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Developmental neurocognitive pathway of psychosis proneness and the impact of cannabis use

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Résumé

Cette thèse fait la promotion d'une nouvelle approche ciblant le risque de psychose qui consiste à identifier les enfants et les jeunes adolescents de la communauté appartenant à différentes trajectoires développementales d'expériences psychotiques. Une identification très précoce du risque de psychose chez des jeunes de la communauté pourrait ainsi diminuer la période où les symptômes cliniques ne sont pas traités, mais aurait également le potentiel de prévenir efficacement l'émergence de symptômes avérés, et ce, si les facteurs de risque sont identifiés.

Étant donné que la consommation de cannabis s'avère un important facteur de risque de la psychose et le contexte actuel où les états en sont à réviser leurs politiques de réglementation du cannabis, il s'avère primordial de mieux comprendre comment la consommation peut mener à la psychose chez les individus vulnérables.

Tout d'abord, j'ai investigué la séquence temporelle entre la consommation de cannabis et les expériences psychotiques chez une population de 4000 adolescents, suivis pendant 4 ans, au moment de l'adolescence où les deux phénomènes s'initient. Ensuite, j'ai examiné, chez des adolescents suivant une trajectoire de vulnérabilité, le rôle d'un moins bon fonctionnement cognitif ainsi que celui d'une exacerbation des symptômes anxieux et dépressifs comme médiateurs du lien entre cannabis et risque de psychose. Enfin, j'ai investigué la présence de marqueurs neurocognitifs précoces (fonctionnels et structurels) qui seraient associés à l'émergence de symptômes psychotiques chez des adolescents, et exploré si la consommation de cannabis pourrait modérer l'ampleur de ces marqueurs.

Les données proviennent de deux cohortes longitudinales suivant des adolescents de la population générale, l'étude Co-Venture (n=4000, âgés de 12 ans, suivis annuellement pendant 4 ans) et l'étude de neuroimagerie IMAGEN (n=2200, âgés de 14 ans, suivis pendant 2 ans), ainsi qu'un sous-échantillon de l'étude Co-Venture ayant complété des mesures de neuroimagerie (n=151, âgés de 12 ans, suivis annuellement pendant 4 ans).

Les résultats ont montré que la consommation de cannabis précédait systématiquement l'augmentation des expériences psychotiques, et non l'inverse. Chez les jeunes suivant une

trajectoire de vulnérabilité, la relation entre la consommation de cannabis et le risque de psychose était davantage expliquée par une augmentation des symptômes de dépression et d'anxiété. Une réduction du volume de l'hippocampe et de l'amygdale en combinaison avec une hyperactivité de ces mêmes régions en réponse à des expressions neutres étaient tous associés à l'émergence de symptômes psychotiques. Or, la consommation de cannabis n'a pas exacerbé les altérations structurelles observées chez les adolescents rapportant des expériences psychotiques.

Ces résultats ont mis en évidence le rôle primordial d'un hyperfonctionnement du système limbique pouvant mener à l'attribution aberrante d'une importance émotionnelle aux stimuli de l'environnement, et ce, chez des adolescents vulnérables. Il semble que le mécanisme par lequel la consommation de cannabis mène à l'émergence de symptômes cliniques passe par son influence sur les symptômes de dépression et d'anxiété ainsi que leurs mécanismes neuronaux sous-jacents d'une hypersensibilité au stress. Enfin, de par ces résultats, cette thèse permet de contribuer au développement de nouvelles interventions visant à réduire la demande de cannabis chez des adolescents vulnérables.

Mots-clés: Expériences psychotiques, adolescence, cannabis, marqueurs de vulnérabilité, imagerie fonctionnelle, imagerie structurelle, devis longitudinaux, symptômes d'anxiété et de dépression, système limbique, saillance exagérée.

Abstract

Following the worldwide initiative on intervening early in clinical high-risk individuals for psychosis, this thesis promotes a novel approach to identify those at risk for psychosis by studying children and adolescents from the community who report different trajectories of subclinical psychosis symptoms (i.e., psychotic-like experiences) without the confounds of iatrogenic effects such as major social and cognitive impairments. Early identification from this approach may not only reduce harm by shortening the duration of untreated symptoms, but may also have the capacity to prevent the emergence of clinically validated symptoms, particularly if early risk factors can be identified.

Considering the long-standing notion that cannabis misuse is an important risk factor for psychosis and that jurisdictions around the world are currently revising their cannabis regulatory policies, there is a need to better understand how cannabis use may lead to psychosis in vulnerable youths.

This thesis examined different mechanisms that may explain the complex relationship between cannabis use and psychosis risk. I first explored the temporal sequence between cannabis use and self-reported psychotic-like experiences in a population-based sample of 4000 adolescents, over a 4-year period when both phenomena have their onset. Second, in vulnerable youths, I investigated the role of impaired cognitive functioning as well as increased affective and anxious symptoms as mediators of the cannabis-to-psychosis relationship. And third, I explored the presence of early neurocognitive markers (both functional and structural) associated with the emergence of psychotic symptoms, and how cannabis use moderates these markers.

Two longitudinal cohorts from the general population, the Co-Venture Study (n=4000, aged 12 years old, followed annually for 4 years) and the neuroimaging IMAGEN Study (n=2200, aged 14 years old, followed for 2 years), as well as the neuroimaging subsample from the Co-Venture Study (n=151, aged 12 years old, followed annually for 4 years) were used.

It was found that an increase in cannabis use always preceded an increase in reported psychotic-like experiences throughout adolescence, but an increase in psychotic-like experiences rarely predicted an increase in cannabis use. Then, in vulnerable adolescents, the

cannabis-to-psychosis risk relationship was better explained by increases in depression and anxiety symptoms relative to changes in cognitive functioning. It was demonstrated that reduced hippocampus and amygdala volumes, combined with hyperactivity of the same regions during neutral cues processing were associated with the emergence of psychotic symptoms in young adolescents reporting psychotic-like experiences. However, cannabis use did not exacerbate the structural alterations observed in youths with psychotic-like experiences.

These findings have improved our understanding of the relationship between cannabis use and vulnerability to psychosis. They have also highlighted the important role of an impaired limbic network leading to an aberrant emotional salience attribution in vulnerable adolescents. Although cannabis use did not exacerbate brain structural alterations observed in vulnerable youths, it appears that cannabis will more likely interfere with depression and/or anxiety symptoms and their associated brain mechanisms underlying vulnerability to stress in the path towards psychosis risk. This thesis may inform the development of new evidence-based interventions that reduce demand for cannabis among vulnerable youths.

Keywords: Psychotic-like experiences, adolescence, cannabis use, vulnerability markers, functional imaging, structural imaging, longitudinal design, depression and anxiety symptoms, limbic system, aberrant salience.

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Abbreviations

Δ^9-THC: Delta-9-tetrahydrocannabinol

2-AG: 2-Arachidonoylglycerol

AIC: Akaike information criterion

APS: Attenuated Psychotic Symptoms

ARMS: At Risk Mental State

AUC: Area under the curve

BIC: Bayesian information criterion

BLIPS: Brief Limited Intermittent Psychotic Symptoms

CB_1: Cannabinoid receptor type 1

CB_2: Cannabinoid receptor type 2

CBT: Cognitive behavioral therapy

CFI: Comparative Fit Index

CI: Confidence interval

CIHR: Canadian Institutes of Health Research

COS: Childhood-onset schizophrenia

CTh: Cortical thickness

DLPFC: Dorsolateral prefrontal cortex

DMN: Default mode network

DSM: Diagnostic and Statistical Manual of Mental Disorders

DTI: Diffusion tensor imaging

ESM: Experience Sampling Method

FAAH: Fatty acid amide hydrolase

FIML: Full Information Maximum Likelihood

fMRI: Functional magnetic resonance imaging

GMM: Growth mixture model

IQ: Intellectual quotient

LMR-LRT: Lo-Mendell-Rubin likelihood ratio test

LSD: Lysergic acid diethylamide

NIMH: National Institutes of Health Research

NMDA: N-methyl-D-aspartate

PCP: Phencyclidine

PET: Positron emission tomography

PFC: Prefrontal cortex

PLE(s): Psychotic-like experiences

PS: Psychotic Symptoms

RDoC: Research Domain Criteria

RI-CLPM: Random-intercept cross-lagged panel model

RMSEA: Root Mean Square Error of Approximation

ROC: Receiver operating characteristic

SDQ: Strengths and Difficulties Questionnaire

SES: Socioeconomic status

SPM8: Statistical Parametric Mapping, version 8

SRMR: Standardized Root Mean Square Residual

SWM: Spatial working memory

ToM: Theory of Mind

VBM: Voxel-based morphometry

WHO: World Health Organization

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1. Introduction

In Canada, mental illnesses rank among the top seven major health conditions in terms of costs in direct healthcare and rank third on the total annual economic burden (Ball et al., 2009). Schizophrenia, one of the most severe mental disorders, was found to be the third most disabling condition, of all medical conditions, in a 14-country survey of physical and mental illnesses (Ustun et al., 1999). The neurodevelopmental theory of psychosis has stimulated a large worldwide initiative of early treatment for harm reduction.

Psychosis is a complex condition that results from the interaction between a plethora of environmental risk factors and genetic liability. There is a long-standing notion that cannabis misuse represents one of these risk factors (Andreasson et al., 1987). Considering that jurisdictions around the world are revising their cannabis regulatory policies and that these changes might impact the prevalence of users, there is a pressing need to develop strategies that address this preventable risk factor in vulnerable youths. So far, most of the cannabis-to-psychosis evidence has provided information about a distal (i.e., long-term) relationship between cannabis use initiated during adolescence and the onset of a first-episode psychosis during adulthood, approximately a decade later (Andreasson et al., 1987; Arseneault et al., 2002; Kelley et al., 2016). Preventive strategies for harm reduction of cannabis use in at-risk youths may benefit from understanding the more proximal (i.e., over a shorter period) temporal relationship between cannabis use and psychosis symptomatology at a time during adolescence when both these phenomena have their onset (Study 1). Moreover, a deeper understanding of the neurocognitive mechanisms by which cannabis use can lead to psychotic symptoms in susceptible youths may help design more targeted preventive interventions (Study 2).

At the same time, understanding the neurofunctional and neurostructural correlates of these neurocognitive mechanisms could help in further refining our understanding of the complex mechanism implicated in the cannabis-to-psychosis relationship (Study 3 and 4). With its four independent studies, this doctoral thesis will provide new insights into the early markers of a developmental path towards emerging clinical symptoms of psychosis. Moreover, this thesis will thoroughly address the relationship between cannabis use and psychosis from a developmental perspective. I hope that the findings of this work will help design and promote

evidence-based interventions to reduce the demand for cannabis among youths. Achieving this could lead to population-based risk reduction for major psychiatric conditions.

1.1 Psychotic disorders

Approximately 3% of the worldwide population is affected by a psychotic disorder (Perala et al., 2007). This prevalence includes schizophrenia and other psychotic disorders (e.g., delusional disorder, schizophreniform disorder), affective psychosis and psychosis induced by substance use (Perala et al., 2007). Schizophrenia, the chronic form of psychotic disorders, has an estimated lifetime prevalence of 0.5% to 1.0% (J. McGrath et al., 2008; Saha et al., 2008). Despite their low prevalence, psychotic disorders, particularly schizophrenia, represent a considerable social and economic burden. In fact, the first episode of psychosis is generally triggered towards the end of adolescence and the beginning of adulthood (18-30 years old) (Angermeyer and Kuhn, 1988), thus leading to a significant loss in productivity for those affected by the chronic form of the disorder. Compared to the general population, individuals with schizophrenia have a life expectancy reduced by 20%, which represents 15-20 years (Crump et al., 2013). In Canada, as of 2004, the direct healthcare costs and the indirect costs for loss of productivity caused by schizophrenia are estimated at 7 billion dollars per year (Goeree et al., 2005). According to the World Health Organization (WHO), schizophrenia is among the top 10 causes of morbidity in developed countries (Salomon et al., 2012).

In part because of their multidimensional nature, the treatment of psychotic disorders is complex and often suboptimal. First, there are positive symptoms, perceived as an excess or an alteration of normal functioning. This set of symptoms includes hallucinations and delusional ideas (tenacious false beliefs), but also disorganized thinking (evident in speech) as well as disorganized behaviors (Association, 2013). Additionally, there are negative symptoms, which are usually associated with a loss of normal functions. The main fields of negative symptoms consist of blunted affect, anhedonia, avolition, alogia and asociality (Kirkpatrick et al., 2006). In addition to these two dimensions, there are also cognitive deficits, observed in 70% to 75% of individuals with a psychotic disorder (Kalkstein et al., 2010; Nuechterlein et al., 2004). These deficits cover a wide range of cognitive domains such as processing speed, attention, working memory, verbal and visual learning, reasoning and problem solving, as well as social cognition (M. F. Green, Nuechterlein, et al., 2004). Although the diagnosis of a psychotic disorder is established based on the presence of positive symptoms, negative symptoms and

disorganization, cognitive deficits remain the best predictors of functional and social outcome (Kalkstein et al., 2010; Nuechterlein et al., 2004).

Despite the fact that, more than a hundred years ago, with Kraepelin and Bleuler, schizophrenia was characterized as a combination of symptom clusters clinically different from neurosis, the etiology of this disorder remains undetermined. Nevertheless, research from the last decades has highlighted diverse risk factors (e.g., perinatal and developmental) and antecedents associated with the emergence of a psychotic disorder (Matheson et al., 2011; Radua et al., 2018). Antecedents, in contrast to risk factors, are defined as premorbid deviations in development that may consist in early expressions of the disorder (Matheson et al., 2011). Among the variety of perinatal factors thought to be implicated in the risk for psychosis, only season of birth in the Northern hemisphere demonstrated sufficient evidence for an association with psychosis. On one hand, there is strong evidence of an association of psychotic disorders with developmental risk factors such as ethnic minority status (second- and first-generation immigrants) and urbanicity. As suggested by Radua et al. (2018), the effect of these risk factors might be explained by low socio-economic status, substance use, discrimination and social isolation. On the other hand, childhood trauma and an infection with Toxoplasma gondii only presented suggestive evidence of an association. Finally, when reviewing the literature on antecedents, the authors confirmed that trait anhedonia, low premorbid intellectual quotient (IQ) and minor physical anomalies were strongly associated with psychotic disorders (Radua et al., 2018). All of these risk factors and antecedents will either have an additive or interactive effect with a genetic vulnerability in the developmental pathway towards a first episode of psychosis.

1.1.1 The neurodevelopmental hypothesis of psychosis

The neurodevelopmental model, put forth in the 1980s by Feinberg (1982), Weinberger (1987) and Murray (1987), suggests that the psychotic condition (i.e., schizophrenia and other psychotic disorders) represents the last phase of a long abnormal neurodevelopmental process which began years prior to the diagnosis. The model also stipulates that the starting point is the presence of a prenatal or perinatal anomaly that then interacts with the neurodevelopmental processes of childhood and adolescence (Rapoport et al., 2005; Weinberger, 1987; Woods, 1998). According to the first formulation of the model, it would be possible to distinguish

psychotic disorders from other psychiatric disorders not by the location or the cause of the prenatal or the perinatal anomaly, but by the interaction of the anomaly with the normal maturation of the brain (Weinberger, 1987). The neurodevelopmental model was inspired notably by the development of neurological disorders, such as epilepsy, but also by experimental studies of lesions in animals showing a latency period between the moment the lesion occurred (before or right after birth) and the moment where the effects on the behavior were felt (Lipska and Weinberger, 2002). In short, the model rests on the theory that the behavioral manifestations of a cerebral lesion vary depending on the cerebral maturation (Weinberger, 1987). Thus, psychotic symptoms seem to appear when 'damaged' neural systems would normally reach their physiological maturity, which occurs around the end of adolescence and the beginning of adulthood.

The most recent formulations of the neurodevelopmental model, today largely accepted by the scientific community, recognize the role of social and behavioral factors such as living in an urban environment, social isolation, immigration status, substance use, traumas (Brew et al., 2018; Radua et al., 2018; Semple et al., 2005) and their interaction with cerebral maturation towards an increasingly deviant developmental trajectory (Broome et al., 2005). The prenatal and perinatal anomaly, or the genetic vulnerability, are considered the first 'hit' towards a risk for psychosis. A second hit (e.g., trauma, stress, substance misuse) during late childhood or adolescence, which also influences the normal maturation of the brain, would then be necessary to provoke a first episode of psychosis (Rapoport et al., 2012).

1.2 Psychosis as a continuum

At the turn of the 21st century, the notion of psychosis as a continuum was put forth by several clinicians and researchers, one of which is Jim van Os (2000; 2009). Even though a dichotomic definition of psychosis is still used for clinical purposes, psychosis is considered best represented, within the population, as an extended psychosis phenotype. This notion of continuum is based on the fact that reporting psychotic symptoms is not necessarily associated with the presence of the disorder (van Os et al., 2009). For instance, an elevated prevalence of psychotic symptoms is observed within various psychiatric populations. Among the following five psychiatric dimensions: mood disorders, anxiety disorders, eating disorders, impulse control disorders and substance use disorders; the mood, anxiety and eating disorders were all

associated with psychotic symptoms (J. J. McGrath et al., 2016). In fact, it is increasingly recognized that the presence of psychotic symptoms amongst non-psychotic psychiatric disorders represents a clinical marker of greater severity. Recent studies have shown that youths with a psychopathology that also report psychotic symptoms, compared to those with a psychopathology but without psychotic symptoms, present a more pessimistic prognosis, a poorer social and functional outcome, a greater use of healthcare services and a higher risk of suicidal behavior or suicide attempts (Kelleher et al., 2014; Wigman et al., 2012).

This notion of a continuum amongst different psychiatric populations as well as the elevated prevalence of psychiatric comorbidity (one fifth of patients who fulfill the criteria of a DSM diagnosis also fulfill the criteria of at least two other diagnoses) have promoted new initiatives, one of which is the 'Research Domain Criteria (RDoC)' project launched by the National Institutes of Mental Health (NIMH). The RDoC's main objective is to develop a new nosological system that incorporates, along with information on symptoms; genetic, physiologic, neuroimaging and cognitive neuroscience information. Within this perspective, the research needs to distance itself from the categorical approach of psychiatry and instead focus on the dimensional approach, where symptoms and risk factors overlap (Adam, 2013).

In addition to this continuum observed in psychiatric populations, the presence of psychotic symptoms or their milder expression (i.e. psychotic-like experiences) among non-psychiatric populations has long been observed (van Os et al., 2009). There is accumulating evidence for an extended psychosis phenotype that can go from psychotic-like experiences observed in the general population, to a diagnosis of psychosis, through a high-risk clinical state. In this perspective of an extended psychosis phenotype, predisposition to psychosis, a potentially transitory state of development, may become abnormally persistent, thus reaching a clinical state according to the level of environmental risk factors to which a person is exposed (van Os et al., 2009).

1.2.1 Proof of a continuum

Following the formulation of the continuum theory, one of its promotors, van Os (2009), reviewed the different evidence for a continuum that opposes the categorical approach of

psychotic disorders. This evidence was then classified in epidemiologic, psychopathologic, etiologic and predictive proof.

First, this evidence reports on an epidemiological validity. Epidemiological validity consists of the distribution of a phenomenon agreeing perfectly with its theoretical model. Following this concept, the categorical approach of psychosis does not align with the fact that the prevalence in the general population of all psychotic symptoms, no matter the associated level of distress, corresponds to approximately 5% to 7% (Linscott and van Os, 2013; J. J. McGrath et al., 2015), which is far superior to the estimated rate of all psychotic disorders of 3% (Perala et al., 2007). The prevalence of psychotic symptoms associated with a degree of distress and treatment seeking but without a diagnosis, is estimated at 4% (van Os et al., 2009). Therefore, the information on prevalence leans more towards a semi-normal distribution of psychotic symptoms in the population. Hence, the higher the severity of symptoms, the lower the prevalence (van Os et al., 2009).

Second, it is important to discuss the psychopathological validity of a continuum. Psychotic disorders are perceived as a correlation or an aggregation of many symptom dimensions, notably positive, negative, emotional and cognitive symptoms (McGorry et al., 1998). As a result, following the continuum construct, these correlations must also apply to non-clinical forms of psychotic symptoms. Studies in individuals with different psychotic symptoms severity (without a diagnosis) have shown a close connection between positive symptoms and emotional symptoms (Fusar-Poli, Nelson, et al., 2014; Lancefield et al., 2016). Similarly, other studies have observed that cognitive deficits of lesser magnitude than those observed in patients with a diagnosis, were already present among the non-clinical population that reported certain symptoms (Cullen et al., 2010; Fusar-Poli, Deste, et al., 2012).

Third, in order to assume the concept of a continuum, risk factors and demographic variables associated with psychotic disorders must also correlate with the non-clinical forms of psychotic symptoms. This is known as etiological validity. For instance, being part of an ethnic minority (Johns et al., 2002; Laurens et al., 2008), childhood abuse (Kelleher et al., 2008) and the use of cannabis or other substances (Mackie et al., 2011; Mackie et al., 2013) is known to influence the rate of psychotic symptoms reported in the general population. This also applies to specific genetic factors, but this will not be discussed in the present thesis (Pain et al., 2018).

Fourth, the most important component that the notion of a continuum must fulfill is predictive validity. If a continuum exists, it would be possible to observe the transition from a non-clinical state where the individual reports a few psychotic symptoms to the first episode of psychosis. Different cohort studies have demonstrated that reporting psychotic symptoms during adolescence, without necessarily having an associated distress, increases the risk for a later psychotic disorder diagnosis by 4 to 16 times (Dominguez et al., 2011; Kaymaz et al., 2012; Poulton et al., 2000; Welham et al., 2009; Werbeloff et al., 2012). In addition to being a predictor of a transition towards the first episode of psychosis, psychotic symptoms reported during adolescence can also lead to other forms of psychopathologies (Kelleher et al., 2012). Therefore, psychotic symptoms observed amongst the general population are important indicators for a multiple psychiatric disorders, but they mostly serve as an index for a vulnerability to more severe forms of psychopathology, such as psychotic disorders and comorbidities.

1.2.2 The extended psychosis phenotype

There are many approaches to evaluate the presence of psychotic symptoms in clinical and non-clinical populations based on different degrees of risk of developing a psychotic disorder. These approaches were developed to better understand the etiological processes underlying psychosis and its comorbidities, but mostly to promote and improve prevention.

1.2.2.1 Genetic risk

The genetic risk approach consists of studying the non-affected family members of schizophrenia patients. This strategy allows for the identification of 'intermediary' endophenotypes attributed to vulnerability genes while excluding the confounding factors of the illness (e.g., medication, low education). According to a Swedish epidemiological study conducted on a national scale, the genetic risk increases the risk of developing any psychotic disorder by 2.8 to 3.8 times in individuals with one of two parents affected (X. Li et al., 2007). In comparison, the specific risk of developing schizophrenia increases from a factor of 5 to 9 when one of the two parents is affected (X. Li et al., 2007). Unaffected siblings have increased risks of 4.8 and 7.3 of receiving a diagnosis of any psychotic disorder and schizophrenia respectively (X. Li et al., 2009). Furthermore, the risk of schizophrenia is 40 to 50 times higher in monozygotic twins when one twin is affected (Karlsson, 1982). Meta-analyses of twin studies

and a national cohort study estimated that the heritability (percentage of variance explained by genetic factors) of psychotic disorders varies from 50% to 80% (Cardno et al., 1999; Chou et al., 2017; Lichtenstein et al., 2009; Sullivan et al., 2003). Therefore, part of the variance is explained by environmental factors.

Although the genetic risk approach is informative on many levels, it does not allow for the systematic identification of individuals at risk of a transition towards a clinical diagnosis. In fact, the majority of new cases of schizophrenia do not have an affected family member. This affirmation is based on the notion that the probability that the disorder is sporadic, meaning that the affected individual does not have an affected family member, greatly depends on the prevalence of the disorder. With a relatively simple mathematical model where heritability is also considered, the proportion of individuals with a diagnosis of schizophrenia who do not have an affected family member is estimated at 63% or 81%, depending on the chosen prevalence (either 0.5% or 1%) (Gottesman and Erlenmeyer-Kimling, 2001; Yang et al., 2010). In short, this approach prevents the identification of a large portion of individuals who are potentially at risk.

1.2.2.2 Clinical high-risk

Psychosis risk can also be studied in individuals at clinical high-risk (also known as 'at risk mental state' – ARMS). These individuals do not fulfill all the DSM criteria in terms of frequency and severity in order to receive a clinical diagnosis. In the classification of clinical high-risk, individuals either report attenuated symptoms in the last month where symptom frequency and severity would require clinical attention ('attenuated psychotic symptoms' – APS) (Tsuang et al., 2013), or they report validated psychotic symptoms that were brief or intermittent in the last weeks ('brief limited intermittent psychotic symptoms' – BLIPS) (Yung et al., 2008). These inclusion criteria are generally based on the presence of positive symptoms (Yung and Nelson, 2013), although the level of social functioning, cognition and negative symptoms also represent important endophenotypes of the psychosis spectrum. Therefore, other criteria are sometimes used, notably the presence of a declining cognitive functioning with regards to language, attention and thoughts (Klosterkotter et al., 2001). The clinical high-risk approach was not included in the DSM-5 as a new diagnostic entity, but was incorporated in the investigation priorities section in the following years (Tsuang et al., 2013). To emphasize the

importance of the clinical high-risk approach, two recent meta-analyses by Fusar-Poli et al. (2012; 2016) gathering a total of 60 longitudinal studies demonstrated that the different criteria of clinical high-risk (APS and BLIPS) confer a 20% to 30% higher risk of developing a first-episode psychosis in the two or three years following the first consultations for attenuated or brief symptoms. These numbers have favored the emergence of numerous clinical trials testing the use of omega-3, antipsychotics, cognitive-behavioral therapies and supportive counselling on the transition towards a first episode (Stafford et al., 2013). Although some of these clinical trials may be promising, it is worth noting that the clinical high-risk state, characterized by active treatment seeking, corresponds to a late period of development when aberrant thinking styles are becoming crystallized.

1.2.2.3 Psychotic-like experiences

At one end of the extended psychosis phenotype are children and adolescents from the community who report psychotic-like experiences. These experiences are defined as perceptual abnormalities and mild delusional thoughts that fall well below the DSM-5 diagnostic criteria of psychosis (Kelleher and Cannon, 2016; van Os et al., 2009). In fact, the assessment of psychotic-like experiences in most cohort studies is based on their presence or absence (Kelleher et al., 2011; Laurens et al., 2007; Poulton et al., 2000). Limited information is collected on their frequency, severity and associated distress which differentiate these experiences from DSM-5 validated psychotic symptoms (see Annex I for an example of questionnaire assessing psychotic-like experiences). In theory, psychotic-like experiences enable the targeting of individuals well before they present important cognitive and social deficits or need to seek treatment for their symptoms. The primary aim of this approach is to cast a wide net in the identification of vulnerabilities to psychosis regardless of whether the individual comes from mental health care services or not. Although the transition rate towards a first-episode psychosis is lower than the transition rate in clinical high-risk individuals (A. E. Simon et al., 2014), preventing the emergence of validated symptoms could have a positive impact on many psychopathologies, since psychotic symptoms are associated with a greater severity in psychiatric disorders.

A recent epidemiological study by the WHO looking at 18 countries reported a lifetime prevalence of psychotic-like experiences estimated at 6% among adults (J. J. McGrath et al.,

2015). However, in strictly adolescent populations, this prevalence can reach up to 20% (Kelleher et al., 2012). As a result, a portion of these psychotic-like experiences is only transitory.

Psychotic-like experiences are not all reported with the same prevalence, nor at the same degree of severity. Ideas of mistrust remain the most commonly reported experiences, while hallucinations have a lower reported prevalence (Wigman, Vollebergh, et al., 2011). Regarding associated severity, hallucinations, delusional ideas and mistrust are associated with more symptoms of general psychopathology, while grandiose ideas and strange or paranormal beliefs are not (Wigman, Vollebergh, et al., 2011). Apart from the different types of psychotic-like experiences, the number of reported experiences is not the only factor determining an eventual need for treatment, but the persistence of these experiences over time is also associated with an eventual need for treatment (Kaymaz and van Os, 2010). Indeed, in an 8-year longitudinal design following adolescents, Dominguez et al. (2011) demonstrated that the risk of psychosis increases in a dose-response manner according to the persistence of reported psychotic-like experiences. The risk of psychosis was shown to be 1.5 times higher in youths reporting psychotic-like experiences once (on a total of three follow-ups) compared to those who never reported any. The risk was 5 times higher for those reporting these experiences twice during the study and 9.9 times higher for those reporting them at the three study time points.

Since 2010, three European cohort studies (n>3600) of teenagers from the community demonstrated that the development of psychotic-like experiences follows three primary trajectories: a trajectory with very few experiences that diminish over time (>80% of teenagers), a trajectory that reaches a high peak fairly quickly and then diminishes gradually until the end of adolescence (8%) and finally, a trajectory that begins with intermediate experiences and consistently increases every year (8%) (Mackie et al., 2011; Mackie et al., 2013; Wigman, van Winkel, et al., 2011). These results stress the importance of evaluating the longitudinal development of psychotic-like experiences, specifically during adolescence, in order to distinguish those with a more persistent trajectory that could necessitate clinical attention from those with transitory or non-problematic experiences.

1.3 Cannabis

1.3.1 Cannabis as a risk factor for psychosis

1.3.1.1 A risk in the general population

In Canada, following an important rise in the 1990s, cannabis use in adolescents has become stabilized in the last decade (2008-2014) and has even diminished in the last few years (Adlaf, 2004; Chapados et al., 2016). Reported use in the last 12 months by North American youths (Canada, United States) aged 15 to 24 is at 26% to 36% (Azofeifa et al., 2016; Canada, 2017; Chapados et al., 2016), which is among the highest rates in the Occident (Spithoff and Kahan, 2014; Traoré et al., 2014). An important concern at the moment are the changes in the state and federal legislation on cannabis use for medical and recreational purposes and their impact on the prevalence of cannabis use. In North America, in addition to Canada and its legalisation expected in October 2018, nine American states have recently legalized the recreational use of cannabis (i.e., Alaska, California, Colorado, Maine, Massachusetts, Nevada, Oregon, Vermont, Washington, and Washington D.C.). It is worth mentioning that the majority of the well-designed studies specifically investigated change in cannabis use from pre- to post-medical cannabis laws but did not consider recreational use laws (Sarvet et al., 2018; Wall et al., 2016; Williams et al., 2017). No clear change in cannabis use was found among youths and adults pre- to post-medical cannabis laws when compared to the change in states that did not modify their policy. Nevertheless, some studies did notice that cannabis use rates were more elevated in states that were about to legalize medical cannabis use relative to states that would not, reflecting a positive association between increased consumption rates and overall acceptance of the general population towards cannabis (Sarvet et al., 2018). Another concern is the fact that the concentration of delta-9-tetrahydrocannabinol (Δ^9-THC), the main psychoactive agent of cannabis, has markedly increased since the 1970s. While the concentration of Δ^9-THC was between 0.5% and 4% in the 1970s, it can now reach up to 15% or more (Cascini et al., 2012; ElSohly et al., 2016).

Randomized, double-blind, placebo-controlled, crossover studies have consistently demonstrated that administration of Δ^9-THC to non-psychiatric participants induces a variety of positive- and negative-like symptoms, disorganized thinking as well as cognitive deficits,

therefore reproducing the complex phenomenology of psychosis (Sherif et al., 2016). In some individuals, it has also been observed that cannabis use can induce a transient psychotic disorder mimicking the positive symptoms of psychosis that warrant clinical attention (Fiorentini et al., 2011). Furthermore, for those who experienced a cannabis-induced psychotic disorder, the risk of subsequent transition to a schizophrenia disorder is even more elevated. A nationwide Finnish study of 18,478 cases revealed that the eight-year cumulative risk of receiving a schizophrenia-spectrum diagnosis was 46% for those with a cannabis-induced psychotic disorder at admission (Niemi-Pynttari et al., 2013).

Recent systematic reviews of cross-sectional observation studies have detailed the relationship between cannabis and psychosis. Cannabis use is associated with an increased risk of developing psychotic symptoms or receiving a diagnosis of a psychotic disorder that is estimated at 1.5 to 3 (Moore et al., 2007; Semple et al., 2005). Notably, both randomized controlled trials of Δ^9-THC administration and epidemiological studies have highlighted that the magnitude of reported symptoms and psychosis risk is influenced by a dose-response relationship of cannabis use (Marconi et al., 2016; Moore et al., 2007; Sherif et al., 2016). For instance, the risk of any psychotic outcome in all types of cannabis users (e.g., occasional, regular, heavy) is estimated at 1.40 (95% CI, 1.20-1.65), while the risk for more regular cannabis users (i.e., more frequently than every week) is estimated at 2.09 (95% CI, 1.54-2.84) (Moore et al., 2007).

There is also significant evidence from local and national surveys suggesting that the age of onset of cannabis use influences the relationship between cannabis and psychotic symptoms (Saha et al., 2011; van Gastel et al., 2012). These findings are consistent with those of prospective studies demonstrating that initial use at age 15 is associated with an increased risk of reporting clinically validated psychotic symptoms compared to an onset of cannabis use by adulthood (i.e. 18 years old) (Arseneault et al., 2002).

Cannabis use generally begins during adolescence while the prodromal state and diagnosis of psychosis typically arise later on during early adulthood. Consequently, a majority of longitudinal studies have only tested a unidirectional association between cannabis and psychosis, and therefore suggested that cannabis use precedes subsequent psychotic symptoms (Andreasson et al., 1987; Arseneault et al., 2002; Fergusson et al., 2003; Kelley et al., 2016; van

Os et al., 2002). However, to properly investigate the temporal precedence between cannabis and psychotic symptoms, it is necessary to test for both possible temporal directions within the research protocol. Among the few studies that have explored a bidirectional relationship, all found a relationship between previous cannabis use and subsequent psychotic symptoms, and while some also reported that early psychotic experiences preceded future cannabis use (Ferdinand et al., 2005; Griffith-Lendering et al., 2013), others did not (Henquet et al., 2005; Kuepper et al., 2011). The major difference between studies showing a bidirectional relationship and those showing a unidirectional one consists of the developmental period covered by the follow-up period. Studies restricting the longitudinal follow-up to the adolescent period were more likely to find a relationship between cannabis use and psychotic symptoms in both directions (Ferdinand et al., 2005; Griffith-Lendering et al., 2013). Considering that (i) proneness to psychosis is already measurable during early adolescence with psychotic-like experiences, (ii) that earlier onset of cannabis use is associated with a greater risk for any psychotic outcome, and (iii) given the potential negative effect of cannabis on the developing brain, there is a need to further explore the temporal relationship between cannabis use and psychotic symptoms during this crucial developmental period that is adolescence.

1.3.1.2 A higher risk among the extended psychosis phenotype

There is increasing evidence confirming that the vulnerability to psychosis acts as a moderator of the cannabis-to-psychotic symptoms relationship. A randomized double-blind placebo-controlled trial showed, compared to placebo, an increased sensitivity of both cognitive effects and effects on positive symptoms to Δ^9-THC administration in patients with schizophrenia compared to individuals without a psychiatric diagnosis (D'Souza et al., 2005). Moreover, in studies using an experience sampling method (ESM), a diary technique that collects information from the participant's experience in the stream of daily life (Delespaul, 1995), both vulnerable individuals and psychosis patients, compared to healthy controls, were more likely to report unusual perceptions and hallucinatory experiences directly following an episode of cannabis use (Henquet et al., 2010; Verdoux et al., 2003).

When investigating the long-term relationship between proneness to psychosis and cannabis use, a prospective follow-up of 2,437 youths demonstrated that, among those with a vulnerability for psychosis, baseline cannabis use was associated with a 24% increased risk of

developing psychotic symptoms at the end of the follow-up period, while for youths without a predisposition that had used cannabis, the risk increased to 6% (Henquet et al., 2005). Other evidence of the interplay between cannabis consumption and psychosis proneness have shown that cannabis use precipitates the first episode of psychosis in vulnerable individuals. A meta-analysis of 80 studies (n>20,000 schizophrenia patients) has demonstrated that cannabis use is associated with an earlier age of psychosis onset (2 years younger), after controlling for the confounding effects of sex, chronicity of use and use of other psychoactive substances (Large et al., 2011; Myles et al., 2012).

Similarly to what is observed in the general population, both frequency of use and early onset seem to be important risk factors for vulnerable individuals. For example, a large cohort study of adolescents observed that the use of cannabis before the age of 14 as well as occasional use predicted a positive change in the reported experiences in individuals following an increasing trajectory of psychotic-like experiences compared to those whose trajectory of psychotic-like experiences remained low during adolescence (Mackie et al., 2013). Thus, it seems possible to identify, right at the beginning of adolescence, vulnerability trajectories to the effects of cannabis. In a retrospective study, Kelley et al. (2016) reported that the steeper the growth in cannabis use during the five years prior to the diagnosis, the higher the risk ('hazard ratio') of transitioning towards a first-episode psychosis.

Together, these results suggest that the development from vulnerability to psychosis towards the emergence of clinically validated symptoms is mediated by an abnormal sensitivity to the psychotropic effects of cannabis.

1.3.2 The endocannabinoid system

In order to understand or at least propose potential mechanisms on how cannabis use increases the risk for subsequent psychotic symptoms, it is necessary to explore the effects of cannabis on the brain. The discovery of the endocannabinoid system in the early 1990s has since greatly improved our comprehension of Δ^9-THC action mechanisms (Matsuda et al., 1990). The endocannabinoid system is composed of at least 5 ligands (the most studied are anandamide and 2-arachidonoylglycerol (2-AG)) and at least 3 receptors, of which CB_1 and CB_2 are better characterized (Mechoulam and Parker, 2013; Pertwee, 2008b). CB_1 is the most abundant G

protein-coupled receptor in the brain (Di Marzo et al., 2004). CB_2 receptors are primarily located at the periphery on immune cells (Galiegue et al., 1995). They are also expressed on central nervous system neurons, but in lower concentrations than CB_1 receptors (Fernandez-Ruiz et al., 2007). Moreover, GPR55 was recently identified as another endocannabinoid receptor as it was shown to be activated by both exogenous and endogenous cannabinoids (Ryberg et al., 2007). However, the psychoactive effects of Δ^9-THC are mainly mediated by CB_1 receptors. The fatty acid amide hydrolase (FAAH), a membrane-bound enzyme, which is responsible for the degradation of anandamide and thus plays a role in neurotransmission, is also part of the endocannabinoid system (Cravatt et al., 1996).

Endocannabinoids, unlike other neurotransmitters, are synthesized on demand at the postsynaptic dendrite and act at the presynaptic nerve terminal to inhibit transmitter release (R. I. Wilson and Nicoll, 2001). These endocannabinoids are primarily found at the GABAergic and the glutamatergic synapses, which suggests that the endocannabinoid system plays an important role in neurotransmission regulation (Fernandez-Espejo et al., 2009). In fact, it has been proposed that neurons regulate their excitation and inhibition input by releasing endocannabinoids (Murray et al., 2007).

1.3.2.1 The endocannabinoid system and its relationship with psychotic disorders

A high density of CB_1 receptors is found in the cerebral cortex, hippocampus, amygdala, hypothalamus, basal ganglia and cerebellum. Consequently, in both animal and human studies, these receptors are implicated in a variety of functions such as cognition, anxiety, appetite, movement, pain and reward (Mechoulam and Parker, 2013). Interestingly, endocannabinoids are critically involved in key functions known to be impaired in psychotic disorders such as emotion processing, learning and memory encoding (e.g. amygdala, prefrontal cortex, and hippocampus), but also in brain plasticity and motor learning (basal ganglia and cerebellum) (Fernandez-Ruiz and Gonzales, 2005; Kuhnert et al., 2013; Puighermanal et al., 2009). In addition, the endocannabinoid system modulates numerous neurodevelopmental processes, notably neural migration and maturation, differentiation of progenitor cells as well as axon elongation and synaptogenesis (Harkany et al., 2008; Malone et al., 2010). In humans, the density of CB_1 increases abruptly in the frontal cortex, the striatum and in the hippocampus during childhood and until the beginning of adulthood (Mato et al., 2003), which suggests that

endocannabinoids have an increasingly essential role over time in the normal maturation of cognitive processes.

A completely different set of evidence has highlighted the elevated density of CB_1 receptors located in the prefrontal cortex, the hippocampus and in the basal ganglia in post-mortem studies of schizophrenia patients' brains (B. Dean et al., 2001). Moreover, a recent positron emission tomography (PET) study found increases in CB_1 receptor binding in the striatum and corticolimbic circuitry among patients with schizophrenia compared to healthy subjects (Ceccarini et al., 2013). Furthermore, this increased binding was directly associated with negative and depression symptoms in unmedicated schizophrenia patients (Ceccarini et al., 2013).

1.3.3 The cannabis-to-psychosis brain mechanisms

The administration of exogenous cannabinoids, whether consisting of Δ^9-THC or other compounds, can disrupt normal neuronal transmission as well as brain maturation processes particularly during adolescence. Considering that Δ^9-THC is a partial agonist of the CB_1 receptor, frequent cannabis use can induce an excessive and prolonged stimulation of this receptor (Pertwee, 2008a). Excessive stimulation of CB_1 in the hippocampus, cerebellum, basal ganglia and cortex is responsible for the cognitive and motor effects associated with cannabis intoxication. Excessive stimulation of CB_1 may also be linked to certain symptoms and cognitive deficits of psychotic disorders. One of the largest PET studies to date on this question has demonstrated that Δ^9-THC, relative to other substances of abuse, modestly increased striatal dopamine in human subjects following its administration (Bossong et al., 2015). Consequently, it is unlikely that the primary or sole mechanism by which cannabis use is associated with a higher risk of psychosis originates from a striatal hyperdopaminergia. Other mechanisms are required.

1.3.3.1 The psychopathological mechanisms of cannabis

The high comorbidity between anxiety, depressive disorders and the extended psychosis phenotype (Fusar-Poli, Nelson, et al., 2014), as well as the elevated prevalence of anxiety and depression symptoms in cannabis users (Leweke and Koethe, 2008) suggest that the relationship between cannabis and risk of developing psychosis can be partly explained by these

affective and anxious symptoms (Reeves et al., 2014). This mechanistic hypothesis has also been promoted by animal studies showing that mice lacking CB_1 receptors present a higher sensitivity to displaying depressive-like and anxiogenic responses during stressful tasks. This in turn suggests an important role for the endocannabinoid system in the regulation of mood and anxiety (Viveros et al., 2005).

The anxiogenic and depressogenic effects of heavy cannabis use and cannabis use disorders have been well-documented (Crippa et al., 2009; Kedzior and Laeber, 2014; Lev-Ran et al., 2014). Both animal and human studies have shown that Δ^9-THC and other synthetic cannabinoids either attenuate or exacerbate anxiety and fear-related behaviors (Viveros, Marco and File, 2005). It has been suggested that low doses of Δ^9-THC have an anxiolytic effect whereas high doses have an anxiogenic effect. Interestingly, a recent randomized placebo-controlled trial in humans demonstrated that increasing negative affect (e.g., anxiety, worry, depression) mediates how Δ^9-THC administration leads to paranoia (Freeman et al., 2015). In fact, Δ^9-THC is thought to exacerbate anxiety and anhedonia via its action as an agonist on CB_1 receptors which are densely expressed in the amygdala, hippocampus, anterior cingulate cortex and prefrontal cortex; key regions in the regulation of fear-related behaviors, mood and anxiety (Viveros, Marco and File, 2005).

Regarding the relationship between vulnerability to psychosis and anxious and depressive symptoms, epidemiological studies have shown that the prevalence of an anxiety disorder or an affective disorder among individuals at clinical high-risk for psychosis ranges from 32% to 53% (Addington et al., 2011; Kelleher et al., 2012; McAusland et al., 2017) and from 35% to 37% (Addington et al., 2011; Kelleher et al., 2012) respectively. Symptoms of anxiety and depression generally precede the first psychotic episode (Fusar-Poli, Nelson, et al., 2014; Tien and Eaton, 1992). In fact, it has been suggested that these symptoms are the first to be observed prior to a first-episode psychosis and that they prompt individuals at clinical high-risk to seek treatment (Stowkowy et al., 2013). Unfortunately, these comorbid anxiety and depression symptoms are associated with psychotic symptoms of a greater severity. For example, among individuals at clinical high-risk for psychosis, those with a diagnosed anxiety disorder, major depression disorder, or both have reported more feelings of distrust and paranoia compared to individuals at clinical high-risk but without any other psychiatric diagnoses

(McAusland et al., 2017). In his theory of hallucinations' formation, Slade (1976) proposes that environmental stressors provoke alterations in emotional regulation, thus promoting anxiety symptomatology, which in turn leads to hallucinations among vulnerable individuals. Therefore, the negative and menacing interpretations of these hallucinations result in more hallucinations and delusional ideas.

1.3.3.2 The neurocognitive mechanisms of cannabis

When investigating potential mediating factors of the relationship between cannabis use and psychotic symptoms, some authors have proposed that impairments in cognitive development due to cannabis misuse exacerbate psychotic symptoms (Solowij and Michie, 2007). This hypothesis originates from a combination of empirical findings. First, randomized controlled trials have demonstrated the acute cognitive effects resulting from Δ^9-THC administration. Second, longitudinal observational studies have shown mild to moderate lasting effects of cannabis use on cognitive functioning. Third, studies in the extended psychosis phenotype have highlighted impaired cognitive abilities.

As mentioned in section 1.3.1.1, multiple randomized controlled trials with a cross-over design have been conducted using a setup where each healthy participant received either a placebo or Δ^9-THC in one or the other of two sessions. These studies have found impaired cognitive functioning in attention, working memory and episodic memory in association with the administration of Δ^9-THC (D'Souza et al., 2005; D'Souza et al., 2004). A recent literature review encompassing over 40 studies investigating the acute effects of cannabis use further confirmed these results: cannabis intoxication generally results in small to moderate deficits in verbal memory, attention and processing speed (Broyd et al., 2016). Notably, results from experimental studies have highlighted a greater sensitivity to the cognitive effects of cannabis in schizophrenia patients relative to healthy controls. Indeed, following administration of Δ^9-THC, performance scores on a recall task decreased more drastically in patients suffering from schizophrenia in comparison to non-psychiatric individuals (D'Souza et al., 2005).

An increasing number of studies of cognitive capacities has also been evaluating social cognition, that is, all mental processes underlying social interactions. These processes consist of emotion recognition and processing, attribution style, social perceptions and knowledge, as well as mental states attribution (i.e., theory of mind) (M. F. Green et al., 2008). Among the

studies that have explored the acute effect of cannabis use on the performance of social cognition tests, most reported a decreased capacity to recognize emotional facial expressions (Ballard et al., 2012; Bossong et al., 2013; Hindocha et al., 2015; Hindocha et al., 2014), and more specifically threatening emotions such as fear and anger (Ballard et al., 2012; Bayrakci et al., 2015; Bossong et al., 2013). However, other studies did not report an impaired capacity to recognize emotions (Fusar-Poli et al., 2009; Phan et al., 2008). Consequently, it appears probable, but not certain, that exposure to Δ^9-THC can result in difficulties in recognizing emotional facial expressions. Unfortunately, the number of studies on the effects of cannabis on other domains of social cognition, such as attribution style and theory of mind, is insufficient to conclusively determine the effects of this substance on these sub-domains.

Regarding the long-term effects of cannabis use, a significant number of longitudinal studies have observed a decline in cognitive performances in terms of attention, memory, processing speed and executive functions in regular users, even when premorbid cognitive functioning was taken into account (Auer et al., 2016; Castellanos-Ryan et al., 2017; Fried et al., 2005; Meier et al., 2012; Meier et al., 2018; Morin et al., 2018; Tapert et al., 2002). This cognitive decline was measured several years after cannabis use initiation. Moreover, these long-term effects of cannabis on cognition were evident even when taking into consideration a reduction in cannabis use in the last months during which the cognitive tests were performed. The cognitive effects of cannabis use are also influenced by the period of development where the majority of the use happened. In fact, the growing literature on adolescents confirms that (i) for an equivalent use, the cognitive deficits seem more pronounced in youths than in adults (Meier et al., 2012), (ii) the deficits observed in adolescents are of the same magnitude as those in adults, but they appear following even less extensive use in youths (Castellanos-Ryan et al., 2017; Morin et al., 2018), or (iii) a combination of both. Put together, these results suggest that adolescence is a period that is sensitive to the cognitive effects of cannabis. Naturally, there are other factors that moderate the cognitive effects of cannabis such as genetic factors, however, they will not be discussed in this thesis.

At the neurobiological level, animal studies suggest that Δ^9-THC impairs cognitive functioning by disrupting normal endocannabinoids neurotransmission in the hippocampus and prefrontal cortex (Egerton et al., 2006). Intrahippocampal administration of Δ^9-THC was shown to disrupt the short-term memory of learned behaviors via its direct action on hippocampal CB_1

receptors (Wise et al., 2009). Considering the cooperation between the hippocampus and prefrontal cortex regions that is needed for the performance of working memory tasks, it is suggested that exogenous cannabinoids may also have deleterious effects on prefrontal neurotransmission (Egerton, Allison, Brett and Pratt, 2006). For instance, it has been proposed that prefrontal alterations underlying cognitive impairments are due to dopamine hypoactivity following cannabis exposure (Egerton, Allison, Brett and Pratt, 2006). Together, these findings suggest that the neurobiological effects of cannabis exposure closely resemble the brain dysfunctions that characterize psychotic disorders.

Regarding the cognitive deficits present in psychotic disorders, different studies have shown that a decline in cognitive function is not secondary to positive or negative symptoms, but is already present before the diagnosis (Reichenberg, 2005). A meta-analysis of studies on cognitive function, including a total of 1,188 individuals at clinical high-risk, has confirmed that the effect size of cognitive impairments varies between -0.54 (moderate effects) and -0.18 (small effects) (Fusar-Poli, Deste, et al., 2012). The following cognitive domains accounted for the worst performances: social cognition ranking first (both emotion identification and theory of mind), visual and verbal memory as well as working memory. Another important meta-analysis has demonstrated similarities in cognitive impairments among individuals at clinical high-risk and at genetic risk (Bora et al., 2014). Other than the intelligence quotient (IQ), working memory and social cognition (this domain has not been evaluated), performances in other domains were similar between the two risk groups.

It is worth noting that some of these cognitive functioning deficits are not limited to the prodrome period but are instead identifiable very early on during development. Studies on schizophrenia patients' offspring (Niemi et al., 2003) and meta-analyses of retrospective studies in high-risk individuals who subsequently developed schizophrenia (Dickson et al., 2012) have reported mild to moderate deficits on IQ, attention and working memory being present before the age of 16. In fact, lower IQ, which is considered an antecedent to psychotic disorders, was shown to be measurable as early as age 13 (Dickson, Laurens, Cullen and Hodgins, 2012). Moreover, youths aged 9 to 12 reporting psychotic-like experiences presented with a moderate to large level of decline in working memory (effect size: Cohen's d, -0,95), inhibitory control (Cohen's d, -0,62), verbal memory (Cohen's d, -0,54) and general IQ (Cohen's d, -0,55) (Cullen et al., 2010).

Although social cognition impairments seem to be the core of the extended psychosis phenotype, only a few studies have evaluated whether these deficits could already be identified as early as childhood or adolescence. Among a total of four studies, three have shown that youths aged 9 to 16 with a vulnerability to psychosis (either unaffected family members of a patient or individuals reporting psychotic-like experiences), in comparison to same-age healthy volunteers, had more difficulties correctly identifying emotional facial expressions (i.e., joy, sadness, anger, fear or neutral) (Dickson et al., 2014; Eack et al., 2010; Roddy et al., 2012; A. Thompson et al., 2011). Two of the four studies concluded that the lower performances by youths with a vulnerability to psychosis were explained by the fact that many neutral faces were being perceived as expressing a negative emotion (Eack et al., 2010; Dickson, Calkins, Kohler, Hodgins and Laurens, 2014). On theory of mind (ToM) paradigms, young adolescents reporting psychotic-like experiences performed worse than healthy controls (Barragan et al., 2011; Clemmensen et al., 2016; Clemmensen et al., 2014). It was demonstrated that the ToM deficits in youths with psychotic-like experiences were specifically explained by an excessive attribution of one's own intentions or self-referential meaning to others, as opposed to impaired representational abilities. This implies that the individual is unaware that others can have their own mental states (Clemmensen et al., 2014; Clemmensen et al., 2016). Interestingly, this excessive ToM or HyperToM is thought to help differentiate those with an autism diagnosis from those with positive psychotic symptoms (Abu-Akel and Bailey, 2000).

Together, these studies highlight the presence of similarities between the cognitive endophenotypes of psychosis and the cognitive deficits induced by the regular use of cannabis, suggesting a potential causal relationship between the cognitive effects of cannabis and the risk of developing clinically validated psychotic symptoms during adolescence.

1.3.4 The use of other substances as risk factors

Besides cannabis, among licit and illicit substances, alcohol, lysergic acid diethylamide (LSD), cocaine, amphetamines (and methamphetamine), phencyclidine (PCP) and ketamine all induce effects that resemble the positive and negative symptoms of psychotic disorders (Paparelli et al., 2011). Chronic alcohol use can sometimes induce hallucinations (Jordaan and Emsley, 2014), amphetamine, similarly to cannabis, specifically promotes paranoia (McKetin, 2018), while LSD is more likely to induce visual illusions and hallucinations (De Gregorio et

al., 2016), and PCP and ketamine produce a variety of negative symptoms (Pomarol-Clotet et al., 2006). These substances all have their own specific mechanisms of inducing symptoms, which have contributed to the pharmacological theories of psychotic disorders. For instance, LSD mainly acts on the brain via serotoninergic receptors 5-HT, while amphetamine and cocaine act directly on dopamine receptors, and PCP and ketamine bind to the N-methyl-D-aspartate (NMDA) receptor of the glutamate system (Paparelli, Di Forti, Morrison and Murray, 2011). The mechanisms by which chronic alcohol intake produces hallucinations is less clear (Soyka et al., 2005). On the contrary, nicotine and opiates do not promote psychotic symptoms (Paparelli et al., 2011; Smith et al., 2002), even though nicotine is believed to confound the relationship between cannabis use and psychotic symptoms (Gage et al., 2014). Considering the modest use of LSD, amphetamines, cocaine, PCP and ketamine in North American adolescent samples (Traoré et al., 2014), the effects of these substances on subsequent psychosis risk were not investigated in this thesis.

1.4 Neurocognitive endophenotypes of the extended psychosis phenotype

Accumulating neuroimaging literature from the last two decades has highlighted, in patients suffering from a psychotic disorder, the presence of various brain functioning and anatomic abnormalities linked to the cognitive deficits that are associated with the disease. This area of research aiming to understand the neural processes underlying cognitive impairments is crucial for improving the current use of pharmacotherapies and the development of new targeted preventive therapies.

1.4.1 Brain functional correlates of the extended psychosis phenotype

Investigating the neural correlates of the extended psychosis phenotype during cognitive functioning can provide information on the early altered neural processes during or even prior to significant cognitive impairments. In meta-analyses of studies investigating the functional correlates of psychosis vulnerability across a variety of cognitive tasks, hypofunctionality of the prefrontal cortex is considered as the central feature (Dutt et al., 2015; Fusar-Poli, 2012;

Smieskova et al., 2010) similarly to what is observed in schizophrenia (Hill et al., 2004). Altered activity patterns across tasks in both the inferior parietal lobule and the superior temporal gyrus were also recognized as important features of clinical high-risk individuals (Dutt et al., 2015). It is worth mentioning that a weaker deactivation of the default mode network (DMN) is observed among at-risk individuals during different cognitively-demanding tasks (Falkenberg et al., 2015; Fryer et al., 2013), which may represent a general characteristic of psychosis proneness.

Neuroimaging results have demonstrated that the functional abnormalities observed in individuals at risk for psychosis are similarly located, but in the milder range, to the altered neural processes evident in patients with a diagnosis. For instance, in a meta-analysis of 15 functional imaging studies using working memory paradigms, relatives of patients with schizophrenia displayed reduced activation within the prefrontal cortex (right middle and right inferior frontal gyri) as well as increased activation within the frontopolar area, the inferior parietal lobule and the thalamus (Zhang et al., 2016). It has been suggested that the regions showing hyperactivity might be recruited as compensatory mechanisms to maintain task performance. The hypofunctionality observed in the middle and inferior frontal gyri, regions implicated in central executive control as well as information manipulation and reorganization for encoding (Petrides, 2000), is thought to represent a marker for psychosis liability irrespective of the clinical expression of symptoms. Similar functional alterations were observed in clinical high-risk individuals. Studies have reported both hypo- (Wolf et al., 2015) and hyperactivation (Bendfeldt et al., 2015; Yaakub et al., 2013) of the prefrontal cortex during the completion of working memory tasks; such hypo- and hyperactivation are thought to depend on the task's cognitive load where a high load is associated with hypoactivations (Van Snellenberg et al., 2006).

Another important cognitive impairment associated with the extended psychosis phenotype is episodic memory which has been shown to elicit a reduced activity from the medial temporal lobe (e.g., parahippocampal gyrus, hippocampus) during both the stimulus encoding and retrieval phase in high-risk individuals and first-episode patients (Allen et al., 2012; Allen et al., 2011; Francis et al., 2016; Thermenos et al., 2007; Valli et al., 2011). Interestingly, Allen et al. (2012) observed that during encoding, the parahippocampal activation was positively

correlated with the number of target words correctly identified in the recall phase. Although it is less consistent than the hypoactivity from the temporal cortex, studies have also highlighted a dysfunctional response from the lateral prefrontal cortex during episodic memory in vulnerable individuals (Allen et al., 2011; Bonner-Jackson et al., 2007; Whyte et al., 2006). Reduced activity in prefrontal and medial temporal regions has been reported in patients with a psychosis diagnosis (Achim and Lepage, 2005) and is thought to explain the memory deficits associated with the condition.

When investigating response inhibition, a component of the cognitive control system, using either go/no-go, stop-signal, or Stroop analog tasks, various functional magnetic resonance imaging (fMRI) studies have found decreased striatal activations in psychosis-prone individuals compared to controls. These studies also reported decreased activations in the dorsal anterior cingulate cortex and the inferior frontal gyrus (Colibazzi et al., 2016; Fryer et al., 2018; Sambataro et al., 2013; Vink et al., 2006), regions implicated in inhibition of an automatic response and response conflict (Hung et al., 2018). In a young population sample of 11- to 13-year-olds from the community reporting psychotic-like experiences, Jacobson et al. (2010) observed reduced activity in prefrontal (e.g., inferior and middle frontal gyrus, anterior cingulate cortex) and temporal regions during a stop-signal task. Interestingly, Fryer et al. (2018) showed that clinical high-risk individuals as well as first-episode psychosis patients, when compared to healthy comparison subjects, presented similarly impaired activity patterns between Go and No-go trials, therefore suggesting that the extended psychosis phenotype is characterized by a general deficit in responding appropriately to the context, rather than by a specific response inhibition deficit.

Another core feature of psychosis is dysfunctional reinforcement learning, which constitutes a domain that is not typically assessed in studies of behavioral cognitive functioning but has been widely investigated using functional neuroimaging. A recent meta-analysis of fMRI studies demonstrated that psychosis spectrum disorders are associated with a blunted response from the striatum during anticipation of reward, which might explain why patients manifest impaired learning of stimulus-reinforcement associations (Radua et al., 2015). Five studies have been performed in first-degree relatives and clinical high-risk individuals using the Monetary Incentive Delay task to evaluate reward anticipation, and four of them have found a

reduced activity in the ventral striatum compared to matched healthy controls (de Leeuw et al., 2015; Grimm et al., 2014; Hanssen et al., 2015; Juckel et al., 2012; Z. Li et al., 2018). This blunted response of the striatum is thought to reflect an overall tonic elevated dopaminergic signalling which is observed in psychosis or an imbalance in dopamine transmission during the reward anticipation and receipt processes (Heinz and Schlagenhauf, 2010).

In a meta-analysis of cognitive abilities, social cognition was highlighted as the most impaired domain in vulnerable individuals compared to healthy control subjects (Fusar-Poli, Deste, et al., 2012). At the functional imaging level, emotional processing arises from interactions between prefrontal regions that act as the center for emotion control and limbic regions known to promote emotional reactivity (Davis and Whalen, 2001; Etkin et al., 2011). Individuals at both clinical and genetic high-risk presented with abnormal activations in frontolimbic areas during the experience of both negative emotions (Habel et al., 2004; H. J. Li et al., 2012; Modinos et al., 2015; Pulkkinen et al., 2015; Wolf et al., 2015) and neutral facial expressions (Seiferth et al., 2008), similarly to what is observed in diagnosed patients (Anticevic et al., 2012; H. Li et al., 2010). Notably, the most consistent finding has been observed using functional connectivity analyses, which demonstrated that the prodrome is associated with impaired negative coupling between the ventro-lateral prefrontal cortex and the amygdala during the processing of emotional stimuli (Modinos et al., 2010; Pulkkinen et al., 2015). Interestingly, among the few neuroimaging studies investigating the early neural correlates of psychosis proneness prior to the onset of more impairing validated psychotic symptoms, studies by Modinos et al. (2010; 2012) showed that youths that had been self-reporting psychotic-like experiences exhibited similar reduced activation of the medial prefrontal cortex and amygdala during passive viewing and reappraisal of negative pictures compared to low-risk youths.

Fewer studies have examined the neural correlates underlying ToM processes within the extended psychosis phenotype. They have shown that psychosis proneness is associated with an overactivation of the ToM network, which includes parts of the DMN (e.g., medial prefrontal cortex, posterior cingulate cortex, precuneus and temporoparietal cortex), while inferring others' beliefs (Brune et al., 2011; Derntl et al., 2015; Takano et al., 2017; Wang et al., 2015).

Together, these findings on the neurocognitive endophenotypes of the vulnerability to psychosis highlight the central role of a functionally impaired lateral prefrontal cortex and its

connections with the parietal, temporal, striatal and limbic systems. However, at the moment, it is still difficult to differentiate the neural markers associated with a common genetic vulnerability to psychosis from those associated with either a transition to a first-episode psychosis or from clinically validated symptoms. Moreover, within the perspective of early prevention, it is still difficult to identify the main early neurodevelopmental markers that may help early identification of this susceptibility to psychosis.

1.4.1.1 Similarities with functional correlates of cannabis use

A meta-analysis of whole-brain functional neuroimaging studies of the residual effects of cannabis use highlighted, among regular users, a significantly increased activation in fronto-temporal regions as well as decreased activation in the occipital cortex, insula and frontal motor areas across a variety of cognitive tasks (e.g., memory, attention, reward processing, inhibitory control and emotion processing) (Blest-Hopley et al., 2018). Moreover, it appears that the specific recruitment of the prefrontal cortex and the hippocampus can differentiate users from non-users during the completion of cognitive tasks (Martin-Santos et al., 2010). These results reflect abnormal activity across regions that are part of the executive-control, the default mode and the salience/limbic network in cannabis users. This is similar to what has been observed in psychosis patients and psychosis-prone individuals. Specifically, in adolescent cannabis users, the meta-analysis found brain hyperactivations that were limited to the striatum, the insula as well as the parietal cortex. Greater task-related activation in these regions is thought to underlie the increased processing required to maintain normal performance (Martin-Santos et al., 2010).

1.4.2 Brain structural correlates of the extended psychosis phenotype

Meta-analyses of voxel based morphometry (VBM) and volumetric studies in clinical and genetic high-risk individuals have consistently reported reduced gray matter density and volume in temporo-prefrontal regions (Boos et al., 2007; Chan et al., 2011; Fusar-Poli et al., 2011; Fusar-Poli, Radua, et al., 2012; Fusar-Poli, Smieskova, et al., 2014; Palaniyappan et al., 2012). Specifically, these reductions are observed in the medial prefrontal cortex, the anterior cingulate cortex, the parahippocampal gyrus, the amygdala and the hippocampus (Boos, Aleman, Cahn, Hulshoff Pol and Kahn, 2007; Chan, Di, McAlonan and Gong, 2011; Fusar-Poli et al. 2011; Fusar-Poli, Radua, McGuire and Borgwardt, 2012; Palaniyappan, Balain and Liddle,

2012; Fusar-Poli, Smieskova, Serafini, Politi and Borgwardt, 2014). These alterations in high-risk individuals are less widespread throughout the brain in comparison to the density reductions in total gray matter, and in a number of temporal, frontal, and parietal regions observed in psychosis patients. Moderate volume decreases are also found in the hippocampus, the amygdala, the thalamus and the nucleus accumbens of psychosis patients (Haijma et al., 2013; Honea et al., 2005; van Erp et al., 2016). It has been shown that reduced gray matter volumes and density are more pronounced in high-risk subjects who later develop a psychotic disorder, compared to those who do not (Borgwardt et al., 2007; Fusar-Poli et al., 2011; Koutsouleris et al., 2009; Takahashi et al., 2009). For instance, in a sample from the NAPLS consortium of 274 clinical high-risk individuals followed longitudinally, those who converted to a first-episode psychosis experienced a more rapid gray matter loss specifically in regions of the frontal cortex (i.e., superior and middle frontal gyri as well as medial orbitofrontal cortex) compared to both healthy matched controls and non-converters (Cannon et al., 2015).

When specifically investigating white matter integrity, diffusion tensor imaging (DTI) studies revealed that recent-onset and clinical high-risk populations show structural dysconnectivity between brain regions (Karlsgodt et al., 2012; Samartzis et al., 2014; Vijayakumar et al., 2016). For instance, the majority of these studies have observed a general pattern of reduced fractional anisotropy (a measure used to reflect fiber density) in clinical high-risk individuals (Vijayakumar et al., 2016). Although the pattern of white matter abnormalities seems slightly inconsistent between studies, the tracts most severely affected consist of the inferior and superior longitudinal fasciculi, the corpus callosum as well as various fronto-temporal and fronto-limbic tracts (e.g., uncinate fasciculus, cingulum bundle) (Karlsgodt et al., 2012; Samartzis et al., 2014; Vijayakumar et al., 2016). The location of these reduced white matter integrities are in line with the main volumetric and gray matter density reductions observed in fronto-temporal regions (Boos, Aleman, Cahn, Hulshoff Pol and Kahn, 2007; Chan, Di, McAlonan and Gong, 2011; Fusar-Poli et al. 2011; Fusar-Poli, Radua, McGuire and Borgwardt, 2012; Palaniyappan, Balain and Liddle, 2012; Fusar-Poli, Smieskova, Serafini, Politi and Borgwardt, 2014).

A few studies have further investigated the early anatomical markers of this susceptibility to psychosis during late childhood and adolescence prior to the onset of

confounding factors such as substance misuse, medication and major social impairment. For instance, Jacobson et al. (2010) and Cullen et al. (2013) found both increases and decreases in gray matter density mainly located in the temporal cortex and to a lesser extent in the parietal and frontal cortices. The prospective study of childhood-onset schizophrenia (COS) may supplement these findings on the specific neurodevelopmental processes that can fail during adolescence. Indeed, COS and the more common adult onset schizophrenia share similar symptoms, genotype, cognitive deficits as well as brain abnormalities. On a whole-brain perspective, COS appears to present with an exaggeration of the normal maturation processes (i.e., cortical loss) seen in typically developing children (Ordonez et al., 2016). More specifically, it was shown that the network with the most significant abnormal cortical growth in COS, relative to healthy comparisons subjects, was the cingulo-fronto-temporal cortex (Alexander-Bloch et al., 2014). Inversely, various longitudinal studies in COS have demonstrated a fixed, but robust reduction in hippocampal volume that is evident at disease onset (Ordonez et al., 2016). This finding is consistent with results from a meta-analysis in clinical high-risk individuals showing no reduction in hippocampal volume before transition to psychosis (Walter, Suenderhauf, Harrisberger, et al., 2016), suggesting that unchanging small hippocampus volume results from very early neurodevelopmental alterations.

1.4.2.1 Similarities with structural correlates of cannabis use

Using volumetry and VBM techniques, studies have found that chronic cannabis use is associated with reduced hippocampus and amygdala volumes in both adults and adolescents (Koenders et al., 2016; Lorenzetti et al., 2015; Rocchetti et al., 2013; Weinstein et al., 2016). Moreover, an earlier age of cannabis use initiation may be associated with more prominent structural alterations in adults. It was demonstrated that whole-brain gray matter volumes were reduced only in participants who started using cannabis before age 17 (Cohen et al., 2012; W. Wilson et al., 2000). The effects of cannabis on white matter integrity have been less studied and have produced more inconsistent results thus far (Arnone et al., 2008; Ashtari et al., 2009; Gruber et al., 2011).

1.5 Objectives and hypotheses of the independent studies of this thesis

Psychotic-like experiences that can be measured in youth community samples offer an interesting approach to study early characteristics of the extended psychosis phenotype, which may subsequently inform novel targeted prevention strategies. The two broad objectives of this dissertation were to (i) further explore the temporal and mechanistic relationships between psychotic-like experiences and cannabis use at a time when both phenomena have their onset, and (ii) investigate both the functional and structural brain correlates underlying the cognitive endophenotypes of psychotic-like experiences. All studies used a prospective design.

Considering the limited number of studies that have adequately tested for the different potential temporal relationships between cannabis and psychosis outcome, the first study aimed to simultaneously investigate the common vulnerability, secondary cannabis use, secondary psychotic symptoms, and bidirectional hypotheses in the general population during an important developmental period that is adolescence. This study was designed to repetitively examine the proximal (short-term) temporal associations (12-month intervals), as opposed to the distal temporal associations often reported in other cohort studies (> 5-year intervals), to better capture the complex and dynamic relationships between early cannabis use and psychotic-like experiences. Testing these proximal temporal associations will allow future research to propose and validate more concrete mechanisms of this relationship. I hypothesized that the most robust association between cannabis use and psychotic-like experiences would be cannabis use preceding psychotic-like experiences and the possibility for a weaker association in the direction of psychotic-like experiences preceding subsequent cannabis use.

The specific objective of the second study was to explore the potential mechanisms of the relationship between cannabis use and psychotic-like experiences in individuals following a psychosis vulnerability trajectory, amongst whom the effects of cannabis are likely to be more important. The mechanisms tested were the psychopathological and neurocognitive pathways underlying cannabis use in increasing psychotic-like experiences. I hypothesized that impaired cognitive abilities, relative to increased depression and anxiety symptoms, would better explain the relationship between cannabis use and increasing psychotic-like symptoms.

The third study aimed to identify brain functional correlates of psychotic-like experiences in youths prior to more impairing cognitive deficits, to onset of regular substance use and to distress. I explored the brain functional activity associated with a variety of cognitive tasks known to be impaired in at-risk individuals such as response inhibition, emotion processing and reward processing. As one of the most replicated findings in functional neuroimaging studies of vulnerable and diagnosed individuals, prefrontal hypoactivity during executive functioning was thought to be an important early marker of a psychosis vulnerability. Therefore, I hypothesized that youths with psychotic-like experiences would present with a reduced activation within the dorso-lateral prefrontal cortex during response inhibition. In addition, considering that deficits in behavioral tasks of social cognition relative to other domains are listed as the most impaired in high-risk individuals, I also expected to find abnormal brain activation during an emotion processing task, located in fronto-limbic regions, in youths reporting psychotic-like experiences. Finally, I hypothesized that a blunted response from the striatum would be observed during the anticipation of reward in adolescents with psychotic-like experiences. As a secondary objective, I tested whether these early neural markers of abnormal activity were also associated with the emergence of clinically validated psychotic symptoms two years later in the total sample of youths (n>1,000).

Finally, the fourth study aimed to complement the third one in investigating early brain structural alterations associated with elevated psychotic-like experiences. Moreover, this fourth study integrated findings from the first and second studies as I also tested the specific effect of early onset cannabis use on brain cortical thickness and volume maturation during early adolescence, and the interaction between early cannabis use and psychotic-like experiences on brain maturation. I expected to find reduced cortical thickness and volume in temporo-frontal regions in youths reporting elevated psychotic-like experiences. I also hypothesized that modest interaction effects of cannabis and psychotic-like experiences on brain maturation would be found, considering that I examined early onset occasional use of cannabis, and not regular use.

2. Testing temporal precedence between cannabis use and psychotic symptoms in the adolescent general population: article no.1

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Josiane Bourque participated in data collection, database management, and quality control. She decided upon the analytic strategy, conducted the analyses, interpreted the results, and wrote the first draft of the manuscript.

Mohammad H. Afzali contributed to database management and quality control. He was implicated in the decision for the analytic strategy and revised the manuscript.

Patricia Conrod designed the main project where this analysis comes from, was implicated in the interpretation of results, and critically revised the manuscript.

All authors have reviewed and approved the final version of this manuscript.

Association of cannabis use and adolescent psychotic symptoms

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RESEARCH LETTER

INTRODUCTION

Considering that jurisdictions are moving towards cannabis legalization and the anticipated changes to the Canadian policy planned for July 2018, there is a need to understand whether cannabis use has a causal role in the development of psychiatric diseases, such as psychosis. Prospective studies report a temporal precedence of cannabis use before later onset of psychosis (Marconi, Di Forti, Lewis, Murray and Vassos, 2016), but the evidence is limited with respect to causality due to studies only assessing psychosis symptoms (PS) at a single follow-up and by relying on analytic models that might confound intra-individual processes with initial between-person differences. In the absence of an experimental design, random-intercept cross-lagged panel models (RI-CLPMs) provide the most rigorous test of causal predominance between 2 outcomes by quantifying the temporal association over multiple follow-up periods and by dissociating within-person and between-person variance (Hamaker, Kuiper and Grasman, 2015). Using this approach, we investigated year-to-year associations between cannabis use and PS over 4 years in youths aged 13 years at study onset.

METHODS

The analysis capitalizes on the developmentally-informed Coventure cohort (O'Leary-Barrett et al., 2017), which includes 76% of all grade 7 students attending 31 secondary schools in the greater Montreal, Quebec, Canada, area, representing 15% of all schools in the area and each of their respective school districts in size and deprivation indices within 1.5 SD. A total of 3966 adolescents actively assented to be part of the study and completed a confidential annual web-based survey from age 13 to 16 years involving self-report of past-year PS and cannabis use and PS. Psychosis symptoms were assessed with the Adolescent Psychotic-Like Symptoms Screener (Laurens, Hodgins, Maughan, Murray, Rutter and Taylor, 2007), and cannabis use frequency was assessed with a 6-point scale (0 indicates never, 5 indicates every day).

Reliability of substance use was evaluated using a sham drug item. Students with at least 1 data point were included in the analysis. A "missing completely at random test" using the R-

package "MissMech" (https://CRAN.R-project.org/package=MissMech) confirmed that the data were missing at random.

The RI-CLPM uses a multilevel approach to test for within-person differences that inform on the extent to which an individual's increase in cannabis use precedes an increase in this individual's PS (and vice versa) (Hamaker et al., 2015). The models were implemented in MPLUS 8 (http://www.statmodel.com), with $\alpha = .05$, using the full information maximum likelihood (FIML) method.

RESULTS

The final sample included 3720 adolescents (mean [SD] age, 12.8 [0.4] years; 1828 [49.1%] female). A basic model containing only autoregressive paths, random intercepts, and within-time correlations across variables was first tested, followed by a transactional model that also contained cross-lagged associations (Figure). The χ^2 difference test favoured the transactional model ($\Delta\chi^2 = 22.15$, 6 *df*; $P = .001$).

The transactional model revealed statistically significant positive cross-lagged associations, at every time point, from cannabis use to PS reported 12 months later, over and above the random intercepts of PS and cannabis use (between-person differences). These cross-lagged associations were similar in size to the autoregressive link (annual stability) between PS from ages 15 to 16 years. Psychosis symptoms at age 15 years had a statistically significant positive association with cannabis use at age 16 years. All autoregressive links and within-time correlations at ages 14, 15, and 16 years were also statistically significant.

DISCUSSION

This analysis demonstrates a predominant association at the individual level of cannabis use frequency with increased PS, and not the opposite, in the general population at a developmental stage when both phenomena have their onset. One limitation was that cannabis use and PS were not confirmed with clinician or collateral reports. However, previous work has shown positive predictive values ranging from 80% to 100% from 3 self-report items to identify interview-verifiable PS (Kelleher, Harley, Murtagh and Cannon, 2011). Furthermore, self-report

is the most efficient way to assess substance use when there are no consequences to reporting because collateral reports and biologic measures are not sensitive to the sporadic nature of adolescent substance use (Clark and Winters, 2002).

Considering that PS are associated with risk for psychosis, as well as nonpsychotic disorders, these results emphasize the need for targeted cannabis use prevention as jurisdictions revise their cannabis regulatory policies. Promoting evidence-based interventions and policies that reduce access to and demand for cannabis among youths could lead to population-based reductions in risk for major psychiatric conditions.

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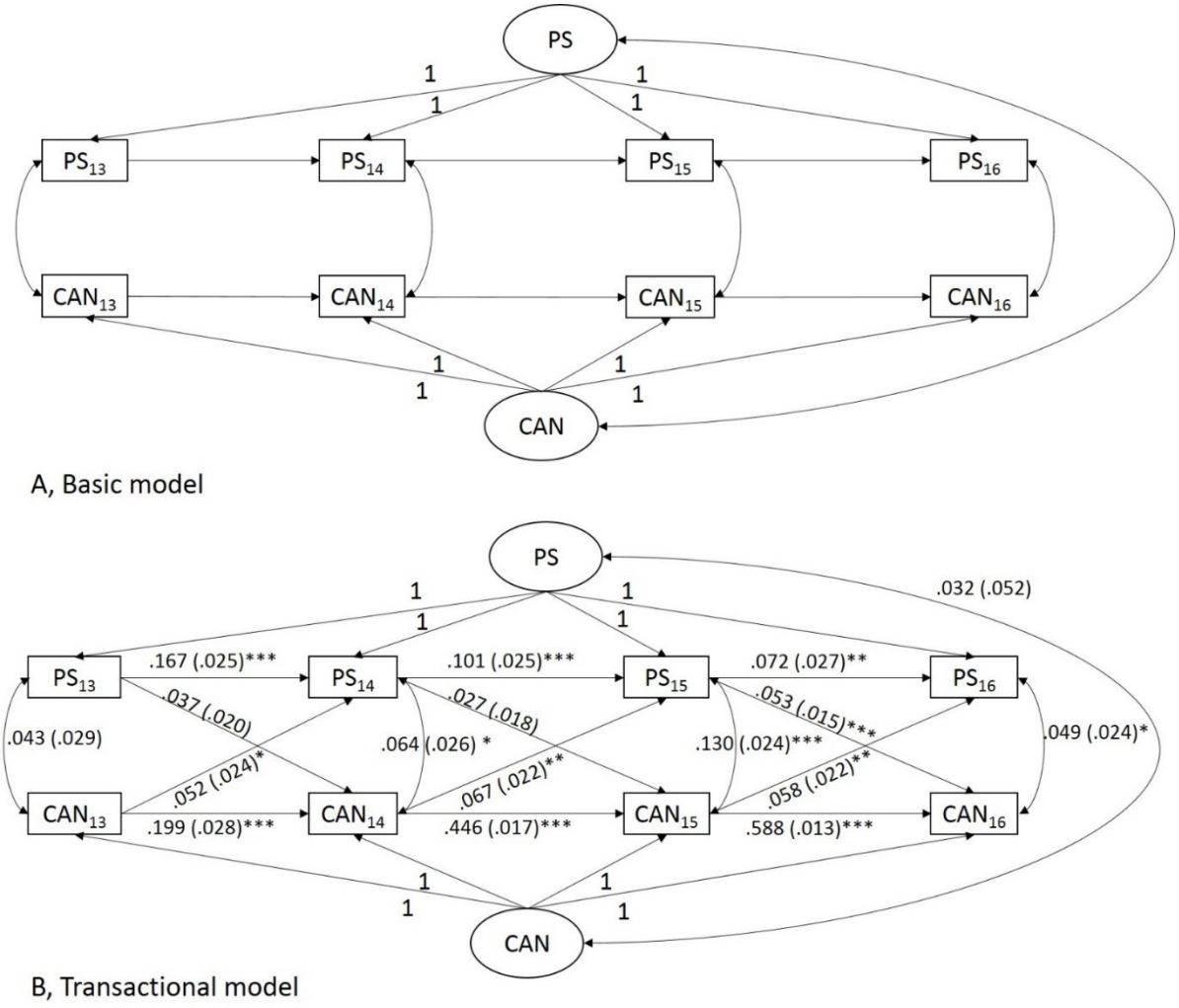
Figure. The Basic and Transactional Versions of the Random-Intercept Cross-Lagged Panel Model Between Cannabis Use Frequency and Psychosis Symptoms (PS) During Adolescence (Age Range; 13-16 Years).



Abbreviations: CAN, Cannabis; RMSEA, Root Mean Square Error of Approximation; CFI, Comparative Fit Index; SRMR, Standardized Root Mean Square Residual.

CAN_{13} represents cannabis use frequency at grade 7 (i.e., age 13 years).

A, The basic model includes random intercepts (trait-like stability, also known as between-person differences), autoregressive paths (stability within a specific variable across time points), and cross-sectional correlations at each time point (within-time correlations across variables) but does not include cross-lagged paths (directional lagged associations between variables).

B, The transactional model includes random intercepts, autoregressive paths, cross-sectional correlations, and cross-lagged paths. Only standardized parameter estimates are reported in the model. Both the basic model and transactional model fitted the data well according to all 4 fit measures. For the basic model, $\chi^2 = 48.22$, 15 *df*, $P < .001$ (RMSEA, 0.02; CFI, 0.99; and SRMR, 0.02); for the transactional model, $\chi^2 = 26.07$, 9 *df*, $P = .002$ (RMSEA, 0.02; CFI, 1.00; and SRMR, 0.01). The χ^2 difference test favoured the transactional model ($\Delta\chi^2 = 22.15$, 6 *df*; $P = .001$).

The first time point occurred at a mean age of 12.8 years. Twelve months separate each assessment. In total, 3226 (86.7%) and 3510 (94.4%) of participants had a minimum of 2 time points out of 4 on PS and cannabis use, respectively.

*$P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

2.1 Cannabis-to-psychosis risk relationship: from the general population to the extended psychosis phenotype

This first manuscript provides evidence of a causal relationship between cannabis use and psychotic symptoms in the general population. While investigating the proximal temporal relationship between cannabis use and the development of psychotic symptoms during a developmental period where both phenomena have their onset, this study found that, at the individual's level, an increase in cannabis use at a given year over the mean cannabis use systematically precedes an increase in the individual's psychotic symptoms 12-month later over the overall mean of reported psychotic symptoms. However, an increase in the individual's psychotic symptoms was rarely found to precede increases in cannabis use.

One important strength of the study's analytic design is that it tested and distinguished intra-individual (within-person) from inter-individual (between-person) processes. A widely used example to describe the difference between within- and between-person processes is the evidence that an individual is more likely to experience a heart attack during exercise (within-person effect), while at the same time people who exercise more tend to, as a group, have lower risk of cardiac failure (between-person effect) (Curran and Bauer, 2011). These two processes give complementary (and, in this example, opposing) information about the complex and multi-level nature of the potential relations between variables. In the field of psychiatric and psychological research, causal and mechanistic theories are often based on within-person processes, such as the relationship between cannabis use and psychosis. However, multiple longitudinal studies have not taken the opportunity to specifically differentiate within- from between-person processes to better inform the relationship (Curran and Bauer, 2011). The random-intercept cross-lagged panel model (RI-CLPM) represents an important advancement from regular cross-lagged panel models (which are often used to repetitively test causal relationships between variables), as it allows to single out between-person variance with the random intercepts such that the lagged relationships (used to test causal relationship) pertain to within-person processes (Hamaker et al., 2015). In fact, considering that the RI-CLPM modeled the association of the trait-like stability between cannabis use and psychotic symptoms (i.e., the correlation between the overall mean of cannabis consumption and psychotic symptoms) and

that this association was not found to be significant, our findings are less likely to be accounted for by pre-existing common vulnerability to cannabis use or by psychosis proneness. Therefore, this study's findings are highly novel and support a causal hypothesis.

The following descriptive table (which was not included in this manuscript because of space limitation associated with research letters) provides information on cannabis use and psychotic symptoms prevalence. Even though only a small proportion (ranging from 1% to 7%) of the sample was considered regular user (i.e. at least weekly), this first manuscript still showed a significant association between cannabis use and psychotic symptoms. Therefore, this association is likely to be driven not only by regular use, but also by more occasional use. Table 1 also highlights the significantly increased proportion of reporting any psychotic symptoms in cannabis users versus non-users at all time points except at baseline (i.e., Grade 8 to 10). Even though the effects were observed among the whole community sample, I suspect that the cannabis-to-psychotic symptoms association is driven by a subsample of youths that may be more prone to the psychotropic effects of cannabis. As previously discussed in the section 1.3.1.2 of the Introduction, the risk for future psychotic outcome is most increased among cannabis users with a vulnerability to psychosis (i.e., those reporting some symptoms at baseline) (Henquet et al., 2005).

Table 1. Descriptive statistics of the sample in the first manuscript.

Prevalence	Grade 7 13 years	Grade 8 14 years	Grade 9 15 years	Grade 10 16 years
Psychotic symptoms				
% reporting at least one PS (1 item)	68.4	61.7	58.9	51.7
% reporting significant PS (based on a previously validated threshold)[1]	12.6	12.5	10.7	8.9
Cannabis use				
% reporting no cannabis use	95.9	90.3	80.1	71.3
% reporting cannabis use at least weekly	0.9	2.0	5.4	7.3

% reporting cannabis use at least occasionally	4.1	9.7	19.9	28.7
Proportion of youths reporting any psychotic symptoms among users and nonusers				
Among cannabis users (at least occasionally), % reporting any PS	46.6[a]	57.5[a]	62.9[a]	55.7[a]
Among nonusers, % reporting any PS	41.3[a]	49.7[b]	53.8[b]	49.6[b]

PS, Psychotic symptoms.

[1]Based on previous studies by our team and Cannon's team (Jacobson et al., 2010; Kelleher et al., 2011), to identify youths with significant psychotic symptoms, which symptoms were validated by consensus ratings from the Structured Interview for Prodromal Syndromes, the following criteria were applied: a total score ≥ 2 on the questionnaire used to assess psychotic symptoms and a score ≥ 0.5 on the auditory hallucination item.

Different superscript letters refer to significant differences ($p < .05$) between nonusers and users, at a specific grade (e.g. Grade 7). Within a specific grade, if the two scores are labeled with the same letter, the scores are not statistically different. If the two scores are labeled with different letters, the scores are statistically different.

The analytic design used in this study has one specific limitation which was not mentioned in the published manuscript. As discussed, the primary aim of the RI-CLPM is to confirm or disconfirm the predominant influence of one variable over another by testing the different relationships (within-time correlations, autoregressive links and cross-lagged regression links) between the two. Considering its particular design, the RI-CLPM is therefore ill-suited to add other variables into the model and to control for potential confounding factors or moderators. In the specific case of the cannabis-to-psychotic symptoms relationship, use of other substances was suggested to potentially confound this association (Gage et al., 2014). Within our community sample, only alcohol and cigarette use could have acted as potential confounders considering that the rate of use of other illicit substances was too low to have any influence on the model results.

Various cross-sectional and longitudinal studies have accounted for use of both cigarette and alcohol when investigating the relationship between cannabis and psychosis risk. Cigarette

use has been associated with an increased emergence of psychotic disorders in longitudinal studies (Gurillo et al., 2015; Kendler et al., 2015). However, unlike cannabis, experimental studies of nicotine administration using a placebo controlled crossover design did not demonstrate an acute increase in positive and negative symptoms following nicotine administration (Smith et al., 2002). Still, cigarette use may be a marker associated with diverse psychosis risk factors such as low SES or family adversity, and in that sense, it was hypothesized to confound the relation between cannabis use and psychosis risk (Gage et al., 2014). Evidence from large cohort studies (n>35,000) demonstrated that cigarette exposure did not alter the association between cannabis use and psychotic symptoms or psychotic disorders (Jones et al., 2018; Vaucher et al., 2018). As for alcohol use, a systematic review by Moore et al. (2007) and other studies have revealed that factors such as alcohol use do not impact the association between cannabis and psychotic outcome (Degenhardt et al., 2001).

Considering the major strengths of this RI-CLPM but also its limitation as a two-variable model, a valid use of this analysis is as a post-hoc test to understand causal predominance following previous empirical evidence of a temporal relationship between two variables. Another interesting option that I propose to the scientific community is to utilize the RI-CLPM in combination with the more flexible multilevel model that also distinguishes within- from between-person variance and tests the lagged relationships while controlling for covariates. This second option would (i) inform the investigator of a potential temporal relationship between variables while also accounting for covariates, and (ii) give more details about the most plausible directionality between the variables (e.g., *a* mostly preceding *b*, *b* mostly preceding *a*, or a bidirectional relationship).

Following the demonstration of a temporal precedence of cannabis use over later psychotic symptoms occurrence in the general population, in the second manuscript, I further investigated this relationship in individuals following a developmental trajectory of persistent or increasing psychotic-like experiences, drawn from the general population of high school students of the greater Montreal area. Considering that mild psychotic symptoms or psychotic-like experiences can be transitory, to adequately study psychosis proneness and the developmental processes implicated in it, a dimensional approach can be useful to explore the different developmental trajectories of psychotic-like experiences. In fact, it has already been

demonstrated that reporting persistent psychotic-like experiences during adolescence is associated with a 10-fold increased risk of developing a psychotic disorder compared to those whose psychotic-like experiences are transitory (Dominguez et al., 2011). This approach allows for the identification of the most at-risk youths among those reporting psychotic-like experiences and may explore the longitudinal mediators of psychosis outcomes. Moreover, using this trajectory design, it is possible to highlight potential differences in cannabis use prevalence within an enriched subsample and compare it to those with very few psychotic-like experiences.

The main objective of this second study was to explore the potential mechanisms that would explain the cannabis-to-psychotic symptoms association specifically within the most at-risk youths, that is, those following an increasing or persistent trajectory. I tested two mediational hypotheses: (i) impaired cognitive functioning and (ii) increased affective or anxious symptoms. These hypotheses originate from both animal and human studies highlighting the role of the endocannabinoid system and the influence of cannabis exposure on neurotransmission in brain regions involved in emotion regulation and cognitive functioning such as memory (Viveros, Marco and File, 2005; Wise, Thorpe and Lichtman, 2009). Moreover, it is now recognized that a high comorbidity exists between depressive, anxiety symptoms and the extended psychotic phenotype (Fusar-Poli, Nelson, et al., 2014). Finally, the cognitive endophenotypes of a psychosis vulnerability have been well-characterized (Fusar-Poli, Deste, et al., 2012).

3. Testing potential mechanisms of the cannabis-to-psychosis risk relationship during adolescence: article no.2

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Josiane Bourque participated in data collection, database management, and quality control. She decided upon the analytic strategy, conducted the analyses, interpreted the results, and wrote the first draft of the manuscript.

Mohammad H. Afzali contributed to database management and quality control. He was implicated in interpreting the results and revised the manuscript.

Maeve O'Leary-Barrett participated in data collection and revised the manuscript.

Patricia Conrod designed the main project where this analysis comes from, contributed to choosing the analytic strategy, was implicated in the interpretation of results, and critically revised the manuscript.

All authors have reviewed and approved the final version of this manuscript.

Cannabis use and psychotic-like experiences trajectory during early adolescence: the coevolution and potential mediators

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ABSTRACT

Background: The authors sought to model the different trajectories of psychotic-like experiences (PLE) during adolescence and to examine whether the longitudinal relationship between cannabis use and PLE is mediated by changes in cognitive development and/or change in anxiety or depression symptoms.

Methods: A total of 2,566 youths were assessed every year for 4-years (from 13- to 16-years of age) on clinical, substance use and cognitive development outcomes. Latent class growth models identified three trajectories of PLE: low decreasing (83.9%), high decreasing (7.9%), and moderate increasing class (8.2%). We conducted logistic regressions to investigate whether baseline levels and growth in cannabis use were associated with PLE trajectory membership. Then, we examined the effects of potential mediators (growth in cognition and anxiety/depression) on the relationship between growth in cannabis use and PLE trajectory.

Results: A steeper growth in cannabis use from 13- to 16-years was associated with a higher likelihood of being assigned to the moderate increasing trajectory of PLE [odds ratio, 2.59; 95% confidence interval (CI), 1.11–6.03], when controlling for cumulative cigarette use. Growth in depression symptoms, not anxiety or change in cognitive functioning, mediated the relationship between growth in cannabis use and the PLE moderate increasing group (indirect effect: 0.07; 95% CI, 0.03–0.11).

Conclusions: Depression symptoms partially mediated the longitudinal link between cannabis use and PLE in adolescents, suggesting that there may be a preventative effect to be gained from targeting depression symptoms, in addition to attempting to prevent cannabis use in youths presenting increasing psychotic experiences.

Keywords: Psychotic-like experiences; trajectory; cannabis use; mediation; depression symptoms; anxiety symptoms; cognitive function.

INTRODUCTION

In the perspective of an extended psychosis phenotype, a promising approach was proposed by Kelleher et al. (2011) and Laurens et al. (2007) to study children and young adolescents from the general population who report subclinical psychotic-like experiences (PLE), without the confounds of iatrogenic effects, such as medication, and major social and cognitive impairment. Developmentally sensitive designs can provide important insights into environmental risk factors, such as early onset and rapid growth in cannabis use, associated with subclinical PLE.

Psychotic-like experiences are defined as perceptual abnormalities (e.g., mild hallucinatory experiences) and delusional thoughts that fall well below DSM-5 diagnostic criteria of psychosis (Kelleher and Cannon, 2016; van Os, Linscott, Myin-Germeys, Delespaul and Krabbendam, 2009). The prevalence of PLE in the general population is estimated at 6%-10% (van Os, et al., 2009) and rises to 13%-15% in adolescent samples (Laurens, Hodgins, Maughan, Murray, Rutter and Taylor, 2007; Poulton et al., 2000). Of note, having reported these experiences is associated with increased odds (4─16) to develop a psychotic disorder over the longer term (Poulton et al., 2000; Werbeloff et al., 2012), particularly if PLE are persistent overtime (Dominguez, Wichers, Lieb, Wittchen and van Os, 2011) . Besides psychotic illnesses, PLE during adolescence become increasingly associated with general Axis I disorders (Fisher et al., 2013; Kelleher et al., 2012). Based on a developmentally informed longitudinal design, Mackie et al. (2011; 2013) demonstrated using data from two large community-based samples that PLE consistently follow three developmental trajectories across adolescence: a low decreasing (>80% of youths), an increasing (8%) and a systematically elevated trajectory (5%). Altogether, these results stress the importance of studying the longitudinal development of PLE, specifically in youth, in order to distinguish those with a more persistent trajectory of psychotic experiences considered to be of more clinical significance from those whose PLE may be transitory or nonproblematic and may never come to clinical attention.

According to two meta-analyses examining the increased risk for psychotic symptoms and diagnoses in cannabis users, the magnitude of the effect appears to be dose-dependent, influenced by age of cannabis use initiation, and premorbid psychosis vulnerability (Moore et al., 2007; Semple, McIntosh and Lawrie, 2005). These effects remained significant when

accounting for tobacco use. Specifically, on the temporal relation between cannabis use and psychotic symptoms, prospective studies demonstrated that cannabis use increases the risk of later incident psychotic symptoms, and not the opposite (Kuepper et al., 2011). However, most of studies focusing on the association between cannabis and psychotic symptoms have used binary classification (i.e. any level of users vs. nonusers) or cumulative consumption to describe cannabis use behaviors (Arseneault et al., 2002; Di Forti et al., 2014; Moore et al., 2007). Unfortunately, static descriptions of the association between these variables do not allow to disentangle the impact of different rates of cannabis use growth in early onset relative to late onset users on psychotic symptomatology development. To our knowledge, only one study has modeled change in cannabis use from a more dynamic perspective (Kelley et al., 2016) which can help to clarify the developmental pathways between patterns of consumption and psychotic symptoms. Considering the imminent Canadian cannabis legalization, the relationship between cannabis use and PLE needs to be addressed more thoroughly from a Canadian community-based cohort.

When investigating potential mediating factors of the relationship between cannabis and psychotic experiences, some authors have proposed that impairments in cognitive development due to cannabis misuse exacerbates psychotic experiences (Solowij and Michie, 2007). Indeed, low premorbid cognitive functioning is associated with and predates the onset of a psychotic disorder (Reichenberg, 2005). A meta-analysis of studies on clinically high-risk individuals for psychosis concluded that alterations in cognitive functions were present in the following domains: social cognition, episodic and working memory, verbal fluency, and executive functioning (effect sizes ranging from -0.55 to -0.22, respectively) (Fusar-Poli et al., 2012). A study investigating 9- to 12-year olds reporting PLE found impairments in working memory, inhibitory control, verbal memory, and IQ functions in these preteenagers (effect sizes ranging from -0.95 to -0.54) (Cullen et al., 2010). In addition, regular cannabis use has been shown to negatively impact executive functioning, inhibitory control, and attention performance in youth populations specifically (Castellanos-Ryan et al., 2016; Fontes et al., 2011; Meier et al., 2012). From a neurophysiological perspective, cannabis exposure in youths is associated with structural alterations of the medial temporal (i.e., amygdala and hippocampus), frontal and cerebellar regions (Volkow et al., 2016), alterations that are known to precede a diagnosis of psychosis (Fusar-Poli et al., 2011). Altogether, these studies underline certain similarities

between the cognitive endophenotypes of psychosis and the resulting cognitive deficits from cannabis use (Solowij and Michie, 2007), suggesting a potential causal relationship between cannabis-induced cognitive changes and psychosis during adolescence.

In the same vein, the important comorbidity between anxiety and depressive disorders with subclinical symptoms of psychosis (Fusar-Poli, Nelson, Valmaggia, Yung and McGuire, 2014) as well as the elevated prevalence of anxiety and depression in cannabis users (Leweke and Koethe, 2008) have led the scientific community to investigate potential mediational effects (Reeves et al., 2014). Anxiety and depression symptoms often precede the onset of psychosis (Fusar-Poli et al., 2014), while the anxiogenic and depressogenic effects of heavy cannabis use and cannabis use disorders have been well-documented (Kedzior and Laeber, 2014; Lev-Ran et al., 2014).

The goals of the present study were twofold. Our first aim was to investigate the relationship between cannabis use and PLE trajectory (Mackie, Castellanos-Ryan and Conrod, 2011; Mackie et al., 2013; Wigman et al., 2011) by focusing on the dynamic modeling of adolescent cannabis use (early onset and growth) in a Canadian sample of 13-year olds followed for 3 years. The second goal was to test whether the longitudinal relationship between cannabis use and PLE is mediated by changes in cognitive functioning or by change in anxiety and/or depression symptoms across adolescence.

METHODS

Participants

A total of 3,826 Grade 7 adolescents (mean, (SD); 12.8 years old (0.4); 49.2% girls) from 31 secondary schools in the greater Montreal area participated in this study. The schools were initially recruited to take part in an ongoing cluster randomized controlled trial evaluating the effectiveness of school-based personality-targeted interventions on substance use and cognitive outcomes (O'Leary-Barrett et al., 2017).

The participants were invited to complete a confidential annual web-based survey during class time (from Grade 7 to Grade 10, from 13- to 16-years old) to assess clinical, cognitive, and psychoactive substance use information. Twelve months separated each assessment. Quality control and reliability of the data were evaluated using a sham drug item, reverse items on various questionnaires and scripts to detect inconsistent or unlikely reporting. Data on cognitive

tasks were further quality controlled with the exclusion of participants whose performance was below what could be expected by chance or outside a normal response range (e.g., reaction time). Confidentiality was assured by emphasizing that parents and teachers would not have access to the survey results and by automatically anonymizing the assessments. Details of the exclusion criteria are reported in the Supplement material. Ethical approval was obtained from the CHU Sainte-Justine Research Ethics Committee in Montreal. Depending on the school, either passive or active parental consent was obtained. All students actively assented to participate.

Among the 3,826 adolescents who were invited to complete the survey annually, 3,612 (94.4%) passed the quality control of the different questionnaires and reported minimal demographic information (sex, age, socioeconomic status - SES). Of these, 2,566 youths (71.0%) were included in the final analyses as they had at least two data points out of four on every measures of interest for this study (i.e. psychotic experiences, substance use, cognitive functioning, anxiety and depression symptoms). Attrition was predicted by older age (p = .018) as well as higher baseline levels of externalizing behaviors (p = .001), higher frequency of cannabis use (p = .028), poorer IQ (p = .001), and poorer response inhibition (p = .004) performance. However, attrition was not predicted by either sex (p = .795), baseline SES (p = .998), the different PLE trajectories (p = .617), baseline depressive (p= .476) and anxiety symptoms (p = .257), baseline delayed memory performance (p = .132), nor baseline working memory performance (p = .058).

Measures

*Dependent variable***.** Psychotic-like experiences (e.g. hallucinations, delusional beliefs, suspiciousness, strange experiences, and feelings of grandiosity) in the past 12 months were assessed with nine items, five of which were adapted from the Diagnostic Interview Schedule (Costello, 1982). All items were previously validated in community samples of children and adolescents (Laurens et al., 2007; Laurens, Hobbs, Sunderland, Green and Mould, 2012). The list of items is reported in the Supplement material. Participants were asked to rate their response to different statements on a 3-point scale (0 = not true; 1 = somewhat true; 2 = certainly true). Individual item scores were summed to obtain a global score of PLE. Kelleher et al. (2011) reported that three questions (i.e. auditory and visual hallucinations, feeling of being spied upon)

presented positive predictive power (ranging from 80% to 100%) for interview-verifiable PLE. Cronbach's α ranged from .80 to .83 between baseline and third follow-up.

Independent variable. Self-reported cigarette and cannabis use frequency were assessed with a modified and validated version of the 'Detection of alcohol and drug problems in adolescents' questionnaire (Germain et al., 2013). Participants were asked to rate their frequency of use over the previous 12 months on a 6-point scale (0 = Never, 5 = Every day).

Potential mediators. Depressive and anxiety symptoms severity in the past 12 months were measured using the depression and anxiety subscales of the Brief Symptoms Inventory (Derogatis, 1993). Global cognitive functioning (IQ) was assessed with the Cultures Figures Task, a modified version of the Cattel's Culture Fair Test (Cattell, 1949) which evaluates perceptual reasoning. Spatial working memory (SWM) was measured with the "Find the Phone" task which is based on the Self-Order Pointing Task (Cragg and Nation, 2007). Delayed memory recall (30 minutes) was assessed with digital analogue of the Dot Location test of the Child Memory Scales (Cohen, 1997). Response inhibition was measured with an adaptation of the Go/No-Go Passive Avoidance Learning Paradigm (Newman and Kosson, 1986) represented by the total number of commission errors across all the no-go trials.

Covariates. Baseline SES was assessed using the Family Affluence Scale for Adolescents (Currie, Elton, Todd and Platt, 1997) and baseline externalizing behaviors (i.e. conduct and hyperactivity problems) with the Strengths and Difficulties Questionnaire (SDQ) (Goodman, Renfrew and Mullick, 2000). The SDQ is a brief behavioral screening questionnaire for 3-16 years olds assessing internalizing (i.e. emotional and peer relationships problems) and externalizing behaviors. Participants provided information about their gender and age. For a more detailed description of the study measures, see Appendix S1 accompanying the online version of this article.

Statistical analyses

Data were analyzed using MPLUS version 7.3. First, group-based trajectories of PLE were estimated using growth mixture models (GMM). Models were fitted beginning with a one-trajectory model and moving to a four-trajectory model, all with random starting values. The best-fitting model was established using the Bayesian Information Criterion (BIC), the Akaike Information Criterion (AIC), the Lo-Mendell-Rubin Likelihood Ratio Test (LMR-LRT), and

entropy. Missing data on the dependent variable (PLE score) were handled through Full Information Maximum Likelihood.

Second, we examined whether change in cannabis use from 13-to-16 years was associated with the PLE trajectories. We estimated growth of cannabis use across the four different time points with unconditional latent-growth curve models. Goodness-of-fit indicators included the comparative fit index (CFI) and the standardized root mean square residual (SRMR) where, as Hu and Bentler (1999) proposed, a model with CFI $> .95$ and SRMR $< .08$ is considered to have a good fit. We extracted the intercept and slope values for each participant from the unconditional latent-growth models. Then, we conducted multinomial and binary logistic regressions with random cannabis intercept and slope factors to predict the posterior probabilities of PLE trajectory membership.

Third, to investigate whether the relationship between growth in cannabis use and PLE trajectory (i.e. the moderate increasing trajectory vs. the low increasing trajectory) is mediated by change in anxiety or depression symptoms or cognitive functioning, we estimated growth of these mediators using unconditional latent-growth curve model across the four time points. Then, linear regressions were used to estimate the relationship between growth in cannabis and growth of potential mediators (*a* pathway), and logistic regressions to test the relationship between growth in cannabis use, growth in potential mediators and PLE trajectory membership (*c* and *b* pathways). A bias corrected bootstrap procedure (5,000 bootstrap resamples) was used to obtain 95% confidence interval (CI) for direct and indirect effects (Imai, Keele and Tingley, 2010).

All the regression models included a cluster-level variable (i.e. schools) to account for the non-independence of observations.

RESULTS

Psychotic-like experiences trajectories

Consistent with previous trajectory modeling of PLE, a three-class trajectory model (Figure 1) fitted the data best (BIC = 39,532.6, AIC = 39,456.6, entropy = 0.87, LMR-LRT: $p = .004$) compared to a two-class model. Although moving from a three- to a four-class model produced small decreases in both the BIC and the AIC (BIC = 39,209.9, AIC = 39,110.5), we opted for the three-class model as the LMR-LRT coefficient was no longer significant ($p = .113$)

and a group from the four-class model was relatively small (3.8%, N = 98) (For model fit information see Table S1). The trajectories include a low decreasing class (N = 2,152, 83.9%) who presented mild, slightly decreasing psychotic experiences, a high decreasing class (N = 203, 7.9%), who presented initially elevated levels of PLE which decreased over the subsequent time points, and a moderate increasing class (N = 211, 8.2%) characterized by intermediate levels of PLE at baseline (a total score of 5, meaning that most of these individuals endorsed five different items to a mild extent) that increased over time.

Table 1 presents demographic, substance use, cognitive, and clinical characteristics of the PLE trajectory groups at both baseline and third follow-up.

Unconditional growth models for the independent variable and potential mediators

Linear growth functions provided good fit indicators for cannabis use, cognitive functioning and symptoms severity data (Table 2). The growth curve factor means and variances were all significantly different from 0 at $p < .01$. All models showed an overall tendency to increase from 13- to 16-years old (except for the SWM and response inhibition data for which the number of errors is decreasing with age). Please refer to Figures S1 and S2, accompanying the online version of this article, for the visualization of the variables' linear growth functions.

Association between change in cannabis use and PLE trajectory

Both the unadjusted and adjusted models for cumulative cigarette use show that a steeper growth in cannabis use frequency was associated with greater odds (Odds ratios ranging from 2.59 to 3.28) of belonging to the moderate increasing trajectory relative to the other two groups (Table 3). However, the intercept of cannabis use frequency (mean = 0.05; suggesting onset for a small proportion of individuals but low level of use) was not associated with the PLE classes in any of the models.

Testing potential mediators

Indirect pathways were estimated when both *a* and *b* pathways were significant. In the cognitive functioning mediations, among the different *a* pathways, growth in cannabis use was only significantly associated with growth in commission errors of the response inhibition task ($\beta = .12$; 95% CI, 0.03-0.21), that is, a slower improvement in response inhibition with time.

For *b* pathways, none of the cognitive growth factors were significantly associated with the moderate increasing trajectory of PLE, except for a marginal effect of growth in response inhibition (β =.12; 95% CI, 0.00-0.24), that is, a slower improvement in response inhibition with time was associated with the moderate increasing trajectory of PLE. The specific indirect effect from growth in cannabis use to the moderate increasing trajectory through growth in response inhibition performance was also marginally significant (0.01; 95% CI, 0.00-0.03).

Among the potential psychopathologic mediators, we showed that positive growths on depression and anxiety measures were significantly associated with membership of the moderate increasing PLE trajectory (depression: β = 0.25; 95% CI, 0.17-0.32; anxiety: β = 0.40; 95% CI, 0.28-0.53). Furthermore, growth in cannabis use frequency was positively related to growth in depression symptoms (β = 0.29; 95% CI, 0.15-0.42), not anxiety. The specific indirect effect from growth in cannabis use to the moderate increasing trajectory through growth in depressive symptoms was 0.07 (95% CI, 0.03-0.11), and explained 12.1% of the direct effect (Table 4). We further examined the potential confounding of early depression levels on the indirect effect by adding baseline depression symptoms as a covariate, and obtained a significant indirect effect of 0.05 (95% CI, 0.01-0.08).

DISCUSSION

Using a large community sample and yearly assessments of substance use, cognitive function and psychiatric symptoms, this unique study contributes to the literature on cannabis use as a risk factor for early psychotic symptoms by identifying mediators of the relationship between growth in cannabis use frequency and PLE trajectory. The data confirm the presence of three distinct PLE trajectory classes manifesting during adolescence (13-16 years old): low decreasing (83.9%), moderate increasing (8.2%) and high decreasing trajectories (7.9%). The proportion of individuals assigned to each class matched those reported by Wigman et al. (2011) and by our previous studies (Mackie et al., 2011; 2013). However, in addition to the three trajectories, Wigman and colleagues identified a relatively low prevalence fourth group for which PLE were consistently elevated over time. In the current study, the four-class trajectory model, which was not the best fitting and most parsimonious model, included that same low prevalence trajectory with persistently elevated PLE (3.8%). The major difference between the samples is that Mackie's team observed no high decreasing trajectory; instead they observed an

'elevated' trajectory that declined abruptly by 14.5 years of age. According to the present and Wigman's results, it seems that Mackie's 'elevated' trajectory might be a combination of both a high early decreasing trajectory with a persistently elevated trajectory. It could be hypothesized that this 'elevated' trajectory may emerge in different samples, such as older populations, or larger samples.

One of the novel components of this study was the way in which adolescents' developing cannabis use was modeled using a developmentally sensitive analytic strategy. Contrary to other studies examining the longitudinal relationship between cannabis and psychotic symptoms using age of cannabis onset or cumulative use data (Arseneault et al., 2002; Di Forti et al., 2014), our models allow for the estimation of interindividual variability in patterns of change over time and thus, help to disentangle the impact of different rates of cannabis use growth relative to onset of use on the development of psychotic symptomatology. Previous findings linking cannabis use to increasing PLE (Mackie et al., 2011; 2013) were only able to test the impact of cannabis use onset. Our study demonstrated that, when accounting for the growth in cannabis use frequency, use at baseline or early initiation was not related to any PLE trajectory. Rather, it was the growth in cannabis use frequency that was significantly associated with membership to the moderate increasing PLE trajectory relative to the other two groups, suggesting a gradient of effect between increasing cannabis use and increasing PLE. Adolescents were shown to be at 159% increased odds of being classified in the increasing PLE trajectory for every unit increment in the cannabis frequency scale (which ranges from no use, occasional use, once a month, once a week, couple times per week, to every day). Altogether, these findings are consistent with a recent study evaluating the different patterns of change in cannabis use on subsequent psychosis onset (Kelley et al., 2016). The authors reported that (a) the steeper the growth in cannabis use in the few years before conversion to psychosis, the higher the risk of conversion, and (b) those with an early onset of cannabis use who follow a decreasing trajectory of use have a similar risk of psychosis onset to nonusers (Kelley et al., 2016). Therefore, it seems that both age of onset and cumulative use information are insufficient measures and are likely to underestimate the real-life impact of cannabis use on psychotic symptoms.

While mounting evidence supports the potential role of cigarette use as a confounding factor when investigating the link between cannabis and psychosis (Gage et al., 2014), we showed that growth in cannabis use was still associated with increasing PLE when controlling

for cigarette use. Accordingly, this is consistent with meta-analyses showing that cannabis use is an independent risk factor for psychotic symptoms (Moore et al., 2007; Semple, McIntosh and Lawrie, 2005).

Individual patterns of change over time in cognitive functioning and affective symptoms were similarly modeled in our adolescent sample to test for a potential mediation of the longitudinal link between cannabis use and increasing PLE. Our results show that apart from a marginal effect of response inhibition, there was no association between change in cognitive functioning and PLE trajectory membership. Those with a poorer growth on response inhibition performance were more likely to be classified in the moderate increasing PLE group. These results seem to be inconsistent with the emerging literature on adolescents with PLE (Cullen et al., 2010), studies on schizophrenia patients' offspring (Niemi, Suvisaari, Tuulio-Henriksson and Lonnqvist, 2003), and meta-analyses of high-risk individuals who will subsequently develop schizophrenia (Dickson, Laurens, Cullen and Hodgins, 2012), all reporting mild to moderate deficits in various cognitive domains during adolescence, particularly IQ, memory, executive functions, attention, as well as processing speed. However, most of the above-cited literature looked at cross-sectional differences in cognition between at-risk and low-risk youths and did not use longitudinal, multi-level modeling to examine this relationship. Our findings only mildly support the mediating role of altered cognitive development on the relationship between cannabis and PLE, with growth in response inhibition performance being the only cognitive domain shown to be associated with cannabis use and mediating its relationship to PLE. These results are in accordance with recent findings from our team demonstrating that cannabis use has a neurotoxic effect that is specific to response inhibition, as opposed to a general impact on cognitive functioning (Morin et al., in press).

In the same vein, we demonstrated that steeper growths in anxiety and depression symptoms were associated with the increasing trajectory of PLE relative to the low decreasing trajectory (control group), suggesting that both anxiety and depression symptoms evolve concomitantly with increasing PLE. The results are consistent with research from the IMAGEN study demonstrating that a limbic hypersensitivity to neutral facial expressions, a core feature of both depression and anxiety disorders (Bourke, Douglas and Porter, 2010; Cooney, Atlas, Joormann, Eugene and Gotlib, 2006), was associated with the presence of psychotic symptoms at 2-year follow-up (Bourque et al., 2017). Additionally, we showed that there was a significant

indirect effect from growth in cannabis use to the increasing PLE trajectory through growth in depressive symptoms. These findings are in accordance with three previous studies in young adults showing cross-sectional mediation or moderation relationships from depressive/anxiety symptoms on the link between cannabis use and psychotic experiences (Najolia, Buckner and Cohen, 2012; Reeves et al., 2014; Spriggens and Hides, 2015). Interestingly, these results are also supported by the reported acute effects of cannabis. Indeed, Freeman et al. (2015) showed that it is not the cognitive deficits exacerbated by intravenous administration of THC that lead to paranoia, rather it is the increase in negative affect (anxiety, worry, depression, and negative thoughts) that result in paranoiac symptoms. However, it should be noted that the indirect effect from growth in depression symptoms was modest and might be better captured using other measures of this cannabis effect (e.g., such as cognitive or neural indices) or more specific self-report depression symptoms (e.g., insomnia or poor concentration). These questions could be addressed in future studies examining the coevolution of specific depressive symptoms with cannabis use and/or PLE. The clinical implications of these results nevertheless highlight the need for reducing cannabis use in high-risk adolescents, as well as the importance of addressing depressive symptoms in programs aimed at preventing increasing PLE in high-risk youths.

The main limitation of the study is that substance use and symptoms severity were based on self-report, which is susceptible to bias. However, previous work has shown good sensitivity and specificity using the same items to identify interview-verifiable PLE (Kelleher, Harley, Murtagh and Cannon, 2011). Similarly, self-reported measures of substance use have previously demonstrated excellent discriminant (Clark and Winters, 2002), and predictive validity (White and Labouvie, 1989) with regards to adolescent substance-related behaviors problems. Other potential limitations are the lack of cannabis potency information and the low prevalence of regular cannabis users (20% of 16-year olds used at least on a monthly basis) in this sample, however, the study was designed and powered to detect small effects of cannabis, while controlling for other covariates.

CONCLUSION

Using a developmentally sensitive design, this study was able to examine the longitudinal emergence and development of psychotic experiences and cannabis use in a young Canadian community sample. Moreover, this study contributes to our knowledge of the role of

depression symptoms, cannabis use and psychotic experiences in developmental psychopathology pathways. Further research needs to replicate the present findings by investigating more closely into the sequence of events between the three phenomena.

KEY POINTS

- The magnitude of the increased risk for psychotic symptoms in cannabis users appears to be dose-dependent, influenced by age of cannabis use initiation, and premorbid psychosis vulnerability.
- The present results show that growth in cannabis use frequency during adolescence, not early onset of use (before 14 years old) was related to an increasing trajectory of psychotic-like experiences, even when controlling for cigarette use.
- The present study supports the role of increasing depression symptoms as a mediating factor between growth in cannabis use and an increasing trajectory of psychotic-like experiences in adolescents.
- There is a need for reducing cannabis use in high-risk adolescents, as well as addressing depressive symptoms in programs aimed at preventing increasing psychotic-like experiences in high-risk youths.

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Table 1. Demographic, substance use, cognitive, and clinical characteristics at baseline (13 years old) and third follow-up (16 years old) of the different PLE trajectory classes.

	Baseline			Third follow-up		
	PLEs trajectory classes					
Characteristics	Low decreasing N=2,152 (83.9%)	Moderate increasing N=211 (8.2%)	High decreasing N=203 (7.9%)	Low decreasing N=2,152 (83.9%)	Moderate increasing N=211 (8.2%)	High decreasing N=203 (7.9%)
Demographic						
Sex [x]: male, (%)	51.7[a]	41.7[b]	45.3[a,b]	—	—	—
Age, mean (SD)	12.82 (0.43)[a]	12.82 (0.46)[a]	12.79 (0.41)[a]	15.76 (0.39)[a]	15.76 (0.45)[a]	15.76 (0.39)[a]
SES, mean (SD)	5.37 (1.64)[a]	5.44 (1.72)[a]	5.28 (1.79)[a]	5.95 (1.66)[a]	5.72 (1.73)[a]	5.84 (1.80)[a]
Substance use						
Cigarette use [x], already used (%)	3.3[a]	2.4[a]	3.9[a]	16.4[a]	27.3[b]	19.3[a,b]
Cannabis use [x], already used (%)	3.1[a]	1.9[a]	3.9[a]	24.1[a]	40.2[b]	28.8[a]
Cognition						
IQ (unstandardized score), mean (SD)	17.13 (2.16)[a]	16.83 (2.09)[a]	16.93 (2.13)[a]	18.69 (2.20)[a]	18.34 (2.28)[a]	18.29 (2.09)[a]
SWM (number of errors), mean (SD)	14.87 (9.87)[a]	15.8 (10.14)[a]	16.44 (10.18)[a]	9.57 (8.54)[a]	10.17 (7.99)[a]	10.03 (8.30)[a]
Delayed recall (performance score), mean (SD)	6.20 (1.78)[a]	6.25 (1.71)[a,b]	5.84 (1.74)[b]	11.39 (3.81)[a]	11.00 (3.89)[a]	11.05 (4.40)[a]
Response inhibition (number of commissions errors), mean (SD)	16.80 (11.22)[a]	17.54 (11.35)[a,b]	19.65 (11.30)[b]	10.05 (9.86)[a]	13.04 (12.26)[b]	10.36 (10.54)[a,b]
Psychiatric symptoms						

Psychotic-like experiences, mean (SD)	2.13 (2.04)[a]	5.66 (3.66)[b]	10.78 (2.88)[c]	1.39 (1.82)[a]	8.17 (4.53)[b]	2.43 (2.41)[c]
Depression, mean (SD)	3.79 (4.44)[a]	5.94 (5.92)[b]	7.50 (7.45)[c]	4.82 (5.34)[a]	8.56 (7.41)[b]	6.76 (7.02)[c]
Anxiety, mean (SD)	2.21 (3.09)[a]	3.93 (4.61)[b]	5.09 (5.51)[c]	2.47 (3.60)[a]	4.92 (5.39)[b]	3.82 (5.12)[b]
Emotional problems, mean (SD)	2.36 (2.07)[a]	3.17 (2.48)[b]	3.73 (2.77)[c]	2.60 (2.29)[a]	3.73 (2.81)[b]	3.30 (2.63)[b]
Peer problems, mean (SD)	1.56 (1.56)[a]	1.94 (1.81)[b]	2.39 (1.97)[c]	1.62 (1.50)[a]	2.60 (2.10)[b]	2.23 (1.82)[b]
Externalizing problems, mean (SD)	5.54 (3.20)[a]	6.83 (3.34)[b]	7.53 (3.75)[b]	5.78 (3.22)[a]	7.70 (3.53)[b]	6.95 (3.25)[b]

PLE, Psychotic-like experiences; SD, Standard deviation; IQ, Intelligence quotient; SWM, Spatial working memory task.

Unless specified by ɤ, ANOVAs were used for comparing group means. When specified by ɤ, Chi-squared tests were used to compare proportions for categorical variables.

Different superscript letters refer to significant differences ($p < .05$, Bonferroni corrected) between the groups at a specific time point (e.g. Cannabis use at baseline). For instance, within a specific characteristic of a specific time point, if two scores are labeled with the same letter, the scores are not statistically different. If two scores are labeled with different letters, the scores are statistically different.

Table 2. Model fit indices and factor means and variances of the unconditional latent-growth curve models (from 13- to 16-years old).

	Model Fit Information				Growth factor means		Growth factor variances	
	$\chi^2_{(5)}$	CFI	SRMR	RMSEA	Intercept	Slope	Intercept	Slope
Independent variable								
Cannabis use frequency	26.07	0.95	0.04	0.04	0.04	0.14	0.05	0.08
Potential mediators								
IQ (unstandardized score)	5.95	1.00	0.02	0.01	17.03	0.53	1.91	0.13
SWM (number of errors)	47.07	0.97	0.03	0.06	14.76	-1.88	37.09	2.05
Delayed memory recall (performance)[a]	0.18 (1)	1.00	0.00	0.00	6.16	0.40	1.16	0.19
Response inhibition (number of commission errors)	78.29	0.93	0.05	0.08	16.11	-2.30	45.70	2.98
Anxiety severity	17.50	0.99	0.03	0.03	2.53	0.11	6.38	0.72
Depression severity	58.75	0.96	0.04	0.06	4.29	0.44	15.27	1.86

CFI, Comparative Fit Index; SRMR, Standardized root mean square residual; RMSEA, Root mean square error of approximation; IQ, Intelligence quotient; SWM, Spatial working memory. χ^2 (5): degrees of freedom are in parenthesis.

[a]All the unconditional latent-growth curve models were estimated over the four time points (i.e. 13–16 years old), except for the unconditional latent-growth curve model of delayed memory recall growth which was estimated over three time points (i.e. 13-15 years old) because performances plateaued at the 3rd follow-up (i.e. 16 years old) and thus the variance was reduced.

The growth curve factor means were all significantly different from 0 at $p < .001$ and showed an overall tendency to increase from 13- to 16-years old (except for the SWM and response inhibition data for which the number of errors is decreasing with age). Growth curve factor variances were also all significantly different from 0 at $p < .01$.

Table 3. Multinomial logistic regression models of cannabis use growth over 13-to-16 years old predicting youth's membership in the PLEs trajectory class.

Cannabis use	Trajectory class comparisons		
	High decreasing vs Low decreasing OR (95% CI)	Moderate increasing vs Low decreasing OR (95% CI)	Moderate increasing vs High decreasing OR (95% CI)
Model 1			
Cannabis, intercept	1.01 (0.33-3.03)	0.38 (0.09-1.66)	0.37 (0.06-2.29)
Cannabis, slope	1.00 (0.53-1.87)	3.26 (1.50-7.07)**	3.28 (1.47-7.27)**
Model 2 adjusted for cumulative cigarette use			
Cannabis, intercept	0.95 (0.28-3.17)	0.28 (0.05-1.54)	0.29 (0.04-2.40)
Cannabis, slope	0.92 (0.48-1.73)	2.59 (1.11-6.03)*	2.82 (1.23-6.48)*

Abbreviations: PLE, Psychotic-like experiences; OR, odds ratio; CI, confidence interval.

Model 1 and 2 were covaried for sex, age as well as baseline SES and externalizing behaviors.

*$p < .05$, **$p < .01$.

Table 4. Mechanisms of cannabis use on psychotic-like experiences trajectory.

Mediator	Path a Estimate (95% CI)	Path b Estimate (95% CI)	Path c' Estimate (95% CI)	Indirect path Estimate (95% CI)
Symptoms				
Growth in anxiety	.07 (-.01, .16)	.40 (.28, .53)***	.63 (.18, 1.08)**	—
Growth in depression	.29 (.15, .42)***	.25 (.17, .32)***	.59 (.13, 1.05)*	**.07 (.03, .11)****
Cognitive functioning				
Growth in IQ	-.01 (-.04, .02)	-.21 (-.72, .30)	.66 (.20, 1.12)**	—
Growth in SWM (number of errors)	.07 (-.04, .17)	.01 (-.14, .15)	.66 (.20, 1.12)**	—
Growth in delayed memory recall[a]	.02 (-.01, .04)	-.21 (-.63, .21)	.66 (.20, 1.12)**	—
Growth in response inhibition (number of commission errors)	.12 (.03, .21)**	.12 (.00, .24)~	.64 (.19, 1.10)**	.01 (.00, .03)

CI, Confidence interval; IQ, Intellectual quotient; SWM, Spatial working memory.

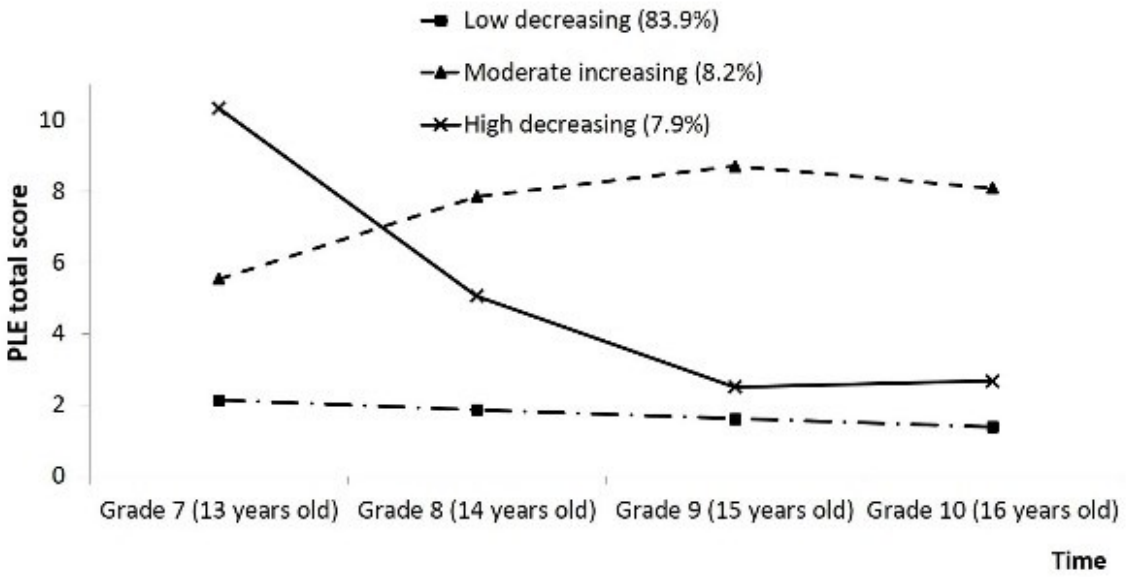
All models included age, sex as well as baseline sociodemographic status, externalizing behaviors and cannabis use (intercept) as covariates. The outcome (trajectory of psychotic-like experiences) is coded: 1 = moderate increasing trajectory, and 0 = low decreasing trajectory (control group). Mediation/indirect effects were examined only when mediators had significant (or marginal) a and b pathways.

Indirect effects were tested with MacKinnon's products of coefficients method with a logistic outcome. Indirect estimates in boldface represent significant indirect pathways.

[a]All growth factors (slopes) were estimated from unconditional latent-growth curve models over the four time points (i.e. 13–16 years old), except for the delayed recall memory growth which was estimated over three time points (i.e. 13–15 years old) because performances plateaued at the 3rd follow-up (i.e. 16 years old) and thus the variance was reduced.

*$p < .05$; **$p < .01$; ***$p < .001$. ~ Marginal effect: $.07 > p > .05$.

Figure 1. Developmental trajectories of psychotic-like experiences between 13- to 16-years old.



PLE, psychotic-like experiences.

3.1 A closer look at the neurocognitive alterations associated with psychosis risk

This second manuscript highlights the prominent role of affective symptoms over impaired cognitive functioning underlying the relationship between cannabis use and increasing psychotic-like experiences in adolescents. However, the way we have modeled cannabis use, potential mediators, and trajectories of psychotic-like experiences (i.e., growth from 13- to 16-years old on every variable), does not allow testing for temporal precedence between cannabis use and potential mediators or between potential mediators and psychotic-like experiences. For instance, a mediational model that would have tested whether the relationship between cannabis use at age 14 and elevated psychotic-like experiences at age 16 is explained by a mediator measured at age 15 may have been informative on the specific sequence of events. However, this model would not have informed on how these respective phenomena change during adolescence, and whether they evolve concomitantly or not. Our mediation analysis revealed that growth in cannabis use, psychotic-like experiences and affective symptoms seem strongly related as they appear to evolve in parallel.

It is important to mention that the relationship between growth in cannabis use and increasing psychotic-like experiences was marginally explained by an altered development of cognitive abilities, namely response inhibition capacities. These results are somewhat surprising considering that meta-analyses on the long-term effects of cannabis use have demonstrated that, following regular cannabis use, the most impaired cognitive domains are memory and working memory, attention and processing speed (Ganzer et al., 2016; Grant et al., 2003; Schoeler et al., 2016; Schreiner and Dunn, 2012). It is worth noting that longitudinal studies specifically following adolescent samples did observe a significant decline in executive functions and response inhibition capacities which was predicted by both increasing cannabis use and an early age of onset (< 15 years old) (Castellanos-Ryan et al., 2017; Morin et al., 2018).

Although informative on the behavioral mechanisms of the relationship between cannabis and psychotic-like experiences, this second study does not provide further information on the neurophysiological processes underlying this complex relationship. Consequently, the third study aimed to investigate the abnormal neurophysiological processes associated with

psychotic-like experiences. Unfortunately, the sample used in this third study did not allow for the investigation of whether cannabis use further alters these neurophysiological processes in youths with psychotic-like experiences (because there was no reported use at baseline).

Considering the important mediational role of increased depression symptoms found in the second study, I examined, as part of the third study, the functional neural correlates of emotion processing in youths reporting psychotic-like experiences. On one hand, emotion processing, as part of the social cognition domain, has been found to be altered in patients with psychosis (Fusar-Poli et al., 2012). On the other hand, abnormal processing of facial expressions has also been known to be a core feature of major depressive disorders and depressive symptoms. For instance, individuals with depression tend to exhibit an increased emotional salience to negative emotions compared to healthy controls (Naranjo et al., 2011). By evaluating the neural processes implicated in emotion processing, the third study aimed to highlight the altered functional correlates underlying the developmental relationship between psychotic-like experiences and depressive symptoms.

Another potential neurophysiological mechanism that warrants future research would be impaired reinforcement learning since individuals that report depression symptoms also show an abnormal positive motivational salience. Studies of reward processing have observed a blunted reward response from the striatum in patients with a major depression disorder (Whitton et al., 2015). A similar blunted response from the ventral striatum during anticipation of reward seems to characterize psychosis spectrum disorders and explains why psychosis patients manifest impaired learning of stimulus-reinforcement associations (Radua et al., 2015).

Following on the finding of marginally impaired response inhibition capacities in youths with increasing psychotic-like experiences, the third study also examined whether the underlying neural processes could be altered in youths with such experiences. These results would then add to the limited literature where Jacobson et al. (2010) showed that reduced cerebral (i.e., frontal and temporal cortices) activity during successful and failed inhibition consisted of an early marker of psychotic-like experiences.

Altogether, the results of this third study may shed light onto the early brain functional markers associated with a vulnerability to psychosis.

4. Brain functional correlates underlying neurocognitive impairments associated with a vulnerability to psychosis: article no.3

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Josiane Bourque contributed to the idea of this project in youths with psychotic-like experiences and helped choosing the analytic strategy for this manuscript. She conducted the analyses, interpreted the results, and wrote the first draft of this manuscript.

Philip A. Spechler conducted the cross-validated logistic regressions.

Stéphane Potvin participated in the decision on the analytic strategy, helped results interpretation, and critically revised the manuscript.

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Hugh Garavan contributed specifically to the idea of this project in youths with psychotic-like experiences, helped with the machine learning analyses, and critically revised the manuscript.

Patricia Conrod contributed specifically to the idea of this project in youths with psychotic-like experiences, participated in the decision on the analytic strategy, helped results interpretation, and critically revised the manuscript.

All authors have reviewed and approved the final version of this manuscript.

Functional neuroimaging predictors of self-reported psychotic symptoms in adolescents

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ABSTRACT

Objective: This study investigated the neural correlates of psychotic-like experiences in youths during tasks involving inhibitory control, reward anticipation, and emotion processing. A secondary aim was to test whether these neuro-functional correlates of risk were predictive of psychotic symptoms 2 years later.

Method: Functional imaging responses to three paradigms – the stop-signal, monetary incentive delay, and faces tasks – were collected in youths at age 14, as part of the IMAGEN study. At baseline, youths from London and Dublin sites were assessed on psychotic-like experiences, and those reporting significant experiences were compared with matched control subjects. Significant brain activity differences between the groups were used to predict, with cross-validation, the presence of psychotic symptoms in the context of mood fluctuation at age 16, assessed in the full sample. These prediction analyses were conducted with the London-Dublin subsample (N=246) and the full sample (N=1,196).

Results: Relative to control subjects, youths reporting psychotic-like experiences showed increased hippocampus/amygdala activity during processing of neutral faces and reduced dorsolateral prefrontal activity during failed inhibition. The most prominent regional difference for classifying 16-year-olds with mood fluctuation and psychotic symptoms relative to the control groups (those with mood fluctuations but no psychotic symptoms and those with no mood symptoms) was hyperactivation of the hippocampus/amygdala, when controlling for baseline psychotic-like experiences and cannabis use.

Conclusions: The results stress the importance of the limbic network's increased response to neutral facial stimuli as a marker of the extended psychosis phenotype. These findings might help to guide early intervention strategies for at-risk youths.

INTRODUCTION

There is evidence of a continuity between clinical and subclinical phenotypes of psychosis that is measurable in the general population (van Os, Linscott, Myin-Gerneys, Delespaul and Krabbendam, 2009) and in individuals with a psychiatric diagnosis (McGrath et al., 2016). On a clinical level, individual differences in psychosis proneness are expressed across a number of psychiatric conditions besides schizophrenia, namely mood, anxiety, eating, impulse control, and substance use disorders (McGrath et al., 2016). At a subclinical level this liability is characterized by "attenuated" or "brief" psychotic symptoms that might not coexist with other diagnostic criteria (frequency and intensity) to meet full diagnosis, yet sufficient impairment is observed to motivate treatment seeking (Yung, Nelson, Thompson and Wood, 2010). This clinical high-risk state has been shown to be a robust risk factor for progression to clinically significant psychiatric disorders (Fusar-Poli et al., 2012), but does not necessarily predict to one specific disorder and instead is predictive of a number of psychopathologies that include psychotic symptoms (Lin et al., 2015).

At the far end of the extended psychosis continuum are children and adolescents from the community who report psychotic-like experiences (i.e., perceptual abnormalities and delusional thoughts) prior to the onset of more-impairing psychotic symptoms. These preclinical experiences, even though they are common in children and young adolescents (7% to 23% [Kelleher et al., 2012]), are associated with increased risk for psychotic or other axis I disorders over the longer term (Kelleher et al., 2012; Poulton et al., 2000). Studying young adolescents prone to such experiences will help to identify etiologic processes implicated in psychosis proneness, without the confounds of diverse risk factors and iatrogenic effects, such as substance misuse, medication, and social impairment (Mackie et al., 2013). Investigating the neural correlates of this preclinical psychosis proneness during cognitive functioning can shed light on early altered neural processes prior to significant cognitive impairments.

However, the vast majority of functional magnetic resonance imaging (fMRI) studies have focused on adults with a clinical risk to psychosis, not on young adolescents reporting psychotic-like experiences. These studies have mostly investigated the neural circuits implicated in executive functioning, social cognition and reinforcement learning. Recent fMRI studies in individuals with psychosis spectrum symptoms have shown significant reduced activation in the dorsolateral prefrontal cortex (DLPFC) during executive functioning (e.g., working memory,

inhibitory control) relative to low-risk control subjects (Colibazzi et al., 2016; Wolf et al., 2015). These results are consistent with findings of DLPFC hypoactivation in patients with clinical diagnoses of psychosis or bipolar disorder during tasks involving working memory and response inhibition (Keener and Phillips, 2007; Minzenberg, Laird, Thelen, Carter and Glahn, 2009), suggesting that the brain markers associated with psychosis proneness cross diagnostic boundaries.

Social cognition, which encompasses emotion processing and theory of mind processes, has also been identified as a domain that might differentiate individuals at clinical risk for psychosis from low-risk individuals (Fusar-Poli et al., 2012). Neuroimaging studies show that the experience of high-arousal negative emotions is associated, in individuals at clinical risk relative to healthy control subjects, with both reduced (Modinos et al., 2015) and increased (Wolf et al., 2015) activation of frontolimbic areas, depending on the contrast used (Anticevic et al., 2012), while viewing neutral material is more consistently associated with increased activation of this network (Modinos et al., 2015; Seiferth et al., 2008).

Another core feature of psychosis, dysfunctional reinforcement learning, has been shown to be shared with distinct diagnostic categories, such as major depressive and bipolar disorders (Whitton, Treadway and Pizzagalli, 2015). A recent meta-analysis of fMRI studies demonstrated that psychosis spectrum disorders are associated with a blunted response from the ventral striatum during anticipation of reward, which might explain why patients manifest impaired learning of stimulus-reinforcement associations (Radua et al., 2015). Functional MRI studies with clinically at-risk individuals have shown modestly reduced activity in frontostriatal regions during reward anticipation, relative to control subjects (Juckel et al., 2012; Wotruba et al., 2014).

Among the very few neuroimaging studies investigating the early neural correlates of preclinical psychosis proneness prior to the onset of more-impairing psychotic symptoms, those by Modinos et al. (2010; 2012) showed that community youths self-reporting psychotic-like experiences had reduced activation of the medial prefrontal cortex, insula, and amygdala during passive viewing and reappraisal of negative pictures relative to low-risk youths. In a quite young sample of 11- to 13-year-olds reporting these experiences, Jacobson et al. (2010) observed reduced activity in prefrontal and temporal regions during a response inhibition task. However, the sample was small (11 in the at-risk group). Consequently, we intended to extend these

findings in another community sample of young adolescents with psychotic-like experiences. Of note, considering that psychotic-like experiences are, for most individuals, transient and not persistent (van Os et al., 2009), it is crucial to understand to what extent these early neural abnormalities relate to a subsequent psychosis vulnerability in terms of clinically validated symptoms.

The primary aim of the present exploratory study was to identify brain correlates of psychotic-like experiences in youths prior to exposure to regular substance use, by means of fMRI measures of emotion processing, inhibitory control, and reward anticipation. The data are from the IMAGEN study, in which two sites, London and Dublin, assessed these preclinical experiences in participants when they were 14 years old. The secondary aim was to validate whether these brain correlates predicted emergence of psychotic symptoms in the context of mood fluctuation symptoms at age 16 in the full IMAGEN sample. We hypothesized that psychotic-like experiences would be associated with reduced activity in the executive network during response inhibition, altered activity in frontolimbic regions during processing of emotional and nonemotional stimuli, as well as modest reductions in ventral striatum activity during anticipation of reward.

METHODS

Participants

In the large European multicenter IMAGEN study, 2,257 14-year-old adolescents were recruited through high schools from eight sites across the United Kingdom, Ireland, France, and Germany. Parents and adolescents gave written informed consent to the study procedures. All procedures were approved by each local institutional ethics committee. A detailed description of the study recruitment and assessment procedure, exclusion criteria, data storage and safety, as well as imaging acquisition protocol may be found elsewhere (Schumann et al., 2010).

Measures

For a more detailed description of the study measures, see the data supplement accompanying the online version of this article.

Psychotic-like experiences. At baseline, the 14-year-olds from London and Dublin completed the self-report Adolescent Psychotic-Like Symptoms Screener (Kelleher, Harley,

Murtagh and Cannon, 2011), which contains seven items evaluating perceptual abnormalities and delusional thoughts in the past 6 months. Participants were asked to rate their responses to different statements on a 1-point scale (0=not true, 0.5=somewhat true, 1=certainly true). Based on previous studies by Cannon's team (Kelleher et al., 2011; Jacobson et al., 2010), to identify youths with significant psychotic-like experiences, we used the following criteria: a total score ≥2 and a score ≥0.5 on the auditory hallucination (this item revealed 88% probability of predicting which individuals would be classified as "at risk", as determined by consensus ratings from the Structured Interview for Prodromal Syndromes).

Among 410 adolescents from the London and Dublin sites (mean age=14.3 years, SD=0.4; 51.7% girls), 300 had complete fMRI and behavioral information. Among them, 27 were classified as having significant psychotic-like experiences. None had yet started using cannabis, and they reported minimal alcohol and cigarette use (<3-5 times in the previous year). By means of an in-house groupwise matching script designed by the IMAGEN consortium, the group was matched (on sex, handedness, imaging site, general IQ, and puberty development) to a control group five times as large (135 adolescents), who had a total score ≤ 1 and a score of 0 on the auditory hallucination question.

Psychotic symptoms at age 16. For the secondary objective of the study, psychotic symptoms were evaluated with the self-report Development and Well-Being Assessment interview (www.dawba.com) (Goodman, Ford, Richards, Gatward and Meltzer, 2000), a computer-based package of questionnaires designed to generate DSM-IV-TR psychiatric diagnoses for 5- to 16-year-olds. The schizophrenia module was not administered to participants at age 16; the bipolar module was more developmentally appropriate for this age group. Therefore, all participants answered initial screening questions assessing mood dysregulation ("rapid mood changes" and "abnormally high mood"), and if they gave a positive, they were then asked three specific items assessing the presence of visual and auditory hallucinations and delusional beliefs. Among the 300 individuals from London and Dublin with complete baseline assessments, 246 (82.0%) completed the bipolar module at age 16 and were further divided into three groups: those who endorsed mood dysregulation plus hallucinatory/delusional symptoms (i.e., group with mood and psychotic symptoms, N=12), those reporting mood dysregulation without hallucinatory/delusional symptoms (i.e., group with

mood symptoms only, N=80) and those who did not endorse the mood dysregulation criteria (i.e., no mood symptoms group, N=154).

Additionally, we conducted similar analyses on the full IMAGEN sample. Among the 1,602 participants reassessed at 16 years old, 1,196 had complete fMRI and behavioral information and were divided into three groups: those with mood and psychotic symptoms (N=72), those with mood symptoms only (N=451), and those without any mood symptoms (N=673).

Neuroimaging tasks. We report results from three task-based fMRI paradigms: 1) the faces task, to assess emotional processing, 2) the stop-signal task, to evaluate motor inhibitory control, and 3) a modified version of the monetary incentive delay task, to examine reward anticipation. The block-design faces task, known to elicit prefrontal and amygdala activations (Grosbras and Paus, 2006), uses video clips displaying a neutral expression progressively turning into an angry or a second neutral expression. A control condition displays expanding/contracting circles. In the event-related adaptation of the stop-signal task used to measure activation of the frontostriatal network (Chevrier, Noseworthy and Schachar, 2007), a motor response to high-frequency go signals (80% of trials) has to be inhibited when, infrequently and unexpectedly (in randomised 20% of trials), a stop signal appears after the go signal. In the modified monetary incentive delay task, participants had to respond to a target in order to win a previously indicated amount of points (three trial types: no win, small win, and large win). In the anticipation phase, which elicits striatal and medial prefrontal activity (Knutson, Adams, Fong and Hommer, 2001), participants were presented with cues signaling the amount of reward that could be won in a given trial.

Data Analysis

fMRI. To test differences in brain activity between the groups reporting and not psychotic-like experiences on each of the contrasts of interests (faces: angry *vs.* neutral and neutral *vs.* control; stop-signal: stop success *vs.* baseline and stop failure *vs.* baseline; monetary incentive delay: anticipation of large reward *vs.* no reward), we conducted two-sample *t* tests, using a whole-brain approach in SPM8 (Wellcome Trust Centre for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Following the recommendations of Eklund et al. (2016) for controlling type 1 error, we used the new version of AFNI's 3dClustSim

(https://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim.html) to calculate a voxel-wise threshold correcting for multiple comparisons and controlling for family-wise error rate. Significant voxels were required to be part of a cluster of more than 24 contiguous voxels, giving a 0.05% probability of a cluster surviving due to chance. For our secondary objective, we used a more liberal threshold: significant voxels were required to be part of a cluster of at least 10 contiguous voxels. Then we created regions of interest based on the regions' coordinates and extracted the mean contrast value (betas) for each region of interest and for each subject.

Machine learning procedure. For our secondary objective, we aimed to classify the youths according to 16-year-olds' psychotic outcomes with fMRI information. We conducted cross-validated logistic regressions with elastic-net regularization to model this relationship. Cross-validation is used to evaluate how well a predictive model generalizes to out-of-sample observations. On one hand, leave-one-out cross-validations were used during classification of the groups within the smaller London-Dublin subsample; on the other hand, *k*(10)-fold cross-validations were used during classification of the groups within the full sample. Cross-validation analysis within the London-Dublin subsample allowed testing of the predictive capacity of the brain markers while controlling for baseline psychotic-like experiences. Considering that the sample size of the groups was much larger in the full sample, we were able to control for more predictors, such as developmental risk factors for psychotic symptoms (i.e., cannabis, alcohol and cigarette use, as well as internalizing and externalizing behaviors (Goodman, Renfrew and Mullick, 2000)), assessed at age 14.

Elastic-net regularization is used to achieve better prediction performance by penalizing the regression coefficients in an attempt to minimize overfit. Elastic-net regularization is an example of a sparse regression method, which imposes a hybrid of both L1- and L2-norm penalties (i.e., penalties on the absolute [L1 norm] and squared [L2 norm] values of the regression coefficients). Model performance was evaluated by using the area under the curve (AUC) of the receiver-operating characteristic (ROC), which quantifies the predicted sensitivity (true positive rate) as a function of false positive rate (1-specificity).

RESULTS

Demographic and Clinical Characteristics at Age 14

Reported in Table 1 are the means of the variables used to match the 27 adolescents with the 135 controls subjects without psychotic-like experiences (no significant differences between the groups). Furthermore, the groups were not different on age or on alcohol, cigarette, and cannabis use in the previous year.

Task Activation Differences Between Groups

Between-group differences were present in small clusters in the three tasks (Table 2). Only two significant clusters of activity differences survived the cluster-corrected threshold of 24 contiguous voxels: a hyperactivation of the right anterior hippocampus/amygdala during passive viewing of neutral/ambiguous faces and a reduced activity in the right DLPFC during failure to inhibit a motor response in youths with psychotic-like experiences (Figure 1).

Prediction of Psychotic-Related Symptoms at Age 16

First, from the London-Dublin subsample, we differentiated youths reporting both mood- and psychotic-related symptoms at 16 (N=12) from those reporting no mood symptoms (N=154). The final model returned from this analysis had a mean AUC of 0.709 (95% CI=0.706-0.713, $p<0.01$) (Figure 2A). This model included all brain regions that survived the more liberal threshold of 10 contiguous voxels (all regions reported in Table 2) and controlled for psychotic-like experiences score at age 14 as well as demographic information (i.e., age, sex, handedness, and site). All features were present in at least 9 folds (out of 10) of the final model. In addition to psychotic-like experiences, the most robust brain classifiers were cerebellum activity during processing of angry faces and the hippocampus/amygdala activity during neutral faces processing (Table 3, model A). The performance of each domain on its own (i.e., brain activity vs. psychotic-like experiences) is displayed in Figure S1 in the online data supplement. We could not significantly distinguish youths with mood symptoms only (N=80) from the other two groups, i.e., the group with both mood and psychotic symptoms (AUC=0.532, 95% CI=0.525-0.539, p=0.36) and the group with no mood symptoms (AUC=0.453, 95% CI=0.450-0.456, p=0.90).

In the second set of prediction analyses, using the full IMAGEN sample, we differentiated youths reporting both mood- and psychotic-related symptoms at age 16 (N=72) from those reporting no mood symptoms (N=673) and from those with mood symptoms only

(N=451). The final models returned from this analysis had mean AUC values of 0.633 (95% CI=0.630-0.636, p<0.0001) and 0.615 (95% CI=0.614-0.617, p=0.001), respectively (Figure 2, models B and C). These models included all brain regions that survived the more liberal threshold of 10 contiguous voxels and controlled for internalizing and externalizing behaviors, use of cigarettes, alcohol, and cannabis, as well as demographic information (i.e., puberty development index, handedness, age, sex, and site). In the classification of the mood and psychotic symptoms group relative to the no mood symptoms group, only internalizing and externalizing behaviors, cigarette and cannabis use, hippocampus/amygdala and cerebellum activity during neutral faces processing, and cerebellum activity during angry faces processing were present in at least 9 folds of the final model (Table 3, model B). However, when classifying the group with mood and psychotic relative to the group with mood symptoms only, we found that all features were present in at least 9 folds of the final model, with cerebellum activity during angry faces processing, fusiform activity during anticipation of reward, internalizing behaviors, cigarette and cannabis use, and hippocampus/amygdala activity during neutral face processing making the strongest contribution to group classification (Table 3, model C).

Finally, we differentiated individuals with mood symptoms only (N=451) from those reporting no mood symptoms (N=673) with a mean AUC of 0.553 (95% CI=0.552-0.553, p=0.002), barely better than chance (Figure 2D). All features except the DLPFC activity during failed response inhibition were present in at least 9 folds of the final model. The most important classifiers were internalizing and externalizing behaviors, cannabis use, reduced activity from the cerebellum during neutral faces processing, puberty development scale, and site (Table 3, model D).

DISCUSSION

At age 14, across the brain networks implicated in emotion processing, response inhibition, and reward anticipation, the cluster-corrected markers of psychotic-like experiences included an increased response from the hippocampus/amygdala during processing of neutral material as well as reduced activity from the DLPFC during failed inhibition. Of note, hyperactivity from the hippocampus/amygdala during the processing of neutral faces further discriminated individuals with mood- and psychotic-related symptoms at 2-year follow-up relative to the other groups in both the London-Dublin subsample and the full IMAGEN sample,

even when controlling for baseline psychotic-like experiences as well as cannabis and cigarette use. The cross-validation models best discriminated the group with mood and psychotic symptoms from the group with no mood symptoms, in comparison to discriminating the group with mood symptoms only from the group with no mood symptoms.

One of the most replicated neural markers of psychosis and clinical high-risk states is hypofunctioning of the PFC and DLPFC during executive functioning (Fusar-Poli et al., 2007). Our results support findings from other community-based studies of youths reporting psychosis-spectrum symptoms showing reduced PFC activity during working memory and response inhibition tasks (Jacobson et al., 2010; Wolf et al., 2015). However, the activity of the DLPFC during the stop-signal task was a weak brain classifier for adolescents reporting both mood and psychotic symptoms relative to the other groups. A possible explanation might be that reduced DLPFC activation is directly related not to positive or mood symptoms, but more to disorganized symptoms or cognitive deficits (which were not assessed by our screening tools) (Goghari, Sponheim and MacDonald, 2010; Wolf et al., 2015). Consequently, DLPFC alterations would appear to be a promising neurofunctional marker of the clinical risk for psychosis when, in addition to positive and negative symptoms, significant cognitive impairments are observed, but not a robust marker in youths reporting psychotic-like experiences prior to a cognitive decline. It is worth mentioning that the use of a working memory task instead of response inhibition could have yielded more significant DLPFC results because working memory paradigms, in comparison to Stroop or Go-NoGo tasks, consistently elicit a more widespread locus of significant activation in the DLPFC and anterior cingulate cortex in both healthy control subjects and schizophrenia patients (Minzenberg et al., 2009).

The current exploratory study stresses the importance of an observed increased activity in the limbic network in the extended psychosis phenotype. Both fMRI and perfusion studies have highlighted increased hippocampal activity at rest and across cognitive tasks in clinically at-risk individuals (Allen et al., 2016; Fusar-Poli et al., 2007). Interestingly, Schobel et al. (2013) demonstrated that baseline hypermetabolism of the hippocampus in clinical high-risk individuals is directly related to a subsequent volume loss (via a hyperglutamatergic state), thereby supporting the heightened hippocampus activity as a highly promising early marker of vulnerability to psychotic disorders. In the context of emotion processing, a recent meta-analysis showed that the apparent deficit in amygdala activity observed in individuals with a psychotic

disorder during the viewing of negative material may be explained by an elevated amygdala response to neutral material (Anticevic et al., 2012). These findings have led some authors to propose that abnormalities in salience attribution might be core to the extended psychosis phenotype, rather than stress reactivity per se (Reininghaus et al., 2016). Thus, the increased neural response to neutral information may reflect an atypical assignment of motivational salience to these stimuli (Kapur, 2003). Results from other cognitive studies showing an impaired decoding of facial expressions in patients with psychosis and high-risk populations further suggest that the abnormal neural activity in the current study might be due to an erroneous identification of neutral faces specifically. For instance, children and adolescents reporting psychotic-like experiences overattribute significance (i.e., negative valence) to neutral faces (Dickson, Calkins, Kohler, Hodgins and Laurens, 2014). Since impaired emotion recognition is linked to declining social functioning in high-risk populations (van Rijn et al., 2011), it represents a potential target for strategies to prevent psychosis symptoms in at-risk youths, prior to subsequent impaired social functioning.

Since cerebellar activity significantly contributed to the classification of youths with mood- and psychotic-related symptoms relative to the other groups, even in the absence of a marked difference in functional activity between individuals with and without psychotic-like experiences at age 14, its role in emotion processing in the psychosis spectrum remains elusive but deserves to be clarified in the future.

No cluster-corrected differences in brain activity between 14-year-olds with and without psychotic-like experiences were observed during reward anticipation. Even when a more liberal cluster threshold was used, significant activity related to reward anticipation did not robustly contribute to discriminate the groups at age 16. These findings are inconsistent with recent fMRI studies showing a blunted response from the ventral striatum during reward processing in psychosis and high-risk individuals (Lancaster et al., 2016; Radua et al., 2015). A possible explanation for this negative result may be given by the finding by Radua et al. (2015) of a negative correlation between striatal activity and the severity of negative symptoms in both patients and individuals at clinical risk for psychosis. Here, only positive experiences/symptoms were assessed.

Limitations

The use of an extended risk phenotype (i.e., youths self-reporting psychotic-like experiences) may constitute both a strength and weakness. While it might be too liberal to predict vulnerability to specific disorders, particularly those with very low prevalence, one advantage of this approach is that it might capture a dimension of vulnerability that is implicated in a number of different psychopathological outcomes. The current study also did not investigate interactions with family, substance misuse, and genetic data, which might further clarify how this extended phenotype is implicated in future psychiatric outcomes. Another potential limitation to the study is that the use of the bipolar module at age 16 may have underestimated the emergence of psychotic symptoms in the group with no mood symptoms. However, the prevalence of psychotic symptoms is low at the end of adolescence (e.g., 5%-7%) (van Os et al., 2009). Finally, the timeframe for studying outcomes was relatively brief and might predate the typical age of onset of psychotic disorders; however, this might also be considered a strength, as we were able to detect relevant brain-related abnormalities before psychotic experiences begin to cause significant functional and cognitive impairment and substance misuse, and require medical intervention.

CONCLUSIONS

The results of the present study suggest that an aberrant neural response to nonsalient stimuli may be an important early vulnerability marker for psychosis, at least in the context of mood fluctuations. These findings might help to guide early intervention strategies for at-risk youths. It has yet to be determined whether individual differences in emotional reactivity to nonsalient stimuli can be modified in young adolescents and whether such modifications have any clinical significance for high-risk youths.

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Table 1. Baseline demographic, clinical, and substance use characteristics of 14-year-olds with psychotic-like experiences and control subjects

Characteristic	Group with PLE (N=27)	Control group (N=135)	P Value[a]
Demographic			
Sex: female, (%)[b]	66.7%	65.2%	.88
Age at testing, mean (SD)	14.26 (0.31)	14.35 (0.38)	.24
Imaging site: London, (%)[b]	59.3%	64.4%	.61
Right handed, (%)[b]	92.9%	91.0%	.89
Puberty status, mean (SD)	3.73 (0.72)	3.69 (0.69)	.77
Cognition			
Verbal IQ, mean (SD)	107.28 (13.64)	110.25 (13.43)	.31
Abstract reasoning IQ, mean (SD)	106.60 (16.70)	107.34 (14.04)	.82
Substance use (previous year)			
Cigarette use, mean (SD)	0.43 (1.17)	0.40 (1.18)	.92
Alcohol use, mean (SD)	2.25 (1.84)	1.90 (1.84)	.37
Cannabis use, mean (SD)	0.00 (0.00)	0.08 (0.48)	.36

Abbreviations: SD, standard deviation; PLE, Psychotic-like experiences.

[a] All p-values in the table are 2-tailed, uncorrected.

[b] Unless specified by [b], t-tests were used for comparing group means. When specified by [b], Chi-squared tests were used to compare proportions for categorical variables.

Table 2. Regions showing differences in fMRI contrasts between 14-year-olds with psychotic-like experiences (PLE) and control subjects

Task, Contrast, and Region	Direction	T-Value	MNI coordinates x	y	z	Voxels	Effect size (Cohen's *d*)
Faces task							
Angry > Neutral							
Cerebellum L	CT > PLE	3.58	-3	-79	-38	10	
Neutral > Control							
Hippocampus/amygdala R	PLE > CT	4.68	30	-13	-17	25[b]	0.987
Middle temporal gyrus R/ temporal pole	PLE > CT	4.19	54	5	-20	10	
Cerebellum L	PLE > CT	3.88	-42	-49	-32	11	
Inferior frontal gyrus, orbital part L	CT > PLE	4.18	-30	32	-20	13	
Lingual gyrus R	CT > PLE	4.15	21	-55	-5	12	
Fusiform gyrus L	CT > PLE	4.14	-33	-31	-17	12	
Stop-signal task[c]							
Stop failure > Baseline							
Middle frontal gyrus R	CT > PLE	4.65	30	38	40	37[b]	0.980
Caudate nucleus L	CT > PLE	4.41	-15	8	19	10	
Monetary incentive delay task							
Anticipation large win > No win							
Anterior/middle cingulate gyrus R	PLE > CT	3.77	3	29	31	13	
Fusiform gyrus L	CT > PLE	4.40	-27	-37	-23	15	

Abbreviations: MNI, Montreal Neurological Institute space; L, left; R, right; CT, Control group reporting no significant psychotic-like experiences; PLE, Group reporting significant psychotic-like experiences.

[b]Cluster is corrected at $p<0.05$ according to AFNI 3dClustSim. Other brain regions presented survived the more liberal cluster threshold of ≥ 10 contiguous voxels.

[c]In the stop-signal task, there was no significant difference for the contrast examining greater activation during stop success than at baseline.

Table 3. Beta weights for prediction of symptoms at age 16 from brain activation at age 14

Predictor	**Mean Beta[b]**
Model A: classification of mood and psychotic symptoms vs. no mood symptoms in London-Dublin subsample	
Demographic information	
Age	0.101
Sex (male)	-0.079
Site	0.105
Handedness (right-handed)	-0.182
Symptoms	
Psychotic-like experiences at baseline	0.577
Brain regions of interest	
DLPFC during failed inhibition	0.021
Caudate during failed inhibition	-0.088
Cerebellum during angry faces processing	0.276
Hippocampus/amygdala during neutral faces processing	0.253
Middle temporal during neutral faces processing	0.070
Cerebellum during neutral faces processing	-0.234
Inferior frontal during neutral faces processing	-0.126
Lingual gyrus during neutral faces processing	-0.142
Fusiform gyrus during neutral faces processing	-0.077
ACC/MCC during anticipation of reward	0.066
Fusiform gyrus during anticipation of reward	-0.216

Predictor	Mean Beta[b]
Model B: classification of mood and psychotic symptoms vs. no mood symptoms in full sample	
Demographic and substance use information	
Cannabis use in the previous year	0.137
Lifetime cigarette use	0.150
Symptoms	
Internalizing behaviors	0.307
Externalizing behaviors	0.084
Brain regions of interest	
Cerebellum during angry faces processing	0.092
Hippocampus/amygdala during neutral faces processing	0.073
Cerebellum during neutral faces processing	-0.090

Predictor	Mean Beta[b]
Model C: classification of mood and psychotic symptoms vs. mood symptoms only in full sample	
Demographic and substance use information	
Age	0.027
Sex (male)	0.188
Site	0.023
Handedness (right-handed)	-0.020
Puberty development score	0.077
Cannabis use in the previous year	0.250
Lifetime cigarette use	0.268
Alcohol use in the previous year	-0.171
Symptoms	
Internalizing behaviors	0.297

Externalizing behaviors	0.098
Brain regions of interest	
DLPFC during failed inhibition	0.100
Caudate during failed inhibition	-0.142
Cerebellum during angry faces processing	0.317
Hippocampus/amygdala during neutral faces processing	0.192
Middle temporal during neutral faces processing	0.100
Cerebellum during neutral faces processing	-0.066
Inferior frontal during neutral faces processing	-0.101
Lingual gyrus during neutral faces processing	-0.158
Fusiform gyrus during neutral faces processing	-0.135
ACC/MCC during anticipation of reward	-0.005
Fusiform gyrus during anticipation of reward	-0.306

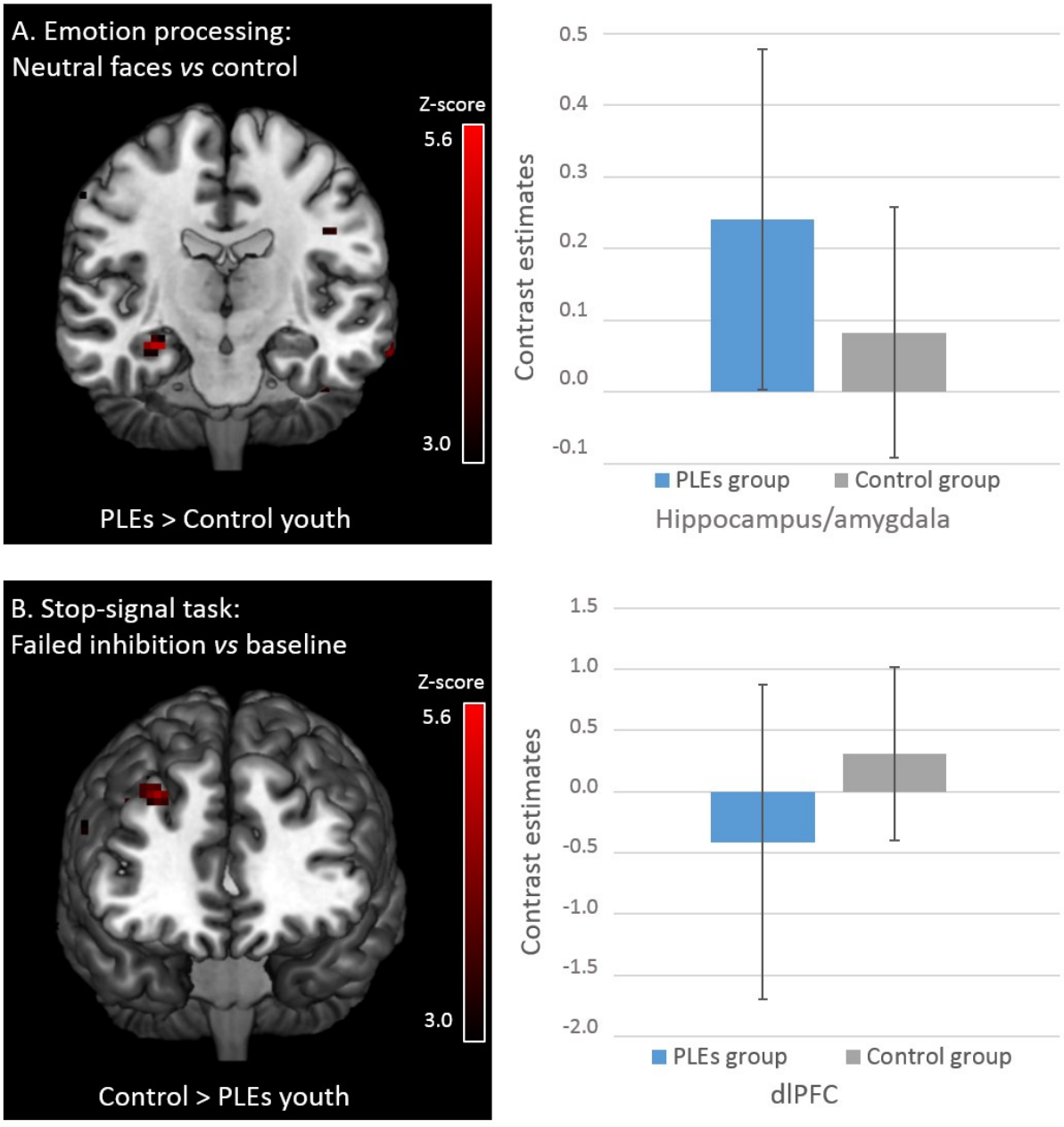
Predictor	**Mean Beta[b]**
Model D: classification of mood symptoms only vs. no mood symptoms in full sample	
Demographic and substance use information	
Age	-0.024
Sex (male)	-0.053
Site	-0.097
Handedness (right-handed)	0.041
Puberty development score	0.096
Cannabis use in the previous year	0.140
Lifetime cigarette use	-0.057
Alcohol use in the previous year	0.058
Symptoms	
Internalizing behaviors	0.154

Externalizing behaviors	0.100
Brain regions of interest	
Caudate during failed inhibition	0.062
Cerebellum during angry faces processing	-0.083
Hippocampus/amygdala during neutral faces processing	-0.029
Middle temporal during neutral faces processing	-0.025
Cerebellum during neutral faces processing	-0.132
Inferior frontal during neutral faces processing	0.036
Lingual gyrus during neutral faces processing	0.071
Fusiform gyrus during neutral faces processing	0.039
ACC/MCC during anticipation of reward	0.025
Fusiform gyrus during anticipation of reward	0.088

Abbreviations: DLPFC, dorsolateral prefrontal cortex; ACC/MCC, anterior/middle cingulate cortex.

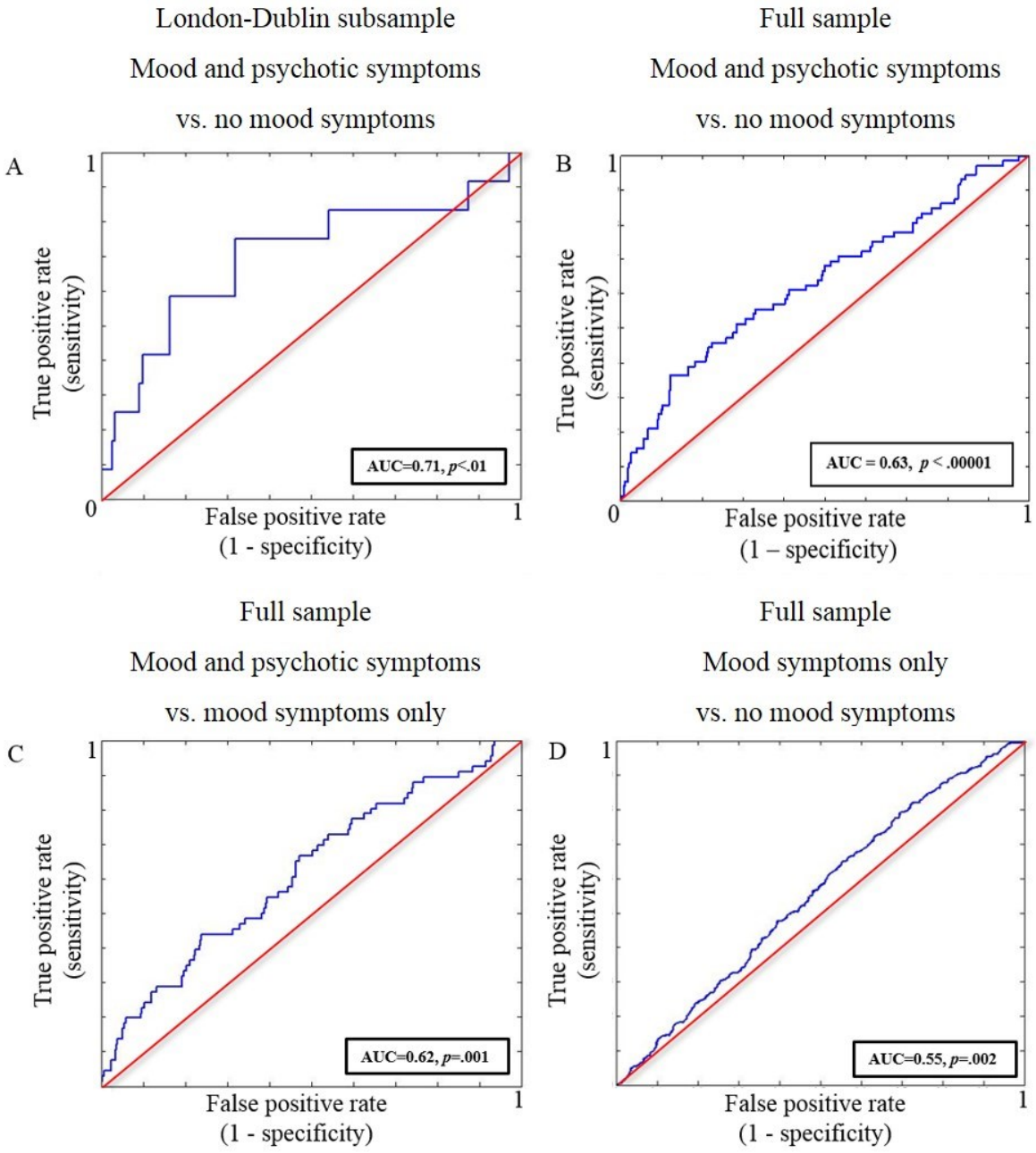
[b]Beta weights were averaged over 10 outer folds for features that were present in at least 9 folds (out of 10) of the final model

Figure 1. Cluster-corrected brain activation differences between 14-year-olds with psychotic-like experiences (PLEs) (N=27) and control subjects (N=135)



Errors bars in the graphs are standard deviations.

Figure 2. Receiver-operating characteristic (ROC) curves for prediction of symptoms at age 16 from brain activation at age 14



4.1 Investigating limbic network structural changes in at-risk youths and their interaction with cannabis

Findings from the third study highlight that among various cognitive processes (inhibitory control, emotion processing and reward processing), altered brain functioning during an emotion processing task appears to be an important early marker of vulnerability to psychosis. Although emotion processing represents only one aspect of social cognition, this result perfectly agrees with the finding that social cognition is the most impaired domain of cognition (Hedges' g = -0.55; 95% CI, -0.73 -0.36) in prodromal psychosis (Fusar-Poli, Deste, et al., 2012). Impaired social cognition (e.g. altered attributional style, emotional processing and meta-representation) has been shown to be implicated in both the formation and maintenance of psychotic symptoms such as delusions (Garety and Freeman, 1999). Moreover, a recent meta-analysis concluded that social cognition, compared to other neurocognitive domains, was more strongly related to functional outcomes in patients with psychosis (Fett et al., 2011).

While we observed intact negative emotion processing in youths reporting psychotic-like experiences, we found a limbic hyperactivity specific to the processing of neutral or ambiguous faces. Moreover, we showed that limbic hyperactivity is an important predictor of emerging psychotic symptoms after two years in the specific context of abnormal mood fluctuations.

Following on these functional results, in the fourth study, I decided to investigate whether an altered structural maturation in these regions could also be observed in youths reporting psychotic-like experiences at an early developmental period. This specific analysis is further supported by various studies in individuals at both genetic and clinical high-risk showing a consistent atrophy of hippocampus and amygdala volume (Boos et al., 2007; D. J. Dean et al., 2016; Fusar-Poli, Radua, et al., 2012; Ganzola et al., 2014; Witthaus et al., 2010). Together, results of the third and fourth study provide information on the relationship between altered brain function and anatomy in two independent vulnerable samples. Moreover, in the fourth study, as a secondary objective, I have opted not to limit my search for structural markers to the limbic network, and have added a whole-brain component which considers the various findings of density or volume reductions in temporo-frontal regions associated with psychosis proneness

(Chan et al., 2011; Fusar-Poli et al., 2011; Thermenos et al., 2013). For the whole-brain analyses, I chose cortical thickness analyses, over VBM or volumetry, as these analyses reflect the size and density of neurons in the cortical columns (Xiao et al., 2015), a more informative neurobiological characteristic relative to volumetry or gray matter density.

Moreover, I decided to turn a limitation of the third study into an important strength of the fourth study. Considering that there were no cannabis users at age 14 who also reported significant psychotic-like experiences in the IMAGEN sample (study 3), I could not test whether early onset cannabis use was moderating the altered brain functioning in at-risk youths. Fortunately, the Montreal subsample of the fourth study, which comes from the vast community sample used in both study 1 and 2, allowed the testing of such an interaction on brain volume and cortical thickness maturation.

Finally, another strength of the fourth study versus the third one is that the findings of early structural brain markers of psychotic-like experiences were not dependent of other psychopathological symptoms such as abnormally high mood and rapid mood changes.

5. Brain structural maturation processes in youths at risk for psychosis, and the moderating role of cannabis use: article no. 4

This manuscript will be submitted to Schizophrenia Bulletin.

Josiane Bourque overviewed the data collection and managed the project's research assistants. She contributed to database management and quality control. She decided upon the analytic strategy, conducted the analyses, interpreted the results, and wrote the first draft of the manuscript.

Sean Spinney participated in data collection, management, processing, and quality control. He was also implicated in the analyses.

Flavie Laroque participated in the quality control of the processed data and contributed to the statistical analyses.

Rachel Sharkey participated in data management and processing.

Marco Leyton designed the main project where this analysis comes from and critically revised the manuscript.

Alain Dagher designed the main project where this analysis comes from and critically revised the manuscript.

Stéphane Potvin participated in the decision on the analytic strategy, helped results interpretation, and critically revised the manuscript.

Patricia Conrod designed the main project where this analysis comes from, was implicated in the interpretation of results, and critically revised the manuscript.

All authors have reviewed and approved the final version of this manuscript.

Structural brain abnormalities associated with psychotic-like experiences in youths and the impact of early onset cannabis use

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ABSTRACT

Investigating the neural correlates of adolescents reporting a mild form of psychotic symptoms (i.e., psychotic-like experiences – PLE) provides a unique opportunity to explore whether brain abnormalities can be observed at an early developmental stage without the confounds of diverse iatrogenic effects. Following on previous findings by our team of a limbic hyperactivity during an emotion processing task associated with emerging psychotic symptoms during adolescence, this study aimed to explore whether youths reporting PLE show altered developmental changes of hippocampus and amygdala volumes and whole brain cortical thickness (CTh). This study also examined whether early onset cannabis use moderates this potential pathogenic process. Thirty young adolescents selected from a population-based longitudinal study in which they reported elevated PLE were compared to 102 same-age healthy controls following two sessions of structural neuroimaging. Subcortical volume-based reconstruction was done using FreeSurfer while whole brain CTh was extracted with Civet 2.0. Linear mixed effect models were implemented using R (volume analyses) and Surfstat (CTh analyses). Reduced amygdala volume across time as well as a modest decrease of hippocampal volume with time were associated with elevated PLE in youths. Thicker cortices in the right parahippocampal gyrus and the right inferior temporal and occipital gyri were associated with cannabis use in the whole sample. Only a modest cannabis by PLE group interaction was observed in the left parahippocampal gyrus. Our results suggest that an atrophy in both the hippocampus and the amygdala may represent important early vulnerability markers for psychosis proneness. Further research are needed to investigate the temporal relationship between structural and functional deficits within the limbic network of vulnerable youths.

Key words: Structural neuroimaging; Psychosis continuum; Cortical thickness; Volumetry; Longitudinal development; Adolescents; Psychosis proneness.

INTRODUCTION

The elevated morbidity and mortality rates (Simon 2018) as well as the frequent poor functional outcome (Lieberman 1993) associated with psychotic disorders have stimulated a worldwide initiative on harm reduction by intervening early. This initiative has resulted in an increasing amount of studies identifying clinically high-risk adults ("at-risk mental state") reporting either attenuated or brief limited intermittent psychotic symptoms (Tsuang et al., 2013; Yung et al., 2008) in order to explore which factors are associated with a transition to a full-blown episode and test the efficacy of pharmacological and psychological therapies on reducing transition rates. Earlier identification would have the potential to not only reduce harm by shortening the duration of untreated symptoms, but to delay the emergence of clinically validated symptoms. In this perspective, a novel approach targets children and adolescents from the community who report subclinical expressions of psychosis such as psychotic-like experiences (PLE - i.e., perceptual abnormalities and delusional thoughts that fall well below DSM diagnostic criteria) (Kelleher et al., 2011; Laurens et al., 2007), without the confounds of diverse iatrogenic effects such as major social and cognitive impairments.

It is estimated that 5% to 7% of the population will experience PLE at least once in their lifetime (Linscott and van Os, 2013; van Os et al., 2009). This prevalence is increased at 21%-23% in populations of children and young adolescents (Kelleher et al., 2012), suggesting that for a proportion of individuals, these PLE decline from childhood to adulthood (van Os et al., 2009). Nonetheless, various cohort studies have demonstrated that PLE are associated with an increased risk of developing a psychotic disorder (Dominguez et al., 2011; Poulton et al., 2000; Welham et al., 2009) or other axis I disorders (Kelleher 2012) during adulthood. Studying the neurobiological bases of PLE during a critical developmental period will help to understand the early etiological processes implicated in the development of psychosis.

Patients with a psychotic disorder have consistently shown significant brain structural abnormalities. A recent meta-analysis of the ENIGMA Schizophrenia Working Group in 2028 patients has demonstrated that the most important volume reductions among subcortical structures were observed in the hippocampus and amygdala (van Erp et al., 2016). These results have been replicated in both non-affected family members of diagnosed patients and clinically high-risk individuals (Boos et al., 2007; Dean et al., 2016; Fusar-Poli et al., 2012; Ganzola et

al., 2014; Witthaus et al., 2010), where the largest volume difference with healthy controls was located in the hippocampus (Boos et al., 2007).

At the whole brain level, meta-analyses of voxel-based morphometry (VBM) and volumetric studies have observed in schizophrenia patients significant gray matter density and volume reductions on the whole cortex, temporal, and frontal lobes, as well as increased ventricles volume (Haijma et al., 2013; Honea et al., 2005). Similarly, but to a milder extent, reviews and meta-analyses of magnetic resonance imaging (MRI) studies in high-risk individuals have reported density and volumetric reductions in temporo-prefrontal regions (Chan et al., 2011; Fusar-Poli et al., 2011; Thermenos et al., 2013).

It is however unclear whether psychosis vulnerability in the form of self-reported PLE during late childhood and early adolescence is also associated with neurodevelopmental abnormalities. Among the few cross-sectional studies in that particular population, psychotic-like experiences were associated with both increased and decreased gray matter density in regions of the temporal and frontal cortex (Cullen et al., 2013; Jacobson et al., 2010). A recent neuroimaging study from our team demonstrated that hyperactivity within the hippocampus and amygdala during passive viewing of videos depicting dynamic neutral facial expressions was significantly associated with PLE and predicted the emergence of more significant psychotic symptoms two years later (Bourque, Spechler, et al., 2017), providing further evidence of alterations in the brain limbic system in psychosis proneness. Evaluating longitudinal changes within this brain system is an important next step in this area to be able to understand the abnormal neurodevelopmental processes involved in the vulnerability to psychosis.

One important developmental risk factor for both psychotic symptoms and PLE (Bourque et al., 2018; Semple et al., 2005) is cannabis use which has also been demonstrated to interfere with the developing brain. Chronic cannabis use is associated with reduced hippocampal and amygdala volumes in both adults and adolescents (Ashtari et al., 2011; Cousijn et al., 2012; Koenders et al., 2016; Lorenzetti et al., 2015; Yucel et al., 2008). An earlier age of onset may be associated with even more prominent structural alterations in adults (Cohen et al., 2012; Wilson et al., 2000). Notably, cannabis use has been shown to interact with psychosis vulnerability on whole brain structural maturation (French et al., 2015).

The present study intended to extend the preliminary findings of PLE associated brain alterations in a community sample of youths (12-14 years of age) followed until age 15. The primary aim was thus to investigate the relationship between PLE and developmental changes of hippocampal and amygdala structures, and if early onset cannabis use moderates this potential pathogenic process. The secondary aim was to explore, by means of a whole brain analysis, further abnormal maturation in cortical thickness associated with PLE, and also test whether cannabis would moderate the association.

METHODS

Participants

High schools in the greater Montreal area were initially recruited to take part in an ongoing cluster randomized controlled trial (RCT) evaluating the effectiveness of school-based personality-targeted interventions on substance use and cognitive functioning outcomes (O'Leary-Barrett et al., 2017). This RCT included a total of 3,966 Grade 7 students assessed annually until Grade 11 on behavioral, clinical, and psychoactive substance use self-reported questionnaires. Quality control and reliability of the data were evaluated using a sham drug item and scripts to detect inconsistent or unlikely reporting.

A subsample of 151 Grade 7 or 8 students (mean, (SD); 13.6 years old (0.6); 54.3% girls) was further invited to take part in an ongoing prospective neuroimaging study evaluating the effects of alcohol and other drugs use on the developing brain (Bourque et al., 2016). Participants were invited to three MRI sessions: the first one at ages 12 to 14 (Grades 7 or 8), the second one at age 15 (Grade 9), the third one at age 17 (Grade 11). The present study reports on the two first time points, as the last MRI session is still ongoing. A total of 132 participants (87.4%) were included in the final analyses. Confidentiality was assured by emphasizing that parents would not have access to the questionnaires results and by anonymizing the assessments. Ethical approval was obtained from the CHU Sainte-Justine Research Ethics Committee in Montreal. All participants actively assented to participate while their parent consented to the study procedures.

Measures

Psychotic-like experiences

Psychotic-like experiences (e.g., perceptual abnormalities, delusional thoughts, suspiciousness, and feelings of grandiosity) in the past 12 months were assessed with nine items, five of which were adapted from the Diagnostic Interview Schedule (Costello, 1982). All items were previously validated in community samples of children and adolescents (Kelleher et al., 2011; Laurens et al., 2007). Moreover, these items were previously used by our team to predict the emergence of psychotic symptoms in adolescents (Bourque et al., 2017). Participants were asked to rate their response to different statements on a 3-point scale (0=not true; 1=somewhat true; 2=certainly true). Individual item scores were summed to obtain a global score of PLE. The list of items is reported in the Supplement material.

Substance use

Cannabis and cigarette use frequency were assessed with a modified and validated version of the 'Detection of alcohol and drug problems in adolescents' questionnaire (Germain et al., 2013). Participants were asked to rate their frequency of use over the previous 12 months on a 6-point scale (0 = Never, 5 = Every day).

Covariates

Considering our previous results showing the concomitant development of anxiety and depression symptoms with both psychotic-like experiences and cannabis use during adolescence (Bourque, Afzali, et al., 2017), this study's models controlled for internalizing symptoms. Mean internalizing behaviors (across the time points) were assessed using the Strengths and Difficulties Questionnaire, a brief behavioral screening questionnaire designed for 3 to 16 years olds (Goodman et al., 2000). Intellectual quotient (IQ) was measured with the Cultures Figures Task, a modified version of the Cattel's Culture Faire Test (Cattell, 1949) which evaluates abstract reasoning. Participants also provided information about their sex and age. When including the moderating effect of cannabis in the models, we also controlled for baseline cannabis use as well as mean use of cigarette (Gage et al., 2014).

MRI

All MRI scanning was performed on a 3 T Siemens Magnetom Trio Scanner. T1-weighted images were acquired using an ultrafast gradient echo 3D sequence (MPRAGE)

(Repetition time = 2.3 s, Echo time = 2.96 ms, 1mm thickness, voxel size = 1 x 1 x 1 mm^3, flip angle = 9°, matrix size = 256 x 256 mm, number of slices = 192).

Data Processing

Subcortical volume processing for the region of interest (ROI) analyses was conducted with the longitudinal stream in Freesurfer software, version 6.0.0 (http://surfer.nmr.mgh.harvard.edu). The subcortical segmentation procedure assigns a neuroanatomic label to each voxel of the MRI volume using a probabilistic atlas and a Bayesian classification rule. The longitudinal stream creates an unbiased within-subject template image for automatic surface reconstruction and segmentation of the individual's different time points (Reuter et al., 2012). Using the results from the unbiased templates can reduce variability in the processing procedure and improve the sensitivity of the longitudinal analysis. Subcortical segmentation and volume extraction were obtained for left and right hippocampus and amygdala, as well as intracranial volume (ICV).

Whole brain cortical image analysis was conducted with the cortical thickness analysis pipeline, CIVET (version 2.0) (http://www.bic.mni. mcgill.ca/ServicesSoftware/CIVET-2-0-0 Introduction). T1-weighted MRI images were corrected for non-uniformity artifacts using the N3 algorithm, masked and registered into stereotaxic space, and then segmented into gray matter, white matter and cerebral spinal fluid using an advanced neural net classifier (Cocosco et al., 2003; Zijdenbos et al., 2002). The white and gray matter surfaces were extracted using the Constrained Laplacian-based Automated Segmentation with Proximities algorithm (Kim et al., 2005). The resulting surfaces were resampled to a stereotaxic surface template to provide vertex based measures of cortical thickness. For each participant, cortical thickness was then measured in native space using the linked distance between the two surfaces across 81,924 vertices and a 20 mm surface smoothing kernel was applied to the data (Lerch et al., 2008). Three independent investigators (JB, SS, FL) then carried out a visual quality control to ensure that there were no aberrations in the automated processing pipeline.

Statistical Analyses

Following reports on developmental trajectory of PLE (Mackie et al., 2011; Mackie et al., 2013; Bourque, Afzali, et al., 2017), we estimated PLE trajectories using growth mixture

models (MPLUS version 8.0) in the RCT final cohort of 3,848 adolescents. Models were fitted beginning with a one-trajectory model and moving to a four-trajectory model, all with random starting values. A three-class trajectory model fitted the data best (For model fit information see Table S1). In the subsample who also participated in the MRI sessions, based on the posterior probabilities of group membership, 102 (77.3%) were classified in the low decreasing group; 20 (15.2%) in the high decreasing group; and 10 (7.6%) in the moderate increasing group (Figure S1). To increase our power of detecting brain anomalies associated with PLE, we decided to combine the high decreasing and moderate increasing trajectories into one group who reported elevated PLE at some developmental stage (n=30) and compare them to the low decreasing group who consistently reported low levels of PLE (n=102).

We used the R-package *lme4* (Bates et al., 2012) to perform linear mixed effects (LME) analyses predicting the longitudinal development of the mean left and right hippocampal and amygdala volumes with PLE group status, time, cannabis use and their interactions as independent variables. LME are well suited for data with imperfect timing and missing data, while maximizing statistical power (Bernal-Rusiel et al., 2013). Each model (i.e., hippocampus, amygdala) consisted of three iterative steps. Every iterative steps included the main effects of PLE group status, time and cannabis use as well as the following covariates: ICV, both a linear and non-linear effect of age, sex, baseline cannabis use, mean cigarette use, mean IQ and mean internalizing symptoms; in addition to a random intercept for participants to account for within-subject variability. As the first step, the full model also estimated the 2-way interactions between PLE group, time and cannabis, as well as their 3-way interaction. In the case the 3-way interaction was not significant, the second step removed that interaction term. The final step further removed non-significant 2-way interaction terms. To correct for multiple comparisons, we used a Bonferroni correction of $p<0.025$ considering that we modeled both amygdala and hippocampus volumes.

Statistical analyses of whole-brain cortical thickness were implemented in SurfStat (http://www.math.mcgill.ca/keith/surfstat/), a statistical toolbox created for MATLAB (The MathWorks, Inc., Nathan, MA, USA). LME models were performed at every vertex including the exact same variables as the subcortical volume analysis, except for ICV. Considering that ICV is not highly predictive of cortical thickness, it has not been recommended to adjust for

ICV when using thickness measurements (Westman et al., 2013). Corrections for multiple comparisons across the whole brain were performed using random-field theory (RFT) analysis (for peaks and clusters), set at $p \leq .05$.Whole brain cortical thickness was analysed with the same iterative steps used for the volume analyses.

RESULTS

Demographic and clinical characteristics of PLE groups at baseline and first follow-up

Demographic, clinical, cognitive, and substance use characteristics are detailed in Table 1. The high and low PLE groups were not different on age at testing, handedness, IQ, as well as cigarette and cannabis use at both baseline and first follow-up. They differed on the proportion of girls and on internalizing problems at the first follow-up, and these variables were included as covariates in the analyses.

ROI volumetric analyses

Amygdala volume: Among the three iterations of the LME model, we showed a significant and consistent negative effect of PLE group status that survived the Bonferroni correction ($p < 0.02$) (Table 2). Youths with elevated PLE exhibited an overall smaller amygdala volume (standardized coefficient: -0.18) than their low PLE peers across both time points. We did not find any significant main effect of cannabis and time as well as no significant 2-way and 3-way interactions.

Hippocampus volume: In the first iterations of the LME model, we observed a significant interaction between PLE group status and time that survived the multiple comparison correction ($p < 0.02$, standardized coefficient: -0.03). However, as we removed the non-significant interaction terms in the last iteration, this effect of PLE group by time no longer survived the corrected alpha threshold ($p = 0.05$). This modest interaction implies that a slight increase in hippocampus volume characterizes youths with low PLE while a slight decrease in hippocampus volume is observed in youths reporting high PLE, with time (Figure 1). The main effects of cannabis, PLE group and time, as well as the other interaction terms were not related to significant change in hippocampus volume.

Whole brain cortical thickness analyses

Following the same iterative steps as for the volume analyses, we did not find a significant 3-way interaction between PLE group status, cannabis use and time on whole brain cortical thickness. Consequently, this 3-way interaction was removed from the second iterative step. Among the 2-way interactions, we found a significant PLE group by cannabis use interaction at the peak-level in the left parahippocampal gyrus (x=-34, y=-25, z=-20; t-value=5.03; p-value<0.001) (Figure 2A). Although significant, the interaction coefficient value had a very small effect size (standardized coefficient: 0.02). Both groups with high and low PLE showed a similar slight increase in cortical thickness as cannabis use increases, but with different intercepts (Figure 2B). Youths with high PLE presented with lower cortical thickness of the parahippocampal gyrus compared to youths reporting low PLE, independent of cannabis use status. There were no significant interactions between PLE group and time nor between cannabis use and time.

In the last iterative step, which includes all the main effect and the significant interaction term, we found a significant positive main effect of cannabis use at the peak-level in the right parahippocampal gyrus (x=35, y=-32, z=-16; t-value=4.74; p=0.004) and at the cluster-level in the right inferior temporal and occipital gyri (x=46, y=-67, z=-8; p=0.018; 465 vertices) (Figure 3A). Cannabis use was associated with increased cortical thickness in these regions. We extracted the model's parameter estimates and found that the main effect of cannabis in these regions was already present at baseline (Figure 3B). There was also a main negative effect of time on cortical thickness of various frontal, parietal, and occipital structures (Figure 3C), but no main effect of PLE group status.

DISCUSSION

Using a longitudinal design in a community sample of young adolescents, this study contributed to the literature on the early (amygdala atrophy) and developmental (a slight accelerated decrease in time of hippocampal volume) brain correlates associated with a psychosis vulnerability. Cannabis use was associated with early vulnerability markers, such as increased cortical thickness in temporo-occipital regions.

Our findings of an amygdala volume reduction are in accordance with both a large cross-sectional study and a prospective study showing volume atrophy of this structure in adolescents and young adults at heightened risk for psychosis compared to their healthy peers (Bhojraj et al., 2011; Roalf et al., 2017). Consistently to what we observed, the studies demonstrated that the amygdala volume showed a similar longitudinal maturation between at-risk and healthy control individuals, suggesting that a smaller volume is explained by early (i.e., gestation and childhood) developmental deficits (Bhojraj et al., 2011). Moreover, a review by Ganzola and colleagues (2014) highlights that amygdala volume loss is evident in childhood and continues in adolescence, yet late maturational processes in vulnerable individuals may help recover volume reductions, as it is observed in adults at clinical high risk.

Although we did not observe main effects of PLE group status and time on hippocampus volume change, we did find a significant modest effect for an interaction between these variables, suggesting that youths with high PLE presented a time-dependent decrease in hippocampus volume relative to their low PLE peers. This finding is consistent with other longitudinal neuroimaging studies showing an initially normal hippocampus volume followed by a progressive decline in individuals with psychotic symptoms (Ho et al., 2017), irrespective of transition status (Walter et al., 2012). It is hypothesized, that compared to the amygdala development, the altered maturation of hippocampal tissue becomes evident later in adolescence (Ganzola et al., 2014). Consequently, the present study's finding may represent the onset of an abnormal developmental trajectory.

Monozygotic and dizygotic twin studies have shown that although brain volume, and particularly hippocampus volume, is affected by genetic factors, a substantial variability originates from environmental factors (Baare et al., 2001; Borgwardt et al., 2010; van Erp et al., 2004; van Haren et al., 2004). These results help explain the slightly altered hippocampus development observed in youths with high PLE as a consequence of developmental risk factors. However, early onset cannabis use was not one of these factors. It may be worthwhile exploring the effect of stress-related factors on brain maturational processes, as recent findings demonstrated that individuals with a familial risk for psychosis who also report childhood adversity show smaller amygdala and hippocampus volumes, relative to those with no childhood adversity (Barker et al., 2016).

Interestingly, in an independent sample of young adolescents reporting PLE (aged 14), we previously demonstrated that an important functional predictor of emerging psychotic symptoms was a hyperactivity of both the amygdala and hippocampus during neutral faces processing (Bourque, Spechler, et al., 2017). Considering the role of the hippocampus in coding contextually salient information (Maren et al., 2013) and the role of the amygdala in aversive processing (Costafreda et al., 2008), it could be hypothesized that an abnormal contextual association of the situation and the way how this association is remembered lead to an aberrant emotional salience. Together, it appears that hyperactivity and volume loss of the limbic system are related processes in the developmental pathway to psychosis risk. This hypothesis is supported by both animal and human studies showing increased glutamate levels and hypermetabolism of the CA1 hippocampus region predicting hippocampal atrophy during the progression to psychosis (Lieberman et al., 2018; Schobel et al., 2013). The present findings of smaller amygdala (the emotion center) and hippocampus (memory, contextual associations) in youths with elevated PLE may suggest an altered functioning in these regions that would pave the way towards mild expressions of delusional ideas.

Contrary to our hypothesis, the frequency of cannabis use was not shown to be associated with further structural alterations in the hippocampus nor the amygdala. At the whole brain level, we found only a modest interaction effect between cannabis use and PLE group status in the left parahippocampal gyrus' cortical thickness. Cannabis use was shown to be associated with increased cortical thickness in both high and low PLE groups, suggesting that this increased cortical thickness consists of a vulnerability marker among cannabis users. This finding does not agree with a vast cohort study showing significant interaction between vulnerability to psychosis and cannabis on cortical maturation (French et al., 2015). This discrepancy could be explained by the limitation of our design: recruitment of occasional users and a short follow-up period. Considering the hypothesis that brain functional changes might predate structural changes, future studies should explore how cannabis use might be related to developmental changes in brain function and then, how such changes might relate to developmental changes in structure over the longer term.

Regarding the main effects of cannabis use on brain structure, we showed that cannabis was associated with increased cortical thickness in regions of the right parahippocampal gyrus

and the right inferior temporal and occipital gyri. A further investigation of cortical thickness at baseline demonstrated that these alterations were evident in future cannabis users. This implies that cannabis use is not responsible for this increased cortical thickness, instead it represents an early vulnerability marker. In a neuroimaging study of the IMAGEN group, larger brain volumes as well as increased cortical thickness were previously shown to be predictive of subsequent cannabis use in adolescents (Spechler et al., 2018). The authors have proposed that the increased volume and cortical thickness indicate a delayed neurodevelopmental maturation in future cannabis users. As part of the extended limbic system, the parahippocampal gyrus is implicated, along with the hippocampus, in memory encoding and retrieval (Diana et al., 2010). Moreover, its most posterior part, juxtaposing the fusiform gyrus, is involved in visual awareness, visuospatial processing, and faces recognition (Mullally and Maguire, 2011). The inferior temporal and occipital gyri form the ventral stream of visual processing. They are known to process object features as well as face characteristics (Kravitz et al., 2013).

An important limitation to the present study was that cannabis use and PLE were not confirmed with clinician or collateral reports. However, previous work has shown positive predictive values ranging from 80% to 100% from 3 self-report items to identify interview-verifiable PLE. Furthermore, self-report is the most efficient way to assess substance use when there are no consequences to reporting because collateral reports and biologic measures are not sensitive to the sporadic nature of adolescent substance use (Clark and Winters, 2002). Another potential limitation is the low prevalence of cannabis users in this sample (6% at baseline and 22% at follow-up) as well as their low frequency of use, which may partly explain the absence of deleterious effects of cannabis. Although the timeframe for studying brain maturation was relatively brief, it was enough to observe significant time effects at the whole brain level, and a modest interaction effect between time and PLE group status on hippocampus volume.

This study was able to examine the effects of PLE and cannabis use on the longitudinal development of brain structure during early adolescence. The results suggest that an atrophy in both the hippocampus and the amygdala may represent important early vulnerability markers for psychosis proneness. Further research needs to replicate the present findings and investigate the temporal relationship between structural and functional deficits within the extended limbic network in vulnerable youths.

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Table 1. Demographic, clinical, cognitive and substance use characteristics of adolescents with high and low psychotic-like experiences at baseline and first follow-up

Characteristics	Baseline			First follow-up		
	High PLE group (N=30)	Low PLE group (N=102)	P Value[a]	High PLE group (N=30)	Low PLE group (N=102)	P Value[a]
Demographic						
Sex: female, (%)	73.3%	50.0%	.02[b]	—	—	—
Age at testing, mean (SD)	13.66 (0.58)	13.63 (0.68)	.86	15.00 (0.42)	14.90 (0.45)	.31
Right handed, (%)	91.2%	86.7%	.46[b]	—	—	—
Cognition						
Abstract reasoning IQ (raw score), mean (SD)	16.47 (3.26)	16.55 (3.03)	.90	17.11 (3.41)	18.18 (2.50)	.13
Symptoms						
Internalizing symptoms, mean (SD)	5.40 (3.85)	4.02 (3.38)	.06	6.26 (3.80)	3.90 (2.92)	<.01
Substance use						
Cigarette use, mean (SD)	0.13 (0.43)	0.10 (0.60)	.79	0.46 (0.88)	0.19 (0.63)	.13
Cannabis use, mean (SD)	0.17 (0.46)	0.08 (0.53)	.43	0.64 (1.10)	0.30 (0.92)	.10

Abbreviations: PLE, psychotic-like experiences; SD, standard deviation.

[a]All p-values in the table are two-tailed, uncorrected.

[b]Determined by means of chi-squared tests. By default, all other p-values are determined by means of *t* tests.

Table 2. Linear mixed effect models predicting the longitudinal development of hippocampus and amygdala volumes

Model		Amygdala volume			Hippocampus volume		
		β	S.E.	*p*	β	SE	*p*
1st iteration	PLE group	-0.17	0.07	**0.013**	-0.08	0.07	0.239
	Time	-0.04	0.03	0.225	0.01	0.01	0.217
	Cannabis	0.11	0.07	0.147	-0.02	0.03	0.468
	Time*PLE group	0.02	0.03	0.598	-0.03	0.01	**0.016**
	Cannabis*PLE group	-0.02	0.05	0.721	0.02	0.02	0.333
	Cannabis*Time	0.00	0.03	0.917	0.00	0.01	0.932
	Cannabis*Time*PLE group	0.01	0.03	0.769	0.01	0.01	0.261
2nd iteration	PLE group	-0.17	0.07	**0.013**	-0.08	0.07	0.245
	Time	-0.04	0.03	0.235	0.01	0.01	0.158
	Cannabis	0.11	0.07	0.155	-0.03	0.03	0.353
	Time*PLE group	0.02	0.03	0.583	-0.03	0.01	**0.017**
	Cannabis*PLE group	-0.01	0.04	0.805	0.04	0.02	0.083
	Cannabis*Time	0.00	0.03	0.898	0.00	0.01	0.834
3rd iteration	PLE group	-0.18	0.07	**0.011**	-0.08	0.07	0.269
	Time	-0.04	0.03	0.238	0.01	0.01	0.212
	Cannabis	0.11	0.06	0.080	-0.01	0.02	0.776
	Time*PLE group	—	—	—	-0.02	0.01	0.053[a]
	Cannabis*PLE group	—	—	—	—	—	—
	Cannabis*Time	—	—	—	—	—	—

Abbreviations: PLE, psychotic-like experiences.

Standardized coefficients are reported. Bonferroni corrected p-values are in **bold**.

[a]Did not survive the Bonferroni correction of $p<0.025$.

Figure 1. PLE group by time interaction on hippocampus volume

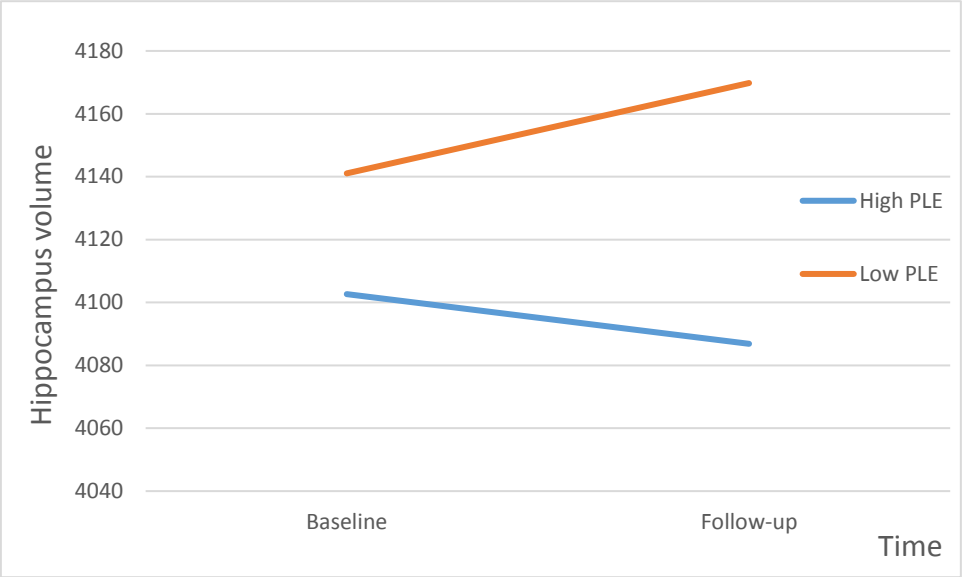
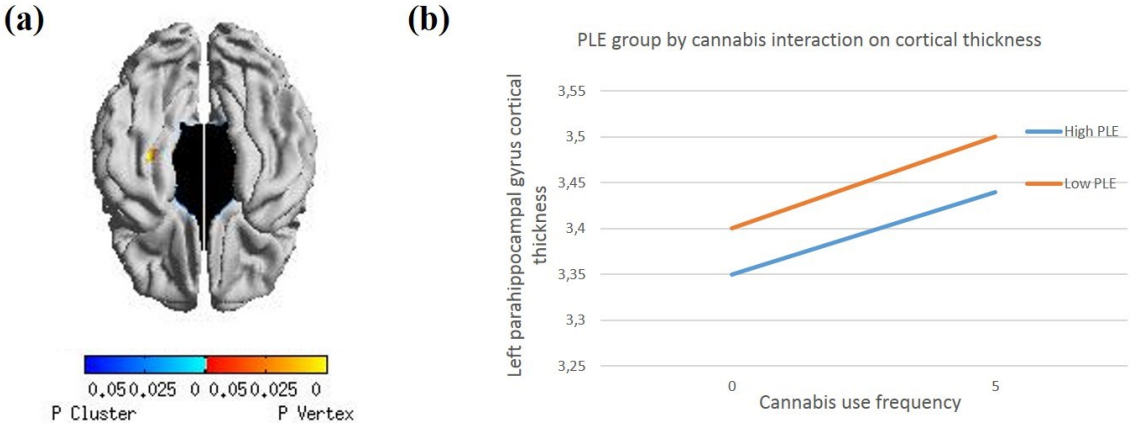


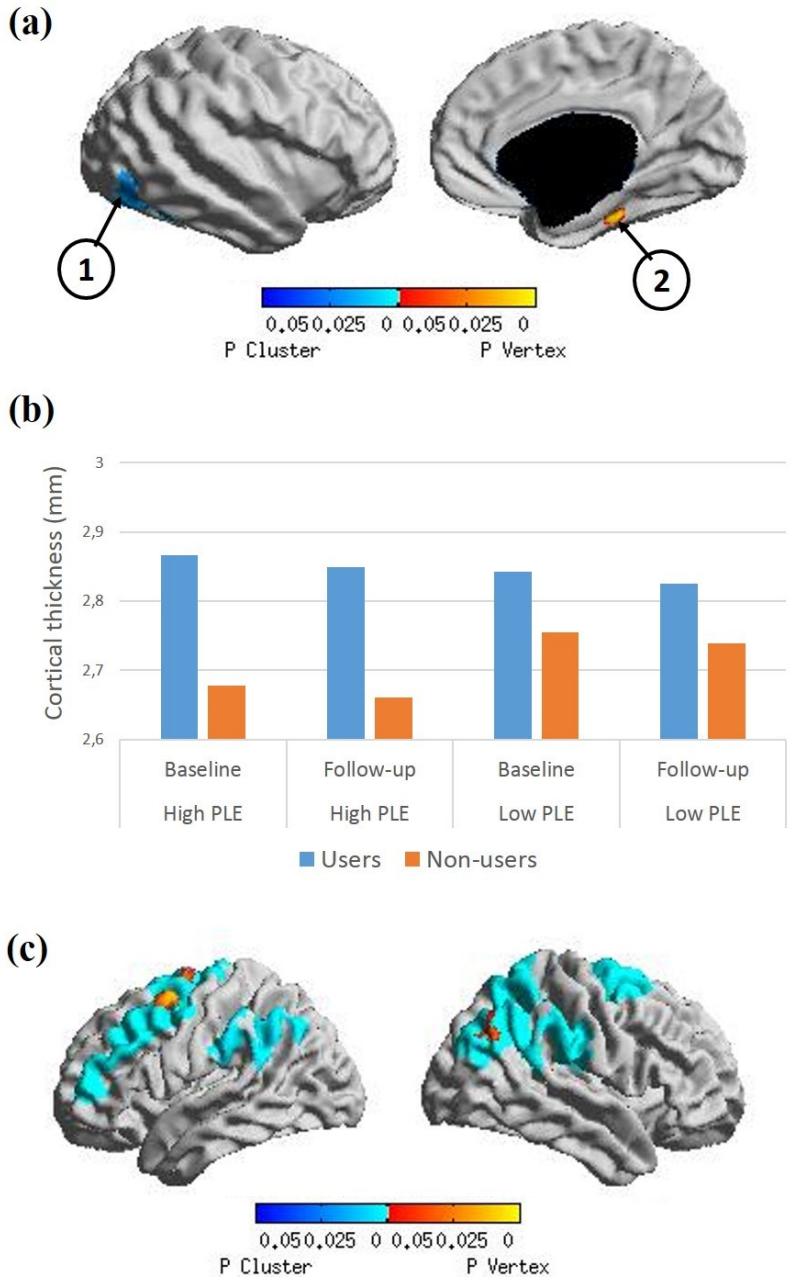
Figure 2. Altered brain cortical thickness patterns associated with a cannabis use by PLE group interaction



(a) Cannabis use by PLE group interaction in the left parahippocampal gyrus.

(b) Cortical thickness of the left parahippocampal gyrus increases as cannabis use frequency increases for both high and low PLE groups. High PLE youths show a smaller intercept than low PLE youths. 0=No use, 5=Every day use.

Figure 3. Altered brain cortical thickness patterns associated with cannabis use and time



(a) Significantly increased cortical thickness in cannabis users. (1) Significant cluster encompassing regions of the right inferior temporal and occipital gyri. (2) Significant effect at the peak-level in the left parahippocampal/fusiform gyrus.

(b) Cortical thickness of the significant cluster reported in **a** (inferior temporal and occipital gyri) according to PLE groups, status of cannabis user and time.

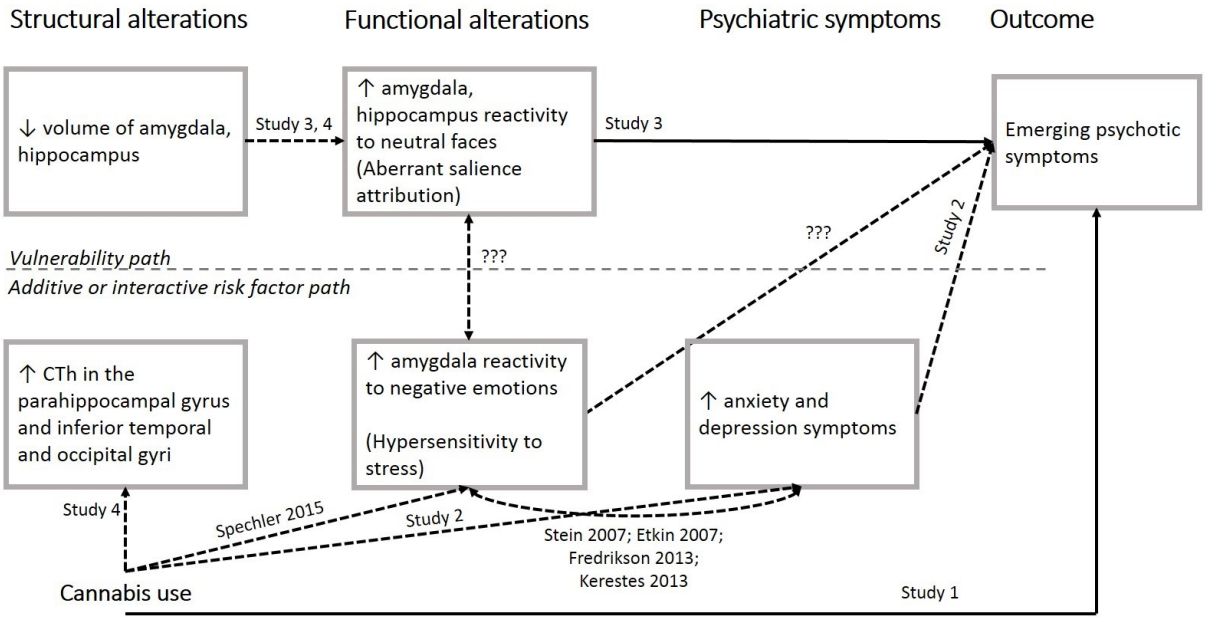
(c) Significantly decreased cortical thickness associated with time.

6. Discussion

The results of this thesis have important theoretical implications for our understanding of early vulnerability markers for psychosis and the developmental mechanisms underlying such vulnerability. Together, they stress the role of the affective (limbic) network and associated depression and anxiety symptoms in early developmental processes of a psychosis vulnerability. Moreover, cannabis use was shown to be causally linked to psychosis vulnerability and this relationship appears to be mediated by depression and anxiety symptoms. These findings could help clinicians and communities identify youths vulnerable to both psychosis spectrum diseases and to the psychotropic effects of cannabis. Furthermore, understanding the process by which cannabis influences psychosis risk will help develop targeted prevention strategies for those at risk.

A summary and an integration of the findings presented in this thesis are displayed in Figure 1. While some temporal precedence was investigated with respect to some of the relationships outlined in this figure, not all were confirmed and therefore their pathways that have yet to be confirmed temporally are identified with dash lines.

Figure 1. Pathways for the vulnerability-stress model of psychosis



Abbreviations: CTh, Cortical thickness.

6.1 Cannabis use on the causal pathway to emerging psychotic symptoms

The general layout of Figure 1 is based on the finding of temporal precedence between cannabis use and psychotic symptoms from the first study. The analytic strategy chosen for this first study allowed for the simultaneous evaluation of four main hypotheses on the association between cannabis use and psychotic symptoms: (1) the common vulnerability hypothesis, (2) the secondary substance use hypothesis such as the self-medication hypothesis, (3) the secondary psychotic outcome hypothesis, and (4) the bidirectional hypothesis (Mueser et al., 1998). First, the RI-CLPM model showed that the overall variability of cannabis use and psychotic symptoms throughout adolescence (i.e., trait-like stability or between-person effects) were not significantly correlated with each other when within-person effects were also tested. This implies that common factors underlying these variabilities are less likely to explain the relationship between cannabis use and psychosis. Although it is difficult to disprove the common factor hypothesis, the present results are consistent with meta-analyses and systematic reviews of the cannabis-to-psychosis outcome relationship demonstrating that, while controlling for a wide range of common factors or potential confounding variables (low SES, other forms of psychopathology, other substance use, premorbid cognitive deficits, etc), cannabis use still preceded psychotic symptoms (Degenhardt and Hall, 2006; Moore et al., 2007).

Consistent with other cohort studies, the secondary substance use hypothesis as well as the self-medication hypothesis were not supported by our findings (Arseneault et al., 2002; Henquet et al., 2005; van Os et al., 2002). Moreover, our findings are not consistent with a purely bidirectional hypothesis where cannabis use promotes the emergence of psychotic symptoms, and psychotic symptoms equally promote further cannabis use. Instead, our results agree with the secondary psychotic outcome hypothesis considering that we found that an increase in cannabis use always preceded an increase in psychotic-like experiences, while an increase in psychotic-like experiences rarely preceded an increase in cannabis use.

It is worth mentioning that other cohort studies have not evaluated the bidirectional hypothesis given that only few of them have used a RI-CLPM or similar approach. Most of them have usually only tested the relationship from one direction – cannabis to psychosis (Arseneault et al., 2002; Fergusson et al., 2003; Kelley et al., 2016; Moore et al., 2007). Among the few studies that have investigated both directions of this relationship, both Henquet et al. (2005) and Kuepper et al. (2011) found that the predisposition to psychosis at baseline did not significantly predict later cannabis use, when controlling for baseline cannabis use. However, two studies of Dutch adolescent samples, showed that cannabis use predicted future psychotic symptoms and vice versa (Ferdinand et al., 2005; Griffith-Lendering et al., 2013). One important difference between the studies reporting a bidirectional relationship and those that did not is the age of the samples. Studies focusing on the adolescent developmental period were more likely to find a relationship between cannabis use and psychotic symptoms in both directions whereas studies in adult populations only determined that cannabis predicts subsequent psychotic outcome.

Based on these results and our own, the most consistent finding overall is that cannabis use is on the causal pathway to psychotic symptoms. This agrees with human and animal studies, which have highlighted that the endocannabinoid system is going through significant changes during adolescence (Mato, Del Olmo and Pazos, 2003) and that these changes may lead to different sensitivities to cannabis exposure (Chadwick et al., 2013). Considering the important role of the endocannabinoid system on affect regulation and anxiety-like behaviors (Viveros, Marco and File, 2005), early cannabis use may lead to psychotic symptoms through the exacerbation of depression and anxiety symptomatology in youths. These mechanisms will be further discussed in the following section.

6.2 Cannabis use may lead to emerging psychotic symptoms via an hypersensitivity to stress and associated psychopathological symptoms

6.2.1 Psychopathological symptoms

Prior to discussing the main results of the second study, it is worth noting that we replicated the different developmental trajectories of psychotic-like experiences in youths in a

third independent sample (Mackie et al., 2011; Wigman et al., 2011; Mackie et al., 2013). A highly consistent finding is the specific influence of cannabis use on psychotic-like experiences among youths following an increasing trajectory (Bourque et al., 2017; Mackie et al., 2011; Mackie et al., 2013), suggesting that this group is more prone to use cannabis and/or more sensitive to its psychotropic effects. These findings have important developmental and clinical implications as they highlight a small portion of the normal population (≤ 8%) for whom delaying and reducing cannabis use may have an important positive impact on their reported psychotic-like experiences and, potentially, on subsequent clinically validated psychotic symptoms.

The main finding of the second study of this thesis is that increasing affective symptoms during adolescence partly explains the relationship between increasing cannabis use and increasing psychotic-like experiences. An additional result which was not directly discussed in the published manuscript is the fact that anxiety symptoms were found to be strongly associated (even more so than depression symptoms) with the increasing trajectory of psychotic-like experiences (path *b*) and almost significantly associated with growth in cannabis use (path *a*: 0.07, 95% CI: -0.01, 0.16). These findings are in direct agreement with three previous studies in young adults showing the cross-sectional mediation or moderation of depression and anxiety symptoms on the relationship between cannabis use and psychotic experiences (Najolia et al., 2012; Reeves et al., 2014; Spriggens and Hides, 2015). Consequently, it would be relevant to consider anxious symptoms to be implicated in the process linking adolescent cannabis use and increasing psychotic-like experiences.

However, this study's findings cannot confirm or disconfirm whether anxious and/or depressed individuals are more likely to become regular cannabis users or whether regular cannabis use during adolescence promotes anxiety and depression symptoms, which then positively influence comorbid symptoms such as increasing psychotic-like experiences. Longitudinal studies of the general population indicate little evidence for an elevated risk of cannabis use and cannabis dependence among individuals reporting depression or anxious symptoms beforehand (Degenhardt et al., 2003; Lev-Ran et al., 2014; Mammen et al., 2018). Most cohort studies demonstrated contradictory evidence that the regular use of cannabis (i.e., weekly and daily) and cannabis use disorders are associated with increased odds of reporting

lasting symptoms of anxiety and depression years later (Kedzior and Laeber, 2014; Lev-Ran et al., 2014; Mammen et al., 2018; Patton et al., 2002). Studies have also highlighted a significant, but weaker relationship between relatively low levels of cannabis use (i.e., approximately once a month) and anxiety and affective disorders (Cheung et al., 2010). This supports our results of a longitudinal relationship between increasing use of cannabis and increasing self-reported anxiety and depression symptoms from an adolescent sample where the frequency of use is relatively low (20% of 16-year-olds used at least on a monthly basis).

When investigating the relationship between cannabis use and anxiety and depression symptoms, specifically within the extended psychosis phenotype, the literature is scarce. On one hand, studies on the motives for cannabis use suggest that depression or anxious symptoms promote or motivate consumption, once these symptoms have had their onset. The most frequently reported reasons for cannabis use in both psychosis-prone and diagnosed individuals are to experience a high (enhancement of positive affect) and to cope with stress, anxiety and dysphoria (Dekker et al., 2009; B. Green, Kavanagh, et al., 2004; Hides et al., 2009). Moreover, a quantitative comparison of the motives for cannabis use within our adolescent cohort revealed that, while controlling for the most common reason to use (i.e., social motives), those following a developmental trajectory of increasing psychotic-like experiences, relative to those following a trajectory of low psychotic-like experiences, use cannabis for both conformity (i.e., to fit in a group) and coping with depressive thoughts (unpublished results).

On the other hand, Henquet et al. (2010) have used experience sampling methods (ESM) to demonstrate that neither positive nor negative affect (e.g. feeling anxious, lonely, insecure) were present in the hour preceding cannabis use in patients with psychosis. One hypothesis that may bridge together the ESM results and motives to use may be that patients and at-risk individuals are not more likely to use directly after a short episode of negative affect, but rather a general trait of anxious or depressed behaviors is providing them with reasons to use. Interestingly, several studies have observed that frequent cannabis use in individuals with trait anxiety leads to subsequent increases in anxiety symptoms (Buckner et al., 2009; Buckner et al., 2011; Zvolensky et al., 2018). It could thus be hypothesized that individuals with specific personality traits, such as hopelessness and anxiety sensitivity, are more prone to experience the anxiogenic and depressogenic effects of cannabis, which in turn, promote emerging psychotic

symptoms. One hypothesis to be tested is whether youths at risk for emotional disorders and psychosis exhibit a greater vulnerability to the psychotropic or anxiogenic and depressogenic effects of cannabis.

6.2.2 Hypersensitivity to stress

Considering (i) that disturbed affective processing underlies anxiety and depression symptoms (Thomas et al., 2001), and (ii) the high density of CB_1 receptors in the amygdala (Katona et al., 2001), it is plausible that cannabis use could exacerbate anxiety and depression symptoms via its action on the generation and regulation of affect. Evidence from both acute and long-term residual effects of cannabis use support this hypothesis of an induced hypersensitivity to stress. Regarding the acute effects of cannabis, functional imaging studies of Δ^9-THC administration in either healthy adults or chronic users showed opposite effects of Δ^9-THC intoxication on the amygdala's response to fearful faces: either an attenuated response (Bossong et al., 2013; Gruber et al., 2009; Phan et al., 2008) relative to happy faces was observed, or a greater response compared to neutral stimuli (Bhattacharyya et al., 2017). This latter study demonstrated that the amygdala's heightened response was independent of other effects induced by Δ^9-THC, such as psychotic symptoms (Bhattacharyya et al., 2017). The discrepancy between these results may be explained in part by the use of different control conditions in the fMRI emotion processing task as well as the use of a higher dose of Δ^9-THC in Bhattacharrya and colleagues' study. Interestingly, findings from animal studies suggest that the anxiolytic and anxiogenic effects of cannabis intoxication are dose-dependent. For instance, larger doses of Δ^9-THC and other exogenous cannabinoids were shown to inhibit GABAergic signalling in the amygdala (Katona et al., 2001), an effect that was amplified in a threatening environment (Patel et al., 2005). Consequently, large doses of Δ^9-THC appear to lower the threshold of amygdala responsivity (by inhibiting inhibitory transmission – an anxiogenic process), while lower doses appear to play an anxiolytic role.

A large neuroimaging study of cannabis use during adolescence (n=140) has further examined whether the mid- to long-term residual effects of cannabis use, as opposed to the acute effects, influence emotion processing (Spechler et al., 2015). The authors found increased reactivity of the amygdala (bilaterally) to angry faces relative to neutral ones in cannabis-

experimented youths compared to non-users. An important strength of this study is that the sample of users (n=70) was carefully matched to a same-size control group among the whole initial cohort of approximately 2000 participants. Both groups of users and non-users did not differ on sex, pubertal development, IQ, psychopathology or alcohol and cigarette use. Consequently, the authors are confident that the observed differences in amygdala response are associated with cannabis status. Altogether, cannabis use may increase threat processing especially in a stressful context (Spechler et al., 2015). This mechanism of action is likely to explain the relationship between cannabis use and both anxiety and depression symptoms.

However, as displayed in Figure 1, it is not clear whether it is the presence of anxiety and depression symptoms or the observed hypersensitivity to stress that directly leads to the development of psychotic symptoms. On one hand, studies have shown that anxiety and depression symptoms often precede the onset of psychosis (Fusar-Poli et al., 2014) and are often the first symptoms to be noticed in high-risk individuals (Stowkowy, Colijn and Addington, 2013). On the other hand, an increased experience of stress also precedes the onset of a psychotic episode. Considering that these two concepts are closely related to one another, it is difficult to determine which one is a proxy for the other in the path towards psychotic symptoms.

6.3 Structural vulnerability markers of adolescent cannabis use

In order to complement the findings of the behavioral and neurophysiological effects of cannabis use, the effects of adolescents' cannabis consumption on brain structure were investigated. Findings from the fourth study revealed that cannabis use during early adolescence marginally interacts with psychotic-like experiences but does not interact with time in its relationship with the maturation of subcortical brain volume and the change in whole brain cortical thickness. These findings are in line with our initial hypotheses, as we expected to observe only modest cannabis by psychotic-like experiences effects. However, we were surprised that the modest interaction was specifically found in the parahippocampal gyrus. Since we did observe that youths with elevated psychotic-like experiences presented reduced volumes of the amygdala and the hippocampus, two regions with high density of CB_1 receptors (Herkenham et al., 1990), we expected to find more pronounced volume atrophy of these regions

in youths who also used cannabis compared to non-users. Among the few studies that have looked at the interaction between the vulnerability to psychosis and cannabis use, some have found no evidence of an increased susceptibility in vulnerable individuals to the harmful effect of cannabis on gray matter density when controlling for confounding effects (Buchy et al., 2016; Stone et al., 2012), while others observed regional- or male-limited deleterious effects of cannabis in at-risk individuals (French et al., 2015; Rapp et al., 2013; Welch et al., 2011).

The number of cannabis users in our sample was modest (6% at baseline and 22% at follow-up) and their mean frequency of use was considered occasional (less often than every week). Consequently, it is not surprising that the low frequency of cannabis use may not have had long-term deleterious effect on brain structures. However, an important study by our group demonstrated that even in the case of occasional use, cannabis can have lasting neurotoxic effects on cognitive performance in high school teens (Morin et al., 2018). Cannabis use during any given year predicted poorer performance on executive functioning (inhibitory control and working memory) assessed one year later, while controlling for a common vulnerability to impaired cognitive functioning and cannabis use. Therefore, it appears that functional imaging, in contrast to structural imaging, has the potential to highlight impairments in brain function that would be associated with cannabis use and moderated by psychosis vulnerability. It is worth noting that the fMRI literature on the subject is practically inexistent (Buchy et al., 2015). Analyses of this interaction using functional imaging are underway in the young adolescent subsample of the fourth study as well as within an older adolescent subsample considered at risk for psychosis (17- to 18-year-olds), at an age where cannabis use is more frequent and prevalent.

In the fourth study, we observed an increase in the cortical thickness of the parahippocampal gyrus and of the inferior temporal and occipital gyri which was positively associated with the frequency of cannabis use. This finding represents an early vulnerability marker since this effect was not moderated over time and was shown to be already present at baseline. Consistently with a recent IMAGEN study aiming at predicting the onset of cannabis use among a community sample of adolescents, larger brain volumes as well as increased regional cortical thickness were shown to be predictive of subsequent cannabis use in boys and girls (Spechler et al., 2018). The increased cortical thickness found in our study may thus indicate a delayed neurodevelopmental maturation of the paralimbic system and its connected

regions which would be associated with a future status of cannabis use. However, it is unclear whether this potential vulnerability marker helps explain the cannabis-to-psychosis symptoms relationship. For this reason, in Figure 1, I did not draw an arrow linking the cortical thickness findings associated with cannabis use to the emergence of psychotic symptoms. This relationship would need to be tested in future studies.

6.4 Aberrant emotional salience characterizes the vulnerability path towards emerging psychotic symptoms

The initial aberrant salience theory proposes that the development of delusions and paranoia originates from the misattribution of motivational or emotional significance to stimuli that would normally be considered irrelevant in context (Kapur et al., 2005). The stimuli which have been attributed an aberrant salience may thus be allocated more cognitive and attentional resources. Delusions would originate from the individual's own explanation of this experience of aberrant salience (Winton-Brown et al., 2014). In the literature, abnormal salience processing in psychosis can be assessed using different tasks. A review by Winton-Brown and colleagues (2014) suggests that salience processing can be conceptualized as either a positive motivational salience, measured with reward prediction and prediction error paradigms, or as an aversive emotional salience, assessed with classical conditioning of threat prediction or emotion processing tasks.

Preclinical studies have demonstrated that the processing of positive motivational salience involves cortico-striatal dopamine signaling (Bromberg-Martin et al., 2010). Heightened dopamine signalling in the striatum also appears to be involved in both the pathophysiology and the etiology of psychosis (O. D. Howes et al., 2012), as it is associated with the transition to a full-blown episode in high-risk individuals (O. Howes et al., 2011). It has been proposed that phasic increases in striatal dopamine signaling of psychosis patients result in an over-attribution of motivational salience to unexpected and irrelevant cues (O. D. Howes and Nour, 2016). Regarding the neural correlates of positive motivational salience attribution, functional imaging studies have identified altered activity from the ventral striatum,

the anterior cingulate cortex and the insula (Schmidt et al., 2016; Smieskova et al., 2015; Walter, Suenderhauf, Smieskova, et al., 2016). The anterior cingulate cortex and the insula form the salience network (Sridharan et al., 2008; Uddin, 2015) which mediates the switching between the activation of the central executive network (i.e., task-related network) and the default-mode network (Uddin, 2015). Both the anterior cingulate cortex and the insula are involved in prediction error processing and updates of an outcome's probability (Palaniyappan and Liddle, 2012). These processes are likely to be followed by the learning of stimulus-reinforcement associations and motor actions (Schmidt et al., 2016).

However, our results from the third study do not agree with an abnormal brain response to reward-related cues. This third study reported limited (that did not survive the cluster threshold) increased activity from the anterior cingulate cortex during anticipation of a large reward in youths with psychotic-like experiences compared to individuals reporting low psychotic-like experiences. This difference in brain activity between the groups did not significantly contribute to classifying those reporting emerging psychotic symptoms 2 years later. Consequently, these findings suggest that an abnormal positive motivational salience attribution is not related to an early vulnerability to psychosis.

As opposed to the underlying mechanisms of positive motivational salience, the potential mechanisms of aversive emotional salience have been less characterized. To date, most of the findings come from emotion processing tasks highlighting the disrupted role of the limbic system (Anticevic et al., 2012). In fact, psychosis patients report increased amygdala activity during neutral expression processing (Anticevic et al., 2012). The results from the third study directly contribute to this increasing literature. Hyperactivity from both the hippocampus and the amygdala that is specific to the processing of neutral (ambiguous) faces was found in young adolescents reporting psychotic-like experiences, suggesting an aberrant emotional salience. This limbic hyperactivity predicted subsequent reporting of clinically validated psychotic symptoms, making it an important early vulnerability marker of psychosis risk.

The functional alterations of the hippocampus and amygdala associated with psychotic-like experiences observed in the third study are potentially related to the structural atrophy found in these same regions in the independent sample of vulnerable youths in the fourth study. It

would be interesting to further assess the developmental relationship between limbic hyperactivity and volume atrophy within an at-risk youth sample.

Interestingly, a few studies have tried to link the hyperdopaminergic theory of psychosis with the abnormal activity from the limbic system. Both animal and human studies indicate that augmented hippocampus activity occurs downstream of the increased striatal dopaminergic signalling associated with psychosis, via glutamatergic afferents from the ventral part of the hippocampus to the nucleus accumbens (Lodge and Grace, 2006, 2011). According to Lodge's review (2011), the ventral hippocampus' action on dopamine firing is context-dependent. For instance, in an environment of potentially high reward or high punishment, an elevated ventral hippocampus activity leads to a large dopamine response, while in a neutral or non-threatening environment, the ventral hippocampus down-regulates the dopamine response. Thus, hyperactivity from the hippocampus, that is consistently observed among the extended psychosis phenotype, is thought to underlie the hyperdopaminergic state and the faulty attribution of positive motivational and aversive emotional salience to stimuli in a non-emotional or non-arousing context.

Moreover, it was shown, both in animal models of schizophrenia and human patients, that individuals with the disorder fail to reduce hippocampus activity with repetitive viewing of the same emotional stimulus compared to healthy controls (Barkus et al., 2014; Holt et al., 2005). Decreased hippocampus activity in healthy individuals is considered as a normal short-term habituation strategy. Therefore, this failed hippocampus suppression with repeated presentations of a stimulus in patients may lead to increased aversive emotional salience and elevated allocation of attentional resources to cues that would normally become irrelevant considering their repetitive and thus, predictive nature (Barkus et al., 2014).

Together, our results of abnormal limbic activity suggest that among the regions implicated in emotional salience, functional alterations (and potentially volume atrophy) of the hippocampus and amygdala may be responsible for the aberrant emotional salience attribution observed in the developmental path towards emerging psychotic symptoms (Figure 1). Our results do not support abnormal positive motivational salience processing as an early developmental marker for psychosis vulnerability.

6.4.1 Aberrant emotional salience versus increased emotional salience

At the functional imaging level, anxiety disorders have been well-characterized by an enhanced reactivity of the amygdala to negative emotional responses, traumatic scripts and stressful cues, reflecting an overall exaggerated fear response or an increased aversive emotional salience (Etkin and Wager, 2007; Fredrikson and Faria, 2013). In addition, increased amygdala and hippocampus activity during negative and arousing stimuli have been reported in depressed patients (Jaworska et al., 2015; Kerestes et al., 2014). As opposed to a general phenomenon of hypersensitivity to stress reported in these disorders, the findings from the third study pointed to a potential specific marker of psychosis risk which is an aberrant emotional salience attribution to otherwise irrelevant or neutral (ambiguous) information. Consequently, it appears that increased emotional salience attribution and aberrant emotional salience attribution could be separate processes that lead to different vulnerabilities to psychopathology.

Another hypothesis proposes that, although aberrant emotional salience to neutral and irrelevant stimuli and increased emotional salience to aversive cues are different processes, one might further impair the other. This potential relationship is displayed in Figure 1: an arrow initiating from hypersensitivity to stress points to aberrant salience processing. Studies have consistently reported an elevated emotional reactivity to stress in individuals vulnerable to psychosis (genetic and clinical high-risk individuals) (Myin-Germeys and van Os, 2007). In fact, an increased affective response to the small stressors of daily life predicts changes in positive symptoms and is associated with the development of psychosis. Therefore, further research is required to determine whether this altered stress-sensitivity that is common among a few psychiatric disorders can specifically lead to an aberrant emotional salience of neutral and ambiguous cues, which in turn would promote the vulnerability path to psychosis.

6.5 Clinical implications for the results of this thesis

An early targeted intervention approach to psychosis risk management offers many advantages over the clinical high-risk or first-episode approach. Specifically, considering the

recognition of the involvement of early onset cannabis use in psychosis risk, one advantage is the potential to delay or prevent some cases of psychosis by delaying or preventing onset of heavy cannabis use, particularly in those most at-risk. Furthermore, considering that psychotic disorders typically develop by 18-30 years of age (Tandon et al., 2009), identifying at-risk individuals by mid-adolescence would allow for a wider timeframe of other potentially helpful prevention strategies.

6.5.1 Early identification

In the different studies of this thesis, I have used two related approaches to identify youths with a vulnerability to psychosis: (i) those reporting significant psychotic-like experiences (i.e., determined by a validated threshold) during adolescence, or (ii) those following an increasing developmental trajectory of psychotic-like experiences during high-school years. Considering the transitory nature of these experiences (van Os et al., 2009), the latter approach is better suited to characterize developmental factors associated with psychosis proneness. It is worth mentioning that this identification approach used in the second study is now undergoing a validation process. In an ongoing project recently funded by the Canadian Institutes of Health Research (CIHR), our team (Stéphane Potvin, Patricia Conrod) is following youths up until age 21 according to the three different psychotic-like experiences trajectories measured during the beginning of adolescence to quantify the proportion of those in the increasing trajectory moving towards clinically validated symptoms relative to the other trajectories (using the Comprehensive Assessment of At-Risk Mental States - CAARMS) (Yung et al., 2005). So far, in a sample of 78 recruited individuals out of the planned 198, we observed that approximately 16.7% of those following the increasing trajectory have reported psychotic symptoms during the semi-structured interview, while this proportion was 0% in both other groups. These numbers further validate the pertinence of the trajectory approach in the investigation of psychosis proneness and outcomes.

Given that the questionnaire used to repetitively measure psychotic-like experiences includes only 9 items, the trajectory method could easily be applied in pediatric clinical settings and schools to help health professionals identify youths with specific needs and vulnerabilities. However, in some settings, longitudinal assessments are considered costly, time-consuming,

and human resources-consuming, consequently the applicability of this strategy may not always be optimal. According to the results from the second study and from Mackie et al. (2011; 2013), it would be possible to distinguish youths following the increasing trajectory from ones on the other trajectories based on the psychotic-like experiences reported by 15-16 years old (please refer to the second study's Figure 1, page 72). In fact, our findings highlight that by age 15 to 16, those with transient psychotic-like experiences report a similar score of psychotic-like experiences as the majority of youths who consistently report low levels. This idea might thus be more useful for healthcare providers due to the limited amount of time they spend with patients. However, this cross-sectional risk identification does not necessarily allow for early prevention because by this age, it becomes more difficult to efficiently prevent the use of cannabis or other substances in vulnerable individuals.

Another strategy to avoid using longitudinal assessments in risk identification would be to promote further research into the characterization of the different trajectory groups. Using newly designed machine learning algorithms could highlight the most important features at baseline (in our case, 12-13 years old) to accurately predict trajectory membership. Results from this analysis would have the potential to identify at-risk adolescents (those eventually following an increasing trajectory of psychotic-like experiences) from an even younger age, if the predictive features were to be evaluated in clinical practice. This last strategy would allow for an opportunity for targeted prevention during an interesting time window. Such an early intervention has the potential to decrease the likelihood of psychotic-like experiences becoming persistent, to increase early resilience to environmental stressors and to delay or prevent adolescent risk factors associated with these experiences, such as substance use.

6.5.2 Prevention strategies

To date, efforts have mostly been made on developing and testing interventions for individuals at clinical high-risk for psychosis. The majority of studies have tested the efficacy of cognitive behavioral therapy (CBT) in this population (E. Thompson et al., 2015) after CBT had been shown to be effective in helping schizophrenia patients cope with symptom-related distress (Pilling et al., 2002; Sensky et al., 2000) and in reducing the risk of relapse (Gumley et al., 2003). The CBT model of intervention is also indicated for concurrent substance use and

psychosis risk since the model was originally developed for mood disorders and was then adapted and validated to be highly effective in substance-dependent populations (Stewart and Conrod, 2008). A recent meta-analysis of 11 trials including 1,246 participants showed a significant effect for CBT in reducing transition to psychosis at 12 months follow-up (risk ratio 0.54, 95% CI, 0.34-0.86) (Stafford et al., 2013). These CBT interventions have common components, including an engagement phase, psychotic symptoms normalization, social skills training, cognitive restructuring and psycho-education (Addington et al., 2012; Stafford et al., 2013).

To my knowledge, only one study, a case series report, has tested the impact of a CBT intervention on children and adolescents (9- to 14-year-olds) from the community reporting psychotic-like experiences, and not clinically validated symptoms. This cognitive behavioral intervention aimed to reduce emotional problems, help the management of psychotic-like experiences, and improve adaptive coping strategies (Maddox et al., 2013) before the development of an at-risk mental state, which is associated with persistent and distressing psychotic symptoms. In fact, results from a longitudinal study suggest that distress, poor coping, and negative appraisals are associated with the persistence of psychotic-like experiences in youths (Lin et al., 2011). This newly developed CBT includes cognitive therapy techniques for emotional and behavioral problems in youths as well as re-appraisal strategies from adult psychosis CBT. The authors noted reductions among all 4 cases in emotional problems, in the frequency of psychotic-like experiences, and most importantly, reductions in associated distress (Maddox et al., 2013).

Although limited, these results are encouraging for the future development or adaptation of a CBT intervention in this population. The findings of this thesis help identify the potential processes underlying emotional problems associated with psychotic-like experiences. Consequently, this information (i.e., aberrant salience attribution) could help in the design of a more targeted preventive strategy.

In addition, this thesis' results highlight the need to address motivational pathways to cannabis use. Descriptive statistics from the second study revealed that the rates of cannabis use in youths reporting increasing psychotic-like experiences were almost double those of healthy adolescents reporting very low experiences (40.2% already used vs 24.1%) (Study 2, Table 1,

page 67). Unpublished results from the same cohort also outlined specific reasons to use cannabis in those following an increasing trajectory (i.e., fit in a group and cope with depression symptoms). This data suggest that youths at risk of psychosis are more likely to use cannabis, and when they do use it, they appear to be more susceptible to the psychotic-inducing effects of cannabis. Therefore, interventions designed to protect these at-risk youths must aim to both reduce the likelihood of taking up regular cannabis use and target the underlying motivational factors that initially attract at-risk youths to cannabis. Unfortunately, even though several authors have acknowledged the need to target substance misuse (e.g. cannabis) in this at-risk population (Valmaggia et al., 2014), relatively few intervention trials have paid direct attention to this complicating factor.

It is worth noting that these notions (e.g., aberrant salience attribution, motives to use cannabis, and associated anxiety and depression symptoms) are now being integrated into a new CBT initiative, developed by our team, for the prevention of increasing psychotic-like experiences and cannabis misuse. The development and upcoming testing of this preventive strategy was funded by the CIHR.

6.6 General limitations

A limitation of this thesis is that I was not able to properly test for an interaction between cannabis use and psychotic-like experiences using brain measures. As discussed previously, the lack of early onset cannabis users (i.e., at age 14) who also reported psychotic-like experiences in the IMAGEN sample prevented me from investigating their interaction on brain function (Study 3). Fortunately, in the fourth study, I was able to explore that interaction on brain volume and cortical thickness. However, I only tested for the interaction among youths reporting elevated psychotic-like experiences at some point during adolescence and not specifically among those following an increasing trajectory of psychotic-like experiences during adolescence. This latter group is considered to be at a greater risk for psychosis, and therefore more vulnerable to the psychotropic effects of cannabis, but it could not be evaluated due to its small sample size (n=10). Considering the young age of our samples and thus the low frequency of use, a more likely finding would have been more pronounced functional alterations, as

opposed to structural anomalies, in cannabis users with psychotic-like experiences. This needs to be investigated in subsequent studies. It is worth mentioning that only a few cross-sectional neuroimaging studies were able to test for the interaction between cannabis and schizophrenia (Bourque et al., 2013; Potvin et al., 2007), and between cannabis and psychosis risk (Buchy et al., 2015) certainly because of the large sample size required for this design.

Another important limitation is that I did not assess behavioral performance of social cognitive functioning in youths with psychotic-like experiences. In fact, in the second study, I only investigated whether the relationship between cannabis and trajectories of psychotic-like experiences could be explained by non-social cognitive deficits. Social cognition was not included in the cognitive battery used in the Co-Venture study considering that the primary aim of that randomized controlled trial was to explore whether delaying or preventing substance use in adolescence would positively influence IQ, memory and executive functioning (O'Leary-Barrett et al., 2017). This thesis would have benefitted from the investigation of emotion processing and identification, as well as how the performance of these tasks would be related to the observed functional and structural alterations of the limbic system associated with psychosis proneness. Although the neuroimaging results of the present thesis do not support alterations in the default-mode network of vulnerable youths, in part because this network was not specifically investigated, a great addition to this thesis would have been a thorough exploration of self-reflection and ToM processes at both the behavioral and functional level. Indeed, self and other distinction as well as the attribution of one's own intention to others' mental states consist in early vulnerability markers of psychosis proneness (Clemmensen et al., 2014; Clemmensen et al., 2016). Furthermore, excessive ToM has been suggested to represent a specific marker for psychotic symptoms (Abu-Akel and Bailey, 2000).

It is worth noting that although the identification of psychosis vulnerability via the psychotic-like experiences approach is not considered a limitation per se, this approach may be subjected to critiques from the clinical milieu. For instance, in the last version of the DSM, it was decided not to include the "attenuated psychosis risk syndrome" as a diagnostic entity considering that this new diagnosis might lead to inappropriate treatments (Tsuang et al., 2013). Still, the DSM-5 task force has emphasized the need for future research on the topic before it is included (Tsuang et al., 2013). Studies of psychosis transition in clinical high-risk individuals have shown that the rate of transition has gradually decreased over the years. This lower rate in

recent studies may be explained by at-risk individuals being referred earlier, which may prolong the time before a transition to a full-blown episode, or by a dilution effect, meaning that more individuals from the general population reporting psychotic experiences are directly referred to these early psychosis intervention clinics (Yung and Nelson, 2013). Considering that a diagnosis of a mental health disorder creates stigma for the individual, and that treatment approaches, particularly pharmacotherapy, can lead to adverse health effects, the psychotic-like experiences approach may not be suitable from a clinical and treatment perspective.

However, from the perspective of early prevention and public health, the psychotic-like experiences approach can be used to promote selective or targeted prevention strategies, which are considered more efficient and less costly than universal prevention programmes (Conrod et al., 2006). These early prevention strategies are less likely to create stigma considering that a significant portion of the general adolescent population (20% - Kelleher et al., 2012) could be invited to discuss the normal phenomenon of having psychotic-like experiences. As it was demonstrated with selective preventive interventions for alcohol and drug use (Conrod et al., 2010; Conrod et al., 2008; Mahu et al., 2015), an early identification of psychotic-like experiences in addition to the implementation of efficient preventive strategies have the potential to delay the development of clinically validated psychotic symptoms.

6.7 Future directions

6.7.1 Understanding the mechanisms underlying aberrant salience

Aberrant salience is frequently mentioned in studies involving psychosis patients and psychosis-prone individuals completing emotion processing tasks, therefore termed aberrant emotion salience. The neural correlates of this dysfunctional emotion processing are heterogeneous. Studies have reported both an under-recruitment and hyper-recruitment of the limbic system during the processing of aversive content. A meta-analysis of functional imaging studies in patients with psychosis has demonstrated that the origin of the heterogeneity between findings originates from the use of different reference conditions (Anticevic et al., 2012). Consequently, the under-recruitment of the amygdala during aversive stimuli processing was explained by the use of a neutral condition as reference, which was shown to elicit increased

amygdala activation. Therefore, when subtracting amygdala activation from one condition to the other, studies reported no significant increase in activation for aversive stimuli, or even decreased activation. Inversely, hyperactivity from the amygdala during aversive emotion processing was observed in studies that did not use the neutral condition as reference, but instead used a baseline (e.g., rest) condition (Anticevic et al., 2012). The finding of increased amygdala activity during neutral expression processing in patients further contributes to the aberrant emotional salience hypothesis of psychosis.

Based on these results and our own, this exaggerated brain response to neutral cues could be portrayed as a dysfunction of emotion identification in which individuals interpret facial expressions as being more negative. This hypothesis is supported by neuroimaging evidence showing amygdala hyperactivation (i.e., increased cerebral blood flow) at rest in patients reporting paranoia symptoms compared to healthy control subjects (Pinkham et al., 2015). This systematic amygdala hyperactivation implies that environmental and daily life stimuli may be attributed more negative weight in patients. This theory fits well with the fact that trauma and child adversity are important risk factors for psychosis and other forms of psychopathology. However, behavioral studies of emotion recognition have found a lower accuracy in identifying facial expressions in first-episode psychosis patients, as opposed to a specific bias towards a negative interpretation (Barkl et al., 2014). In fact, lower identification accuracy was observed for disgust, fear, surprise, sadness and happiness. Thus, the underlying mechanism of aberrant salience appears to be more complex than a specific bias towards a negative interpretation.

As previously discussed in section 6.4, aberrant salience attribution can also be investigated in the context of reward learning with cue conditioning paradigms (also known as positive motivational salience). These tasks use two types of conditioned stimuli: one that is paired with the unconditioned stimulus (reward) to assess adaptive salience, and one that serves as the neutral comparator to assess aberrant motivational salience. Both neuroimaging and behavioral studies in individuals with a diagnosis of psychosis have demonstrated inappropriate striatal and limbic activation as well as increased galvanic skin responses to neutral cues, suggesting aberrant reward learning (Jensen et al., 2008; Romaniuk et al., 2010). These findings suggest that a general pattern of assigning erroneous or inappropriate contextual associations to the stimuli underlies the observed aberrant salience attribution. Interestingly, the hippocampus

plays a major role in coding contextually salient information (Maren et al., 2013). Therefore, it could be hypothesized that abnormal hippocampus activity characterises both aberrant emotional and motivational processes, and that the general underlying mechanism would be altered contextual associations of the situation and the way these associations are remembered.

Future studies need to explore more extensively the brain mechanisms of aberrant salience to better understand the different contexts in which aberrant salience attribution could be found. To do so, the next step would be to examine the functional connectivity within the limbic network during various tasks measuring aberrant salience. Then, it would be interesting to evaluate the connectivity of both the amygdala and hippocampus with other networks known to be dysfunctional in psychosis, such as the striatal, salience, default-mode and control-executive networks.

6.7.2 The role of sleep disturbances

Poor sleep or sleep disturbances are often reported in adolescent community samples (Crowley et al., 2007) and are comorbid with both internalizing and externalizing symptoms (Gregory et al., 2011). In fact, sleep disturbances such as insomnia has been used as a transdiagnostic process considering its high prevalence in various psychiatric disorders (Harvey et al., 2011). One such psychiatric disorder is substance use disorder. The relationship between sleep problems and substance misuse appears to be complex. Some studies have shown that sleep problems during childhood and adolescence can predict the early onset of substance use (Pieters et al., 2015; Wong et al., 2009; Wong et al., 2015), while others have demonstrated that regular substance use leads to extended sleep onset latency, more nighttime awakenings, as well as decreased rapid-eye-movement (REM) sleep (Schierenbeck et al., 2008).

In the case of cannabis use, interesting recent findings over the last decades have supported the role of the endocannabinoid system in regulating sleep and circadian rhythms (Prospero-Garcia et al., 2016). For instance, the endocannabinoid system has been shown to promote both REM and non-rapid-eye-movement (NREM) sleep by direct activation or blockade of CB_1 receptors (Pava et al., 2016; Prospero-Garcia et al., 2016). Moreover, modifications in the expression of CB_1 receptors were associated with different sleep-wake cycles, and a lack of sleep was associated with dysregulations within the endocannabinoid

system (Vaughn et al., 2010). In an experimental study with humans, Δ^9-THC alone did not influence nocturnal sleep on the day of its administration, but it did increase feelings of sleepiness the following day (Nicholson et al., 2004). However, in daily cannabis users, Δ^9-THC administration leads to a decrease in overall nighttime sleep (Gorelick et al., 2013). Together, these results highlight a potential involvement of the endocannabinoid system in sleep regulation (Babson et al., 2017). It could be hypothesized that sleep disturbances during adolescence play a role in the cannabis use pathway towards anxiety and depression symptoms, and in turn, psychosis proneness.

A proposed mechanism for this relationship would be the influence of sleep quality on emotional response to stimuli (Chuah et al., 2010; Gujar et al., 2011; Rosales-Lagarde et al., 2012). A selective interruption of REM sleep, but not an interruption of NREM sleep, was associated with enhanced emotional reactivity to threatening stimuli in comparison to the emotional response during the baseline condition (no sleep interruptions) (Rosales-Lagarde et al., 2012). Moreover, at the neurofunctional level, the authors found an opposite pattern of brain activity during task completion in those with REM sleep interruptions compared to those with NREM sleep interruptions. They observed a reduction in temporo-frontal activation during threat processing relative to the baseline condition in participants with NREM sleep interruptions, while the activation of this network slightly increased relative to baseline in those with REM sleep interruptions, suggesting an elevated emotional response when REM sleep is altered. Resting-state connectivity studies have highlighted an elevated connectivity within the limbic network during sleep deprivation relative to a sleep-rested state which was also associated with increased amygdala activation in a subsequent emotional-distraction task (Krause et al., 2017). Moreover, in an experimental sleep deprivation protocol, the "lack of sleep" condition and not the "sleep rested" condition, resulted in a similar processing of emotional and neutral cues (by the dorsolateral prefrontal cortex and the amygdala) according to fMRI and EEG measures (E. B. Simon et al., 2015). The sleep deprivation condition was also associated with reduced amygdala-prefrontal connectivity that may be responsible for the hypothesized impairment in emotion regulation. The authors suggested that sleep deprivation may decrease the threshold for emotional activation leading to a loss of neutral cue processing (Simon, et al., 2015).

This hypersensitivity to emotions or emotional bias towards neutral cues from impaired sleep fit our hypothesized mechanism of increased emotional salience in explaining the relationship between cannabis use and emerging psychotic symptoms. It has yet to be determined how poor sleep, as a cause or consequence of cannabis use, might be mechanistically related to psychosis proneness. However, one limitation of this new research program would be the recruitment of regular cannabis users considering the effects of cannabis use on disturbed sleep patterns are more likely to be observed among regular users, relative to occasional users.

6.7.3 Differential pathways for different developmental trajectories of psychotic-like experiences

Following the interesting results of the second study, it would be relevant to further understand how and why a portion of the population with psychotic-like experiences grow out of these experiences by mid-adolescence while another subsample continuously reports having these experiences throughout adolescence. To date, we have limited information as to whether fundamental differences exist between the high decreasing and the moderate increasing trajectories. For instance, a steep growth in both anxiety and depression symptoms during adolescence is associated with the moderate increasing trajectory, while results from Table 1 (Study 2, page 67) show that the high decreasing trajectory present with consistently elevated depression and anxiety symptoms (at both baseline and third follow-up). At the third and last follow-up (i.e., age 16), the two groups showed similarly elevated externalizing, general internalizing and anxiety symptoms. From this limited characterization, although the two groups present with similar environmental risk factors (comorbid psychopathological symptoms) but not similar rates of substance use, it appears that youths in the high decreasing group are resilient to persistence of psychotic-like experiences. The data suggest that they may have developed adapted coping strategies to deal with psychotic-like experiences, yet these coping mechanisms did not help reduce other types of symptoms. It could also be hypothesized that, for some of these individuals, these psychotic-like experiences resolve on their own. The level of associated distress and ways of rationalization might influence how these experiences resolve. These hypotheses raise further questions as to which protective factors can help resolve or cope with

psychotic-like experiences and may promote new research into a limited literature (Radua et al., 2018; Schlosser et al., 2012).

Future research should also explore how these different developmental trajectories of psychotic-like experiences eventually link to the clinical high-risk state. As previously discussed, a research project from our team, funded by the CIHR, is following youths from the different trajectories up until age 21 to quantify the proportion of each trajectories that would score significantly on a semi-structured interview assessing the clinical high-risk state (i.e., CAARMS).

6.8 Conclusion

This thesis highlights the major role of the limbic system in the developmental neurocognitive pathway towards the emergence of psychotic symptoms. Both volume reduction and hyperactivity of the hippocampus and amygdala were highlighted as early brain vulnerability markers of psychotic-like experiences and were associated with an aberrant emotional salience attribution to neutral expressions. Results of this thesis also demonstrate that cannabis use during adolescence precedes increases in psychotic-like experiences through cannabis' influence on depression and anxiety symptoms. Based on these findings and on the current literature, this thesis proposes a risk pathway for cannabis in which cannabis use exacerbates the brain response to aversive and threatening cues, a mechanism often associated with both anxiety and depression symptoms. The developmental neurocognitive and risk pathways proposed by this thesis should help inform the development of adapted prevention strategies in vulnerable youths.

Further studies are needed to quantify the relationship between the occurrence of psychotic-like experiences and the development of clinical high-risk states. Such research could help in bridging community prevention strategies with pediatric and adult clinical interventions. The findings also highlight the need to deeply assess social cognition, and not only emotion processing, when identifying vulnerable individuals. Addressing social cognition impairments could benefit these at-risk youths from a wide psychopathological background, such as depression, anxiety and/or psychotic symptoms. Finally, the potential underlying mechanisms of an aberrant salience attribution should be further investigated to adequately prevent and treat the associated symptoms.

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Annex I : Psychotic-like experiences questionnaire

The next items ask about thoughts or beliefs that you could have had DURING THE PAST 12 months. Remember to answer all the times as best you can even if you are not absolutely certain or the items seem irrelevant!

	Not true	**Somewhat true**	**Certainly true**
1. Some people believe that their thoughts can be read. Have other people ever read your thoughts?	□	□	□
2. Have you ever believed that you were being sent special messages through the television?	□	□	□
3. Have you ever thought that you were being followed or spied upon?	□	□	□
4. Have you ever heard voices that other people can't hear?	□	□	□
5. Have you ever felt that you were under the control of some special power?	□	□	□
6. Have you ever known what another person was thinking even though that person wasn't speaking?	□	□	□
7. Have you ever felt as though your body had been changed in some way that you could not understand?	□	□	□
8. Do you have any special powers that other people don't have?	□	□	□
9. Have you ever seen something or someone that other people could not see?	□	□	□

Annex II: Supplement material of Study 2

Methods. Participants, Measures.

Participants

Participants with intellectual deficiency (IQ < 70), aged 14 in Grade 7 (have repeated a school year), and those whose dyslexia is significant enough that one will not be able to complete the test battery within 75 minutes were excluded.

Measures

Dependent variable

All nine items begin with the following statement: 'The next items ask about thoughts or beliefs that you could have had DURING THE PAST 12 months'. Five items were adapted from the Diagnostic Interview Schedule (Costello, 1982): (1) 'Some people believe that their thoughts can be read. Have other people ever read your thoughts?', (2) 'Have you ever believed that you were being sent special messages through the television?', (3) 'Have you ever thought that you were being followed or spied upon?', (4) ' Have you ever heard voices that other people cannot hear?', (5) 'Have you ever felt as though your body had been changed in some way that you could not understand?'. Four additional questions, validated in community samples of children and adolescents (Laurens et al., 2007) were included: (6) 'Have you ever felt that you were under the control of some special power?', (7) 'Have you ever known what another person was thinking even though that person wasn't speaking?', (8) 'Do you any some special powers that other people do not have?', (9) 'Have you ever seen something or someone that other people could not see?'.

Potential mediators

The Brief Symptoms Inventory (BSI) includes 7 items for depression and 5 items for anxiety (Derogatis, 1993). Each item is rated on 5-point scale ranging from 0 (Not at all) to 4 (Extremely) and summed together to form a global score of depression and anxiety separately.

Spatial working memory (SWM) was measured by counting the number of times a previously chosen stimulus (phone) was selected on a giving trial; therefore, a lower score indicates a better performance (Cragg and Nation, 2007).

For delayed memory recall, participants are asked to recall a previously learned visual sequence 30 minutes later (Cohen, 1997).

During the response inhibition task, the participant is asked to learn, by trial and error, to respond to "good" numbers and to withhold a response to "wrong" numbers by rewarding correct or punishing wrong go and no-go responses (Newman and Kosson, 1986). Response inhibition was evaluated with the number of commission errors across the trials.

Covariates

The items of the Family Affluence Scale (FAS) consisted of factual information, such as the amount of weekly received pocket money (ranging from 0 to 2, 2 being 15$ or more), the number of cars in their household (ranging from 0 to 4, 4 being more than 3 cars); whether the child had a personal cellphone, computer, bedroom (yes or no); and whether they go on family vacations at least once a year (yes or no) (Currie, Elton, Todd and Platt, 1997). Each item was summed to form the index of their family's affluence level.

Table S1. Criteria for deciding the number of classes within the growth mixture model of the main sample (2,566 adolescents).

No. of classes	AIC	BIC	Entropy	LMR-LRT *p* value
2	40 206.5	40 259.1	0.87	0.229
3	39 456.6	39 532.6	0.87	0.004
4	39 110.5	39 209.9	0.88	0.113

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LMR-LRT, Lo-Mendell-Rubin Likelihood Ratio Test.

Figure S1. Main population trajectory of cannabis use frequency between 13- to 16-years old.

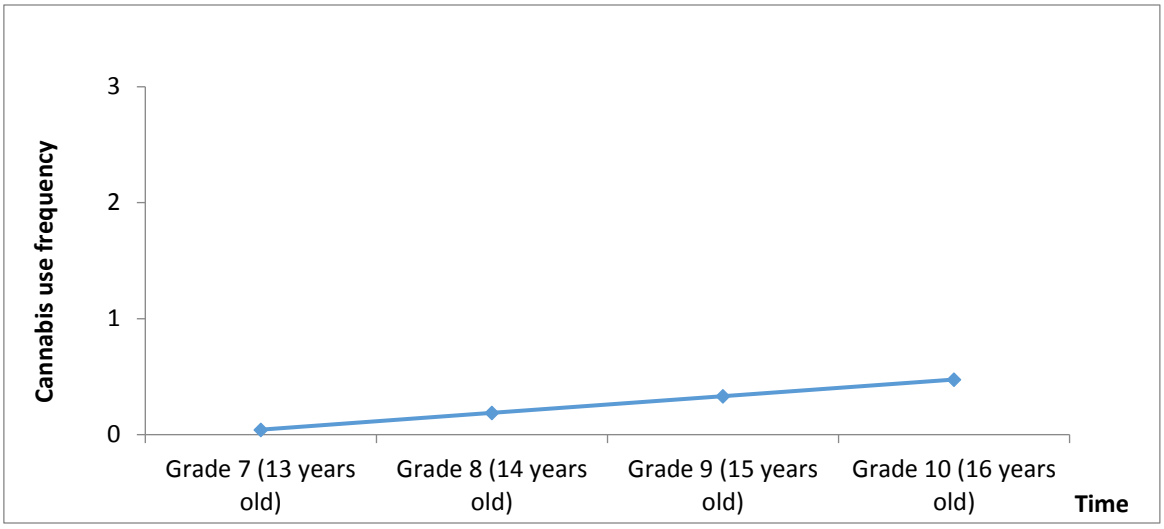
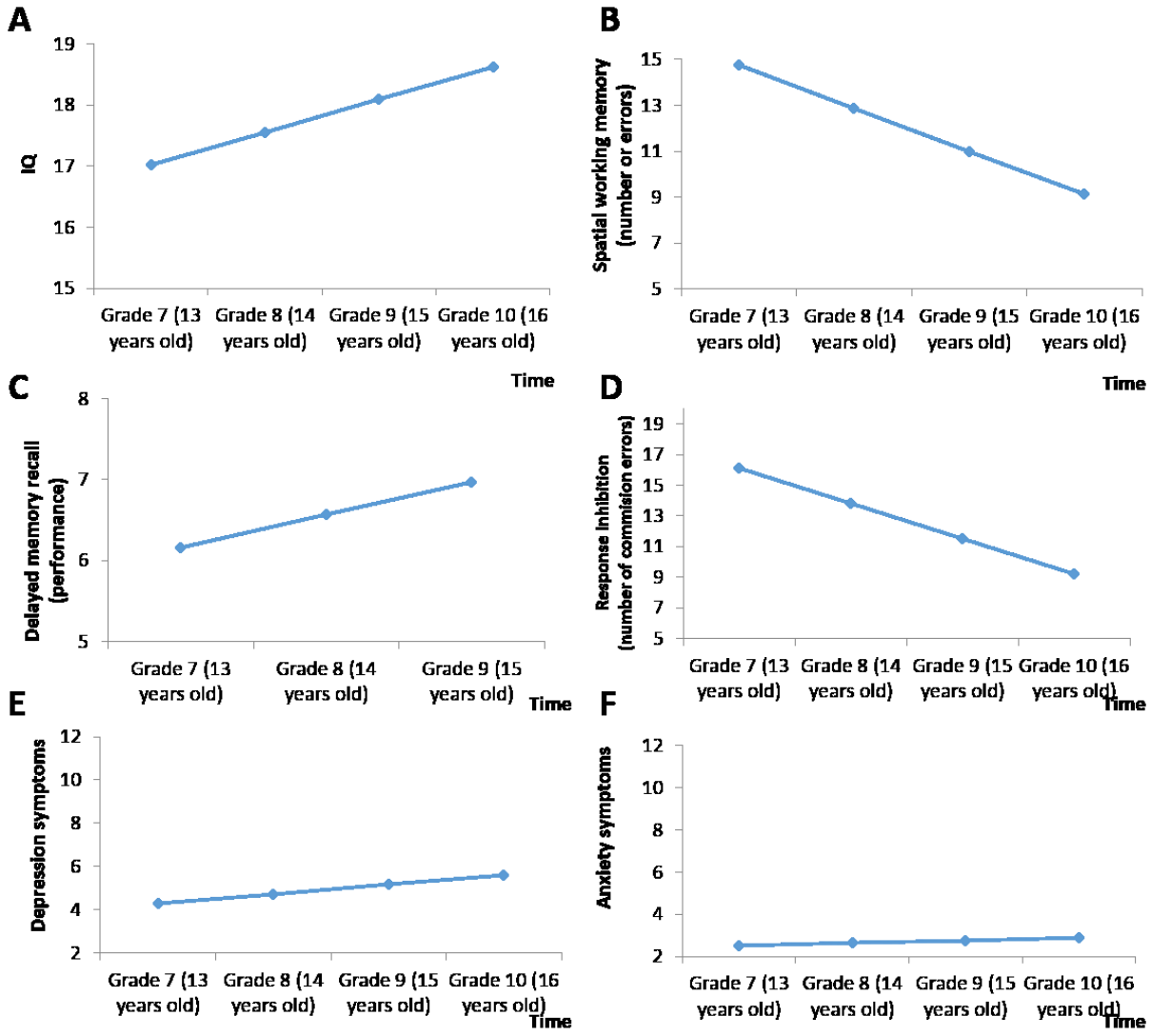


Figure S2. Main population trajectory of the potential mediators between 13- to 16-years old.



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Annex III: Supplement material of Study 3

Supplemental Methods

Procedures

In this 2-year prospective study, all participants completed, at baseline, a home-based assessment on clinical and demographic information and were further invited to perform cognitive tasks while their brain responses were measured with fMRI. Importantly, a subsample of 410 adolescents from London and Dublin sites further completed a baseline assessment of psychotic-like experiences. Then, 1602 participants from all sites were re-assessed two years later (i.e. 16 years old) through a home-based assessment.

Information about the magnetic resonance imaging (MRI) procedure (image acquisition sequence, standardization across MRI scanner) can be found elsewhere (Schumann et al., 2010). All images were acquired on 3 Tesla scanners of different manufacturers (Siemens, Philips, General Electric, Bruker).

Further description of measures

Psychotic-like experiences

The Adolescent Psychotic-Like Symptoms Screener's items begin with the following statement: 'The next items ask about thoughts or beliefs that you could have had DURING THE PAST 6 months'. The following 4 items were adapted from the Diagnostic Interview Schedule (Costello, 1982): (i) 'Some people believe that their thoughts can be read', (ii) 'Have you ever believed that you were being sent special messages through the TV?', (iii) 'Have you ever thought that you were being spied upon?', (iv) ' Have you ever heard voices that no-one else could hear?'. Three additional items, validated in community samples of children and adolescents (Laurens et al., 2007, Kelleher, Harley, Murtagh and Cannon, 2011) were included: (v) 'Have you ever felt that you were under the control of some special power?', (vi) 'Do you have some special powers that other people do not have?', (vii) 'Have you ever seen something or someone that other people could not see?'.

Twenty-seven 14-year olds reporting significant psychotic-like experiences were matched to a group of healthy controls five times as large. The matching script's function was to find a group of matched adolescents, among the 300 youth with complete fMRI and behavioral information,

whose parameter averages did not differ more than 5% above or below the parameter averages of the 27 adolescents with these experiences.

As for the relationship between psychotic-like experiences assessed at age 14 and emerging psychotic symptoms assessed at age 16 with the bipolar module in the London-Dublin subsample, of the twenty-seven 14-year-olds reporting significant psychotic-like experiences, follow-up information was available for 23. Of these, 6 (26.1%) had both mood and psychotic related symptoms, 6 had only mood symptoms, and 11 reported no mood symptoms. Of the 135 adolescents reporting no psychotic-like experiences at 14 years old, follow-up information was available for 109. Of these, 3 (2.8%) had both mood and psychotic related symptoms, 33 had only mood symptoms, and 73 reported no mood symptoms.

Functional imaging

All participants underwent two 45-min MRI sessions. Before each session, participants familiarized themselves with the scanner and the tasks in a practice session. In the scanner, they received a brief visual and verbal reminder of the instructions before the tasks.

The faces task is derived from Grosbras and Paus (2006), where dynamic angry faces are displayed. Participants passively viewed blocks of short black and white video clips (2-5s) of three conditions: neutral faces, angry faces, and control (non-biological motion). Each block includes four to seven video clips. In both the angry and neutral conditions, the faces were always neutral at the beginning and progressively turned angry or stayed neutral. Video clips were preferred to static faces as they allow a better recruitment of cerebral regions implicated in facial processing (Arsalidou, Morris and Taylor, 2011). The control condition (Beauchamp, Lee, Haxby and Martin, 2002) consisted of contracting and expanding concentric circles with black and white contrasts matching the contrast and motion characteristics of the faces clips. Ten 18-sec blocks were presented (5 blocks of angry faces, 5 blocks of neutral faces), interleaved with nine blocks of the control condition, for a total of 6 minutes.

The fMRI adaptation (Rubia et al., 2001) of the stop-signal task (Logan, Schachar and Tannock, 1997) measures activity in brain areas related to the inhibition of an already planned motor response as well as error detection. On a total of 480 trials, a motor response to high frequency go signals (arrows pointing left or right) has to be inhibited when infrequently and unexpectedly, a stop signal appears after the go signal (arrow pointing upwards). Indeed, participants were

asked to try and withhold their response when an upwards arrow followed the go-stimuli, however, they were explicitly reminded to try and respond as fast as possible to the go stimuli. Stopping difficulty is manipulated across trials by varying the delay between the onset of the go arrow and the stop arrow (stop-signal delay). Therefore, the task is individually titrated to force every subject to fail on 50% of stop trials, making every subject work at the edge of their own inhibitory capacity, and therefore adjusting for differences in success levels between subjects and groups, making it ideal for developmental studies. This 16-minute task included 80 stop trials (16.7% of trials). Between three and seven go trials separated two stop trials. Stimulus duration in go trials was 1,000 ms and varied in stop trials (0-900ms) in accordance with the tracking algorithm (initial delay = 250ms). For this task, first-level analysis included the movement realignment regressors plus 5 task-specific regressors: (i) successful inhibitions, (ii) errors of commission, (iii) incorrect responses on go trials, (iv) late responses on go trials, and (v) correct responses on go trials.

A modified version of the monetary incentive delay task was used to assess brain response to reward anticipation (Knutson, Adams, Fong and Hommer 2001; Knutson, Fong, Adams, Varner and Hommer, 2001), in which each trial included a reward anticipation phase, a reward response phase, and a feedback phase. Considering that the ventral striatum hypoactivation during reward anticipation is the most replicated finding in chronic and first-episode psychosis patients as well as in individuals at clinical risk for psychosis in paradigms exploring reinforcement learning (Radua et al., 2015), the current study only focused on the anticipation phase. First, participants are presented with cues (ranging from 4.0-4.5 sec) signaling the amount of reward that could be won on a given trial (large reward = 10 points, small reward = 2 points, no reward = 0 points). Then they are instructed to respond to the response cue. Participants' outcome (score) is dependent upon their performance in this simple reaction time task. The duration of the response cue is adjusted so that 66% of the trials produce a positive feedback. Specifically, the duration of the response cue presentation varies from 250 to 400 ms and is adjusted in every trial to the participant's performance by subtracting 10 milliseconds if the success rate is greater than 66% of the trials, and adding 10 ms if the success rate is inferior to 66%. Points were converted to sweet food snacks following testing (5 points per M&M). In total, participants completed 22 trials per condition. For this task, first-level analysis included the movement realignment regressors plus 6 regressors for successful trials: (i) anticipation of large reward, (ii) anticipation

of small reward, (iii) anticipation of no reward, (iv) large reward feedback, (v) small reward feedback, (vi) no reward feedback, and the same 6 regressors for unsuccessful trials.

Further description of data analysis

fMRI

Functional MRI data were pre-processed and analysed with SPM8 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm). Time series data were slice-time corrected using the first slice as the reference, realigned to the mean volume, non-linearly warped onto MNI space using a custom EPI template, and spatially smoothed with a 3D Gaussian kernel (5 mm full-width half maximum). Estimated movement parameters (18: 3 translational, 3 rotations, 3 quadratic, 3 cubic translations, 3 translations shifted 1 TR before and 3 shifted 1 TR later) were added as nuisance variables in first-level analysis. Each fMRI time series underwent automatic spike detection and any artifactual time points were regressed out of each subject's data. Activation maps were computed using a general linear model with an auto-regressive noise model. The regressors modeling the experimental conditions were convolved using SPM's default hemodynamic response function.

To control for multiple comparisons type 1 error following recommandations by Eklund et al. (2016), we performed Monte Carlo simulations computed with AFNI's 3dClustSim. Assuming a per voxel probability threshold of p=0.001, mean residual smoothing of 8.96mm, 9.04mm, and 8.21mm in x, y and z estimated with "spm_est_smoothness" function in SPM, after 10,000 simulations, significant voxels were required to be part of cluster of more than 24 contiguous voxels giving a 0.05% probability of a cluster surviving due to chance.

For our secondary objective (predicting psychotic outcome at age 16 with brain information), we created regions of interest's masks based on the regions' coordinates using the MarsBaR SPM toolbox (Brett, Anton, Valabregue and Poline, 2002), and extracted the mean contrast value (betas) for each region of interest and for each subject.

Machine learning procedure

The elastic-net has two key parameters, alpha and lambda. The alpha balances the application of the L1- and L2-norm penalties, and the lambda controls the magnitude of shrinkage applied to the regression coefficients. These parameters are tuned within a nested *k*-fold cross-validation

scheme in order to maintain the independence of the final model used in evaluating the originally set-aside *k*-fold observations (or single observation during leave-one-out cross-validation).

Supplemental Results

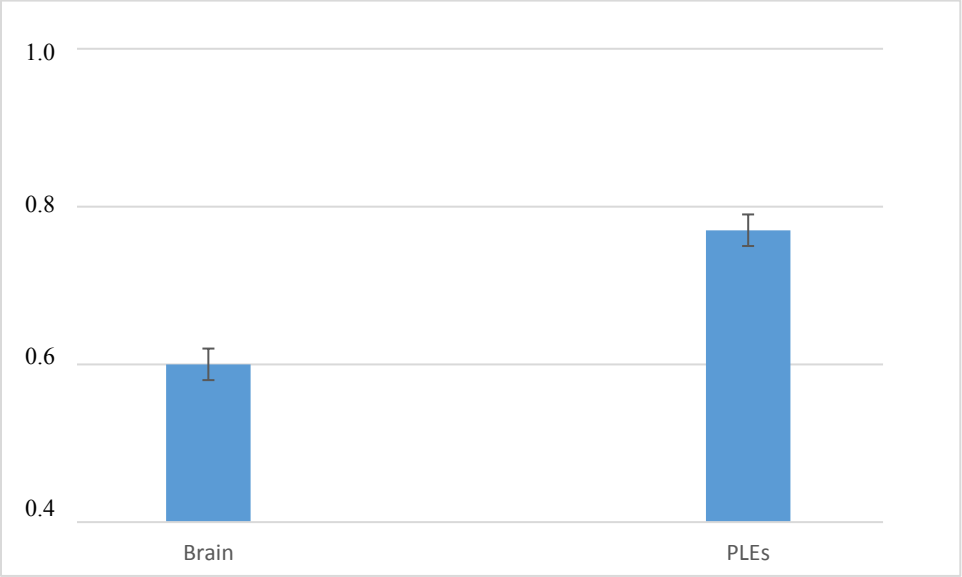
Task activation differences between groups

In the faces task, the angry relative to control contrast was also investigated to help the interpretation of the neutral relative to control contrast's findings. However, no cluster of significant activity differences in the angry relative to control contrast survived the cluster threshold of 24 contiguous voxels. Even when using a more liberal cluster threshold of 10 contiguous voxels for the prediction analyses, no significant activity differences were observed, except for an increased activity from the left cerebellum (x=-3, y=-79, z=-38 T-value=3.58 cluster=10 voxels) in healthy controls relative to those reporting psychotic-like experiences.

Prediction of psychotic-related symptoms at age 16

Following our accurate classification of youths reporting both mood- and psychotic-related symptoms at 16 (N=12) from those reporting no mood symptoms (N=154) in the London-Dublin subsample, we investigated the performance of each domain (i.e., brain activity and baseline psychotic-like experiences) on its own. Psychotic-like experiences at age 14 were more robust classifiers than brain regions, however, brain information still helped the classification (AUC > 0.6) (Figure 1S).

Figure S1. Classification accuracy for individual domains in the London-Dublin subsample.



Abbreviations: PLE, Psychotic-like experiences.

The bars represent standard deviations.

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Annex IV: Supplement material of Study 4

Methods. Measures, Statistical analysis.

Measures

Psychotic-like experiences (e.g., perceptual abnormalities, delusional thoughts, suspiciousness, and feelings of grandiosity) in the past 12 months were assessed with nine items. All nine items begin with the following statement: 'The next items ask about thoughts or beliefs that you could have had DURING THE PAST 12 months'. Five items were adapted from the Diagnostic Interview Schedule (Costello, 1982): (1) 'Some people believe that their thoughts can be read. Have other people ever read your thoughts?', (2) 'Have you ever believed that you were being sent special messages through the television?', (3) 'Have you ever thought that you were being followed or spied upon?', (4) ' Have you ever heard voices that other people cannot hear?', (5) 'Have you ever felt as though your body had been changed in some way that you could not understand?'. Four additional questions, validated in community samples of children and adolescents (Laurens et al., 2007) were included: (6) 'Have you ever felt that you were under the control of some special power?', (7) 'Have you ever known what another person was thinking even though that person wasn't speaking?', (8) 'Do you any some special powers that other people do not have?', (9) 'Have you ever seen something or someone that other people could not see?'.

Statistical analysis

The best-fitting growth mixture model (GMM) was established using the Bayesian Information Criterion (BIC), the Akaike Information Criterion (AIC), the Lo-Mendell-Rubin Likelihood Ratio Test (LMR-LRT), and entropy. Missing data on the dependent variable (PLE score) were handled through Full Information Maximum Likelihood. Table S1 reports on model fit information.

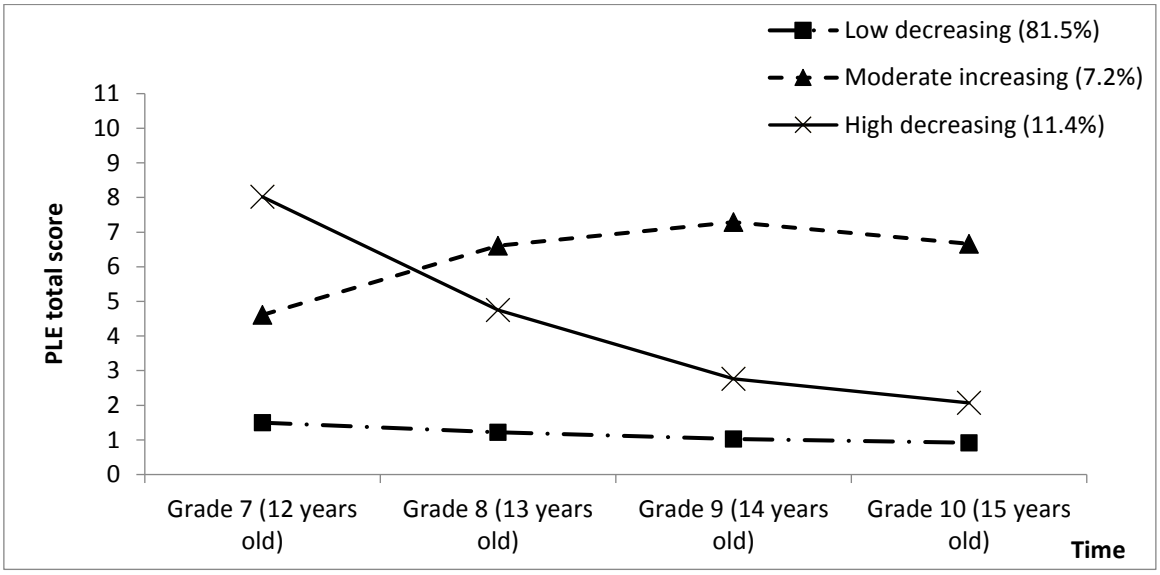
The three-class trajectory model, compared to the two-class model, fitted the data best according to both BIC and AIC (Table S1). Although moving from a three- to a four-class model produced small decreases in both the BIC and the AIC (BIC = 45,126.50, AIC = 45,026.41), we opted for the three-class model as the LMR-LRT coefficient was not longer significant (p = .266).

Table S1. Criteria for deciding the number of classes within the growth mixture model of the main sample (3,848 adolescents).

No. of classes	AIC	BIC	Entropy	LMR-LRT *p* value
2	46 398.45	46 448.50	0.90	<0.001
3	45 598.41	45 673.47	0.85	0.005
4	45 026.41	45 126.50	0.85	0.266

Abbreviations: AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; LMR-LRT, Lo-Mendell-Rubin Likelihood Ratio Test.

Figure S1. Developmental trajectories of psychotic-like experiences between 12- to 15-years old.



PLE, Psychotic-like experiences.

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