019). Despite mixed reports regarding PLEs during adulthood (Chapman, Kwapil, Eckblad, & Zinser, 1994; Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Werbeloff et al., 2012), a meta-analysis of PLEs experienced at any age did not show a significant increase in risk (Kaymaz et al., 2012). Indeed, when two of the six studies in that analysis were subsequently excluded due to unrepresentative samples, their results achieved significance. This exclusion was composed of two studies that assessed PLEs in adulthood and equated to 37% of their primary sample (Chapman et al., 1994; Werbeloff et al., 2012), leaving a 56% representation of adolescent PLEs. In addition to more psychotic outcomes following adolescent PLEs, nearly a third of those with a

psychotic disorder had PLEs during adolescence in our sample. This is higher than the previous estimate of 23.2% (Healy et al., 2019). Together this suggests that screening for adolescent PLEs has the potential to identify a significant portion of those who, if trajectory not altered, would develop a psychotic disorder. While the degree of PLE persistence (Mackie, Castellanos-Ryan, & Conrod, 2010), distress (Karcher et al., 2022), and co-occurring cannabis use (Denissoff et al., 2022) can signify someone at greater risk for psychosis, further research is needed to identify in what contexts could intervention be beneficial (Soneson et al., 2020).

As anticipated, heterogeneity was substantial in this review. Criteria for PLEs varied widely between assessment tools used, including the number of items, item content, timeframe, structure, and symptom threshold. Our effort to statistically explore its effect on the performance of the assessments, though limited in power, revealed a significant effect in having a clinician verify experiences. Although predictive validity on individual items is generally poor (Kelleher, Harley, Murtagh, & Cannon, 2011; Granö et al., 2016), past evidence has suggested that self-report can reliably identify the presence of clinician verified PLEs (Kelleher et al., 2011; Laurens, Hobbs, Sunderland, Green, & Mould, 2012). Self-report auditory hallucinations are a noted exception to this discordance between individuals and clinicians; however, they are only experienced in an estimated 44% of those with PLEs (McGrath et al., 2015). These findings advise against the use of any single self-report PLE item for prognostic value, even in light of the finding that auditory hallucinations alone can signify an increased risk (Welham et al., 2009). Even in the estimation of PLE prevalence, interview or self-report has been identified as a significant source of heterogeneity (Linscott & van Os, 2013). In this research, it has been suggested that the higher prevalence estimates seen with self-report may be due to an increased number of false positives (van Os et al., 2009; Schultze-Lutter et al., 2014; Staines et al., 2022). The effect of self-report versus clinician verified PLEs can be qualitatively described by comparing the performance of the Psychotic-Like Symptom Interview (PLIKSi) to the self-report PROD-screen. Both assessments inquired about the prevalence of hallucinations (auditory and visual) and delusions (of grandiosity, persecution, reference, spied on, thought insertion and withdrawal) in the past year. However, the PROD-screen identified a much greater proportion of PLEs (30.5% vs.

4.5%) and had a significantly lower, non-overlapping effect on predicting future psychotic disorder than the PLIKSi, despite the stricter threshold of three positive items for the PROD-screen. A previous assessment of the PROD-screen also confirmed substantial differences with an interviewers' evaluation of the same items (Granö et al., 2016). It is possible that interview-based assessments perform better than self-report because the interviewer can more objectively assess the degree to which social and environmental contexts play into a self-perceived PLE, something that varies between individuals (Larøi et al., 2014). Furthermore, a clinician may incorporate the degree of persistence and distress into their subjective assessment, further validating their assessment. The search for other sources of statistical heterogeneity were unsuccessful. This may be due to insufficient power to detect an effect, a true lack of effect, or interactions between the investigated features. It is also possible that unexplored features play a role which could include the recency of PLEs that the assessment inquires, threshold number of symptoms, gender, or other demographic characteristics of the samples.

Strengths & Limitations. A strength of this review is its focus on exploring reasons for heterogeneity, particularly regarding features of the PLE assessment tool and its delivery. The finding that interview-based assessments may provide greater prognostic value for psychotic outcomes can be applied to help standardize the assessment of PLEs. However, online surveys are an invaluable method of capturing large samples, especially when measuring risk in the general population. Highlighting this potential relationship can still inform clinicians and researchers on how to approach PLE assessment and interpret its findings. While this meta-analysis can be credited with conducting a robust systematic search of peer reviewed literature, the inclusion of only six studies provides quite modest statistical power to truly detect this effect or other sources of variability. While true that low power conservatively biases the estimate of heterogeneity (I^2) and bolsters our significant finding of PLE assessment type, it also makes it more difficult to pinpoint its specific sources. Therefore, the non-significant sources of heterogeneity we explored cannot be ruled out.

The limited number of studies in this review also provides the opportunity for bias to more greatly affect our assessment of the relationship between child and adolescent

PLEs and subsequent psychotic disorder. Specifically, the few included studies made it unsuitable to assess publication bias, which can be a concern with published studies. Furthermore, within-study bias becomes a greater concern, particularly regarding the follow-up of cohorts as two studies had each lost 27% of baseline participants by follow-up (Welham et al, 2009; Dominguez et al., 2011) and one study having lost 40% (Zammit et al., 2013). A subsequent analysis of the MUSP cohort noted that those lost to follow-up were more likely to be of lower socioeconomic standing, of older age, be a tobacco user, and have poorer mental health at baseline (McGrath et al., 2010). This result likely biased our assessment of this relationship to be more conservative, supporting its significant findings. Alternatively, significant heterogeneity questions the validity of our estimate for this relationship. True heterogeneity implies real differences between what studies are assessing, and meta-analyzing these studies may simply be a collation of inherently different phenomena, leading to inaccurate conclusions about the generalized topic. However, this will remain true until heterogeneity can be adequately resolved, something this review attempts to contribute to. Furthermore, our estimate for the increased risk for psychotic disorders matches the general consensus from both primary research and review levels (Healy et al., 2019; Staines et al., 2022), suggesting that a potential lack of validity would only affect the OR estimate and not the significance of the relationship. Despite these effects of significant heterogeneity among a small number of studies, synthesis of the existing literature is necessary for identifying emerging themes and clarifying inconsistencies to advance our understanding of the topic, which we believe is justly achieved in this review.

Addressing methods taken by this review, the manner of dichotomization follows previously applied methods used for PLEs (Kaymaz et al., 2012; Healy et al., 2019), facilitating comparison between these studies. By establishing only the highest level of exposure as significant, it also reduces heterogeneity between studies. In turn, however, this reduces the PLE assessment tool from its intended use, potentially altering how its findings are interpreted. Future research should evaluate how various features of PLEs interact with other known risk factors to create a more informative and transdisciplinary evaluation of psychosis risk in the general population.

2.6. Conclusion

Children and adolescents who experience PLEs are at an increased risk for developing a psychotic disorder, and sizable portion of those with a psychotic disorder experienced PLEs in childhood and adolescence. Monitoring PLEs during this time has the potential to improve detection of those who are on a path towards psychosis development, which may be better achieved during interview compared with a self-report questionnaire. More research is needed to clarify what modulates someone's trajectory after PLEs first occur.

2.7. Tables

Table 2.1: Description of population-based longitudinal studies assessing psychotic-like experiences in children and adolescents at baseline and psychotic outcome at follow-up.

Study ID	Study description	Sample size (*n*)	Mean age at baseline – follow-up (years)	Baseline PLE assessment	PLE categories (assessment score, when specified)	Follow-up assessment of psychotic disorder
Poulton et al., 2000	DMHD birth cohort (1972-1973) assessed at age 11 for delusions and hallucinatory experiences and at age 26 for schizophreniform disorder.	761	11–26	DISC-C: schizophrenia section (5-item, lifetime), each item rated by a psychiatrist as no (0); yes, likely (1); and yes, definitely (2).	No symptoms (0) Weak symptoms (1) Strong symptoms (2+)	DSM-IV: Schizophreniform disorder
Dhossche et al., 2002	Subset of Dutch cohort assessed at age 11-18 (1989) for self-reported hallucinations and 9 years later for psychiatric diagnoses.	779	14–23	Youth Self-Report: one question on current auditory hallucinations rated not true (0), sometimes true (1), or very true (2).	PLE- PLE+	CIDI DSM-IV: Brief psychotic disorder or schizophrenic, schizophreniform, schizoaffective, or delusional disorder.
Welham et al., 2009	MUSP birth cohort (1981-1983) assessed at age 14 for psychotic-like symptoms and age 21 for non-affective psychotic disorder.	3563	12–21	Youth Self-Report: One question on current auditory hallucinations rated never, rarely, sometimes, or often.	PLE- (never/rarely) PLE+ (sometimes/ often)	CIDI DSM-IV: Non-affective psychotic disorder or past diagnosis of schizophrenia.

Study ID	Study description	Sample size (*n*)	Mean age at baseline – follow-up (years)	Baseline PLE assessment	PLE categories (assessment score, when specified)	Follow-up assessment of psychotic disorder
Dominguez et al., 2011	Subset of EDSP cohort (1970-1981) who were 14-17 at T0, assessed for psychotic experiences at T0, T1, and T2 (range = 3.5 years) and psychotic disorder at T3 (4.9 years after T2).	845	15–23	SCL-90-R: paranoid ideation (6-item) and psychoticism (10-item) past two-week self-report symptoms, with each item rated from "not at all" (0) to "extremely" (4). TS identified as the 90th percentile of scores at timepoint.	Persistence: Level 0 (no TS) Level 1 (TS x1) Level 2 (TS x2) Level 3 (TS x3)	DIA-X/M-CIDI: Diagnosis of psychotic disorder at T3 based on the presence of (i) positive psychotic symptoms, (ii) help-seeking behaviour, and (iii) impairment.
Zammit et al., 2013	ALSPAC birth cohort (1991-1992) assessed at age 12 for PLEs and age 18 for psychotic disorder.	4060	12–18	PLIKSi: 11-item semi-structured interview assessing hallucinations, delusions, and experiences of thought interference since age 12.	None Suspected Definite	Definite psychotic experiences occurring monthly over past six months and causing distress, dysfunction, or help-seeking behaviour.
Denissoff et al., 2022	NFBC birth cohort (1985-1986) assessed at age 15-16 for PLEs, followed up until psychosis diagnosis or until age 33.	6552	15–33	PROD-screen: 12-item self-report questionnaire for past 6-month prevalence of PLEs, with each item rated no (0) or yes (1).	PLE- (≤ 2) PLE+ (3+)	ICD-10 diagnosis of psychosis obtained from clinical registry.

Note. ALSPAC, Avon Longitudinal Study of Parents and Children; CIDI, Composite International Diagnostic Interview; DISC-C, Diagnostic Interview Schedule for Children for DSM-III; DMHD, Dunedin Multidisciplinary Health and Development Study; EDSP, Early Developmental Stages of Psychopathology; MUSP, Mater-University Study of Pregnancy; NFBC, Northern Finland Birth Cohort; PLEs, Psychotic-like experiences; PLIKSi, Psychotic-Like Symptom Interview; SCL-90-R, Self-report Symptom Checklist-90-R, TS, top score.

Table 2.2: Descriptive statistics and reported results of population-based longitudinal studies assessing the relationship between psychotic-like experiences in children and adolescents at baseline and psychotic outcome at follow-up.

Study ID	Sample size	Exposure instrument Exposure types	Exposed *n* (%)	Psychotic outcome *n* (% exposure type)	Dichotomized psychotic outcome *n* (% exposure type)	Dichotomized unadjusted OR (95% CI)	Original OR reported by study (95% CI)
Poulton et al., 2000	761	DISC-C: No symptoms Weak symptoms Strong symptoms	 654 95 (12.5%) 12 (1.6%)	 13 (1.99%) 9 (9.47%) 3 (25.0%)	 22 (2.94%) 3 (25.0%)	**11.02 (2.79 – 43.51)**	Strong symptoms: **16.4 (3.9 – 67.8)**
Dhossche et al., 2002	779	Youth Self-Report: PLE- PLE+	 740 39 (5.0%)	 3 (0.41%) 0 (0%)		-	-
Welham et al., 2009	3563	Youth Self-Report: PLE- PLE+	 3112 451 (12.7%)	 38 (1.22%) 18 (3.99%)		**3.36 (1.90 – 5.94)**	males = **5.09 (2.18 – 11.84)** females = **2.27 (1.01 – 5.12)**
Dominguez et al., 2011	845	SCL-90-R: Persistence level 0 Persistence level 1 Persistence level 2 Persistence level 3	 666 132 (15.6%) 33 (3.9%) 14 (1.7%)	 23 (3.45%) 6 (4.55%) 4 (12.1%) 3 (21.4%)	 23 (3.45%) 13 (7.26%)	**2.19 (1.09 – 4.42)**	 Level 1 = 1.5 (0.6 – 3.7) Level 2 = **5.0 (1.6 – 15.9)** Level 3 = **9.9 (2.5 – 39.8)**
Zammit et al., 2013	4060	PLIKSi: None Suspected Definite	 3590 289 (7.1%) 181 (4.5%)	 36 (1.00%) 11 (3.81%) 15 (8.29%)	 47 (1.21%) 15 (8.29%)	**7.37 (4.04 – 13.45)**	 Definite = **12.7 (6.2 – 26.1)**
Denissoff et al., 2022	6552	PROD-screen: PLE- PLE+	 4552 2000 (30.5%)	 73 (1.60%) 81 (4.05%)		**2.59 (1.88 – 3.57)**	CE+ = **3.86 (1.83 – 8.11)** CE- = **2.41 (1.61 – 3.62)**
Meta-analysis	16560	Dichotomized PLE- Dichotomized PLE+	13698 2862 (17.3%)		206 (1.50%) 130 (4.54%)	**3.80 (2.31 – 6.26)**	-

Note. CE, cannabis exposure; DISC-C, Diagnostic Interview Schedule for Children; SCL-90-R, Self-Report Symptom Checklist-90-Revised; PLIKSi, Psychosis-Like Symptom Interview. Bold values indicate $p < 0.05$.

Table 2.3. Univariate regression results for sources of heterogeneity predicting strength of relationship between child and adolescent PLEs and subsequent psychotic disorder.

Independent variable	Adjusted R^2	β	SE	*t*	*p*
Assessment type	0.83	6.48	1.43	4.52	**.020**
Item count	-0.15	-0.23	0.34	-0.68	.544
More than hallucinations	-0.22	2.42	4.70	0.52	.642
Baseline age	0.56	-1.66	0.68	-2.45	.092
Follow-up time	-0.32	0.07	0.43	0.15	.889
Remaining sample	-0.31	0.03	0.13	0.21	.847
Region	-0.06	3.15	3.57	0.88	.443

Note. Categorical variables were coded in the following format: assessment type (questionnaire = 0, interview = 1), more than hallucinations (no = 0, yes = 1), region (Europe = 1, Australia & New Zealand = 2). Bold values indicate $p < .05$.

2.8. Figures

Figure 2.1: Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow chart of study screening process.

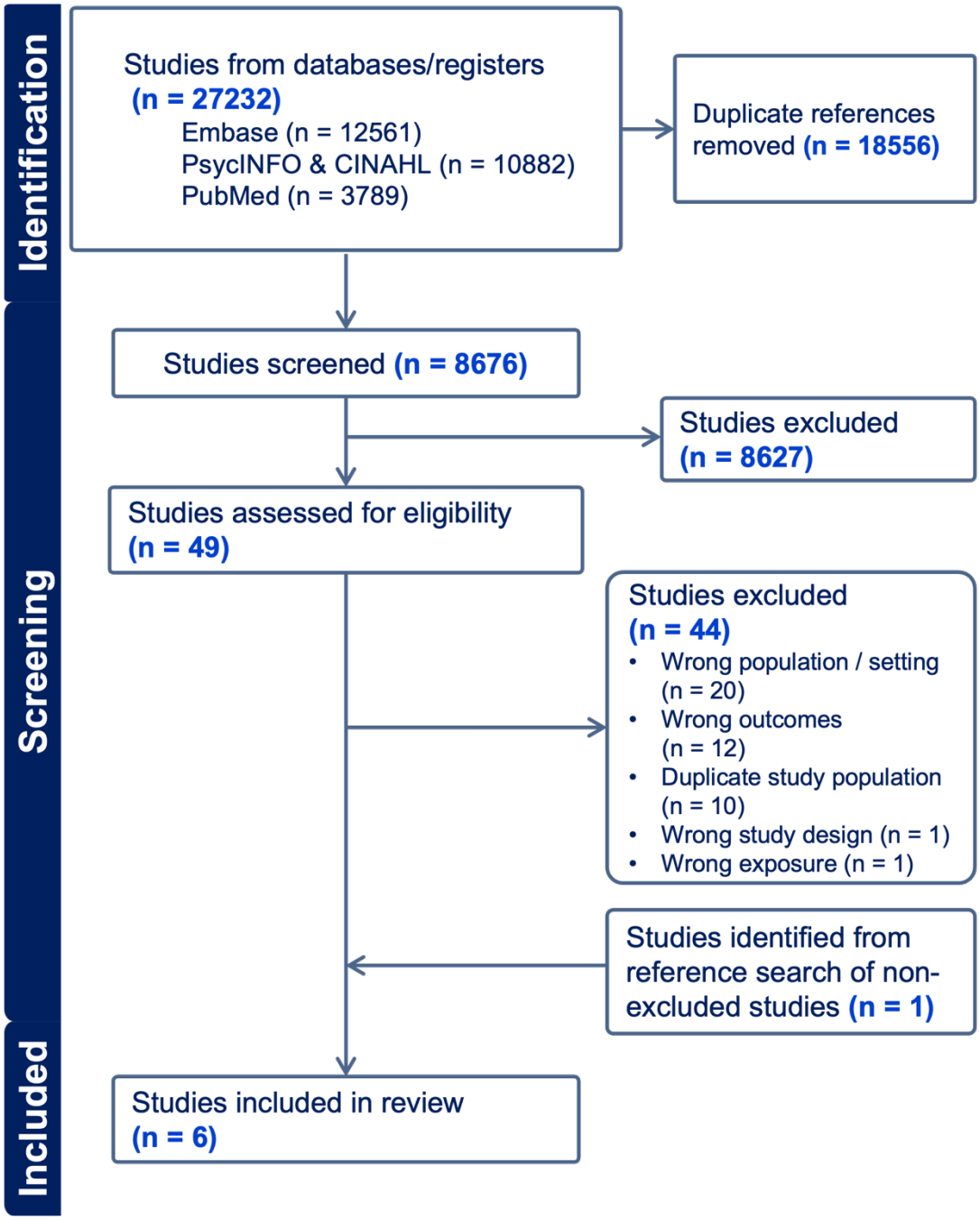
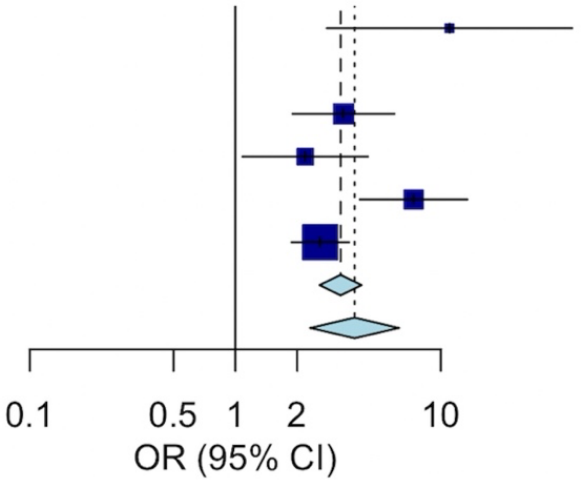


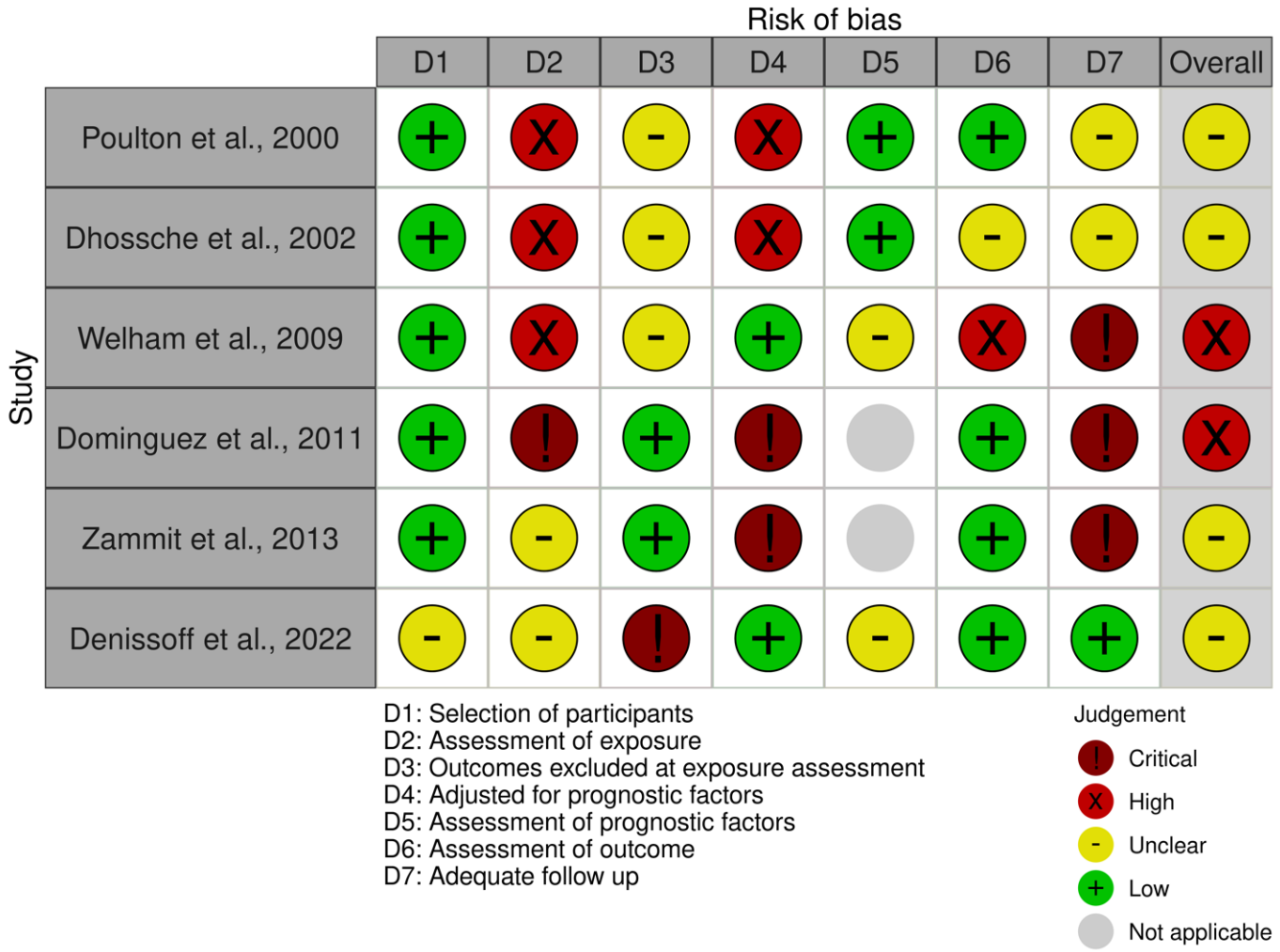
Figure 2.2: Forest plot of unadjusted odds ratios for the relationship between dichotomized exposure of childhood and adolescent psychotic-like experiences and subsequent psychotic disorder.

Source	OR (95% CI)
Poulton et al., 2000	11.02 [2.79; 43.54]
Dhossche et al., 2002	0.00
Welham et al., 2009	3.36 [1.90; 5.94]
Dominguez et al., 2011	2.19 [1.09; 4.42]
Zammit et al., 2013	7.37 [4.04; 13.45]
Denissoff et al., 2022	2.59 [1.88; 3.57]
Total (common effect)	3.25 [2.57; 4.11]
Total (random effect)	3.80 [2.31; 6.26]



Heterogeneity: $\chi^2_4 = 13.29$ ($P = .010$), $I^2 = 70\%$

Figure 2.3. Risk Of Bias In Non-randomized Studies - of Exposures (ROBINS-E) table.



Chapter 3. Bridging Concepts

Chapter 2 highlighted a high prevalence of child and adolescent PLEs in the non-help-seeking population and significant variability in the ability for these PLEs to predict the development of clinical psychosis. Despite these findings, there remains a notable gap in understanding the neurobiological underpinnings of PLEs and the pathophysiological context that may confer their associated risk for psychotic outcomes. Disruptions in neurotransmitter systems, neuroinflammation, and neurodevelopmental processes have all been implicated in the pathophysiology of psychotic disorders. However, it is not clear if these characteristics are present among adolescents experiencing PLEs. By examining if similar disruptions are present in this population, researchers may be better informed to develop interventions that address these specific neurobiological vulnerabilities or identify patients whose PLEs are markers of possible later development of psychotic disorders.

Adolescent cannabis use is highly prevalent amongst adolescents, with a 43% prevalence for past 12-month use in Canada (Canada, 2023). It has been shown that adolescent cannabis use increases the frequency of PLEs (Miettunen et al., 2008; van Gastel et al., 2013; Bourque et al., 2017; Hides et al., 2009; Stefanis et al., 2004), and together with the experience of PLEs further increases the risk of psychosis compared to PLEs alone (Denissoff et al., 2022). Alone, adolescent cannabis use has also been implicated as a risk factor for the development of a psychotic disorder (Large et al., 2011; Kiburi et al., 2021; Marconi et al., 2016; Matheson et al., 2023). This suggests that cannabis use during adolescence may influence the pathophysiology of psychotic disorders, including the subclinical/extended psychosis spectrum.

The connection between early cannabis use and an increased risk of developing a psychotic disorder may be related to altered brain development. Cannabis interacts with the endocannabinoid system, which plays a crucial role in regulating developmental processes such as synaptic pruning and myelination (Patel et al., 2021). Disruption of this system by cannabinoids during critical periods of brain development in adolescence may alter neurodevelopmental trajectory and this is believed to mediate the increased risk for psychosis (Miller et al., 2019; Poulia et al., 2019).

One of the possible mechanisms linking cannabis use and PLEs is increased excitability in the prefrontal cortex and hippocampus, which allows for a pro-inflammatory environment. Chronic activation of CB1 receptors by THC leads to increased net excitability in these brain regions through long-term depression of pre-synaptic GABAergic interneuron activity (Chiu et al., 2010; Jappy et al., 2016; Bloomfield et al., 2016). This heightened excitability promotes the production of pro-inflammatory cytokines such as IL-6, which can further degrade GABAergic signaling and maintain a state of neuroinflammation (Dugan et al., 2009; Rezaei et al., 2024; Zamberletti et al., 2015). This pro-inflammatory environment disrupts normal neuronal function and may contribute to the development of PLEs. Another mechanism involves THC-activated glial cells inducing premature pruning of excitatory synapses in the PFC. In the CNS, THC binds to CB2 receptors primarily on glial cells, leading to their activation, increased release of pro-inflammatory cytokines, and further glial cell recruitment (Miller & Stella, 2008). Chronic activation by THC results in premature glial-mediated synaptic pruning in the PFC, reducing the number of excitatory synapses (Miller et al., 2019). This altered synaptic pruning disrupts the normal development of the PFC, which is crucial for cognitive and executive functions, and may highlight another mechanism for the increased risk psychosis by adolescent THC exposure. It is currently unclear whether these mechanisms are ongoing among adolescents reporting PLEs, one of the earliest expressions of psychosis risk.

Chapter 4 details an observational magnetic resonance study to explore metabolic markers of neuroinflammation in adolescents reporting PLEs and the potential influence of cannabis use. This study interviews a community sample of 15- and 16-year-olds to assess the presence of PLEs and gather information about their cannabis use habits and employs ^{1}H MRS to quantify metabolic markers of neuroinflammation inf the PFC and hippocampus. This empirical investigation aims to fill the gap regarding the neuroinflammatory balance associated with early psychosis proneness (i.e., adolescent PLEs) and contribute to the broader understanding of how adolescent cannabis use may influence this phenomenon and, by extension, the development of psychosis.

Chapter 4. A Preliminary Analysis of Spectroscopic Markers of Neuroinflammation in Adolescents Reporting Psychotic-Like Experiences and the Influence of Cannabis Use

This chapter presents a preliminary analysis of a study that has continuing recruitment beyond the date of analysis. This analysis was created and executed by Isaiah Burton under the guidance of his co-supervisors, Dr. Phil Tibbo and Dr. Candice Crocker. Isaiah was responsible for all aspects of conducting this analysis, including data cleaning and quality control, building of statistical models, and interpretation of findings. The manuscript on this dataset will be drafted after data collection and analysis has been conducted on the complete dataset.

4.1. Abstract

Adolescent psychotic-like experiences (PLEs) are a risk factor for subsequent psychosis, and the use of cannabis during this time increases the likelihood of both. Proton magnetic resonance spectroscopy (^{1}H MRS) has identified similar neurometabolic alterations in those at ultra-high risk for psychosis and among adolescent-onset heavy cannabis users, including altered levels of myoinositol and N-acetyl aspartate (NAA) in the left hippocampus and frontal lobe, which may suggest shared mechanisms of neuroinflammation. It is currently unclear how the neurometabolic alterations associated with adolescent PLEs are influenced by cannabis use. This preliminary analysis of an ongoing single-voxel ^{1}H MRS study assessed the relationship between past 6-month cannabis use (CU6+/-) and PLEs (PLE+/-) in population-representative adolescents and assessed the relationships of each with concentrations of myoinositol, total NAA, and total choline in the left hippocampus and prefrontal cortex. Among seventy-three (n=73) 15- and 16-year-olds, PLEs were reported in 20.8% (5/24) of CU6+ participants and 12.2% (6/49) of CU6- participants. This relationship did not achieve statistical significance (($\beta = 0.634 \pm 0.665$, $p = .34$), however an exploratory analysis revealed a relationship between past 1-month exposure to delta-9-tetrahydrocannabidiol (THC) and PLE score ($p = .007$). PLE+ was associated with a reduced hippocampal myoinositol concentration after correcting for handedness, other substance use, and externalizing behavioural difficulties ($p = .047$), whereas no neurometabolic relationships were found for CU6 status. These findings suggest that adolescent PLEs are not associated with recent cannabis use but may be associated with a reduced concentration or activation of astrocytes in the hippocampus. Furthermore, recent adolescent cannabis use does not affect metabolic markers of neuroinflammation. Future research should compare hippocampal myoinositol with specific markers of glial activation to better understand the significance of reduced hippocampal myoinositol in the context of neuroinflammatory demand.

Keywords. Adolescent cannabis use, choline (Cho), community sample, myoinositol (mI), N-acetyl aspartate (NAA), neurometabolites, non-clinical, proton magnetic resonance spectroscopy, psychotic experiences, subclinical

4.2. Introduction

Subclinical positive psychotic symptoms, or psychotic-like experiences (PLEs), encompass a broad range of symptoms that can be generally classified into perceptual abnormalities (e.g., auditory or visual), delusional (e.g., paranoid) or disorganized thinking and behaviour (Staines et al., 2022; Nelson et al., 2012). These experiences do not meet a clinical classification as they do not meet their specific definition criteria nor cause a functional decline. A lifetime PLE prevalence has been widely reported in the general population with a range of 5-27%, however they are more common in younger populations than in adulthood (Bourgin et al., 2020; Monshouwer et al., 2022; Nordguard et al., 2019; Linscott & van Os, 2013). Most individuals who report PLEs do not develop a psychotic disorder (Kaymaz et al., 2012), however considering the presence of shared risk factors (e.g., genetic, substance use/abuse, psychopathological), PLEs are thought to reflect a subclinical extension of the spectrum for psychotic phenotypes (Staines et al., 2022; Kelleher & Cannon 2012; van Os & Linscott 2012) and thus share neurobiological mechanisms (Healy et al., 2019).

Within the population experiencing PLEs, risk status for a psychotic disorder can be further stratified based on the individual's age, PLE frequency, level of distress duration of symptoms, and genetic risk. The highest degree of risk for a psychotic disorder is often termed the ultra-high-risk state (UHR), where the experiences meet specific criteria for distress, frequency, and duration, and are experienced during the developmental window where the onset of psychosis is most likely (ages 15-25) (Nelson et al., 2014). Contrary to UHR, there is less consensus on the criteria for PLEs. The age in which PLEs are experienced is an important criterion for psychosis risk; adolescents with PLEs are at a significantly increased risk for psychosis compared to adults who experience PLEs (Kaymaz et al., 2012). This population also experiences PLEs at a higher prevalence (8–17%) than the adult population (5-6%) and are below the age of typical psychosis onset in young adulthood (van Os et al., 2009; Kelleher et al., 2012; Maijer et al., 2018; Solmi et al., 2022). Monitoring adolescent PLEs in the general population has been proposed to identify a greater proportion of psychosis prone trajectories; however, heterogeneity in study designs, PLE assessment, and resulting

conclusions on the psychosis-prone dimensions of PLEs have limited reliable PLE assessment in clinical practice (Healy et al., 2019; Lee et al., 2016; Staines et al., 2022). As one of the earliest specific phenotypical expressions of the psychosis spectrum, an improved understanding of adolescent PLEs, its biological underpinnings and environmental mediators is important.

A highly implicated environmental moderator in psychosis proneness is cannabis use, with supporting evidence from all stages of the psychosis spectrum (Matheson et al., 2023; Kiburi et al., 2021). Among PLEs, a recent meta-analysis reported significant moderating effects of lifetime and weekly cannabis use on PLE status in subjects under the age of 18 (Matheson 2023). The frequency of cannabis use has been associated with increased PLEs, with its use as an anxiety coping mechanism moderating PLE-associated cannabis use problems in first- and second-year undergraduate students (Bernusky et al., 2023). Adolescent cannabis use has also been implicated in the earlier onset of subclinical psychotic symptoms, functional decline, and clinical diagnosis of a psychotic disorder (Kiburi et al., 2021).

Cannabis-dose relationships and adolescent PLE research has reported effect sizes generally weaker than among the clinical population, producing mixed reports of an effect when correcting for demographics, other substance use, and/or behavioural difficulties (Degenhardt et al., 2018; Ryan et al., 2020; Bechtold et al., 2016; Dolphin et al., 2015; van Gastel et al., 2013). A dose-dependent effect of cannabis use on PLEs appears to be restricted to adolescents and not adults (Vinkers et al., 2013), stronger association among those assessed at a younger age (Matheson et al., 2023; Konings et al., 2008; Stefanis et al., 2004), and the loss of a significant association with lifetime cannabis use when age of onset is corrected for (Brañas et al., 2016; Konnigs et al., 2008; Jones et al., 2017). This points to a specific vulnerability in adolescence for the interaction between cannabis use and psychosis risk and neurobiological investigations may provide insight into the pathophysiology of psychosis development (Crocker et al., 2017), which may highlight potential targets for intervention.

Neuroimaging studies have been a valuable tool in mapping the psychosis associated effects of adolescent cannabis use. Particular focus has been given to magnetic resonance spectroscopy (MRS), a non-invasive neuroimaging technique able to quantify

in-vivo concentrations of various molecules (Frangou et al., 1996). Proton MRS (^{1}H MRS) is the most frequently used in this research and is best suited for a high-resolution quantification of metabolites (Frangou et al., 1996; Shen et al., 2020). Common metabolites measured with ^{1}H MRS include N-acetyl aspartate (NAA), N-acetyl-aspartyl glutamate (NAAG), total choline (tCho), myoinositol (mI), creatine (Cr), phosphocreatine (PCr). NAA and NAAG (total NAA; tNAA) are synthesized in neurons, with roles in myelin synthesis, mitochondrial energy production, and modulation of glutamate transmission, reflecting neuronal health and density (Baslow et al., 2000; Moore & Galloway, 2002; Moffett et al., 2007; Paslakis 2014; Crocker et al., 2017). Myoinositol (mI), highly concentrated in astrocytes, is involved in osmotic balance, energy production, membrane integrity, and signal transduction, representing astrocyte activity (Chang et al., 1998; Hattingen et al., 2008; Crocker et al., 2017). Total choline (tCho) includes cytosolic and membrane-bound forms, essential for membrane synthesis, acetylcholine production, and lipid metabolism, with concentrations affected by overall membrane turnover (Taybati et al., 2012). Creatine (Cr) and phosphocreatine (PCr) form total creatine (Cr+PCr), serving as an energy reservoir and a marker of metabolic activity (Chen et al., 2023). Together, these metabolites can provide valuable insight to the underlying metabolic state of a brain region.

Concentrations of these metabolites in specific brain regions are affected in the psychosis spectrum and adolescent-onset cannabis use. One of these regions is the prefrontal cortex (PFC), a region critical for executive cognitive functions and working memory. Elevated myoinositol concentrations have been reported in UHR subjects (Romeo et al., 2020) and use of cannabis during adolescence has been associated with altered prefrontal NAA metabolism (Hermann et al., 2007; Prescot et al., 2011). Affected choline metabolism has also been demonstrated in the PFC of long-term cannabis users (Orihuel et al., 2023), however in the psychosis spectrum, this alteration may not precipitate until clinical disorder has developed (Romeo et al., 2020; Bernier et al., 2016; Brecke et al., 2019). The hippocampus is another brain region implicated in the relationship between adolescent cannabis use and psychosis risk, as its roles in long-term memory, learning, and response to stress are negatively impacted in each. Indeed, both heavy adolescent cannabis users (Blest-Hopley et al., 2020b) and individuals in UHR

status (Romeo et al., 2020) demonstrate reduced myoinositol concentrations in the hippocampus and reduced hippocampal NAA is also has been reported in UHR and FEP subjects (Whitehurst et al., 2020).

Neuroinflammation has been proposed to explain the effect of adolescent cannabis use on psychosis risk (Romeo et al., 2022; Morris et al., 2022; Corsi-Zueli et al., 2022; Miller et al., 2019). Neuroinflammation in the central nervous system (CNS) typically involves the activation of glial cells such as microglia, astrocytes, and oligodendrocytes (Domingues et al., 2016; Yang & Zhou, 2018). Astrocytes support neuronal function and maintain the blood-brain barrier (Barres et al., 2008), while oligodendrocytes are responsible for myelinating axons – essential for efficient neural communication (Nave & Werner, 2014). During neuroinflammation, microglia release pro-inflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6) which can lead to further activation of astrocytes and oligodendrocytes, resulting in both protective and potentially harmful effects (Yang & Zhou, 2018). Chronic neuroinflammation can disrupt normal brain function and contribute to various neuropsychiatric disorders (Breke, 2019; Hong et al., 2016). Reflecting this in the psychosis spectrum, increased systemic concentrations of these cytokines are associated with FEP, a relationship moderated by cannabis use before the age of 17 (Corsi-Zuelli et al., 2022).

The primary psychoactive cannabinoid in cannabis, delta-9-tetrahydrocannabidiol (THC) exerts its effects in the CNS by binding to cannabinoid receptors type 1 and 2 (CB1R and CB2R, respectively) (Di Marzo et al., 2015). CB1R is mainly located on neuronal cells in regions such as the PFC (Chiu et al., 2010) and hippocampus (Jappy et al., 2016; Bloomfield et al., 2016). Chronic activation of CB1R by THC has been shown to increase net prefrontal and hippocampal excitability through long-term depression of pre-synaptic GABAergic interneuron activity (Chiu et al., 2010; Jappy et al., 2016; Bloomfield et al., 2016). Increased net excitability in these regions may permit a pro-inflammatory environment that contributes to this chronic change in excitability, as increased prefrontal excitability in associated with IL-6 production (Garcia-Oscos et al., 2012), a cytokine that further degrades GABAergic interneuron signalling (Dugan et al., 2009; Rezaei et al., 2024). Additionally, THC treatment in mice was found to be associated with the reduced expression of glutamate receptor subunits and IL-10 (an anti-

inflammatory cytokine) and the increased expression of astrocytes and pro-inflammatory cytokines (Zamberletti et al., 2015). Prefrontal excitability is critical in the development of schizophrenia, as it may contribute to the dysregulation of the hippocampus-PFC circuitry observed in the disorder (O'Donnell et al., 2008; Gruter et al., 2015; Ando et al., 2012).

CB2Rs in the brain are most extensively expressed on glial cells and are involved in the neuroinflammatory response by regulating glial cell activity (Miller & Stella, 2008). THC exposure in adolescent mice has been shown to induce premature glial-mediated synaptic pruning in the PFC (Miller et al., 2019). Increased cytokine signaling and glial recruitment is also linked to changes in dopamine turnover in the hippocampus and frontal cortex (Borovcanin et al., 2017; Misiak et al., 2021), further connecting inflammation and neurotransmitter dysregulation. As both altered inflammatory cytokine balance and changes in dopaminergic capacity may predict the development of psychosis in CHR individuals (Zhang et al., 2022; Howes et al., 2012), the inflammatory functions of CB2R signalling appears to be an important contributor to psychosis risk. Therefore, it is possible that THC-mediated signaling through CB1R and CB2R biologically connect the metabolic changes resulting from adolescent cannabis use to altered glial activity (Yang et al., 2023; Jeon et al., 2021; Dietz et al., 2020; Brecke et al., 2019) and dysregulated prefrontal synaptic pruning (Yuksel et al., 2021). Together, this data provides a plausible mechanism for the increased risk observed with adolescent cannabis use.

There has not previously been an ^{1}H MRS investigation into adolescent PLEs to provide insight into a potential state of regional neuroinflammation. Further, no investigations have yet looked into how adolescent cannabis use may contribute to this neuroinflammatory state to increase the risk for psychosis. In the clinical population, a spectroscopic investigation exists for the effects of substance use and was not specific to adolescent cannabis exposure (Bernier et al., 2016). This presents gaps in our understanding of how early indicators of psychosis risk may be reflected in underlying neurobiology and how adolescent cannabis use may induce or accelerate a progression of this pathophysiology.

This present study seeks to investigate the shared neurometabolic correlates of PLEs and cannabis use as reported in the general adolescent population. Use of a population-based adolescent sample has the benefit of examining various degrees and patterns of cannabis exposure and increases the generalizability of findings, important for research in a subclinical population with limited healthcare interactions and opportunities for assessment. Here I report on an interim analysis of a subsample for a study that will continue recruitment beyond the defence date. The approach taken in this analysis seeks to first demonstrate a relationship between adolescent PLEs and cannabis use in this sample, then individually identify relationships for each with the neurometabolic markers of interest in brain regions previously implicated in this relationship. If the latter provided evidence of a shared mechanism, a post hoc investigation of the shared metabolites(s) including both PLE and cannabis use variables will be conducted. That is, Aim #1 will seek to assess the association between self-report PLEs and cannabis use reported within the past 6-months (CU6), Aim #2 will assess the effect of self-report PLEs on myoinositol (mI), total choline (tCh), and NAA+NAAG (tNAA) in the prefrontal cortex and hippocampus (HIP), and Aim #3 will be to assess the same neurometabolic effects of past 6-month cannabis use (CU6) among a population-representative sample of 15- and 16-year olds.

Based on the degree of existing evidence, I hypothesize that a positive report of PLEs will be associated with CU6 group membership. Although difficult to predict neurometabolic relationships given the novelty of this present analysis, I predict PLEs to be associated with reduced myoinositol in the frontal lobe and hippocampus, with hippocampal myoinositol also being reduced by CU6 status, highlighting the convergence of metabolic effects on astrocyte function. Given the preliminary nature of this analysis, it is essential that all results be interpreted conservatively and assumed to be pending validation in a more statistically powerful sample. This caveat, however, will not impede a theoretical discussion of results.

4.3. Methods

Design of this research study and the materials used received approval from the research ethics board (REB) of Nova Scotia Health (NSHA) (REB FILE #1027507). This

research study represents a subset of the materials and methods used for the larger Working Group 3 (WG3) of the Canadian Cannabis and Psychosis Research Team (CCPRT).

4.3.1. Participants & Procedures

Inclusion & Exclusion Criteria. Youth, 15 and 16 years of age, were recruited from the Halifax Regional Municipality (HRM). Exclusion criteria included individuals who had been diagnosed with or receiving care for a neurological or psychiatric disorder, have a first degree relative with schizophrenia or bipolar disorder, have experienced a previous significant head injury or seizure, or regular stimulant use. These criteria were maintained to control for factors with the potential to confound the data. This study also required participants to be able to read and speak English, as this was the only language the interview component was offered in. Subjects were also excluded based on safety and suitability for MRI (e.g., braces, permanent retainer).

Recruitment. Participants were recruited through convenience sampling methods which included postering, social media advertising, direct outreach, and snowballing. Study posters were posted on telephone poles near schools, parks, and recreation centres. The posters asked interested 15- and 16-year-olds to scan a QR code using their smartphone, which took them to an online form on REDCap (Research Electronic Data Capture, Vanderbilt Consortium) (Harris et al., 2009; Harris et al., 2019) allowing them to provide their name, consent to be contacted, preferred method of contact, and how they first heard about the study (poster, Instagram, friend/family referral, or other). Posters were also circulated directly to organizations who were willing to make them visible at no cost, including the Halifax Public Libraries, one YMCA location, local fast-food locations, and the Delmore Buddy Daye Learning Institute.

Instagram (Meta, Melno Park, CA, USA) and TikTok (ByteDance Ltd., Bejing, China) pages were created and used as a resource for recruitment (CCPRT Halifax, n.d.a; CCPRT Halifax, n.d.b.). In addition to displaying the posters, these pages shared an REB-approved 60-second promotional video in a youth-friendly format that acted out the steps involved in participation from the perspective of a participant. On Instagram, this video was promoted using Instagram's algorithm-based advertising for professional accounts,

allowing for the selection of a target demographic: 13–18-year-olds in Nova Scotia. From the advertisement, users were directed to the study's Instagram profile where they could access the REDCap link. The Instagram page was linked to the TikTok page in similar fashion which was the flow for this strictly organic traffic (i.e., no advertising).

Direct outreach involved leveraging contacts from members of the research team including community/sports organizations. Participants were also contacted from the ongoing Canadian Underage Substance use Prevention (CUSP) Trial, a multi-site national study that aims to assess adolescent risk behaviour for subsequent substance misuse. As per the REB approval, only those who participated in CUSP and had given consent to be contacted for future research were contacted. Community outreach consisted of the writer and/or two other team members engaging with the youth population in Downtown Halifax, directing anyone interested to the REDCap contact's page.

Snowball sampling was introduced to bolster recruitment. Participants were asked to share their experience participating with their peers in hope of encouraging further inquiries for participation. Despite the tendency for this sampling method to bias towards clusters of similar socioeconomic standing (Parker et al., 2019), recent analyses of its use post-pandemic have shown success with recruiting diverse samples (Leighton et al., 2021; Rubbi et al., 2023). In the context of the aforementioned recruitment strategies, snowball sampling was deemed an acceptable supplement.

Procedures. Upon arrival, individuals participated in an informed consent discussion. A verbal overview of the information was given to the youth including the motives for this research, the risks and benefits of participating, how their data would be stored and used, and about their right to withdraw consent at any point. They were then asked to read an REB-approved informed consent package. Capacity to consent was assessed by asking the participant questions about the study procedures. After reading the consent form package and being given the opportunity to have any questions addressed, those who decided to participate provided written consent. Despite their status as a minor, there is no set age for capacity to consent to medical treatment, research or release of information in Nova Scotia. This allows minors to provide consent for research participation if they are capable of understanding the risks and consequences that they

could be exposed to (Chapter 4: Consent, Capacity and Substitute Decision-Makers, Province of Nova Scotia, 2013).

The interview component inquired about participants' demographic characteristics, substance use history, and psychological health through a battery outlined below. Participants then immediately underwent an MRI scan for the collection of spectroscopic metabolite data via MRS in bilateral frontal lobe and hippocampal (HIP) brain regions. Details on the interview assessments and imaging protocol are further described in sections 4.3.3 and 4.3.4, respectively.

4.3.2. Interview Assessment

Demographics & Assessment Scales. A semi-structured, author-compiled demographics interview with school-life questions gathered data on the participant's age, grade, ethnicity, sex, gender, and socio-demographic characteristics (including living situation, parental education, lifetime school suspensions, and estimated frequency of truancy). The frequency, duration, and purpose for taking any medications and supplements was also recorded.

The Family Affluence Scale (FAS) III (Hartley et al., 2016) questionnaire was used as a validated measure of SES. The FAS-III was developed and validated through qualitative cognitive interviews and focus groups with Scottish 11, 13, and 15-year-olds (Hartley et al., 2016). The FAS-III reflects European and North American consumption patterns, discriminates SES within ultra-rich and ultra-poor environments, and maintains its independence from accurate knowledge of parental occupation or education. This assessment outlines eight self-report items: up to 6 points for "yes" to six yes/no questions and unlimited values for "How many times did you and your family travel outside of Canada for holiday/vacation last year?" and "How many bathrooms (room with a bath or shower) are in your home?", with higher scores indicating a higher SES.

The Adolescent Sleep Wake Scale (ASWS) (Essner et al., 2015), modified from the original 28 item (LeBourgeois et al., 2005), was utilized to assess subjective ratings of sleep quality. Recognizing the unique patterns of adolescent sleep (e.g., decreased duration and inconsistency of sleep [Wolfson & Clarkson, 1998; Leger et al., 2012], their heightened vulnerability to sleep disturbances [Palmer, 2020], and significance of sleep to their mental health [Essner et al., 2015; Palmer, 2020; Tarokh et al., 2014]), evaluation of

subjective sleep quality in this study was to better contextualize and provide insight to their physical, emotional, and cognitive development. Each item is self-report evaluation of a dimension of sleep-wake behaviours where the respondent indicates the perceived frequency of that behaviour (6-point Likert-scale ranging from never to always) with higher scores indicating better-quality sleep. Essner's (2015) analysis demonstrated that the three elected factors possess fair to good internal consistency (Cronbach's alpha: Falling Asleep and Reinitiating Sleep [FARS] = 0.80, Return to Wakefulness [RTW] = 0.89, Going to Bed [GTB] = 0.64) and each item possesses strong factor loading coefficients (range: 0.51–0.87) in a heterogenous sample of 12-18-year-olds (Essner et al., 2015), suggesting this version of the ASWS is both reliable and constructively valid.

The 10-item Edinburgh Handedness Inventory (EHI) (Oldfield, 1971) was used to objectively assess handedness. This was necessary for MRS analyses to control for functional lateralization reflected in the metabolites measured (Braun et al., 2002), and for the possibility of an influence of handedness on psychiatric disturbance (Rodriguez et al., 2010). This self-report questionnaire asks participants to indicate their preferred hand (or lack thereof) for 10 activities of daily living (e.g., writing, throwing, using a spoon), producing a total score quantifying the degree of handedness. The total score ranges from -100 to 100, with 100 indicating complete right-hand dominance, -100 indicating complete left-hand dominance. While Oldfield (1971) originally intended for scores between +/-40 to indicate ambidexterity, a subsequent psychometric validation suggests a threshold of +/-60 or +/-70 for mixed-handedness (Komarc et al., 2014).

Psychological Assessment Scales. Designed specifically for school-aged children, the Adolescent Psychotic-like Symptom Screener (APSS) was used to characterize PLEs in this study (Kelleher et al., 2011). This 7-item self-report questionnaire assesses the lifetime occurrence of psychotic experiences (never = 0, maybe = 0.5, definitely = 1) in the following categories: mind reading, TV/radio communication, spying, auditory hallucinations, controlled, visual hallucinations, and grandiosity. Following the authors' validation, a score of 2 or more (i.e., at least two PLE categories) is defined as PLE+ exposure. This threshold has shown a sensitivity of 70% and specificity of 82.6% when compared with the 2- to 4-hour K-SADS interview (Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present

and Lifetime Version; DSM-5-TR; APA, 2022). On individual items, positive predicted values (PPV) for any interview-confirmed definite experience ranged from 40.0–100%, with negative predicted values (NPV) ranging from 74.1–88.4% (Kelleher et al., 2011). Together, this suggests the APSS is sufficiently reliable and valid for use in the context of this study.

The Strengths and Difficulties Questionnaire (SDQ) was administered as a validated measure of behavioural difficulties (Goodman et al., 1998). The self-report version used in this study was specifically designed for completion by adolescents to maintain high agreement (Spearman's rho = 0.43, $p < .01$) with the same assessment made by parents and teachers (Goodman et al., 1998). This 25-item behavioural screening tool evaluates problematic behaviour over the past six months by asking youth to evaluate their agreement ("not true" = 0, "somewhat true" = 1, and "certainly true" = 2) with statements about their behaviour. Items are summed to produce a total SDQ score, which itself is the sum of five 5-item behavioural sub scores: hyperactivity, emotional symptoms, conduct problems, peer problems, and prosocial. Summing the emotional symptoms and peer problems subscales indicate a score for internalizing problems (SDQ-Int), and the sums of hyperactivity and conduct problems produce an externalizing score (SDQ-Ext). For analysis in the general population, SDQ-Int and SDQ-Ext are recommended over their substituent domains because of their improved discriminatory capacity and agreement with parental assessment in low-risk samples (Goodman et al., 2010). In children, these two domains have also shown to be a risk factor for the subsequent development of both PLEs (Gin et al., 2021; Laurens et al., 2020) and schizophrenia (Hodgins et al., 2014). Furthermore, because hallucinatory PLEs are more common than delusions in the general population and thought to reflect a lower risk for psychopathology (Linszen et al., 2022), the SDQ emotional symptoms (SDQ-Em) subscale was also of interest to this study as it is the only SDQ subscale able to differentiate children with definite hallucinatory-only PLEs from definite PLEs of multiple modalities (Laurens et al., 2020).

Substance Use Assessments. Lifetime exposure to various substances was recorded with the Chemical Use/Abuse/Dependence Scale (CUAD) (McGovern & Morrison, 1992). This semi-structured interview asked participants to describe their

substance use habits using frequency (less than monthly = 1, once or more per month = 2, once or more per week = 3, 3 times or more per week = 4, daily = 5), typical amount consumed per use, typical mode of consumption (oral = 1, inhaled = 2, smoked = 3, injected = 4), and duration of use at this rate and quantity (less than a month = 1, more than a month = 2, six months or longer = 3). Participants were specifically asked about the following substances to gather this data: alcohol, amphetamines, cannabis, cocaine, hallucinogens, inhalants, opioids, phencyclidine (PCP), sedatives/hypnotics/anxiolytics, and other(s). For each substance exposure, the CUAD can determine a dependency score based on 17 true/false questions regarding problematic use habits, which can be summed to produce a substance severity score. The CUAD has demonstrated excellent reliability (1-week test-retest reliability: $r = 0.95$) and acceptable validity (80% true positive hit rate) for identifying substance use disorder (McGovern & Morrison, 1992). In the present study, any level of frequency of alcohol use signified alcohol exposure. Similarly, any substance use excluding alcohol, cannabis, and nicotine were used to identify other substance exposures. In addition, for all participants who indicated prior cannabis exposure, the date since last use was recorded. This allowed participants to be categorized by their history of cannabis use: i) no use ever (or single use longer than 1 year ago), ii) discontinued use (i.e., use on multiple occasions, but not in the past year), iii) use within the past year, iv) use within the past 6-months, v) use within the past 1-month. Use within the past 6-months was designated as recent cannabis users (CU6+/-) and, among these cannabis users, use within the past 1-month (CU1+/-) was defined. Current use of tobacco/nicotine products was also evaluated by asking participants if they currently smoke tobacco cigarettes or use electronic nicotine products.

The Timeline Follow Back (TLFB) is a structured interview used to collect detailed information on participants' cannabis use habits over the past 30 days (Sobell et al., 1996; Robinson et al., 2014). For each instance of cannabis use on a given day, this assessment collects information on the time(s) of day of use, the method(s) of administration (e.g., joint, bong, vaporizer, edible, etc.), the number and type of units consumed (e.g., one joint, two gummies, 5 "pulls" from vaporizer, etc.), the quantity of cannabis product per unit, and the social context (i.e., alone or shared with others) For routine users, a "typical" cannabis use day was also characterized with this information

and extrapolated over typical use days, in addition to recording information on non-typical use days. Participants were asked to estimate these measures to the best of their ability or provide a range from which the average could be taken. The TLFB consistently reports high agreement with biological measures of cannabis use as measured in urine, with a meta-analysis reporting this agreement to be between 87.3% and 90.9% (Hjorthøj et al., 2012). During this assessment, participants were also asked about the strain(s) or name(s) of cannabis products consumed and the concentrations of THC and CBD in each, if known.

4.3.3. ^{1}H MRS Acquisition

Imaging Protocol. Imaging took place at the BIOmedical Translational Imaging Centre (BIOTIC) at the Halifax Infirmary (QEII Health Sciences Complex, Halifax, NS, Canada). Images were acquired using a 3 Tesla (T) GE Healthcare Model M750 whole-body magnetic resonance imager (GE Healthcare MR750, Milwaukee, WI, USA) with a Nova Medical 3T 32-Channel Head Coil (Nova Medical, Wilmington, MA, USA). 3-dimensional T1-weighted images were acquired using sagittal Inverse Recovery Fast Spoiled Gradient Recalled Echo (IR-FSPGR) to produce high resolution whole brain images (TE = 2.94 ms, TR = 6.716ms, FOV = 256mm isotropic, matrix size = 256x256, flip angle = 11°, slice thickness = 1 mm isotropic, number of excitations = 1).

A single voxel MRS approach was applied to four volumes of interest (VOI): left and right prefrontal cortex (PFC) and hippocampal (HIP) regions. All voxels were 20x20x20 mm^3 in size. PFC VOI were centred in the dorsomedial prefrontal region, encompassing predominantly white matter (WM) tracts with inclusion of the superior edge of the anterior cingulate cortex (ACC) and medial edge of the superior frontal sulcus (Figure 1a). HIP VOI were centred just anterodorsally from the middle of the hippocampus, ensuring no inclusion of the cerebellum and brain stem (Figure 1b). The MRS sequences were acquired using a Spin Echo, full Intensity Acquired Localized (SPECIAL) Point-Resolved Spectroscopy (PRESS) sequence (TE= 35 ms, TR= 3000 ms, FOV = 240 mm^2 isotropic, CSI matrix = 1, acquisition time = 456 sec, bandwidth= 2.0 kHz, water suppression with chemical shift selective [CHESS] pulses, averages = 128, water-unsuppressed acquisitions = 8). The modification of the PRESS RF sequence to

include spin echo with an adiabatic pulse better protects against field inhomogeneity within the volume of interest (VOI), allowing for the use of shorter TEs and improved signal identification than with PRESS alone (Mlynárik et al., 2006). This was viewed as essential in this study as it allowed for a more optimal balance between spectral quality and scan time, an important consideration for adolescents who are known to have greater difficulties staying stationary for extended scans (Jensen et al., 2017). Prior to each voxel acquisition, higher order shimming (HOS) of the magnetic field was done to optimize pre-scan linewidth. As time permitted, pre-scans and HOS were repeated to achieve a linewidth of < 10 Hz for PFC and < 12 Hz for HIP voxels.

Spectral Processing. Grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) fractions within the VOI were estimated using Advanced Normalization Tools (ANTS) (Avants et al., 2014) tissue segmentation on the T1-weighted image. Preprocessing, fitting, quantification, and quantitation of the MRS data were achieved with FSL-MRS version 2.1.19 (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl), an end-to-end MRS analysis software from FMRIB Software Library (Clarke et al., 2021). FSL-MRS was favoured over the more widespread LCModel (Provencher et al., 2001) for its user-independent pre-processing, simulated and fully customizable basis set, and use of highly sophisticated fitting algorithms. More specifically, FSL-MRS benefits from a weighted singular value decomposition (SVD) coil combination using a Bayesian maximum likelihood model. This method identifies noise across spectra which is applied to better identify signal and significantly improve SNR compared to the standard averaging as done in LCModel (Rodgers & Robson, 2010). Furthermore, since basis set composition has been shown to affect spectral fit and quality (Demler et al., 2023), and updated basis sets are no longer provided for LCModel, this degree of flexibility allowed for further spectral refinement that is not afforded by LCModel. All default FSL-MRS preprocessing parameters were used, which have been described elsewhere (Clarke et al., 2021). In brief, this process entailed frequency-phase correction to correct for data drift, removal of any residual water in suppressed peaks, eddy-current correction (ECC) to correct phase shift, and SVD-weighted coil combination.

Spectral Quality Control. Parameters for spectra-level quality control were experimented with to maximize spectral inclusion while maintaining a baseline standard of signal and metabolite resolution. HIP spectra were consistently observed to produce poorer signal-to-noise ratios of the NAA signal (SNR) and linewidths than for PFC voxels in the same subject. This could be reflecting greater field inhomogeneities within the voxel due to the greater magnetic susceptibility artifacts in its subcortical location (i.e., tissue and air-filled spaces, including the brain stem, ear canal, and sinuses) which was unable to be consistently mitigated with HOS (Weygand at al., 2016). Different criteria for each region were also experimented with that were comparable to criteria used in studies with similar imaging parameters, voxel locations, and participant ages (Blest-Hopley et al., 2020b; Valkenboroughs et al., 2021; Tennous et al., 2021, Prescot et al., 2011). This included SNR thresholds of 5, 10, and 15, and linewidth thresholds of 15 and 20 Hz. It was observed that restricting linewidths to ≤15 Hz and SNRs to ≥10 respectively excluded 49% (63/129) and 18% (23/129) of available HIP spectra, many of which included ideal SNRs and well-resolved metabolite peaks. This compared to only a 5.9% (8/135) exclusion of PFC spectra with the same criteria. A similar effect saw an SNR of ≥15 exclude 33% (42/129) of HIP spectra and only 6.7% (9/135) of PFC spectra. Loosening the SNR criterion to ≥5 provided little to no benefit compared to an SNR of 10. Further visual inspection of the spectra was able to identify that a loosening of PFC linewidth thresholds from 15 Hz to 17 Hz was able to include four additional PFC spectra.

The spectra-level quality control parameters decided upon were SNR ≥10 for all spectra, linewidth ≤17 Hz for PFC spectra, and ≤20 Hz for HIP spectra. Furthermore, spectra with an uncertain quantification of metabolites were excluded from analysis, as identified by a percent Cramer-Rao lower bound (CRLB%) greater than 20%. SNR, linewidth, and metabolite CRLB% for all spectra were visually inspected to ensure no inclusion of poorly fitted and quantified data.

Monthly MRS acquisitions of the ^{1}H-MRS Spectroscopy Phantom (GE Healthcare, Milwaukee, WI, USA) were performed throughout the course of the study to assess variation and drift in metabolite concentrations over time (Woo et al., 2009). With respect to the metabolites of interest in this study (tNAA, tCh, mI), visual inspection of

mean absolute metabolite concentrations, their standard deviations, and the trend over time revealed no drift in quality that would require correction.

4.3.4. Statistical Analysis & Considerations

Power Analysis. G*Power version 3.1.9.6 statistical software (Faul et al., 2009) was used to evaluate the minimum expected sample size to provide sufficient power to accomplish each of the three aims. This calculation required a desired α (0.05), power (0.8), and expected effect size and allowed for manipulation of the test family (t-test), statistical test, and number of tails (two). Addressing Aim #1, there are limited number of studies that report adolescent PLE and cannabis-use observations in mid-adolescent samples (aged 14–17), either assessing lifetime use (Denissoff et al., 2022; Stainton et al., 2021; Bourque et al., 2017) or past-year use (Hides et al., 2009). Further, only one of these studies reported on PLE status based on a validated score cut-off (Denissoff et al., 2022). While these studies may serve to provide the best estimates for this analysis, a true determination of sample size for this specific research question cannot be calculated based on the available evidence. Denissoff and colleagues (2022) reported PLEs identified by the PROD-screen and lifetime cannabis exposure in a birth cohort of 15- and 16-year-olds (n=6552). The equation presented by Chinn (2000) allowed for manual computation of the effect size, and a G*Power point biserial correlation test determined the total necessary sample to be 17 participants. The next most similar study did not find an association between past-year cannabis use and scores on the positive scale on the Community Assessment of Psychic Experiences (CAPE-P) (Hides et al., 2009), which yields a required sample of 1008 with at least 72 cannabis users using an independent difference in means calculation. Similar conclusions were drawn from a separate study comparing CAPE-P scores with lifetime cannabis use (Stainton et al., 2021), in which the calculation suggests a total sample size of 8454 participants with at least 1117 cannabis users. Furthermore, another study observed different trajectories of PLEs between ages 13 and 16: low/stable, increasing, and decreasing trajectories (Bourque et al., 2017). At age 16, comparing lifetime cannabis exposure in the increasing group (40.3%) to the low (16.4%) and decreasing (28.6%) groups suggests a total sample size of 21 participants. The drastically different effects provided by these studies reflect the considerable

heterogeneity in criteria for identifying PLEs and provides little guidance on a reliably sized sample for this study.

Estimating the sample size required to detect a difference in neurometabolites between PLE groups (Aim #2) was also not feasible as this study is the first investigation into the effect of subclinical psychotic symptoms on neurometabolite concentrations in humans. However, addressing the effect of cannabis on MRS-identified neurometabolites, Blest-Hopley and colleagues (2020b) (n=43) identified a significant effect of adolescent-onset cannabis use on left hippocampal myoinositol among young adults (18–34 years-old). An independent difference in means statistical test yields a minimum required sample of 72 with at least 37 cannabis users to address this aim with sufficient power. Another relevant study found reduced myoinositol and NAA in the ACC of a younger sample of heavy adolescent-onset cannabis users (Prescot et al., 2011) that suggest sample sizes of 74 and 82 to detect differences in NAA and myoinositol, respectively. However, the effects expected to be observed in this present analysis were not expected to be as strong since the investigations by Blest-Hopley (2020b) and Prescot (2011) were among heavy long-term cannabis users and age- and sex-matched controls. Therefore, conducting a similar analysis in the general population would require an even larger sample to achieve the same power.

Following 16 months of recruitment, data was available for a total of 73 participants, thus a preliminary analysis on a subset of data obtained from an ongoing study.

Data Preparation. All data was imported into RStudio v2024.04.0+735 (RStudio Team, 2020) based on R version 4.3.2 (R Core Team, 2023) for analyses. Linear regression-based imputation was applied only to missing interview datapoints that formed a total or average score. The larger score excluding the dependent score was calculated and subsequently used as the predictor. All other missing interview data and features of substance use indicated as “not known” were imputed as the variable mean. Imputation was preferred over maximum likelihood-based handling of missing data in regression analyses as it better protects against model overfitting and dissolution, a crucial goal for this restricted sample. Means and standard deviations (s.d.) of interview and metabolite

data were calculated for the two PLE exposure groups, the four PLE/CU6 exposure groups, and the entire sample.

Considerations for Imaging Analysis. Investigating the potential effect of brain lateralization, a paired sample t-test revealed that all metabolites were significantly elevated in the right PFC (5.6 – 16.8%, $p < 1e\text{-}6$) and left HIP (7.0 – 12.4%, $p < .02$) compared to left PFC and right HIP, respectively. Given the uncertainty of interhemispheric effects in relation to PLEs, analysis of hemispheres individually was preferred to maintain goodness-of-fit and interpretation quality. Analyzing only a single hemisphere in this pilot sample also reduced the number of imaging hypotheses, lessening the reliance on correction methods for Type I errors. The left PFC data was chosen due to a ubiquitous decrease in variance across metabolites in the left hemisphere compared to the right in this sample (20.4% mean decrease in s.d.). Although left HIP VOI did not demonstrate such a difference in variance, other studies have reported specific sensitivities of left hippocampal mI to external influences (Husarova et al., 2012; Njau et al., 2016; Valkenborghs et al., 2022). Furthermore, a left hemisphere bias of metabolic dysfunction is also implicated in the psychosis spectrum (Molina et al., 2005; Lieberman et al., 2018). Therefore, data from only the left hemisphere was chosen for subsequent analyses.

Main Analysis. For Aim 1, a logistic binomial generalized linear model (GLM) was applied to assess the relationship between adolescent PLEs (dependent) and CU6 status (independent) using an inverse Gaussian family to handle positively skewed data (Dunn & Smyth, 2018). For Aims 2 and 3, multiple linear regression models were used to predict the effects of adolescent PLEs and CU6 on regional neurometabolite concentrations, maintaining subject handedness as a required covariate. A post hoc analysis depended on the identification of a regional neurometabolite significantly affected by both adolescent PLEs and CU6 status. For each significant regional neurometabolite, the combined effect of adolescent PLEs and CU6 status on its concentration assessed by multiple linear regression was sought to reveal the contributions of both to variance in the metabolite's concentration.

Results were reported as the regression coefficient (β), standard error (± S.E.), and p-value, with a significance threshold of 0.05. False discovery rate (FDR) corrections were applied to adjust for multiple testing. Given the preliminary nature of the analyses, uncorrected p-values were reported alongside corrected p-values due to the potential conservativeness of FDR corrections.

Exploratory Analysis. A prominent obstacle to investigating the biological effects of cannabis use is the significant heterogeneity across use habits. The Government of Canada recently identified eight different cannabis use products used by Canadians (Canada, 2024), many of which can be consumed in different ways, each with their own standard use habits (Shauer et al., 2020). The result is a wide range of THC exposure patterns that are difficult to reflect in standard categorical measures of cannabis use habits. Acknowledging the arbitrariness and potential lack of insight from a 6-month threshold for recency of cannabis use, it was thought useful to additionally explore the effects of estimated THC exposure (THCe), or past-month THC dosage, in mg over the past 30 days, calculated from the TLFB. THCe from flower consumption was calculated by multiplying the quantity (g/unit) by the frequency (number of units) by the stated concentration percentage (assumed to be percent by mass), divided by the number of people the cannabis product was shared with. THCe from edible consumption was calculated similarly, however participants often reported the quantity in mg of THC, eliminating the need for a concentration term. Unlike flower and edibles, vaporizers are not designed to be consumed entirely in a single use, so participants would report the number of "puffs" consumed, the total quantity of concentrate, and less often, the THC concentration. To quantify THCe for vaporizers, two assumptions were necessary: i) all puffs are equal in volume and ii) 1 gram of oil contains 200 puffs. Insufficient literature on the topic renders the second assumption merely an estimate (straingenie.com/thc-dosage-calculator). This allowed THCe to be calculated by multiplying the fraction of vaporizer consumed (number of puffs divided by 200 times the quantity of concentrate in grams) by THC concentration. THCe was calculated for each mode of cannabis consumption for each day and summed to produce a total 30-day THCe. When not known by the participant, THC concentration was imputed as the mean concentration for the respective mode of consumption.

Exploratory analyses addressed the heterogeneity in cannabis use habits by calculating THCe over the past 30 days. THCe was calculated for flower, edibles, and vaporizers, considering the amount, frequency, concentration, and sharing practices. APSS score replacing PLE status was also conducted to assess this relationship in a dose-dependent manner. Furthermore, analyses with SDQ externalizing scores replacing PLE status were conducted. This was to explore the concept of PLEs being one manifestation of global psychiatric vulnerability that may be modified by cannabis use in adolescence. For APSS and SDQ-Ext explorations, ordinal regression models were used due to the graded nature of the score distributions.

Sensitivity Analysis. Sensitivity analyses were conducted for relationships that approached or achieved significance by adding covariates and reassessing relationships. To manage model complexity in this small sample, a list of candidate covariates was selected based on previously hypothesized or demonstrated relationships with PLE or cannabis use. These variables were assessed through t-tests to determine their inclusion based on demonstrated effects. For Aims 1 and 2, potential covariates included age, sex, ethnicity, FAS total, subjective sleep quality, SDQ-Em, SDQ-Int, SDQ-Ext, and other substance use. CU6 status was assessed for effects of spectral acquisition characteristics (SNR, FWHM, and tissue fractions), age, sex, FAS total, parental migration status, and other substance use. Significant findings indicated that PLE status was affected by SDQ-Ext, other substance use excluding tobacco/nicotine, SDQ-Int, and ethnicity (Table 1). CU6 status was affected by other substance use (Table 1). SDQ-Ext was preferred over SDQ-Int due to its stronger effect, and ethnicity was excluded to maintain model simplicity. Significant relationships from Aim 1 (main and were reassessed with adjustments for other substance use and SDQ-Ext scores. Aim 2 findings were adjusted for other substance use, SDQ-Ext, and handedness, while significant Aim 3 findings were adjusted for other substance use and handedness.

4.4. Results

4.4.1. Sample Description

Recruitment. 74 participants were eligible for inclusion and were recruited to participate between Dec 2022 and Apr 2024. At the consent discussion, a second screen of study eligibility identified an additional exclusion (language considerations), thus 73 participants subsequently completed the interview and participated in imaging. Four participants did not complete the full-length imaging protocol (partial imaging data collected), and one MRS file was lost during the data transfer process. The sample sizes of the imaging data collected, in the order of collection, are: T1-w (n = 72), left PFC MRS (n = 70), left HIP MRS (n = 68). Incomplete imaging was due to insufficient time (n = 2), intolerance to scanner environment (n = 1), and the presence of braces (n = 1).

Data Skewness. Initial histogram inspection revealed positive skewness for most interview variables, with negative skewness observed for handedness and alcohol use, and balanced distributions for SDQ-Ext and SDQ total. Among substance users (cannabis, alcohol, and other), all features of use for that substance were negatively skewed. Imaging metrics followed similar trends between PFC and HIP regions: slight positive skewness for metabolite concentrations, strong right skewness for metabolite CRLB%, and balanced distributions for tissue fractions. However, SNR and FWHM were positively skewed in PFC spectra but were more balanced in HIP spectra.

Demographic Characteristics. A description of this population-based adolescent sample by PLE and CU6 statuses are provided in Table 4.1, and by combined status in Table 4.2. This was a predominantly female sample by sex and gender (female: n = 43 [58.9%], male: n = 24 [32.9%], non-binary: n = 6 [8.2%]). Participants all attended school and were in either grade 11 (n = 46 [63.0%]) or grade 10 (n = 17 [23.2%]), or other (n = 10 [13.7%]). With respect to parental migration status, 56.2% (n = 41) of participants had two parents who were born in Canada, 19.1% (n = 14) had one, and 24.7% (n = 18) did not have either parent born in Canada. At least one parent was reported to have attained post-secondary education in 79.5% (n = 58) of the sample.

Lifetime suspensions from school were reported by 23.3% (n = 17) of participants, and 45.2% (n = 33) admitted to truancy from class at an estimated average of 30.6 occasions per school year (SD = 48.5, range: 1–200). Twelve participants (16.4%) were currently taking prescribed medications at the time of participation, including oral contraceptives (n = 5), steroid inhalers (n = 4), and others (n = 7). Missing demographics data for one item from one participant (ASWS item #4) was imputed with ordinal regression. Among demographic variables assessed to be affected by PLE status (age, sex, ethnicity, FAS, ASWS Total), ethnically white-identifying participants (60.3% [44/73]) were more greatly represented in the PLE- group (64.5% [40/62]) than in the PLE+ group (36.4% [4/11]) (t = 2.15, p = .035). The remaining demographic variables were not associated with PLE status. By CU6 status, no effects were observed for age (p = .199) sex (p = .328), FAS (p = .618), nor parental migration status (p = .676).

Figure 4.2 displays the distribution of APSS scores by CU6 status. A score of 2+ indicating PLE+ status was true for 15.1% (n = 11) of this sample. By APSS item, definite and possible experiences were reported for spying (definite: n = 8; possible: n = 26), auditory hallucinations (definite: n = 7; possible: n = 12), visual hallucinations (definite: n = 3, possible: n = 9), mind reading (definite: n = 2; possible: n = 18), TV/radio communication (definite: n = 2; possible: n = 5), under special control (definite: n = 1; possible: n = 4), and grandiosity (possible: n = 1). Any single definite experience was reported by 12 participants, with two of these participants not meeting the total score threshold for PLE+. Both of these participants had a score of 1.5, with definite scores for spying and auditory hallucinations, and possible scores for mind reading and visual hallucinations, respectively. Alternatively, one PLE+ participant did not report any definite experience but reported possible experiences for spying, auditory hallucinations, visual hallucinations, and mind reading.

SDQ item #8 was missing for one participant and was predicted from an ordinal regression of total SDQ-emotions scores minus the missing item. SDQ-Int and SDQ-Ext scores were significantly associated with PLE status (SDQ-Int: t = 2.31, p = .024; SDQ-Ext: t = 3.26, p = .002), both higher among PLE+ participants (SDQ-Int: mean = 8.4, range: 3–15; SDQ-Ext: mean = 9.5, range: 6–13) than among PLE- (SDQ-Int: mean = 5.8, range: 0–18; SDQ-Ext: mean = 6.1, range: 0–13). The association observed for SDQ-

Em did not reach statistical significance (p = .08). SDQ scores were not affected by CU6 status.

Substance Use Characteristics. Lifetime cannabis use on more than one occasion or single-use within the past year was reported by 38.4% (n = 28) of the sample, with 32.9% (n = 24) having last used cannabis in the last six months and these participants comprised the CU6+ exposure group. Among CU6+ participants, 66.7% (16/24) had used cannabis in the past 30 days (CU1+ group). Frequency of cannabis use by CU6+ participants were described as less than once a month (33.3%; 8/24), more than monthly but less than weekly (25%; 6/24), at least weekly but no more than thrice weekly (12.5%; 3/24), and daily (29.2%; 7/24). All participants who used more than three times a week used daily.

Features of cannabis use collected from CU1+ participants for exploratory analyses are reported in Table 4.3. CU1+ participants tended to report using cannabis for all 30 (37.5%; 6/16) or for less than 5 (50%; 8/16) of the previous 30 days, with the other two participants having used for 18 and 28 days in the past month. Most CU1+ participants reported consuming cannabis in the form of flower (75%; 12/16), with considerable representation from users of vaporizers (37.5%; 6/16). Three CU1+ participants (18.8%) reported using multiple methods of THC consumption in the past 30-days: all three used flower and vaporizers, one also used edibles, and another used hash/kief. Exactly half of CU1+ users could report the potency of THC in the product(s) they used: 22.8% mean THC for flower (6/12), 95.8% mean THC for vaporizer, and 100mg THC per edible unit (1/2). Imputing mean THC potency for participants who did not know, the average exposure to THC over the past 30-days (THCe) was 10778 mg (SD = 19294 mg), ranging from 5 mg to 72618 mg. Expressing this as a function of 1-gram joint-equivalents at 15% THC, this equates to a 30-day average of 71.9 joint-equivalents (SD = 128.6, range: 0.03 to 484.1). The primary consumption methods that provided participants with the most THCe included flower (68.8%; 11/16), vaporizer (25%; 4/16), and edibles (6.3%, 1/16).

Recreational alcohol use was common, reported by 63.0% (n = 46) of all participants. Nearly all CU6+ users reported consuming alcohol (91.7%; 22/24), compared to just 49% (24/49) in CU6- participants. Use of other substances was much

less common (23.3%; 17/73) and significantly associated with CU6+ (t = 3.90, $p < .001$) but not PLE status (t = 1.11, $p = .272$). Other substance use included nicotine vaporizers (n = 16), hallucinogens (n = 9), tobacco cigarettes (n = 7), cocaine (n = 4), sedatives/hypnotics/anxiolytics (n = 4), opiates (n = 2), and amphetamines (n = 1). Further excluding nicotine and tobacco products from other substances, all remaining other-substance users had used at least hallucinogens (9/9) and demonstrated a significant bias towards PLE+ (4/9; t = 2.73, $p = .008$) and CU6+ (8/9; t = 2.89, $p = .004$) statuses and was used as the primary variable for other substance use.

4.4.2. ^{1}H MRS Spectral Quality

Initial experimentation with MRS acquisition was necessary to accommodate imaging in this adolescent sample. As a result, MRS data for the first participant was demonstrated to be significantly unlike the rest, with most metabolite peaks unable to be resolved from the noise after various re-fitting attempts and was therefore excluded from analysis. MRS data for an additional participant was lost during the data transfer process. That allowed 68 PFC and 66 HIP spectra to reach quality assessment. Spectra-level quality criteria eliminated 1 PFC and 16 HIP spectra. All metabolites from included spectra had a CRLB% less than 20% and were therefore included in analyses.

A description of the included spectra by region and PLE status are shown in Table 4.4, and by region and CU6 status in Table 4.5. The quality of PFC spectra was markedly superior to HIP spectra, evidenced by a higher mean SNR and lower mean FWHM (Table 4.4). Comparing the PFC and HIP data included in analyses, there were no statistical differences in demographic (age, sex, lateralization/handedness, ethnicity, FAS, ASWS Total), psychological (SDQ scores), substance use (non-cannabis/alcohol and non-cannabis/alcohol/nicotine other substance use), or main exposure status variables (PLE & CU6) between the data available in these regions. Furthermore, spectral characteristics investigated (SNR, FWHM, tissue fractions, and lateralization/handedness) did not demonstrate an effect on PLE nor CU6 status.

4.4.3. Aim 1: Adolescent PLEs & Cannabis Use

PLEs were reported in 20.8% (5/24) of CU6+ participants and in 12.2% (6/49) of CU6- participants. Mean APSS scores were similar between groups; CU6+: 0.85 (SD =

1.27), CU6-: 0.82 (SD = 0.98) (Figure 4.2). Modelling this relationship demonstrated CU6 status not to be predictive of PLE status alone (β = 0.634 ± 0.665, *p* = .34) nor in combination with other substance use and SDQ-Ext as predictors (β = 0.065 ± 0.910, *p* = .943). An ad hoc Chi square test to account for limitations in the small sample confirmed no relationship (*p* = .54).

In exploratory analyses (Figure 4.3), replacing CU6 with THCe as the predictor in a subset of CU1+ participants demonstrated an effect on PLE status that did not achieve statistical significance (β = 0.103 ± 0.061, *p* = .091). Including the primary method of THC consumption as a predictor was unable to improve the model (β = 0.080 ± 0.058, *p* = .173). This analysis revealed that no participants in this sample with a non-flower primary method of THC consumption experienced a PLE.

Analysing APSS score as the PLE outcome did not yield a significant relationship with CU6 status (β = -0.300 ± 0.470, *p* = .528), but did with THCe in CU1+ participants (β = 0.151 ± 0.056, *p* = .007). Adding the primary method of THC consumption maintained this significant finding (β = 0.143 ± 0.057, *p* = .012). Exploring this model further by replacing the primary method of consumption with covariates from the main analysis demonstrated a significant effect with less error than the previous two models (β = 0.147 ± 0.055, *p* = .008). A final model that reincorporated the primary method as a fourth predictor identified a similar but less certain degree of significance (β = 0.146 ± 0.056, *p* = .01).

Externalizing Difficulties. To explore whether externalizing difficulties more strongly associated with cannabis use variables, SDQ-Ext was used as the main outcome variable and demonstrated no relationship with CU6 status (β = 0.239 ± 0.438, *p* = .586). However, there was a significant effect of THCe predicting higher SDQ-Ext scores in CU1+ participants (β = 0.069 ± 0.032, *p* = .034) that did not reach the threshold for significance after controlling for primary method of consumption (β = 0.060 ± 0.033, *p* = .069). A subsequent model using other substance use and PLE status as predictors alongside THCe produced the strongest relationship (β = 0.092 ± 0.040, *p* = .022) (Figure 4.4) that maintained significance following inclusion of primary consumption method (β = 0.087 ± 0.040, *p* = .032).

4.4.4. Aim 2: Adolescent PLEs & Neurometabolites

Metabolite concentrations by region and PLE status are displayed in Table 4.6 and Figure 4.5. A base model where metabolite concentrations were estimated by PLE status and handedness identified no relationships in the PFC region and a nearly significant effect of PLE+ on reduced myoinositol in the HIP region ($\beta = -3.087 \pm 1.536$, $p = .050$, $q = .402$). Adding other substance use to this model allowed for the effect of HIP myoinositol to reach uncorrected significance ($\beta = -3.328 \pm 1.634$, $p = .047$, $q = .380$). These findings were consistent in a third model that added SDQ-Ext as a fourth predictor ($\beta = -3.479 \pm 1.729$, $p = .050$, $q = .402$).

Exploration with APSS score as the main predictor did not identify any significant relationships with metabolite concentrations in either region, regardless of covariates. The same was found in a similar analysis of SDQ-Ext with PLE status as the fourth predictor in the third model.

4.4.5. Aim 3: Adolescent Cannabis Use & Neurometabolites

Metabolite concentrations by region and CU6 status are illustrated in Table 4.7 and Figure 4.6. In the two main analysis models that covaried by handedness with and without other substance use, CU6 did not demonstrate any relationship with metabolite concentrations (myoinositol, tNAA, tCh) that approached even uncorrected statistical significance. The condition of identifying a metabolite independently influenced by both PLEs and CU6 was therefore not satisfied to permit the post hoc analysis.

4.5. Discussion

The present study aimed to investigate the possible relationships between adolescent psychotic-like experiences (PLEs), cannabis use, and neurometabolite concentrations in the left prefrontal cortex and hippocampus, as measured with ^{1}H MRS. To the best of my knowledge at the time of writing, this is the first investigation seeking to provide evidence for a converging neurometabolic mechanism between cannabis use and PLE pathophysiology in adolescents. Preliminary analysis of this ongoing study was unable to identify a significant association between past 6-month cannabis use and APSS-identified PLEs. Examining the effects of each on neurometabolite concentrations in the

left prefrontal cortex and hippocampus identified an inverse relationship between PLEs and hippocampal myoinositol when controlling for other substance use and externalizing behavioural difficulties. Past 6-month cannabis use did not demonstrate a relationship with the metabolites investigated. These early results suggest that recent cannabis use is not associated with self-reported PLEs among population-representative adolescents, with no evidence of a shared neurometabolic mechanism in the left prefrontal cortex and hippocampus.

4.5.1. Adolescent PLEs & Cannabis Use

Although past 6-month users were identified as PLE+ (20.8%) more frequently than non-users (12.2%), this relationship did not achieve statistical significance in this study. Meta-analyses on the topic generally report that a relationship between adolescent cannabis use and PLEs exists (Matheson et al., 2023; Linscott & van Os, 2013); however, mixed results on the study level suggest the relationship may be modulated by various factors. It is possible that our finding of no relationship between adolescent cannabis use and PLEs is genuine despite power concerns, as is suggested by our large uncorrected p-value (p = .34) from this analysis, aligning with a past report of no concurrent relationship (Stainton et al., 2021; Degenhardt et al., 2018; Dolphin et al., 2015).

While our findings did not demonstrate that correcting for other substance use and externalizing difficulties to reveal a relationship between PLEs and cannabis use, other substance use was significantly associated with both PLEs and cannabis use. It is possible that the use of other substances, and not cannabis use, is responsible for past findings of a relationship between cannabis use and PLEs in adolescents. Previous research has shown that the concurrent use of substances such as alcohol, tobacco, and other illicit drugs can complicate the assessment of cannabis's specific impact on psychotic-like experiences (PLEs) (Linscott & van Os 2013; Matheson et al., 2023; Vaughan et al., 2006; McGrath et al., 2016). For instance, Linscott and van Os (2013) found that exposure to any substance doubled the risk for psychotic experiences, indicating that poly-substance use is a critical factor to consider when examining psychotic outcomes. Matheson et al. (2023) observed that young people who used substances were nearly twice as likely to experience PLEs compared to non-users, with alcohol, tobacco, and amphetamine use each significantly contributing to this increased risk. Additionally, Vaughn (2006)

demonstrated that poly-substance use, was related to higher levels of paranoid ideation and psychotic symptoms, indicating that the combined effects of multiple substances can exacerbate psychotic-like symptoms more than cannabis use alone. Together, this may suggest that other substance use be both a proxy for cannabis use and the predominant driver of its apparent relationship with adolescent PLEs. Indeed, the frequent and more intense use of other substances during adolescence shows a dose-dependent relationship with the severity of PLEs (Marconi et al., 2016; Degenhardt et al., 2018).

Other dimensions of psychopathology are also involved in this relationship. Although externalizing difficulties did not differ by cannabis use status, exploratory analyses revealed a significant linear relationship with past-month THC exposure within past-month cannabis users. Unlike its relationship with APSS scores, where scores rapidly increased only among those most exposed to THC, SDQ externalizing scores were relatively high and increasing across the spectrum of exposure. This may suggest that externalizing difficulties, such as aggression and conduct problems, may be more indicative of underlying psychopathology that contributes to psychosis risk independently of cannabis use. Research has shown that externalizing behaviors are significant predictors of psychosis (Gin et al., 2021). Reflecting this, delinquent and aggressive behaviours in childhood are associated with psychosis in early adulthood (Welham et al., 2009). Hastings (2019) and Cannon (2001) also demonstrated that these early behaviors increase psychosis risk, especially when combined with other risk factors such as social withdrawal.

In addition to externalizing difficulties, internalizing difficulties such as anxiety and depression also play a significant role in psychosis risk (Gin et al., 2021). Indeed, this was evidenced in this present analysis with an association between internalizing SDQ scores and PLE status, although this was not chosen as a covariate due to the stronger effect of externalizing psychopathology and their close relationship together demonstrating global psychiatric vulnerability (Sunderland et al., 2021). Therefore, it may be that a general psychopathological burden may serve as the underlying risk factors for psychosis over the psychotic dimension of PLEs alone.

Extending these findings further, it is likely that the interplay between different substances and their reciprocal effects on psychopathology could contribute to the

observed PLEs in adolescents. Childhood behavioral problems are linked with earlier onset and higher frequency of substance use, including cannabis, alcohol, and tobacco (Miettunen et al., 2013; Oshri et al., 2011; Storr et al., 2011; Coffey et al., 2022). For example, children exhibiting aggressive and delinquent behaviours are more likely to engage in substance use at an earlier age (Storr et al., 2011; Coffey et al., 2002). Internalizing difficulties have been shown to mediate the relationship between substance use and psychotic symptoms, suggesting that adolescents with higher levels of anxiety and depression are more vulnerable to the psychosis-inducing effects of substances (Henquet et al., 2005). In the other direction, early substance use can also predict subsequent psychopathology in adolescents (Friedman et al., 1987; Ernst et al., 2006; Gau et al., 2018). Therefore, there appears to be influences of both self-medication of psychopathology through the use substances (Khantzian, 1985; Khantzian, 1997) and an effect of substances on psychiatric vulnerability.

These relationships can be further complicated by early childhood exposures like maltreatment and victimization (Fisher et al., 2013a), behavioural difficulties (Gin et al., 2021), and substance use (Abajobir et al., 2017; Boyda et al., 2018; Mackie et al., 2011) which also increase the risk of PLEs. Furthermore, genetic components have also been linked with externalizing difficulties (Barr & Dick, 2019), internalizing difficulties (Ensink et al., 2019), substance use (Salmanzadeh et al., 2021), and psychosis risk (O'Donnovan et al., 2009). It is therefore possible that this collection of factors may specifically contribute to a general psychopathological burden, creating a trajectory towards both substance use and increased psychosis risk (Storr et al., 2011; Coffey et al., 2002; Merrin et al., 2022; Guxen et al., 2007). That is, this broader risk profile, influenced by the combined effects of multiple substances and underlying behavioral tendencies, likely contributes to the increased risk of psychosis more than cannabis use alone.

Cannabis Use Recency vs. THC Exposure. Exploratory analysis revealed a significant correlation with increasing past-month cannabis exposure and APSS scores within past-month cannabis users (for which this data was available). Considering that THC is the primary active component in cannabis and a mediator of pro-psychotic mechanism *in vitro* (Miller et al., 2019) and symptoms *in vivo* (Englund et al., 2016;

Martin-Santos et al., 2012), our quantification of a continuous THC exposure likely provided improved dimensionality over any past 6-month exposure in its ability to characterize the psychotogenic effects of adolescent cannabis use. Given the variability in product potency, methods, and patterns of cannabis use (Canada, 2024; Bonar et al., 2017), it is not immediately clear whether, for example, a frequent light user is differentially exposed to or engaging in more pathogenic use habits than less frequent users of larger amounts. While some authors have differentially highlighted cannabis use frequency (Marconi et al., 2016; Hines et al., 2020; Hides et al., 2009), duration/onset of use (Jones et al., 2017; Konings et al., 2008; Stefanis et al., 2004), and potency (Di Forti et al., 2014; Di Forti et al., 2015; Di Forti et al., 2019) as the primary mediators of the dose-response relationship, others have provided evidence against their influences when correcting for other risk factors (Ryan et al., 2020). One study in particular saw the loss of an effect of average THC potency when adjusting for frequency of use (Hines et al., 2020). In a similar effect, only high potency cannabis was associated with FEP in a large urban sample, with risk further increasing with the frequency of high-potency cannabis use (Di Forti et al., 2015). This suggests an interaction between cannabis use features that can modulate its role on psychosis risk, an interaction that was not captured in a 6-month recency measure of cannabis use.

4.5.2. Adolescent PLEs & Neurometabolites

This analysis provided evidence for a relationship between adolescent PLEs and reduced hippocampal myoinositol concentrations, with this relationship reaching statistical significance when accounting for other drug use and externalizing behavioural difficulties. No significant relationships were observed with the other metabolites (tCh and tNAA) or in the PFC.

Our finding of reduced myoinositol in the hippocampus is quite unique among investigations on subclinical psychotic symptoms in this region. In a sample of 25 UHR subjects, Shakory (2018) saw no difference in myoinositol concentrations. Conversely, Bossong (2019) and colleagues conducted a longitudinal study of 86 UHR participants and found that elevated hippocampal myoinositol was a significant indicator of subsequent psychotic disorder compared to both non-progressors and healthy controls. Further, a meta-analysis on UHR samples saw no difference in the hippocampus, but

elevated myoinositol in the DLPFC that was not evident among just CHR subjects (Romeo et al., 2020), which may implicate a role of genetics in myoinositol sensitivity as well.

Heterogeneity between these two samples and the distinctness of our study population could help explain these disparate findings. Heterogeneity exists in the inclusion of UHR subjects, as these studies employed differing criteria for severity, frequency, and duration of symptoms. Shakorky (2018) defined risk with the Structured Interview for Psychosis-Risk (SIPS) (Miller et al., 1999; Miller et al., 2002), while Bossong (2019) included participants based on UHR status from the Comprehensive Assessment of At-Risk Mental State (CAARMS) (Yung et al., 1998; Yung et al., 2005). Although assessing highly similar concepts via interview assessment (APS, BLIPS, and GRD), SIPS has a slightly less restrictive threshold for paranoid thinking (whereby "mild" severity can signify APS), and a lower requirement for symptom frequency (at least once per week) (Perkins et al., 2004; Fusar-Poli et al., 2016). However, the longer window for clinical deterioration permitted by CAARMS allowed it to identify slightly more UHR individuals than with SIPS in a side-by-side comparison (Fusar-Poli et al., 2016). Compared to our population-based analysis, both of these UHR samples from case-control studies similarly represent populations further at-risk. As a result, our findings, though seemingly contradictory, may not be so, given the distinct risk profile of our subjects.

The insignificant findings for tNAA and tCho in our sample of PLE-reporting 15–16-year-olds are similar to those for the medial PFC (Da Silva 2018a; Wang 2020) and hippocampus (Shakory et al., 2018; Bossong et al., 2018; Wang et al., 2020) in higher risk populations. One meta-analysis suggested a potential decrease in hippocampal tNAA among UHR subjects; however, this finding became insignificant after restricting analysis to just CHR (Romeo et al., 2020). This may suggest that diverging neuropathological trajectories exist for psychotic disorder development based on prior risk status, a notion that has been extensively acknowledged (Lizano et al., 2019; de Wit et al., 2016; Sugranyes et al., 2020; Assaf et al., 2022; Liberg et al., 2016; Bartholomeusz et al., 2017). However, it is currently unclear how genetic risk factors that are present in the

PLE-reporting adolescent population may be reflected by tNAA concentrations in the hippocampus.

4.5.3. Adolescent Cannabis Use & Neurometabolites

This analysis did not identify any metabolites in the frontal lobe nor hippocampus that were affected by past-6-month cannabis use. This finding came in contrary to the hypothesis of reduced hippocampal myoinositol proposed for our sample, as had been previously observed among heavy adolescent-onset cannabis users (Blest-Hopely et al., 2020b). This could be further indicative of the cumulative effects of sustained cannabis use, as this analysis was conducted on young adults (ages 18-34) who had been using cannabis more than three days per week over the previous two years, whereas our sample was population-based and included many mixed/infrequent users. This may also contribute to our discordance with the finding of reduced NAA/Cr ratio in the DLPFC of a late-adolescent sample of heavy cannabis users (Hermann et al., 2007). However, a real effect on creatine could also contribute to this difference as it was not assessed in our study. Although reduced prefrontal creatine has not previously been demonstrated in the subclinical population, they are reduced in FEP patients (Tibbo et al., 2013), raising this possibility. An analysis of THC exposure on neurometabolites could have further assessed the metabolic effect of cumulative (recent) adolescent cannabis use, however this was not suitable in this preliminary analysis due to the limited number of CU1+ MRS data. As the first MRS analysis in this young of a sample of general-population cannabis users, these results may simply be reflecting a lack of effect of cannabis use recency on hippocampal and prefrontal metabolism at this age and degree of cannabis exposure. This will be clarified, along with a more detailed assessment of specific features of cannabis use, when total recruitment has been satisfied and a more in-depth statistical analysis is permitted.

In the PFC, our results also do not align with the report of reduced NAA and myoinositol in the ACC of heavy late-adolescent users (Prescot et al., 2011). However, in addition to being an older sample with a greater cannabis-use burden, it cannot be ruled out that their inclusion of a predominantly grey matter region in the frontal lobe may have contributed to this difference in findings. Evidence is mixed regarding a differential effect of cannabis use in white and grey matter and is likely further dependent on the

region (Mashhoon et al., 2013; Hirjak et al., 2021; Hermann et al., 2007; Chang et al., 2006). For example, a sample of heavy cannabis users displayed lower mI/Cr ratios in global white matter (Silveri et al., 2011), and in a predominantly white matter section covering the left thalamus not seen in temporal or parieto-occipital cortices nor in controls (Mashhoon et al., 2013). However, the latter analysis included only white matter-predominant voxels, and no group by region by tissue type interaction was assessed. Furthermore, while grey matter volume reductions are reported in a combined structural/functional MRI study of heavy cannabis users (Hirjak et al., 2021), this study did not search for white matter correlates. Together, this suggests there may be a regional difference to the effects of heavy adolescent cannabis use on white and grey matter, a potential influence that could not have been identified in this study.

4.5.4. Implications for Neuroinflammation in Adolescent PLEs

The heterogeneity reported in the literature on the significance of myoinositol changes in the extended psychosis phenotype is supportive of a progressive dysregulation of neuroinflammatory processes that contribute to risk for psychosis. That is, it is possible that the decrease in hippocampal myoinositol seen in this lower-risk sample and the increase in hippocampal myoinositol among UHR subjects noted in other research (Romeo et al., 2020) may be reflecting a progressive breakdown of its signalling as additional risk is conferred through chronic neuroinflammation.

Myoinositol is widely available in the cell and mitochondrial membranes of astrocytes with notable roles in glucose metabolism and energy production (Brand et al., 1994; Downes & Macphee, 1990; Abdali et al., 2015). A reduction in hippocampal myoinositol could therefore be suggestive of early astrocytic cell loss or impaired energy metabolism that reduces astrocyte activity. This suggests that the risk for psychosis identified by PLEs in adolescents may be the result of an altered neuroinflammatory state where glial cells are in an early phase of dysfunction, leading to a lower level of astrocyte activity or reactivity. This hypothesis aligns with the findings that initial glial cell dysfunction, particularly in the hippocampus, is a precursor to more pronounced inflammatory responses as the risk for psychosis increases (Misiak et al., 2021; Zhang et al., 2022; Lieberman et al., 2018). Our findings also suggest tNAA and tCh may not be affected, implying that neuronal integrity is likely maintained. The stability of these

metabolites also supports the initial hypothesis of weak neuroinflammatory aberrations in PLE-reporting adolescents, where this alteration in the neuroinflammatory balance is primarily affecting the availability or reactivity of glial cells rather than a robust neuroinflammatory response on neurons and synapses.

Within the elevated risk profile of UHR subjects, the evidence for increased hippocampal myoinositol suggests a heightened state of astrocyte activation and inflammation. At this stage, elevated myoinositol could indicate the initiation of neuroinflammatory signalling resulting in glial cell proliferation (Shakory et al., 2018). This is supported by elevated serum concentrations of IL-6 in UHR subjects (Misiak et al., 2021), and a lower IL-1B/IL-6 ratio predictive of progression to psychosis (Zhang et al., 2022). Changes in global mitochondrial function have also been identified in UHR subjects, where increased global glial cell activity correlates with decreased mitochondrial activity (Da Silva et al., 2018b), further marking a role of a dysregulated neuroinflammatory response in subclinical psychosis pathology. Together, this suggests that the difference in neuropathological environments between adolescents with PLEs and those at UHR status could be the initiation or escalation of neuroinflammatory signalling in the context of an impaired neuroinflammatory response. However, it is not known whether adolescents with PLEs also display changes in inflammatory signalling. That is, reduced myoinositol could also be explained by lower levels of inflammatory signalling that are the reason for the reduced astrocyte activity, rather than an impairment of astrocyte function in an unaltered cytokine profile. However, the finding of high-risk genetic variants in enzymes that are concentrated in astrocytes responsible for glutamate metabolism (Xin et al., 2016) and elevated hippocampal Glx concentrations in the hippocampus of UHR subjects suggest that astrocytic dysfunction may already be apparent in this population (Romeo et al., 2020).

Furthermore, our results add to existing evidence implicating the hippocampus among earliest affected brain structure in the development of psychosis risk (Lieberman et al., 2018), where altered PFC metabolism may only start to become apparent in a greater state of risk, as in the UHR population. The subsequent inclusion of the PFC and the identification of global mitochondrial deficiency in UHR subjects could implicate a direction of psychopathological development, whereby a heightened neuroinflammatory

state beginning in the hippocampus propagates to distal connections (Da Silva et al., 2018b; Lieberman et al., 2018). This progression of chronic neuroinflammation is further supported in the clinical population, as the reduced prefrontal myoinositol concentrations in this population may arise from glial cell desensitization following chronic exposure to pro-inflammatory cytokines. In fact, glial desensitization is a specific effect of long-term IL-6 exposure (Recasens et al., 2021). Despite reduced glial activity, elevated serum IL-6 levels correlate with longer illness duration and treatment resistance, suggesting persistent inflammation impacts brain function even as glial responses diminish (Ganguli et al., 1994; Lin et al., 1998; Da Silva et al., 2018b; Plaven-Sigray et al., 2018; Cotter et al., 2001; Dietz et al., 2020). The inverse relationship between glial activity and negative symptoms in FEP further supports this mechanism of chronic inflammation and glial desensitization (Dunleavy et al., 2022).

Influence of Cannabis Use. If PLE status reflects a state of impaired neuroinflammatory processes or capacity as is suggested by our results, there does not appear to be a contributing role of cannabis at this level of risk. In context with the available clinical evidence, it is more likely that chronic adolescent cannabis use influences the pathophysiology of psychosis only after neuroinflammatory processes have become truly dysregulated. CB1 receptors on glial cells function to modulate neuroinflammatory and apoptotic responses (Howlett et al., 2002; Leonard & Ariciglu, 2023). Our finding of no relationship between recent adolescent cannabis use and neurometabolites suggests that this low threshold of exposure does not significantly affect inflammatory processes. However, prolonged activation of these receptors by THC could lead to a reduced sensitivity of glial cells to endogenous signals, impairing their neuroprotective functions, a mechanism previously demonstrated in an animal model (Burston et al., 2010). If true that adolescent PLEs reflect just an impairment of neuroinflammatory capacity and not a state of ongoing inflammation, the insignificance of recent cannabis use on PLEs may also suggest its insignificance on inducing inflammation. Alternatively, in the context of neuroinflammation already in-progress, chronic cannabis use could exacerbate this pathology through further desensitization of glial cells. Even among adolescents with PLEs, it is possible that a THC-mediated desensitization of glial cells primes an environment with an even further diminished

capacity to respond to pro-inflammatory signals. Therefore, while not influencing the presentation of PLEs, this mechanism would contribute to a neural environment of greater psychosis risk, a theory well suited to explain the acceleration of psychosis onset among adolescent users.

4.5.5. Strengths and Limitations

Study Design. This study's design benefits from a population-representative adolescent sample, enhancing the relevance of findings for public health, particularly in reporting population prevalences (e.g., PLE and CU6 statuses) and assessing clinical risk in subclinical populations with infrequent healthcare encounters. However, the underpowered sample may have hindered the ability to identify meaningful relationships. Without a case-control design, increased variability around the variable of interest limits statistical precision, leading to greater error estimates and wider confidence intervals. This limitation may have influenced the finding of no relationship between cannabis-use recency and PLEs, despite a notable difference in PLE prevalence by cannabis use status.

Recruitment strategies included postering, community outreach, social media, and contact lists from ongoing studies, supplemented by snowball recruitment. Snowball sampling, while prone to sampling bias (Parker et al., 2019), was acceptable given recent successes in recruiting diverse samples post-pandemic (Leighton et al., 2021; Rubbi et al., 2023). The urban setting, necessary for participant presence, may have biased the sample toward urban-dwelling adolescents, who are linked with higher rates of psychotic experiences (Saxena et al., 2022; Bouter et al., 2023; Beyer et al., 2024) and cannabis use outcomes (Schell et al., 2022; Kuepper et al., 2011; Hasin et al., 2018), complicating the isolation of cannabis use effects.

High ethnic diversity strengthens findings by reflecting various demographic statuses but complicates external validity due to increased PLE reporting among ethnic minorities. This relationship, although not included as a covariate to maintain model simplicity, still presents a possible influence on assessed relationships (Leaune et al., 2019). Furthermore, a cross-sectional design, while limiting causal inference, aided participant retention and generalizability. This is crucial in adolescent PLE research with high loss-to-follow-up rates (Welham et al., 2009; Dominguez et al., 2011; Zammit et al., 2013).

Study Assessments. Internal validity was maintained through validated questionnaires and assessments, with interviews led by graduate students likely improving honest self-reporting of cannabis use and minimizing authority bias. However, reliance on self-report measures, like the APSS and TLFB, introduces biases such as social desirability and recall bias, affecting data accuracy (Camerini et al., 2018; Grimm et al., 2010; Latkin et al., 2017). Misreporting of cannabis use, whether underreported due to illegality or overreported to align with perceived study goals, therefore poses a limitation. Future research should incorporate objective measures of cannabis use, such as saliva or urine samples, and interview-assessed PLEs for more accurate insights.

The APSS is a self-report assessment of PLEs that, as evidenced in Chapter 2, is not as strong at identifying psychosis risk states than interview-based assessments. The choice for the APSS came prior to the Chapter 2 analysis, and its high average positive and negative predictive values for each item compared to interview (72.6% and 78.2%, respectively) suggests the APSS is a reasonably reliable self-report questionnaire (Kelleher et al., 2011). Furthermore, the APSS's classification of PLE+ may have influenced findings, as it does not distinguish between symptom severity. Differences in presentation regarding cannabis use and neurometabolic markers might be clearer with more stringent criteria, like UHR/CHR status. PLE assessment heterogeneity also impacts external validity, suggesting a need for more commonly used measures like the PLIKSi. Considering the importance of participant perception of commitment (de Jong et al., 2022), the goal was to make the interview less demanding, using easily administered surveys suitable for large samples and short clinical visits.

The TLFB's limited data on THC exposure, restricted to past 30-days, limited exploratory analyses with THC exposure. The small sample and elimination of spectra during quality control further constrained statistical modeling. Future research should explore THCe's relationship with PLEs and neurometabolic markers.

^{1}H MRS. There are a number of strengths to the application of ^{1}H MRS in this study. The use of FSL-MRS software provides distinct advantages over the more widely used LCModel. Instead of necessitating a metabolite basis set that had to have been previously acquired under the same conditions (including scanner manufacturer, echo time, field strength, and set metabolites), FSL-MRS uses its advanced software to

simulate a basis set with the desired conditions. This is especially advantageous as it allows researchers to adapt a basis set to a field-specific research standard, important for the cross-comparison of results between studies since basis set composition can critically affect the concentrations and relationships observed in MRS imaging (Demler et al., 2023). Further to this effect, this analysis reported the MRS methods and results in accordance with recently established recommendations (Near et al., 2021; Lin et al., 2021; Wilson et al., 2019), contributing to the potential reproducibility and validation of these presented findings.

The voxels that were included in this analysis also provided some useful insight. In addition to assessing implicated brain regions in different functional regions (hippocampus and frontal lobe), these voxels contained a differing predominance of tissue type (grey matter and white matter, respectively). This allowed for insight into multiple emerging ideas regarding the regional- and tissue-specific bias for adolescent PLE neurobiology and the effect of cannabis use. However, because both tissue types were not assessed in each region, nor was there a correction for tissue type, no conclusions could be definitively drawn from this data, simply hypotheses and directions for future research. Furthermore, full inclusion of a previously implicated PFC region, like the ACC or the DLPFC, would have provided more supplemental insight to the insignificant findings in this prefrontal WM-predominant region, particularly regarding hypotheses on the propagation of psychosis risk and the influence of cannabis.

A drawback to the use of ^{1}H MRS in its current state is the inability to distinguish the cell-specific metabolite concentrations within a voxel (Crocker et al., 2017). While measuring overall metabolite concentrations within a voxel, it cannot distinguish between contributions from different cell types, such as neurons and glial cells, nor can it distinguish contributions from the extracellular matrix. This limitation hinders the ability to make precise conclusions about the cellular mechanisms underlying the observed metabolic changes.

Voxel placement and inclusion present further considerations. The small head sizes of adolescent participants posed a challenge, leading to variable voxel placement. Smaller head sizes can result in difficulties in consistently placing voxels in the same anatomical locations across participants, introducing variability in the data. This

variability may affect the reliability of the findings, as slight differences in voxel placement can lead to differences in the measured metabolite concentrations. Furthermore, due to the voxel placement order of 1) R PFC, 2) L PFC, 3) R HIP, 4) L HIP, the number of available voxels prior to quality control decreases in this order. This is due to the scan length – at nearly 60 minutes, not every participant was able to be scanned for the full-length protocol, resulting in less hippocampal scans than frontal scans. The significant number of L HIP spectra that were excluded during quality control likely also reflects participant restlessness at this point near the end of the protocol and, likely to some degree, researcher fatigue. This also further necessitates validation of our finding in the hippocampus.

Using a 3T magnet offers both strengths and limitations to this study. The primary strength lies in the enhanced SNR and improved spectral resolution at 3T compared to lower strengths, which facilitate more accurate quantification of small metabolites (Wilson et al., 2019; Di Costanzo et al., 2007). This higher resolution helps better distinguish between closely spaced peaks and overlapping resonances. However, a limitation of a stronger magnet includes the potential for increased susceptibility artifacts and chemical shift dispersion (Wilson et al., 2019). This can complicate the interpretation of spectra, particularly in regions with complex tissue composition like the hippocampus. Additionally, while 3T provides a good balance between SNR and practicality, it does not achieve the same level of metabolite differentiation as higher field strengths (e.g., 7T), potentially limiting the detection of subtle metabolic changes. A comparison of metabolite quantification under 3T and 7T conditions found prefrontal tNAA and tCh concentrations to be significantly higher with 7T and CRLB% for both significantly lower (Terpstra et al., 2016). The same was also found for tNAA in the cerebellum (Terpstra et al., 2016). While this could be suggested as a reason for the lack of relationship between PLEs and tNAA in the hippocampus as is seen across the psychosis spectrum, the vast majority of these studies were conducted under 3T conditions. Whether hippocampal tNAA concentrations may be marginally impacted in adolescents with PLEs is arguably less important to understanding the pathophysiology of psychosis than the increase in effect size of tNAA alterations with more severe psychotic states,

which should be identified under similar imaging conditions. Overall, the use of 3T is well suited for this research.

The choice of SPECIAL-PRESS is another strong suit and follows recent recommendations to improve MRS research homogeneity (Wilson et al., 2019). PRESS is recommended over STEAM (stimulated echo acquisition mode), another widely used RF sequence, because while STEAM uses three 90-degree excitation pulses, PRESS uses one excitation pulse and two 180-degree refocusing pulses. The planar refocusing pulses in PRESS produces a perpendicular spin echo in addition to the stimulated echo, whereas STEAM only utilizes one plane of the magnetic field for signal detection. Under the same TE, field strength, and number of acquisitions, PRESS can therefore provide two times the signal compared to STEAM (Wilson et al., 2019). However, the downside to PRESS is that the refocusing pulses are of lower bandwidth and therefore cause greater chemical shift displacement in less homogenous magnetic fields. In turn, this adds more uncertainty to metabolite quantification with the same TE as STEAM. This effect was mitigated with the use of the adiabatic pulses provided by the SPECIAL modification, as these pulses have a substantially greater bandwidth than the traditional PRESS pulses (*Adiabatic Pulse – An overview*, 2004; Wilson et al., 2019). Field inhomogeneity still nonetheless posed a challenge in our acquisition of hippocampal voxels, contributed to by its proximity to air/tissue interfaces (e.g., ear canal and sinuses), its deeper location, and participant restlessness.

CHESS is the most common method of water suppression used in ^{1}H MRS psychosis research. This method uses frequency-selective RF pulses to selectively excite water protons followed by a gradient pulse to dephase the water signal (Buonocore & Maddock, 2015). Other methods used include VAPOR (variable power RF pulses with optimized relaxion delays) and MEGA (Mescher-Garwood). Both methods provide advantages over CHESS in preventing water sideband distortions, but their applications are more complicated, and in the case of MEGA, requires precise frequency calibration with the metabolite(s) to be enhanced. In this study, the quantified metabolites included myoinositol (~3.6 ppm), tCh (~3.2 ppm) and tNAA (~2.0 ppm). As the smallest and closest to the water peak, it is possible that myoinositol could have been affected by water sideband distortions. Mitigating this effect, this study doubled the recommended

acquisitions for analyzing a 20x20x20mm voxel at 3T, thereby improving the reliability signal detection across all metabolites (Wilson et al., 2019).

Finally, the inability to incorporate both hemispheres due to sample size constraints was another limitation. Bilateral measurements would have provided a more complete picture of the neurometabolic effects, as asymmetries in metabolite concentrations between the hemispheres could be relevant for understanding the underlying neurobiology of PLEs and cannabis use. This study's finding of significantly more variance in the right hippocampus could have revealed a lateralization of psychosis risk and/or the effects of cannabis use, which could have been commented on in context of a leftward bias in the psychosis spectrum. Increasing the sample size in future studies would allow for the inclusion of both hemispheres in a multi-level random effects model, providing more comprehensive data.

4.6. Conclusion

To conclude, past 6-month cannabis use did not demonstrate an effect on PLEs in this cross-sectional analysis of a population-representative adolescent sample. Alternatively, a restricted exploratory analysis among past-month cannabis users suggested positive relationship between THC exposure and self-report PLEs. Assessing neurometabolic alterations, adolescents reporting PLEs showed a decreasing trend for left hippocampal myoinositol, and no trends were found among past 6-month cannabis users. These findings suggest that adolescents experiencing PLEs may exhibit impaired neuroinflammatory capacity in the hippocampus. While also suggesting adolescent cannabis use may not be associated with PLEs, it may be that THC exposure better encompasses the psychotogenic properties of adolescent cannabis use and requires further investigation. Future research should attempt to quantify THC exposure in context with other patterns of cannabis use in humans to isolate specific use habits that may prime a neurobiological environment for increased psychosis risk. This could allow for a more widespread application of informed harm reduction strategies in the subclinical/nonclinical adolescent population.

4.7. Tables

Table 4.1. Sample description of demographic, psychological, and substance use characteristics.

Sample Characteristic	Total (n=73)	PLE+ (n=11)	PLE- (n=62)	Test statistics	CU6+ (n=24)	CU6- (n=49)	Test statistics
Demographics							
Age, mean (SD)	15.8 (0.6)	16.0 (0.8)	15.7 (0.6)	t = 1.26, *p* = .212	15.9 (0.7)	15.7 (0.6)	t = 1.30, *p* = .199
Sex				t = -0.39, *p* = .689			t = -0.94, *p* = .348
Females, % (n)	65.8% (4)	72.7% (8)	64.5% (40)		75% (18)	61% (30)	
Males, % (n)	31.5% (23)	27.3% (3)	32.3% (20)		25% (6)	34.7% (17)	
Undisclosed, % (n)	2.7% (2)	0% (0)	3.2% (2)		0% (0)	4.1% (2)	
Ethnicity				**t = 2.15, *p* = .035**			
White, % (n)	60.3% (44)	36.4% (4)	64.5% (40)		66.7% (16)	57.1% (28)	
Other, % (n)	24.7% (18)	27.3% (3)	24.2% (15)		12.5% (3)	30.6% (15)	
Mixed, % (n)	15.1% (11)	36.4% (4)	11.3% (7)		20.8% (5)	12.1% (6)	
Parental migrant status							t = 0.42, *p* = .676
All born in Canada	56.2% (41)	45.5% (5)	58.1% (36)		58.3% (14)	55.1% (27)	
Mixed	19.2% (14)	27.3% (3)	17.7% (11)		20.8% (5)	18.4% (9)	
All migrated to Canada	24.7% (18)	27.3% (3)	24.2% (15)		20.8% (5)	26.5% (13)	
FAS, mean (SD)	7.2 (1.8)	6.4 (0.8)	7.3 (1.9)	t = -1.69, *p* = .095	7.0 (2.2)	7.3 (1.6)	t = -0.50, *p* = .618
ASWS, mean (SD)	3.6 (0.8)	3.1 (0.8)	3.7 (0.8)	t = -1.94, *p* = .056	3.7 (0.9)	3.5 (0.8)	
Psychological							
APSS, mean (SD)	0.83 (1.08)	2.95 (1.11)	0.45 (0.46)		0.85 (1.27)	0.82 (0.98)	$\beta = -0.300 \pm 0.47$, *p* = .528

Sample Characteristic	Total (n=73)	PLE+ (n=11)	PLE- (n=62)	Test statistics	CU6+ (n=24)	CU6- (n=49)	Test statistics
SDQ Externalizing, mean (SD)	6.59 (3.37)	9.45 (2.50)	6.08 (3.26)	**t = 3.26, *p* = .002**	6.88 (3.43)	6.45 (3.36)	
SDQ Internalizing, mean (SD)	6.21 (3.47)	8.36 (3.78)	5.82 (3.30)	**t = 2.31, *p* = .024**	6.67 (4.44)	5.98 (2.90)	
SDQ Emotions, mean (SD)	3.88 (2.31)	5.00 (2.86)	3.68 (2.16)	t = 1.78, *p* = .08	3.92 (2.62)	3.86 (2.17)	
Substance Use							
Cannabis							
Lifetime, % (n)	38.6% (28)	45.5% (5)	37.1% (23)		-	-	
CU6+/Past 6-months, % (n)	32.9% (24)	45.5% (5)	30.6% (19)	β = 0.07 ± 0.91, *p* = .940	-	-	
CU1+/Past 1-month, % (n)	21.9% (16)	36.4% (4)	19.4% (12)		-	-	
Discontinued, % (n)	5.5% (4)	0% (0)	6.5% (4)		-	-	
Alcohol, % (n)	63.0% (46)	63.6% (7)	62.9% (39)	t = 0.05, *p* = .964	91.7% (22)	49% (24)	**t = 3.85, *p* < .001**
Tobacco/nicotine, % (n)	23.3% (17)	36.4% (4)	21.0% (13)	t = 0.96, *p* = .348	54.2% (13)	8.2% (4)	**t = 5.01, *p* < .001**
Other, % (n)	12.3% (9)	36.4% (4)	8.1% (5)	**t = 2.73, *p* = .008**	33.3% (8)	2% (1)	**t = 4.12, *p* < .001**

Note. APSS, Adolescent Psychotic-like Symptom Screener; ASWS, Adolescent Sleep-Wake Scale; FAS, Family Affluence Scale (III); SDQ, Strengths & Difficulties Questionnaire.

Table 4.2. Description of demographic, psychological, and substance use characteristics by combined PLE and 6-month cannabis use status.

Sample Characteristic	PLE+/CU6+ (n=5)	PLE+/CU6- (n=6)	PLE-/CU6+ (n=19)	PLE-/CU6- (n=43)
Demographics				
Age, mean (SD)	16.0 (0.7)	16.0 (0.9)	15.9 (0.7)	15.7 (0.5)
Sex				
Females, % (n)	100% (5)	50.0% (3)	68.4% (13)	62.8% (27)
Males, % (n)	0% (0)	50.0% (3)	31.6% (6)	32.6% (14)
Undisclosed, % (n)	0% (0)	0% (0)	0% (0)	4.7% (2)
Ethnicity				
White, % (n)	60% (3)	16.7% (1)	68.4% (13)	57.1% (27)
Other, % (n)	0% (0)	50% (3)	15.8% (3)	30.6% (12)
Mixed, % (n)	40% (2)	33.3% (2)	15.8% (3)	12.1% (4)
Parental migrant status				
All born in Canada	50% (3)	33.3% (2)	57.9% (11)	558.1% (25)
Mixed	20% (1)	33.3% (2)	21.1% (4)	16.3% (7)
All migrated to Canada	20% (1)	33.3% (2)	21.1% (4)	25.6% (11)
FAS, mean (SD)	6.2 (0.4)	6.5 (1.0)	7.3 (2.4)	7.4 (1.6)
ASWS, mean (SD)	3.5 (0.8)	2.8 (0.7)	3.7 (0.8)	3.6 (0.8)
Psychological				
APSS, mean (SD)	2.80 (1.52)	3.08 (0.74)	0.34 (0.47)	0.50 (0.45)
SDQ Externalizing, mean (SD)	9.00 (2.55)	9,83 (2.64)	6.32 (3.46)	5.98 (3.19)
SDQ Internalizing, mean (SD)	8.40 (4.67)	8.33 (3.33)	6.21 (4.39)	5.65 (2.72)
SDQ Emotions, mean (SD)	5.20 (2.86)	4.83 (3.13)	3.58 (2.52)	3.72 (2.02)
Substance Use				
Cannabis				
Lifetime, % (n)	100% (5)	0% (0)	100% (19)	9.3% (4)
CU6+/Past 6-months, % (n)	-	-	-	-
CU1+/Past 1-month, % (n)	80% (4)	-	63.2% (12)	-
Discontinued, % (n)	0% (0)	0% (0)	0% (0)	9.3% (4)
Alcohol, % (n)	100% (5)	33.3% (2)	91.7% (17)	51.2% (22)
Tobacco/nicotine, % (n)	40% (2)	66.7% (4)	0% (0)	2.3% (1)
Other, % (n)	80% (4)	0% (0)	33.3% (4)	2.3% (1)

Note. APSS, Adolescent Psychotic-like Symptom Screener; ASWS, Adolescent Sleep-Wake Scale; FAS, Family Affluence Scale (III); SDQ, Strengths & Difficulties Questionnaire.

Table 4.3. Features of cannabis use from past 1-month users (CU1+).

Feature of Cannabis Use	Total (n=16)	PLE+ (n=4)	PLE- (n=12)	Test statistics
THCe, g (range)	10.778 (0.005, 72.618)	30.409 (8.600, 72.618)	4.234 (0.005, 31.161)	$\beta = 0.080 \pm 0.058$, $p = .173$
Joint equivalents (range)	71.9 (< 0.1, 484.1)	202.7 (57.3, 484.1)	28.2 (< 0.1, 207.7)	
Days of consumption	15.2 (1, 30)	30 (30, 30)	10.3 (1, 30)	
Uses flower, % (n)	75% (12)	100% (4)	66.7% (8)	
Uses vaporizer, % (n)	37.5% (6)	0% (0)	50% (6)	
Uses other, % (n)	18.8% (3)	0% (0)	25% (3)	

Note. THCe, THC exposure (past 30-days). Joint equivalents: assumed 1g cannabis at 15% THC.

Table 4.4. ^{1}H MRS spectra description by self-reported psychotic-like experiences.

Spectra characteristic	PFC				HIP			
	Total (n=67)	PLE+ (n=11)	PLE- (n=56)	Test statistics	Total (n=50)	PLE+ (n=8)	PLE- (n=42)	Test statistics
Sex				t = -0.5, *p* = .620				t = -0.66, *p* = .510
Females, % (n)	64.2% (43)	72.7% (8)	62.5% (35)		62% (31)	75% (6)	59.5% (25)	
Males, % (n)	32.8% (22)	27.3% (3)	33.9% (19)		34% (17)	25% (2)	35.7% (15)	
Undisclosed, % (n)	3% (2)	0% (0)	3.6% (3)		4% (2)	0% (0)	4.8% (2)	
Handedness				t = -1.76, *p* = .084				t = -1.44, *p* = .156
Right, % (n)	62.7% (42)	45.5% (5)	66.1% (37)		64% (32)	50% (4)	66.7% (28)	
Mixed, % (n)	35.8% (24)	45.5% (5)	33.9% (19)		34% (17)	37.5% (3)	33.3% (14)	
Left, % (n)	1.5% (1)	9.1% (1)	0% (0)		2% (1)	12.5% (1)	0% (0)	
SNR, mean (SD)	44.63 (16.70)	41.50 (13.36)	45.24 (17.3)	t = -0.68, *p* = .501	19.95 (4.45)	21.38 (5.01)	19.68 (4.35)	t = 0.99, *p* = .328
FWHM, mean Hz (SD)	7.88 (2.37)	8.08 (0.86)	7.84 (2.57)	t = 0.30, *p* = .766	14.74 (2.30)	13.96 (2.63)	14.88 (2.23)	t = -1.04, *p* = 0.302
CSF, mean (SD)	0.019 (0.018)	0.019 (0.019)	0.019 (0.018)	t = -0.05, *p* = .964	0.041 (0.017)	0.044 (0.014)	0.041 (0.018)	t = 0.39, *p* = .701
GM, mean (SD)	0.349 (0.075)	0.345 (0.080)	0.350 (0.075)	t = -0.19, *p* = .852	0.594 (0.060)	0.604 (0.059)	0.593 (0.061)	t = 0.50, *p* = .618
WM, mean (SD)	0.631 (0.086)	0.633 (0.102)	0.631 (0.084)	t = 0.07, *p* = .945	0.364 (0.066)	0.352 (0.056)	0.366 (0.068)	t = -0.56, *p* = .578

Note. CSF, cerebrospinal fluid; FWHM, full-width at half-max; GM, grey matter; SNR, signal-to-noise ratio; WM, white matter.

Table 4.5. ^{1}H MRS spectra description by past 6-months cannabis use status.

Spectra characteristic	PFC				HIP			
	Total (n=67)	CU6+ (n=24)	CU6- (n=43)	Test statistics	Total (n=50)	CU6+ (n=21)	CU6- (n=29)	Test statistics
Sex				t = -1.15, *p* = .256				t = -0.86, *p* = .393
Females, % (n)	64.2% (43)	75% (18)	58.1% (25)		62% (31)	71.4% (15)	55.2% (16)	
Males, % (n)	32.8% (22)	25% (6)	37.2% (16)		34% (17)	28.6 (6)	37.9% (11)	
Undisclosed, % (n)	3% (2)	0% (0)	4.7% (2)		4% (2)	0% (0)	6.9% (2)	
Handedness				t = -0.82, *p* = .414				t = -1.66, *p* = .103
Right, % (n)	62.7% (42)	54.2% (13)	67.4% (29)		64% (32)	47.6% (10)	75.9% (22)	
Mixed, % (n)	35.8% (24)	45.8% (11)	30.2% (13)		34% (17)	52.4% (11)	20.7% (6)	
Left, % (n)	1.5% (1)	0% (0)	2.3% (1)		2% (1)	0% (0)	3.4% (1)	
SNR, mean (SD)	44.63 (16.70)	43.49 (14.35)	45.26 (18.01)	t = -0.41, *p* = .681	19.95 (4.45)	19.59 (4.45)	20.21 (4.51)	t = -0.48, *p* = .631
FWHM, mean Hz (SD)	7.88 (2.37)	7.53 (1.39)	8.07 (2.77)	t = -0.89, *p* = .377	14.74 (2.30)	15.17 (2.19)	14.42 (2.36)	t = 1.15, *p* = 0.257
CSF, mean (SD)	0.019 (0.018)	0.017 (0.014)	0.020 (0.020)	t = -0.62, *p* = .539	0.041 (0.017)	0.044 (0.020)	0.040 (0.015)	t = 0.89, *p* = .378
GM, mean (SD)	0.349 (0.075)	0.341 (0.055)	0.354 (0.085)	t = -0.69, *p* = .491	0.594 (0.060)	0.603 (0.051)	0.588 (0.066)	t = 0.88, *p* = .385
WM, mean (SD)	0.631 (0.086)	0.642 (0.061)	0.625 (0.098)	t = 0.77, *p* = .444	0.364 (0.066)	0.353 (0.058)	0.372 (0.071)	t = -1.04, *p* = .304

Note. CSF, cerebrospinal fluid; FWHM, full-width at half-max; GM, grey matter; SNR, signal-to-noise ratio; WM, white matter

Table 4.6. ^{1}H MRS metabolites description by self-reported psychotic-like experiences.

	PFC				HIP			
Metabolite	Total (n=67)	PLE+ (n=11)	PLE- (n=56)	Test statistics	Total (n=50)	PLE+ (n=8)	PLE- (n=42)	Test statistics
tNAA, mm/Kg mean (SD)	26.76 (2.45)	26.67 (2.45)	26.78 (2.47)	β = 0.02 ± 0.89, *p* = .986	26.14 (3.33)	27.13 (2.89)	25.95 (3.41)	β = 1.57 ± 1.41, *p* = .269
mI, mm/Kg mean (SD)	16.72 (3.11)	16.59 (1.29)	16.74 (3.36)	β = -0.47 ± 1.13, *p* = .678	25.20 (4.00)	22.88 (2.15)	25.64 (4.13)	**β = -3.33 ± 1.63, *p* = .047**
tCh, mm/Kg mean (SD)	4.55 (0.60)	4.49 (0.45)	4.56 (0.63)	β = -0.08 ± 0.22, *p* = .736	6.12 (0.86)	6.56 (0.76)	6.87 (0.88)	β = -0.41 ± 0.36, *p* = .261

Note. mI, myoinositol; tCh, total choline; tNAA, total n-acetyl aspartate.

Table 4.7. ^{1}H MRS metabolites description by past 6-months cannabis use status.

	PFC				HIP			
Metabolite	Total (n=67)	CU6+ (n=11)	CU6- (n=56)	Test statistics	Total (n=50)	CU6+ (n=8)	CU6- (n=42)	Test statistics
tNAA, mm/Kg mean (SD)	26.76 (2.45)	26.24 (1.87)	27.05 (2.70)	β = -0.03 ± 0.03, *p* = .351	26.14 (3.33)	26.72 (3.11)	25.72 (3.47)	β = 0.07 ± 0.04, *p* = .149
mI, mm/Kg mean (SD)	16.72 (3.11)	16.36 (2.23)	16.92 (3.52)	β = -0.05 ± 0.05, *p* = .380	25.20 (4.00)	25.66 (3.24)	24.86 (4.49)	β = 0.04 ± 0.06, *p* = .483
tCh, mm/Kg mean (SD)	4.55 (0.60)	4.51 (0.40)	4.60 (0.69)	β = -0.04 ± 0.04, *p* = .351	6.12 (0.86)	6.97 (0.72)	6.71 (0.95)	β = 0.04 ± 0.04, *p* = .345

Note. mI, myoinositol; tCh, total choline; tNAA, total n-acetyl aspartate.

4.8. Figures

Figure 4.1. Voxel placement in a) left prefrontal cortex and b) hippocampus for proton magnetic resonance spectroscopy.

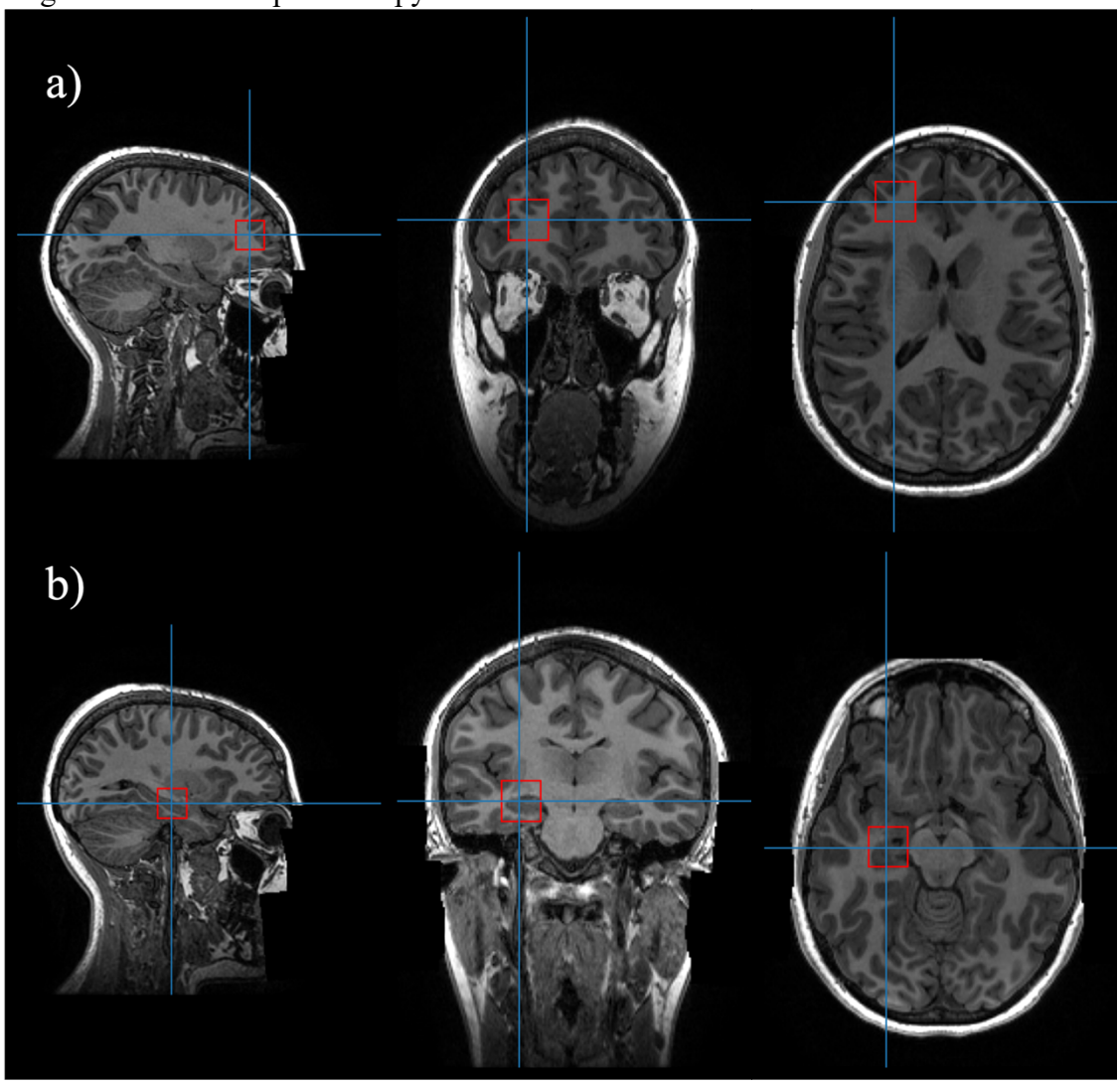
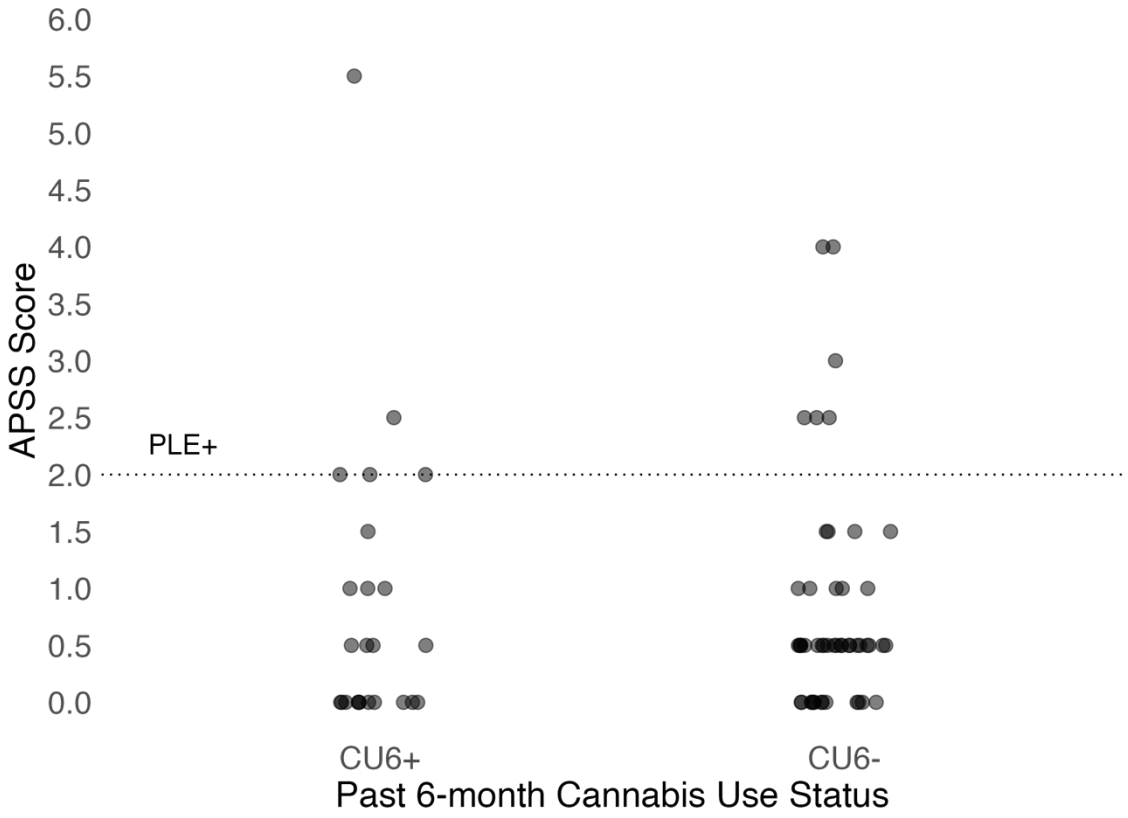
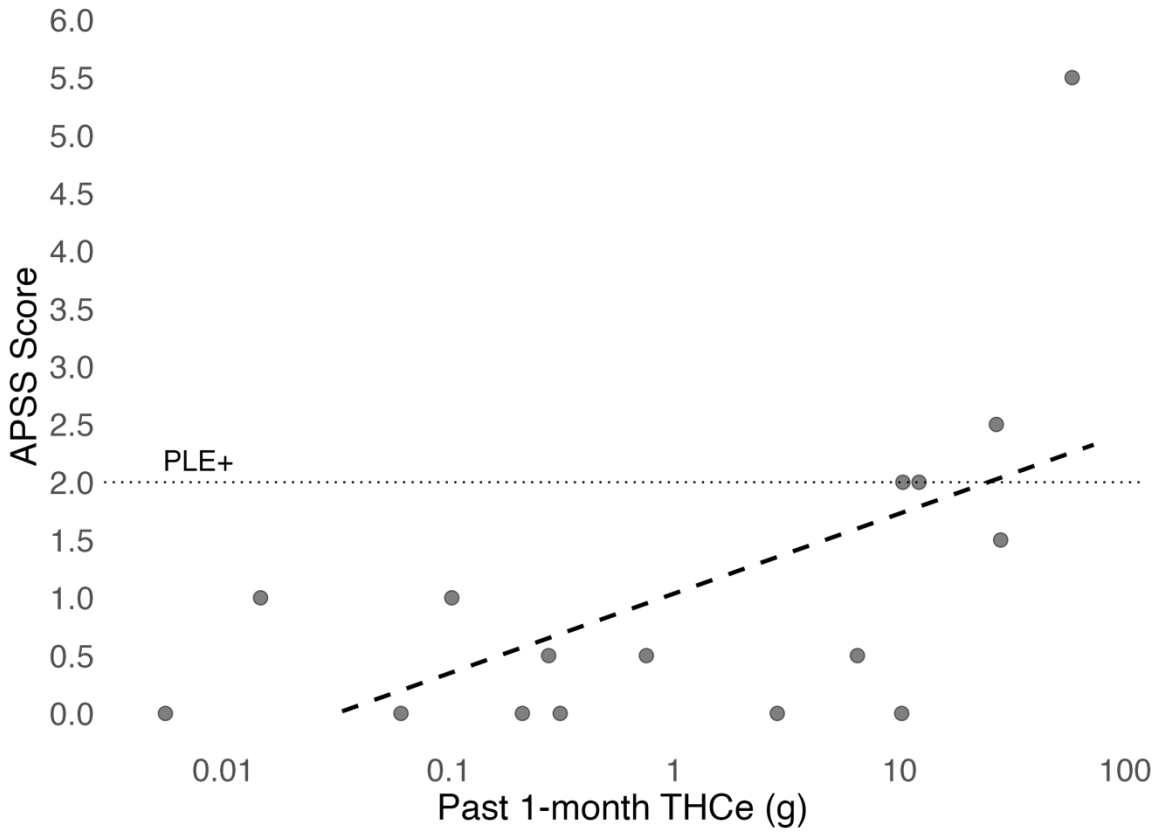


Figure 4.2. Self-reported PLE score from the Adolescent Psychotic-Like Symptom Screener by past 6-month cannabis use status.



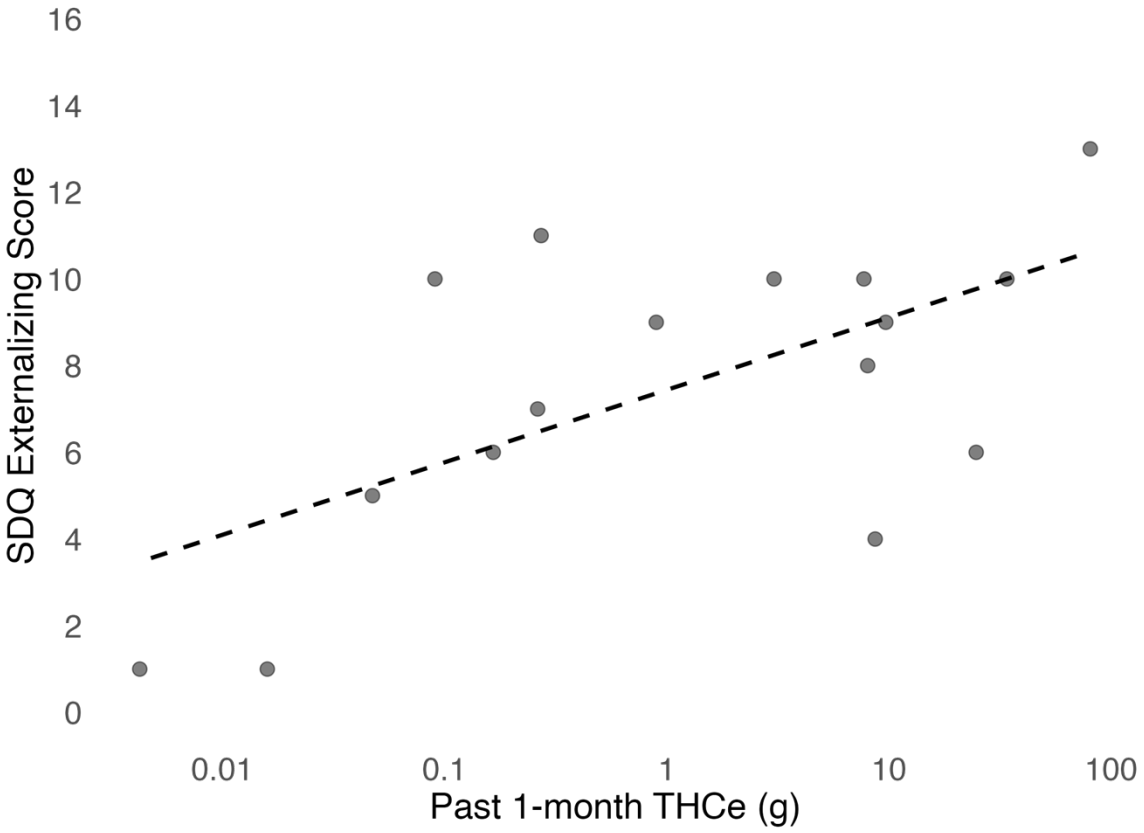
Note. Mean APSS scores (SD): CU6+: 0.85 (1.27); CU6-: 0.82 (0.98). APSS, Adolescent Psychotic-Like Symptom Screener; CU6, past 6-month cannabis use status; SD, standard deviation.

Figure 4.3. Self-reported PLE score from the Adolescent Psychotic-Like Symptom Screener by past-month THC exposure among past-month users.



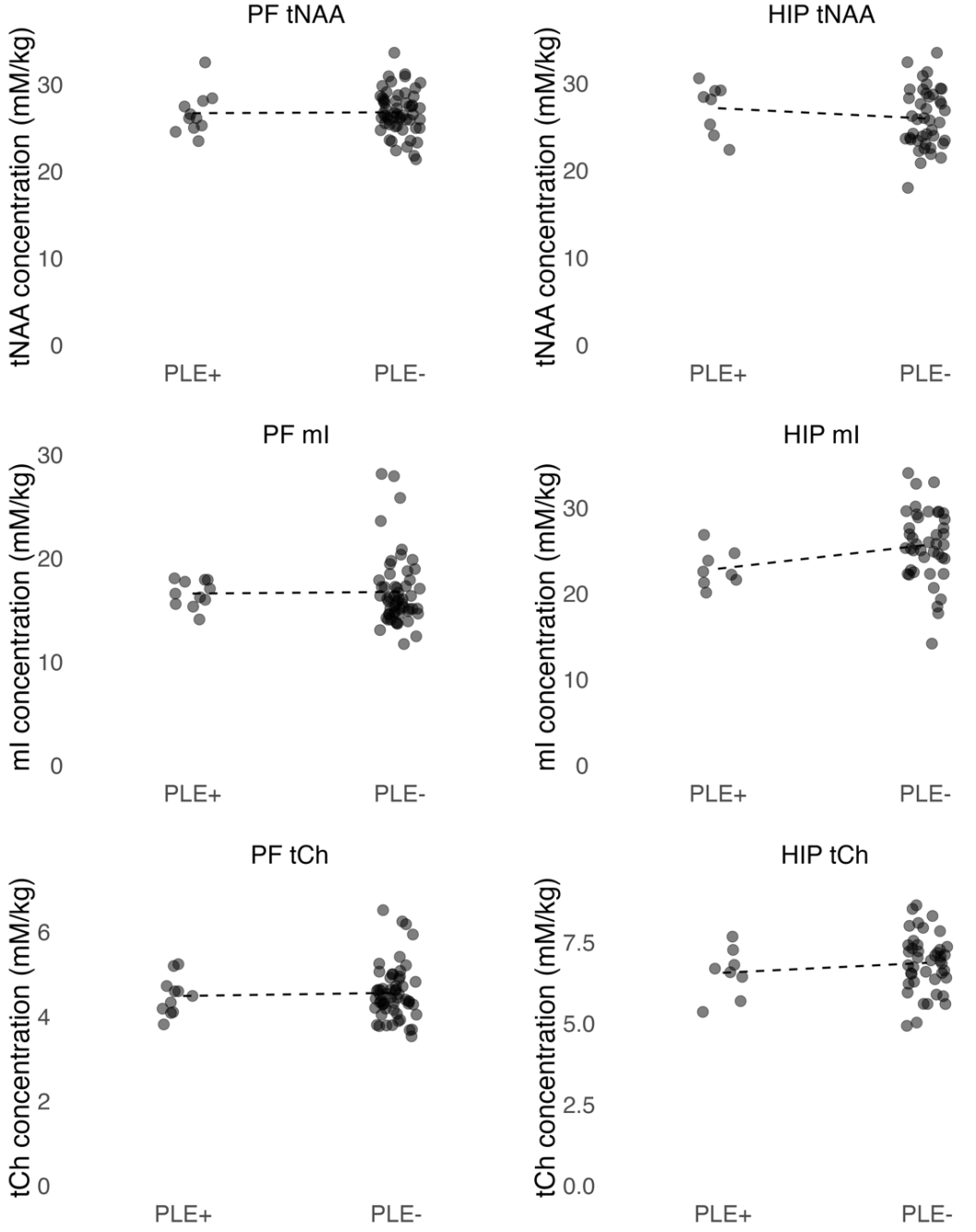
Note. Significant relationship with APSS score (β = 0.147 ± 0.055, p = .008) but not with PLE status (β = -0.300 ± 0.470, p = .528), corrected for externalizing difficulties and other substance use. APSS, Adolescent Psychotic-Like Symptom Screener; PLE, psychotic-like experience; THCe, delta-9-tetrahydrocannabinol exposure (g).

Figure 4.4. Externalizing difficulties score from the Strengths and Difficulties Questionnaire by past-month exposure to delta-9-tetrahydrocannabinol among past-month cannabis users.



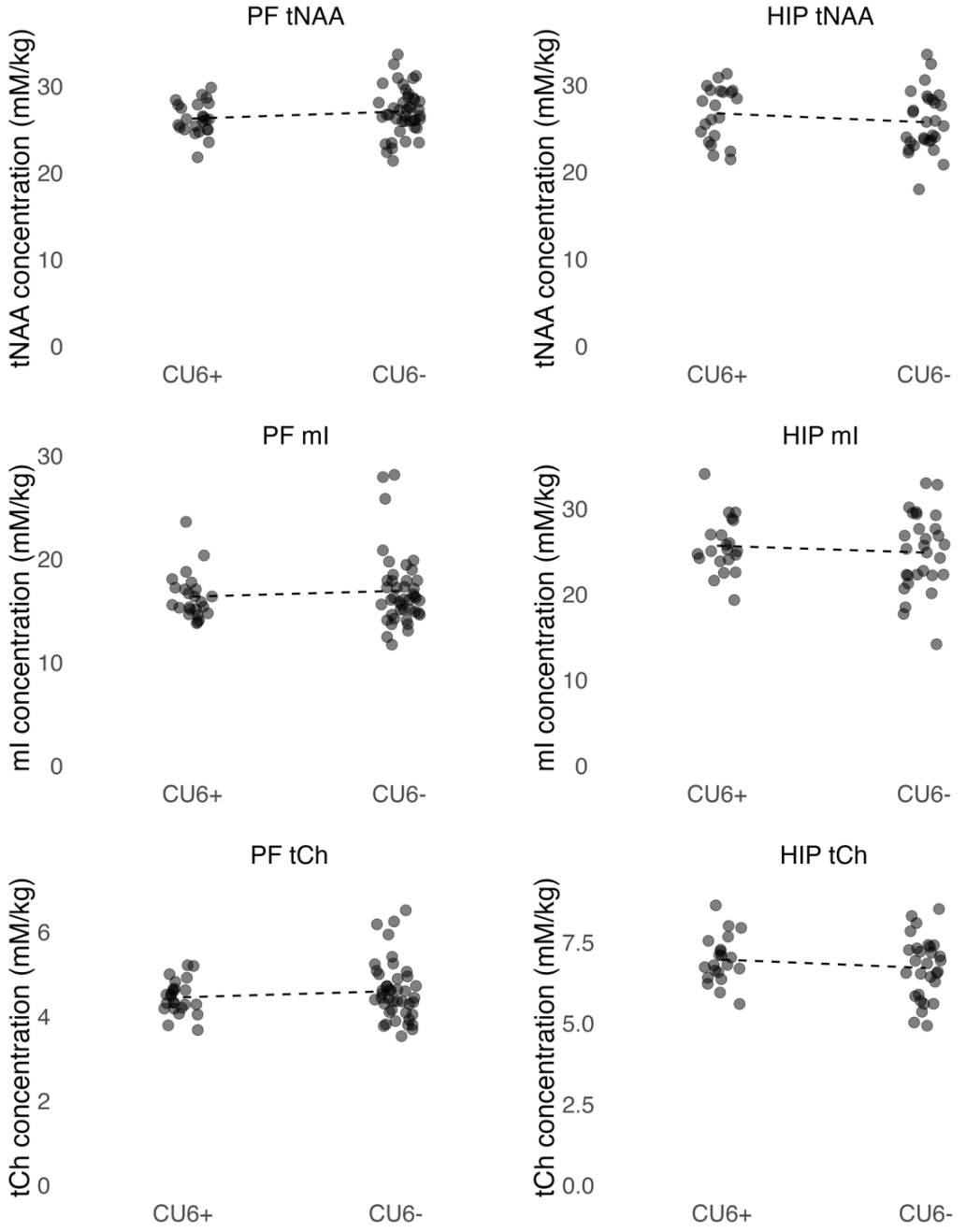
Note. β = 0.092 ± 0.040, *p* = .022. Corrected for PLE status and other substance use. SDQ, Strengths and Difficulties Questionnaire; THCe, delta-9-tetrahydrocannabinol exposure (g).

Figure 4.5. Concentration of MRS-identified neurometabolites in left prefrontal cortex and hippocampus by self-reported psychotic-like experiences.



Note. Significant relationship with HIP mI (β = -3.479 ± 1.729, p = .050), corrected for handedness, externalizing difficulties, and other substance use. HIP, hippocampus; mI, myoinositol; MRS, magnetic resonance spectroscopy; PF, prefrontal; PLE, psychotic-like experiences; tCh, total choline; tNAA, total N-acetyl aspartate.

Figure 4.6. Concentration of MRS-identified neurometabolites in left prefrontal cortex and hippocampus by past 6-month cannabis use status.



Note. No significant relationships identified. CU6, past 6-month cannabis use; HIP, hippocampus; mI, myoinositol; MRS, magnetic resonance spectroscopy; PF, prefrontal; tCh, total choline; tNAA, total N-acetyl aspartate.

Chapter 5: Discussion

5.1. Overview of Findings

This thesis project sought to examine the nature of PLEs in children and adolescence from a clinical and neurobiological perspective, with the goal of better characterizing low-level psychosis risk in the extended psychosis spectrum and to assess the evidence for early neuroinflammatory mechanisms of disease progression. As discussed in Chapter 2, PLEs are relatively common in adolescence and the vast majority of those who experience them will not develop a psychotic disorder. They are, however, still at an increased risk compared to adolescents not experiencing PLEs, with interviewer-verified experiences conferring significantly more risk than self-reported PLEs. As supported in Chapter 4, this increase in risk associated with adolescent PLEs may arise from alterations in neuroinflammatory balance in the hippocampus, where reduced myoinositol concentrations alongside unaltered tNAA and choline concentrations could be reflective of diminished glial cell activity or reactivity. Yet, this is true only for the method of PLE assessment used for this analysis (i.e., APSS), as significant heterogeneity exists between PLE assessments' ability to indicate psychotic risk.

Chapters 1 and 3 discussed the implications of adolescent cannabis use in the risk of PLEs and psychosis development, with evidence suggesting it may progress or accelerate the psychopathology of the psychosis spectrum through mechanisms of neuroinflammation. This motivated the co-investigation of spectroscopic markers of neuroinflammation of cannabis use alongside PLEs in Chapter 4. No relationship was found between PLEs and cannabis use status in a community-based adolescent sample, and cannabis use was not associated with the neurometabolites investigated in the left hippocampus and a white-matter predominant voxel of the left PFC. Given the small sample and resultingly few PLE-reporting adolescents in this analysis, the lack of metabolic relationships with cannabis use was not supportive of assessing a differential relationship between adolescent PLEs and neurometabolites by cannabis use status. These preliminary findings suggest there is no effect of cannabis use on the co-occurrence of PLEs in adolescents, clinically nor through neurometabolic/inflammatory mechanisms. Strong, significant relationships for other substance use with both PLEs and cannabis use

may be indicative of these substances being more consequential for the increase in psychosis risk, although its direct effect on neurometabolites were not assessed. Externalizing behavioural difficulties were also found to be associated with PLE status, although not with the neurometabolites investigated. This is supportive of adolescent PLEs highlighting a state of global psychiatric burden, although possibly with a distinct mechanism for psychotic risk.

5.2. PLEs & Substance Use Adolescents

The systematic review and meta-analysis provide an updated insight into the epidemiology of PLEs in the child and adolescent population. Notably, this work showed that PLEs were observed in 17.8% of samples, nearly double the most recent meta-analytical estimate of 9.3% (Healy et al., 2019). Although our findings were heavily influenced by one study using the PROD-screen, excluding this study still identified a prevalence of 8.9%, confirming that PLEs are a common experience in the child and adolescent population. These were studies conducted in non-help seeking adolescents and importantly, over 95% of those reporting PLEs did not develop a psychotic disorder in early adulthood. Therefore, while highlighting PLEs during childhood and adolescence as a common phenomenon, most individuals who experience them are not on a psychotic illness trajectory. This fits under the current perspective of psychotic phenotypes existing on a spectrum with varying degrees of psychotic(-like) features and burden, including a nonclinical expression. This also highlights the complexity of identifying who may be at risk of developing a psychotic disorder even with risk behaviours, one of which is cannabis use.

Recent cannabis use in adolescence does not appear to be universally associated with PLEs in adolescence, evidenced by a lack of association with past-6-month cannabis use in the Chapter 4 analysis. It is possible that cumulative exposure to THC during adolescence better reflects this relationship, as the restricted exploratory analysis found past-month total THC exposure to be associated with the severity of PLEs in a dose-dependent manner. This was especially noticeable among those most greatly exposed to THC (Chapter 4 Figure 3) and may implicate an effect only among the most chronic users. While a finding worthy of further exploration, the restricted sample (N = 16) for

this analysis limits a definitive conclusion. Furthermore, as exposure was only calculated for past-month use, it is not a true reflection of total exposure but rather recent exposure.

Focusing on the primary finding, the lack of relationship between adolescent cannabis use and PLEs may be genuine. Suggested by Ryan and colleagues (2020), previous reports of a relationship may reflect a broader limitation in the literature where the presence of cannabis- and PLE-associated confounding factors are the reasons for implicating adolescent cannabis use in psychosis risk. This would imply that the corrections made for concurrent psychopathology and substance use in the Chapter 4 analysis may have successfully mitigated these confounding effects on adolescent PLEs. Therefore, no relationship may exist between the two.

Additional psychopathological burden is a common characteristic among adolescents experiencing PLEs, often reflected through both internalizing and externalizing behaviors. Both were significantly associated with PLEs in the Chapter 4 analysis as well as in prior research (Laurens et al., 2020; Gin et al., 2021; Healy et al., 2019). Externalizing psychopathology represents general impulsivity and a disinhibition of behaviour (Achenbach, 1978), a common feature of several psychiatric conditions including oppositional defiant disorders, conduct disorders, attention-deficit and hyperactivity disorders (ADHD), and SUDs (Krueger et al., 2009; Gin et al., 2020). Conversely, internalizing psychopathology encompasses a spectrum of emotional and affective disturbances characterized by inhibitory behavioral processes such as emotional dysregulation, and withdrawal (Achenbach, 1978), common in mood disorders such as anxiety and major depression (Willemsen et al., 2012). Interpreting PLEs to reflect a dimension of psychoticism, these dimensions demonstrate bidirectional relationships with each other in longitudinal studies (Downs et al., 2013; Lancefield et al., 2016; Gin et al., 2020). Although PLEs tend to be biased towards psychotic outcomes (Healy et al., 2019), their subclinical nature and overlap with other dimensions of psychopathology support the existence of a broader spectrum of psychiatric vulnerability. This multidimensional spectrum suggests that PLEs may be influenced by various risk factors that differentially impact these overlapping dimensions of psychopathology (Staines et al., 2022; van Os et al., 2017; Spiteri-Staines et al., 2024), a perspective that may represent a more optimal approach to comprehensive clinical prognostication in mental healthcare settings.

This perspective may be useful to explain the frequent presentation of other substance use with adolescent PLEs (Ryan et al., 2020; Dolphin et al., 2015; Matheson et al., 2023; Degenhardt et al., 2016; Degenhardt et al., 2018), something also observed in Chapter 4. Studies consistently show that adolescents experiencing PLEs are more likely to engage in substance use both cross sectionally (Ryan et al., 2020; Dolphin et al., 2015; Matheson et al., 2023) and longitudinally (Healy et al., 2019; Cederlof et al., 2017; Fisher et al., 2013b; Dhossche et al., 2002). On one hand, this may reflect the psychotic vulnerability that substance use imposes on the developing adolescent brain. However, the association of PLEs with other dimensions of psychopathology also may implicate substance use more broadly to neuropsychiatric vulnerability across these dimensions. A recent meta-analysis by Matheson (2023) found significant moderating effects for various substance use types on the prevalence of adolescent PLEs, including alcohol (regression coefficient = 0.44), tobacco (0.24), amphetamines (0.07), in addition to lifetime (0.19) and weekly (0.04) cannabis use (Matheson et al., 2023). These findings are also supported in Chapter 4, where participants (adolescents) where the prevalence of PLEs was much higher among tobacco (86%) and other substance users (44%) compared to non-users of these substances (8% and 11%, respectively). Although, this was not the case for alcohol use, where a PLE prevalence of 15% was found in both groups. Longitudinally, tobacco and alcohol use have been linked to increased impulsivity and poorer emotional control—traits commonly associated with externalizing psychopathology (Degenhardt et al., 2016). Therefore, it is possible that substance use in this demographic could exacerbate existing psychopathological burden. However, mixed findings exist for this direction of effect on externalizing psychopathology (Griffith-Lendering et al., 2011; Oshri et al., 2011; Miettunen et al., 2013), and cannabis use may only exacerbate certain aspects of internalizing difficulties (Colder et al., 2019), suggesting the influence of other factors as well.

Another implicated theory for this relationship is the self-medication hypothesis (Khantzian, 1985; Khantzian, 1997). That is, substance use in adolescents with PLEs may reflect an attempt to self-medicate distressing symptoms associated with their PLEs. Childhood externalizing difficulties, and internalizing difficulties in female children, both predict substance use by mid adolescence (Miettunen et al., 2013; Oshri et al., 2011).

Regarding cannabis use, PLEs reported at age-13 and age-16 are associated with the onset of cannabis within the following 3 years (Griffith-Lendring et al., 2013), and age-16 externalizing difficulties predicted CUD at age-30 (Farmer et al., 2015). Cross-sectional studies suggest tobacco use to provide relief from attentional and affective dysfunctions (Ghricke et al., 2007), and early-adulthood alcohol use problems show a positive relationship with shared aspects of childhood internalizing and externalizing problems (Foster et al., 2018). These findings suggest that self-medication from psychopathology could be a motivator for the use of substances. However, even among the longitudinal findings, causation cannot be effectively determined in the absence of more robust analysis techniques. For example, Bernusky and colleagues (2023) applied a chained-mediation path analysis for this purpose, cross-sectionally measuring PLEs, anxiety, motives for cannabis use, and cannabis use problems in young adults. This study did not find an association between PLEs and cannabis use problems, however identified a significant pathway from PLEs to anxiety and anxiety coping motives, and from these mediators to cannabis use problems in a single model (Bernusky et al., 2023). Using this method of analysis with variables collected at different timepoints in a longitudinal study could more robustly assess causative pathways between PLEs, substance use, and motives for substance use.

Given the substantial proportion of disordered substance users who do not show early psychopathology (Farmer et al., 2015), it is possible that both self-medication and elevated psychiatric vulnerability are unique influences on an adolescent's decision to consume psychoactive substances. The relative degree of each may vary by substance type and developmental window. In the adult population, while PLEs predicted subsequent tobacco, alcohol, and cannabis use, it was only tobacco and alcohol use that predicted subsequent PLEs (Degenhardt et al., 2018). This is different in adolescents, whereby any cannabis, alcohol, or tobacco use at age-16 predicted age-18 emergence of PLEs (Gage et al., 2014), suggesting cannabis confers a specific neuropsychiatric vulnerability during adolescence. However, this window of vulnerability may be narrow, as age-13 cannabis use was not shown to predict age-16 PLEs (Griffith-Lendring et al., 2013). The lack of a cross-sectional relationship between past-6-month cannabis use and

PLEs in the Chapter 4 analysis of 15- and 16-year-olds could also be explained, in part, by a narrow developmental vulnerability for the effects of cannabis.

5.3. Neurometabolic Markers of Inflammation in Adolescent PLEs

The findings of reduced myoinositol concentrations in the left hippocampus among adolescents reporting psychotic-like experiences (PLEs) suggest early astrocytic dysfunction. This aligns with evidence that subcortical alterations, particularly in the hippocampus, are common across the psychosis spectrum, including its subclinical stages (Sahakyan et al., 2020; Sasabayashi et al., 2020; Karcher et al., 2023; Allen et al., 2012; Whitehurst et al., 2020; Lieberman et al., 2018). Myoinositol, a marker of glial cell activity, particularly astrocytes, plays crucial roles in cellular osmoregulation and energy metabolism (Brand et al., 1994; Downes & Macphee, 1990; Abdali et al., 2015). The reduction of myoinositol suggests early-stage astrocytic dysfunction or impaired energy metabolism, which may predispose a neural environment for more severe inflammatory responses and neurobiological changes as additional risk factors, such as chronic cannabis use or genetic predisposition, accumulate.

The presence of reduced myoinositol without significant changes in tNAA or tCh indicates that glial cell dysfunction may be occurring before significant neuronal damage or loss. This pattern of findings supports the hypothesis that astrocytic dysfunction and early metabolic changes are among the first detectable neurobiological alterations in the psychosis spectrum (Lieberman et al., 2018; Dietz et al., 2020; Watkins & Andrews, 2016). The significant effect of myoinositol restricted to the hippocampus also aligns with the notion that the hippocampus is one of the earliest brain regions affected in the progression of psychotic disorders (Lieberman et al., 2018; Whitehurst et al., 2020; Grace, 2012; Schobel et al., 2013; Bossong et al., 2019). The stable tNAA and tCh levels suggest that while neuronal health is maintained at this stage, glial cell function may already be compromised. This early dysfunction could predispose individuals to more severe neuroinflammatory responses and subsequent neurodegenerative changes as the disorder progresses.

These findings also suggest that adolescents with PLEs may be experiencing glutamate dysfunction in the hippocampus, which have shown to be responsible for early

metabolic changes in the psychosis prodrome (Lieberman et al., 2018). This glutamate dysfunction might be indicative of altered glutamate transmission affecting metabolism before significant neuronal health declines that would lead to atrophic changes (Lieberman et al., 2018). This could position common PLEs in the adolescent population as reflecting a state of altered glutamate transmission that impacts metabolism but has not yet progressed to a chronic state that would result in hippocampal neuronal deficits. An MRS assessment of glutamate concentrations in this population would help evaluate this hypothesis. Furthermore, the prevalence of PLEs that do not precede psychosis in adolescents (Chapter 2) and the small sample size in Chapter 4 make it unclear if this metabolic state is reflective of common PLEs or is more strongly occurring in those in the psychosis prodrome. Examining the spread of myoinositol concentrations between groups does not suggest this to be the case, but limited power prevents a firm conclusion, and this needs to be assessed in the full sample.

The absence of significant relationships between recent cannabis use and neurometabolites in our adolescent sample contrasts with findings in chronic, heavy users where significant neurobiological changes are more evident. Studies in heavy cannabis users report reduced hippocampal myoinositol and decreased NAA/Cr ratio in the DLPFC (Blest-Hopely et al., 2020b; Hermann et al., 2007). These discrepancies likely arise from differences in the duration and intensity of cannabis use. Our population-based sample, which includes many infrequent users, might not capture the cumulative effects of sustained cannabis use. This highlights the importance of considering the cumulative impact and interaction of cannabis use with neuroinflammatory processes in understanding its role in psychosis risk.

The apparent stability of tNAA and tCh levels also suggests the resilience of the adolescent brain to early neurotoxic impacts of cannabis use, at least in the context of PLEs. However, the observed inverse relationship between hippocampal myoinositol and PLEs suggests that early neuroinflammatory changes are already at play, albeit at a stage where neuronal integrity likely remains unaffected. This finding emphasizes the potential for early interventions targeting neuroinflammatory processes to mitigate psychosis risk. The role of cannabis in this neuroinflammatory context is complex and appears to be influenced by the duration and frequency of use. Chronic use, especially during critical

periods of brain development, may exacerbate underlying neuroinflammatory conditions, thereby increasing psychosis risk. However, our findings suggest that recent use does not significantly alter neurometabolite levels in a way that would predispose adolescents to psychosis.

5.4. Barriers to Knowledge

A reoccurring theme in this body of research is the significant heterogeneity in PLE assessment in the psychosis spectrum. PLE assessments can vary by the number of items (1 to 42+), item content (e.g., auditory/visual hallucinations, paranoid thinking, disorganized behaviour, negative symptoms), timeframe for symptom occurrence (past 2-weeks to lifetime), assessment structure (self-report or structured interview), and item threshold for risk status (1 to 3, with varying criteria for frequency and/or distress). Including the analysis in Chapter 2, past meta-analyses have also identified significant heterogeneity between studies of adolescent PLEs (Healy et al., 2019), especially in regard to the definitions and assessments, with 41 different assessment tools having been identified (Lee et al., 2016).

Although the analysis in Chapter 2 was only able to identify the assessment structure as a source of heterogeneity in the predictive value of assessments, it is possible that the varying item content may be the most consequential. Although this feature was incorporated into that analysis, the limited number of studies prevented a thorough investigation, as only the presence of non-hallucinatory PLEs was assessed for an effect. The variability in item content between assessments reflects a more profound issue regarding the phenomenon of PLEs and the perspective taken to conceptualize them. On one hand, it has been suggested that only positive PLEs specifically reflect the psychosis spectrum (Kelleher et al., 2011), with negative and thought-based experiences reflecting more of a global psychiatric burden. Alternatively, other lines of research implicate these additional dimensions with the phenomenon, as they hold additional value for the prediction of psychosis onset (Daalman et al., 2011; Morrison et al., 2004; Davies et al., 2001). The issue with whether an experience may be classified as psychotic-like inherently depends on the purpose for interest into the phenomenon. That is, are these experiences thought to be normal or indicative of underlying pathological mechanisms,

and how does one establish such boundaries (Lee 2016)? This conceptual issue is a significant factor in the existence of the many different PLE assessments and resulting assessments of prevalence and risk.

While PLEs are thought to be relatively common amongst adolescents, often times transient and non-distressing, it is not entirely clear which aspects of this phenomenon may be reflected in altered neurometabolic processes. Chapter 4 was able to identify reduced hippocampal myoinositol among PLE-reporting adolescents, but an inadequate sample and a lack of a detailed characterization of PLEs prevents the assessment of PLE features on this mechanism. That is, it remains to be seen to what degree this altered metabolism may be modified by total PLE burden, specific experiences, dimensional categories, or other underlying confounding factors in the sample (e.g., ethnicity, internalizing difficulties, or further unidentified factors). It is also unclear how this neurometabolic context differs between different trajectories of PLEs. It has been hypothesized that PLEs may reflect one of three contexts: i) neurological disturbances and vulnerability to psychotic disorders, ii) psychopathological impairment in non-psychotic dimensions that result in psychotic-like disturbances, and iii) a benign and transient phenomenon with no association with psychopathology (Yung et al., 2009; Lee et al., 2016). Assuming that PLEs could reflect either a normal or disturbed psychopathology requires a deeper investigation into both the features of the experience itself (i.e., features directly incorporated into the assessment, such as the number of symptoms, prognostic value of individual symptoms, frequency, distress, timeframe, etc.), modulating environmental factors, and underlying neurological changes. This would permit a better understanding of what these experiences truly represent in a clinical context and aid in the development of a standardized assessment tool.

Various methods of ^{1}H MRS imaging was also a common theme in this area of research, which alone have the potential to significantly alter findings before considering additional variations in study design. Differences that can significantly affect the interpretation of findings include voxel size and location, inclusion of hemispheres, choice of RF sequence, and echo times. Voxel size and location can vary between MRS studies on the same region and are important considerations when comparing findings. The size of the voxel directly affects SNR, as larger voxels have a greater quantity of the

metabolites of interest, allowing a stronger signal to be captured with no appreciable difference in noise (Provencher, 2001). Location is also important, as varying voxel dimensions and volumes around the region of interest will include different structures. This could explain the different conclusions drawn from Modinos (2018) and Fuente-Sandoval (2016). Both studies employed a 3T MEGA-PRESS protocol (TE = 68ms) of the ACC in UHR subjects to assess GABA concentrations, using either a 40 x 25 x 30mm (Modinos et al., 2018) or a 30 x 25 x 25mm voxel (Fuente-Sandoval et al., 2016). Despite similar tissue composition between voxels, calculations for tissue correction, and units of concentration, Fuente-Sandoval (2016) reported a significant increase in GABA concentration that was not identified by Modinos and colleagues (2018). Examining the spectral data, a higher mean SNR (21.9 vs. 18.9) and spectral resolution (6.8 vs. 12.0 Hz) came from the study by Modinos (2018). While seemingly highlighting a superior approach, the increased size of the voxel worsens the spatial localization of findings, presenting a trade-off between the accurate detection and localization of metabolites. Echoing Da Silva and authors (2019), standardizing voxel locations for commonly analyzed regions would improve the integration of findings and our understanding of underlying metabolism.

The selection of hemispheres can impact the detectability and interpretation of metabolites. From childhood to adulthood, the timing of brain development occurs along spatial gradients in a left-to-right, caudal-to-rostral, and deep-to-superficial manner (Corballis & Morgan, 1978; Howes & Shatalina, 2022; Pinto et al., 2013). Early leftward maturation is believed to reflect the bias for language processing, with language lateralization already present in children as young as 5-years (Ahmed et al., 2003; Corballis & Morgan, 1978). Adolescence marks a critical shift in neurodevelopment where the rapid dendritic branching and synapse formation characteristic in children yields to the strengthening of certain connections and the pruning of others (Drzewiecki et al., 2016; Crain et al., 1973; Zecevic et al., 1989; Rakic et al., 1986; Bourgeois et al., 1993; Howes & Shatalina, 2022). The accelerated development of the left hemisphere is thought to be more sensitive to disruptions from environmental, genetic, and neurobiological factors and may underlie the bias for leftward disruptions seen in

neurodevelopmental disorders like autism spectrum and psychotic disorders (Sussman & Lewandowski, 1990; Molina et al., 2005; van Veelen et al., 2010).

For consideration in this present research, metabolism in the left hemisphere is consistently more strongly altered than in the right across the psychosis spectrum and is therefore an important consideration for imaging analyses (Bustillo et al., 2020; de Jong et al., 2022). While analysis of both hemispheres can identify the bilateral effect of a particular region while separating the contributions of each hemisphere when analyzed correctly, this analysis may diminish the contributing effects of either hemisphere if the difference between the two hemispheres or their effects on the neurobiological measure are small. This consideration leads some studies to analyze hemispheres in isolation (Sahakyan et al., 2020; Bustillo et al., 2020; Martinez-Granados et al., 2008; Nenadic et al., 2015) or may only analyze a single hemisphere (as was done in Chapter 4 to manage multiple hypothesis testing) (Wood et al., 2003; Jessen et al., 2006; Shakory et al., 2018; Howes et al., 2019; Bossong et al., 2019), something that is not always clear when findings are reported. Furthermore, much of this distinction needs to be lost to facilitate meta-analysis, where conclusions are often generalized bilaterally (Romeo et al., 2020; Whitehurst et al., 2020; Brugger et al., 2011). Not accounting for these differences in analysis can hamper conclusions that can be drawn with the integration of these studies, particularly in ^{1}H MRS meta-analyses where study-level findings and conclusions are frequently more diverse.

Echo time is another consideration that can dramatically affect metabolite quantification. As different molecules have different T_1 relaxation times, the signal detected for a given metabolite will vary at different time points following excitation (Mlynarik et al., 2001). For example, the studies by Wood (2003) and Jessen (2006) employed highly similar 1.5T protocols for the quantification of metabolites in the left DLPFC of UHR subjects. While Wood and colleagues (2003) reported an increase in the NAA/Cr ratio for this region, Jessen (2006) reported a decrease. Although potentially influenced by different voxel sizes, this alone would be less likely to affect the observed relationship so substantially. The difference in TE (135 vs. 272 ms) affects the detection of both NAA and Cr since their respective signals are differentially aligned with the magnetic field at these times. The not only affects the absolute quantification of each

metabolite but becomes compounded when assessing one metabolite as a ratio with another. This can make it quite difficult to interpret these findings regarding underlying metabolism and suggests against using these ratios, even in light of relative Cr stability in this population (Romeo et al., 2020).

PRESS is both recommended and widely used for this research (Wilson et al., 2019); however, other signal sequences have been used which may affect the quality of spectra. For example, Natsubori and researchers (2014) used STEAM to quantify metabolites in the ACC of UHR subjects in a similar context as the use of PRESS by Egerton et al., (2014). Aside from TE (a choice modified by the sequence), most other imaging parameters were similar or identical (e.g., TR, voxel size and position, tissue fractions). While both studies arrived at the same conclusions – no change in NAA, Glx, mI, and Cho concentrations – the mean SNR with PRESS (~21) was far superior to that with STEAM (11.7), demonstrating a benefit of the refocusing pulses with PRESS. Furthermore, because the lack of refocusing pulses allows STEAM to use a reduced TE, this provides another source of variability on metabolite signals. This poses a conceptual challenge to meta-analysis of this data among many others using PRESS, as it questions the phenomenological value of this data in context of alternately acquired data, highlighting the importance of standardized imaging practices.

5.4. Future Directions

Clinical Directions. Building on the systematic review from Chapter 2, a future meta-analysis could focus on the entire subclinical extension of the psychosis spectrum with minimal exclusion or inclusion criteria. This study would aim to indiscriminately include all relevant population samples: any PLE(s), distressing/persisting PLEs, UHR and CHR individuals, and healthy controls. Instead of differentiating studies by these categories, the lack of restricting criteria would allow for coding of significant potential sources of heterogeneity in the definition and assessment of experiences, such as item content, degree of persistence in the sample, proportion of experience type, timeframe for symptom presentation, age group, and source of samples among others. By adopting this bottom-up approach to identify subclinical psychotic risk, this research could provide a more multifaceted understanding of factors influencing psychotic risk. Depending on the

number of studies identified, it may also be beneficial to incorporate the influence of environmental risk factors. This can help clarify the various trajectories of subclinical psychotic risk from a more spectrum-based approach.

Future research should also seek to implement a standardized measure of THC exposure in a case-control study that categorizes participants into heavy users, light/infrequent users, and non-users. This study design would more accurately assess the dose-response relationship between adolescent cannabis use and PLEs and its association with neurometabolites. By differentiating groups based on exposure levels, this research could clarify whether the relationships differ by total exposure, addressing the hypothesis from Chapter 4 that cumulative THC exposure might be a more relevant factor than recent use in influencing PLEs. This would contribute to resolving ambiguities regarding the impact of cannabis use method on PLEs, as the recent rise in vaporizer use poses new questions about its neuropsychiatric effects compared to other methods.

Building on the findings mentioned, a longitudinal study could explore the contexts in which interventions might be beneficial for individuals showing signs of PLEs. This study would investigate how different contexts of exposure, influenced by known effects and interactions such as cannabis use, genetic risk, and additional psychopathologies, correlate with the risk for clinical deterioration. Such research could potentially redefine intervention strategies by identifying high-risk combinations akin to current UHR criteria and determining which might benefit from preventive measures. This would enhance clinical assessments by integrating comprehensive evaluations of environmental and psychopathological factors, potentially leading to early interventions tailored to individual risk profiles.

Neuroimaging Directions. Informed by the findings in Chapter 4 regarding myo-inositol levels in adolescent PLEs, a cross-sectional study utilizing both MRS and PET is proposed to further investigate the neurobiological underpinnings of PLEs. The study could specifically focus on elucidating the relationship between altered myoinositol levels and potential neuroinflammatory processes within the brain. The selection of MRS and PET is driven by the need to directly correlate metabolic changes detected through MRS, such as variations in myo-inositol within the hippocampus, with markers of glial activation observed via PET imaging. Incorporation of these imaging modalities with an

assessment of circulating cytokines would also be complimentary. This research would be able to substantiate this preliminary hypothesis of impaired inflammatory capacity by comparing the density of activated astrocytes to inflammatory demand. To do this, participants would need to be recruited from the general population, with demographics-matched PLE+ and PLE- groups to ensure sufficient power. Furthermore, imaging should focus on regions identified throughout the pathophysiology of psychotic disorders, including the hippocampus, ACC, DLPFC, frontal WM, and basal ganglia. By correlating these imaging modalities, the study aims to refine our understanding of how glial activity and neuroinflammation contribute to the clinical presentation of PLEs, potentially guiding targeted interventions and preventive strategies for at-risk youth.

A longitudinal study assessing the impact of adolescent cannabis use on hippocampal neurometabolites over time could provide crucial insights into the neurodevelopmental effects of cannabis. Incorporating a within-subjects design, this study would assess changes in hippocampal, frontal WM, and prefrontal regions to explore how these relationships evolve in individuals more prone to psychosis. By integrating multimodal imaging techniques, including structural imaging like diffusion tensor imaging to assess the integrity of WM tracts, the study could investigate potential correlations between psychotic risk and neuroanatomical changes. Specifically, this could assess how varying exposures and patterns of cannabis use might alter the neuroinflammatory demand to increase the risk for psychosis

5.6. Strengths & Limitations

This thesis sought to take a nuanced exploration of psychotic-like experiences (PLEs) among adolescents by integrating a systematic literature review with empirical research, focusing on both the diagnostic complexities and the neurobiological underpinnings associated with these phenomena. The analysis of assessment tools advances the discourse on standardizing assessment criteria, which is crucial for enhancing the reliability of early detection and intervention strategies. This effort not only aligned with suggestions by Healy (2019) and Lee (2016) to address the variability in diagnostic practices but also aimed to fill the gaps these studies were unable to clarify,

particularly regard to assessment criteria that more sensitively identify psychosis-prone trajectories.

A notable strength of this thesis is its focused examination of the relationship between cannabis use and the neurobiological marker myo-inositol. This investigation enriches our understanding of how specific environmental factors interact with biological processes, potentially influencing the onset and progression of PLEs. While this focus yields detailed insights into a targeted pathway, it simultaneously narrows the research scope. This limitation is evident as the thesis does not sufficiently account for other significant factors such as genetic predispositions, the influence of multiple substances, and broader environmental impacts like the degree of urbanicity, all of which could play crucial roles in the etiology of PLEs.

Additionally, while the thesis provides valuable perspectives on subclinical populations and identifies potential biomarkers for early detection, it does not thoroughly explore the transition from subclinical to clinical states of psychosis. This gap presents a future opportunity to delve into how early interventions could be precisely targeted to prevent the escalation of early symptoms into more severe psychiatric conditions. Understanding these transitions is essential for developing effective preventative strategies that could significantly alter the developmental trajectory of individuals at risk of developing psychosis.

In sum, while the thesis significantly contributes to the field by addressing key dimensions of PLEs through an integrated review and empirical methodology, its insights are constrained by a focus on specific elements. Broadening the research to encompass a wider range of influencing factors and employing longitudinal designs to track the evolution of PLEs would greatly enrich the findings. Such advancements would provide a more comprehensive understanding of the onset and progression of psychotic disorders, potentially leading to more effective and targeted clinical interventions. This expanded approach would build on the current thesis by addressing its limitations and setting a trajectory for future research that could profoundly impact adolescent psychiatric research.

5.6. Conclusion

This thesis has explored PLEs within the child and adolescent population, providing insights into the prevalence and variability of these experiences as potential early markers of psychiatric vulnerability. The systematic review highlighted that PLEs affect a substantial portion of youth, providing further support for a broad spectrum of psychotic psychopathology that includes subclinical experiences. Through meta-analysis, the varied prognostic value of PLEs was emphasized, underscoring the necessity for standardized assessment methods to accurately identify and support at-risk individuals. This review also identified that interview-based PLE assessments can detect a subclinical risk status with a greater proportion of psychosis-prone trajectories than from self-report PLE assessments. The empirical component of this work investigated the neurometabolic correlates of PLEs, particularly focusing on the impact of the environmental factor of adolescent cannabis use. It was found that adolescent PLEs were associated with reduced myoinositol concentrations and, in the context of unchanged neuronal health and membrane turnover, may indicate a reduced capacity for astrocytes to participate in neuroinflammation. Future research should expand on these findings with larger samples and advanced neuroimaging techniques to delineate neurobiological changes associated with the nature of PLEs and their influence on a diminished neuroinflammatory capacity. Moreover, the development of risk modification strategies that are both specific and beneficial to adolescents with PLEs in the context of mitigating environmental risk factors could modify long-term mental health outcomes and alleviate a portion of the psychotic burden in the general population. Overall, this thesis contributes to enhancing the prediction and prevention strategies for psychotic disorders, aiming to improve outcomes for at-risk youth by attempting to bridge the gap between empirical evidence and clinical practice.

References

Abajobir, A. A., Kisely, S., Scott, J. G., Williams, G., Clavarino, A., Strathearn, L., & Najman, J. M. (2017). Childhood Maltreatment and Young Adulthood Hallucinations, Delusional Experiences, and Psychosis: A Longitudinal Study. *Schizophrenia Bulletin*, *43*(5), 1045–1055. https://doi.org/10.1093/schbul/sbw175

Abdallah, C. G., De Feyter, H. M., Averill, L. A., Jiang, L., Averill, C. L., Chowdhury, G. M. I., Purohit, P., de Graaf, R. A., Esterlis, I., Juchem, C., Pittman, B. P., Krystal, J. H., Rothman, D. L., Sanacora, G., & Mason, G. F. (2018). The effects of ketamine on prefrontal glutamate neurotransmission in healthy and depressed subjects. *Neuropsychopharmacology*, *43*(10), 2154–2160. https://doi.org/10.1038/s41386-018-0136-3

Abush, H., Ghose, S., Van Enkevort, E. A., Clementz, B. A., Pearlson, G. D., Sweeney, J. A., Keshavan, M. S., Tamminga, C. A., & Ivleva, E. I. (2018). Associations between adolescent cannabis use and brain structure in psychosis. *Psychiatry Research: Neuroimaging*, *276*, 53–64. https://doi.org/10.1016/j.pscychresns.2018.03.008

Achenbach, T. M., & Edelbrock, C. S. (1978). The classification of child psychopathology: A review and analysis of empirical efforts. *Psychological Bulletin*, *85*(6), 1275–1301. https://doi.org/10.1037/0033-2909.85.6.1275

Adiabatic Pulse—An overview | ScienceDirect Topics. (2004). Retrieved July 22, 2024, from https://www.sciencedirect.com/topics/medicine-and-dentistry/adiabatic-pulse

Ajnakina, O. (2017). *FIRST EPISODE PSYCHOSIS*. King's College London. Retrieved February 18, 2024, from https://kclpure.kcl.ac.uk/portal/en/studentTheses/first-episode-psychosis

Allen, P., Luigjes, J., Howes, O. D., Egerton, A., Hirao, K., Valli, I., Kambeitz, J., Fusar-Poli, P., Broome, M., & McGuire, P. (2012). Transition to Psychosis Associated With Prefrontal and Subcortical Dysfunction in Ultra High-Risk Individuals. *Schizophrenia Bulletin*, *38*(6), 1268–1276. https://doi.org/10.1093/schbul/sbr194

Andó, R. D., Bíró, J., Csölle, C., Ledent, C., & Sperlágh, B. (2012). The inhibitory action of exo- and endocannabinoids on [3H]GABA release are mediated by both CB1 and CB2 receptors in the mouse hippocampus. *Neurochemistry International*, *60*(2), 145–152. https://doi.org/10.1016/j.neuint.2011.11.012

Andreou, C., Eickhoff, S., Heide, M., de Bock, R., Obleser, J., & Borgwardt, S. (2023). Predictors of transition in patients with clinical high risk for psychosis: An umbrella review. *Translational Psychiatry*, *13*(1), 1–11. https://doi.org/10.1038/s41398-023-02586-0

Arciniegas, D. B. (2015). Psychosis. *Continuum : Lifelong Learning in Neurology*, *21*(3 Behavioral Neurology and Neuropsychiatry), 715–736. https://doi.org/10.1212/01.CON.0000466662.89908.e7

Aricioglu, F., Ozkartal, C. S., Unal, G., Dursun, S., Cetin, M., & Müller, N. (2016). Neuroinflammation in Schizophrenia: A Critical Review and The Future. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology*, *26*(4), 429–437. https://doi.org/10.5455/bcp.20161123044657

Armando, M., Nelson, B., Yung, A. R., Ross, M., Birchwood, M., Girardi, P., & Fiori Nastro, P. (2010). Psychotic-like experiences and correlation with distress and depressive symptoms in a community sample of adolescents and young adults. *Schizophrenia Research*, *119*(1–3), 258–265. https://doi.org/10.1016/j.schres.2010.03.001

Assaf, R., Ouellet, J., Bourque, J., Stip, E., Leyton, M., Conrod, P., & Potvin, S. (2022). A functional neuroimaging study of self-other processing alterations in atypical developmental trajectories of psychotic-like experiences. *Scientific Reports*, *12*(1), 16324. https://doi.org/10.1038/s41598-022-20129-3

Atakan, Z. (2012). Cannabis, a complex plant: Different compounds and different effects on individuals. *Therapeutic Advances in Psychopharmacology*, *2*(6), 241–254.

Avants, B. B., Tustison, N., & Johnson, H. (2014). *Advanced Normalization Tools (ANTS)*.

Bagot, K. S., Milin, R., & Kaminer, Y. (2015). Adolescent Initiation of Cannabis use and Early-Onset Psychosis. *Substance Abuse*, *36*(4), 524–533. https://doi.org/10.1080/08897077.2014.995332

Bakhshaie, J., Sharifi, V., & Amini, J. (2011). Exploratory Factor Analysis of SCL90-R Symptoms Relevant to Psychosis. *Iranian Journal of Psychiatry*, *6*(4), 128–132.

Bang, M., Park, J. Y., Kim, K. R., Lee, S. Y., Song, Y. Y., Kang, J. I., Lee, E., & An, S. K. (2019). Psychotic conversion of individuals at ultra-high risk for psychosis: The potential roles of schizotypy and basic symptoms. *Early Intervention in Psychiatry*, *13*(3), 546–554. https://doi.org/10.1111/eip.12518

Barragan, M., Laurens, K. R., Navarro, J. B., & Obiols, J. E. (2011). 'Theory of Mind', psychotic-like experiences and psychometric schizotypy in adolescents from the general population. *Psychiatry Research*, *186*(2), 225–231. https://doi.org/10.1016/j.psychres.2010.07.051

Barres, B. A. (2008). The Mystery and Magic of Glia: A Perspective on Their Roles in Health and Disease. *Neuron*, *60*(3), 430–440. https://doi.org/10.1016/j.neuron.2008.10.013

Bartholomeusz, C. F., Cropley, V. L., Wannan, C., Di Biase, M., McGorry, P. D., & Pantelis, C. (2017). Structural neuroimaging across early-stage psychosis: Aberrations in neurobiological trajectories and implications for the staging model. *Australian & New Zealand Journal of Psychiatry*, *51*(5), 455–476. https://doi.org/10.1177/0004867416670522

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

Beiser, M., Erickson, D., Fleming, J. A. E., & Iacono, W. (1993). Establishing the Onset of Psychotic Illness. *The American Journal of Psychiatry*, *150*, 1349–1354. https://doi.org/10.1176/ajp.150.9.1349

Bernier, D., Bartha, R., McAllindon, D., Hanstock, C. C., Marchand, Y., Dillen, K. N. H., Gallant, M., Good, K. P., & Tibbo, P. G. (2016). Illness versus substance use effects on the frontal white matter in early phase schizophrenia: A 4Tesla (1)H-MRS study. *Schizophrenia Research*, *175*(1–3), 4–11. https://doi.org/10.1016/j.schres.2016.04.022

Bernusky, H. C. R., Tibbo, P. G., Conrod, P. J., Yunus, F. Md., Keough, M. T., Thompson, K. D., Krank, M. D., Hadwin, A. F., & Stewart, S. H. (2023). Do Anxiety Symptoms Mediate the Association Between Cannabis Use Frequency and Psychotic-Like Experiences in Emerging Adult Undergraduates? *The Canadian Journal of Psychiatry*, *68*(11), 860–869. https://doi.org/10.1177/07067437231176900

Bertolino, A., Esposito, G., Callicott, J. H., Mattay, V. S., Van Horn, J. D., Frank, J. A., Berman, K. F., & Weinberger, D. R. (2000). Specific Relationship Between Prefrontal NeuronalN-Acetylaspartate and Activation of the Working Memory Cortical Network in Schizophrenia. *American Journal of Psychiatry*, *157*(1), 26–33. https://doi.org/10.1176/ajp.157.1.26

Beyer, M., Brick, T. R., & Kühn, S. (2024). Urbanicity and psychotic experiences: Social adversities, isolation and exposure to natural environments predict psychosis. *Journal of Environmental Psychology*, *96*, 102293. https://doi.org/10.1016/j.jenvp.2024.102293

Bhattacharyya, S., Atakan, Z., Martin-Santos, R., Crippa, J. A., Kambeitz, J., Prata, D., Williams, S., Brammer, M., Collier, D. A., & McGuire, P. K. (2012). Preliminary report of biological basis of sensitivity to the effects of cannabis on psychosis: AKT1 and DAT1 genotype modulates the effects of δ-9-tetrahydrocannabinol on midbrain and striatal function. *Molecular Psychiatry*, *17*(12), 1152–1155. https://doi.org/10.1038/mp.2011.187

Bhavsar, V., Jauhar, S., Murray, R. M., Hotopf, M., Hatch, S. L., McNeill, A., Boydell, J., & MacCabe, J. H. (2018). Tobacco smoking is associated with psychotic experiences in the general population of South London. *Psychological Medicine*, *48*(1), 123–131. https://doi.org/10.1017/S0033291717001556

Bie, B., Wu, J., Foss, J. F., & Naguib, M. (2018). An overview of the cannabinoid type 2 (CB2) receptor system and its therapeutic potential. *Current Opinion in Anaesthesiology*, *31*(4), 407–414. https://doi.org/10.1097/ACO.0000000000000616

Bissonnette, J. N., Francis, A. M., MacNeil, S., Crocker, C. E., Tibbo, P. G., & Fisher, D. J. (2022). Glutamate and N-Acetylaspartate Alterations Observed in Early Phase Psychosis: A Systematic Review of Proton Magnetic Resonance Spectroscopy Studies. *Psychiatry Research: Neuroimaging*, *321*, 111459. https://doi.org/10.1016/j.pscychresns.2022.111459

Blest-Hopley, G., Colizzi, M., Giampietro, V., & Bhattacharyya, S. (2020a). Is the Adolescent Brain at Greater Vulnerability to the Effects of Cannabis? A Narrative Review of the Evidence. *Frontiers in Psychiatry*, *11*, 859. https://doi.org/10.3389/fpsyt.2020.00859

Blest-Hopley, G., O'Neill, A., Wilson, R., Giampietro, V., Lythgoe, D., Egerton, A., & Bhattacharyya, S. (2020b). Adolescent-onset heavy cannabis use associated with significantly reduced glial but not neuronal markers and glutamate levels in the hippocampus. *Addiction Biology*, *25*(6), e12827. https://doi.org/10.1111/adb.12827

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

Bloomfield, M. A. P., Morgan, C. J. A., Egerton, A., Kapur, S., Curran, H. V., & Howes, O. D. (2014). Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biological Psychiatry*, *75*(6), 470–478. https://doi.org/10.1016/j.biopsych.2013.05.027

Bonar, E. E., Goldstick, J. E., Collins, R. L., Cranford, J. A., Cunningham, R. M., Chermack, S. T., Blow, F. C., & Walton, M. A. (2017). Daily associations between cannabis motives and consumption in emerging adults. *Drug and Alcohol Dependence*, *178*, 136–142. https://doi.org/10.1016/j.drugalcdep.2017.05.006

Bossong, M. G., Antoniades, M., Azis, M., Samson, C., Quinn, B., Bonoldi, I., Modinos, G., Perez, J., Howes, O. D., Stone, J. M., Allen, P., & McGuire, P. (2019). Association of Hippocampal Glutamate Levels With Adverse Outcomes in Individuals at Clinical High Risk for Psychosis. *JAMA Psychiatry*, *76*(2), 199–207. https://doi.org/10.1001/jamapsychiatry.2018.3252

Bourgin, J., Tebeka, S., Mallet, J., Mazer, N., Dubertret, C., & Le Strat, Y. (2020). Prevalence and correlates of psychotic-like experiences in the general population. *Schizophrenia Research*, *215*, 371–377. https://doi.org/10.1016/j.schres.2019.08.024

Bourque, J., Afzali, M. H., O'Leary-Barrett, M., & Conrod, P. (2017). Cannabis use and psychotic-like experiences trajectories during early adolescence: The coevolution and potential mediators. *Journal of Child Psychology and Psychiatry*, *58*(12), 1360–1369. https://doi.org/10.1111/jcpp.12765

Bouter, D. C., Ravensbergen, S. J., Lakerveld, J., Hoogendijk, W. J. G., & Grootendorst-van Mil, N. H. (2023). Associations between the urban environment and psychotic experiences in adolescents. *Schizophrenia Research*, *260*, 123–131. https://doi.org/10.1016/j.schres.2023.08.016

Boyda, D., McFeeters, D., Dhingra, K., & Rhoden, L. (2018). Childhood maltreatment and psychotic experiences: Exploring the specificity of early maladaptive schemas. *Journal of Clinical Psychology*, *74*(12), 2287–2301. https://doi.org/10.1002/jclp.22690

Bramness, J. G., Gundersen, Ø. H., Guterstam, J., Rognli, E. B., Konstenius, M., Løberg, E.-M., Medhus, S., Tanum, L., & Franck, J. (2012). Amphetamine-induced psychosis—A separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry*, *12*(1), 221. https://doi.org/10.1186/1471-244X-12-221

Brañas, A., Barrigón, M. L., Garrido-Torres, N., Perona-Garcelán, S., Rodriguez-Testal, J. F., Lahera, G., & Ruiz-Veguilla, M. (2016). U-shaped curve of psychosis according to cannabis use: New evidence from a snowball sample. *Journal of Psychopharmacology*, *30*(12), 1331–1338. https://doi.org/10.1177/0269881116660712

Brand, A., Richter-Landsberg, C., & Leibfritz, D. (1994). Multinuclear NMR Studies on the Energy Metabolism of Glial and Neuronal Cells. *Developmental Neuroscience*, *15*(3–5), 289–298. https://doi.org/10.1159/000111347

Braun, C. M. J., Boulanger, Y., Labelle, M., Khiat, A., Dumont, M., & Mailloux, C. (2002). Brain metabolic differences as a function of hemisphere, writing hand preference, and gender. *Laterality*, *7*(2), 97–113. https://doi.org/10.1080/13576500143000212

Brecke, V. (2019). *Exploring Glial Marker Activation and Neuroinflammation in Schizophrenia: A multimodal Approach*.

Brucato, G., Masucci, M. D., Arndt, L. Y., Ben-David, S., Colibazzi, T., Corcoran, C. M., Crumbley, A. H., Crump, F. M., Gill, K. E., Kimhy, D., Lister, A., Schobel, S. A., Yang, L. H., Lieberman, J. A., & Girgis, R. R. (2017). Baseline demographics, clinical features and predictors of conversion among 200 individuals in a longitudinal prospective psychosis-risk cohort. *Psychological Medicine*, *47*(11), 1923–1935. https://doi.org/10.1017/S0033291717000319

Brugger, S., Davis, J. M., Leucht, S., & Stone, J. M. (2011). Proton Magnetic Resonance Spectroscopy and Illness Stage in Schizophrenia—A Systematic Review and Meta-Analysis. *Biological Psychiatry*, *69*(5), 495–503. https://doi.org/10.1016/j.biopsych.2010.10.004

Brunelin, J., Fecteau, S., & Suaud-Chagny, M.-F. (2013). Abnormal Striatal Dopamine Transmission in Schizophrenia. *Current Medicinal Chemistry*, *20*(3), 397–404.

Buonocore, M. H., & Maddock, R. J. (2015). Magnetic resonance spectroscopy of the brain: A review of physical principles and technical methods. *Reviews in the Neurosciences*, *26*(6), 609–632. https://doi.org/10.1515/revneuro-2015-0010

Burston, J. J., Wiley, J. L., Craig, A. A., Selley, D. E., & Sim-Selley, L. J. (2010). Regional enhancement of cannabinoid CB1 receptor desensitization in female adolescent rats following repeated Δ9-tetrahydrocannabinol exposure. *British Journal of Pharmacology*, *161*(1), 103–112. https://doi.org/10.1111/j.1476-5381.2010.00870.x

Bustillo, J. R., Upston, J., Mayer, E. G., Jones, T., Maudsley, A. A., Gasparovic, C., Tohen, M., & Lenroot, R. (2020). Glutamatergic hypo-function in the left superior and middle temporal gyri in early schizophrenia: A data-driven three-dimensional proton spectroscopic imaging study. *Neuropsychopharmacology*, *45*(11), 1851–1859. https://doi.org/10.1038/s41386-020-0707-y

Calabrese, J., & Al Khalili, Y. (2024a). Psychosis. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK546579/

Camerini, A.-L., & Schulz, P. (2018). Social Desirability Bias in Child-Report Social Well-Being: Evaluation of the Children's Social Desirability Short Scale Using Item Response Theory and Examination of Its Impact on Self-Report Family and Peer Relationships. *Child Indicators Research*, *11*, 1–16. https://doi.org/10.1007/s12187-017-9472-9

Canada, H. (2023, June 1). *Summary of results for the Canadian Student Tobacco, Alcohol and Drugs Survey 2021* [Surveys]. https://www.canada.ca/en/health-canada/services/canadian-student-tobacco-alcohol-drugs-survey/2021-2022-summary.html

Canada, H. (2024, January 12). *Canadian Cannabis Survey 2023: Summary* [Surveys]. https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/canadian-cannabis-survey-2023-summary.html

Cannon, M., Walsh, E., Hollis, C., Kargin, M., Taylor, E., Murray, R. M., & Jones, P. B. (2001). Predictors of later schizophrenia and affective psychosis among attendees at a child psychiatry department. *The British Journal of Psychiatry*, *178*(5), 420–426. https://doi.org/10.1192/bjp.178.5.420

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

Carney, R., Cotter, J., Firth, J., Bradshaw, T., & Yung, A. R. (2017). Cannabis use and symptom severity in individuals at ultra high risk for psychosis: A meta-analysis. *Acta Psychiatrica Scandinavica*, *136*(1), 5–15. https://doi.org/10.1111/acps.12699

Carpenter, W. T. (2013). How the Diagnosis of Schizophrenia Impeded the Advance of Knowledge (and What to Do About It). In S. M. Silverstein, B. Moghaddam, & T. Wykes (Eds.), *Schizophrenia: Evolution and Synthesis*. MIT Press. http://www.ncbi.nlm.nih.gov/books/NBK569652/

Casadio, P., Fernandes, C., Murray, R. M., & Di Forti, M. (2011). Cannabis use in young people: The risk for schizophrenia. *Neuroscience & Biobehavioral Reviews*, *35*(8), 1779–1787. https://doi.org/10.1016/j.neubiorev.2011.04.007

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., Taylor, A., Arseneault, L., Williams, B., Braithwaite, A., Poulton, R., & Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. *Biological Psychiatry*, *57*(10), 1117–1127. https://doi.org/10.1016/j.biopsych.2005.01.026

Castillejos, M. C., Martín-Pérez, C., & Moreno-Küstner, B. (2018). A systematic review and meta-analysis of the incidence of psychotic disorders: The distribution of rates and the influence of gender, urbanicity, immigration and socio-economic level. *Psychological Medicine*, *48*(13), 2101–2115. https://doi.org/10.1017/S0033291718000235

Catone, G., Marotta, R., Pisano, S., Lennox, B., Carotenuto, M., Gritti, A., Pascotto, A., & Broome, M. R. (2017). Psychotic-like experiences in help-seeking adolescents: Dimensional exploration and association with different forms of bullying victimization – A developmental social psychiatry perspective. *International Journal of Social Psychiatry*, *63*(8), 752–762. https://doi.org/10.1177/0020764017733765

Cerdá, M., Wall, M., Feng, T., Keyes, K. M., Sarvet, A., Schulenberg, J., O'Malley, P. M., Pacula, R. L., Galea, S., & Hasin, D. S. (2017). Association of State Recreational Marijuana Laws With Adolescent Marijuana Use. *JAMA Pediatrics*, *171*(2), 142–149. https://doi.org/10.1001/jamapediatrics.2016.3624

Champagne, F. A. (2010). Early Adversity and Developmental Outcomes: Interaction Between Genetics, Epigenetics, and Social Experiences Across the Life Span. *Perspectives on Psychological Science*, *5*(5), 564–574. https://doi.org/10.1177/1745691610383494

Chang, L., Cloak, C., Yakupov, R., & Ernst, T. (2006). Combined and Independent Effects of Chronic Marijuana Use and HIV on Brain Metabolites. *Journal of Neuroimmune Pharmacology*, *1*(1), 65–76. https://doi.org/10.1007/s11481-005-9005-z

Chang, L., Ernst, T., Osborn, D., Seltzer, W., Leonido-Yee, M., & Poland, R. E. (1998). Proton Spectroscopy in Myotonic Dystrophy: Correlations With CTG Repeats. *Archives of Neurology*, *55*(3), 305–311. https://doi.org/10.1001/archneur.55.3.305

Chang, W. C., Wong, C. S. M., Chen, E. Y. H., Lam, L. C. W., Chan, W. C., Ng, R. M. K., Hung, S. F., Cheung, E. F. C., Sham, P. C., Chiu, H. F. K., Lam, M., Lee, E. H. M., Chiang, T. P., Chan, L. K., Lau, G. K. W., Lee, A. T. C., Leung, G. T. Y., Leung, J. S. Y., Lau, J. T. F., … Bebbington, P. (2017). Lifetime Prevalence and Correlates of Schizophrenia-Spectrum, Affective, and Other Non-affective Psychotic Disorders in the Chinese Adult Population. *Schizophrenia Bulletin*, *43*(6), 1280–1290. https://doi.org/10.1093/schbul/sbx056

Chapman, L. J., Chapman, J. P., Kwapil, T. R., Eckblad, M., & Zinser, M. C. (1994). Putatively psychosis-prone subjects 10 years later. *Journal of Abnormal Psychology*, *103*(2), 171–183. https://doi.org/10.1037/0021-843X.103.2.171

Chen, H.-R., DeGrauw, T., & Kuan, C.-Y. (2022). (Phospho)creatine: The reserve and merry-go-round of brain energetics. *Neural Regeneration Research*, *18*(2), 327–328. https://doi.org/10.4103/1673-5374.346470

Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., Kolachana, B. S., Hyde, T. M., Herman, M. M., Apud, J., Egan, M. F., Kleinman, J. E., & Weinberger, D. R. (2004). Functional Analysis of Genetic Variation in Catechol-O-Methyltransferase (COMT): Effects on mRNA, Protein, and Enzyme Activity in Postmortem Human Brain. *The American Journal of Human Genetics*, *75*(5), 807–821. https://doi.org/10.1086/425589

Chhetri, D. R. (2019). Myo-Inositol and Its Derivatives: Their Emerging Role in the Treatment of Human Diseases. *Frontiers in Pharmacology*, *10*. https://doi.org/10.3389/fphar.2019.01172

Chiang, J. J., Lam, P. H., Chen, E., & Miller, G. E. (2022). Psychological stress during childhood and adolescence and its association with inflammation across the lifespan: A critical review and meta-analysis. *Psychological Bulletin*, *148*(1–2), 27–66. https://doi.org/10.1037/bul0000351

Chiappelli, J., Rowland, L. M., Wijtenburg, S. A., Muellerklein, F., Tagamets, M., McMahon, R. P., Gaston, F., Kochunov, P., & Hong, L. E. (2015). Evaluation of Myo-Inositol as a Potential Biomarker for Depression in Schizophrenia. *Neuropsychopharmacology*, *40*(9), 2157–2164. https://doi.org/10.1038/npp.2015.57

Chinn, S. (2000). A simple method for converting an odds ratio to effect size for use in meta-analysis. *Statistics in Medicine*, *19*(22), 3127–3131. https://doi.org/10.1002/1097-0258(20001130)19:22<3127::aid-sim784>3.0.co;2-m

Chiu, C. Q., Puente, N., Grandes, P., & Castillo, P. E. (2010). Dopaminergic Modulation of Endocannabinoid-Mediated Plasticity at GABAergic Synapses in the Prefrontal Cortex. *Journal of Neuroscience*, *30*(21), 7236–7248. https://doi.org/10.1523/JNEUROSCI.0736-10.2010

Chouinard, V.-A., Kim, S.-Y., Valeri, L., Yuksel, C., Ryan, K. P., Chouinard, G., Cohen, B. M., Du, F., & Öngür, D. (2017). Brain bioenergetics and redox state measured by 31P magnetic resonance spectroscopy in unaffected siblings of patients with psychotic disorders. *Schizophrenia Research*, *187*, 11–16. https://doi.org/10.1016/j.schres.2017.02.024

Chun, C. A., Cooper, S., & Ellman, L. M. (2020). Associations of psychotic-like experiences, related symptoms, and working memory with functioning. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *63*(1), e20. https://doi.org/10.1192/j.eurpsy.2020.21

Churchwell, J. C., Lopez-Larson, M., & Yurgelun-Todd, D. A. (2010). Altered Frontal Cortical Volume and Decision Making in Adolescent Cannabis Users. *Frontiers in Psychology*, *1*. https://doi.org/10.3389/fpsyg.2010.00225

Cichocka, M., Kozub, J., Karcz, P., & Urbanik, A. (2016). Differences in Metabolite Concentrations Between the Hemispheres of the Brain in Healthy Children: A Proton Magnetic Resonance Spectroscopy Study (1HMRS). *Journal of Child Neurology*, *31*(11), 1296–1301. https://doi.org/10.1177/0883073816653784

Ciranka, S., & van den Bos, W. (2019). Social Influence in Adolescent Decision-Making: A Formal Framework. *Frontiers in Psychology*, *10*. https://doi.org/10.3389/fpsyg.2019.01915

Clarke, P. (2008). When can group level clustering be ignored? Multilevel models versus single-level models with sparse data. *Journal of Epidemiology & Community Health*, *62*(8), 752–758. https://doi.org/10.1136/jech.2007.060798

Clarke, W. T., Stagg, C. J., & Jbabdi, S. (2021). FSL-MRS: An end-to-end spectroscopy analysis package. *Magnetic Resonance in Medicine*, *85*(6), 2950–2964. https://doi.org/10.1002/mrm.28630

Coffey, C., Lynskey, M., Wolfe, R., & Patton, G. C. (2000). Initiation and progression of cannabis use in a population-based Australian adolescent longitudinal study. *Addiction*, *95*(11), 1679–1690. https://doi.org/10.1046/j.1360-0443.2000.951116798.x

Colder, C. R., Lee, Y. H., Frndak, S., Read, J. P., & Wieczorek, W. F. (2019). Internalizing symptoms and cannabis and alcohol use: Between- and within-person risk pathways with coping motives. *Journal of Consulting and Clinical Psychology*, *87*(7), 629–644. https://doi.org/10.1037/ccp0000413

Colyer-Patel, K., Romein, C., Kuhns, L., Cousijn, J., & Kroon, E. (2024). Recent Evidence on the Relation Between Cannabis Use, Brain Structure, and Function: Highlights and Challenges. *Current Addiction Reports*, *11*, 1–13. https://doi.org/10.1007/s40429-024-00557-z

Cooper, Z. D., & Haney, M. (2009). Comparison of subjective, pharmacokinetic, and physiologic effects of marijuana smoked as joints and blunts. *Drug and Alcohol Dependence*, *103*(3), 107–113. https://doi.org/10.1016/j.drugalcdep.2009.01.023

Corcoran, C. M., Mittal, V. A., & Woods, S. W. (2021). Attenuated Psychosis Syndrome Should Be Moved to the Main Section in DSM-5-TR. *JAMA Psychiatry*, *78*(8), 821–822. https://doi.org/10.1001/jamapsychiatry.2021.0838

Coronado, C., Wade, N. E., Aguinaldo, L. D., Hernandez Mejia, M., & Jacobus, J. (2020). Neurocognitive Correlates of Adolescent Cannabis Use: An Overview of Neural Activation Patterns in Task-Based Functional MRI Studies. *Journal of Pediatric Neuropsychology*, *6*(1), 1–13. https://doi.org/10.1007/s40817-020-00076-5

Corsi-Zuelli, F., Marques, L., Roza, D. L. da, Loureiro, C. M., Shuhama, R., 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

Cotter, D., Mackay, D., Landau, S., Kerwin, R., & Everall, I. (2001). Reduced Glial Cell Density and Neuronal Size in the Anterior Cingulate Cortex in Major Depressive Disorder. *Archives of General Psychiatry*, *58*(6), 545–553. https://doi.org/10.1001/archpsyc.58.6.545

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

Covey, D., Mateo, Y., Sulzer, D., Cheer, J. F., & Lovinger, D. M. (2017). Endocannabinoid modulation of dopamine neurotransmission. *Neuropharmacology*, *124*, 52–61. https://doi.org/10.1016/j.neuropharm.2017.04.033

Crocker, C. E., Cookey, J., & Tibbo, P. G. (2017). Chapter 36—Neuroimaging Findings in Adolescent Cannabis Use and Early Phase Psychosis. In V. R. Preedy (Ed.), *Handbook of Cannabis and Related Pathologies* (pp. 345–356). Academic Press. https://doi.org/10.1016/B978-0-12-800756-3.00041-7

Currie, C., Molcho, M., Boyce, W., Holstein, B., Torsheim, T., & Richter, M. (2008). Researching health inequalities in adolescents: The development of the Health Behaviour in School-Aged Children (HBSC) Family Affluence Scale. *Social Science & Medicine*, *66*(6), 1429–1436. https://doi.org/10.1016/j.socscimed.2007.11.024

Currie, C. & Weltgesundheitsorganisation (Eds.). (2004). *Young people's health in context: Health Behaviour in School-aged Children (HBSC) study ; international report from the 2001/2002 survey*. World Health Organization, Regional Office for Europe.

D. Howes, O., Fusar-Poli, P., Bloomfield, M., Selvaraj, S., & McGuire, P. (2012). From the Prodrome to Chronic Schizophrenia: The Neurobiology Underlying Psychotic Symptoms and Cognitive Impairments. *Current Pharmaceutical Design*, *18*(4), 459–465. https://doi.org/10.2174/138161212799316217

Da Silva, T., Hafizi, S., Andreazza, A. C., Kiang, M., Bagby, R. M., Navas, E., Laksono, I., Truong, P., Gerritsen, C., Prce, I., Sailasuta, N., & Mizrahi, R. (2018). Glutathione, the Major Redox Regulator, in the Prefrontal Cortex of Individuals at Clinical High Risk for Psychosis. *International Journal of Neuropsychopharmacology*, *21*(4), 311–318. https://doi.org/10.1093/ijnp/pyx094

Da Silva, T., Wu, A., Laksono, I., Prce, I., Maheandiran, M., Kiang, M., Andreazza, A. C., & Mizrahi, R. (2018). Mitochondrial function in individuals at clinical high risk for psychosis. *Scientific Reports*, *8*(1), 6216. https://doi.org/10.1038/s41598-018-24355-6

Danese, A., Caspi, A., Williams, B., Ambler, A., Sugden, K., Mika, J., Werts, H., Freeman, J., Pariante, C. M., Moffitt, T. E., & Arseneault, L. (2011). Biological embedding of stress through inflammation processes in childhood. *Molecular Psychiatry*, *16*(3), 244–246. https://doi.org/10.1038/mp.2010.5

Das, T. K., Dey, A., Sabesan, P., Javadzadeh, A., Théberge, J., Radua, J., & Palaniyappan, L. (2018). Putative Astroglial Dysfunction in Schizophrenia: A Meta-Analysis of 1H-MRS Studies of Medial Prefrontal Myo-Inositol. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00438

de Bartolomeis, A., Barone, A., Vellucci, L., Mazza, B., Austin, M. C., Iasevoli, F., & Ciccarelli, M. (2022). Linking Inflammation, Aberrant Glutamate-Dopamine Interaction, and Post-synaptic Changes: Translational Relevance for Schizophrenia and Antipsychotic Treatment: a Systematic Review. *Molecular Neurobiology*, *59*(10), 6460–6501. https://doi.org/10.1007/s12035-022-02976-3

de Jong, Y., Boon, A. E., Gouw, D., van der Gaag, M., & Mulder, C. L. (2022). Improving screening methods for psychosis in an adolescent help-seeking population using the Child Behavior Checklist (CBCL) and the Youth Self Report (YSR) versus the Prodromal Questionnaire -16 items version (PQ-16). *Child and Adolescent Psychiatry and Mental Health*, *16*(1), 25. https://doi.org/10.1186/s13034-022-00459-w

de Wit, S., Wierenga, L. M., Oranje, B., Ziermans, T. B., Schothorst, P. F., van Engeland, H., Kahn, R. S., & Durston, S. (2016). Brain development in adolescents at ultra-high risk for psychosis: Longitudinal changes related to resilience. *NeuroImage: Clinical*, *12*, 542–549. https://doi.org/10.1016/j.nicl.2016.08.013

Degenhardt, L., Saha, S., Lim, C. C. W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Andrade, L. H., Bromet, E. J., Bruffaerts, R., Caldas-de-Almeida, J. M., de Girolamo, G., Florescu, S., Gureje, O., Haro, J. M., Karam, E. G., Karam, G., Kovess-Masfety, V., Lee, S., Lepine, J.-P., … McGrath, J. J. (2018). The associations between psychotic experiences, and substance use and substance use disorders: Findings from the World Health Organisation World Mental Health Surveys. *Addiction (Abingdon, England)*, *113*(5), 924–934. https://doi.org/10.1111/add.14145

Demler, V., Sterner, E. F., Wilson, M., Zimmer, C., & Knolle, F. (2023). *The impact of spectral basis set composition on estimated levels of cingulate glutamate and its associations with different personality traits* (p. 2023.07.12.23292540). medRxiv. https://doi.org/10.1101/2023.07.12.23292540

Denissoff, A., Mustonen, A., Miettunen, J., Alakokkare, A.-E., Veijola, J., Scott, J. G., Sami, M. B., & Niemelä, S. (2022). Trajectories of adolescent psychotic-like experiences and early cannabis exposure: Results from a Finnish Birth Cohort Study. *Schizophrenia Research*, *246*, 95–102. https://doi.org/10.1016/j.schres.2022.06.014

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

Di Biase, M. A., Zalesky, A., O'keefe, G., Laskaris, L., Baune, B. T., Weickert, C. S., Olver, J., McGorry, P. D., Amminger, G. P., Nelson, B., Scott, A. M., Hickie, I., Banati, R., Turkheimer, F., Yaqub, M., Everall, I. P., Pantelis, C., & Cropley, V. (2017). PET imaging of putative microglial activation in individuals at ultra-high risk for psychosis, recently diagnosed and chronically ill with schizophrenia. *Translational Psychiatry*, *7*(8), e1225–e1225. https://doi.org/10.1038/tp.2017.193

Di Forti, M. D., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., Rodriguez, V., Jongsma, H. E., Ferraro, L., Cascia, C. L., Barbera, D. L., Tarricone, I., Berardi, D., Szöke, A., Arango, C., Tortelli, A., Velthorst, E., Bernardo, M., Del-Ben, C. M., … Ven, E. van der. (2019a). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): A multicentre case-control study. *The Lancet Psychiatry*, *6*(5), 427–436. https://doi.org/10.1016/S2215-0366(19)30048-3

Di Marzo, V., & Piscitelli, F. (2015). The Endocannabinoid System and its Modulation by Phytocannabinoids. *Neurotherapeutics*, *12*(4), 692–698. https://doi.org/10.1007/s13311-015-0374-6

Dietz, A. G., Goldman, S. A., & Nedergaard, M. (2020). Glial cells in schizophrenia: A unified hypothesis. *The Lancet. Psychiatry*, *7*(3), 272–281. https://doi.org/10.1016/S2215-0366(19)30302-5

Doggui, R., Elsawy, W., Conti, A. A., & Baldacchino, A. (2021). Association between chronic psychoactive substances use and systemic inflammation: A systematic review and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *125*, 208–220. https://doi.org/10.1016/j.neubiorev.2021.02.031

Dolphin, L., Dooley, B., & Fitzgerald, A. (2015). Prevalence and correlates of psychotic like experiences in a nationally representative community sample of adolescents in Ireland. *Schizophrenia Research*, *169*(1–3), 241–247. https://doi.org/10.1016/j.schres.2015.09.005

Domingues, H. S., Portugal, C. C., Socodato, R., & Relvas, J. B. (2016). Oligodendrocyte, Astrocyte, and Microglia Crosstalk in Myelin Development, Damage, and Repair. *Frontiers in Cell and Developmental Biology*, *4*. https://doi.org/10.3389/fcell.2016.00071

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

Downes, C. P., & Macphee, C. H. (1990). Myo-Inositol metabolites as cellular signals. *European Journal of Biochemistry*, *193*(1), 1–18. https://doi.org/10.1111/j.1432-1033.1990.tb19297.x

Dudley, R., Aynsworth, C., Cheetham, R., McCarthy-Jones, S., & Collerton, D. (2018). Prevalence and characteristics of multi-modal hallucinations in people with psychosis who experience visual hallucinations. *Psychiatry Research*, *269*, 25–30. https://doi.org/10.1016/j.psychres.2018.08.032

Dugan, L. L., Ali, S. S., Shekhtman, G., Roberts, A. J., Lucero, J., Quick, K. L., & Behrens, M. M. (2009). IL-6 Mediated Degeneration of Forebrain GABAergic Interneurons and Cognitive Impairment in Aged Mice through Activation of Neuronal NADPH Oxidase. *PLOS ONE*, *4*(5), e5518. https://doi.org/10.1371/journal.pone.0005518

Dugré, J. R., Potvin, S., Dellazizzo, L., & Dumais, A. (2021). Aggression and delinquent behavior in a large representative sample of high school students: Cannabis use and victimization as key discriminating factors. *Psychiatry Research*, *296*, 113640. https://doi.org/10.1016/j.psychres.2020.113640

Dunleavy, C., Elsworthy, R. J., Upthegrove, R., Wood, S. J., & Aldred, S. (2022). Inflammation in first-episode psychosis: The contribution of inflammatory biomarkers to the emergence of negative symptoms, a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *146*(1), 6–20. https://doi.org/10.1111/acps.13416

Dunn, P. K., & Smyth, G. K. (2018). Chapter 11: Positive Continuous Data: Gamma and Inverse Gaussian GLMs. In P. K. Dunn & G. K. Smyth (Eds.), *Generalized Linear Models With Examples in R* (pp. 425–456). Springer. https://doi.org/10.1007/978-1-4419-0118-7_11

Ebert, T., Heinz, D. E., Almeida-Corrêa, S., Cruz, R., Dethloff, F., Stark, T., Bajaj, T., Maurel, O. M., Ribeiro, F. M., Calcagnini, S., Hafner, K., Gassen, N. C., Turck, C. W., Boulat, B., Czisch, M., & Wotjak, C. T. (2021). Myo-Inositol Levels in the Dorsal Hippocampus Serve as Glial Prognostic Marker of Mild Cognitive Impairment in Mice. *Frontiers in Aging Neuroscience*, *13*, 731603. https://doi.org/10.3389/fnagi.2021.731603

Egerton, A., Chaddock, C. A., Winton-Brown, T. T., Bloomfield, M. A. P., Bhattacharyya, S., Allen, P., McGuire, P. K., & Howes, O. D. (2013). Presynaptic Striatal Dopamine Dysfunction in People at Ultra-high Risk for Psychosis: Findings in a Second Cohort. *Biological Psychiatry*, *74*(2), 106–112. https://doi.org/10.1016/j.biopsych.2012.11.017

Eggins, P. S., Hatton, S. N., Hermens, D. F., Hickie, I. B., & Lagopoulos, J. (2018). Subcortical volumetric differences between clinical stages of young people with affective and psychotic disorders. *Psychiatry Research: Neuroimaging*, *271*, 8–16. https://doi.org/10.1016/j.pscychresns.2017.11.015

Ellman, L. M., Schiffman, J., & Mittal, V. A. (2020). Community Psychosis Risk Screening: An Instrument Development Investigation †. *Journal of Psychiatry and Brain Science*, *4*(3). https://doi.org/10.20900/jpbs.20200019

Englund, A., Atakan, Z., Kralj, A., Tunstall, N., Murray, R., & Morrison, P. (2016). The effect of five day dosing with THCV on THC-induced cognitive, psychological and physiological effects in healthy male human volunteers: A placebo-controlled, double-blind, crossover pilot trial. *Journal of Psychopharmacology*, *30*(2), 140–151. https://doi.org/10.1177/0269881115615104

Ensink, J. B. M., de Moor, M. H. M., Zafarmand, M. H., de Laat, S., Uitterlinden, A., Vrijkotte, T. G. M., Lindauer, R., & Middeldorp, C. M. (2020). Maternal environmental risk factors and the development of internalizing and externalizing problems in childhood: The complex role of genetic factors. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *183*(1), 17–25. https://doi.org/10.1002/ajmg.b.32755

Ermel, J. A., Moran, E. K., Culbreth, A. J., & Barch, D. M. (2019). Psychotic like experiences as part of a continuum of psychosis: Associations with effort-based decision-making and reward responsivity. *Schizophrenia Research*, *206*, 307–312. https://doi.org/10.1016/j.schres.2018.10.026

Ernst, M., Luckenbaugh, D. A., Moolchan, E. T., Leff, M. K., Allen, R., Eshel, N., London, E. D., & Kimes, A. (2006). Behavioral Predictors of Substance-Use Initiation in Adolescents With and Without Attention-Deficit/Hyperactivity Disorder. *Pediatrics*, *117*(6), 2030–2039. https://doi.org/10.1542/peds.2005-0704

Essner, B., Noel, M., Myrvik, M., & Palermo, T. (2015). Examination of the Factor Structure of the Adolescent Sleep–Wake Scale (ASWS). *Behavioral Sleep Medicine*, *13*(4), 296–307. https://doi.org/10.1080/15402002.2014.896253

Fagerström, K. O. (1978). Measuring degree of physical dependence to tobacco smoking with reference to individualization of treatment. *Addictive Behaviors*, *3*(3–4), 235–241. https://doi.org/10.1016/0306-4603(78)90024-2

Falkenberg, L. E., Westerhausen, R., Craven, A. R., Johnsen, E., Kroken, R. A., L⊘berg, E.-M., Specht, K., & Hugdahl, K. (2014). Impact of glutamate levels on neuronal response and cognitive abilities in schizophrenia. *NeuroImage: Clinical*, *4*, 576–584. https://doi.org/10.1016/j.nicl.2014.03.014

Farmer, R. F., Seeley, J. R., Kosty, D. B., Gau, J. M., Duncan, S. C., Lynskey, M. T., & Lewinsohn, P. M. (2015). Internalizing and externalizing psychopathology as predictors of cannabis use disorder onset during adolescence and early adulthood. *Psychology of Addictive Behaviors*, *29*(3), 541–551. https://doi.org/10.1037/adb0000059

Fatani, B. Z., Aldawod, R., Alhawaj, A., Alsadah, S., Slais, F. R., Alyaseen, E. N., Ghamri, A. S., Banjar, J., & Qassaim, Y. A. (2017). Schizophrenia: Etiology, Pathophysiology and Management - A Review. *The Egyptian Journal of Hospital Medicine*, *69*(6), 2640–2646. https://doi.org/10.12816/0042241

Faul, F., Erdfelder, E., Buchner, A., & Lang, A.-G. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behavior Research Methods*, *41*(4), 1149–1160. https://doi.org/10.3758/BRM.41.4.1149

Fergusson, D. M., Lynskey, M. T., & Horwood, L. J. (1996). The short-term consequences of early onset cannabis use. *Journal of Abnormal Child Psychology*, *24*(4), 499–512. https://doi.org/10.1007/BF01441571

Ferretjans, R., de Souza, R. P., Panizzutti, B., Ferrari, P., Mantovani, L., de Campos-Carli, S. M., Santos, R. R., Guimarães, F. C., Teixeira, A. L., Gama, C. S., & Salgado, J. V. (n.d.). Cannabinoid receptor gene polymorphisms and cognitive performance in patients with schizophrenia and controls. *Brazilian Journal of Psychiatry*, *44*, 26–34. https://doi.org/10.1590/1516-4446-2020-1650

Fisher, H. L., Schreier, A., Zammit, S., Maughan, B., Munafò, M. R., Lewis, G., & Wolke, D. (2013a). Pathways Between Childhood Victimization and Psychosis-like Symptoms in the ALSPAC Birth Cohort. *Schizophrenia Bulletin*, *39*(5), 1045–1055. https://doi.org/10.1093/schbul/sbs088

Fisher, H. L., Caspi, A., Poulton, R., Meier, M. H., Houts, R., Harrington, H., Arseneault, L., & Moffitt, T. E. (2013b). Specificity of childhood psychotic symptoms for predicting schizophrenia by 38 years of age: A birth cohort study. *Psychological Medicine*, *43*(10), 2077–2086. https://doi.org/10.1017/S0033291712003091

Flückiger, R., Ruhrmann, S., Debbané, M., Michel, C., Hubl, D., Schimmelmann, B. G., Klosterkötter, J., & Schultze-Lutter, F. (2016). Psychosis-predictive value of self-reported schizotypy in a clinical high-risk sample. *Journal of Abnormal Psychology*, *125*(7), 923–932. https://doi.org/10.1037/abn0000192

Fonseca-Pedrero, E., Lucas-Molina, B., Pérez-Albéniz, A., Inchausti, F., & Ortuño-Sierra, J. (2020). Psychotic-like experiences and cannabis use in adolescents from the general population. *Adicciones*, *32*(1), 41–51. https://doi.org/10.20882/adicciones.1149

Fortea, A., Batalla, A., Radua, J., van Eijndhoven, P., Baeza, I., Albajes-Eizagirre, A., Fusar-Poli, P., Castro-Fornieles, J., De la Serna, E., Luna, L. P., Carvalho, A. F., Vieta, E., & Sugranyes, G. (2021). Cortical gray matter reduction precedes transition to psychosis in individuals at clinical high-risk for psychosis: A voxel-based meta-analysis. *Schizophrenia Research*, *232*, 98–106. https://doi.org/10.1016/j.schres.2021.05.008

Foster, K. T., Hicks, B. M., & Zucker, R. A. (2018). Positive and negative effects of internalizing on alcohol use problems from childhood to young adulthood: The mediating and suppressing role of externalizing. *Journal of Abnormal Psychology*, *127*(4), 394–403. https://doi.org/10.1037/abn0000337

Frangou, S., & Williams, S. C. R. (1996). Magnetic resonance spectroscopy in psychiatry: Basic principles and applications. *British Medical Bulletin*, *52*(3), 474–485. https://doi.org/10.1093/oxfordjournals.bmb.a011561

Freyberg, Z., Ferrando, S. J., & Javitch, J. A. (2010). Roles of the Akt/GSK-3 and Wnt Signaling Pathways in Schizophrenia and Antipsychotic Drug Action. *American Journal of Psychiatry*, *167*(4), 388–396. https://doi.org/10.1176/appi.ajp.2009.08121873

Friedman, A. S., Utada, A. T., Glickman, N. W., & Morrissey, M. R. (1987). Psychopathology as an Antecedent to, and as a "Consequence" of, Substance Use, in Adolescence. *Journal of Drug Education*, *17*(3), 233–244. https://doi.org/10.2190/F7VJ-3MTA-HF62-0DQC

Fusar-Poli, P., Borgwardt, S., Crescini, A., Deste, G., Kempton, M. J., Lawrie, S., Mc Guire, P., & Sacchetti, E. (2011). Neuroanatomy of vulnerability to psychosis: A voxel-based meta-analysis. *Neuroscience & Biobehavioral Reviews*, *35*(5), 1175–1185. https://doi.org/10.1016/j.neubiorev.2010.12.005

Fusar-Poli, P., Cappucciati, M., Borgwardt, S., Woods, S. W., Addington, J., Nelson, B., Nieman, D. H., Stahl, D. R., Rutigliano, G., Riecher-Rössler, A., Simon, A. E., Mizuno, M., Lee, T. Y., Kwon, J. S., Lam, M. M. L., Perez, J., Keri, S., Amminger, P., Metzler, S., … McGuire, P. K. (2016). Heterogeneity of Psychosis Risk Within Individuals at Clinical High Risk: A Meta-analytical Stratification. *JAMA Psychiatry*, *73*(2), 113–120. https://doi.org/10.1001/jamapsychiatry.2015.2324

Fusar-Poli, P., Howes, O. D., Allen, P., Broome, M., Valli, I., Asselin, M.-C., Montgomery, A. J., Grasby, P. M., & McGuire, P. (2011). Abnormal prefrontal activation directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. *Molecular Psychiatry*, *16*(1), 67–75. https://doi.org/10.1038/mp.2009.108

Fusar-Poli, P., Tantardini, M., De Simone, S., Ramella-Cravaro, V., Oliver, D., Kingdon, J., Kotlicka-Antczak, M., Valmaggia, L., Lee, J., Millan, M. J., Galderisi, S., Balottin, U., Ricca, V., & McGuire, P. (2017). Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. *European Psychiatry*, *40*, 65–75. https://doi.org/10.1016/j.eurpsy.2016.09.003

Gage, S. H., Hickman, M., Heron, J., Munafò, M. R., Lewis, G., Macleod, J., & Zammit, S. (2014). Associations of cannabis and cigarette use with psychotic experiences at age 18: Findings from the Avon Longitudinal Study of Parents and Children. *Psychological Medicine*, *44*(16), 3435–3444. https://doi.org/10.1017/S0033291714000531

Gage, S. H., Jones, H. J., Burgess, S., Bowden, J., Davey Smith, G., Zammit, S., & Munafò, M. R. (2017). Assessing causality in associations between cannabis use and schizophrenia risk: A two-sample Mendelian randomization study. *Psychological Medicine*, *47*(5), 971–980. https://doi.org/10.1017/S0033291716003172

Gage, S. H., Zammit, S., & Hickman, M. (2013). Stronger evidence is needed before accepting that cannabis plays an important role in the aetiology of schizophrenia in the population. *F1000 Medicine Reports*, *5*, 2. https://doi.org/10.3410/M5-2

Galletly, C., Clark, L., McFarlane, A., Searle, A., Sawyer, M., Sim, M., Baghurst, P., & van Hooff, M. (2016). Childhood lead exposure, childhood trauma, substance use and subclinical psychotic experiences–a longitudinal cohort study. *Psychiatry Research*, *239*, 54–61. https://doi.org/10.1016/j.psychres.2016.02.066

Gamma-Aminobutyric Acid (GABA) and the Endocannabinoids: Understanding the Risks and Opportunities | IntechOpen. (n.d.). Retrieved July 18, 2024, from https://www.intechopen.com/chapters/78043

Ganguli, R., Yang, Z., Shurin, G., Chengappa, K. N. R., Brar, J. S., Gubbi, A. V., & Rabin, B. S. (1994). Serum interleukin-6 concentration in schizophrenia: Elevation associated with duration of illness. *Psychiatry Research*, *51*(1), 1–10. https://doi.org/10.1016/0165-1781(94)90042-6

Garcia-Oscos, F., Salgado, H., Hall, S., Thomas, F., Farmer, G. E., Bermeo, J., Galindo, L. C., Ramirez, R. D., D'Mello, S., Rose-John, S., & Atzori, M. (2012). The Stress-Induced Cytokine Interleukin-6 Decreases the Inhibition/Excitation Ratio in the Rat Temporal Cortex via Trans-Signaling. *Biological Psychiatry*, *71*(7), 574–582. https://doi.org/10.1016/j.biopsych.2011.11.018

Garver, D. L., Tamas, R. L., & Holcomb, J. A. (2003). Elevated Interleukin-6 in the Cerebrospinal Fluid of a Previously Delineated Schizophrenia Subtype. *Neuropsychopharmacology*, *28*(8), 1515–1520. https://doi.org/10.1038/sj.npp.1300217

Gastel, W. A. van, MacCabe, J. H., Schubart, C. D., Vreeker, A., Tempelaar, W., Kahn, R. S., & Boks, M. P. M. (2013). Cigarette smoking and cannabis use are equally strongly associated with psychotic-like experiences: A cross-sectional study in 1929 young adults. *Psychological Medicine*, *43*(11), 2393–2401. https://doi.org/10.1017/S0033291713000202

Gau, S. S. F., Chong, M.-Y., Yang, P., Yen, C.-F., Liang, K.-Y., & Cheng, A. T. A. (2007). Psychiatric and psychosocial predictors of substance use disorders among adolescents: Longitudinal study. *The British Journal of Psychiatry*, *190*(1), 42–48. https://doi.org/10.1192/bjp.bp.106.022871

GBD 2019 Mental Disorders Collaborators. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet. Psychiatry*, *9*(2), 137–150. https://doi.org/10.1016/S2215-0366(21)00395-3

Gee, D. G., & Cannon, T. D. (2011). Prediction of conversion to psychosis: Review and future directions. *Brazilian Journal of Psychiatry*, *33*, s129–s142. https://doi.org/10.1590/S1516-44462011000600002

Gehricke, J.-G., Loughlin, S. E., Whalen, C. K., Potkin, S. G., Fallon, J. H., Jamner, L. D., Belluzzi, J. D., & Leslie, F. M. (2007a). Smoking to self-medicate attentional and emotional dysfunctions. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco*, *9 Suppl 4*, S523-536. https://doi.org/10.1080/14622200701685039

Gehricke, J.-G., Loughlin, S. E., Whalen, C. K., Potkin, S. G., Fallon, J. H., Jamner, L. D., Belluzzi, J. D., & Leslie, F. M. (2007b). Smoking to Self-Medicate Attentional and Emotional Dysfunctions. *Nicotine & Tobacco Research*, *9*(Suppl_4), S523–S536. https://doi.org/10.1080/14622200701685039

Gender differences in the experience of psychotic-like experiences and their associated factors: A study of adolescents from the general population—ClinicalKey. (n.d.-a). Retrieved May 17, 2024, from https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0920996421000505?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0920996421000505%3Fshowall%3Dtrue&referrer=https:%2F%2Fpubmed.ncbi.nlm.nih.gov%2F

Genetic Risk and Outcome of Psychosis (GROUP), a multi site longitudinal cohort study focused on gene–environment interaction: Objectives, sample characteristics, recruitment and assessment methods—Korver—2012—International Journal of Methods in Psychiatric Research—Wiley Online Library. (n.d.). Retrieved June 17, 2024, from https://onlinelibrary-wiley-com.ezproxy.library.dal.ca/doi/full/10.1002/mpr.1352

Gerritsen, C., Iyengar, Y., DaSilva, T., Koppel, A., Rusjan, P., Bagby, R. M., & Mizrahi, R. (2020). Personality traits in psychosis and psychosis risk linked to TSPO expression: A neuroimmune marker. *Personality Neuroscience*, *3*, e14. https://doi.org/10.1017/pen.2020.14

Gin, K., Stewart, C., & Jolley, S. (2021a). A systematic literature review of childhood externalizing psychopathology and later psychotic symptoms. *Clinical Psychology & Psychotherapy*, *28*(1), 56–78. https://doi.org/10.1002/cpp.2493

Gin, K., Stewart, C., & Jolley, S. (2021b). A systematic literature review of childhood externalizing psychopathology and later psychotic symptoms. *Clinical Psychology & Psychotherapy*, *28*(1), 56–78. https://doi.org/10.1002/cpp.2493

Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. (2022a). *The Lancet Psychiatry*, *9*(2), 137–150. https://doi.org/10.1016/S2215-0366(21)00395-3

Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. (2022b). *The Lancet Psychiatry*, *9*(2), 137–150. https://doi.org/10.1016/S2215-0366(21)00395-3

Glutamate hypothesis in schizophrenia—Uno—2019—Psychiatry and Clinical Neurosciences—Wiley Online Library. (n.d.). Retrieved July 6, 2024, from https://onlinelibrary.wiley.com/doi/full/10.1111/pcn.12823

Gold, A. L., Steuber, E. R., White, L. K., Pacheco, J., Sachs, J. F., Pagliaccio, D., Berman, E., Leibenluft, E., & Pine, D. S. (2017). Cortical Thickness and Subcortical Gray Matter Volume in Pediatric Anxiety Disorders. *Neuropsychopharmacology*, *42*(12), 2423–2433. https://doi.org/10.1038/npp.2017.83

Goodman, A., Lamping, D. L., & Ploubidis, G. B. (2010). When to use broader internalising and externalising subscales instead of the hypothesised five subscales on the Strengths and Difficulties Questionnaire (SDQ): Data from British parents, teachers and children. *Journal of Abnormal Child Psychology*, *38*(8), 1179–1191. https://doi.org/10.1007/s10802-010-9434-x

Goodman, R., Meltzer, H., & Bailey, V. (1998). The strengths and difficulties questionnaire: A pilot study on the validity of the self-report version. *European Child & Adolescent Psychiatry*, *7*(3), 125–130. https://doi.org/10.1007/s007870050057

Grace, A. A. (2012). Dopamine System Dysregulation by the Hippocampus: Implications for the Pathophysiology and Treatment of Schizophrenia. *Neuropharmacology*, *62*(3), 1342–1348. https://doi.org/10.1016/j.neuropharm.2011.05.011

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

Greenland, S. (2000). Principles of multilevel modelling. *International Journal of Epidemiology*, *29*(1), 158–167. https://doi.org/10.1093/ije/29.1.158

Grent-'t-Jong, T., Gross, J., Goense, J., Wibral, M., Gajwani, R., Gumley, A. I., Lawrie, S. M., Schwannauer, M., Schultze-Lutter, F., Navarro Schröder, T., Koethe, D., Leweke, F. M., Singer, W., & Uhlhaas, P. J. (2018). Resting-state gamma-band power alterations in schizophrenia reveal E/I-balance abnormalities across illness-stages. *eLife*, *7*, e37799. https://doi.org/10.7554/eLife.37799

Griffith-Lendering, M. F. H., Huijbregts, S. C. J., Mooijaart, A., Vollebergh, W. A. M., & Swaab, H. (2011). Cannabis use and development of externalizing and internalizing behaviour problems in early adolescence: A TRAILS study. *Drug and Alcohol Dependence*, *116*(1), 11–17. https://doi.org/10.1016/j.drugalcdep.2010.11.024

Griffith-Lendering, M. F. H., Wigman, J. T. W., Prince van Leeuwen, A., Huijbregts, S. C. J., Huizink, A. C., Ormel, J., Verhulst, F. C., Os, J., Swaab, H., & Vollebergh, W. A. M. (2013). Cannabis use and vulnerability for psychosis in early adolescence-a TRAILS study. *Addiction*, *108*(4), 733–740. https://doi.org/10.1111/add.12050

Griffith-Lendering, M. F. H., Wigman, J. T. W., Prince van Leeuwen, A., Huijbregts, S. C. J., Huizink, A. C., Ormel, J., Verhulst, F. C., van Os, J., Swaab, H., & Vollebergh, W. A. M. (2013). Cannabis use and vulnerability for psychosis in early adolescence—A TRAILS study. *Addiction (Abingdon, England)*, *108*(4), 733–740. https://doi.org/10.1111/add.12050

Grimm, P. (2010). Social Desirability Bias. In *Wiley International Encyclopedia of Marketing*. John Wiley & Sons, Ltd. https://doi.org/10.1002/9781444316568.wiem02057

Grüter, T., Wieschollek, V., Dubovyk, V., Aliane, V., & Manahan-Vaughan, D. (2015). Altered neuronal excitability underlies impaired hippocampal function in an animal model of psychosis. *Frontiers in Behavioral Neuroscience*, *9*. https://doi.org/10.3389/fnbeh.2015.00117

Guindon, J., & Hohmann, A. G. (2008). Cannabinoid CB2 receptors: A therapeutic target for the treatment of inflammatory and neuropathic pain. *British Journal of Pharmacology*, *153*(2), 319–334. https://doi.org/10.1038/sj.bjp.0707531

Guxens, M., Nebot, M., & Ariza, C. (2007). Age and sex differences in factors associated with the onset of cannabis use: A cohort study. *Drug and Alcohol Dependence*, *88*(2), 234–243. https://doi.org/10.1016/j.drugalcdep.2006.10.018

Hagler, M. A., Ferrara, M., Yoviene Sykes, L. A., Li, F., Addington, J., Bearden, C. E., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Perkins, D. O., Mathalon, D. H., Seidman, L. J., Tsuang, M. T., Walker, E. F., Powers, A. R., Allen, A. R., Srihari, V. H., & Woods, S. W. (2023). Sampling from different populations: Sociodemographic, clinical, and functional differences between samples of first episode psychosis individuals and clinical high-risk individuals who progressed to psychosis. *Schizophrenia Research*, *255*, 239–245. https://doi.org/10.1016/j.schres.2023.03.047

Hájos, N., & Freund, T. F. (2002). Pharmacological separation of cannabinoid sensitive receptors on hippocampal excitatory and inhibitory fibers. *Neuropharmacology*, *43*(4), 503–510. https://doi.org/10.1016/S0028-3908(02)00157-0

Hanna, R. C., Shalvoy, A., Cullum, C. M., Ivleva, E. I., Keshavan, M., Pearlson, G., Hill, S. K., Sweeney, J. A., Tamminga, C. A., & Ghose, S. (2016). Cognitive Function in Individuals With Psychosis: Moderation by Adolescent Cannabis Use. *Schizophrenia Bulletin*, *42*(6), 1496–1503. https://doi.org/10.1093/schbul/sbw030

Hanssen, M., Bak, M., Bijl, R., Vollebergh, W., & van Os, J. (2005). The incidence and outcome of subclinical psychotic experiences in the general population. *The British Journal of Clinical Psychology*, *44*(Pt 2), 181–191. https://doi.org/10.1348/014466505X29611

Harris, P. A., Taylor, R., Minor, B. L., Elliott, V., Fernandez, M., O'Neal, L., McLeod, L., Delacqua, G., Delacqua, F., Kirby, J., & Duda, S. N. (2019). The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics*, *95*, 103208. https://doi.org/10.1016/j.jbi.2019.103208

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Hartley, J. E. K., Levin, K., & Currie, C. (2016). A new version of the HBSC Family Affluence Scale - FAS III: Scottish Qualitative Findings from the International FAS Development Study. *Child Indicators Research*, *9*, 233–245. https://doi.org/10.1007/s12187-015-9325-3

Hartmann, J. A., Nelson, B., Amminger, G. P., Spark, J., Yuen, H. P., Kerr, M. J., Polari, A., Wallis, N., Blasioli, J., Dixon, L., Carter, C., Loewy, R., Niendam, T. A., Shumway, M., & McGorry, P. D. (2022). Staged treatment in the ultra-high risk for psychosis clinical population: Baseline data of a sequential multiple assignment randomised trial (STEP Study). *Early Intervention in Psychiatry*, *16*(10), 1130–1142. https://doi.org/10.1111/eip.13263

HARVEY, P. D., & STRASSING, M. (2012). Predicting the severity of everyday functional disability in people with schizophrenia: Cognitive deficits, functional capacity, symptoms, and health status. *World Psychiatry*, *11*(2), 73–79.

Harvey, P. D., & Walker, E. F. (1990). Positive and negative symptoms in psychosis—Description, research, and future directions. *Behaviour Research and Therapy*, *28*(3), 256. https://doi.org/10.1016/0005-7967(90)90012-8

Hasin, D. S., Shmulewitz, D., & Sarvet, A. L. (2019). Time trends in US cannabis use and cannabis use disorders overall and by sociodemographic subgroups: A narrative review and new findings. *The American Journal of Drug and Alcohol Abuse*, *45*(6), 623–643. https://doi.org/10.1080/00952990.2019.1569668

Hastings, P. D., Serbin, L. A., Bukowski, W., Helm, J. L., Stack, D. M., Dickson, D. J., Ledingham, J. E., & Schwartzman, A. E. (2020). Predicting psychosis-spectrum diagnoses in adulthood from social behaviors and neighborhood contexts in childhood. *Development and Psychopathology*, *32*(2), 465–479. https://doi.org/10.1017/S095457941900021X

Hattingen, E., Raab, P., Franz, K., Zanella, F. E., Lanfermann, H., & Pilatus, U. (2008). Myo-Inositol: A marker of reactive astrogliosis in glial tumors? *NMR in Biomedicine*, *21*(3), 233–241. https://doi.org/10.1002/nbm.1186

Haug, S., Núñez, C. L., Becker, J., Gmel, G., & Schaub, M. P. (2014). Predictors of onset of cannabis and other drug use in male young adults: Results from a longitudinal study. *BMC Public Health*, *14*(1), 1202. https://doi.org/10.1186/1471-2458-14-1202

Hawes, S. W., Trucco, E. M., Duperrouzel, J. C., Coxe, S., & Gonzalez, R. (2019). Developmental pathways of adolescent cannabis use: Risk factors, outcomes and sex-specific differences. *Substance Use & Misuse*, *54*(2), 271–281. https://doi.org/10.1080/10826084.2018.1517177

Hayatbakhsh, R., Williams, G. M., Bor, W., & Najman, J. M. (2013). Early childhood predictors of age of initiation to use of cannabis: A birth prospective study. *Drug and Alcohol Review*, *32*(3), 232–240. https://doi.org/10.1111/j.1465-3362.2012.00520.x

Healy, C., Link to external site, this link will open in a new tab, 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

Heckers, S., Barch, D. M., Bustillo, J., Gaebel, W., Gur, R., Malaspina, D., Owen, M. J., Schultz, S., Tandon, R., Tsuang, M., Van Os, J., & Carpenter, W. (2016). Structure of the Psychotic Disorders Classification in DSM-5. *Focus*, *14*(3), 366–369. https://doi.org/10.1176/appi.focus.140307

Heinimaa, M., Salokangas, R. k. r., Ristkari, T., Plathin, M., Huttunen, J., Ilonen, T., Suomela, T., Korkeila, J., & Mcglashan, T. h. (2003). PROD-screen – a screen for prodromal symptoms of psychosis. *International Journal of Methods in Psychiatric Research*, *12*(2), 92–104. https://doi.org/10.1002/mpr.146

Heinimaa, M., Salokangas, R. K. R., Ristkari, T., Plathin, M., Huttunen, J., Ilonen, T., Suomela, T., Korkeila, J., & McGlashan, T. H. (2003). PROD-screen—A screen for prodromal symptoms of psychosis. *International Journal of Methods in Psychiatric Research*, *12*(2), 92–104. https://doi.org/10.1002/mpr.146

Henquet, C., Di Forti, M., Morrison, P., Kuepper, R., & Murray, R. M. (2008). Gene-Environment Interplay Between Cannabis and Psychosis. *Schizophrenia Bulletin*, *34*(6), 1111–1121. https://doi.org/10.1093/schbul/sbn108

Henquet, C., Rosa, A., Delespaul, P., Papiol, S., Fañanás, L., Van Os, J., & Myin-Germeys, I. (2009). COMT Val158Met moderation of cannabis-induced psychosis: A momentary assessment study of 'switching on' hallucinations in the flow of daily life. *Acta Psychiatrica Scandinavica*, *119*(2), 156–160. https://doi.org/10.1111/j.1600-0447.2008.01265.x

Henquet, C., Rosa, A., Krabbendam, L., Papiol, S., Faňanás, L., Drukker, M., Ramaekers, J. G., & van Os, J. (2006). An Experimental Study of Catechol-O-Methyltransferase Val158Met Moderation of Δ-9-Tetrahydrocannabinol-Induced Effects on Psychosis and Cognition. *Neuropsychopharmacology*, *31*(12), 2748–2757. https://doi.org/10.1038/sj.npp.1301197

Henshaw, F. R., Dewsbury, L. S., Lim, C. K., & Steiner, G. Z. (2021). The Effects of Cannabinoids on Pro- and Anti-Inflammatory Cytokines: A Systematic Review of In Vivo Studies. *Cannabis and Cannabinoid Research*, *6*(3), 177–195. https://doi.org/10.1089/can.2020.0105

Hermann, D., Sartorius, A., Welzel, H., Walter, S., Skopp, G., Ende, G., & Mann, K. (2007a). Dorsolateral Prefrontal Cortex N-Acetylaspartate/Total Creatine (NAA/tCr) Loss in Male Recreational Cannabis Users. *Biological Psychiatry*, *61*(11), 1281–1289. https://doi.org/10.1016/j.biopsych.2006.08.027

Hermann, D., Sartorius, A., Welzel, H., Walter, S., Skopp, G., Ende, G., & Mann, K. (2007b). Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users. *Biological Psychiatry*, *61*(11), 1281–1289. https://doi.org/10.1016/j.biopsych.2006.08.027

Hermann, D., Sartorius, A., Welzel, H., Walter, S., Skopp, G., Ende, G., & Mann, K. (2007c). Dorsolateral Prefrontal Cortex N-Acetylaspartate/Total Creatine (NAA/tCr) Loss in Male Recreational Cannabis Users. *Biological Psychiatry*, *61*(11), 1281–1289. https://doi.org/10.1016/j.biopsych.2006.08.027

Hides, L., Baker, A., Norberg, M., Copeland, J., Quinn, C., Walter, Z., Leung, J., Stoyanov, S. R., & Kavanagh, D. (2020). A Web-Based Program for Cannabis Use and Psychotic Experiences in Young People (Keep It Real): Protocol for a Randomized Controlled Trial. *JMIR Research Protocols*, *9*(7), e15803. https://doi.org/10.2196/15803

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), 130–135. https://doi.org/10.1016/j.schres.2009.04.001

Higgins, J., Morgan, R., Rooney, A., Taylor, K., Thayer, K., Silva, R., … Sterne, J. (2023). Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E). Launch version, 20 June 2023. Retrieved from https://www.riskofbias.info/welcome/robins-e-tool

Hines, L. A., Freeman, T. P., Gage, S. H., Zammit, S., Hickman, M., Cannon, M., Munafo, M., MacLeod, J., & Heron, J. (2020). Association of High-Potency Cannabis Use With Mental Health and Substance Use in Adolescence. *JAMA Psychiatry*, *77*(10), 1044–1051. https://doi.org/10.1001/jamapsychiatry.2020.1035

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

Hirjak, D., Schmitgen, M. M., Werler, F., Wittemann, M., Kubera, K. M., Wolf, N. D., Sambataro, F., Calhoun, V. D., Reith, W., & Wolf, R. C. (2022). Multimodal MRI data fusion reveals distinct structural, functional and neurochemical correlates of heavy cannabis use. *Addiction Biology*, *27*(2), e13113. https://doi.org/10.1111/adb.13113

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

Ho, B.-C., Wassink, T. H., Ziebell, S., & Andreasen, N. C. (2011). Cannabinoid receptor 1 gene polymorphisms and marijuana misuse interactions on white matter and cognitive deficits in schizophrenia. *Schizophrenia Research*, *128*(1), 66–75. https://doi.org/10.1016/j.schres.2011.02.021

Ho, N. F., Lee, B. J. H., Tng, J. X. J., Lam, M. Z. Y., Chen, G., Wang, M., Zhou, J., Keefe, R. S. E., & Sim, K. (2020). Corticolimbic brain anomalies are associated with cognitive subtypes in psychosis: A longitudinal study. *European Psychiatry*, *63*(1), e40. https://doi.org/10.1192/j.eurpsy.2020.36

Hodgins, S., Piatosa, M. J., & Schiffer, B. (2014). Violence among people with schizophrenia: Phenotypes and neurobiology. *Current Topics in Behavioral Neurosciences*, *17*, 329–368. https://doi.org/10.1007/7854_2013_259

Holcomb, H. H., Lahti, A. C., Medoff, D. R., Weiler, M., & Tamminga, C. A. (2001). Sequential regional cerebral blood flow brain scans using PET with H2(15)O demonstrate ketamine actions in CNS dynamically. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *25*(2), 165–172. https://doi.org/10.1016/S0893-133X(01)00229-9

Hong, H., Kim, B. S., & Im, H.-I. (2016). Pathophysiological Role of Neuroinflammation in Neurodegenerative Diseases and Psychiatric Disorders. *International Neurourology Journal*, *20*(Suppl 1), S2-7. https://doi.org/10.5213/inj.1632604.302

Hoogman, M., Bralten, J., Hibar, D. P., Mennes, M., Zwiers, M. P., Schweren, L. S. J., Hulzen, K. J. E. van, Medland, S. E., Shumskaya, E., Jahanshad, N., Zeeuw, P. de, Szekely, E., Sudre, G., Wolfers, T., Onnink, A. M. H., Dammers, J. T., Mostert, J. C., Vives-Gilabert, Y., Kohls, G., … Franke, B. (2017). Subcortical brain volume differences in participants with attention deficit hyperactivity disorder in children and adults: A cross-sectional mega-analysis. *The Lancet Psychiatry*, *4*(4), 310–319. https://doi.org/10.1016/S2215-0366(17)30049-4

Howes, O. D., Egerton, A., Allan, V., McGuire, P., Stokes, P., & Kapur, S. (2009). Mechanisms Underlying Psychosis and Antipsychotic Treatment Response in Schizophrenia: Insights from PET and SPECT Imaging. *Current Pharmaceutical Design*, *15*(22), 2550–2559.

Howes, O. D., & Kapur, S. (2009). The Dopamine Hypothesis of Schizophrenia: Version III—The Final Common Pathway. *Schizophrenia Bulletin*, *35*(3), 549–562. https://doi.org/10.1093/schbul/sbp006

Howes, O. D., & Shatalina, E. (2022). Integrating the Neurodevelopmental and Dopamine Hypotheses of Schizophrenia and the Role of Cortical Excitation-Inhibition Balance. *Biological Psychiatry*, *92*(6), 501–513. https://doi.org/10.1016/j.biopsych.2022.06.017

Hu, L., Zhou, B.-Y., Yang, C.-P., Lu, D.-Y., Tao, Y.-C., Chen, L., Zhang, L., Su, J.-H., Huang, Y., Song, N.-N., Chen, J.-Y., Zhao, L., Chen, Y., He, C.-H., Wang, Y.-B., Lang, B., & Ding, Y.-Q. (2022). Deletion of Schizophrenia Susceptibility Gene Ulk4 Leads to Abnormal Cognitive Behaviors via Akt-GSK-3 Signaling Pathway in Mice. *Schizophrenia Bulletin*, *48*(4), 804–813. https://doi.org/10.1093/schbul/sbac040

Hu, W., MacDonald, M. L., Elswick, D. E., & Sweet, R. A. (2015). The glutamate hypothesis of schizophrenia: Evidence from human brain tissue studies. *Annals of the New York Academy of Sciences*, *1338*(1), 38–57. https://doi.org/10.1111/nyas.12547

Hua, J. P. Y., Loewy, R. L., Stuart, B., Fryer, S. L., Niendam, T. A., Carter, C. S., Vinogradov, S., & Mathalon, D. H. (2023). Cortical and subcortical brain morphometry abnormalities in youth at clinical high-risk for psychosis and individuals with early illness schizophrenia. *Psychiatry Research: Neuroimaging*, *332*, 111653. https://doi.org/10.1016/j.pscychresns.2023.111653

Hui, S. C. N., Mikkelsen, M., Zöllner, H. J., Ahluwalia, V., Alcauter, S., Baltusis, L., Barany, D. A., Barlow, L. R., Becker, R., Berman, J. I., Berrington, A., Bhattacharyya, P. K., Blicher, J. U., Bogner, W., Brown, M. S., Calhoun, V. D., Castillo, R., Cecil, K. M., Choi, Y. B., … Edden, R. A. E. (2021). Frequency drift in MR spectroscopy at 3T. *NeuroImage*, *241*, 118430. https://doi.org/10.1016/j.neuroimage.2021.118430

Husarova, V., Bittsansky, M., Ondrejka, I., Kerna, V., & Dobrota, D. (2012). Hippocampal neurometabolite changes in depression treatment: A 1H magnetic resonance spectroscopy study. *Psychiatry Research: Neuroimaging*, *201*(3), 206–213. https://doi.org/10.1016/j.pscychresns.2011.07.006

Iwata, Y., Nakajima, S., Plitman, E., Caravaggio, F., Kim, J., Shah, P., Mar, W., Chavez, S., De Luca, V., Mimura, M., Remington, G., Gerretsen, P., & Graff-Guerrero, A. (2019). Glutamatergic Neurometabolite Levels in Patients With Ultra-Treatment-Resistant Schizophrenia: A Cross-Sectional 3T Proton Magnetic Resonance Spectroscopy Study. *Biological Psychiatry*, *85*(7), 596–605. https://doi.org/10.1016/j.biopsych.2018.09.009

Iwata, Y., Nakajima, S., Plitman, E., Mihashi, Y., Caravaggio, F., Chung, J. K., Kim, J., Gerretsen, P., Mimura, M., Remington, G., & Graff-Guerrero, A. (2018). Neurometabolite levels in antipsychotic-naïve/free patients with schizophrenia: A systematic review and meta-analysis of 1H-MRS studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *86*, 340–352. https://doi.org/10.1016/j.pnpbp.2018.03.016

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

Jakabek, D., Yücel, M., Lorenzetti, V., & Solowij, N. (2016). An MRI study of white matter tract integrity in regular cannabis users: Effects of cannabis use and age. *Psychopharmacology*, *233*(19), 3627–3637. https://doi.org/10.1007/s00213-016-4398-3

James, S., & Bondugji, D. (2021). *Gamma-Aminobutyric Acid (GABA) and the Endocannabinoids: Understanding the Risks and Opportunities*. https://doi.org/10.5772/intechopen.99242

Jappy, D., Valiullina, F., Draguhn, A., & Rozov, A. (2016). GABABR-Dependent Long-Term Depression at Hippocampal Synapses between CB1-Positive Interneurons and CA1 Pyramidal Cells. *Frontiers in Cellular Neuroscience*, *10*. https://doi.org/10.3389/fncel.2016.00004

Jauhar, S., Nour, M. M., Veronese, M., Rogdaki, M., Bonoldi, I., Azis, M., Turkheimer, F., McGuire, P., Young, A. H., & Howes, O. D. (2017). A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia. *JAMA Psychiatry*, *74*(12), 1206–1213. https://doi.org/10.1001/jamapsychiatry.2017.2943

Jayasundar, R., & Raghunathan, P. (1997). Evidence for left-right asymmetries in the proton MRS of brain in normal volunteers. *Magnetic Resonance Imaging*, *15*(2), 223–234. https://doi.org/10.1016/S0730-725X(96)00342-6

Jensen, J. E., Auerbach, R. P., Pisoni, A., & Pizzagalli, D. A. (2017). Localized MRS reliability of in vivo glutamate at 3 T in shortened scan times: A feasibility study. *NMR in Biomedicine*, *30*(11), e3771. https://doi.org/10.1002/nbm.3771

Jeon, P., Mackinley, M., Théberge, J., & Palaniyappan, L. (2021). The trajectory of putative astroglial dysfunction in first episode schizophrenia: A longitudinal 7-Tesla MRS study. *Scientific Reports*, *11*(1), 22333. https://doi.org/10.1038/s41598-021-01773-7

Jeong, J. H., Kim, S.-W., Lee, B. J., Kim, J. J., Yu, J.-C., Won, S.-H., Lee, S.-H., Kim, S.-H., Kang, S. H., Kim, E., Chung, Y.-C., & Lee, K. Y. (2022). The factor structure and clinical utility of clinician-rated dimensions of psychosis symptom severity in patients with recent-onset psychosis: Results of a 1-year longitudinal follow-up prospective cohort study. *Psychiatry Research*, *310*, 114420. https://doi.org/10.1016/j.psychres.2022.114420

Jessen, F., Fingerhut, N., Sprinkart, A. M., Kühn, K.-U., Petrovsky, N., Maier, W., Schild, H.-H., Block, W., Wagner, M., & Träber, F. (2013). N-acetylaspartylglutamate (NAAG) and N-acetylaspartate (NAA) in patients with schizophrenia. *Schizophrenia Bulletin*, *39*(1), 197–205. https://doi.org/10.1093/schbul/sbr127

Joe, P., Clemente, J. C., Piras, E., Wallach, D. S., Robinson-Papp, J., Boka, E., Remsen, B., Bonner, M., Kimhy, D., Goetz, D., Hoffman, K., Lee, J., Ruby, E., Fendrich, S., Gonen, O., & Malaspina, D. (2022). An integrative study of the microbiome gut-brain-axis and hippocampal inflammation in psychosis: Persistent effects from mode of birth. *Schizophrenia Research*, *247*, 101–115. https://doi.org/10.1016/j.schres.2021.09.019

Jones, C. M., & McCance-Katz, E. F. (2019). Relationship Between Recency and Frequency of Youth Cannabis Use on Other Substance Use. *Journal of Adolescent Health*, *64*(3), 411–413. https://doi.org/10.1016/j.jadohealth.2018.09.017

Jones, C., & McCance-Katz, E. (2018). Relationship Between Recency and Frequency of Youth Cannabis Use on Other Substance Use. *Journal of Adolescent Health*, *64*. https://doi.org/10.1016/j.jadohealth.2018.09.017

Jones, J. D., Calkins, M. E., Scott, J. C., Bach, E. C., & Gur, R. E. (2017). Cannabis Use, Polysubstance Use, and Psychosis Spectrum Symptoms in a Community-Based Sample of U.S. Youth. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine*, *60*(6), 653–659. https://doi.org/10.1016/j.jadohealth.2017.01.006

Jong, S. T., Stevenson, R., Winpenny, E. M., Corder, K., & van Sluijs, E. M. F. (2023). Recruitment and retention into longitudinal health research from an adolescent perspective: A qualitative study. *BMC Medical Research Methodology*, *23*(1), 16. https://doi.org/10.1186/s12874-022-01802-7

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

Kalman, J. L., Bresnahan, M., Schulze, T. G., & Susser, E. (2019). Predictors of persisting psychotic like experiences in children and adolescents: A scoping review. *Schizophrenia Research*, *209*, 32–39. https://doi.org/10.1016/j.schres.2019.05.012

Karcher, N. R., Barch, D. M., Avenevoli, S., Savill, M., Huber, R. S., Simon, T. J., Leckliter, I. N., Sher, K. J., & Loewy, R. L. (2018). Assessment of the Prodromal Questionnaire–Brief Child Version for Measurement of Self-reported Psychoticlike Experiences in Childhood. *JAMA Psychiatry*, *75*(8), 853–861. https://doi.org/10.1001/jamapsychiatry.2018.1334

Karcher, N. R., Loewy, R. L., Savill, M., Avenevoli, S., Huber, R. S., Makowski, C., Sher, K. J., & Barch, D. M. (2022a). Persistent and distressing psychotic-like experiences using adolescent brain cognitive development[SM] study data. *Molecular Psychiatry*, *27*(3), Article 3. https://doi.org/10.1038/s41380-021-01373-x

Karcher, N. R., Loewy, R. L., Savill, M., Avenevoli, S., Huber, R. S., Makowski, C., Sher, K. J., & Barch, D. M. (2022b). Persistent and distressing psychotic-like experiences using adolescent brain cognitive development[SM] study data. *Molecular Psychiatry*, *27*(3), 1490–1501. https://doi.org/10.1038/s41380-021-01373-x

Karcher, N. R., Modi, H., Kochunov, P., Gao, S., & Barch, D. M. (2023). Regional Vulnerability Indices in Youth With Persistent and Distressing Psychoticlike Experiences. *JAMA Network Open*, *6*(11), e2343081. https://doi.org/10.1001/jamanetworkopen.2023.43081

Karcher, N. R., O'Brien, K. J., Kandala, S., & Barch, D. M. (2019). Resting-State Functional Connectivity and Psychotic-like Experiences in Childhood: Results From the Adolescent Brain Cognitive Development Study. *Biological Psychiatry*, *86*(1), 7–15. https://doi.org/10.1016/j.biopsych.2019.01.013

Kaymaz, N., Drukker, M., Lieb, R., Wittchen, H.-U., Werbeloff, N., Weiser, M., Lataster, T., & van Os, J. (2012). Do subthreshold psychotic experiences predict clinical outcomes in unselected non-help-seeking population-based samples? A systematic review and meta-analysis, enriched with new results. *Psychological Medicine*, *42*(11), 2239–2253. https://doi.org/10.1017/S0033291711002911

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. (2012a). 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., Harley, M., Murtagh, A., & Cannon, M. (2011a). 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., 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. (2012b). Clinicopathological significance of psychotic experiences in non-psychotic young people: Evidence from four population-based studies. *The British Journal of Psychiatry*, *201*(1), 26–32. https://doi.org/10.1192/bjp.bp.111.101543

Kelleher, I., Keeley, H., Corcoran, P., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., & Cannon, M. (2013). Childhood trauma and psychosis in a prospective cohort study: Cause, effect, and directionality. *The American Journal of Psychiatry*, *170*(7), 734–741. https://doi.org/10.1176/appi.ajp.2012.12091169

Kelley, M. E., Wan, C. R., Broussard, B., Crisafio, A., Cristofaro, S., Johnson, S., Reed, T. A., Amar, P., Kaslow, N. J., Walker, E. F., & Compton, M. T. (2016). Marijuana use in the immediate 5-year premorbid period is associated with increased risk of onset of schizophrenia and related psychotic disorders. *Schizophrenia Research*, *171*(1), 62–67. https://doi.org/10.1016/j.schres.2016.01.015

Kelly, B. D., O'Callaghan, E., Waddington, J. L., Feeney, L., Browne, S., Scully, P. J., Clarke, M., Quinn, J. F., McTigue, O., Morgan, M. G., Kinsella, A., & Larkin, C. (2010). Schizophrenia and the city: A review of literature and prospective study of psychosis and urbanicity in Ireland. *Schizophrenia Research*, *116*(1), 75–89. https://doi.org/10.1016/j.schres.2009.10.015

Kenk, M., Selvanathan, T., Rao, N., Suridjan, I., Rusjan, P., Remington, G., Meyer, J. H., Wilson, A. A., Houle, S., & Mizrahi, R. (2015). Imaging Neuroinflammation in Gray and White Matter in Schizophrenia: An In-Vivo PET Study With [18 F]-FEPPA. *Schizophrenia Bulletin*, *41*(1), 85–93. https://doi.org/10.1093/schbul/sbu157

Keshavan, M., Giedd, J., Lau, J., Lewis, D., & Paus, T. (2014). Changes in the adolescent brain and the pathophysiology of psychotic disorders. *The Lancet Psychiatry*, *1*, 549–558. https://doi.org/10.1016/S2215-0366(14)00081-9

Keshavan, M. S., Giedd, J., Lau, J. Y. F., Lewis, D. A., & Paus, T. (2014a). Changes in the adolescent brain and the pathophysiology of psychotic disorders. *The Lancet Psychiatry*, *1*(7), 549–558. https://doi.org/10.1016/S2215-0366(14)00081-9

Keshavan, M. S., Giedd, J., Lau, J. Y. F., Lewis, D. A., & Paus, T. (2014b). Changes in the adolescent brain and the pathophysiology of psychotic disorders. *The Lancet Psychiatry*, *1*(7), 549–558. https://doi.org/10.1016/S2215-0366(14)00081-9

Kessler, R. C., Birnbaum, H., Demler, O., Falloon, I. R. H., Gagnon, E., Guyer, M., Howes, M. J., Kendler, K. S., Shi, L., Walters, E., & Wu, E. Q. (2005). The Prevalence and Correlates of Nonaffective Psychosis in the National Comorbidity Survey Replication (NCS-R). *Biological Psychiatry*, *58*(8), 668–676. https://doi.org/10.1016/j.biopsych.2005.04.034

Ketcherside, A., Noble, L. J., McIntyre, C. K., & Filbey, F. M. (2017). Cannabinoid Receptor 1 Gene by Cannabis Use Interaction on CB1 Receptor Density. *Cannabis and Cannabinoid Research*, *2*(1), 202–209. https://doi.org/10.1089/can.2017.0007

Kiburi, S., Molebatsi, K., Ntlantsana, V., & Lynskey, M. (2021). Cannabis use in Adolescence and Risk of Psychosis: Are there Factors that Moderate this Relationship? A Systematic Review and Meta-Analysis. *Substance Abuse*, *42*, 1–25. https://doi.org/10.1080/08897077.2021.1876200

Kirschner, M., Hodzic-Santor, B., Antoniades, M., Nenadic, I., Kircher, T., Krug, A., Meller, T., Grotegerd, D., Fornito, A., Arnatkeviciute, A., Bellgrove, M. A., Tiego, J., Dannlowski, U., Koch, K., Hülsmann, C., Kugel, H., Enneking, V., Klug, M., Leehr, E. J., … Modinos, G. (2022). Cortical and subcortical neuroanatomical signatures of schizotypy in 3004 individuals assessed in a worldwide ENIGMA study. *Molecular Psychiatry*, *27*(2), 1167–1176. https://doi.org/10.1038/s41380-021-01359-9

Kline, E. R., Ferrara, M., Li, F., Cyril D'Souza, D., Keshavan, M., & Srihari, V. H. (2022). Timing of Cannabis Exposure Relative to Prodrome and Psychosis Onset in a Community-Based First Episode Psychosis Sample. *Journal of Psychiatric Research*, *147*, 248–253. https://doi.org/10.1016/j.jpsychires.2022.01.039

Knolle, F. (n.d.-a). *The impact of spectral basis set composition on estimated levels of cingulate glutamate and its associations with different personality traits*.

Knolle, F. (n.d.-b). *The impact of spectral basis set composition on estimated levels of cingulate glutamate and its associations with different personality traits*.

Kochunov, P., Hong, L. E., Dennis, E. L., Morey, R. A., Tate, D. F., Wilde, E. A., Logue, M., Kelly, S., Donohoe, G., Favre, P., Houenou, J., Ching, C. R. K., Holleran, L., Andreassen, O. A., van Velzen, L. S., Schmaal, L., Villalón-Reina, J. E., Bearden, C. E., Piras, F., … Jahanshad, N. (2022). ENIGMA-DTI: Translating reproducible white matter deficits into personalized vulnerability metrics in cross-diagnostic psychiatric research. *Human Brain Mapping*, *43*(1), 194–206. https://doi.org/10.1002/hbm.24998

Koenders, L., Cousijn, J., Vingerhoets, W. A. M., Brink, W. van den, Wiers, R. W., Meijer, C. J., Machielsen, M. W. J., Veltman, D. J., Goudriaan, A. E., & Haan, L. de. (2016a). Grey Matter Changes Associated with Heavy Cannabis Use: A Longitudinal sMRI Study. *PLOS ONE*, *11*(5), e0152482. https://doi.org/10.1371/journal.pone.0152482

Koenders, L., Cousijn, J., Vingerhoets, W. A. M., Brink, W. van den, Wiers, R. W., Meijer, C. J., Machielsen, M. W. J., Veltman, D. J., Goudriaan, A. E., & Haan, L. de. (2016b). Grey Matter Changes Associated with Heavy Cannabis Use: A Longitudinal sMRI Study. *PLOS ONE*, *11*(5), e0152482. https://doi.org/10.1371/journal.pone.0152482

Komarc, M., Harbichova, I., & Tichy, J. (2014). Psychometric properties of the Edinburgh Handedness Inventory in children. *Ceskoslovenská Psychologie*, *58*, 512–523.

Komoroski, R. A., Heimberg, C., Cardwell, D., & Karson, C. N. (1999). Effects of gender and region on proton MRS of normal human brain. *Magnetic Resonance Imaging*, *17*(3), 427–433. https://doi.org/10.1016/s0730-725x(98)00186-6

Konings, M., Henquet, C., Maharajh, H. D., Hutchinson, G., & Van Os, J. (2008). Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad. *Acta Psychiatrica Scandinavica*, *118*(3), 209–213. https://doi.org/10.1111/j.1600-0447.2008.01202.x

Konings, M., Stefanis, N., Kuepper, R., Graaf, R. de, Have, M. ten, Os, J. van, Bakoula, C., & Henquet, C. (2012). Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk. *Psychological Medicine*, *42*(1), 149–159. https://doi.org/10.1017/S0033291711000973

Korver, N., Quee, P. J., Boos, H. B. M., Simons, C. J. P., & Haan, L. (2012). Genetic Risk and Outcome of Psychosis (GROUP), a multi site longitudinal cohort study focused on gene-environment interaction: Objectives, sample characteristics, recruitment and assessment methods. *International Journal of Methods in Psychiatric Research*, *21*(3), 205–221. https://doi.org/10.1002/mpr.1352

Kosty, D. B., Seeley, J. R., Farmer, R. F., Stevens, J. J., & Lewinsohn, P. M. (2017). Trajectories of cannabis use disorder: Risk factors, clinical characteristics and outcomes. *Addiction*, *112*(2), 279–287. https://doi.org/10.1111/add.13557

Kotaria, N., Kiladze, M., Zhvania, M. G., Japaridze, N. J., Bikashvili, T., Solomonia, R. O., & Bolkvadze, T. (2013). The Protective Effect of Myo-inositol on Hippocamal Cell Loss and Structural Alterations in Neurons and Synapses Triggered by Kainic Acid-Induced Status Epilepticus. *Cellular and Molecular Neurobiology*, *33*(5), 659–671. https://doi.org/10.1007/s10571-013-9930-y

Kraan, T., Velthorst, E., Koenders, L., Zwaart, K., Ising, H. K., Van Den Berg, D., De Haan, L., & Van Der Gaag, M. (2016). Cannabis use and transition to psychosis in individuals at ultra-high risk: Review and meta-analysis. *Psychological Medicine*, *46*(4), 673–681. https://doi.org/10.1017/S0033291715002329

Krabbendam, L., & van Os, J. (2005). Schizophrenia and Urbanicity: A Major Environmental Influence—Conditional on Genetic Risk. *Schizophrenia Bulletin*, *31*(4), 795–799. https://doi.org/10.1093/schbul/sbi060

Kreis, R., Boer, V., Choi, I.-Y., Cudalbu, C., de Graaf, R. A., Gasparovic, C., Heerschap, A., Kršňák, M., Lanz, B., Maudsley, A. A., Meyerspeer, M., Near, J., Öz, G., Posse, S., Slotboom, J., Terpstra, M., Tkáč, I., Wilson, M., & Bogner, W. (2021). Terminology and concepts for the characterization of in vivo MR spectroscopy methods and MR spectra: Background and experts' consensus recommendations. *NMR in Biomedicine*, *34*(5), e4347. https://doi.org/10.1002/nbm.4347

Krystal, J. H., Karper, L. P., Seibyl, J. P., Freeman, G. K., Delaney, R., Bremner, J. D., Heninger, G. R., Bowers, M. B., & Charney, D. S. (1994). Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Archives of General Psychiatry*, *51*(3), 199–214. https://doi.org/10.1001/archpsyc.1994.03950030035004

Ksir, C., & Hart, C. L. (2016). Cannabis and Psychosis: A Critical Overview of the Relationship. *Current Psychiatry Reports*, *18*(2). https://doi.org/10.1007/s11920-015-0657-y

Kuepper, R., van Os, J., Lieb, R., Wittchen, H.-U., & Henquet, C. (2011). Do cannabis and urbanicity co-participate in causing psychosis? Evidence from a 10-year follow-up cohort study. *Psychological Medicine*, *41*(10), 2121–2129. https://doi.org/10.1017/S0033291711000511

Kukull, W. A., & Ganguli, M. (2012). Generalizability. *Neurology*, *78*(23), 1886–1891. https://doi.org/10.1212/WNL.0b013e318258f812

Kummer, K. K., Zeidler, M., Kalpachidou, T., & Kress, M. (2021). Role of IL-6 in the regulation of neuronal development, survival and function. *Cytokine*, *144*, 155582. https://doi.org/10.1016/j.cyto.2021.155582

Lacasa, F., Mitjavila, M., Ochoa, S., & Balluerka, N. (2015). The relationship between attachment styles and internalizing or externalizing symptoms in clinical and nonclinical adolescents. *Anales de Psicología*, *31*, 422. https://doi.org/10.6018/analesps.31.2.169711

Lahti, A. C., Holcomb, H. H., Medoff, D. R., & Tamminga, C. A. (1995). Ketamine activates psychosis and alters limbic blood flow in schizophrenia. *Neuroreport*, *6*(6), 869–872. https://doi.org/10.1097/00001756-199504190-00011

Lancefield, K. S., Raudino, A., Downs, J. M., & Laurens, K. R. (2016). Trajectories of childhood internalizing and externalizing psychopathology and psychotic-like experiences in adolescence: A prospective population-based cohort study. *Development and Psychopathology*, *28*(2), 527–536. https://doi.org/10.1017/S0954579415001108

Landucci, E., Mazzantini, C., Lana, D., Giovannini, M. G., & Pellegrini-Giampietro, D. E. (2022). Neuronal and Astrocytic Morphological Alterations Driven by Prolonged Exposure with Δ9-Tetrahydrocannabinol but Not Cannabidiol. *Toxics*, *10*(2), 48. https://doi.org/10.3390/toxics10020048

Lansing, A., Plante, W. Y., Fennema-Notestine, C., Golshan, S., & Beck, A. N. (2018). Psychotic-spectrum symptoms, cumulative adversity exposure and substance use among high-risk girls. *Early Intervention in Psychiatry*, *12*(1), 74–86. https://doi.org/10.1111/eip.12533

Larøi, F., Luhrmann, T. M., Bell, V., Christian, W. A., Deshpande, S., Fernyhough, C., Jenkins, J., & Woods, A. (2014a). Culture and Hallucinations: Overview and Future Directions. *Schizophrenia Bulletin*, *40*(Suppl 4), S213–S220. https://doi.org/10.1093/schbul/sbu012

Larøi, F., Luhrmann, T. M., Bell, V., Christian, W. A., Deshpande, S., Fernyhough, C., Jenkins, J., & Woods, A. (2014b). Culture and Hallucinations: Overview and Future Directions. *Schizophrenia Bulletin*, *40*(Suppl 4), S213–S220. https://doi.org/10.1093/schbul/sbu012

Laruelle, M., Kegeles, L. S., & Abi-Dargham, A. (2003). Glutamate, Dopamine, and Schizophrenia. *Annals of the New York Academy of Sciences*, *1003*(1), 138–158. https://doi.org/10.1196/annals.1300.063

Latkin, C. A., Edwards, C., Davey-Rothwell, M. A., & Tobin, K. E. (2017). The relationship between social desirability bias and self-reports of health, substance use, and social network factors among urban substance users in Baltimore, Maryland. *Addictive Behaviors*, *73*, 133–136. https://doi.org/10.1016/j.addbeh.2017.05.005

Lau, C.-I., Wang, H.-C., Hsu, J.-L., & Liu, M.-E. (2013a). Does the dopamine hypothesis explain schizophrenia? *Reviews in the Neurosciences*, *24*(4), 389–400. https://doi.org/10.1515/revneuro-2013-0011

Lau, C.-I., Wang, H.-C., Hsu, J.-L., & Liu, M.-E. (2013b). Does the dopamine hypothesis explain schizophrenia? *Reviews in the Neurosciences*, *24*(4), 389–400. https://doi.org/10.1515/revneuro-2013-0011

Laurens, K. R., Hobbs, M. J., Sunderland, M., Green, M. J., & Mould, G. L. (2012). Psychotic-like experiences in a community sample of 8000 children aged 9 to 11 years: An item response theory analysis. *Psychological Medicine*, *42*(7), 1495–1506. https://doi.org/10.1017/S0033291711002108

Laurens, K. R., Tzoumakis, S., Dean, K., Harris, F., Carr, V. J., & Green, M. J. (2020). Population profiles of child-reported psychotic-like experiences and their differential association with other psychopathologies. *British Journal of Clinical Psychology*, *59*(1), 22–38. https://doi.org/10.1111/bjc.12230

Leal-López, E., Sánchez-Queija, I., Rivera, F., & Moreno, C. (2020a). Trends in Cannabis Use among Adolescents in Spain 2006–2018. *Journal of Child & Adolescent Substance Abuse*, *29*(4–6), 221–231. https://doi.org/10.1080/1067828X.2021.1988021

Leal-López, E., Sánchez-Queija, I., Rivera, F., & Moreno, C. (2020b). Trends in Cannabis Use among Adolescents in Spain 2006–2018. *Journal of Child & Adolescent Substance Abuse*, *29*(4–6), 221–231. https://doi.org/10.1080/1067828X.2021.1988021

Leal-López, E., Sánchez-Queija, I., Rivera, F., & Moreno, C. (2020c). Trends in Cannabis Use among Adolescents in Spain 2006–2018. *Journal of Child & Adolescent Substance Abuse*, *29*(4–6), 221–231. https://doi.org/10.1080/1067828X.2021.1988021

Leaune, E., Dealberto, M.-J., Luck, D., Grot, S., Zeroug-Vial, H., Poulet, E., & Brunelin, J. (2019a). Ethnic minority position and migrant status as risk factors for psychotic symptoms in the general population: A meta-analysis. *Psychological Medicine*, *49*(4), 545–558. https://doi.org/10.1017/S0033291718002271

Leaune, E., Dealberto, M.-J., Luck, D., Grot, S., Zeroug-Vial, H., Poulet, E., & Brunelin, J. (2019b). Ethnic minority position and migrant status as risk factors for psychotic symptoms in the general population: A meta-analysis. *Psychological Medicine*, *49*(4), 545–558. https://doi.org/10.1017/S0033291718002271

LeBourgeois, M., & Harsh, J. (2001). A New Research Measure for Children's Sleep. *Sleep*, *24*, A213–A214.

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

Leger, D., Beck, F., Richard, J.-B., & Godeau, E. (2012). Total Sleep Time Severely Drops during Adolescence. *PLOS ONE*, *7*(10), e45204. https://doi.org/10.1371/journal.pone.0045204

Leighton, K., Kardong-Edgren, S., Schneidereith, T., & Foisy-Doll, C. (2021). Using Social Media and Snowball Sampling as an Alternative Recruitment Strategy for Research. *Clinical Simulation in Nursing*, *55*, 37–42. https://doi.org/10.1016/j.ecns.2021.03.006

Lemos, S., Vallina Fernandez, O., Fernández, P., Ortega, J., García, P., Gutiérrez, A., Bobes, J., Garcia Espinosa, A., & Miller, T. (2006). Predictive validity of the Scale of Prodromal Symptoms (SOPS). *Actas Españolas de Psiquiatría*, *34*, 216–223.

Lemos-Giráldez, S., Vallina-Fernández, O., Fernández-Iglesias, P., Vallejo-Seco, G., Fonseca-Pedrero, E., Paíno-Piñeiro, M., Sierra-Baigrie, S., García-Pelayo, P., Pedrejón-Molino, C., Alonso-Bada, S., Gutiérrez-Pérez, A., & Ortega-Ferrández, J. A. (2009). Symptomatic and functional outcome in youth at ultra-high risk for psychosis: A longitudinal study. *Schizophrenia Research*, *115*(2–3), 121–129. https://doi.org/10.1016/j.schres.2009.09.011

Leonard, B. E., & Aricioglu, F. (2023). Cannabinoids and neuroinflammation: Therapeutic implications. *Journal of Affective Disorders Reports*, *12*, 100463. https://doi.org/10.1016/j.jadr.2023.100463

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

Levi, L., Bar-Haim, M., Winter-van Rossum, I., Davidson, M., Leucht, S., Fleischhacker, W. W., Park, J., Davis, J. M., Kahn, R. S., & Weiser, M. (2023). Cannabis Use and Symptomatic Relapse in First Episode Schizophrenia: Trigger or Consequence? Data From the OPTIMISE Study. *Schizophrenia Bulletin*, *49*(4), 903–913. https://doi.org/10.1093/schbul/sbad033

Li, B. S., Regal, J., & Gonen, O. (2001). SNR versus resolution in 3D 1H MRS of the human brain at high magnetic fields. *Magnetic Resonance in Medicine*, *46*(6), 1049–1053. https://doi.org/10.1002/mrm.1297

Liberg, B., Rahm, C., Panayiotou, A., & Pantelis, C. (2016). Brain change trajectories that differentiate the major psychoses. *European Journal of Clinical Investigation*, *46*(7), 658–674. https://doi.org/10.1111/eci.12641

Lieberman, J. A., & First, M. B. (2018). Psychotic Disorders. *New England Journal of Medicine*, *379*(3), 270–280. https://doi.org/10.1056/NEJMra1801490

Lieberman, J. A., Girgis, R. R., Brucato, G., Moore, H., Provenzano, F., Kegeles, L., Javitt, D., Kantrowitz, J., Wall, M. M., Corcoran, C. M., Schobel, S. A., & Small, S. A. (2018). Hippocampal dysfunction in the pathophysiology of schizophrenia: A selective review and hypothesis for early detection and intervention. *Molecular Psychiatry*, *23*(8), 1764–1772. https://doi.org/10.1038/mp.2017.249

Lieberman, J. A., Perkins, D., Belger, A., Chakos, M., Jarskog, F., Boteva, K., & Gilmore, J. (2001). The early stages of schizophrenia: Speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biological Psychiatry*, *50*(11), 884–897. https://doi.org/10.1016/S0006-3223(01)01303-8

Liemburg, E. J., Nolte, I. M., Klein, H. C., & Knegtering, H. (2018). Relation of inflammatory markers with symptoms of psychotic disorders: A large cohort study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *86*, 89–94. https://doi.org/10.1016/j.pnpbp.2018.04.006

Lima, M. G., Tardelli, V. S., Brietzke, E., & Fidalgo, T. M. (2020). Cannabis and Inflammatory Mediators. *European Addiction Research*, *27*(1), 16–24. https://doi.org/10.1159/000508840

Lin, A., Andronesi, O., Bogner, W., Choi, I., Coello, E., Cudalbu, C., Juchem, C., Kemp, G. J., Kreis, R., Krššák, M., Lee, P., Maudsley, A. A., Meyerspeer, M., Mlynarik, V., Near, J., Öz, G., Peek, A. L., Puts, N. A., Ratai, E., … Mullins, P. G. (2021). Minimum Reporting Standards for in vivo Magnetic Resonance Spectroscopy (MRSinMRS): Experts' consensus recommendations. *Nmr in Biomedicine*, *34*(5), e4484. https://doi.org/10.1002/nbm.4484

Lin, A., Kenis, G., Bignotti, S., Tura, G.-J.-B., De Jong, R., Bosmans, E., Pioli, R., Altamura, C., Scharpé, S., & Maes, M. (1998). The inflammatory response system in treatment-resistant schizophrenia: Increased serum interleukin-6. *Schizophrenia Research*, *32*(1), 9–15. https://doi.org/10.1016/S0920-9964(98)00034-6

Linscott, R. J., & Os, J. van. (2010). Systematic Reviews of Categorical Versus Continuum Models in Psychosis: Evidence for Discontinuous Subpopulations Underlying a Psychometric Continuum. Implications for DSM-V, DSM-VI, and DSM-VII. *Annual Review of Clinical Psychology*, *6*(Volume 6, 2010), 391–419. https://doi.org/10.1146/annurev.clinpsy.032408.153506

Linscott, R. J., & Os, J. van. (2013a). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: On the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, *43*(6), 1133–1149. https://doi.org/10.1017/S0033291712001626

Linscott, R. J., & Os, J. van. (2013b). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: On the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, *43*(6), 1133–1149. https://doi.org/10.1017/S0033291712001626

Linscott, R. J., & van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: On the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, *43*(6), 1133–1149. https://doi.org/10.1017/S0033291712001626

Linszen, M. M. J., de Boer, J. N., Schutte, M. J. L., Begemann, M. J. H., de Vries, J., Koops, S., Blom, R. E., Bohlken, M. M., Heringa, S. M., Blom, J. D., & Sommer, I. E. C. (2022). Occurrence and phenomenology of hallucinations in the general population: A large online survey. *Schizophrenia*, *8*(1), 41. https://doi.org/10.1038/s41537-022-00229-9

Lisano, J. K., Kisiolek, J. N., Smoak, P., Phillips, K. T., & Stewart, L. K. (2020). Chronic cannabis use and circulating biomarkers of neural health, stress, and inflammation in physically active individuals. *Applied Physiology, Nutrition, and Metabolism*, *45*(3), 258–263. https://doi.org/10.1139/apnm-2019-0300

Lizano, P., Dhaliwal, K., Lutz, O., Mothi, S. S., Miewald, J., Montrose, D., & Keshavan, M. (2020). Trajectory of neurological examination abnormalities in antipsychotic-naïve first-episode psychosis population: A 1 year follow-up study. *Psychological Medicine*, *50*(12), 2057–2065. https://doi.org/10.1017/S0033291719002162

Loch, A. A., Chianca, C., Alves, T. M., Freitas, E. L., Hortêncio, L., Andrade, J. C., van de Bilt, M. T., Fontoni, M. R., Serpa, M. H., Gattaz, W. F., & Rössler, W. (2017). Poverty, low education, and the expression of psychotic-like experiences in the general population of São Paulo, Brazil. *Psychiatry Research*, *253*, 182–188. https://doi.org/10.1016/j.psychres.2017.03.052

Lopez-Larson, M. P., Bogorodzki, P., Rogowska, J., McGlade, E., King, J. B., Terry, J., & Yurgelun-Todd, D. (2011). Altered prefrontal and insular cortical thickness in adolescent marijuana users. *Behavioural Brain Research*, *220*(1), 164–172. https://doi.org/10.1016/j.bbr.2011.02.001

Lorenzetti, V., Alonso-Lana, S., Youssef, G., Verdejo-Garcia, A., Suo, C., Cousijn, J., Takagi, M., Yücel, M., & Solowij, N. (2017). Adolescent Cannabis Use: What is the Evidence for Functional Brain Alteration? *Current Pharmaceutical Design*, *22*(42), 6353–6365. https://doi.org/10.2174/1381612822666160805155922

Lorenzetti, V., Hoch, E., & Hall, W. (2020). Adolescent cannabis use, cognition, brain health and educational outcomes: A review of the evidence. *European Neuropsychopharmacology*, *36*, 169–180. https://doi.org/10.1016/j.euroneuro.2020.03.012

Lowe, D. J. E., Sasiadek, J. D., Coles, A. S., & George, T. P. (2019). Cannabis and mental illness: A review. *European Archives of Psychiatry and Clinical Neuroscience*, *269*(1), 107–120. https://doi.org/10.1007/s00406-018-0970-7

Luzi, S., Morrison, P. D., Powell, J., Di Forti, M., & Murray, R. M. (2008). What is the mechanism whereby cannabis use increases risk of psychosis? *Neurotoxicity Research*, *14*(2), 105–112. https://doi.org/10.1007/BF03033802

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., O'Leary-Barrett, M., Al-Khudhairy, N., Castellanos-Ryan, N., Struve, M., Topper, L., & Conrod, P. (2013). Adolescent bullying, cannabis use and emerging psychotic experiences: A longitudinal general population study. *Psychological Medicine*, *43*(5), 1033–1044. https://doi.org/10.1017/S003329171200205X

Mackie, C. J., Wilson, J., Freeman, T. P., Craft, S., Escamilla De La Torre, T., & Lynskey, M. T. (2021). A latent class analysis of cannabis use products in a general population sample of adolescents and their association with paranoia, hallucinations, cognitive disorganisation and grandiosity. *Addictive Behaviors*, *117*, 106837. https://doi.org/10.1016/j.addbeh.2021.106837

Mackie, K. (2006). Mechanisms of CB1 receptor signaling: Endocannabinoid modulation of synaptic strength. *International Journal of Obesity*, *30*(1), S19–S23. https://doi.org/10.1038/sj.ijo.0803273

Magnetic resonance spectroscopy: Neurochemistry and treatment effects in affective disorders—PubMed. (n.d.). Retrieved July 1, 2024, from https://pubmed.ncbi.nlm.nih.gov/12397837/

Maijer, K., Begemann, M. J. H., Palmen, S. J. M. C., Leucht, S., & Sommer, I. E. C. (2018). Auditory hallucinations across the lifespan: A systematic review and meta-analysis. *Psychological Medicine*, *48*(6), 879–888. https://doi.org/10.1017/S0033291717002367

Malhi, G. S., Valenzuela, M., Wen, W., & Sachdev, P. (2002). Magnetic Resonance Spectroscopy and its Applications in Psychiatry. *Australian & New Zealand Journal of Psychiatry*, *36*(1), 31–43. https://doi.org/10.1046/j.1440-1614.2002.00992.x

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

Malone, D. T., Hill, M. N., & Rubino, T. (2010). Adolescent cannabis use and psychosis: Epidemiology and neurodevelopmental models. *British Journal of Pharmacology*, *160*(3), 511–522. https://doi.org/10.1111/j.1476-5381.2010.00721.x

Mamah, D., Mutiso, V. N., & Ndetei, D. M. (2021). Psychotic-like experiences among 9,564 Kenyan adolescents and young adults. *Psychiatry Research*, *302*, 113994. https://doi.org/10.1016/j.psychres.2021.113994

Mam-lam-Fook, C., Danset-Alexandre, C., Pedron, L., Amado, I., Gaillard, R., & Krebs, M.-O. (2017). Neuropsychology of subjects with ultra-high risk (UHR) of psychosis: A critical analysis of the literature. *L'Encéphale*, *43*(3), 241–253. https://doi.org/10.1016/j.encep.2017.02.001

Maniglio, R. (2015). Association between peer victimization in adolescence and cannabis use: A systematic review. *Aggression and Violent Behavior*, *25*, 252–258. https://doi.org/10.1016/j.avb.2015.09.002

Manterola, A., Chara, J. C., Aguado, T., Palazuelos, J., Matute, C., & Mato, S. (2022). Cannabinoid CB1 receptor expression in oligodendrocyte progenitors of the hippocampus revealed by the NG2-EYFP-knockin mouse. *Frontiers in Neuroanatomy*, *16*, 1030060. https://doi.org/10.3389/fnana.2022.1030060

Mapping the onset of psychosis: The Comprehensive Assessment of At-Risk Mental States—PubMed. (n.d.). Retrieved June 25, 2024, from https://pubmed.ncbi.nlm.nih.gov/16343296/

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016a). Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophrenia Bulletin*, *42*(5), 1262–1269. https://doi.org/10.1093/schbul/sbw003

Marconi, A., Di Forti, M., Lewis, C. M., Murray, R. M., & Vassos, E. (2016b). Meta-analysis of the Association Between the Level of Cannabis Use and Risk of Psychosis. *Schizophrenia Bulletin*, *42*(5), 1262–1269. https://doi.org/10.1093/schbul/sbw003

Marenco, S., Bertolino, A., & Weinberger, D. R. (2006). In Vivo NMR Measures of NAA and the Neurobiology of Schizophrenia. In J. R. Moffett, S. B. Tieman, D. R. Weinberger, J. T. Coyle, & A. M. A. Namboodiri (Eds.), *N-Acetylaspartate* (Vol. 576, pp. 227–240). Springer US. https://doi.org/10.1007/0-387-30172-0_16

Marsman, A., van den Heuvel, M. P., Klomp, D. W. J., Kahn, R. S., Luijten, P. R., & Hulshoff Pol, H. E. (2013a). Glutamate in Schizophrenia: A Focused Review and Meta-Analysis of 1H-MRS Studies. *Schizophrenia Bulletin*, *39*(1), 120–129. https://doi.org/10.1093/schbul/sbr069

Marsman, A., van den Heuvel, M. P., Klomp, D. W. J., Kahn, R. S., Luijten, P. R., & Hulshoff Pol, H. E. (2013b). Glutamate in schizophrenia: A focused review and meta-analysis of ^{1}H-MRS studies. *Schizophrenia Bulletin*, *39*(1), 120–129. https://doi.org/10.1093/schbul/sbr069

Martínez-Granados, B., Brotons, O., Martínez-Bisbal, M. C., Celda, B., Martí-Bonmati, L., Aguilar, E. J., González, J. C., & Sanjuán, J. (2008). Spectroscopic metabolomic abnormalities in the thalamus related to auditory hallucinations in patients with schizophrenia. *Schizophrenia Research*, *104*(1), 13–22. https://doi.org/10.1016/j.schres.2008.05.025

Martin-Santos, R., A. Crippa, J., Batalla, A., Bhattacharyya, S., Atakan, Z., Borgwardt, S., Allen, P., Seal, M., Langohr, K., Farre, M., Zuardi, AW., & K. McGuire, P. (2012). Acute Effects of a Single, Oral dose of d9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) Administration in Healthy Volunteers. *Current Pharmaceutical Design*, *18*(32), 4966–4979. https://doi.org/10.2174/138161212802884780

Mashhoon, Y., Jensen, J. E., Sneider, J. T., Yurgelun-Todd, D. A., & Silveri, M. M. (2013). Lower Left Thalamic Myo-Inositol Levels Associated with Greater Cognitive Impulsivity in Marijuana-Dependent Young Men: Preliminary Spectroscopic Evidence at 4T. *Journal of Addiction Research & Therapy*, *Suppl 4*, 009. https://doi.org/10.4172/2155-6105.S4-009

Matéos, M., Hacein-Bey, L., Hanafi, R., Mathys, L., Amad, A., Pruvo, J.-P., & Krystal, S. (2023). Advanced imaging in first episode psychosis: A systematic review. *Journal of Neuroradiology*, *50*(5), 464–469. https://doi.org/10.1016/j.neurad.2023.04.001

Matheson, S. L., Laurie, M., & Laurens, K. R. (2023). Substance use and psychotic-like experiences in young people: A systematic review and meta-analysis. *Psychological Medicine*, *53*(2), 305–319. https://doi.org/10.1017/S0033291722003440

Mayo, D., Corey, S., Kelly, L. H., Yohannes, S., Youngquist, A. L., Stuart, B. K., Niendam, T. A., & Loewy, R. L. (2017). The Role of Trauma and Stressful Life Events among Individuals at Clinical High Risk for Psychosis: A Review. *Frontiers in Psychiatry*, *8*. https://doi.org/10.3389/fpsyt.2017.00055

McDonald, C. (n.d.). *Identifying Cannabis Use Motives and their Association with Problematic Cannabis Use*.

McGorry, P. D., Hartmann, J. A., Spooner, R., & Nelson, B. (2018). Beyond the "at risk mental state" concept: Transitioning to transdiagnostic psychiatry. *World Psychiatry*, *17*(2), 133–142. https://doi.org/10.1002/wps.20514

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., Saha, S., Welham, J., El Saadi, O., MacCauley, C., & Chant, D. (2004). A systematic review of the incidence of schizophrenia: The distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Medicine*, *2*, 13. https://doi.org/10.1186/1741-7015-2-13

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., Selvaraj, S., & Howes, O. (2011). Is clinical intervention in the ultra high risk phase effective? *Revista Brasileira De Psiquiatria (Sao Paulo, Brazil: 1999)*, *33 Suppl 2*, s161-174. https://doi.org/10.1590/s1516-44462011000600004

McHugh, M. J., McGorry, P. D., Yuen, H. P., Hickie, I. B., Thompson, A., de Haan, L., Mossaheb, N., Smesny, S., Lin, A., Markulev, C., Schloegelhofer, M., Wood, S. J., Nieman, D., Hartmann, J. A., Nordentoft, M., Schäfer, M., Amminger, G. P., Yung, A., & Nelson, B. (2018). The Ultra-High-Risk for psychosis groups: Evidence to maintain the status quo. *Schizophrenia Research*, *195*, 543–548. https://doi.org/10.1016/j.schres.2017.09.003

McMahon, E. M., Corcoran, P., Keeley, H., Clarke, M., Coughlan, H., Wasserman, D., Hoven, C. W., Carli, V., Sarchiapone, M., Healy, C., & Cannon, M. (2021). Risk and protective factors for psychotic experiences in adolescence: A population-based study. *Psychological Medicine*, *51*(7), 1220–1228. https://doi.org/10.1017/S0033291719004136

Mei, C., van der Gaag, M., Nelson, B., Smit, F., Yuen, H. P., Berger, M., Krcmar, M., French, P., Amminger, G. P., Bechdolf, A., Cuijpers, P., Yung, A. R., & McGorry, P. D. (2021). Preventive interventions for individuals at ultra high risk for psychosis: An updated and extended meta-analysis. *Clinical Psychology Review*, *86*, 102005. https://doi.org/10.1016/j.cpr.2021.102005

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S. E., McDonald, K., Ward, A., Poulton, R., & Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(40), E2657-2664. https://doi.org/10.1073/pnas.1206820109

Merrin, G. J., Leadbeater, B. J., Sturgess, C. M. B., Ames, M. E., & Thompson, K. (2022). Predictors of Early-Onset Cannabis Use in Adolescence and Risks for Substance Use Disorder Symptoms in Young Adulthood. *Journal of Drug Issues*, *52*(2), 182–206. https://doi.org/10.1177/00220426211049356

Merritt, K., Egerton, A., Kempton, M. J., Taylor, M. J., & McGuire, P. K. (2016). Nature of Glutamate Alterations in Schizophrenia: A Meta-analysis of Proton Magnetic Resonance Spectroscopy Studies. *JAMA Psychiatry*, *73*(7), 665–674. https://doi.org/10.1001/jamapsychiatry.2016.0442

Merritt, K., McGuire, P., & Egerton, A. (2013). Relationship between Glutamate Dysfunction and Symptoms and Cognitive Function in Psychosis. *Frontiers in Psychiatry*, *4*, 151. https://doi.org/10.3389/fpsyt.2013.00151

Merritt, K., Mcguire, P., & Egerton, A. (2013). Relationship between Glutamate Dysfunction and Symptoms and Cognitive Function in Psychosis. *Frontiers in Psychiatry*, *4*. https://doi.org/10.3389/fpsyt.2013.00151

Mescher, M., Merkle, H., Kirsch, J., Garwood, M., & Gruetter, R. (1998). Simultaneous in vivo spectral editing and water suppression. *NMR IN BIOMEDICINE*, *11*.

Meyer, U. (2013). Developmental neuroinflammation and schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *42*, 20–34. https://doi.org/10.1016/j.pnpbp.2011.11.003

Miech, R. A. (n.d.). *National Survey Results on Drug Use, 1975-2023:*

Miettunen, J., Murray, G. K., Jones, P. B., Mäki, P., Ebeling, H., Taanila, A., Joukamaa, M., Savolainen, J., Törmänen, S., Järvelin, M.-R., Veijola, J., & Moilanen, I. (2014). Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychological Medicine*, *44*(8), 1727–1738. https://doi.org/10.1017/S0033291713002328

Miettunen, J., Törmänen, S., Murray, G. K., Jones, P. B., Mäki, P., Ebeling, H., Moilanen, I., Taanila, A., Heinimaa, M., Joukamaa, M., & Veijola, J. (2008). Association of cannabis use with prodromal symptoms of psychosis in adolescence. *The British Journal of Psychiatry: The Journal of Mental Science*, *192*(6), 470–471. https://doi.org/10.1192/bjp.bp.107.045740

Milani, A. C. C., Foerster, B., Cogo-Moreira, H., Farias, T. M. de B., Salido, F., Carrete, H., Mello, M. F., & Jackowski, A. P. (2018). A Longitudinal 1H-MRS Study of the Anterior Cingulate Gyrus in Child and Adolescent Victims of Multiple Forms of Violence. *Chronic Stress*, *2*, 2470547018763359. https://doi.org/10.1177/2470547018763359

Miller, A. M., & Stella, N. (2008). CB2 receptor-mediated migration of immune cells: It can go either way. *British Journal of Pharmacology*, *153*(2), 299–308. https://doi.org/10.1038/sj.bjp.0707523

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 Δ9-tetrahydrocannabinol alters the transcriptional trajectory and dendritic architecture of prefrontal pyramidal neurons. *Molecular Psychiatry*, *24*(4), Article 4. https://doi.org/10.1038/s41380-018-0243-x

Miller, T. J., McGlashan, T. H., Rosen, J. L., Somjee, L., Markovich, P. J., Stein, K., & Woods, S. W. (2002). Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: Preliminary evidence of interrater reliability and predictive validity. *The American Journal of Psychiatry*, *159*(5), 863–865. https://doi.org/10.1176/appi.ajp.159.5.863

Miller, T. J., McGlashan, T. H., Woods, S. W., Stein, K., Driesen, N., Corcoran, C. M., Hoffman, R., & Davidson, L. (1999). Symptom Assessment in Schizophrenic Prodromal States. *Psychiatric Quarterly*, *70*(4), 273–287. https://doi.org/10.1023/A:1022034115078

Mills, J. G., Fusar-Poli, P., Morgan, C., Azis, M., & McGuire, P. (2017). People meeting ultra high risk for psychosis criteria in the community. *World Psychiatry*, *16*(3), 322–323. https://doi.org/10.1002/wps.20463

Misiak, B., Bartoli, F., Carrà, G., Stańczykiewicz, B., Gładka, A., Frydecka, D., Samochowiec, J., Jarosz, K., Hadryś, T., & Miller, B. J. (2021). Immune-inflammatory markers and psychosis risk: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *127*, 105200. https://doi.org/10.1016/j.psyneuen.2021.105200

Mlynárik, V., Gambarota, G., Frenkel, H., & Gruetter, R. (2006). Localized short-echo-time proton MR spectroscopy with full signal-intensity acquisition. *Magnetic Resonance in Medicine*, *56*(5), 965–970. https://doi.org/10.1002/mrm.21043

Modinos, G., Richter, A., Egerton, A., Bonoldi, I., Azis, M., Antoniades, M., Bossong, M., Crossley, N., Perez, J., Stone, J. M., Veronese, M., Zelaya, F., Grace, A. A., Howes, O. D., Allen, P., & McGuire, P. (2021). Interactions between hippocampal activity and striatal dopamine in people at clinical high risk for psychosis: Relationship to adverse outcomes. *Neuropsychopharmacology*, *46*(8), 1468–1474. https://doi.org/10.1038/s41386-021-01019-0

Modinos, G., Şimşek, F., Azis, M., Bossong, M., Bonoldi, I., Samson, C., Quinn, B., Perez, J., Broome, M. R., Zelaya, F., Lythgoe, D. J., Howes, O. D., Stone, J. M., Grace, A. A., Allen, P., & McGuire, P. (2018). Prefrontal GABA levels, hippocampal resting perfusion and the risk of psychosis. *Neuropsychopharmacology*, *43*(13), 2652–2659. https://doi.org/10.1038/s41386-017-0004-6

Moffett, J. R., Ross, B., Arun, P., Madhavarao, C. N., & Namboodiri, A. M. A. (2007). *N*-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. *Progress in Neurobiology*, *81*(2), 89–131. https://doi.org/10.1016/j.pneurobio.2006.12.003

Molina, V., Sánchez, J., Reig, S., Sanz, J., Benito, C., Santamarta, C., Pascau, J., Sarramea, F., Gispert, J. D., Misiego, J. M., Palomo, T., & Desco, M. (2005). *N*-acetyl-aspartate levels in the dorsolateral prefrontal cortex in the early years of schizophrenia are inversely related to disease duration. *Schizophrenia Research*, *73*(2), 209–219. https://doi.org/10.1016/j.schres.2004.02.001

Molina-Holgado, E., Vela, J. M., Arévalo-Martín, A., Almazán, G., Molina-Holgado, F., Borrell, J., & Guaza, C. (2002). Cannabinoids Promote Oligodendrocyte Progenitor Survival: Involvement of Cannabinoid Receptors and Phosphatidylinositol-3 Kinase/Akt Signaling. *The Journal of Neuroscience*, *22*(22), 9742–9753. https://doi.org/10.1523/JNEUROSCI.22-22-09742.2002

Momanyi, A. (2023). Effectiveness of School-Based Health Education Programs in Preventing Substance Abuse among Adolescents. *International Journal of Public Health Studies*, *1*(1), Article 1.

Mondino, M., Brunelin, J., & Saoud, M. (2013). N-Acetyl-Aspartate Level is Decreased in the Prefrontal Cortex in Subjects At-Risk for Schizophrenia. *Frontiers in Psychiatry*, *4*, 99. https://doi.org/10.3389/fpsyt.2013.00099

Monshouwer, K., Have, M. ten, Tuithof, M., Dorsselaer, S. van, Bak, M., Gunter, N., Delespaul, P., Os, J. van, & Graaf, R. de. (2023). Prevalence, incidence, and persistence of psychotic experiences in the general population: Results of a 9-year follow-up study. *Psychological Medicine*, *53*(8), 3750–3761. https://doi.org/10.1017/S0033291722002690

Morean, M. E., Krishnan-Sarin, S., Sussman, S., Foulds, J., Fishbein, H., Grana, R., & O'Malley, S. S. (2019). Psychometric Evaluation of the E-cigarette Dependence Scale. *Nicotine & Tobacco Research*, *21*(11), 1556–1564. https://doi.org/10.1093/ntr/ntx271

Moreno-Küstner, B., Martín, C., & Pastor, L. (2018a). Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. *PLoS ONE*, *13*(4), e0195687. https://doi.org/10.1371/journal.pone.0195687

Moreno-Küstner, B., Martín, C., & Pastor, L. (2018b). Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. *PLOS ONE*, *13*(4), e0195687. https://doi.org/10.1371/journal.pone.0195687

Moretti, S., Franchi, S., Castelli, M., Amodeo, G., Somaini, L., Panerai, A., & Sacerdote, P. (2015). Exposure of Adolescent Mice to Delta-9-Tetrahydrocannabinol Induces Long-Lasting Modulation of Pro- and Anti-Inflammatory Cytokines in Hypothalamus and Hippocampus Similar to that Observed for Peripheral Macrophages. *Journal of Neuroimmune Pharmacology*, *10*(2), 371–379. https://doi.org/10.1007/s11481-015-9592-2

Morgan, C., Reininghaus, U., Reichenberg, A., Frissa, S., Team, Selc. study, Hotopf, M., & Hatch, S. L. (2014). Adversity, cannabis use and psychotic experiences: Evidence of cumulative and synergistic effects. *The British Journal of Psychiatry*, *204*(5), 346–353. https://doi.org/10.1192/bjp.bp.113.134452

Morris, G., Sominsky, L., Walder, K. R., Berk, M., Marx, W., Carvalho, A. F., Bortolasci, C. C., Maes, M., & Puri, B. K. (2022). Inflammation and Nitro-oxidative Stress as Drivers of Endocannabinoid System Aberrations in Mood Disorders and Schizophrenia. *Molecular Neurobiology*, *59*(6), 3485–3503. https://doi.org/10.1007/s12035-022-02800-y

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), 210–214. https://doi.org/10.1016/j.schres.2012.08.008

Mourik, K., Decrescenzo, P., Brucato, G., Gill, K. E., Arndt, L., Kimhy, D., Keilp, J. G., & Girgis, R. R. (2017). Various neurocognitive deficits and conversion risk in individuals at clinical high risk for psychosis. *Early Intervention in Psychiatry*, *11*(3), 250–254. https://doi.org/10.1111/eip.12296

Müller, M., Vetter, S., Buchli-Kammermann, J., Stieglitz, R.-D., Stettbacher, A., & Riecher-Rössler, A. (2010). The Self-screen-Prodrome as a short screening tool for pre-psychotic states. *Schizophrenia Research*, *123*(2–3), 217–224. https://doi.org/10.1016/j.schres.2010.08.018

Murgatroyd, C., & Spengler, D. (2011). Epigenetics of Early Child Development. *Frontiers in Psychiatry*, *2*. https://doi.org/10.3389/fpsyt.2011.00016

Murray, R. M., & Di Forti, M. (2016). Cannabis and Psychosis: What Degree of Proof Do We Require? *Biological Psychiatry*, *79*(7), 514–515. https://doi.org/10.1016/j.biopsych.2016.02.005

Mustonen, A., Niemelä, S., Nordström, T., Murray, G. K., Mäki, P., Jääskeläinen, E., & Miettunen, J. (2018). Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. *The British Journal of Psychiatry*, *212*(4), 227–233. https://doi.org/10.1192/bjp.2017.52

Nadri, C., Dean, B., Scarr, E., & Agam, G. (2004). GSK-3 parameters in postmortem frontal cortex and hippocampus of schizophrenic patients. *Schizophrenia Research*, *71*(2), 377–382. https://doi.org/10.1016/j.schres.2004.02.020

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

Nakahara, T., Tsugawa, S., Noda, Y., Ueno, F., Honda, S., Kinjo, M., Segawa, H., Hondo, N., Mori, Y., Watanabe, H., Nakahara, K., Yoshida, K., Wada, M., Tarumi, R., Iwata, Y., Plitman, E., Moriguchi, S., de la Fuente-Sandoval, C., Uchida, H., … Nakajima, S. (2022). Glutamatergic and GABAergic metabolite levels in schizophrenia-spectrum disorders: A meta-analysis of 1H-magnetic resonance spectroscopy studies. *Molecular Psychiatry*, *27*(1), 744–757. https://doi.org/10.1038/s41380-021-01297-6

Nave, K.-A., & Werner, H. B. (2014). Myelination of the Nervous System: Mechanisms and Functions. *Annual Review of Cell and Developmental Biology*, *30*(Volume 30, 2014), 503–533. https://doi.org/10.1146/annurev-cellbio-100913-013101

Near, J., Harris, A. D., Juchem, C., Kreis, R., Marjańska, M., Öz, G., Slotboom, J., Wilson, M., & Gasparovic, C. (2021). Preprocessing, analysis and quantification in single-voxel magnetic resonance spectroscopy: Experts' consensus recommendations. *NMR in Biomedicine*, *34*(5), e4257. https://doi.org/10.1002/nbm.4257

Nelson, B., Fusar-Poli, P., & R. Yung, A. (2012). Can We Detect Psychotic-like Experiences in the General Population? *Current Pharmaceutical Design*, *18*(4), 376–385. https://doi.org/10.2174/138161212799316136

Nelson, B., Fusar-Poli, P., & Yung, A. R. (2012). Can we detect psychotic-like experiences in the general population? *Current Pharmaceutical Design*, *18*(4), 376–385. https://doi.org/10.2174/138161212799316136

Nelson, B., Yuen, K., & Yung, A. R. (2011a). Ultra high risk (UHR) for psychosis criteria: Are there different levels of risk for transition to psychosis? *Schizophrenia Research*, *125*(1), 62–68. https://doi.org/10.1016/j.schres.2010.10.017

Nelson, B., Yuen, K., & Yung, A. R. (2011b). Ultra high risk (UHR) for psychosis criteria: Are there different levels of risk for transition to psychosis? *Schizophrenia Research*, *125*(1), 62–68. https://doi.org/10.1016/j.schres.2010.10.017

Nenadic, I., Maitra, R., Basu, S., Dietzek, M., Schönfeld, N., Lorenz, C., Gussew, A., Amminger, G. P., McGorry, P., Reichenbach, J. R., Sauer, H., Gaser, C., & Smesny, S. (2015). Associations of hippocampal metabolism and regional brain grey matter in neuroleptic-naïve ultra-high-risk subjects and first-episode schizophrenia. *European Neuropsychopharmacology*, *25*(10), 1661–1668. https://doi.org/10.1016/j.euroneuro.2015.05.005

Nichols, T., & Hayasaka, S. (2003). Controlling the familywise error rate in functional neuroimaging: A comparative review. *Statistical Methods in Medical Research*, *12*(5), 419–446. https://doi.org/10.1191/0962280203sm341ra

Njau, S., Joshi, S. H., Leaver, A. M., Vasavada, M., Van Fleet, J., Espinoza, R., & Narr, K. L. (2016). Variations in myo-inositol in fronto-limbic regions and clinical response to electroconvulsive therapy in major depression. *Journal of Psychiatric Research*, *80*, 45–51. https://doi.org/10.1016/j.jpsychires.2016.05.012

Nordgaard, J., Buch-Pedersen, M., Hastrup, L. H., Haahr, U. H., & Simonsen, E. (2019). Measuring Psychotic-Like Experiences in the General Population. *Psychopathology*, *52*(4), 240–247. https://doi.org/10.1159/000502048

Nosková, E., Fajnerová, I., Pajuelo, D., Stopková, P., & Horáček, J. (2023). 1H-MRS of the anterior cingulate cortex in obsessive-compulsive disorder: Metabolic abnormalities in pgACC - controlled study. *European Psychiatry*, *66*(S1), S105–S106. https://doi.org/10.1192/j.eurpsy.2023.295

Nuevo, R., Van Os, J., Arango, C., Chatterji, S., & Ayuso-Mateos, J. L. (2013). Evidence for the early clinical relevance of hallucinatory-delusional states in the general population. *Acta Psychiatrica Scandinavica*, *127*(6), 482–493. https://doi.org/10.1111/acps.12010

O'Donnell, P. (2008). Increased Cortical Excitability as a Critical Element in Schizophrenia Pathophysiology. In P. O'Donnell (Ed.), *Cortical Deficits In Schizophrenia: From Genes to Function* (pp. 219–236). Springer US. https://doi.org/10.1007/978-0-387-74351-6_11

O'Donovan, M. C., Craddock, N. J., & Owen, M. J. (2009). Genetics of psychosis; insights from views across the genome. *Human Genetics*, *126*(1), 3–12. https://doi.org/10.1007/s00439-009-0703-0

Okafor, C. N., Li, M., & Paltzer, J. (2020). Self-reported cannabis use and biomarkers of inflammation among adults in the United States. *Brain, Behavior, & Immunity - Health*, *7*, 100109. https://doi.org/10.1016/j.bbih.2020.100109

Okubo, Y., Suhara, T., Suzuki, K., Kobayashi, K., Inoue, O., Terasaki, O., Someya, Y., Sassa, T., Sudo, Y., Matsushima, E., Iyo, M., Tateno, Y., & Toru, M. (1997). Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature*, *385*(6617), 634–636. https://doi.org/10.1038/385634a0

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*, *9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Olfson, M., Lewis-Fernández, R., Weissman, M. M., Feder, A., Gameroff, M. J., Pilowsky, D., & Fuentes, M. (2002). Psychotic Symptoms in an Urban General Medicine Practice. *American Journal of Psychiatry*, *159*(8), 1412–1419. https://doi.org/10.1176/appi.ajp.159.8.1412

Onaivi, E. S. (2009). Cannabinoid receptors in brain: Pharmacogenetics, neuropharmacology, neurotoxicology, and potential therapeutic applications. *International Review of Neurobiology*, *88*, 335–369. https://doi.org/10.1016/S0074-7742(09)88012-4

Oorschot, M., Lataster, T., Thewissen, V., Bentall, R., Delespaul, P., & Myin-Germeys, I. (2012). Temporal dynamics of visual and auditory hallucinations in psychosis. *Schizophrenia Research*, *140*(1), 77–82. https://doi.org/10.1016/j.schres.2012.06.010

Orihuel, J., Capellán, R., Casquero-Veiga, M., Soto-Montenegro, M. L., Desco, M., Oteo-Vives, M., Ibáñez-Moragues, M., Magro-Calvo, N., Luján, V. M., Morcillo, M. Á., Ambrosio, E., & Higuera-Matas, A. (2023). The long-term effects of adolescent Δ9-tetrahydrocannabinol on brain structure and function assessed through neuroimaging techniques in male and female rats. *European Neuropsychopharmacology*, *74*, 47–63. https://doi.org/10.1016/j.euroneuro.2023.05.005

Ortiz, A. E., Ortiz, A. G., Falcon, C., Morer, A., Plana, M. T., Bargalló, N., & Lázaro, L. (2015). 1H-MRS of the anterior cingulate cortex in childhood and adolescent obsessive–compulsive disorder: A case-control study. *European Neuropsychopharmacology*, *25*(1), 60–68. https://doi.org/10.1016/j.euroneuro.2014.11.007

Os, J. van, 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

Oshri, A., Rogosch, F. A., Burnette, M. L., & Cicchetti, D. (2011). Developmental pathways to adolescent cannabis abuse and dependence: Child maltreatment, emerging personality, and internalizing versus externalizing psychopathology. *Psychology of Addictive Behaviors*, *25*(4), 634–644. https://doi.org/10.1037/a0023151

Ouellet, J., Assaf, R., Afzali, M. H., Nourbakhsh, S., Potvin, S., & Conrod, P. (2024). Neurocognitive consequences of adolescent sleep disruptions and their relationship to psychosis vulnerability: A longitudinal cohort study. *Npj Mental Health Research*, *3*(1), 1–9. https://doi.org/10.1038/s44184-024-00058-x

Ozturk, A., Degaonkar, M., Matson, M. A., Wells, C. T., Mahone, E. M., & Horská, A. (2009). Proton MR Spectroscopy Correlates of Frontal Lobe Function in Healthy Children. *American Journal of Neuroradiology*, *30*(7), 1308–1314. https://doi.org/10.3174/ajnr.A1576

Page, C. E., & Coutellier, L. (2019). Prefrontal excitatory/inhibitory balance in stress and emotional disorders: Evidence for over-inhibition. *Neuroscience & Biobehavioral Reviews*, *105*, 39–51. https://doi.org/10.1016/j.neubiorev.2019.07.024

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Systematic Reviews*, *10*(1), 89. https://doi.org/10.1186/s13643-021-01626-4

Palmer, C. A. (2020). Tired Teens: Sleep Disturbances and Heightened Vulnerability for Mental Health Difficulties. *Journal of Adolescent Health*, *66*(5), 520–521. https://doi.org/10.1016/j.jadohealth.2020.01.023

Pantelis, C., Yücel, M., Wood, S. J., Velakoulis, D., Sun, D., Berger, G., Stuart, G. W., Yung, A., Phillips, L., & McGorry, P. D. (2005). Structural Brain Imaging Evidence for Multiple Pathological Processes at Different Stages of Brain Development in Schizophrenia. *Schizophrenia Bulletin*, *31*(3), 672–696. https://doi.org/10.1093/schbul/sbi034

Park, H. Y., Bang, M., Seo, E., Koo, S. J., Lee, E., Lee, S.-K., & An, S. K. (2022). The stress-vulnerability model on the path to schizophrenia: Interaction between BDNF methylation and schizotypy on the resting-state brain network. *Schizophrenia*, *8*(1), 1–7. https://doi.org/10.1038/s41537-022-00258-4

Parker, C., Scott, S., & Geddes, A. (2019). Snowball Sampling. *SAGE Research Methods Foundations*. http://methods.sagepub.com/foundations/snowball-sampling

Paslakis, G., Träber, F., Roberz, J., Block, W., & Jessen, F. (2014). N-acetyl-aspartate (NAA) as a correlate of pharmacological treatment in psychiatric disorders: A systematic review. *European Neuropsychopharmacology*, *24*(10), 1659–1675. https://doi.org/10.1016/j.euroneuro.2014.06.004

Patel, P. K., Leathem, L. D., Currin, D. L., & Karlsgodt, K. H. (2021). Adolescent Neurodevelopment and Vulnerability to Psychosis. *Biological Psychiatry*, *89*(2), 184–193. https://doi.org/10.1016/j.biopsych.2020.06.028

Patel, S., Khan, S., M, S., & Hamid, P. (n.d.). The Association Between Cannabis Use and Schizophrenia: Causative or Curative? A Systematic Review. *Cureus*, *12*(7), e9309. https://doi.org/10.7759/cureus.9309

Paz, R. D., Tardito, S., Atzori, M., & Tseng, K. Y. (2008). Glutamatergic dysfunction in schizophrenia: From basic neuroscience to clinical psychopharmacology. *European Neuropsychopharmacology*, *18*(11), 773–786. https://doi.org/10.1016/j.euroneuro.2008.06.005

Perälä, J., Suvisaari, J., Saarni, S. I., Kuoppasalmi, K., Isometsä, E., Pirkola, S., Partonen, T., Tuulio-Henriksson, A., Hintikka, J., Kieseppä, T., Härkänen, T., Koskinen, S., & Lönnqvist, J. (2007). Lifetime Prevalence of Psychotic and Bipolar I Disorders in a General Population. *Archives of General Psychiatry*, *64*(1), 19–28. https://doi.org/10.1001/archpsyc.64.1.19

Perkins, D. O. (2004). Evaluating and Treating the Prodromal Stage of Schizophrenia. *Current Psychiatry Reports*, *6*(4), 289–295.

Pesesse, X., Choi, K., Zhang, T., & Shears, S. B. (2004). Signaling by Higher Inositol Polyphosphates: SYNTHESIS OF BISDIPHOSPHOINOSITOL TETRAKISPHOSPHATE ("InsP8") IS SELECTIVELY ACTIVATED BY HYPEROSMOTIC STRESS*. *Journal of Biological Chemistry*, *279*(42), 43378–43381. https://doi.org/10.1074/jbc.C400286200

Petroff, O. A. C. (2007). 6—Metabolic Biopsy of the Brain. In S. G. Waxman (Ed.), *Molecular Neurology* (pp. 77–100). Academic Press. https://doi.org/10.1016/B978-012369509-3.50008-1

Pignon, B., Peyre, H., Ayrolles, A., Kirkbride, J. B., Jamain, S., Ferchiou, A., Richard, J. R., Baudin, G., Tosato, S., Jongsma, H., Haan, L. de, Tarricone, I., Bernardo, M., Velthorst, E., Braca, M., Arango, C., Arrojo, M., Bobes, J., Del-Ben, C. M., … Schürhoff, F. (2022). Genetic and psychosocial stressors have independent effects on the level of subclinical psychosis: Findings from the multinational EU-GEI study. *Epidemiology and Psychiatric Sciences*, *31*, e68. https://doi.org/10.1017/S2045796022000464

Pike Moore, S., Masyn, K. E., Fryer, C., Lee, E., Gunzler, D., Trapl, E., Shang, C., & Sterling, K. L. (2023). Recency measures matter: Variability in reported last use of tobacco and marijuana products among a nationally representative study of U.S. young adults. *Addictive Behaviors*, *144*, 107746. https://doi.org/10.1016/j.addbeh.2023.107746

Pillinger, T., D'Ambrosio, E., McCutcheon, R., & Howes, O. D. (2019). Is psychosis a multisystem disorder? A meta-review of central nervous system, immune, cardiometabolic, and endocrine alterations in first-episode psychosis and perspective on potential models. *Molecular Psychiatry*, *24*(6), 776–794. https://doi.org/10.1038/s41380-018-0058-9

Pinchevsky, G. M., Fagan, A. A., & Wright, E. M. (2014). Victimization Experiences and Adolescent Substance Use: Does the Type and Degree of Victimization Matter? *Journal of Interpersonal Violence*, *29*(2), 299–319. https://doi.org/10.1177/0886260513505150

Planchuelo-Gómez, Á., Lubeiro, A., Núñez-Novo, P., Gomez-Pilar, J., de Luis-García, R., del Valle, P., Martín-Santiago, Ó., Pérez-Escudero, A., & Molina, V. (2020). Identificacion of MRI-based psychosis subtypes: Replication and refinement. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *100*, 109907. https://doi.org/10.1016/j.pnpbp.2020.109907

Plavén-Sigray, P., Matheson, G. J., Collste, K., Ashok, A. H., Coughlin, J. M., Howes, O. D., Mizrahi, R., Pomper, M. G., Rusjan, P., Veronese, M., Wang, Y., & Cervenka, S. (2017). *PET studies of the glial cell marker TSPO in psychosis patients—A meta-analysis using individual participant data* (p. 228742). bioRxiv. https://doi.org/10.1101/228742

Plitman, E., de la Fuente-Sandoval, C., Reyes-Madrigal, F., Chavez, S., Gómez-Cruz, G., León-Ortiz, P., & Graff-Guerrero, A. (2016). Elevated Myo-Inositol, Choline, and Glutamate Levels in the Associative Striatum of Antipsychotic-Naive Patients With First-Episode Psychosis: A Proton Magnetic Resonance Spectroscopy Study With Implications for Glial Dysfunction. *Schizophrenia Bulletin*, *42*(2), 415–424. https://doi.org/10.1093/schbul/sbv118

Poulia, N., Delis, F., Brakatselos, C., Lekkas, P., Kokras, N., Dalla, C., & Antoniou, K. (2020). Escalating low-dose Δ9-tetrahydrocannabinol exposure during adolescence induces differential behavioral and neurochemical effects in male and female adult rats. *European Journal of Neuroscience*, *52*(1), 2681–2693. https://doi.org/10.1111/ejn.14598

Poulton, R., Caspi, A., Moffitt, T., Cannon, M., Murray, R., & Harrington, H. (2000a). Children's self-reported psychotic symptoms and adult schizophreniform disorder. *Archives of General Psychiatry*, *57*, 1053–1058.

Poulton, R., Caspi, A., Moffitt, T. E., Cannon, M., Murray, R., & Harrington, H. (2000b). Children's Self-Reported Psychotic Symptoms and Adult Schizophreniform Disorder: A 15-Year Longitudinal Study. *Archives of General Psychiatry*, *57*(11), 1053. https://doi.org/10.1001/archpsyc.57.11.1053

Pouwels, P. J. W., Brockmann, K., Kruse, B., Wilken, B., Wick, M., Hanefeld, F., & Frahm, J. (1999). Regional Age Dependence of Human Brain Metabolites from Infancy to Adulthood as Detected by Quantitative Localized Proton MRS. *Pediatric Research*, *46*(4), Article 4. https://doi.org/10.1203/00006450-199910000-00019

Power, R. A., Verweij, K. J. H., Zuhair, M., Montgomery, G. W., Henders, A. K., Heath, A. C., Madden, P. a. F., Medland, S. E., Wray, N. R., & Martin, N. G. (2014a). Genetic predisposition to schizophrenia associated with increased use of cannabis. *Molecular Psychiatry*, *19*(11), 1201–1204. https://doi.org/10.1038/mp.2014.51

Power, R. A., Verweij, K. J. H., Zuhair, M., Montgomery, G. W., Henders, A. K., Heath, A. C., Madden, P. a F., Medland, S. E., Wray, N. R., & Martin, N. G. (2014b). Genetic predisposition to schizophrenia associated with increased use of cannabis. *Molecular Psychiatry*, *19*(11), 1201–1204. https://doi.org/10.1038/mp.2014.51

Prescot, A. P., Locatelli, A. E., Renshaw, P. F., & Yurgelun-Todd, D. A. (2011a). Neurochemical alterations in adolescent chronic marijuana smokers: A proton MRS study. *NeuroImage*, *57*(1), 69–75. https://doi.org/10.1016/j.neuroimage.2011.02.044

Prescot, A. P., Locatelli, A. E., Renshaw, P. F., & Yurgelun-Todd, D. A. (2011b). Neurochemical alterations in adolescent chronic marijuana smokers: A proton MRS study. *NeuroImage*, *57*(1), 69–75. https://doi.org/10.1016/j.neuroimage.2011.02.044

Provencher, S. (n.d.). *LCModel1 & LCMgui User's Manual*.

Provencher, S. W. (2001). Automatic quantitation of localized in vivo 1H spectra with LCModel. *NMR in Biomedicine*, *14*(4), 260–264. https://doi.org/10.1002/nbm.698

Psychotic Disorders | New England Journal of Medicine. (n.d.). Retrieved July 4, 2024, from https://www.nejm.org/doi/full/10.1056/NEJMra1801490

Pucci, S., Fasoli, F., Moretti, M., Benfante, R., Di Lascio, S., Viani, P., Daga, A., Gordon, T. J., McIntosh, M., Zoli, M., Clementi, F., & Gotti, C. (2021). Choline and nicotine increase glioblastoma cell proliferation by binding and activating α7- and α9- containing nicotinic receptors. *Pharmacological Research*, *163*, 105336. https://doi.org/10.1016/j.phrs.2020.105336

Ragazzi, T. C. C., Shuhama, R., Menezes, P. R., & Del-Ben, C. M. (2018a). Cannabis use as a risk factor for psychotic-like experiences: A systematic review of non-clinical populations evaluated with the Community Assessment of Psychic Experiences. *Early Intervention in Psychiatry*, *12*(6), 1013–1023. https://doi.org/10.1111/eip.12693

Ragazzi, T. C. C., Shuhama, R., Menezes, P. R., & Del-Ben, C. M. (2018b). Cannabis use as a risk factor for psychotic-like experiences: A systematic review of non-clinical populations evaluated with the Community Assessment of Psychic Experiences. *Early Intervention in Psychiatry*, *12*(6), 1013–1023. https://doi.org/10.1111/eip.12693

Ragazzi, T. C. C., Shuhama, R., Menezes, P. R., & Del-Ben, C. M. (2018c). Cannabis use as a risk factor for psychotic-like experiences: A systematic review of non-clinical populations evaluated with the Community Assessment of Psychic Experiences. *Early Intervention in Psychiatry*, *12*(6), 1013–1023. https://doi.org/10.1111/eip.12693

Raz, N., Gunning-Dixon, F., Head, D., Rodrigue, K. M., Williamson, A., & Acker, J. D. (2004). Aging, sexual dimorphism, and hemispheric asymmetry of the cerebral cortex: Replicability of regional differences in volume. *Neurobiology of Aging*, *25*(3), 377–396. https://doi.org/10.1016/S0197-4580(03)00118-0

Read, J., Bentall, R. P., & Fosse, R. (2009a). Time to abandon the bio-bio-bio model of psychosis: Exploring the epigenetic and psychological mechanisms by which adverse life events lead to psychotic symptoms. *Epidemiology and Psychiatric Sciences*, *18*(4), 299–310. https://doi.org/10.1017/S1121189X00000257

Read, J., Bentall, R. P., & Fosse, R. (2009b). Time to abandon the bio-bio-bio model of psychosis: Exploring the epigenetic and psychological mechanisms by which adverse life events lead to psychotic symptoms. *Epidemiology and Psychiatric Sciences*, *18*(4), 299–310. https://doi.org/10.1017/S1121189X00000257

Reale, M., Costantini, E., & Greig, N. H. (2021). Cytokine Imbalance in Schizophrenia. From Research to Clinic: Potential Implications for Treatment. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/fpsyt.2021.536257

Recasens, M., Almolda, B., Pérez-Clausell, J., Campbell, I. L., González, B., & Castellano, B. (2021). Chronic exposure to IL-6 induces a desensitized phenotype of the microglia. *Journal of Neuroinflammation*, *18*, 31. https://doi.org/10.1186/s12974-020-02063-1

Redirecting. (n.d.). Retrieved July 6, 2024, from https://linkinghub-elsevier-com.ezproxy.library.dal.ca/retrieve/pii/S0165032724005743

Regional enhancement of cannabinoid CB1 receptor desensitization in female adolescent rats following repeated Δ9-tetrahydrocannabinol exposure—Burston—2010—British Journal of Pharmacology—Wiley Online Library. (n.d.). Retrieved July 20, 2024, from https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/j.1476-5381.2010.00870.x

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

Renard, J., Rushlow, W. J., & Laviolette, S. R. (2018). Effects of Adolescent THC Exposure on the Prefrontal GABAergic System: Implications for Schizophrenia-Related Psychopathology. *Frontiers in Psychiatry*, *9*. https://doi.org/10.3389/fpsyt.2018.00281

Renard, J., Vitalis, T., Rame, M., Krebs, M.-O., Lenkei, Z., Le Pen, G., & Jay, T. M. (2016a). Chronic cannabinoid exposure during adolescence leads to long-term structural and functional changes in the prefrontal cortex. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *26*(1), 55–64. https://doi.org/10.1016/j.euroneuro.2015.11.005

Renard, J., Vitalis, T., Rame, M., Krebs, M.-O., Lenkei, Z., Le Pen, G., & Jay, T. M. (2016b). Chronic cannabinoid exposure during adolescence leads to long-term structural and functional changes in the prefrontal cortex. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *26*(1), 55–64. https://doi.org/10.1016/j.euroneuro.2015.11.005

ResearchGate. (n.d.). Retrieved May 17, 2024, from https://www.researchgate.net/publication/233799981_Reliability_and_Validity_of_Family_Affluence_Scale_FAS_II_among_Adolescents_in_Beijing_China/link/0a85e531ede5b1ed39000000/download?_tp=eyJjb250ZXh0Ijp7ImZpcnN0UGFnZSI6InB1YmxpY2F0aW9uIiwicGFnZSI6InB1YmxpY2F0aW9uIn19

Ribolsi, M., Lin, A., Wardenaar, K. J., Pontillo, M., Mazzone, L., Vicari, S., & Armando, M. (2017). Clinical presentation of Attenuated Psychosis Syndrome in children and adolescents: Is there an age effect? *Psychiatry Research*, *252*, 169–174. https://doi.org/10.1016/j.psychres.2017.02.050

Richetto, J., & Meyer, U. (2021). Epigenetic Modifications in Schizophrenia and Related Disorders: Molecular Scars of Environmental Exposures and Source of Phenotypic Variability. *Biological Psychiatry*, *89*(3), 215–226. https://doi.org/10.1016/j.biopsych.2020.03.008

Rigucci, S., Xin, L., Klauser, P., Baumann, P. S., Alameda, L., Cleusix, M., Jenni, R., Ferrari, C., Pompili, M., Gruetter, R., Do, K. Q., & Conus, P. (2018). Cannabis use in early psychosis is associated with reduced glutamate levels in the prefrontal cortex. *Psychopharmacology*, *235*(1), 13–22. https://doi.org/10.1007/s00213-017-4745-z

Ritunnano, R., Kleinman, J., Oshodi, D. W., Michail, M., Nelson, B., Humpston, C. S., & Broome, M. R. (2022). Subjective experience and meaning of delusions in psychosis: A systematic review and qualitative evidence synthesis. *The Lancet Psychiatry*, *9*(6), 458–476. https://doi.org/10.1016/S2215-0366(22)00104-3

ROBINS-E_LAUNCH-VERSION _20jun2023.pdf. (n.d.). Google Docs. Retrieved February 18, 2024, from https://drive.google.com/file/d/17xCWqLVi01PIjffqkC4yJYJnF7VyGNOn/view?usp=drive_link&usp=embed_facebook

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*, *28*(1), 154–162. https://doi.org/10.1037/a0030992

Robinson, S., Sobell, L., Sobell, M., & Leo, G. (2012). Reliability of the Timeline Followback for cocaine, cannabis, and cigarette use. *Psychology of Addictive Behaviors*, *in press*.

Rodgers, C. T., & Robson, M. D. (2010). Receive array magnetic resonance spectroscopy: Whitened singular value decomposition (WSVD) gives optimal Bayesian solution. *Magnetic Resonance in Medicine*, *63*(4), 881–891. https://doi.org/10.1002/mrm.22230

Rodriguez, A., Kaakinen, M., Moilanen, I., Taanila, A., McGough, J. J., Loo, S., & Järvelin, M.-R. (2010). Mixed-Handedness Is Linked to Mental Health Problems in Children and Adolescents. *Pediatrics*, *125*(2), e340–e348. https://doi.org/10.1542/peds.2009-1165

Rodríguez-Muñoz, M., Sánchez-Blázquez, P., Merlos, M., & Garzón-Niño, J. (2016). Endocannabinoid control of glutamate NMDA receptors: The therapeutic potential and consequences of dysfunction. *Oncotarget*, *7*(34), 55840–55862. https://doi.org/10.18632/oncotarget.10095

Rognli, E. B., & Bramness, J. G. (2015). Understanding the Relationship Between Amphetamines and Psychosis. *Current Addiction Reports*, *2*(4), 285–292. https://doi.org/10.1007/s40429-015-0077-4

Rolls, E. T., Loh, M., Deco, G., & Winterer, G. (2008). Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. *Nature Reviews Neuroscience*, *9*(9), 696–709. https://doi.org/10.1038/nrn2462

Romeo, B., Lestra, V., Martelli, C., Benyamina, A., & Hamdani, N. (2022). Cannabis Cessation, Inflammatory Markers and Schizophrenia. *Journal of Dual Diagnosis*, *18*(1), 33–41. https://doi.org/10.1080/15504263.2021.2013697

Romeo, B., Petillion, A., Martelli, C., & Benyamina, A. (2020). Magnetic resonance spectroscopy studies in subjects with high risk for psychosis: A meta-analysis and review. *Journal of Psychiatric Research*, *125*, 52–65. https://doi.org/10.1016/j.jpsychires.2020.03.006

Rose, G. (1981). Strategy of prevention: Lessons from cardiovascular disease. *British Medical Journal (Clinical Research Ed.)*, *282*(6279), 1847–1851.

Rubbi, I., Lupo, R., Lezzi, A., Cremonini, V., Carvello, M., Caricato, M., Conte, L., Antonazzo, M., Caldararo, C., Botti, S., Andretta, V., Lattarulo, P., & Vitale, E. (2023). The Social and Professional Image of the Nurse: Results of an Online Snowball Sampling Survey among the General Population in the Post-Pandemic Period. *Nursing Reports*, *13*(3), Article 3. https://doi.org/10.3390/nursrep13030109

Rubino, T., & Parolaro, D. (2014). Cannabis abuse in adolescence and the risk of psychosis: A brief review of the preclinical evidence. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *52*, 41–44. https://doi.org/10.1016/j.pnpbp.2013.07.020

Rubino, T., Prini, P., Piscitelli, F., Zamberletti, E., Trusel, M., Melis, M., Sagheddu, C., Ligresti, A., Tonini, R., Di Marzo, V., & Parolaro, D. (2015). Adolescent exposure to THC in female rats disrupts developmental changes in the prefrontal cortex. *Neurobiology of Disease*, *73*, 60–69. https://doi.org/10.1016/j.nbd.2014.09.015

Rubino, T., Vigano', D., Realini, N., Guidali, C., Braida, D., Capurro, V., Castiglioni, C., Cherubino, F., Romualdi, P., Candeletti, S., Sala, M., & Parolaro, D. (2008). Chronic Δ9-Tetrahydrocannabinol During Adolescence Provokes Sex-Dependent Changes in the Emotional Profile in Adult Rats: Behavioral and Biochemical Correlates. *Neuropsychopharmacology*, *33*(11), 2760–2771. https://doi.org/10.1038/sj.npp.1301664

Rubino, T., Zamberletti, E., & Parolaro, D. (2012). Adolescent exposure to cannabis as a risk factor for psychiatric disorders. *Journal of Psychopharmacology*, *26*(1), 177–188. https://doi.org/10.1177/0269881111405362

Ruhrmann, S., Schultze-Lutter, F., Salokangas, R. K. R., Heinimaa, M., Linszen, D., Dingemans, P., Birchwood, M., Patterson, P., Juckel, G., Heinz, A., Morrison, A., Lewis, S., Graf von Reventlow, H., & Klosterkötter, J. (2010). Prediction of Psychosis in Adolescents and Young Adults at High Risk: Results From the Prospective European Prediction of Psychosis Study. *Archives of General Psychiatry*, *67*(3), 241–251. https://doi.org/10.1001/archgenpsychiatry.2009.206

Ruzicka, W. B. (2015). Epigenetic Mechanisms in the Pathophysiology of Psychotic Disorders. *Harvard Review of Psychiatry*, *23*(3), 212. https://doi.org/10.1097/HRP.0000000000000048

Ryan, J. E., Veliz, P., McCabe, S. E., Stoddard, S. A., & Boyd, C. J. (2020). Association of early onset of cannabis, cigarette, other drug use and schizophrenia or psychosis. *Schizophrenia Research*, *215*, 482–484. https://doi.org/10.1016/j.schres.2019.10.002

Sahakyan, L., Meller, T., Evermann, U., Schmitt, S., Pfarr, J.-K., Sommer, J., Kwapil, T. R., & Nenadić, I. (2021). Anterior vs Posterior Hippocampal Subfields in an Extended Psychosis Phenotype of Multidimensional Schizotypy in a Nonclinical Sample. *Schizophrenia Bulletin*, *47*(1), 207–218. https://doi.org/10.1093/schbul/sbaa099

Sahin, C., Unal, G., & Aricioglu, F. (2014). Regulation of GSK-3 Activity as A Shared Mechanism in Psychiatric Disorders. *Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology*, *24*(1), 97–108. https://doi.org/10.5455/bcp.20140317063255

Salazar de Pablo, G., Catalan, A., & Fusar-Poli, P. (2020). Clinical Validity of DSM-5 Attenuated Psychosis Syndrome: Advances in Diagnosis, Prognosis, and Treatment. *JAMA Psychiatry*, *77*(3), 311–320. https://doi.org/10.1001/jamapsychiatry.2019.3561

Salazar de Pablo, G., Radua, J., Pereira, J., Bonoldi, I., Arienti, V., Besana, F., Soardo, L., Cabras, A., Fortea, L., Catalan, A., Vaquerizo-Serrano, J., Coronelli, F., Kaur, S., Da Silva, J., Shin, J. I., Solmi, M., Brondino, N., Politi, P., McGuire, P., & Fusar-Poli, P. (2021). Probability of Transition to Psychosis in Individuals at Clinical High Risk: An Updated Meta-analysis. *JAMA Psychiatry*, *78*(9), 970–978. https://doi.org/10.1001/jamapsychiatry.2021.0830

Salazar de Pablo, G., Woods, S. W., Drymonitou, G., de Diego, H., & Fusar-Poli, P. (2021). Prevalence of Individuals at Clinical High-Risk of Psychosis in the General Population and Clinical Samples: Systematic Review and Meta-Analysis. *Brain Sciences*, *11*(11), Article 11. https://doi.org/10.3390/brainsci11111544

Salmanzadeh, H., Ahmadi-Soleimani, S. M., Azadi, M., Halliwell, R. F., & Azizi, H. (2021). Adolescent Substance Abuse, Transgenerational Consequences and Epigenetics. *Current Neuropharmacology*, *19*(9), 1560. https://doi.org/10.2174/1570159X19666210303121519

Salokangas, R. K. R., From, T., Ilonen, T., Luutonen, S., Heinimaa, M., Armio, R.-L., Laurikainen, H., Walta, M., Paju, J., Toivonen, A., Jalo, P., Tuominen, L., & Hietala, J. (2021). Short-term functional outcome in psychotic patients: Results of the Turku early psychosis study (TEPS). *BMC Psychiatry*, *21*, 602. https://doi.org/10.1186/s12888-021-03516-4

Sami, M., Worker, A., Colizzi, M., Annibale, L., Das, D., Kelbrick, M., Eranti, S., Collier, T., Onyejiaka, C., O'Neill, A., Lythgoe, D., McGuire, P., Williams, S. C. R., Kempton, M. J., & Bhattacharyya, S. (2020). Association of cannabis with glutamatergic levels in patients with early psychosis: Evidence for altered volume striatal glutamate relationships in patients with a history of cannabis use in early psychosis. *Translational Psychiatry*, *10*(1), 1–12. https://doi.org/10.1038/s41398-020-0790-1

Sánchez-de la Torre, A., Aguado, T., Huerga-Gómez, A., Santamaría, S., Gentile, A., Chara, J. C., Matute, C., Monory, K., Mato, S., Guzmán, M., Lutz, B., Galve-Roperh, I., & Palazuelos, J. (2022). Cannabinoid CB1 receptor gene inactivation in oligodendrocyte precursors disrupts oligodendrogenesis and myelination in mice. *Cell Death & Disease*, *13*(7), 1–13. https://doi.org/10.1038/s41419-022-05032-z

Sandy. (2013, May 15). Positive symptoms. *NeuRA Library*. https://library.neura.edu.au/schizophrenia/signs-and-symptoms/general-signs-and-symptoms/positive-symptoms/

Sasabayashi, D., Takayanagi, Y., Takahashi, T., Katagiri, N., Sakuma, A., Obara, C., Katsura, M., Okada, N., Koike, S., Yamasue, H., Nakamura, M., Furuichi, A., Kido, M., Nishikawa, Y., Noguchi, K., Matsumoto, K., Mizuno, M., Kasai, K., & Suzuki, M. (2020). Subcortical Brain Volume Abnormalities in Individuals With an At-risk Mental State. *Schizophrenia Bulletin*, *46*(4), 834–845. https://doi.org/10.1093/schbul/sbaa011

Saxena, A., & Dodell-Feder, D. (2022a). Explaining the Association Between Urbanicity and Psychotic-Like Experiences in Pre-Adolescence: The Indirect Effect of Urban Exposures. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.831089

Saxena, A., & Dodell-Feder, D. (2022b). Explaining the Association Between Urbanicity and Psychotic-Like Experiences in Pre-Adolescence: The Indirect Effect of Urban Exposures. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.831089

Schauer, G. L., Njai, R., & Grant-Lenzy, A. M. (2020). Modes of marijuana use – smoking, vaping, eating, and dabbing: Results from the 2016 BRFSS in 12 States. *Drug and Alcohol Dependence*, *209*, 107900. https://doi.org/10.1016/j.drugalcdep.2020.107900

Scheid, M. P., & Woodgett, J. R. (2001). PKB/AKT: Functional insights from genetic models. *Nature Reviews. Molecular Cell Biology*, *2*(10), 760–768. https://doi.org/10.1038/35096067

Schell, C., Godinho, A., & Cunningham, J. A. (2022). Examining the influence of rurality on frequency of cannabis use and severity of consequences as moderated by age and gender. *Addictive Behaviors*, *133*, 107385. https://doi.org/10.1016/j.addbeh.2022.107385

Schobel, S. A., Chaudhury, N. H., Khan, U. A., Paniagua, B., Styner, M. A., Asllani, I., Inbar, B. P., Corcoran, C. M., Lieberman, J. A., Moore, H., & Small, S. A. (2013). Imaging patients with psychosis and a mouse model establishes a spreading pattern of hippocampal dysfunction and implicates glutamate as a driver. *Neuron*, *78*(1), 81–93. https://doi.org/10.1016/j.neuron.2013.02.011

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

Scholes-Balog, K. E., Hemphill, S. A., Heerde, J. A., Toumbourou, J. W., & Patton, G. C. (2020). Childhood social environmental and behavioural predictors of early adolescent onset cannabis use. *Drug and Alcohol Review*, *39*(4), 384–393. https://doi.org/10.1111/dar.13077

Schubart, C. D., Gastel, W. A. van, Breetvelt, E. J., Beetz, S. L., Ophoff, R. A., Sommer, I. E. C., Kahn, R. S., & Boks, M. P. M. (2011). Cannabis use at a young age is associated with psychotic experiences. *Psychological Medicine*, *41*(6), 1301–1310. https://doi.org/10.1017/S003329171000187X

Schubart, C. D., van Gastel, W. A., Breetvelt, E. J., Beetz, S. L., Ophoff, R. A., Sommer, I. E. C., Kahn, R. S., & Boks, M. P. M. (2011). Cannabis use at a young age is associated with psychotic experiences. *Psychological Medicine*, *41*(6), 1301–1310. https://doi.org/10.1017/S003329171000187X

Schultze-Lutter, F., Renner, F., Paruch, J., Julkowski, D., Klosterkötter, J., & Ruhrmann, S. (2014a). Self-reported psychotic-like experiences are a poor estimate of clinician-rated attenuated and frank delusions and hallucinations. *Psychopathology*, *47*(3), 194–201. https://doi.org/10.1159/000355554

Schultze-Lutter, F., Renner, F., Paruch, J., Julkowski, D., Klosterkötter, J., & Ruhrmann, S. (2014b). Self-reported psychotic-like experiences are a poor estimate of clinician-rated attenuated and frank delusions and hallucinations. *Psychopathology*, *47*(3), 194–201. https://doi.org/10.1159/000355554

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

Scott, J., Martin, G., Bor, W., Sawyer, M., Clark, J., & McGrath, J. (2009). The prevalence and correlates of hallucinations in Australian adolescents: Results from a national survey. *Schizophrenia Research*, *107*(2–3), 179–185. https://doi.org/10.1016/j.schres.2008.11.002

Self-Reported Psychotic-Like Experiences Are a Poor Estimate of Clinician-Rated Attenuated and Frank Delusions and Hallucinations | Psychopathology | Karger Publishers. (n.d.). Retrieved February 18, 2024, from https://karger.com/psp/article/47/3/194/284905/Self-Reported-Psychotic-Like-Experiences-Are-a

Selvaraj, S., Bloomfield, P. S., Cao, B., Veronese, M., Turkheimer, F., & Howes, O. D. (2018). Brain TSPO imaging and gray matter volume in schizophrenia patients and in people at ultra high risk of psychosis: An [11C]PBR28 study. *Schizophrenia Research*, *195*, 206–214. https://doi.org/10.1016/j.schres.2017.08.063

Shakoor, S., Zavos, H. M. S., McGuire, P., Cardno, A. G., Freeman, D., & Ronald, A. (2015). Psychotic experiences are linked to cannabis use in adolescents in the community because of common underlying environmental risk factors. *Psychiatry Research*, *227*(2–3), 144–151. https://doi.org/10.1016/j.psychres.2015.03.041

Shakory, S., Watts, J. J., Hafizi, S., Da Silva, T., Khan, S., Kiang, M., Bagby, R. M., Chavez, S., & Mizrahi, R. (2018a). Hippocampal glutamate metabolites and glial activation in clinical high risk and first episode psychosis. *Neuropsychopharmacology*, *43*(11), 2249–2255. https://doi.org/10.1038/s41386-018-0163-0

Sharma, R., Tikka, S. K., Bhute, A. R., & Bastia, B. K. (2022). N-acetyl cysteine in the treatment of cannabis use disorder: A systematic review of clinical trials. *Addictive Behaviors*, *129*, 107283. https://doi.org/10.1016/j.addbeh.2022.107283

Shen, J., Shenkar, D., An, L., & Tomar, J. S. (2020a). Local and Interregional Neurochemical Associations Measured by Magnetic Resonance Spectroscopy for Studying Brain Functions and Psychiatric Disorders. *Frontiers in Psychiatry*, *11*, 802. https://doi.org/10.3389/fpsyt.2020.00802

Sherif, M., Radhakrishnan, R., D'Souza, D. C., & Ranganathan, M. (2016). Human Laboratory Studies on Cannabinoids and Psychosis. *Biological Psychiatry*, *79*(7), 526–538. https://doi.org/10.1016/j.biopsych.2016.01.011

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

Siever, L. J., & Davis, K. L. (2004). The Pathophysiology of Schizophrenia Disorders: Perspectives From the Spectrum. *American Journal of Psychiatry*, *161*(3), 398–413. https://doi.org/10.1176/appi.ajp.161.3.398

Silva, L., Black, R., Michaelides, M., Hurd, Y. L., & Dow-Edwards, D. (2016). Sex and age specific effects of delta-9-tetrahydrocannabinol during the periadolescent period in the rat: The unique susceptibility of the prepubescent animal. *Neurotoxicology and Teratology*, *58*, 88–100. https://doi.org/10.1016/j.ntt.2016.02.005

Silva, T. D., Hafizi, S., Rusjan, P. M., Houle, S., Wilson, A. A., Prce, I., Sailasuta, N., & Mizrahi, R. (2019). GABA levels and TSPO expression in people at clinical high risk for psychosis and healthy volunteers: A PET-MRS study. *Journal of Psychiatry and Neuroscience*, *44*(2), 111–119. https://doi.org/10.1503/jpn.170201

Silveri, M. M., Jensen, J. E., Rosso, I. M., Sneider, J. T., & Yurgelun-Todd, D. A. (2011). Preliminary evidence for white matter metabolite differences in marijuana-dependent young men using 2D *J*-resolved magnetic resonance spectroscopic imaging at 4 Tesla. *Psychiatry Research: Neuroimaging*, *191*(3), 201–211. https://doi.org/10.1016/j.pscychresns.2010.10.005

Simon, A. E., Velthorst, E., Nieman, D. H., Linszen, D., Umbricht, D., & de Haan, L. (2011). Ultra high-risk state for psychosis and non-transition: A systematic review. *Schizophrenia Research*, *132*(1), 8–17. https://doi.org/10.1016/j.schres.2011.07.002

Simon, G. E., Coleman, K. J., Yarborough, B. J., Operskalski, B., Stewart, C., Hunkeler, E., Lynch, F. L., Carrell, D., & Beck, A. (2017). INCIDENCE AND PRESENTATION OF FIRST-EPISODE PSYCHOSIS IN A POPULATION-BASED SAMPLE. *Psychiatric Services (Washington, D.C.)*, *68*(5), 456–461. https://doi.org/10.1176/appi.ps.201600257

Simpson, R., Devenyi, G. A., Jezzard, P., Hennessy, T. J., & Near, J. (2017a). Advanced processing and simulation of MRS data using the FID appliance (FID-A)—An open source, MATLAB-based toolkit. *Magnetic Resonance in Medicine*, *77*(1), 23–33. https://doi.org/10.1002/mrm.26091

Simpson, R., Devenyi, G. A., Jezzard, P., Hennessy, T. J., & Near, J. (2017b). Advanced processing and simulation of MRS data using the FID appliance (FID-A)—An open source, MATLAB-based toolkit. *Magnetic Resonance in Medicine*, *77*(1), 23–33. https://doi.org/10.1002/mrm.26091

Sims, P. A. (n.d.). *Is Faith Delusion*.

Smeets, F., Lataster, T., Dominguez, M.-G., Hommes, J., Lieb, R., Wittchen, H.-U., & van Os, J. (2012). Evidence That Onset of Psychosis in the Population Reflects Early Hallucinatory Experiences That Through Environmental Risks and Affective Dysregulation Become Complicated by Delusions. *Schizophrenia Bulletin*, *38*(3), 531–542. https://doi.org/10.1093/schbul/sbq117

Smigielski, L., Jagannath, V., Rössler, W., Walitza, S., & Grünblatt, E. (2020). Epigenetic mechanisms in schizophrenia and other psychotic disorders: A systematic review of empirical human findings. *Molecular Psychiatry*, *25*(8), 1718–1748. https://doi.org/10.1038/s41380-019-0601-3

Smith, M. J., Thirthalli, J., Abdallah, A. B., Murray, R. M., & Cottler, L. B. (2009). Prevalence of Psychotic Symptoms in Substance Users: A Comparison across Substances. *Comprehensive Psychiatry*, *50*(3), 245–250. https://doi.org/10.1016/j.comppsych.2008.07.009

Smucny, J., Carter, C. S., & Maddock, R. J. (2022). Magnetic resonance spectroscopic evidence of increased choline in the dorsolateral prefrontal and visual cortices in recent onset schizophrenia. *Neuroscience Letters*, *770*, 136410. https://doi.org/10.1016/j.neulet.2021.136410

Social Desirability Bias—An overview | ScienceDirect Topics. (n.d.). Retrieved July 3, 2024, from https://www.sciencedirect.com/topics/psychology/social-desirability-bias

Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., Kim, J. H., Kim, J. Y., Carvalho, A. F., Seeman, M. V., Correll, C. U., & Fusar-Poli, P. (2022). Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*, *27*(1), 281–295. https://doi.org/10.1038/s41380-021-01161-7

Soneson, E., Russo, D., Stochl, J., Heslin, M., Galante, J., Knight, C., Grey, N., Hodgekins, J., French, P., Fowler, D., Lafortune, L., Byford, S., Jones, P. B., & Perez, J. (2020). Psychological interventions for people with psychotic experiences: A systematic review and meta-analysis of controlled and uncontrolled effectiveness and economic studies. *The Australian and New Zealand Journal of Psychiatry*, *54*(7), 673–695. https://doi.org/10.1177/0004867420913118

Song, X., Chen, X., Yuksel, C., Yuan, J., Pizzagalli, D. A., Forester, B., Öngür, D., & Du, F. (2021). Bioenergetics and abnormal functional connectivity in psychotic disorders. *Molecular Psychiatry*, *26*(6), 2483–2492. https://doi.org/10.1038/s41380-020-00993-z

Sözeri-Varma, G., Kalkan-Oğuzhanoglu, N., Efe, M., Kıroglu, Y., & Duman, T. (2013). Neurochemical metabolites in prefrontal cortex in patients with mild/moderate levels in first-episode depression. *Neuropsychiatric Disease and Treatment*, *9*, 1053–1059. https://doi.org/10.2147/NDT.S42627

Spiteri-Staines, A. E., Yung, A. R., Lin, A., Hartmann, J. A., Amminger, P., McGorry, P. D., Thompson, A., Wood, S. J., & Nelson, B. (2024). Non-psychotic Outcomes in Young People at Ultra-High Risk of Developing a Psychotic Disorder: A Long-Term Follow-up Study. *Schizophrenia Bulletin*, sbae005. https://doi.org/10.1093/schbul/sbae005

Squarcina, L., Stanley, J. A., Bellani, M., Altamura, C. A., & Brambilla, P. (2017). A review of altered biochemistry in the anterior cingulate cortex of first-episode psychosis. *Epidemiology and Psychiatric Sciences*, *26*(2), 122–128. https://doi.org/10.1017/S2045796016000895

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), 3297–3308. 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

Stainton, A., Chisholm, K., Woodall, T., Hallett, D., Reniers, R. L. E. P., Lin, A., & Wood, S. J. (2021). Gender differences in the experience of psychotic-like experiences and their associated factors: A study of adolescents from the general population. *Schizophrenia Research*, *228*, 410–416. https://doi.org/10.1016/j.schres.2021.01.008

Stark, T., Di Martino, S., Drago, F., Wotjak, C. T., & Micale, V. (2021). Phytocannabinoids and schizophrenia: Focus on adolescence as a critical window of enhanced vulnerability and opportunity for treatment. *Pharmacological Research*, *174*, 105938. https://doi.org/10.1016/j.phrs.2021.105938

Steen, R. G., Hamer, R. M., & Lieberman, J. A. (2005). Measurement of Brain Metabolites by 1H Magnetic Resonance Spectroscopy in Patients with Schizophrenia: A Systematic Review and Meta-Analysis. *Neuropsychopharmacology*, *30*(11), 1949–1962. https://doi.org/10.1038/sj.npp.1300850

Stefanis, N. C., Delespaul, P., Henquet, C., Bakoula, C., Stefanis, C. N., & Van Os, J. (2004). Early adolescent cannabis exposure and positive and negative dimensions of psychosis. *Addiction*, *99*(10), 1333–1341. https://doi.org/10.1111/j.1360-0443.2004.00806.x

Stefanis, N. C., Hanssen, M., Smirnis, N. K., Avramopoulos, D. A., Evdokimidis, I. K., Stefanis, C. N., Verdoux, H., & Van Os, J. (2002). Evidence that three dimensions of psychosis have a distribution in the general population. *Psychological Medicine*, *32*(2), 347–358. https://doi.org/10.1017/s0033291701005141

Stein, A., Zhu, C., Du, F., & Öngür, D. (2023). Magnetic Resonance Spectroscopy Studies of Brain Energy Metabolism in Schizophrenia: Progression from Prodrome to Chronic Psychosis. *Current Psychiatry Reports*, *25*(11), 659–669. https://doi.org/10.1007/s11920-023-01457-1

Sterne, J.A.C., Hernán, M.A., McAleenan, A., Reeves, B.C., Higgins, J.P.T. Chapter 25: Assessing risk of bias in a non-randomized study. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.4 (updated August 2023). Cochrane, 2023

Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., Lau, J., Carpenter, J., Rücker, G., Harbord, R. M., Schmid, C. H., Tetzlaff, J., Deeks, J. J., Peters, J., Macaskill, P., Schwarzer, G., Duval, S., Altman, D. G., Moher, D., & Higgins, J. P. T. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*, *343*, d4002. https://doi.org/10.1136/bmj.d4002

Stone, J. M., Day, F., Tsagaraki, H., Valli, I., McLean, M. A., Lythgoe, D. J., O'Gorman, R. L., Barker, G. J., McGuire, P. K., & OASIS. (2009). Glutamate dysfunction in people with prodromal symptoms of psychosis: Relationship to gray matter volume. *Biological Psychiatry*, *66*(6), 533–539. https://doi.org/10.1016/j.biopsych.2009.05.006

Stone, J. M., Fisher, H. L., Major, B., Chisholm, B., Woolley, J., Lawrence, J., Rahaman, N., Joyce, J., Hinton, M., Johnson, S., & Young, A. H. (2014). Cannabis use and first-episode psychosis: Relationship with manic and psychotic symptoms, and with age at presentation. *Psychological Medicine*, *44*(3), 499–506. https://doi.org/10.1017/S0033291713000883

Stone, J. M., Howes, O. D., Egerton, A., Kambeitz, J., Allen, P., Lythgoe, D. J., O'Gorman, R. L., McLean, M. A., Barker, G. J., & McGuire, P. (2010). Altered Relationship Between Hippocampal Glutamate Levels and Striatal Dopamine Function in Subjects at Ultra High Risk of Psychosis. *Biological Psychiatry*, *68*(7), 599–602. https://doi.org/10.1016/j.biopsych.2010.05.034

Stopponi, S., Soverchia, L., Ubaldi, M., Cippitelli, A., Serpelloni, G., & Ciccocioppo, R. (2014). Chronic THC during adolescence increases the vulnerability to stress-induced relapse to heroin seeking in adult rats. *European Neuropsychopharmacology*, *24*(7), 1037–1045. https://doi.org/10.1016/j.euroneuro.2013.12.012

Storr, C. L., Wagner, F. A., Chen, C.-Y., & Anthony, J. C. (2011). Childhood predictors of first chance to use and use of cannabis by young adulthood. *Drug and Alcohol Dependence*, *117*(1), 7–15. https://doi.org/10.1016/j.drugalcdep.2010.12.023

Strauss, G. P., Raugh, I. M., Mittal, V. A., Gibb, B. E., & Coles, M. E. (2018). Bullying victimization and perpetration in a community sample of youth with psychotic like experiences. *Schizophrenia Research*, *195*, 534–536. https://doi.org/10.1016/j.schres.2017.08.056

Streck, J. M., Hughes, J. R., Klemperer, E. M., Howard, A. B., & Budney, A. J. (2019). Modes of Cannabis Use: A Secondary Analysis of an Intensive Longitudinal Natural History Study. *Addictive Behaviors*, *98*, 106033. https://doi.org/10.1016/j.addbeh.2019.106033

Subramaniam, P., Prescot, A., McGlade, E., Renshaw, P., & Yurgelun-Todd, D. (2022). Examination of Gamma-Aminobutyric Acid and Glutamate-Glutamine Levels in Association with Impulsive Behavior in Adolescent Marijuana Users. *Drug and Alcohol Dependence*, *233*, 109326. https://doi.org/10.1016/j.drugalcdep.2022.109326

Sugranyes, G., de la Serna, E., Ilzarbe, D., Pariente, J. C., Borras, R., Romero, S., Rosa, M., Baeza, I., Moreno, M. D., Bernardo, M., Vieta, E., & Castro-Fornieles, J. (2021). Brain structural trajectories in youth at familial risk for schizophrenia or bipolar disorder according to development of psychosis spectrum symptoms. *Journal of Child Psychology and Psychiatry*, *62*(6), 780–789. https://doi.org/10.1111/jcpp.13321

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. *American Journal of Psychiatry*, *177*(4), 308–317. https://doi.org/10.1176/appi.ajp.2019.19060654

Sunderland, M., Forbes, M. K., Mewton, L., Baillie, A., Carragher, N., Lynch, S. J., Batterham, P. J., Calear, A. L., Chapman, C., Newton, N. C., Teesson, M., & Slade, T. (2021). The structure of psychopathology and association with poor sleep, self-harm, suicidality, risky sexual behavior, and low self-esteem in a population sample of adolescents. *Development and Psychopathology*, *33*(4), 1208–1219. https://doi.org/10.1017/S0954579420000437

Tajima-Pozo, K., de Castro Oller, M. J., Lewczuk, A., & Montañes-Rada, F. (2015). Understanding the direct and indirect costs of patients with schizophrenia. *F1000Research*, *4*, 182. https://doi.org/10.12688/f1000research.6699.2

Tang, H., Shen, N., Jin, H., Liu, D., Miao, X., & Zhu, L.-Q. (2013). GSK-3β Polymorphism Discriminates Bipolar Disorder and Schizophrenia: A Systematic Meta-Analysis. *Molecular Neurobiology*, *48*(3), 404–411. https://doi.org/10.1007/s12035-013-8414-x

Tannous, J., Cao, B., Stanley, J. A., Zunta-Soares, G. B., Mwangi, B., Sanches, M., & Soares, J. C. (2021). Altered neurochemistry in the anterior white matter of bipolar children and adolescents: A multivoxel 1H MRS study. *Molecular Psychiatry*, *26*(8), 4117–4126. https://doi.org/10.1038/s41380-020-00927-9

Tarasov, V. V., Svistunov, A. A., Chubarev, V. N., Sologova, S. S., Mukhortova, P., Levushkin, D., Somasundaram, S. G., Kirkland, C. E., Bachurin, S. O., & Aliev, G. (2020). Alterations of Astrocytes in the Context of Schizophrenic Dementia. *Frontiers in Pharmacology*, *10*, 1612. https://doi.org/10.3389/fphar.2019.01612

Tarokh, L., Hamann, C., & Schimmelmann, B. G. (2014). Sleep in child and adolescent psychiatry: Overlooked and underappreciated. *European Child & Adolescent Psychiatry*, *23*(6), 369–372. https://doi.org/10.1007/s00787-014-0554-7

Tarter, R. E., Vanyukov, M., Kirisci, L., Reynolds, M., & Clark, D. B. (2006). Predictors of Marijuana Use in Adolescents Before and After Licit Drug Use: Examination of the Gateway Hypothesis. *American Journal of Psychiatry*, *163*(12), 2134–2140. https://doi.org/10.1176/ajp.2006.163.12.2134

Tayebati, S. K., & Amenta, F. (2013). Choline-containing phospholipids: Relevance to brain functional pathways. *Clinical Chemistry and Laboratory Medicine*, *51*(3), 513–521. https://doi.org/10.1515/cclm-2012-0559

Taylor, D. R., Poulton, R., Moffitt, T. E., Ramankutty, P., & Sears, M. R. (2000). The respiratory effects of cannabis dependence in young adults. *Addiction*, *95*(11), 1669–1677. https://doi.org/10.1046/j.1360-0443.2000.951116697.x

Taylor, M., Collin, S. M., Munafò, M. R., MacLeod, J., Hickman, M., & Heron, J. (2017). Patterns of cannabis use during adolescence and their association with harmful substance use behaviour: Findings from a UK birth cohort. *J Epidemiol Community Health*, *71*(8), 764–770. https://doi.org/10.1136/jech-2016-208503

Taylor, M. J., Freeman, D., Lundström, S., Larsson, H., & Ronald, A. (2022). Heritability of Psychotic Experiences in Adolescents and Interaction With Environmental Risk. *JAMA Psychiatry*, *79*(9), 889–897. https://doi.org/10.1001/jamapsychiatry.2022.1947

Taylor, M. J., Godlewska, B. R., Norbury, R., Selvaraj, S., Near, J., & Cowen, P. J. (2012). Early increase in marker of neuronal integrity with antidepressant treatment of major depression: 1H-magnetic resonance spectroscopy of N-acetyl-aspartate. *International Journal of Neuropsychopharmacology*, *15*(10), 1541–1546. https://doi.org/10.1017/S1461145712000272

Tebartz van Elst, L., Valerius, G., Büchert, M., Thiel, T., Rüsch, N., Bubl, E., Hennig, J., Ebert, D., & Olbrich, H. M. (2005). Increased Prefrontal and Hippocampal Glutamate Concentration in Schizophrenia: Evidence from a Magnetic Resonance Spectroscopy Study. *Biological Psychiatry*, *58*(9), 724–730. https://doi.org/10.1016/j.biopsych.2005.04.041

THC Dosage Calculator For THC Oil, THC Vapes, and More. (2019, December 4). Strain Genie. https://straingenie.com/thc-dosage-calculator/

The International Impacts of Alcohol Use Disorder and Nicotine and Tobacco. (n.d.). Oxford Academic. Retrieved July 21, 2024, from https://academic.oup.com/journals/pages/international-impacts-of-alcohol

Théberge, J., Al-Semaan, Y., Drost, D. J., Malla, A. K., Neufeld, R. W. J., Bartha, R., Manchanda, R., Menon, R., Densmore, M., Schaefer, B., & Williamson, P. C. (2004). Duration of untreated psychosis vs. N-acetylaspartate and choline in first episode schizophrenia: A 1H magnetic resonance spectroscopy study at 4.0 Tesla. *Psychiatry Research*, *131*(2), 107–114. https://doi.org/10.1016/j.pscychresns.2004.04.002

Thomas, V. L., Chavez, M., Browne, E. N., & Minnis, A. M. (2020). Instagram as a tool for study engagement and community building among adolescents: A social media pilot study. *Digital Health*, *6*, 2055207620904548. https://doi.org/10.1177/2055207620904548

Thurston, J. H., Sherman, W. R., Hauhart, R. E., & Kloepper, R. F. (1989). myo-Inositol: A Newly Identified Nonnitrogenous Osmoregulatory Molecule in Mammalian Brain. *Pediatric Research*, *26*(5), 482–485. https://doi.org/10.1203/00006450-198911000-00024

Tibbo, P. G., Bernier, D., Hanstock, C. C., Seres, P., Lakusta, B., & Purdon, S. E. (2013). 3-T proton magnetic spectroscopy in unmedicated first episode psychosis: A focus on creatine. *Magnetic Resonance in Medicine*, *69*(3), 613–620. https://doi.org/10.1002/mrm.24291

Tkáč, I., Deelchand, D., Dreher, W., Hetherington, H., Kreis, R., Kumaragamage, C., Považan, M., Spielman, D. M., Strasser, B., & de Graaf, R. A. (2021). Water and lipid suppression techniques for advanced 1H MRS and MRSI of the human brain: Experts' consensus recommendations. *NMR in Biomedicine*, *34*(5), e4459. https://doi.org/10.1002/nbm.4459

Tomko, R. L., Jones, J. L., Gilmore, A. K., Brady, K. T., Back, S. E., & Gray, K. M. (2018). N-acetylcysteine: A potential treatment for substance use disorders. *Current Psychiatry*, *17*(6), 30–55.

Tompson, A. (2015). *Epigenetic predictors of psychotic symptoms in adolescence* [Thesis, Deakin University]. https://dro.deakin.edu.au/articles/thesis/Epigenetic_predictors_of_psychotic_symptoms_in_adolescence/21107674/1

Tor, J., Dolz, M., Sintes, A., Muñoz, D., Pardo, M., de la Serna, E., Puig, O., Sugranyes, G., & Baeza, I. (2018). Clinical high risk for psychosis in children and adolescents: A systematic review. *European Child & Adolescent Psychiatry*, *27*(6), 683–700. https://doi.org/10.1007/s00787-017-1046-3

Trotta, G., Rodriguez, V., Quattrone, D., Spinazzola, E., Tripoli, G., Gayer-Anderson, C., Freeman, T. P., Jongsma, H. E., Sideli, L., Aas, M., Stilo, S. A., La Cascia, C., Ferraro, L., La Barbera, D., Lasalvia, A., Tosato, S., Tarricone, I., D'Andrea, G., Tortelli, A., … EU-GEI WP2 Group. (2023). Cannabis use as a potential mediator between childhood adversity and first-episode psychosis: Results from the EU-GEI case-control study. *Psychological Medicine*, *53*(15), 7375–7384. https://doi.org/10.1017/S0033291723000995

Uno, Y., & Coyle, J. T. (2019). Glutamate hypothesis in schizophrenia. *Psychiatry and Clinical Neurosciences*, *73*(5), 204–215. https://doi.org/10.1111/pcn.12823

Unterrassner, L. (2018). Subtypes of Psychotic-Like Experiences and Their Significance for Mental Health. In *Psychosis—Biopsychosocial and Relational Perspectives*. IntechOpen. https://doi.org/10.5772/intechopen.78691

Valkenborghs, S. R., Hillman, C. H., Al-Iedani, O., Nilsson, M., Smith, J. J., Leahy, A. A., Harries, S. K., Ramadan, S., & Lubans, D. R. (2022). Effect of high-intensity

interval training on hippocampal metabolism in older adolescents. *Psychophysiology*, *59*(11), e14090. https://doi.org/10.1111/psyp.14090

Valmaggia, L. R., Day, F. L., Jones, C., Bissoli, S., Pugh, C., Hall, D., Bhattacharyya, S., Howes, O., Stone, J., Fusar-Poli, P., Byrne, M., & McGuire, P. K. (2014). Cannabis use and transition to psychosis in people at ultra-high risk. *Psychological Medicine*, *44*(12), 2503–2512. https://doi.org/10.1017/S0033291714000117

van Gastel, W. A., Wigman, J. T. W., Monshouwer, K., Kahn, R. S., van Os, J., Boks, M. P. M., & Vollebergh, W. A. M. (2012). Cannabis use and subclinical positive psychotic experiences in early adolescence: Findings from a Dutch survey. *Addiction*, *107*(2), 381–387. https://doi.org/10.1111/j.1360-0443.2011.03626.x

Van Laere, K., Goffin, K., Bormans, G., Casteels, C., Mortelmans, L., de Hoon, J., Grachev, I., Vandenbulcke, M., & Pieters, G. (2009). Relationship of Type 1 Cannabinoid Receptor Availability in the Human Brain to Novelty-Seeking Temperament. *Archives of General Psychiatry*, *66*(2), 196–204. https://doi.org/10.1001/archgenpsychiatry.2008.530

van Os, J. (2003). Is there a continuum of psychotic experiences in the general population? *Epidemiologia E Psichiatria Sociale*, *12*(4), 242–252. https://doi.org/10.1017/s1121189x00003067

van Os, J., & Guloksuz, S. (2017). A critique of the "ultra-high risk" and "transition" paradigm. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *16*(2), 200–206. https://doi.org/10.1002/wps.20423

van Os, J., & Linscott, R. J. (2012). Introduction: The Extended Psychosis Phenotype—Relationship With Schizophrenia and With Ultrahigh Risk Status for Psychosis. *Schizophrenia Bulletin*, *38*(2), 227–230. https://doi.org/10.1093/schbul/sbr188

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

van Veelen, N. M. J., Vink, M., Ramsey, N. F., & Kahn, R. S. (2010). Left dorsolateral prefrontal cortex dysfunction in medication-naive schizophrenia. *Schizophrenia Research*, *123*(1), 22–29. https://doi.org/10.1016/j.schres.2010.07.004

van Winkel, R. & Genetic Risk and Outcome of Psychosis (GROUP) Investigators. (2011). Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: Sibling analysis and proband follow-up. *Archives of General Psychiatry*, *68*(2), 148–157. https://doi.org/10.1001/archgenpsychiatry.2010.152

Vassos, E., Pedersen, C. B., Murray, R. M., Collier, D. A., & Lewis, C. M. (2012). Meta-Analysis of the Association of Urbanicity With Schizophrenia. *Schizophrenia Bulletin*, *38*(6), 1118–1123. https://doi.org/10.1093/schbul/sbs096

Vawter, M. P., Hamzeh, A. R., Muradyan, E., Civelli, O., Abbott, G. W., & Alachkar, A. (2019). Association of Myoinositol Transporters with Schizophrenia and Bipolar

Disorder: Evidence from Human and Animal Studies. *Molecular Neuropsychiatry*, *5*(4), 200–211. https://doi.org/10.1159/000501125

Vinkers, C. H., Van Gastel, W. A., Schubart, C. D., Van Eijk, K. R., Luykx, J. J., Van Winkel, R., Joëls, M., Ophoff, R. A., Boks, M. P. M., Bruggeman, R., Cahn, W., de Haan, L., Kahn, R. S., Meijer, C. J., Myin-Germeys, I., van Os, J., & Wiersma, D. (2013). The effect of childhood maltreatment and cannabis use on adult psychotic symptoms is modified by the *COMT* Val158Met polymorphism. *Schizophrenia Research*, *150*(1), 303–311. https://doi.org/10.1016/j.schres.2013.07.020

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic Advances from the Brain Disease Model of Addiction. *The New England Journal of Medicine*, *374*(4), 363–371. https://doi.org/10.1056/NEJMra1511480

Volkow, N. D., Swanson, J. M., Evins, A. E., DeLisi, L. E., Meier, M. H., Gonzalez, R., Bloomfield, M. A. P., Curran, H. V., & Baler, R. (2016). Effects of Cannabis Use on Human Behavior, Including Cognition, Motivation, and Psychosis: A Review. *JAMA Psychiatry*, *73*(3), 292–297. https://doi.org/10.1001/jamapsychiatry.2015.3278

Vollenweider, F. X., Leenders, K. L., Scharfetter, C., Antonini, A., Maguire, P., Missimer, J., & Angst, J. (1997). Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [18F]fluorodeoxyglucose (FDG). *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *7*(1), 9–24. https://doi.org/10.1016/s0924-977x(96)00039-9

Wainberg, M., Jacobs, G. R., di Forti, M., & Tripathy, S. J. (2021). Cannabis, schizophrenia genetic risk, and psychotic experiences: A cross-sectional study of 109,308 participants from the UK Biobank. *Translational Psychiatry*, *11*(1), 1–9. https://doi.org/10.1038/s41398-021-01330-w

Wang, G. S. (2017). Pediatric Concerns Due to Expanded Cannabis Use: Unintended Consequences of Legalization. *Journal of Medical Toxicology*, *13*(1), 99–105. https://doi.org/10.1007/s13181-016-0552-x

Wang, W. W., Zhou, Q. X., Ma, L., Feng, S. H., Yang, Z. R., Sun, F., & Zhan, S. (2022). [Introduction of a tool to assess Risk of Bias in Non-randomized Studies-of Environmental Exposure (ROBINS-E)]. *Zhonghua Liu Xing Bing Xue Za Zhi = Zhonghua Liuxingbingxue Zazhi*, *43*(1), 98–104. https://doi.org/10.3760/cma.j.cn112338-20201112-01324

Wang, X., Chang, Z., & Wang, R. (2023). Opposite effects of positive and negative symptoms on resting-state brain networks in schizophrenia. *Communications Biology*, *6*(1), 1–12. https://doi.org/10.1038/s42003-023-04637-0

Wang, Y., Xiao, Y., & Xie, W. (2020). Metabolite abnormalities in psychosis risk: A meta-analysis of proton magnetic resonance spectroscopy studies. *Asian Journal of Psychiatry*, *54*, 102220. https://doi.org/10.1016/j.ajp.2020.102220

Waters, F., & Stephane, M. (2014). *The Assessment of Psychosis: A Reference Book and Rating Scales for Research and Practice*. Routledge.

Watkins, C. C., & Andrews, S. R. (2016). Clinical studies of neuroinflammatory mechanisms in schizophrenia. *Schizophrenia Research*, *176*(1), 14–22. https://doi.org/10.1016/j.schres.2015.07.018

Watts, J. J., Garani, R., Da Silva, T., Lalang, N., Chavez, S., & Mizrahi, R. (2020). Evidence That Cannabis Exposure, Abuse, and Dependence Are Related to Glutamate Metabolism and Glial Function in the Anterior Cingulate Cortex: A 1H-Magnetic Resonance Spectroscopy Study. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/fpsyt.2020.00764

Weed, P. F., Filipeanu, C. M., Ketchum, M. J., & Winsauer, P. J. (2016). Chronic Δ9-Tetrahydrocannabinol during Adolescence Differentially Modulates Striatal CB1 Receptor Expression and the Acute and Chronic Effects on Learning in Adult Rats. *Journal of Pharmacology and Experimental Therapeutics*, *356*(1), 20–31. https://doi.org/10.1124/jpet.115.227181

Welham, J., Scott, J., Williams, G., Najman, J., Bor, W., O'Callaghan, M., & McGrath, J. (2009). Emotional and behavioural antecedents of young adults who screen positive for non-affective psychosis: A 21-year birth cohort study. *Psychological Medicine*, *39*(4), 625–634. https://doi.org/10.1017/S0033291708003760

Werbeloff, N., Drukker, M., Dohrenwend, B. P., Levav, I., Yoffe, R., van Os, J., Davidson, M., & Weiser, M. (2012). Self-reported attenuated psychotic symptoms as forerunners of severe mental disorders later in life. *Archives of General Psychiatry*, *69*(5), 467–475. https://doi.org/10.1001/archgenpsychiatry.2011.1580

Weygand, J., Fuller, C. D., Ibbott, G. S., Mohamed, A. S. R., Ding, Y., Yang, J., Hwang, K.-P., & Wang, J. (2016). Spatial Precision in Magnetic Resonance Imaging–Guided Radiation Therapy: The Role of Geometric Distortion. *International Journal of Radiation Oncology*Biology*Physics*, *95*(4), 1304–1316. https://doi.org/10.1016/j.ijrobp.2016.02.059

Whitehurst, T. S., Osugo, M., Townsend, L., Shatalina, E., Vava, R., Onwordi, E. C., & Howes, O. (2020). Proton Magnetic Resonance Spectroscopy of N-acetyl Aspartate in Chronic Schizophrenia, First Episode of Psychosis and High-Risk of Psychosis: A Systematic Review and Meta-Analysis. *Neuroscience & Biobehavioral Reviews*, *119*, 255–267. https://doi.org/10.1016/j.neubiorev.2020.10.001

Wied, C. C. G., & Jansen, L. M. C. (2002). The stress-vulnerability hypothesis in psychotic disorders: Focus on the stress response systems. *Current Psychiatry Reports*, *4*(3), 166–170. https://doi.org/10.1007/s11920-002-0022-9

Wiers, C. E., Shokri-Kojori, E., Wong, C. T., Abi-Dargham, A., Demiral, Ş. B., Tomasi, D., Wang, G.-J., & Volkow, N. D. (2016). Cannabis Abusers Show Hypofrontality and Blunted Brain Responses to a Stimulant Challenge in Females but not in Males. *Neuropsychopharmacology*, *41*(10), 2596–2605. https://doi.org/10.1038/npp.2016.67

Wijtenburg, S. A., & Knight-Scott, J. (2009). The impact of SNR on the reliability of LCmodel and QUEST quantitation in 1H-MRS. *Proceedings of the International Society for Magnetic Resonance in Medicine*, *17*, 2401.

Willemsen, J., & Verhaeghe, P. (2012). Psychopathy and internalizing psychopathology. *International Journal of Law and Psychiatry*, *35*(4), 269–275. https://doi.org/10.1016/j.ijlp.2012.04.004

Wilson, M., Andronesi, O., Barker, P. B., Bartha, R., Bizzi, A., Bolan, P. J., Brindle, K. M., Choi, I.-Y., Cudalbu, C., Dydak, U., Emir, U. E., Gonzalez, R. G., Gruber, S., Gruetter, R., Gupta, R. K., Heerschap, A., Henning, A., Hetherington, H. P., Huppi, P. S., … Howe, F. A. (2019). A Methodological Consensus on Clinical Proton MR Spectroscopy of the Brain: Review and Recommendations. *Magnetic Resonance in Medicine*, *82*(2), 527–550. https://doi.org/10.1002/mrm.27742

Wolfson, A. R., & Carskadon, M. A. (1998). Sleep schedules and daytime functioning in adolescents. *Child Development*, *69*(4), 875–887.

Woo, D.-C., Choi, C.-B., Kim, S.-S., Rhim, H.-S., Jahng, G.-H., Baek, H.-M., Nalcioglu, O., & Choe, B.-Y. (2009). Development of a QA phantom and protocol for proton magnetic resonance spectroscopy. *Concepts in Magnetic Resonance Part B: Magnetic Resonance Engineering*, *35B*(3), 168–179. https://doi.org/10.1002/cmr.b.20144

Woodcock, E. A., Hillmer, A. T., Mason, G. F., & Cosgrove, K. P. (2019). Imaging Biomarkers of the Neuroimmune System among Substance Use Disorders: A Systematic Review. *Molecular Neuropsychiatry*, *5*(3), 125–146. https://doi.org/10.1159/000499621

Xin, L., Mekle, R., Fournier, M., Baumann, P. S., Ferrari, C., Alameda, L., Jenni, R., Lu, H., Schaller, B., Cuenod, M., Conus, P., Gruetter, R., & Do, K. Q. (2016). Genetic Polymorphism Associated Prefrontal Glutathione and Its Coupling With Brain Glutamate and Peripheral Redox Status in Early Psychosis. *Schizophrenia Bulletin*, *42*(5), 1185–1196. https://doi.org/10.1093/schbul/sbw038

Xu, K., Krystal, J. H., Ning, Y., Chen, D. C., He, H., Wang, D., Ke, X., Zhang, X., Ding, Y., Liu, Y., Gueorguieva, R., Wang, Z., Limoncelli, D., Pietrzak, R. H., Petrakis, I. L., Zhang, X., & Fan, N. (2015). Preliminary analysis of positive and negative syndrome scale in ketamine-associated psychosis in comparison with schizophrenia. *Journal of Psychiatric Research*, *61*, 64–72. https://doi.org/10.1016/j.jpsychires.2014.12.012

Yamasaki, S., Usami, S., Sasaki, R., Koike, S., Ando, S., Kitagawa, Y., Matamura, M., Fukushima, M., Yonehara, H., Foo, J. C., Nishida, A., & Sasaki, T. (2018). The association between changes in depression/anxiety and trajectories of psychotic-like experiences over a year in adolescence. *Schizophrenia Research*, *195*, 149–153. https://doi.org/10.1016/j.schres.2017.10.019

Yang, A. C., & Tsai, S.-J. (2017). New Targets for Schizophrenia Treatment beyond the Dopamine Hypothesis. *International Journal of Molecular Sciences*, *18*(8), Article 8. https://doi.org/10.3390/ijms18081689

Yang, Q., & Zhou, J. (2019). Neuroinflammation in the central nervous system: Symphony of glial cells. *Glia*, *67*(6), 1017–1035. https://doi.org/10.1002/glia.23571

Yang, Y. S., Smucny, J., Zhang, H., & Maddock, R. J. (2023). Meta-analytic evidence of elevated choline, reduced N-acetylaspartate, and normal creatine in schizophrenia and their moderation by measurement quality, echo time, and medication status. *NeuroImage: Clinical*, *39*, 103461.

Yildiz-Yesiloglu, A., & Ankerst, D. P. (2006). Neurochemical alterations of the brain in bipolar disorder and their implications for pathophysiology: A systematic review of the in vivo proton magnetic resonance spectroscopy findings. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *30*(6), 969–995. https://doi.org/10.1016/j.pnpbp.2006.03.012

Yoon, S., Shi, Y., Yoon, D., Pei, F., Schoppe-Sullivan, S., & Snyder, S. M. (2020). Child Maltreatment, Fathers, and Adolescent Alcohol and Marijuana Use Trajectories. *Substance Use & Misuse*, *55*(5), 721–733. https://doi.org/10.1080/10826084.2019.1701033

You, H., Shi, J., Huang, F., Wei, Z., Jones, G., Du, W., & Hua, J. (2023). Advances in Genetics and Epigenetics of Developmental Coordination Disorder in Children. *Brain Sciences*, *13*(6), Article 6. https://doi.org/10.3390/brainsci13060940

Yu, W., & Greenberg, M. L. (2016). Inositol depletion, GSK3 inhibition and bipolar disorder. *Future Neurology*, *11*(2), 135–148. https://doi.org/10.2217/fnl-2016-0003

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

Yuksel, C., Chen, X., Chouinard, V.-A., Nickerson, L. D., Gardner, M., Cohen, T., Öngür, D., & Du, F. (2021). Abnormal Brain Bioenergetics in First-Episode Psychosis. *Schizophrenia Bulletin Open*, *2*(1), sgaa073. https://doi.org/10.1093/schizbullopen/sgaa073

Yung, A. R., & McGorry, P. D. (1996). The Prodromal Phase of First-episode Psychosis: Past and Current Conceptualizations. *Schizophrenia Bulletin*, *22*(2), 353–370. https://doi.org/10.1093/schbul/22.2.353

Yung, A. R., Phillips, L. J., McGorry, P. D., McFarlane, C. A., Francey, S., Harrigan, S., Patton, G. C., & Jackson, H. J. (1998). Prediction of psychosis: A step towards indicated prevention of schizophrenia. *British Journal of Psychiatry*, *172*(S33), 14–20. https://doi.org/10.1192/S0007125000297602

Yung, A. R., Stanford, C., Cosgrave, E., Killackey, E., Phillips, L., Nelson, B., & McGorry, P. D. (2006). Testing the Ultra High Risk (prodromal) criteria for the prediction of psychosis in a clinical sample of young people. *Schizophrenia Research*, *84*(1), 57–66. https://doi.org/10.1016/j.schres.2006.03.014

Yung, A. R., Yuen, H. P., Berger, G., Francey, S., Hung, T.-C., Nelson, B., Phillips, L., & McGorry, P. (2007). Declining Transition Rate in Ultra High Risk (Prodromal) Services: Dilution or Reduction of Risk? *Schizophrenia Bulletin*, *33*(3), 673–681. https://doi.org/10.1093/schbul/sbm015

Zádor, F., Joca, S., Nagy-Grócz, G., Dvorácskó, S., Szűcs, E., Tömböly, C., Benyhe, S., & Vécsei, L. (2021). Pro-Inflammatory Cytokines: Potential Links between the Endocannabinoid System and the Kynurenine Pathway in Depression. *International Journal of Molecular Sciences*, *22*(11). https://doi.org/10.3390/ijms22115903

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

Zaman, T., Malowney, M., Knight, J., & Boyd, J. W. (2015). Co-Occurrence of Substance-Related and Other Mental Health Disorders Among Adolescent Cannabis Users. *Journal of Addiction Medicine*, *9*(4), 317. https://doi.org/10.1097/ADM.0000000000000138

Zamberletti, E., Gabaglio, M., Prini, P., Rubino, T., & Parolaro, D. (2015). Cortical neuroinflammation contributes to long-term cognitive dysfunctions following adolescent delta-9-tetrahydrocannabinol treatment in female rats. *European Neuropsychopharmacology*, *25*(12), 2404–2415. https://doi.org/10.1016/j.euroneuro.2015.09.021

Zammit, S., Kounali, D., Cannon, M., David, A. S., Gunnell, D., Heron, J., Jones, P. B., Lewis, S., Sullivan, S., Wolke, D., & Lewis, G. (2013). Psychotic Experiences and Psychotic Disorders at Age 18 in Relation to Psychotic Experiences at Age 12 in a Longitudinal Population-Based Cohort Study. *American Journal of Psychiatry*, *170*(7), 742–750. https://doi.org/10.1176/appi.ajp.2013.12060768

Zammit, S., Owen, M. J., Evans, J., Heron, J., & Lewis, G. (2011). Cannabis, COMT and psychotic experiences. *The British Journal of Psychiatry*, *199*(5), 380–385. https://doi.org/10.1192/bjp.bp.111.091421

Zarghami, T. S., Zeidman, P., Razi, A., Bahrami, F., & Hossein-Zadeh, G.-A. (2023). Dysconnection and cognition in schizophrenia: A spectral dynamic causal modeling study. *Human Brain Mapping*, *44*(7), 2873–2896. https://doi.org/10.1002/hbm.26251

Zavos, H. M. S., Freeman, D., Haworth, C. M. A., McGuire, P., Plomin, R., Cardno, A. G., & Ronald, A. (2014). Consistent Etiology of Severe, Frequent Psychotic Experiences and Milder, Less Frequent Manifestations: A Twin Study of Specific Psychotic Experiences in Adolescence. *JAMA Psychiatry*, *71*(9), 1049–1057. https://doi.org/10.1001/jamapsychiatry.2014.994

Zhang, T., Tang, X., Li, H., Woodberry, K. A., Kline, E. R., Xu, L., Cui, H., Tang, Y., Wei, Y., Li, C., Hui, L., Niznikiewicz, M. A., Shenton, M. E., Keshavan, M. S., Stone, W. S., & Wang, J. (2020). Clinical subtypes that predict conversion to psychosis: A canonical correlation analysis study from the ShangHai At Risk for Psychosis program. *The Australian and New Zealand Journal of Psychiatry*, *54*(5), 482–495. https://doi.org/10.1177/0004867419872248

Zhang, T., Zeng, J., Wei, Y., Ye, J., Tang, X., Xu, L., Hu, Y., Cui, H., Xie, Y., Tang, Y., Liu, X., Liu, H., Chen, T., Li, C., & Wang, J. (2022). Changes in inflammatory balance correlates with conversion to psychosis among individuals at clinical high-risk: A prospective cohort study. *Psychiatry Research*, *318*, 114938. https://doi.org/10.1016/j.psychres.2022.114938

Zhang, Y., Catts, V. S., Sheedy, D., McCrossin, T., Kril, J. J., & Shannon Weickert, C. (2016). Cortical grey matter volume reduction in people with schizophrenia is associated with neuro-inflammation. *Translational Psychiatry*, *6*(12), e982–e982. https://doi.org/10.1038/tp.2016.238

Zhao, L., Xiao, H., Gao, X., Wang, R., Liu, R., & Zhang, P. (2015). 1H-MRS Analysis for Prefrontal Cortex, Hippocampus and Thalamus of Adolescent Patients with Depression. *Journal of Medical Imaging and Health Informatics*, *5*(6), 1229–1232. https://doi.org/10.1166/jmihi.2015.1507

Zvonarev, V., Fatuki, T. A., & Tregubenko, P. (n.d.). The Public Health Concerns of Marijuana Legalization: An Overview of Current Trends. *Cureus*, *11*(9), e5806. https://doi.org/10.7759/cureus.5806

Appendix A.

Modifications made to registered PROSPERO protocol.

Exploring for sources of heterogeneity was initially planned as a sensitivity analysis contingent on $I^2 \geq 50\%$. However, the original PROSPERO protocol for this review was registered prior to the identification of the meta-analysis conducted by Healy (2019) and colleagues where significant heterogeneity was previously established. To extend upon their findings, we felt that a directed search for sources of heterogeneity in the prediction of psychotic outcomes was well justified, which is why it was incorporated as integral to fulfilling the second research objective. As I^2 was determined to be 70%, this amendment did not change the originally planned analyses. The identification of Healy (2019) also influenced our addition of population attributable fraction (PAF) to the second research aim.

In addition to being able to update this figure with new insights, we agree that this metric is complimentary to odds ratio (OR). While OR depicts the odds of experiencing an outcome given an exposure, PAF quantifies how much of the exposure was experienced in those with the outcome. We felt its addition was well suited to further describe the relationship between PLEs and subsequent psychotic disorder.

The CINAHL database was also added to the search protocol after initial registration following consult with the evidence synthesis librarian. This was simple to implement as it could be searched alongside PsycINFO. During full-text review, it became apparent that perhaps the initial exclusion criteria were too stringent as they would have allowed only one study to be included. In addition to no longer excluding based on a loss to follow-up greater than 20% and inclusion of psychiatric disorders at baseline, the minimum acceptable age for baseline assessment was changed from 12 to 11 and the maximum age at follow-up from 30 to 35. Psychiatric disorders were permitted at baseline as it is generally not common for psychotic disorders to be present in childhood and early adolescence (Solmi et al., 2022).

In addition, to enhance the rigor of this systematic review, two researchers independently extracted data instead of one reviewer extracting data and the other verifying. Furthermore, the tool used to assess risk of bias was changed from the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data to the Risk Of Bias in

Non-randomised Studies – of Exposure (ROBINS-E) assessment (Higgins et al., 2023), which follows the most recent Cochrane Methods recommendations (Sterne *et al*., 2023).

Appendix B.

Search strategy used for (a) PubMed, (b) Embase, and (c) PsycINFO and CINAHL databases.

a)

1	affective disorders, psychotic/ or psychotic disorders/ or exp schizophrenia/
2	(psychosis or psychoses or psychotic* or schizophreni*).ti,ab,kf.
3	1 or 2
4	Prodromal Symptoms/
5	3 and 4
6	((psychosis or psychoses or psychotic* or schizophreni*) adj3 (Subthreshold or "sub threshold" or sub-threshold or subclinical or "sub clinical" or sub-clinical or nonclinical or non-clinical or "non clinical" or prodromal or prone* or subtle)).ti,ab,kf.
7	((psychosis or psychotic or hallucinat* or delusion* or psychotic-like or psychoticlike) adj2 (experience* or attenuat*)).ti,ab,kf.
8	5 or 6 or 7
9	(follow-up or follow up or transition or conversion or longitudinal or incidence or predict* or cohort or risk).mp.
10	8 and 9

b)

1	‘schizophrenia’/exp OR ‘psychotic disorder’/exp
2	psychosis:ti,ab,kw OR psychoses:ti,ab,kw OR psychotic*:ti,ab,kw OR schizophreni*:ti,ab,kw OR ‘affective psychotic’:ti,ab,kw OR ‘affective psychos?s’:ti,ab,kw OR ‘non-affective psychotic’:ti,ab,kw OR ‘non-affective psychos?s’:ti,ab,kw
3	#1 OR #2
4	prodromal AND (‘symptom’/exp OR symptom)
5	#3 AND #4
6	((psychos?s OR psychotic* OR schizophreni*) NEAR/3 (subthreshold OR 'sub threshold' OR 'sub-threshold' OR subclinical OR 'sub clinical' OR 'sub-clinical' OR nonclinical OR 'non-clinical' OR 'non clinical' OR prodromal OR prone* OR subtle)):ti,ab,kw
7	#5 OR #6 OR #7
8	‘follow-up’ OR ‘follow up’ OR ‘followup’ OR transition OR conversion OR longitudinal OR incidence OR predict* OR ‘cohort study’ OR risk
9	#8 AND #9

c)

1	((DE "Psychosis" OR DE "Affective Psychosis" OR DE "Brief Psychotic Disorder" OR DE "Childhood Onset Psychosis" OR DE "Childhood Onset Schizophrenia" OR DE "Chronic Psychosis" OR DE "Delusional Disorder" OR DE "Paranoid Psychosis" OR DE "Shared Paranoid

	Disorder" OR DE "Postpartum Psychosis" OR DE "Reactive Psychosis" OR DE "Schizophrenia" OR DE "Acute Schizophrenia" OR DE "Catatonic Schizophrenia" OR DE "Childhood Onset Schizophrenia" OR DE "Paranoid Schizophrenia" OR DE "Process Schizophrenia" OR DE "Schizoaffective Disorder" OR DE "Schizophrenia (Disorganized Type)" OR DE "Schizophreniform Disorder" OR DE "Undifferentiated Schizophrenia" OR DE "Paranoid Schizophrenia") OR (DE "Affective Psychosis")) OR (TI (psychosis) OR AB (psychosis) OR KW (psychosis) OR TI (psychoses) OR AB (psychoses) OR KW (psychoses) OR TI (psychotic) OR AB (psychotic) OR KW (psychotic) OR TI (schizophreni*) OR AB (schizophreni*) OR KW (schizophreni*))
2	DE "Prodrome"
3	#1 AND #2
4	TI (((psychosis or psychoses or psychotic* or schizophreni*) N3 (Subthreshold or "sub threshold" or "sub-threshold" or subclinical or "sub clinical" or "sub-clinical" or nonclinical or "non-clinical" or "non clinical" or prodromal or prone* or subtle))) OR AB (((psychosis or psychoses or psychotic* or schizophreni*) N3 (Subthreshold or "sub threshold" or "sub-threshold" or subclinical or "sub clinical" or "sub-clinical" or nonclinical or "non-clinical" or "non clinical" or prodromal or prone* or subtle))) OR KW (((psychosis or psychoses or psychotic* or schizophreni*) N3 (Subthreshold or "sub threshold" or "sub-threshold" or subclinical or "sub clinical" or "sub-clinical" or nonclinical or "non-clinical" or "non clinical" or prodromal or prone* or subtle)))
5	TI (((psychosis or psychotic or hallucinat* or delusion* or "psychotic-like" or psychoticlike) N2 (experience* or attenuat*))) OR AB (((psychosis or psychotic or hallucinat* or delusion* or "psychotic-like" or psychoticlike) N2 (experience* or attenuat*))) OR KW (((psychosis or psychotic or hallucinat* or delusion* or "psychotic-like" or psychoticlike) N2 (experience* or attenuat*)))
6	"follow-up" or "follow up" or transition or conversion or longitudinal or incidence or predict* or cohort or risk
7	S3 OR S4 OR S5
8	S6 AND S7

Appendix C.

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Pg. 33
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Pg. 34
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Pg. 35, 36
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pg. 36
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Appendix A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Pg. 36, 37
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Pg. 38, 39
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Pg. 37, 38

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Pg. 38
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Pg. 38-40
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Pg. 39
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Pg. 39, 40
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Pg. 39, 40
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Pg. 40
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Pg. 40 & Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2.3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2.2 & Fig. 2.2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2.2 & Fig. 2.2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A (see pg. 40)

Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pg. 42-44
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pg. 45, 46
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Pg. 42-44, 47
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	N/A