Psychotic-like Experiences in Childhood and Adolescence: A Cognitive Neuropsychiatric Approach

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I, Jasmine Harju-Seppänen, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

0.1 Abstract

Psychotic-like experiences (PLEs) include experiences such as hallucinations and delusional thinking that can occur in the absence of a clinical disorder. PLEs peak in middle childhood but appear to spontaneously remit in most children. Nevertheless, their presence, and particularly their persistence, are associated with an increased risk of developing later psychosis and poor psychiatric and social outcomes. However, the mechanisms by which they are generated during childhood are unclear. Existing models of psychosis cite early life experience and childhood neurodevelopment as important but often examine these retrospectively. Furthermore, they suggest mechanisms for how psychotic experiences are generated that are assumed to apply across the lifespan. This assumption has remained untested, however. Consequently, in this thesis, I investigated neurocognitive mechanisms of PLEs in 9-10 year-old-children using data from the Adolescent Brain Cognitive Development (ABCD) study. In Study 1, I examined whether the established mechanistic risk factors in adult psychosis – affective symptoms, traumatic experiences, cognitive function, structural brain changes – are associated with PLEs using network analysis, finding only that depression-related symptoms were associated with PLEs. In Study 2, I tested whether fMRI activation in striatal reward pathways was associated with PLEs in children, as this is an established finding in adults. This study found no strong evidence for alteration to striatal reward pathways with a high likelihood that it was absent, rather than undetectable. Given the prognostic and aetiological important of persistence of PLEs, in Study 3, I tested affective, trauma-related, cognitive and striatal reward activation predictors of 1-year PLE persistence. Only depressive symptoms were substantial predictors. Depressive symptoms emerged as the strongest predictor of PLEs at this developmental stage, both cross-sectionally and longitudinally. The findings indicate that PLEs in childhood are not a ‘mini psychosis syndrome’ and developmental-stage specific models of psychotic experiences in children are required.

0.2 Impact statement

This thesis aimed to examine the neuropsychiatric mechanisms underlying psychotic-like experiences (PLEs) in childhood and adolescence in order to inform existing theoretical models of psychosis. The empirical chapters involve analyses on data from the Adolescent Brain Cognitive Development (ABCD) study, an ongoing longitudinal cohort study based in the US. The ABCD study recruited over 10,000 children aged 9-10 and aims to follow them up for 10 years, and is regarded as one of the largest studies to have collected such an extensive range of outcomes.

The results of this doctoral thesis indicate that several of the main risk factors and hypothesised mechanisms associated with adult psychosis seem absent at this developmental stage, although depressive symptoms are reliably associated with childhood PLEs and the persistence of PLEs. This suggests that childhood PLEs may not be generated in the same manner as adult PLEs, which not only has theoretical implications in terms of highlighting the need for further consideration of psychosis models and the psychosis continuum in children, but also has potential clinical implications.

In terms of early identification, it suggests that screening for PLEs alone may be insufficient in identifying those who will transition to psychosis later in life. These findings also have implications for intervention, as the findings suggest that that depression should be a key clinical target in young people who are presenting with psychosis-spectrum experiences. Moreover, the lack of association with reward system activation calls into question whether antipsychotics are likely to be the most effective treatment approach for reducing positive symptoms in childhood and early adolescence. As such, further research is required which investigates these potential clinical implications.

One of the main benefits of using open datasets such as the ABCD study is the fact that it enables an open science approach which allows additional transparency and reproducibility of the results. The analysis code used for all analyses in the present thesis have been made publicly available online at https://github.com/

jasmine-hs/Thesis, making the findings reproducible by others. This has also created a learning resource for other researchers and a code base for additional analyses and extension of the research on the ABCD dataset reported here.

0.3 Acknowledgements

I would first like to thank my primary supervisor Dr Vaughan Bell for all of the guidance and the many early morning meetings. I would also like to thank my supervisors Dr Liam Mason and Professor Elvira Bramon for their support over the past few years.

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Finally, I would like to thank my mom for her constant support, and Calum for putting up with me for all of these years.

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Chapter 1

Introduction

The general introduction begins with a brief description of psychosis, and then progresses to provide an overview of psychotic-like experiences (PLEs), the focus of this thesis. This includes prevalence rates and definitions of key terms used throughout. Secondly, the introduction outlines the current evidence base regarding the developmental course of PLEs, and reviews literature regarding associations between PLEs and later development of psychosis and other psychiatric disorders. This is followed by a description of the existing theoretical models of psychosis. Finally, the primary overarching aims of the research in this thesis are outlined, and the specific objectives and methods used for each empirical study (Chapters 2-4) are provided.

1.1 Psychosis

"Psychosis" is an umbrella term. Both the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) and International Classification of Diseases (ICD-10) (Organization, 2004) use it to refer to a clinical presentation consisting of hallucinations, delusions, disorganised thought or behaviour, negative symptoms, and functional impairment (Biedermann & Fleischhacker, 2016). Whilst psychosis is regarded as the defining feature of schizophrenia spectrum and other psychotic disorders, it can also be present in other conditions such as mood disorders (Arciniegas, 2015). Schizophrenia is often referred to as "non-affective psychosis", however when psychosis is present in other disor-

ders such as schizoaffective disorder and major depression with psychosis then it is typically termed "affective psychosis" (Barch & Ceaser, 2012). Childhood-onset schizophrenia (COS; defined as onset before 13) has been argued to represent a more rare and severe form than adult- or early-onset schizophrenia- after age 18 and 13-18, respectively (Nicolson & Rapoport, 1999), and its prevalence rate is less than 1 in 10,000 (Burd & Kerbeshian, 1987). This contrasts from a median point prevalence rate of 3.8 per 1000 reported for psychotic disorders in the adult population (Moreno-Küstner, Martín, & Pastor, 2018). This finding was also supported by a large-scale meta-analysis recently performed by Solmi et al. (2021). The authors pooled data from population-based studies to estimate the peak age of onset and the proportion of individuals with mental disorders at various ages. The results showed that the median onset of schizophrenia spectrum disorders and primary psychotic disorders is 25, and the earliest peak onset is at 20.5 years. Only a minority of individuals have an onset of psychosis prior to age 18 (12.3%). This can be seen in Figure 1.1 below.

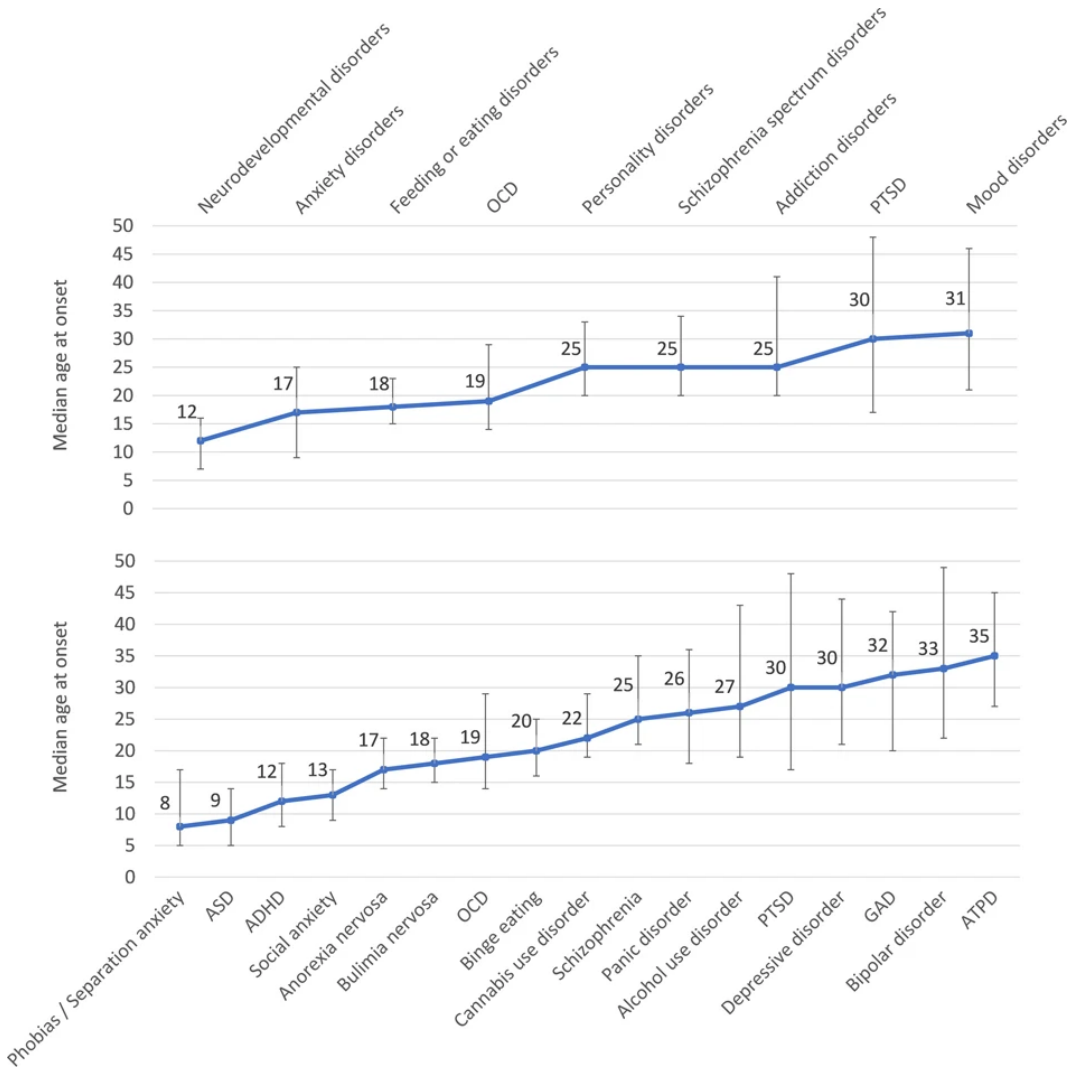


Figure 1.1: Meta-analytic median age at onset of mental disorders, from Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., [...] Fusar-Poli, P. (2021). Age at onset of mental disorders worldwide:large-scale meta-analysis of 192 epidemiological studies. Molecular Psychiatry

Duration of untreated psychosis (DUP) has been associated with poorer outcomes, including more severe positive and negative symptoms, as well as lower chance of remission (Howes et al., 2021). As such, there is an interest in early identification of individuals who may develop psychosis. The concept of "ultra-high risk" (UHR) individuals was presented when new intervention approaches were developed in the 1990s, with the aim of identifying individuals who are at a high risk of developing first episode psychosis (FEP) (Yung et al., 1996). This led to

the establishment of Early Intervention in Psychosis (EIP) programmes, which target young people with psychotic symptoms or who are deemed to be at "ultra-high risk" (Csillag et al., 2016). This high-risk state has also been referred to as "At Risk Mental State" (ARMS) and "Clinical High Risk" (CHR; Fusar-Poli, Byrne, Badger, Valmaggia, and McGuire (2013), as well as "prodromal", having evolved to describe the pre-psychotic phase, where individuals present with potentially prodromal symptoms (Fusar-Poli, Borgwardt, et al., 2013). A prodrome refers to "an early or premonitory manifestation of impending disease, before specific symptoms begin" (Gennaro & Gould, 1979), and the concept of a prodrome of schizophrenia dates back to Bleuler (Bleuler, 1950). The proposed trajectory of psychosis is displayed below in Figure 1.2 and will be discussed in further detail later on in the thesis.

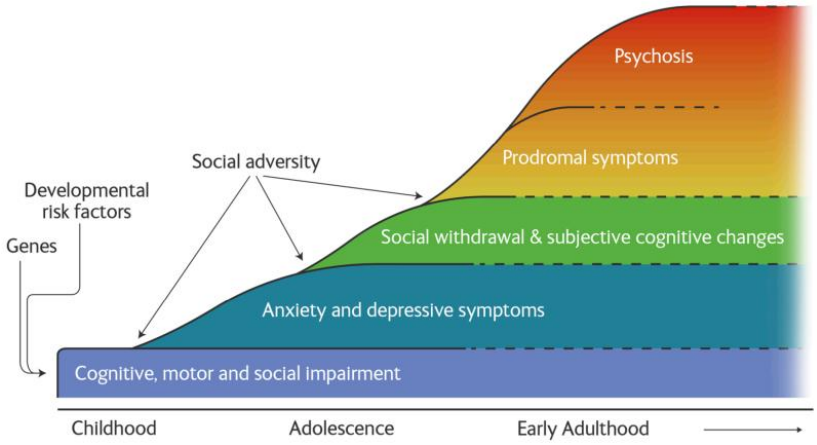


Figure 1.2: Howes, O. D., & Murray, R. M. (2014, May). Schizophrenia: an integrated sociodevelopmental-cognitive model. Lancet, 383(9929), 1677–1687

However, early identification of individuals who will go on to develop psychosis remains challenging, in large part due to one reason: these unusual experiences are not limited to clinical populations. These experiences are often (but not exclusively) referred to as "psychotic-like experiences" (PLEs) when they occur in the general population (see Section 1.4 for a detailed account of the variation in terminology, and its implications).

1.2 Psychotic-like experiences and the psychosis continuum

Several studies demonstrate that non-clinical populations also report unusual experiences and beliefs (PLEs). This was first observed by Meehl (1962), and subsequently updated in Meehl (1990). He outlined a model of the cause of schizophrenia, in which he described how genetically influenced alterations in neural transmission could result in in clinical schizophrenia. This was then followed by seminal studies conducted by Verdoux et al. (1998) and van Os, Hanssen, Bijl, and Ravelli (2000). Verdoux et al. (1998) carried out a survey in a primary care setting and found that individuals with no history of a psychiatric disorder reported "delusional" ideas. Additionally, the prevalence of PLEs appeared to be negatively correlated with age. Similarly, van Os et al. (2000) observed that, whilst psychosis is typically defined dichotomously for clinical purposes, these symptoms may also apply to the general population. 4.2% of participants were rated as displaying evidence of delusions or hallucinations by a psychiatrist, and 17.5% of them were found to report an experience akin to the clinical psychosis concept. As a result of studies such as these, it is now accepted that a proportion of the healthy adult population experiences PLEs – 5-6% according to a review by van Os, Linscott, Myin-Germeys, Delespaul, and Krabbendam (2009). This includes experiences such as hearing voices, which is often regarded as a hallmark symptom of psychosis (Beavan, Read, & Cartwright, 2011). The two most frequently used methods to assess psychotic-like experiences (PLEs) are 1) a structured interview which is performed by a non-clinician interviewer and 2) a structured self-report measure such as the "PLIKS" (Nordgaard, Buch-Pedersen, Hastrup, Haahr, & Simonsen, 2019).

As outlined above, psychosis was initially regarded as a dichotomous entity. However, the observation that PLEs occur often in the general population has led to the argument that hallucinations and delusions are dimensional phenomena which lie on continua with normal experiences (Johns & van Os, 2001), and psychosis represents one end of the continuum, rather than a discrete categorical entity. Johns and

van Os (2001) were among the first to argue for the existence of a psychosis continuum. Their argument was based on the following lines of evidence: 1) Prevalence of Symptoms of Psychosis 2) Similarity in Underlying Dimensional Representation 3) Familial clustering and longitudinal associations 4) Associations with demographic risk factors.

1.2.0.1 Implications of a psychosis continuum

A psychosis continuum implies that the experiences that are seen in patients with psychotic disorders can be measured in non-clinical populations, and assumes that PLEs are not exclusively associated with a psychotic disorder (van Os et al., 2009). As such, the prevalence of PLEs can be high, whilst the prevalence of a clinical disorder is low, as depicted in Figure 1.3 below.

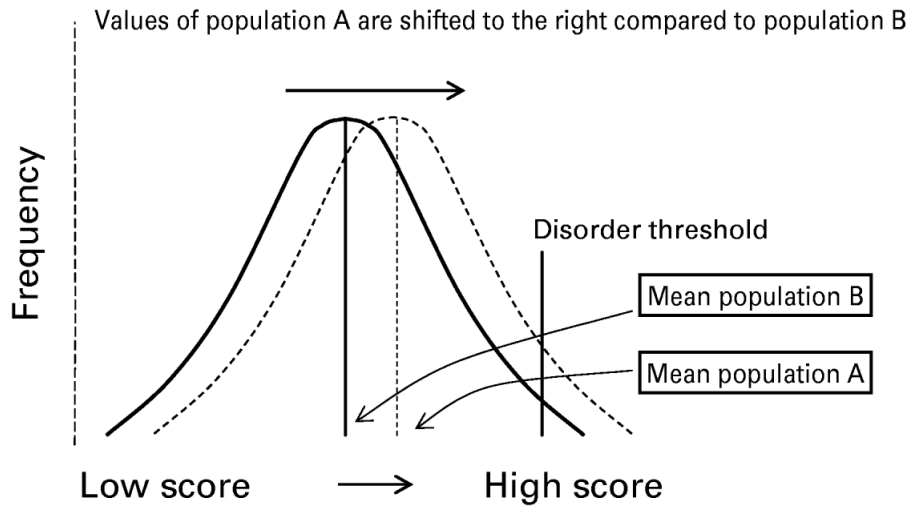


Figure 1.3: Psychosis continuum, from van Os, J., Linscott, R., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychological Medicine, 39(2), 179-195.

The concept of a psychosis continuum has facilitated the development of a clinical staging model (McGorry, Hickie, Yung, Pantelis, & Jackson, 2006; Hartmann, Nelson, Ratheesh, Treen, & McGorry, 2019). In summary, in this model, stage 0 refers to individuals with genetic risk. PLEs reported in the general population have frequently been referred to as stage 1a when present with non-specific gen-

eral psychopathologies such as depressive and anxiety symptoms. Stage 1b refers to the presence of more specific PLEs, and individuals who are deemed to be in a clinical or ultra-high risk state. The remaining stages are as follows: stage 2 (above-threshold PLEs), persistent symptoms (stage 3) and severe non-remitted psychotic disorders (stage 4) (Mennigen & Bearden, 2020).

The proposed existence of a psychosis continuum is not without controversy (David, 2010; Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010). There have also been questions regarding whether a fully- or quasi dimensional model is a more accurate (DeRosse & Karlsgodt, 2015), which will be discussed further in Section 1.7.

1.3 Phenomenology of Psychotic-like Experiences

The idea of a continuum suggests a phenomenological continuity, which make PLEs an important area to study, particularly in early detection and prevention of psychosis. However, they remain poorly understood (Lee et al., 2016). Phenomenological studies can be highly informative because they can provide novel information about the nature of these experiences. This has been illustrated by a number of recent studies examining the phenomena in those with both psychotic (Coughlan, Humphries, Clarke, Healy, & Cannon, 2021; Upthegrove et al., 2016; Woods, Jones, Alderson-Day, Callard, & Fernyhough, 2015) and non-psychotic disorders (Wallis et al., 2020), as well as those with PLEs (Johns et al., 2014). The majority of the literature investigates the phenomenology of voice hearing, despite studies indicating that these experiences encompass a broad range (Coughlan et al., 2021). Moreover, there is a paucity of research examining the phenomenology of these experiences in young people, which are a key group to study given their higher prevalence of PLEs. Given this, they are an important group to investigate to elucidate the association between PLEs and psychopathology, due to the fact that it is more commonly reported in this population (Coughlan et al., 2021). The study of children and young people longitudinally also offers an optimal study design and the developmental nature of PLEs is discussed further in Section 1.5.

In one of the few studies that examine the phenomenology of PLEs in adolescence, Cadario et al. (2012) report a qualitative analysis of early signs of becoming unwell and use of mental health services. 12 young people with a first episode of psychosis and their carers detailed a range of difficulties, and described experiencing a range of psychotic symptoms, including affective disturbances, unusual physical sensations, hallucinations and delusions. However, the PLEs themselves were only outlined briefly.

1.4 Terminology and measurement of PLEs

A recent review by Hinterbuchinger and Mossaheb (2021) has clearly highlighted the challenges in investigating PLEs. There is a great deal of heterogeneity in the literature in terms of how PLEs have been defined and assessed, which has been proposed to contribute to the variation in estimated prevalence rates (Hinterbuchinger & Mossaheb, 2021; Lee et al., 2016).

Alongside PLEs, several terms have been used interchangeably in the literature, such as "subclinical psychotic symptoms", "schizotypy", "unusual experiences", "sub-psychotic experiences", and so forth (Hinterbuchinger & Mossaheb, 2021; Kusztrits et al., 2021). However, "PLE" is the main term that will be adopted throughout the thesis. This is due to numerous factors. Firstly, it is the most commonly used term in this field. Secondly, it has been suggested as a terminology that minimises the stigma that is connected to psychotic episodes (Kusztrits et al., 2021). Thirdly, unlike terms such as "schizotypy", which imply a stable trait-like characteristic, the term PLEs reflects their transient nature, as they resolve in 80% of young people, as shown in a meta-analysis by Linscott and Os (2013).

Unsurprisingly, the use of the term "PLE" has developed over time. It was initially used specifically to refer to "subschizophrenic" symptoms on a continuum from normal experiences to "genuine" psychotic symptoms (Strauss, 1969) and has since been adopted to refer to "psychotic symptoms in absence of illness" (Kelleher & Cannon, 2011), or psychotic symptoms in non-clinical populations (Linscott & van Os, 2010).

Similarly to the PLE terminology, there is substantial variation in terms of assessment methods. Lee et al. (2016) performed a systematic review on definitions and assessments of PLEs. The review highlighted the absence of a "gold-standard" measure for assessing PLEs and identified three main approaches to measuring PLEs: assessment tools using pre-set criteria, assessment tools with a predetermined threshold, and assessment tools without a predetermined threshold or criteria. A total of 41 assessment tools for PLEs were identified. The most common of these tools was the Magical Ideation Scale (MIS; Eckblad and Chapman (1983)), which was adopted by 21.1% of the studies. This was followed by the Community Assessment of Psychic Experience (CAPE, 16.7%), Konings, Bak, Hanssen, van Os, and Krabbendam (2006)) and Launay-Slade Hallucination Scale (LSHS, 14.1% Launay and Slade (1981)). In other words, just as the terminology captures a range of experiences, assessments do so also. Preti, Cella, Raballo, and Vellante (2012) have presented a pyramid model of the risk for psychosis and argued that different definitions of PLEs are distinguished by degrees of distress and insight (illustrated in Figure 1.4 below).

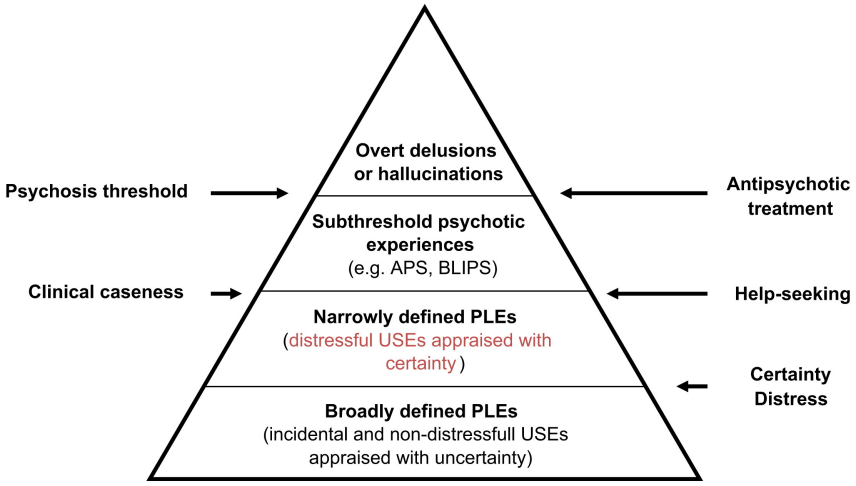


Figure 1.4: Stage model of psychosis development, from Preti, A., Cella, M., Raballo, A., & Vellante, M. (2012). Psychotic-Like or Unusual Subjective Experiences? The role of certainty in the appraisal of the subclinical psychotic phenotype. Psychiatry Research, 200(2-3), 669-673.

It has also been argued that these different terms assume different models

of psychosis, namely fully- or quasi dimensional models (DeRosse & Karlsgodt, 2015). The quasi-dimensional model is predominantly based on research done by Meehl (Meehl, 1962, 1989). Meehl suggested that a "dominant autosomal schizogene" leads to an aberration in synaptic signal selectivity which in turn produces a defect in neurointegrative processes which he termed "schizotaxia" (Meehl, 1962). Meehl argued that schizotaxia could then give rise to schizotypy, which was necessary, but not sufficient for the emergence of schizophrenia. As such, this quasi-dimensional model proposes a continuum of psychosis which ranges from personality characteristics (i.e., magical thinking) to clinically significant symptoms of psychotic disorders (i.e., delusions). However, Meehl believed that only a small percentage of the population could be represented across the psychosis continuum, as he thought only 10% of the population carried the so-called "schizogene". Of course this contrasts with our current understanding, with compelling evidence that psychotic disorders are genetically complex and highly polygenic with a combination of both common low-risk and rare high-risk genetic variants involved (Ripke et al., 2014; Singh, Neale, & Daly, 2020; The Schizophrenia Working Group of the Psychiatric Genomics Consortium, Ripke, Walters, & O'Donovan, 2020), Meehl's quasi-dimensional model is partly supported by studies of schizotypal personality (see the review by Kwapil and Barrantes-Vidal (2015)). The fully-dimensional model, on the other hand, is primarily based on work by Claridge (Claridge, 1972, 1987). This model proposes that psychotic symptoms exist along a continuum in the full population, rather than in a subset of individuals. Based on the current literature, it remains unclear which of two models best reflects the existing data. However, in practice, the majority of recent work on the psychosis continuum does not directly refer to these models, rather, they implicitly ascribe to one of them based on the measure used (DeRosse & Karlsgodt, 2015). For instance, the Schizotypal Personality Questionnaire (SPQ; Raine (1991)) is typically regarded to be based on the quasi-dimensional model, whereas the Community Assessment of Psychic Experience (CAPE Stefanis et al. (2002)) is viewed as a measure based on the fully dimensional model. Nevertheless, little is known regarding the extent to which the

measurements obtained from these scales differ. Assessments of non-clinical populations using these scales use the terms "schizotypy" and "sub-clinical psychotic symptoms" and "PLEs" interchangeably (DeRosse & Karlsgodt, 2015).

See Figure 1.5 for a diagram illustrating the quasi- and fully-dimensional approach.

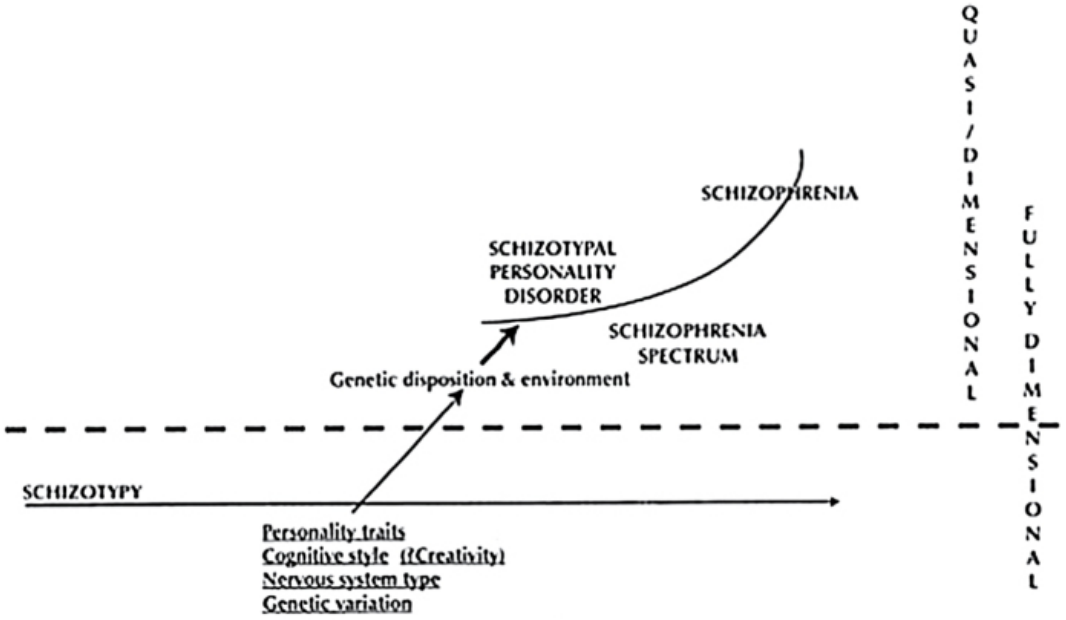


Figure 1.5: Quasi- and fully-dimensional model of psychosis, from Claridge, G., Beech, T. (1995). Fully and quasi-dimensional constructions of schizotypy. In A. Raine, T. Lencz, S. A. Mednick (Eds.), Schizotypal Personality (1st ed., pp. 192–216). Cambridge University Press.

1.5 Developmental course of Psychotic-like Experiences

1.5.1 Prevalence of Psychotic-like Experiences across the life course

Interestingly, the prevalence of PLEs also appears to vary across the life course; whilst psychotic disorders are more common in adulthood than childhood, the inverse is true for PLEs. Whilst the early studies examining the prevalence was con-

ducted in adults and reported a median prevalence of 5.3% in van Os et al. (2009), subsequent studies have indicated that PLEs are more common on earlier on in life. One of the first reviews to illustrate this was Linscott and Os (2013)'s updated review, which included additional studies on children and adolescents and showed a prevalence rate of 7.2%. However, the terms "childhood" and "adolescence" will be explained before a more comprehensive review of the literature examining the developmental course of PLEs is outlined.

Adolescence is defined as the period between childhood and adulthood and consists of both biological and social changes, as it is typically regarded to start with the onset of puberty, and to end when the individual achieves independence. As such, its definition has long presented a challenge, and the terms "childhood" (also sometimes termed "pre-adolescence" (Garavan et al., 2018)) and "adolescence" have been applied inconsistently throughout the literature. A recent review by Sawyer, Azzopardi, Wickremarathne, and Patton (2018) concluded that a definition of 10-24 years most accurately reflects our current understanding of this phase. Due to this inconsistency in defining these life phases, the ages of the participants in the studies will be specified throughout the thesis. As stated earlier, PLEs appear to be more common earlier on in life, as shown in a meta-analysis by Kelleher, Keeley, et al. (2012), which included 19 population-based studies and reported a median prevalence of 17% among children aged 9–12 years and 7.5% among those aged 13–18 years. This has been illustrated in both cross-sectional, as well as longitudinal studies.

In summary, PLEs appear to be more common earlier in life (Kelleher, Connor, et al., 2012), and the significantly higher prevalence of PLEs in childhood has led some to argue that they may be a behavioural expression of normative neurodevelopmental processes.

1.5.2 Transience of childhood Psychotic-like Experiences

Another noteworthy feature of PLEs in childhood is that they are transient for most individuals. The meta-analysis by Linscott and Os (2013) reported that PLEs were transient for nearly 80% of individuals. More recent studies have also reinforced the

transitory nature of PLEs for the majority of individuals, see the review by Kalman, Bresnahan, Schulze, and Susser (2019).

The transience of childhood PLEs is depicted below in Figure 1.6.

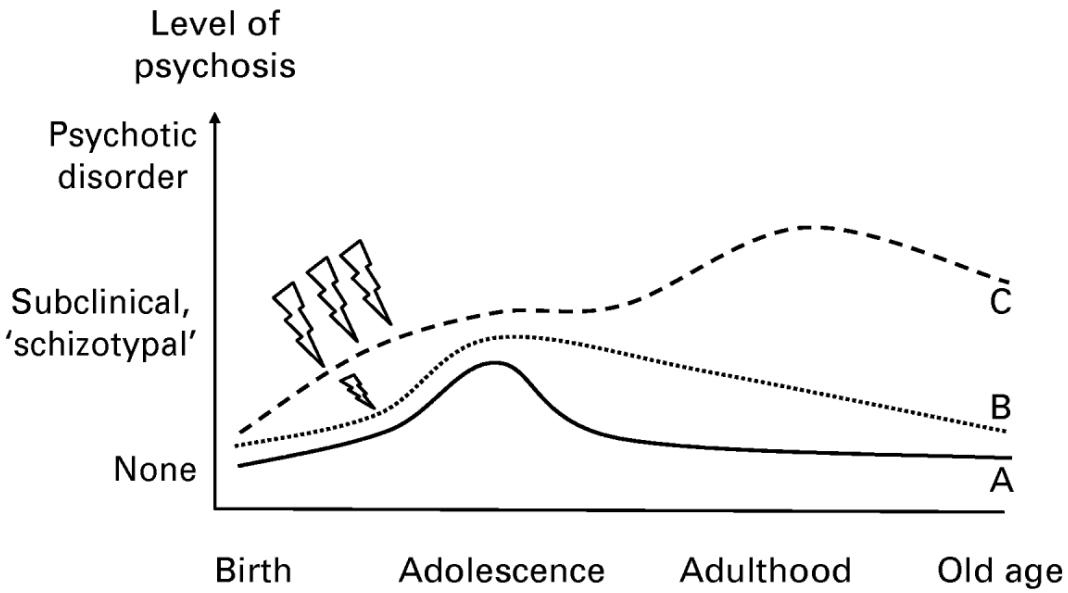


Figure 1.6: Differences in longitudinal trajectories of psychosis proneness, from van Os, J., Linscott, R., Myin-Germeys, I., Delespaul, P., Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychological Medicine, 39(2), 179–195. doi: 10.1017/S0033291708003814

1.6 Clinical implications of Psychotic-like experiences

1.6.1 Association with psychosis

As PLEs during childhood are relatively common, they have been regarded to be benign and of limited prognostic value. Nonetheless, this view began to shift as multiple studies indicated that PLEs in late childhood and adolescence are associated with a range of negative outcomes, including the development of psychotic and non-psychotic disorders later in life. Initially, studies focused on their association with future risk of developing psychotic disorders. A seminal study conducted by Poulton et al. (2000) used data from the Dunedin Multidisciplinary Health and De-

velopment Study, a longitudinal cohort of individuals born between 1st April 1972 and 31st March 1973 in Dunedin, New Zealand. This study performed analyses examining the association between PLEs at age 11 and schizophreniform outcomes at age 26. Both measures were assessed using psychiatric interviews (Diagnostic Interview Schedule for Children, DISC-C at age 11, DIS at age 26). Poulton et al. (2000)'s findings reported that PLEs at age 11 predicted an elevated risk of a schizophreniform diagnosis at age 26 (odds ratio 16.4). The authors acknowledged that the participants had not passed through the entire risk period for psychosis, citing a study by Häfner, Maurer, Löffler, and Riecher-Rössler (1993) which reported that approximately half of the individuals who develop schizophrenia are diagnosed by age 29. As such, Fisher et al. (2013) followed up the Dunedin Cohort at age 38. Their analyses indicated that PLEs at 11 were associated with higher odds of meeting criteria for a schizophrenia diagnosis.

Kaymaz et al. (2012) meta-analysed the results of six cohort studies with a 3-24 year follow-up. Their results indicated that the yearly risk of conversion to frank psychosis in individuals with PLEs was 3.5 higher than for those without. There was also evidence of a dose-response relationship with the persistence of psychotic experiences (see Section 1.6.5 regarding the clinical relevance of persisting PLEs). Their results suggested that there is a weaker association between PLEs and conversion to non-psychotic disorders- more recent studies investigating this have been outlined below in Section 1.6.2.

1.6.2 Association with affective and behavioural disorders

Fisher et al. (2013)'s follow-up study of the Dundein Cohort (outlined above) found that PLEs at age 11 were not only associated with higher odds of developing a psychotic disorder. Individuals who had reported PLEs at age 11 also displayed increased odds of meeting criteria for PTSD at age 38, as well as increased rates of suicide attempts. Similarly, Cederlöf et al. (2017) linked the data from the Child and Adolescent Twin Study in Sweden (CATSS) with the National Patient Register, creating a prospective cohort of 9242 adolescents. Their findings indicated that PLEs at age 15 or 18 were associated with later substance use disorders and sui-

cide attempts. The association between PLEs and subsequent substance use has been replicated in a longitudinal population-based study in Zuid-Holland in the Netherlands (Dhossche, Ferdinand, Van Der Ende, Hofstra, & Verhulst, 2002), and the association between PLEs and suicide has been observed in studies using data from the Swedish Twin Study of Child and Adolescent Development (TCHAD) (Kelleher, Cederlöf, & Lichtenstein, 2014), as well as the Saving and Empowering Young Lives in Europe (SEYLE) study (Kelleher et al., 2013). Trotta et al. (2020) used data from the Environmental Risk Longitudinal Twin Study, a nationally representative birth cohort of 2232 twins, and found that childhood PLEs were associated with a range of mental health outcomes beyond psychosis, including depression, anxiety, suicide attempts and self-harm. Similarly, PLEs at age 14 have been associated with internalising and conduct problems at three-year follow-up in the SALVe cohort, a Swedish cohort study (Isaksson, Vadlin, Olofsdotter, Åslund, & Nilsson, 2020). There is also evidence that this association is bi-directional, with symptoms of common psychiatric disorders increasing the risk of PLEs (Giocondo et al., 2021).

Not only have PLEs been associated with an increased risk of developing an affective disorder later in life, depression and anxiety have also been cited as important in driving anomalous experiences, behavioural responses and cognitive biases that form and maintain psychotic experiences in adults (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Freeman, Garety, Kuipers, Fowler, & Bebbington, 2002). Affective symptoms have also been associated with psychotic experiences in children. In a cohort study of adolescents aged 14–24 years (van Rossum, Dominguez, Lieb, Wittchen, & van Os, 2011) it was reported that, at baseline, most PLEs occurred in the presence of affective dysregulation and PLEs that met a clinically relevant threshold were more likely to occur with higher levels of depressive symptoms. In a study of help-seeking adolescents, Bird, Waite, Rowsell, Fergusson, and Freeman (2017) found that paranoia persistence was associated with anxiety, depression, negative self-belief and affective reactivity, alongside perceptual anomalies, poor sleep, and peer victimisation. However, a large longitudinal study

of PLEs (baseline measurement at 10-11 years) found that depression and anxiety were associated most with the persistent trajectory of PLEs but also the decreasing trajectory, suggest the relationship between PLEs, anxiety and depression is likely to be complex (Wigman, Lin, et al., 2011).

1.6.3 Association with attainment and cognitive function

PLEs have been found to be associated with an even broader range of negative outcomes. Childhood PLEs have been associated with cognitive under-performance, and this has been reported in numerous longitudinal studies. This includes the ALSPAC study, where Hameed, Lewis, Sullivan, and Zammit (2013) found evidence of reduced literacy skills (measured using five different tasks) in children with PLEs. It has also been supported by studies such as Barnes et al. (2021). Further analysis of the ALSPAC study has indicated that children reporting PLEs at age 12 showed reduced attention at age 11, and reduced performance in processing speed at age 8, compared to their peers without PLEs, with some evidence for an associated decline in age-matched cognitive performance between the ages of 8-11 (Niarchou et al., 2013). Davies, Sullivan, and Zammit (2018) also analysed data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. They found that PLEs at age 12 were associated with poorer educational and occupational attainment between the ages of 16-20, even after adjusting for confounding variables. Additionally, they also found evidence that PLEs were linked to impairments in social functioning. Gur et al. (2014), which used data from the Philadelphia neurodevelopmental cohort to perform neurocognitive growth charting, found that individuals with PLEs were neurocognitively behind their chronological age, when compared to young people without PLEs. The authors reported that this delay was present across different domains, ranging between 6-18 months and is present by age 8. Moreover, it appeared to widen across time and the departure from the normal growth curve is particularly marked after age 16. As such, there is evidence that childhood PLEs are associated with reduced cognitive performance on a range of tasks. However, one potential drawback of these findings is that they are drawn from cohort studies that were not designed to be representative of the wider

population, meaning it is possible that some of the association is accounted for by population stratification, whereby individuals who share risk factors for PLEs also share risk factors for poor cognition.

It has been long recognised that cognitive deficits are a key symptom of psychosis, and this dates back to Kraeplin's definition of schizophrenia as "dementia praecox" (Kraepelin, 1919). More recently, there has been a substantial increase in the research examining cognition in psychosis, dating back to the 80s (Barch & Ceaser, 2012). This was in part fuelled by increasing evidence that cognitive function is a strong predictor of quality of life and functioning in psychosis (Nuechterlein et al., 2011). Existing research has illustrated that individuals diagnosed with schizophrenia display reduced performance in a wide range of cognitive tasks (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005). These cognitive deficits appear prior to the onset of schizophrenia, as there is evidence that there is reduced premorbid cognitive functioning (Woodberry, Giuliano, & Seidman, 2008). This includes both general (such as IQ) (Woodberry et al., 2008; Mollon & Reichenberg, 2018) and specific (such as processing speed) cognitive impairments. Meier et al. (2014)'s follow up study of the Dunedin Birth Cohort indicated that individuals with a schizophrenia diagnosis exhibited premorbid impairments in processing speed, and that they also displayed a decline in IQ and a range of cognitive processes from the premorbid to the post-onset period, including processing speed, learning, executive function, and motor function. Evidence for premorbid cognitive deficits is consistent with the neurodevelopmental model of psychosis (outlined further in Section 1.7).

In summary, whilst childhood PLEs are associated with an increased risk of developing psychosis later on in development, they are also associated with an increased risk of developing other psychiatric disorders, as well as a range of non-psychiatric negative outcomes. Despite this, PLEs are merely transient for most individuals (Linscott & Os, 2013). As such, it has been argued that PLEs may be present in different individuals for varying reasons. According to Nelson and Yung (2009) they may be:

1. An expression of underlying and more fundamental disturbance (including self- or ipseity disturbance)

2. Clinical "noise" around a non-psychotic disorder, also termed "incidental PLEs" (Yung et al., 2007)

3. Present in non-clinical individuals, not associated with distress or reduced functioning

The first type of PLE (an expression of underlying and more fundamental disturbance) has been argued to be of particular clinical relevance in terms of risk of transition to psychosis. As such, this type has been investigated in this thesis (through addressing both distress and persistence) in order to understand how PLEs in childhood and adolescence can be integrated into current accounts of the development of psychosis.

1.6.4 Distressing PLEs

Mental disorders are typically diagnosed when there is a dysfunction that is also associated with "significant distress in social, occupational, or other important activities" (American Psychiatric Association, 2013). As described previously, PLEs are not uncommon - especially earlier on in life. As such, it is perhaps unsurprising that they are not inevitably associated with distress (Armando et al., 2010), particularly when taking into account that most individuals reporting PLEs in childhood do not go on to develop psychosis or any other disorder. Moreover, it has been argued that the distress elicited by PLEs is of particular clinical significance- findings from multiple studies indicate that non-clinical voice-hearing is distinguished from psychosis by reduced distress and increased control (Laroi et al., 2012; Johns et al., 2014).

Regardless of their prognostic significance, it has been stated that distressing PLEs in children and young people ought to be a focus of psychological intervention (NICE, 2016). However, it has been argued that the development of effective treatment is hindered by a lack of understanding regarding PLEs and the absence of a recognised conceptual framework for their emergence, persistence and resolution

(Ames et al., 2014). Existing psychological models of the development of psychosis (outlined below in Section 1.7). describe how various risk factors lead to the transition from sub-clinical experiences to a clinical disorder and allude to the importance of affective symptoms (Garety et al., 2001; Garety, Bebbington, Fowler, Freeman, & Kuipers, 2007), however, there has been limited research examining these developmental models in children and young people (Ames et al., 2014).

1.6.5 Persistent PLEs

There are several lines of evidence indicating that persisting PLEs are a marker of more serious and clinically significant levels of psychopathology. Firstly, psychotic disorders are by definition a PLE that persists beyond a certain time, one month in the DSM-5 (American Psychiatric Association, 2013). More severe episodes have greater levels of persistence, and therefore understanding persistence is a key issue in understanding what makes PLEs of clinical concern and are potentially the most relevant mechanisms for psychotic disorders.

As stated earlier, research indicates that childhood PLEs are transient for the vast majority of individuals (Linscott & Os, 2013). Indeed, Hanssen, Bak, Bijl, Vollebergh, and Os (2005) followed up over 4000 individuals from the Netherlands Mental Health Survey and Incidence (NEMESIS) study and found that the vast majority of individuals displayed transience in their PLEs. However, the minority of individuals who did have persisting PLEs were at significantly higher odds of presenting with a need for care. This is similar to the results reported by Dominguez, Wichers, Lieb, Wittchen, and van Os (2011). This study used data from the Early Developmental Stages of Psychopathology (EDSP) study, a prospective cohort study conducted in a general population sample of 845 adolescents aged 14-17 years in Munich, Germany. Participants in this study were assessed four times over a period of 8.4 years, and as in Kaymaz et al. (2012), the researchers argued that there was evidence of a dose-response relationship. Of all the individuals identified as transitioning the clinical psychosis at T3, more than a third (38.3%) had experienced PLEs once at prior time points and a fifth (19.6%) at least twice. Interestingly, a study by Wigman, van Winkel, et al. (2011) found that individuals on a persisting

trajectory of PLEs reported the highest levels of overall distress, as well as distress associated with PLEs, indicating that persistence is linked with distress.

Additionally, depression has been found to be a strong modifier of predictive power for a clinically relevant outcome. Downs, Cullen, Barragan, and Laurens (2013)'s study included 8099 children at baseline (mean age 10.4 years), of which 547 children completed reassessment, on average, two years later. Their findings indicated that children with persisting PLEs displayed a two-fold increase for later internalising and externalising psychopathology in comparison to children with no PLEs, as well as to children with remitting PLEs. These results are consistent with multiple theoretical accounts of psychosis, which are outlined further in Section 1.7.

In summary, current theories of psychosis attempt to explain the maintenance of PLEs, i.e., their persistence, through referring to various mechanisms. For instance, cognitive theories refer to the importance of cognitive processes and affective symptoms (Garety et al., 2001; Freeman et al., 2002), and other models such as Cougnard's psychosis-proneness-persistence-impairment model (Cougnard et al., 2007), pictured below in Figure 1.8 and the Developmental Risk factor model (Murray, Bhavsar, Tripoli, & Howes, 2017) argue that PLEs may become abnormally persistent and clinically relevant depending on the degree of environmental risk the person is additionally exposed to. The psychosis-proneness-persistence-impairment model will be expanded on in further detail in Chapter 4.

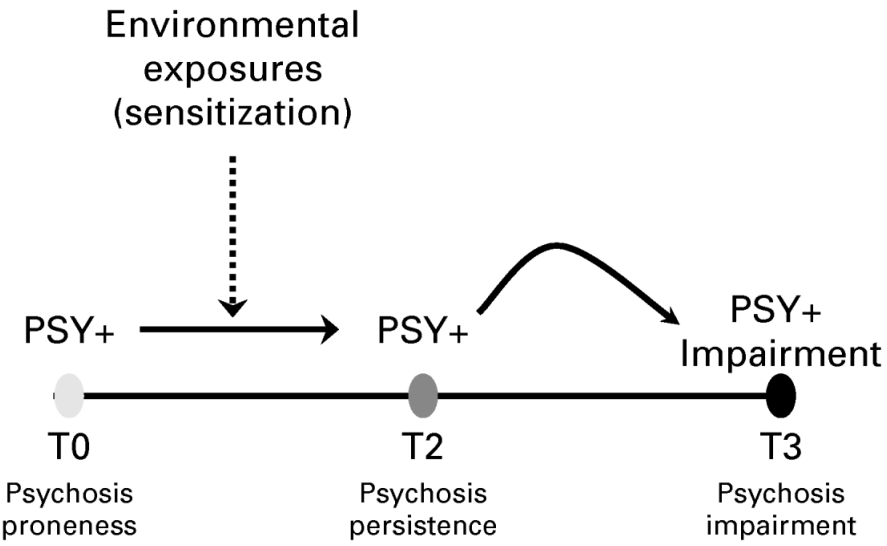


Figure 1.7: Psychosis continuum, from van Os, J., Linscott, R., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. Psychological Medicine, 39(2), 179-195.

1.7 PLEs and models of psychosis

Existing adult models of psychosis cite developmental processes as important in the generation of adult psychosis (Garety et al., 2001; Murray et al., 2017), and suggest that alterations to cognitive processes also present in children (Murray et al., 2017). As such, this indicates that the same processes should generate psychotic experiences in children, and therefore this has testable implications of PLEs in children.

However, there is a lack of research that examines the mechanisms underlying PLEs in childhood and early adolescence. The majority of studies that have attempted to elucidate the processes leading to the generation of PLEs have investigated this after the onset of adolescence, citing mechanisms from adults as a potential explanation (Papanastasiou et al., 2018).

1.7.1 Cognitive models of psychosis

A number of models of psychosis have attempted to explain what maintains psychotic experiences. It has long been argued that the symptoms of psychosis can only be comprehended fully through linking phenomenological experiences, social,

psychological and neurobiological levels of explanation. As such, cognitive models of psychosis have been proposed to be an essential part of this link. This is due to the fact that they provide a psychological description of the experiences, which can then assist in the formation of testable hypotheses regarding the causal processes. Factors from different levels of explanation such as social, individual and neurobiological variables can then be integrated through their effect on cognitive processes (Garety et al., 2001). This has led to the development of multiple cognitive models of psychosis. Perhaps the most influential psychological model is Garety et al. (2001)'s cognitive model of the positive symptoms of psychosis.

Garety et al.'s (2001) model of positive psychotic symptoms

This model proposes that there are two routes to the development of positive symptoms in psychosis. The first path is the result of both cognitive and affective changes, whilst the other path occurs solely through affective disturbance. The researchers argue the first route is more common, and that a triggering event may lead to a predisposed individual to experience a disruption to their cognitive processes. Garety et al. (2001)'s model purports that whilst individuals on both of these routes display cognitive disturbances during the onset of their anomalous experiences, these experiences have not developed into psychotic symptoms at this point. Rather, affective changes also emerge as a direct result of the triggering event and unusual experiences, against the backdrop of a "conducive social cognitive background". Garety et al. (2001) argue that individuals with unusual experiences do not transition to frank psychotic symptoms if they are able to "reject the hypothesis of externality". Garety et al. (2001) also argue that for a small number of individuals the triggering event itself might not lead to a disturbance in information processing, but that they instead cause disrupted affect, and this is what leads to the emergence of biased appraisals or other cognitive processes which cause an externalising appraisal (i.e., the delusion). In these circumstances delusions may occur in the absence of hallucinations or other positive psychotic symptoms. A key aspect to the model is attempting to explain what maintains the psychotic appraisal, or

causes it to persist. Garety et al. (2001) suggest that numerous factors may cause the psychotic appraisal to persist, namely: reasoning processes, dysfunctional schemas and adverse social environments, emotions and cognitive processes linked to emotion and finally, the secondary appraisal. Garety et al. (2001)'s model is illustrated in Figure 1.8.

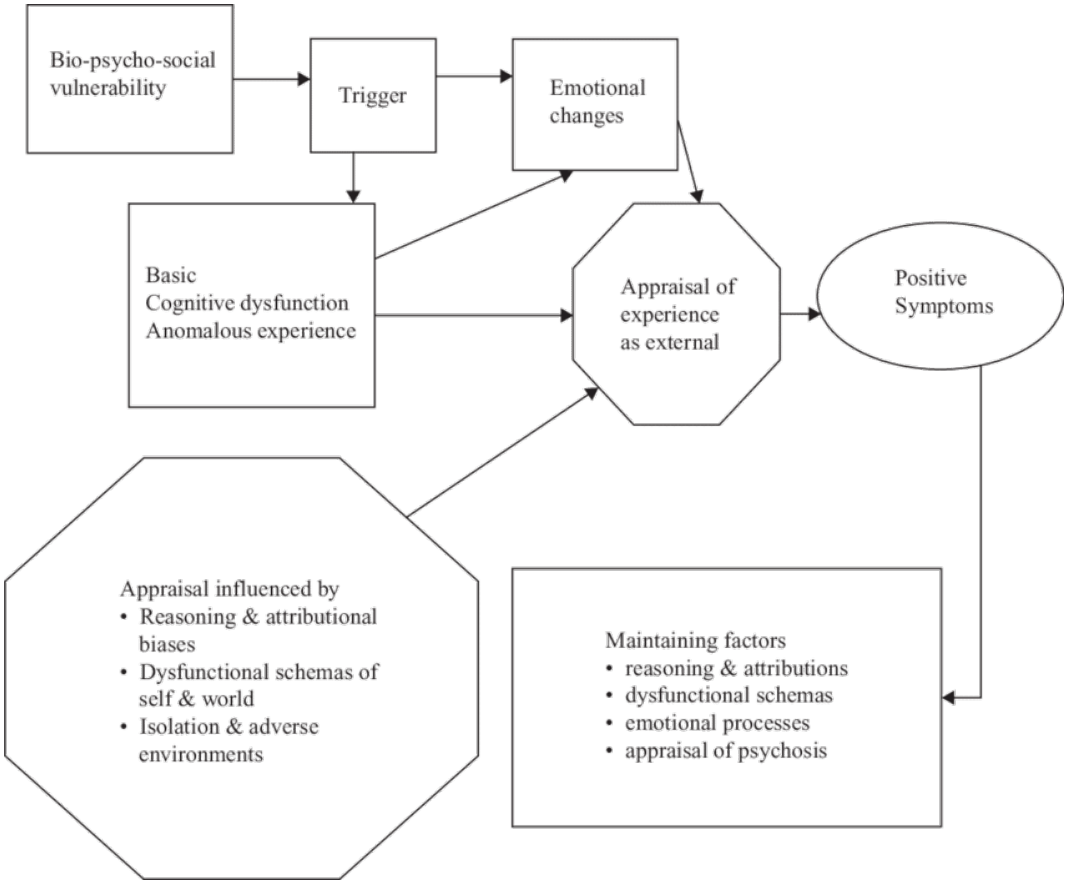


Figure 1.8: Conceptualization of Garety et al.'s (2001) model of positive psychotic symptoms, from "Cognitive, emotional, and social processes in psychosis: Refining cognitive behavioral therapy for persistent positive symptoms," by E. Kuipers, P. Garety, D. Fowler, G. Dunn, and P. Bebbington, 2006, Schizophrenia Bulletin, 32 (Suppl. 1), p. S25, 669-673.

Freeman et al.'s (2002) cognitive model of persecutory delusions

Garety et al. (2001)'s model was the basis of other models more focused on specific psychosis symptoms, such as Freeman et al. (2002). Here, Garety et al. (2001)'s model has been applied to focus specifically on persecutory delusions.

Once again, the authors argue that the model is underpinned by a stress-vulnerability framework, where the emergence of psychotic symptoms rely on an interaction between vulnerability (due to genetic, biological, psychological and social risk factors) and stress (which might also be biological, psychological or social). As such, delusions are formed after a precipitator, but also often occur in the presence of long-term affective dysregulation (such as anxiety and depression).

See Figure 1.9 below for a summary of the maintenance of a persecutory delusion.

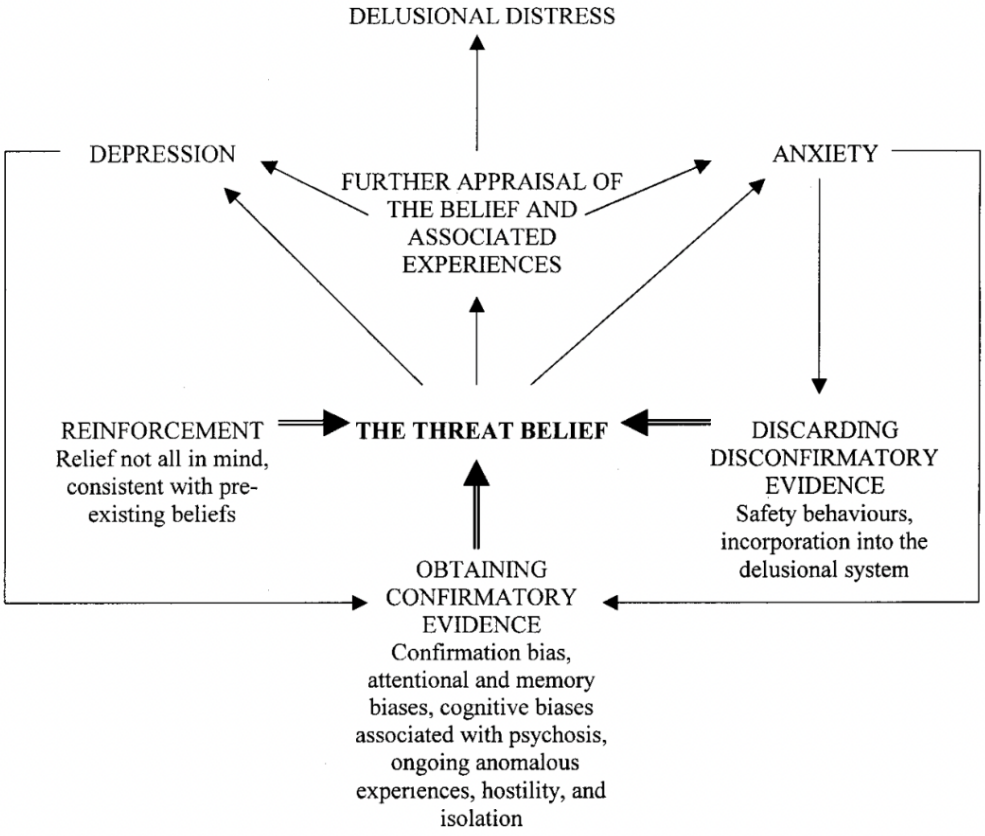


Figure 1.9: Freeman et al.'s (2002) Summary of the maintenance of a persecutory delusion, from Freeman, D., Garety, P. A., Kuipers, E., Fowler, D., & Bebbington, P. E. A cognitive model of persecutory delusions. British Journal of Clinical Psychology, 41(4), 331–347.

Nevertheless, a significant limitation of these cognitive models is that whilst cognitive models cite that early life experiences are crucial for both the development

and persistence of anomalous experiences, they do not attempt to provide well-evidenced mechanisms for how developmental processes lead to adult psychosis and imply that PLEs are generated by processes that should apply equally to PLEs in childhood.

1.7.2 Developmental risk factor model of psychosis

Neurodevelopmental model of schizophrenia

A neurodevelopmental approach to psychosis was first taken by Clouston in 1891 (Clouston, 1891). However, these ideas were quickly displaced by Kraeplin's conceptualisation of "dementia praecox", which described psychosis as an adult onset neurodegenerative disorder (Kraepelin, 1927). This view was prominent for almost a century, as evidenced through Johnstone, Frith, Crow, Husband, and Kreel (1976) interpreting their findings that individuals with chronic schizophrenia had lateral ventricular enlargement and cognitive deficits as being indicative of "dementia praecox". Nevertheless, this view began to change due to studies such as Reveley, Clifford, Reveley, and Murray (1982), which indicated that monozygotic (MZ) twins diagnosed with schizophrenia had larger cerebral ventricles than their twin who did not have a diagnosis. Those with a diagnosis were also more likely to have been exposed to perinatal hazards, suggesting an environmental component. The role of pre- and peri-natal complications was confirmed in a review of studies of discordant and concordant twins (Reveley, Reveley, & Murray, 1984) and non-twin studies (Lewis & Murray, 1987). Subsequent research demonstrated that periventricular bleeding in infants who were premature or exposed to hypoxia frequently resulted in enlarged ventricles (Lewis & Murray, 1987). These findings, combined with the observation that those diagnosed with schizophrenia often displayed neuromotor delays in childhood led Murray and colleagues to argue that schizophrenia is a neurodevelopmental, rather than neurodegenerative disorder (Murray & Lewis, 1987). Although less recognised, this was also argued for by Weinberger (1987), who suggested that schizophrenia is the result of an early life fixed brain lesion interacting with normal maturation of the neural system. The neurodevelopmental hypothesis was further supported by findings from studies such as Jones (1994),

which analysed data from the British 1946 Birth Cohort and reported that individuals who later developed psychosis displayed delayed attainment of development milestones and had poorer educational performance.

Early papers based on this model cited genetic predisposition as key (Jones & Murray, 1991), and stated that early adversity - specifically focusing on obstetric complications (Lewis & Murray, 1987)- would only manifest as psychosis in early adulthood, once normative maturational changes revealed the damage sustained earlier on in life. However, Keshavan, Anderson, and Pettergrew (1994) revived Feinberg's hypothesis that schizophrenia was caused by aberrant synaptic pruning in adolescence (Feinberg, 1982). Hence, the neurodevelopmental model started to incorporate findings regarding disruption during foetal development, childhood and adolescence. This subsequently enabled the impact of other environmental factors to be considered. An early review on this topic by McGrath et al. (2004) indicated that there is substantial heterogeneity in the incidence of schizophrenia in the population, which supported the notion that environmental factors impact schizophrenia risk. Specifically, this risk was linked to area-level factors such as urbanicity (Vassos, Pedersen, Murray, Collier, & Lewis, 2012), rather than just individual-level variables. There was also an increased interest in the role of cannabis as a risk factor for the development of psychosis (Paparelli, Di Forti, Morrison, & Murray, 2011). Research in this area also began to explore the mechanisms underlying the onset of psychosis, with a particular focus on the role of dopamine as the final common pathway leading to the emergence of schizophrenia (Howes et al., 2004). This was based on multiple lines of research, including the observation that there is increased dopamine synthesis capacity in individuals with psychotic disorders, which is detectable even in the prodromal stage (Howes et al., 2009). This is outlined in further detail in Chapter 3.

The Developmental Risk Factor Model

Whilst the neurodevelopmental hypothesis was widely accepted in the early years of the 21st century, findings began to emerge which challenged this account. This included a revived interest in neurodegeneration, fuelled by research demon-

strating that there are progressive brain changes in individuals with schizophrenia (DeLisi et al., 1997; Lieberman, 1999). Others subsequently argued that these changes are the result of a combination of the effects of anti-psychotics, substance use and lifestyle factors (Murray et al., 2016). According to Murray et al. (2017), another threat to the viability of the model emerged from the "uncritical adoption of the reductionist view that schizophrenia is simply a neurodevelopmental disorder" (Insel, 2010). Murray et al. (2017) argue that it is apparent that schizophrenia is not a neurodevelopmental disorder in the same way as autism, rather that neurodevelopmental risk factors interact with environmental risk factors. It has been argued that the neurodevelopmental model and the idea that schizophrenia leads to progressive brain changes are not necessarily mutually exclusive (Olabi et al., 2011). More recent neuroimaging studies have supported the view that those who transition to psychosis display aberrations in neural development. A review by Smieskova et al. (2010) found that individuals who transition from an ultra-high risk state to psychosis display patterns of subtle gray matter abnormalities within frontal and temporal cortices, the limbic system and the cerebellum. Additionally, a meta-analysis found that those with a schizophrenia diagnosis displayed greater decreases in their brain volume, whole brain gray matter, frontal gray and white matter, parietal white matter, and temporal white matter volume and larger increases in lateral ventricular volume (Olabi et al., 2011).

Murray et al. (2017) go on to outline how deficits in neuro- and social cognition emerge due to subtle abnormalities in neural networks, thus causing some children to be placed on a trajectory of increasingly challenging life events, including difficulties academically, socially, which frequently are termed primary negative symptoms later in life. According to Murray et al. (2017), there is a cascade of exposure to environmental stressors, such as substance or victimisation, which causes dysregulated dopamine release. This is supported by literature showing that adverse early life experiences are a risk factor for the development of psychosis (see Varese et al. (2012)'s meta-analysis, which reported that childhood adversity and trauma increases the risk of psychosis with an OR of 2.8). Trauma has been pro-

posed to act as both a risk factor for onset as well as through leading to the emergence of maintaining factors (Mueser, Rosenberg, Goodman, & Trumbetta, 2002). According to the Developmental Risk Factor Model, the alterations in dopamine that have arisen due to environmental stressors in turn cause the aberrant assignment of salience to experiences, which can cause a vicious cycle, whereby stress increases dopamine dysregulation, which then leads to more stress due to the emergence of anomalous experiences. This then causes further dopamine release, and an eventual "hard-wiring" of psychotic interpretations (Howes & Murray, 2014). The neurodevelopmental hypothesis has therefore gradually changed into the Developmental Risk Factor Model, which also takes into account evidence indicating that there is a continuum of sub-clinical psychotic symptoms, or PLEs (Howes & Murray, 2014; Howes, McCutcheon, Owen, & Murray, 2017; Murray & Fearon, 1999). This model purports that a clinical diagnosis is only made if psychotic symptoms pass a certain threshold, consistent with the diagnosis of hypertension or obesity. However, whilst citing developmental processes as key, it is noteworthy that this model does not predict at what age alterations to the striatal dopamine system lead to aberrant salience. More recently, predictive coding accounts of psychosis have been outlined (see Sterzer et al. (2018) for a review). This view proposes that the brain is a hierarchy whose primary goal is to maximise evidence for its model of the world by comparing prior beliefs with sensory data, and using any resultant prediction errors (PEs) to update the model. Nevertheless, it does not attempt to explain why PLEs persist, why psychosis tends to have its onset in adolescence and suggests that PLEs at any age should have a similar explanation in altered dopaminergic prediction error signalling (Sterzer et al., 2018).

1.8 Evidence from children and adolescents

As outlined earlier, it is clear that development is a central but poorly specified component of adult psychosis, and that there is a developmental aspect to PLEs, as their prevalence peaks in childhood and then typically drastically declines at the onset of adolescence. Research indicates that PLEs are transient for most, however, they

can become persistent and clinically relevant in a minority of individuals, approximately 20% according to Linscott and Os (2013). However, this has yet to be integrated into existing cognitive and neurocognitive models of psychosis. Whilst the neurodevelopmental model cites striatal dopamine as the final pathway that generates psychotic symptoms and experiences, evidence for aberrations in dopaminergic functioning is primarily based on adults and it is unclear whether this generalises to children and adolescents, despite them experiencing high levels of PLEs. Only a limited number of studies have investigated PLEs in healthy populations and reward processing, and this has been examined in mid- to late adolescence rather than earlier in development. This includes Papanastasiou et al. (2018) and Bourque, Spechler, et al. (2017), both using the IMAGEN dataset (participants aged 14 at baseline and 19 at follow-up).

Similarly, cognitive models of psychosis also state that early life experiences are vital for the development and persistence of PLEs. Nevertheless, they do not attempt to explain the known developmental trajectory of PLEs and psychosis, and given they are also primarily based on findings from studies in adults, do not seem to be consistent with it. However, there have been some attempts to explore the causal mechanisms underlying PLEs in children and adolescents. This includes Bird, Evans, Waite, Loe, and Freeman (2019). In this sample consisting of a school cohort of 801 adolescents aged 11 to 15, Directed Acyclic Graphs were used to assess causal interactions with paranoia. Findings indicated that there were likely direct causal relationships between paranoia and negative affect, peer difficulties, bullying, and cognitive-affective responses to social media. The interaction between negative affect and paranoia was particularly robust.

Similar findings have been reported in studies with longer periods of follow-up such as Downs et al. (2013), previously outlined in Section 1.6.5, and these results are also consistent with cognitive models that propose that positive psychotic symptoms interact with affective difficulties and perpetuate psychotic and emotional symptoms (Garety et al., 2001; Freeman et al., 2002).

Longitudinal studies that assess PLEs at multiple time points enable re-

searchers to study trajectories of psychotic experiences over time, while also reducing mis-classification error from single time-point assessments (Kalman et al., 2019); other strengths of longitudinal studies, particularly those employing a population neuroscience approach will be outlined below in Section 1.9.

It has been argued that internalising and externalising psychopathology in early life might be causally related to PLEs (Ames et al., 2014). This has been supported by numerous studies, including Mackie, Castellanos-Ryan, and Conrod (2011). They assessed PLEs in 409 adolescents in the UK (mean age 14 years and 7 months) at four time points, each 6 months apart. Mackie et al. (2011) identified three subgroups of PLEs: (1) persistent; (2) increasing; (3) low. Those in the persistent trajectory experienced higher symptom levels of depression and anxiety. They also reported higher levels of victimisation, which is in line with models of psychosis stating that adverse life events are associated with the persistence of PLEs (Garety et al., 2001; Freeman et al., 2002; Cougnard et al., 2007). Moreover, adolescents on the increasing trajectory reported more cigarette use before any increases in PLEs, and also began to engage in substance abuse as PLEs were increasing at later time points. The authors suggested that this represents a group of adolescents who are either susceptible to engaging in both substance misuse and having PLEs, or whose substance misuse indexes future risk for increasing PLEs. Whilst limited by the small sample size, this study is among the first to examine trajectories of PLEs in adolescence, and highlights factors that are related to the persistence of PLEs during this period. These findings are consistent with a study by Wigman, van Winkel, et al. (2011) which was published at around the same time. This study used data from the TRacking Adolescents' Individual Lives Survey (TRAILS), a prospective cohort study among adolescents in the general Dutch population. In a group of individuals followed from 10 to 16 years old, four developmental trajectories of thought problems over time were identified; a low, decreasing, increasing and persistent group. Only the final group was associated with several factors that have been found to predict transition to psychosis, including ethnic minority group status, developmental problems and exposure to trauma be-

tween ages 11 and 16 years. This again indicates that persisting PLEs may be of particular clinical relevance, and the authors argued that persisting PLEs may be the result of dopamine sensitisation (see section 1.7.2 for details regarding the proposed role of dopamine in psychosis). However, Bourque, Afzali, O'Leary-Barrett, and Conrod (2017)'s findings suggested that a three-class trajectory model provided the best fit (low-decreasing, moderate-increasing and high-decreasing), rather than a four-class model as in Wigman, van Winkel, et al. (2011) and Mackie et al. (2011). Nevertheless, Bourque, Afzali, et al. (2017) also emphasised the role of internalising symptomatology, as growths in anxiety and depressive symptoms were associated with the moderate-increasing PLE trajectory (along with growth in cannabis use frequency). Despite this, Thapar et al. (2012)'s study which used data from the ALSPAC cohort reported that whilst individuals in the persistent-class had the highest scores on the majority of the measures (which include demographic characteristics, peri-natal factors, cognition, etc.), none of these measures was able to distinguish between those who belonged in the persistent, intermittent or decreasing group.

Additionally, many of the existing studies are limited by the sample size. Furthermore, while a minority may speculate about the underlying neurocognitive mechanisms, they often do not actually contain neuroimaging measures or validated cognitive measures. This is why, as explained in the next section, a population neuroscience approach is key to understanding the mechanisms leading to the development of disorders such as psychosis.

1.9 Population Neuroscience

The concept of "Population neuroscience" was first outlined in Paus (Paus, 2010, 2012), and has been described as a field that lies at the intersection of cognitive neuroscience, genetics and epidemiology (see Figure 1.10 below).

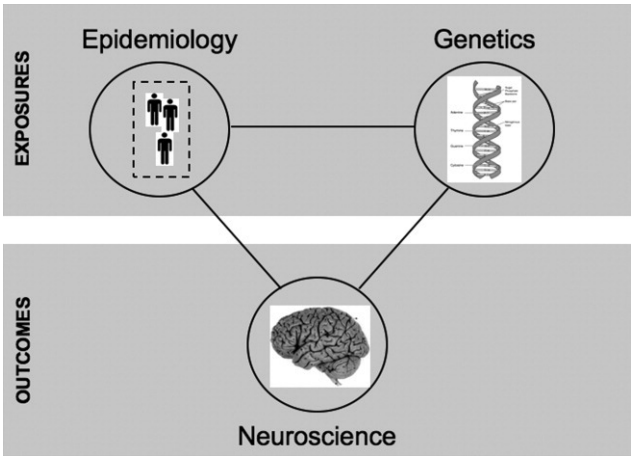


Figure 1.10: Population Neuroscience, from Paus, T. (2010). Population neuroscience: Why and how. Human Brain Mapping, 31(6), 891–903.

The emergence of neuroscientific studies with large samples such as the Human Connectome Project (Glasser et al., 2016), Generation R (Kooijman et al., 2016), GUSTO (Soh et al., 2014), IMAGEN (the IMAGEN consortium et al., 2010), Philadelphia Birth Cohort (Satterthwaite, Connolly, et al., 2016), PING (Jernigan et al., 2016), NCANDA (Brown & Whalen, 2015), UK Biobank (Sudlow et al., 2015), as well as data pooling from ENIGMA (P. M. Thompson et al., 2014) provides researchers with the opportunity to attempt to apply epidemiological principles to neuroscientific investigations (Garavan et al., 2018), which up until recently has relied on small and homogeneous convenience samples (Falk et al., 2013). These samples are limited by a lack of power (Button et al., 2013) as well as a lack of diversity, which in turn limits our ability to elucidate how individual differences in brain structure and function affect cognitive, affective and behavioural outcomes, and how this interacts with the broader environmental context (Falk et al., 2013). This is a problem that is particularly relevant to studies of psychopathology in children, where neurocognitive studies are hard to conduct and have consequently often lacked sufficient statistical power to adequately address relevant hypotheses.

1.10 The Adolescent Brain Cognitive Development (ABCD) Study

The analyses presented in this thesis have been conducted on data from the Adolescent Brain Cognitive Development (ABCD) Study. The ABCD study was initially conceived in order to elucidate how substance use impacts brain development. However, the Collaborative Research on Addiction (CRAN) Institute Directors quickly concluded that the ABCD study needed to examine mental and physical health, as it interacts with substance use (Volkow et al., 2018).

As such, the ABCD study is now a collaborative trans-NIH venture, including -but not limited to- several collaborators such as The National Institute of Mental Health (NIMH), the NIH Office of Behavioral and Social Science Research (OBSSR), The National Institute on Minority Health and Health Disparities (NIMHD) (Volkow et al., 2018). It takes a "population neuroscience" approach and is the largest US study to date of its kind, recruiting 11,875 young people aged 9-10 from 21 sites (detailed information about the sample available in supplement Appendix A). Due to its design, it provides researchers with a unique opportunity to examine the association between brain development and the onset and progression of mental health difficulties. This means that premorbid markers of illness can be identified (Karcher & Barch, 2021), along with sensitive periods for intervention. Another noteworthy aspect about the ABCD study is that half of the sample are from minority groups. This was planned due to the growing diversity within the U.S population (Volkow et al., 2018), but is particularly valuable for this body of work as individuals occupying certain ethnic minority positions are more likely to receive a psychosis diagnosis (Jongsma et al., 2021).

Measurement of PLEs in the ABCD study

As stated earlier, the ABCD study contains a wide range of measures. A detailed description of the rationale and the measures is available, see Barch et al. (2018) for the demographic, physical and mental health assessments, Zucker et al. (2018) for the assessment of culture and environment and Casey et al. (2018) for imaging acquisition across all the sites. Out of measures acquired in the ABCD

study, one specifically assesses PLEs: the Prodromal Questionnaire-Brief Child Version (Karcher et al., 2018).

Categorical diagnostic assessments were also conducted using a validated and computerised Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) for DSM 5 (Kobak, Kratochvil, Stanger, & Kaufman, 2013).

1.11 Chapter conclusion and research proposal

In light of the evidence discussed in this chapter, several areas can be highlighted where further empirical work is needed. In adults, affective changes, poorer cognition, change to brain structure and function, and adverse experiences have all been associated with psychosis. However, the extent to which these reliably associated variables in adults also associate with PLEs in children has yet to be established. Secondly, whilst neurocognitive models of psychosis frequently cite the importance of early life experiences in the generation of psychotic symptoms and imply alterations to affect and cognition during development should play a causal role, the mechanisms by which this occurs have been either omitted or remain untested. The Developmental Risk Factor Model (Murray et al., 2017) proposes that alterations in striatal dopamine underlie the generation of adult psychotic experiences and implies this mechanism applies to all psychotic symptoms regardless of when they might occur during development. Nevertheless, this assumption remains largely untested in children and adolescents. Finally, PLE persistence and distress have been confirmed as important in predicting severity and outcome in children, but further research is needed to elucidate to what extent they are associated with proposed causal mechanisms for psychotic symptoms. Traditionally, addressing these questions has been challenging, due to difficulties in recruiting pre-adolescent participants in sufficient numbers, with robust measures, and with sufficient representativeness to draw strong conclusions. The ABCD dataset provides an ideal opportunity to investigate these questions, due to richness of the data (notably the use of detailed measures of psychosis that takes into account both presence and distress of PLEs), an ample sample size, and the age and diversity of the participants.

Therefore, this thesis reports research that addresses the following questions:

1.11.1 Research Aims

1.11.1.1 Chapter 2: Network Analysis of psychotic-like experiences, depressive symptoms, trauma and neurocognition

Chapter 2 takes a network analysis approach to explore how established factors associated with psychotic symptoms in adults associate with the presence of PLEs in children. A network analysis approach was used as it allows a statistically robust way of investigating the association across multiple variables while providing metrics about the potential importance of each variable within the network. Consequently, this chapter examines how environmental, cognitive and neuroimaging factors interact with PLEs in children.

1.11.1.2 Chapter 3: Reward Processing and Psychotic-like Experiences in childhood

There is substantial evidence in adults that psychotic symptoms are associated with aberrant reward processing. This is the basis of the developmental risk factor model that suggests that developmental adversities will impact on the mid-brain dopamine system that generates PLEs. However, the extent to which alterations to the reward system are associated with PLEs at their peak age in children remains untested. As such, Chapter 3 will investigate whether PLEs and PLE-related distress are associated with alterations in reward processing at age 9-10 as tested using a widely used neuroimaging test of reward – the Monetary Incentive Delay task – in over 6,000 children.

1.11.1.3 Chapter 4: Social, cognitive and affective predictors of the Persistence, Remission and New Incidence of Psychotic-like Experiences

The persistence of PLEs during childhood is a substantial predictor of poor outcome and increased risk for later psychosis. As such, Chapter 4 investigates predictors of

PLE presence and persistence. This will be done through examining two research questions 1) whether social, cognitive and affective predictors of adult psychosis predict the persistence, remission and incidence of PLEs in children and 2) whether reward processing at age 9-10 predicts the persistence, remission and incidence of PLEs at one-year follow-up.

1.11.1.4 Chapter 5: General Discussion and Synthesis

Chapter 5 summarises the findings of this doctoral thesis and integrates it with existing research and models of psychosis, whilst also making suggestions for future research.

Chapter 2

Study 1: Network Analysis of psychotic-like experiences, depressive symptoms, trauma and neurocognition

2.1 Abstract

Network analysis is a novel approach to psychopathology, first originating approximately a decade ago. Rather than assuming the existence of an underlying latent factor which leads to the emergence of mental health symptoms, it proposes that mental health difficulties can be conceptualised as a complex network of symptoms which interact with each other. Network analysis can allow the investigation of risk factors across multiple levels of explanation, whilst accounting for complex patterns of interaction both within and across levels. As such, it presents a valuable approach for understanding psychotic-like experiences (PLEs). Existing theoretical models do not adequately address the developmental nature of PLEs. Whilst they make reference to the existence of a psychosis continuum, they do not take into account that the prevalence of PLEs varies across the life course. PLEs appear to be most common in early life and appear to spontaneously remit in the majority of individuals, suggesting they are part of a transient developmental expression for most. Additionally, whilst existing theoretical models of psychosis argue that psychosis is a neurodevelopmental disorder, they often infer altered neurodevelopment based on findings from adult literature. Similarly, they argue that negative affect and cognition, combined with exposure to stressful life events, play a key role in the mechanism underlying psychosis, but this too is often based on research conducted in adults. The present study sought to use network analysis to examine how PLEs interact with factors from different levels of explanation. This was done using data from the Adolescent Brain Cognitive Development (ABCD) study, an ongoing longitudinal cohort study in the US. The present study used the baseline data from the ABCD study and investigated how PLEs interact with social, neurocognitive and affective factors in a sample of children aged 9-10, in order to explore whether the established components of psychosis in adults is also present in late childhood. The results indicated that PLEs at this age were only strongly associated with depressive symptoms, but not with cognition, cortical thickness or trauma. As such, these findings suggest that the correlates of psychosis in adults do not replicate in children aged 9-10, but develop over time instead.

2.2 Introduction

The idea that adverse events, developmental challenges, and psychological characteristics in childhood contribute to the risk for later development of psychosis is now widely accepted (Holtzman et al., 2013; Malone, Hill, & Rubino, 2010). These findings have been integrated to existing models of psychosis, which cite development as key to the causation of psychotic experiences (Murray et al., 2017). However, these models often retrospectively infer relevant developmental risk factors from adult data and there is still a paucity of research that has actually focused on the developmental and neurodevelopmental differences associated with PLEs in children themselves which should, according to these models, be caused by similar mechanisms (Howes & Murray, 2014). Additionally, existing research often relies on retrospective data gathering, meaning it is not clear whether the relationships between key variables we see in adult psychosis are a reliable guide to the relationships that have important causal influences on PLEs during development.

As outlined in section 1.6.2 in the introductory chapter, affective symptoms and cognition have been associated with PLEs and have been proposed as causes of the development of psychosis. Another important candidate cause of PLEs in children is trauma. The link between psychosis and trauma was first proposed in Jeffries (1977). Morrison, Frame, and Larkin (2003) was also among the first to describe an integrative model of psychosis and trauma, stating that it is likely that traumatic life experience contribute to "faulty self and social knowledge" suggesting that trauma leads to psychosis through influencing cognitive processes. More recently, several empirical studies have been conducted which suggest that trauma may be an important risk factor for the development for psychosis. This includes Arseneault et al. (2011), which analysed data from the Environmental Risk Longitudinal Twin Study, a cohort study which follows over 2000 twins and their families and found that children who experienced maltreatment were more likely to report psychotic symptoms at age 12 (relative risk = 3.16). This remained the case even after adjusting for covariates, and was consistent for early and late childhood trauma. There was also evidence of a dose-response relationship, which is consistent with

studies such as Schreier et al. (2009), which used data from the ALSPAC study and found that victimisation was associated with a two-fold risk of PLEs. In a meta-analysis of the association between childhood trauma and adult psychosis (Varese et al., 2012) concluded that childhood adversity is associated with an increased risk with an overall effect of OR = 2.8.

There is evidence of extensive brain maturation in adolescence and young adulthood (Blakemore, 2008). One of the most notable changes in adolescence occurs in terms of cortical thickness, a measure of the width between the inner surface and outer surface of the grey matter (Dahnke, Yotter, & Gaser, 2013), namely cortical thinning (Tamnes et al., 2010, 2017). Data from the ENGIMA consortium has found evidence of global cortical thinning in individuals diagnosed with schizophrenia (Van Erp et al., 2018; Walton et al., 2018). The evidence from cross-sectional studies is mixed, whilst multiple cross-sectional studies have observed that young people deemed at clinical high risk (CHR-P) for psychosis display atypical cortical thinning (Jung et al., 2011; Kwak et al., 2019), others do not (Hong et al., 2013). The North American Prodrome Longitudinal Study (NAPLS 2), one of the largest longitudinal studies of individuals at CHR-P, reported that individuals who later transitioned to psychosis displayed accelerated cortical thinning (Cannon et al., 2015). Research finding evidence of structural differences in individuals who later go on to develop psychosis is consistent with the neurodevelopmental hypothesis of schizophrenia (Murray et al., 2017), which proposes that there is a disruption to brain maturational processes. In terms of studies including young people from the general population PLEs in childhood and adolescence have also been associated with reduction in temporal lobe volume (Roalf et al., 2017), grey matter volume (Satterthwaite, Wolf, et al., 2016) and asymmetries in subcortical brain volume (Okada et al., 2018). However, these studies were performed in young people who had already entered adolescence, as both Roalf et al. (2017) and Satterthwaite, Wolf, et al. (2016) used data from the Philadelphia Neurodevelopmental Cohort, in which the participant's mean age was 14-15. The sample used by Okada et al. (2018) included late childhood as well as early adolescence as participants were

10.5-13.3 years old. As such, existing studies are exploring the association between brain structure and PLEs beyond the peak age for PLEs. This limits our mechanistic understanding of the development of psychosis. Additionally, it is challenging to infer from structural studies the links with PLEs due to a lack of power caused by small sample sizes. Only 386 individuals were classified as being on the "psychosis spectrum" in Roalf et al. (2017), and Okada et al. (2018)'s sample was comprised of 203 individuals. Furthermore, the majority of research has broadly assessed positive PLEs, such as hearing voices, and not cognitive symptoms (Kalman et al., 2019), which are also associated with psychosis and often precede the onset of the disorder (Mollon, David, Zammit, Lewis, & Reichenberg, 2018).

Overall, whilst there is substantial evidence of cognitive deficits in children with PLEs, there is limited empirical research examining the neural and affective predictors of the presence of PLEs before adulthood. Additionally, existing studies have been criticised for not adequately controlling for confounding variables (Kalman et al., 2019). Moreover, it is important to note that developmental models cite affective dysregulation, trauma and neurocognition as being related. Indeed, trauma and childhood adversity has been proposed to result in changes to cognitive processes, affective regulation as well as changes to brain structure and functioning (Morrison et al., 2003; Garety et al., 2001; Murray et al., 2017). Conversely, it has also been argued that alterations in neural networks can lead to cognitive deficits and challenging life events (Murray et al., 2017) and the environmental stressors in turn cause a vicious cycle in which stress increases dopamine dysregulation and this leads to further stress due to the emergence of anomalous experiences.

Thus, the relationship between proposed mechanisms underlying psychotic experiences is likely to be complex and there are multiple reasons why these have not been well-investigated in children. This includes the statistical challenge of including variables representing large numbers of potentially interacting factors in studies that collect neuroimaging data, which typically involve small sample sizes. Secondly, testing relationships between multiple variables in parallel across psychological and brain structure measures can be complex in standard statistical models.

One potential way of addressing this is network analysis. Network analysis has its roots dating back to 2008 (Borsboom, 2008) and its empirical foundation to 2010 (Cramer, Waldorp, van der Maas, & Borsboom, 2010). Whilst this approach to psychopathology emerged approximately a decade ago, the use of network metrics was well-established in other fields, for example: semantic networks, social networks, and neural networks. It contrasts from traditional measurement models, which regard the symptoms of mental disorders as being caused by an underlying latent variable, depicted in Figure 2.1 below.

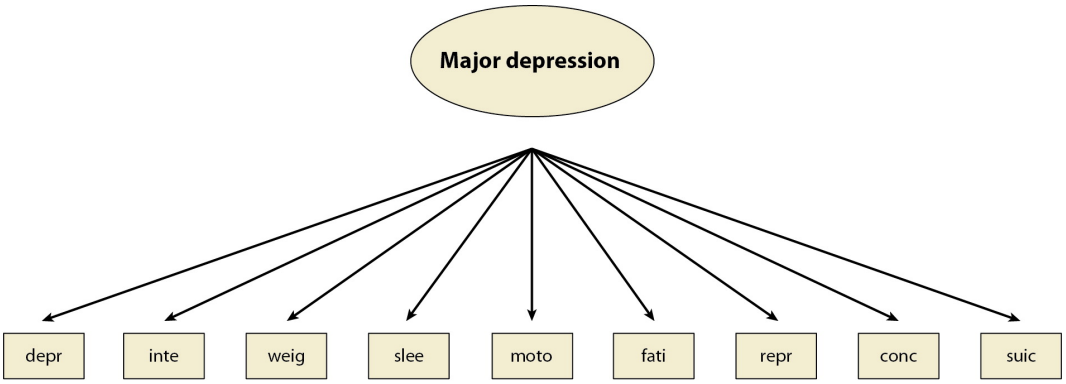
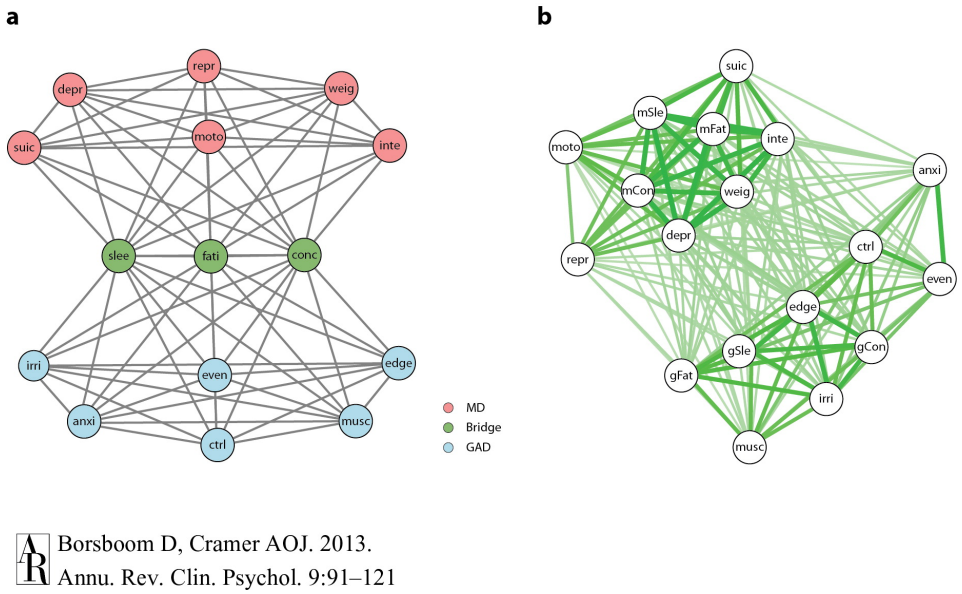


Figure 2.1: Medical disease model approach to Major Depression, from Borsboom, D., & Cramer, A. O. J. (2013). Network analysis: an integrative approach to the structure of psychopathology. Annual Review of Clinical Psychology,9, 91–121.

The network approach, on the other hand, conceptualises symptoms as elements of a complex network which interact (Borsboom & Cramer, 2013) and possibly self-reinforce each other (McNally et al., 2015). In this approach, networks consist of nodes, which represent the variables, and the causal interactions are represented by connections between nodes (referred to as "edges") (Borsboom, 2017) (see Figure 2.2). The majority of network analysis approaches use conditional approaches to define the network structure present in a set of variables. A conditional association between two variables refers to an association whereby the two variables are probabilistically dependent, contingent on all other variables in the data. The measure of conditional association used varied based on the structure of the data,

partial correlations are used for multivariate normal data, whereas logistic regression coefficients are used for binary data. As such, the lack of an edge in a network indicates that two variables are conditionally independent given all or a subset of other nodes present in the network (Borsboom et al., 2021).

Once these nodes and edges are identified, then the topology can be studied using descriptive tools from network science (Newman & Clauset, 2016). Note, edges can be unweighted or weighted, with a weighted edge also conveying information about the magnitude of the association. If the edges in a network are unweighted, all of the lines are the same thickness and the connection between two nodes simply means that the variables are correlated. Whereas if the edges in a network are weighted, the magnitude of the association is reflected in the thickness of the edge (with a thicker line representing a stronger connection). Additionally, green is often used to depict edges where there is a positive association, and red is typically used to denote a negative association. Edges can also be undirected or directed, whereby directed edges contain arrow tips which point in the direction of prediction (McNally, 2021). It has been argued that network models can be used to generate causal hypotheses (Borsboom et al., 2021). This line of argument is based on the view that they represent statistical structures that may reflect causal dynamics. An example of this is networks which represent conditional independence relations, which may connect correlations to causal relationships (Pearl & others, 2000; J. Haslbeck, Ryan, Robinaugh, Waldorp, & Borsboom, 2021). Nevertheless, networks based on correlations and utilising cross-sectional data cannot establish causation as it is unclear whether symptom A predicts symptom B, or vice versa. Furthermore, it remains possible that two nodes are correlated within a network due to the influence of other nodes in the network (McNally, 2021).



Borsboom D, Cramer AOJ. 2013.
Annu. Rev. Clin. Psychol. 9:91–121

Figure 2.2: Network analysis approach to Major Depression, from Borsboom, D., & Cramer, A. O. J. (2013). Network analysis: an integrative approach to the structure of psychopathology. Annual Review of Clinical Psychology,9, 91–121.

The use of network analysis to understand psychosis-related psychopathology has grown quickly (Contreras, Nieto, Valiente, Espinosa, & Vazquez, 2019). Existing studies have used network analysis in individuals with a psychotic disorder (Pappa, Peters, & Bell, 2020; Hardy, O'Driscoll, Steel, van der Gaag, & van den Berg, 2020; Isvoranu et al., 2017; van Rooijen et al., 2017), First Episode Psychosis (Chang et al., 2020; Izquierdo et al., 2021) and to assess symptoms in ultra-high risk individuals (Jimeno et al., 2020). A few studies have also used network analysis to examine PLEs in the general population. This includes examining paranoia in adults from the general population (Bell & O'Driscoll, 2018), and PLEs and distress (J. Murphy, McBride, Fried, & Shevlin, 2018; Wüsten et al., 2018). Additionally, some studies have examined the relationship between PLEs and psychotic symptoms with other symptoms such as dissociation (Černis, Evans, Ehlers, & Freeman, 2021), depressive (Wigman, de Vos, Wichers, van Os, & Bartels-Velthuis, 2017) and autistic symptoms (Isvoranu et al., 2021). In comparison, fewer studies have attempted to incorporate variables from different levels of explanation into psychosis symptom networks. This includes Isvoranu et al. (2020), which incorporated

polygenic risk scores, Isvoranu, Borsboom, van Os, and Guloksuz (2016), which incorporated environmental variables, Gaweda et al. (2021), which included traumatic life events and Fonseca-Pedrero, Ortuño-Sierra, Inchausti, Rodríguez-Testal, and Debbané (2020), which included cognitive measures. This is despite the fact environmental risk factors, cognition and affective symptoms have been consistently shown to increase the risk of experiencing both PLEs and psychosis (Gaweda et al., 2021).

One further challenge in conducting research across social, cognitive and neurocognitive domains in children has been the difficulty in collecting comprehensive, standardised, and well-specified data, meaning many studies have been necessarily too narrow in focus or have small samples (Hevey, 2018). The Adolescent Brain Cognitive Development (ABCD) study (Volkow et al., 2018) was launched to collect neuroimaging, health, social environment and cognitive data from a cohort of over 10,000 children in an attempt to address these challenges. The first phase of this dataset was released in 2018, allowing researchers access to an unprecedented dataset for mental health research.

Accordingly, to answer the question of whether evidenced causal models of adult psychosis are also associated with PLEs in children- and therefore whether the developmental assumptions of models of psychosis stand up in light of robust evidence from children- we completed a network analysis of a relationship between depression and anxiety, trauma, cognition and structural brain changes using the ABCD dataset. To our knowledge, no studies have adopted a network perspective to examine PLEs at age 9-10, despite extensive evidence of the developmental nature of PLEs. This represents a significant gap in the literature, as examining this will enable us to understand to what extent a psychosis-like syndrome 'coalesces' over time and starts to self-maintain from previously disparate components, or whether the components are already unhelpfully related in from an early age in a type of recognisable 'mini syndrome'.

Using this dataset, we aimed to understand how key social, cognitive, environmental and neural factors relate to PLEs in a large sample of young people aged

9-10 – the peak age for the expression of PLEs. We applied network analysis to understand relationships between these factors and to help determine the potential influence of each factor in the overall network.

2.3 Methods

2.3.1 Sample

Data was gathered as part of the Adolescent Brain Cognitive Development study (ABCD study; Volkow et al. (2018), an ongoing longitudinal study consisting of 21 research sites across the US. A baseline cohort of over 10,000 children (aged nine and ten) were recruited, as well as their parents/guardians, and they will be followed up for ten years (Garavan et al., 2018). Institutional review board approval was obtained for each site before data collection. All parents provided written informed consent and all children provided assent (Clark et al., 2018). Data analysis was conducted on the ABCD Study Curated Annual Release 3.0.1. The Pediatric Psychosis Questionnaire (PQ-BC; (Loewy, Pearson, Vinogradov, Bearden, & Cannon, 2011) was available for 11859 individuals at baseline. See the supplement for a detailed description of the sample (Appendix A).

2.3.2 Measures

2.3.2.1 Psychotic-like experiences

PLEs were measured using the Prodromal Questionnaire-Brief Child Version (PQ-BC) (Barch et al., 2018). This is a modified version of the Prodromal Questionnaire Brief Version (PQ-B) (Loewy et al., 2011), a self-report screening measure for psychosis risk syndromes. This study implemented the same approach to PLEs as described in Harju-Seppänen et al. (2021). Hence, a brief summary is provided below. The PB-QC is a 21-item questionnaire which consists of two parts. The first part of the questionnaire asks whether the individual has had particular thoughts, feelings and experiences in the past month, with an overall score ranging from 0-21. The second part of the questionnaire as then to indicate how distressing the experience has been, on a 5-point Likert scale from 0 (if not relevant) to 5 (strongly agree). The

overall distress score ranges from 0-92.

A subset of six items were selected for the network. These were *"Did you hear strange sounds that you never noticed before like banging, clicking, hissing, clapping, or ringing in your ears?"* (auditory hallucination), *"Did you feel that someone else, who is not you, has taken control over the private, personal, thoughts or ideas inside your head?"* (thought insertion), *"Did you suddenly feel that you could not trust other people because they seemed to be watching you or talking about you in an unfriendly way?"* (paranoia), *"Did you honestly believe in things that other people would say are unusual or weird?"* (bizarre beliefs), *"Did you feel that other people might want something bad to happen to you or that you could not trust other people?"* (paranoia) and *"Did you suddenly start to be able to see things that other people could not see or they did not seem to see?"* (visual hallucination). See Appendix B in the supplement for a full list of the items in the PQ-BC.

The coding for each PLE was as follows: 0 (absent) and 1 (present).

2.3.2.2 Depressive Symptoms

Depressive symptoms were measured using the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-5). The ABCD study used a recently validated and computerised version of the KSADS-5 (Kobak et al., 2013). This study used data from the Youth Diagnostic Interview, where symptoms and diagnoses are coded as present or absent (Kobak & Kaufman, 2015). A separate node was included for depressed mood, anhedonia, and irritability. As above, if symptom was present this was coded as 1 and 0 if absent.

2.3.2.3 Cognition

A detailed account of the neurocognitive battery in the ABCD can be found in Luciana et al. (2018). In order to examine cognition, three measures were used in the present study. This included the un-corrected NIH Toolbox List Sorting Working Memory Test Age 7+ v2.0 score (working memory), un-corrected NIH Toolbox Picture Vocabulary Test Age 3+ v2.0 (vocabulary) and the Weschler Intelligence Scale for Children, 5th Edition (WISC-V) Matrix Reasoning Total Scaled Score (fluid intelligence).

Fluid intelligence

The automated version of the Matrix Reasoning sub-test from the Wechsler Intelligence Test for Children-V (WISC-V (Wechsler, 2014)) was used to measure fluid intelligence, as it is well-validated and has shown to be a reliable measure of non-verbal reasoning (Wechsler, 2014). On each trial of the task, the participant is presented with a visuospatial array which consists of a series of stimuli. The series is incomplete, and the participant must indicate which stimuli from a list of four options completes it. The participant completes the task using two iPads. One of these is controlled by the examiner and presents each trial, whilst the other is viewed by the participant. These iPads are synchronised via a Bluetooth connection. Standardised instructions are provided and 32 possible trials are available. Testing ends if the participant fails three consecutive items. The total number of correct items across completed trials (the raw score) is tabulated and translated, using a normative database, into a standard score. The mean of the normative standard score is 10.0 and the standard deviation is 3.0. This corresponds to an IQ score of 100 (in the average range). The Matrix Reasoning test measures the following cognitive processes: fluid reasoning, visual intelligence, part-whole spatial reasoning, perceptual organisation. It has been found to strongly represent the Fluid Reasoning factor of the WISC-V and is correlated (r = 0.67) with general ability (g). Split-half reliability was found to be strong for children in the 9–10 year-old age range (r =0.87), and re-test stability is acceptable (r =0.78) (Luciana et al., 2018). The Total Scaled Score was used in the analysis.

Vocabulary

Vocabulary was measured using the Toolbox Picture Vocabulary Task (TPVT) (Gershon et al., 2014). It measures language and verbal intellect, and is a variant of the Peabody Picture Vocabulary Test (PPTV). The participants are presented with audio files of words and are shown four pictures in a square. One of these pictures represents the concept, idea or object that is referred to in the audio file. The participant is then asked to indicate which picture matches the word. The task uses computerised adaptive testing in order to ensure appropriate item difficulty. The

TPVT has shown good test-retest reliability (ICC = 0.81) and expected age related effects in validation testing in children and young people. It has also been found to show strong convergent validity with the PPTV (Gershon et al., 2014, 2013; Mungas et al., 2014). The un-corrected NIH Toolbox Picture Vocabulary Test score was used in the analysis.

Working Memory

The Toolbox List Sorting Working Memory Test (TLSWMT) is a variant of the letter-number sequencing test (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997), which uses pictures instead of words or letters (Tulsky et al., 2014). In the task, participants are presented with a series of pictures of food or animals of different sizes. Each of these pictures is presented alongside an audio recording of the name. The participant is then asked to repeat the items that were displayed to them, in the order from the smallest to the largest. Initially the TLSWMT only presents pictures from a single category. The participants are presented with a list consisting of two-items, and if they are correct, each subsequent trial increases the number of items by one, until a maximum of seven is reached. Participants are provided with two different trials to provide a correct response at each list length, and proceed to the next length provided they respond correctly to at least one of the items. All participants then continue to the next phase, in which the trials interleave two different categories. For these trials, the participant is asked to organise and repeat the items for one category (i.e., animals), followed by the other category (i.e., food). As in the case of the single category phase, the participants are presented with two opportunities to provide a correct response at each list length in order to continue, up to a maximum length of seven. The experiment scores each response as correct or incorrect. The TLSWMT has been validated in children and adolescents, and has been found to display good test-retest reliability (ICC = 0.86), age-related effects, as well as reasonable convergent validity with the WISC-IV Letter-Number sequencing task (Tulsky et al., 2013). Additionally, the TLSWMT has also been found to display relatively strong correlations with the PPVT, the Delis-Kaplan Executive Function System (D-KEFS) Color-Word Interference Task

and the Wisconsin Card Sort –64 Perseverative Errors, with *r*s ranging from 0.42 to 0.45 (Tulsky et al., 2014). The un-corrected NIH Toolbox List Sorting Working Memory Test Age 7+ v2.0 score was used in the analysis.

2.3.2.4 Cortical Thickness

During the scan session, T1w and T2W images are collected during the structural MRI (sMRI) series. The full imaging acquisition protocol is outlined in Casey et al. (2018). A detailed account of image processing and analysis can be found in Hagler et al. (2019) and is summarised below. The T1w and T2w images are corrected for any gradient non-linearity distortions through the use of scanner-specific, non-linear transformations which are provided by the scanner manufacturers (Jovicich et al., 2006; Wald, Schmitt, & Dale, 2001). Coarse and rigid-body pre-alignment is applied to the T2w images via within-modality registration to atlas brains. Following this, the images are registered to T1w images using mutual information (Wells, Viola, Atsumi, Nakajima, & Kikinis, 1996).

FreeSurfer v5.3 (Fischl, 2012) was used for the cortical surface reconstruction and subcortical segmentation. Cortical thickness (CT) measures were available for individual Desikan-Killiany regions of interests (ROIs) (Desikan et al., 2006) and the ROIs were mapped to the lobes, to obtain a total CT measurement for the right and left frontal, temporal and parietal lobe. The cortical thickness (mm) of each lobe was included in the analysis.

2.3.2.5 Trauma

Trauma was measured using the ABCD Parent Diagnostic Interview for DSM-5 (KSADS) Traumatic events. Each item was coded as 0= no and 1 = yes. A total trauma score was derived through summing the amount of traumatic experience for each individual. See the supplement for a detailed description of a full list of the items included in this measure (Appendix C).

2.3.2.6 Demographic characteristics

The following demographic characteristics of the sample are reported in Section 2.4.1 below: age, gender, ethnicity and household income and parental education.

These items are from the ABCD Parent Demographics Survey. Age at time of interview was collected in months and this was transformed to years. Carers were also asked about the sex of the young person at the young person, and were asked to check all of the races that they considered the young person to be. Additionally, carers were asked about the total combined family income for the past 12 months and the highest educational qualification they had received.

Household income and parental education were transformed using code provided by the NDA https://github.com/ABCD-STUDY/analysis-nda/blob/master/notebooks/general/core_demographics3.0.R

Similarly, ethnicity was transformed using code provided by the NDA https://github.com/ABCD-STUDY/analysis-nda/blob/master/notebooks/general/categorical_extension3.0.R. Whilst not included in the networks, any missing demographic data was imputed for descriptive purposes. See Chapter 3 and Chapter 4 for a description of the imputation process.

2.3.3 Statistical Analysis

2.3.3.1 Network Estimation

A Mixed Graphical Model (MGM) was fitted to the data, as it consisted of a combination of categorical and interval variables. This was done using R package *mgm*, version 1.2.7 (J. M. B. Haslbeck & Waldorp, 2020). It has been reported variables from within the same domain (such as symptoms, or environmental factors) have a tendency to cluster together, whilst the links between-domains is weaker (Santos Jr, Fried, Asafu-Adjei, & Ruiz, 2017; Isvoranu et al., 2017) this may lead to traditional networks missing between-domain links due to a lack of statistical power (Isvoranu et al., 2016). As such, an unregularised network was run, as recommended by Isvoranu et al. (2019) and Epskamp and Fried (2018). All analyses were conducted using R version 3.6.2 (RStudio Team, 2020) on a 64-bit Windows platform.

2.3.3.2 Network visualisation

In network models, the edges between two nodes denotes a partial correlation between the variables, after conditioning on the other variables in the network. Green

edges represent positive partial correlations, whilst red edges represent negative partial correlations. Interactions between categorical variables are represented in grey. Although the estimated network is undirected, it is weighted, as the strength of the edge is represented by the thickness of the edge, with wider edges signifying stronger correlations (Epskamp, Cramer, Waldorp, Schmittmann, & Borsboom, 2012). Networks were visualised using the R-package *qraph*, (Epskamp et al., 2012). The Fruchterman-Reingold algorithm was used, which plots nodes which are more highly correlated close to each other (Fruchterman & Reingold, 1991). The package *bootnet* (Epskamp, Borsboom, & Fried, 2018) was used to estimate the accuracy and stability of the network and centrality indices.

2.3.3.3 Centrality

A number of centrality metrics were estimated for each node. This included strength, betweenness, closeness and expected influence. Strength measures how strongly a node is directly connected to other nodes, using the sum of absolute weights of all edges of a node. Betweenness quantifies how often it lies on the shortest path between two other nodes, and closeness provides information on how many indirect connections there are from that node (Hevey, 2018). Expected influence is the sum of all edges of a node (Robinaugh, Millner, & McNally, 2016).

2.3.3.4 Network accuracy and stability

Bootstrapping was performed in order to examine the accuracy and stability of the estimated networks (Epskamp et al., 2018). First, the accuracy of the network was tested using non-parametric bootstrapping, a process which involves re-sampling subsets of the data in order to calculate a confidence interval (CI). This CI is the range of bootstrapped values from the different subsets. 2500 iterations were performed as in Epskamp et al. (2018). A smaller CI indicates a more precise estimation. The non-parametric bootstrap results include edge weight accuracy as well as testing for significant differences between edge weights.

The stability of the centrality indices were then tested using case-dropping bootstrapping (Epskamp et al., 2018). During this process the model is repeatedly estimated while dropping rows of the data. The correlation stability (CS) coefficient

quantifies the maximum number of cases which can be excluded to retain - with 95% certainty, a correlation of higher than 0.7 with the original centrality.

2.4 Results

2.4.1 Descriptive statistics

The initial sample size consisted of 11,878. Data from participants was excluded based on the following criteria: having a psychiatric diagnosis or taking psychiatric medication (N = 3404), not completing the Prodromal Questionnaire (N = 14), missing depressive symptoms (N = 49), missing information for cortical thickness (N = 103), missing cognitive data (N = 168) and missing trauma data (N = 197).

The final sample consisted of 7934 children. See Table 2.1 for a description of the demographic characteristics. See Appendix D for a description of the endorsement of individual PLEs and distress, as well as the distribution of number of PLEs in the overall sample at baseline. See Appendix D for a correlation matrix including all of the cognitive variables included in the network. In summary, the correlation matrix found that the following variables were strongly correlated: cortical thickness (range 0.53-0.80) and working memory and fluid intelligence (0.65). Working memory and receptive vocabulary were weakly correlated (0.34) and trauma was very weakly correlated to the other continuous measures (-0.04 to 0.02).

	Total (N = 7943)
Age (SD)	9.9 (0.62)
Sex N (%)	
Female	4041 (50.9%)
Household income (USD)	
<50k	1999(25.2%)
>=50k & <100k	2091 (26.4%)
>=100k	3182 (40.1%)
Parental education N (%)	
<HS diploma	506 (6.4%)
HS diploma/ GED	813 (10.2%)
Some college	2201 (27.7%)
Bachelor	2309 (29.1%)
Postgraduate degree	2106 (26.5%)
Ethnicity	
Asian	211 (2.7%)
Black	1182 (14.9%)
Other/mixed	1368 (17.2%)
White	5067 (63.8%)

Table 2.1: Demographic characteristics of participants (N=7934)

2.4.2 Network Estimation

2.4.2.1 Network Structure

The structure of the network is displayed in Figure 2.3. The Fruchterman-Reingold algorithm (Fruchterman & Reingold, 1991) was used for layout, which places highly correlated nodes near each other, and this shows that PLEs are therefore strongly inter-related. All nodes form part of the network, except for trauma. It was not possible to complete a sub-community detection analysis in this network as the graph was not fully connected. A sensitivity analysis was performed in which the network was estimated in all participants (including those with a psychiatric diagnosis or who had indicated they were taking psychiatric medication at baseline) and this can be seen in Appendix D.

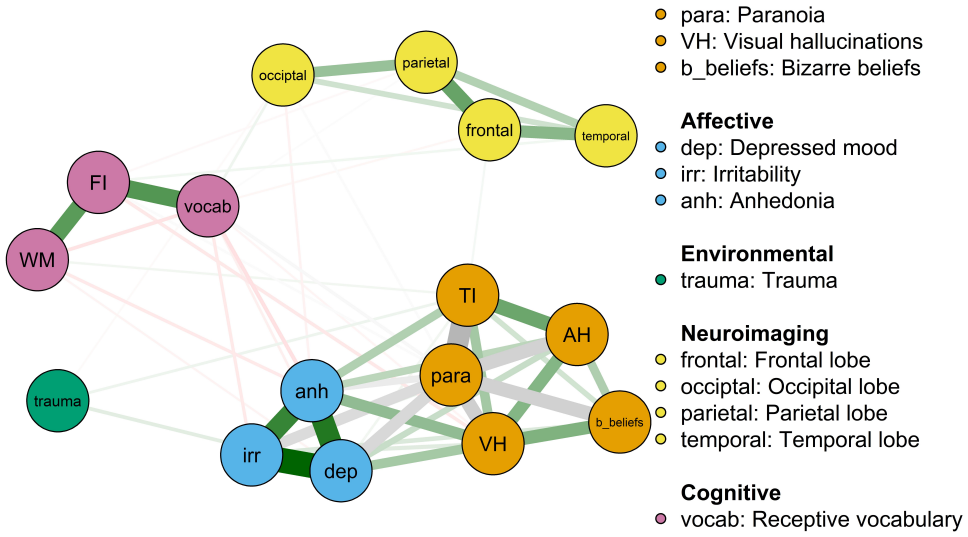


Figure 2.3: Network analysis results

Centrality Metrics

As seen in Figure 2.4 below, the most central and influential node was estimated to be paranoia. This was followed by affective symptoms, namely anhedonia and depressed mood. A table containing the full details of the centrality analyses can be found in Table 2.2.

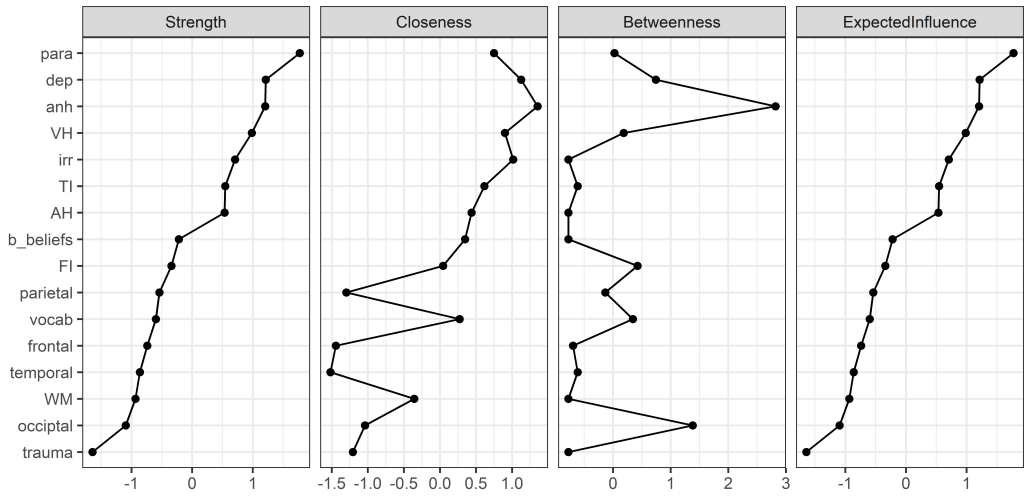


Figure 2.4: Centrality Metrics for network

	Centrality Metrics			
Node	*Betweeness*	*Closeness*	*Strength*	*Expected Influence*
Auditory Hallucination	-0.77	0.44	0.53	0.53
Thought insertion	-0.61	0.62	0.55	0.55
Paranoia	0.02	0.75	1.77	1.77
Visual hallucination	0.18	0.90	0.99	0.99
Bizarre beliefs	-0.77	0.35	-0.22	-0.22
Depressed mood	0.74	1.12	1.21	1.21
Irritability	-0.77	1.02	0.71	0.71
Anhedonia	2.82	1.35	1.21	1.21
Trauma	-0.77	-1.21	-1.64	-1.64
Frontal lobe CT	-0.69	-1.44	-0.74	-0.74
Occipital lobe CT	1.38	-1.04	-1.10	-1.10
Parietal lobe CT	-0.13	-1.30	-0.54	-0.54
Temporal lobe CT	-0.61	-1.52	-0.86	-0.86
Vocabulary	0.34	0.27	-0.60	-0.60
Working memory	-0.77	-0.36	-0.93	-0.93
Fluid inteligence	0.42	0.04	-0.34	-0.34

Table 2.2: Centrality Metrics

2.4.2.2 Reliability of Network Estimates for full network

The model was bootstrapped 2500 times as part of the stability analyses.

Confidence Intervals for edge-weights

As described previously, the edges between nodes have a weight. The 95% CIs around these edge weights can be calculated. The output of the bootstrap analysis can be seen below. The red line represents the edge weights, whereas the grey borders surrounding them are the range of the bootstrapped values. Wide confidence intervals represent low stability and overlapping confidence intervals indicate that the edge weights in question are not likely to significantly differ from one another. The edge-weights and their bootstrapped confidence intervals for edges between PLEs and each other variable and a figure displaying the differences between edge weights can be seen in Appendix D.

Stability of strength centrality metric

The stability of centrality estimates was calculated using case-dropping subset bootstrapping, which involves correlating the metrics from the full sample with metrics obtained after removing an increasing number of cases from the analysis.

The results of this can be seen in the figures below. Whilst the correlation stability coefficients for strength was good, the correlation stability coefficient for betweenness was not. Additionally, closeness did not show any variance and is not displayed in the plot as a result.

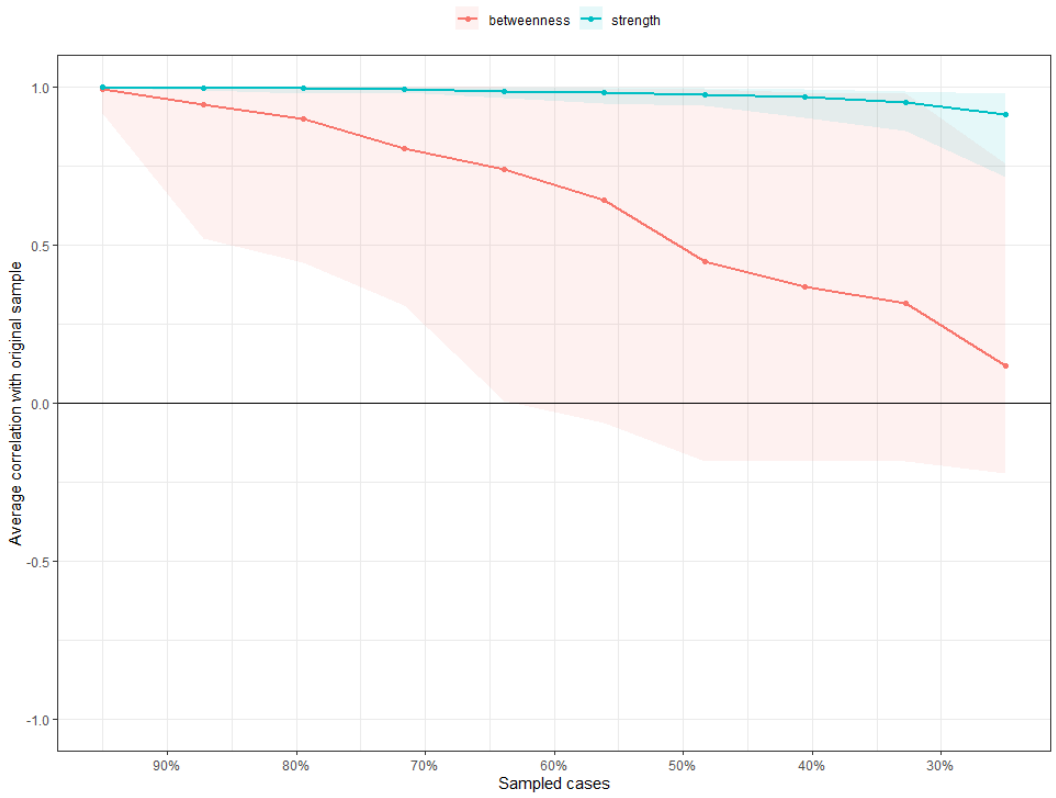


Figure 2.5: Case-drop subset bootstrapping

The results indicates that depressive symptoms are most strongly related to any PLE (paranoia) and are also associated with visual hallucinations and auditory hallucinations. Irritability and anhedonia are more weakly associated than the strongest association with depression but are associated with more nodes. Overall, it suggests that PLEs and affective symptoms are likely to be connected in a dense network that would facilitate cross activation through multiple paths.

2.5 Discussion

The present study outlines the first attempt to understand how key cognitive, environmental and neurocognitive factors relate to PLEs in nine to ten-year olds, which is a peak age for the expression of PLEs. The most central node in the network was paranoia. Depressed mood and anhedonia also scored highly on the centrality metrics, whilst trauma was isolated from the rest of the network. The results of the network analysis showed that PLEs tended to associate strongly and have more connections with each other and affective symptoms, rather than with the broader network. The second analysis examined the network structure when only including PLEs and depressive symptoms. These findings suggested that paranoia is the most central node in this network as well. The stability of the characteristics of the estimated networks varied, suggesting the inferences based on them may not be robust.

The present findings are consistent with previous research which has found that negative affect is associated with paranoia in both adolescents with mental health difficulties (Bird et al., 2017), as well as those from the general population (Bird et al., 2019). Existing models of psychosis have also postulated that negative affect plays a key role in the maintenance of psychosis (Garety et al., 2001; Freeman et al., 2002).

Although not an isolated node, trauma one of the less central variables included in the network. This is despite the fact that it has been found to be significant predictor of a range mental health disorders later in life (Humphreys et al., 2020; van Nierop et al., 2015), and some have argued that is has a particular role in the development of psychosis (Bloomfield et al., 2020). Upon first observation these results may appear inconsistent with Hardy, O'Driscoll, et al. (2020), which reported that post-traumatic stress symptoms were highly central in adult psychosis networks, and (Bird et al., 2021), a network analysis study which found evidence of a robust relationship between paranoia and trauma in young people with mental health difficulties. Nevertheless, there are numerous factors that may explain the non-central role of trauma in the estimated network reported here. Firstly, the method for assess-

ing paranoia varied from Bird et al. (2021), which had a more extensive (18-item) self-report measure. Secondly, only a small minority of the participants were reported to have experienced traumatic events and it may be that traumatic events later in development are more significant or the cumulative effects of later trauma have additive effects. However, this suggests that at a population level, traumatic events are unlikely to be strongly associated with PLEs at this age.

However, it is important to consider the possible impact of measurement issues on these findings. The ABCD used parent report to measure traumatic events and research has suggested that the reliance on a single method of identifying adverse and traumatic experience may bias reporting (Shaffer, Huston, & Egeland, 2008). Indeed, there is evidence of poor agreement between self- and professional- reports of traumatic events. Najman et al. (2020) found that most children who are registered as experiencing maltreatment by professionals subsequently self-report that they experienced little or no maltreatment, and that the majority of children who report experiencing severe maltreatment did not have maltreatment reported to the relevant protection agencies. This suggests that self and other reports of trauma in children may be measuring different phenomena. Notably, the ABCD trauma measure relies on parent report, and work on self-report of traumatic events in children of this age would need to be completed to establish the extent to which these overlap.

Finally, it is possible that there is a developmental effect where the influence of earlier trauma may depend on other modifying factors later in development. A recent meta-analysis by Pastore, de Girolamo, Tafuri, Tomasicchio, and Margari (2020) found a lack of support for the view that trauma alone is associated with conversion to psychosis. Instead, their findings indicated that the cumulative effect of childhood adversity combined with genetic liability for psychosis confers the highest risk for developing psychosis. Moreover, it has been found that multiple other post-incident stressors, including social support protects against the development of PTSD (Platt, Keyes, & Koenen, 2014), and it is possible that this equally applies to other forms of psychopathology that can be outcomes of traumatic events.

In this study, there was evidence of a weak association between receptive vocabulary and paranoia. This is despite the fact that individuals with a schizophrenia diagnosis have been found to display impairments in numerous cognitive tasks (Fioravanti et al., 2005), and these deficits emerge prior to diagnosis (Woodberry et al., 2008; Mollon & Reichenberg, 2018; Meier et al., 2014). To our knowledge, no studies to date have examined the association between paranoia and vocabulary in young people. Barnes et al. (2021) examined the relationship between distressing PLEs and vocabulary in clinically referred young people aged 8-18 and found that distressing PLEs had lower receptive language, however, they did not examine the association specifically with paranoia. Similarly, (Rammos et al., 2021), which used data from 8045 individuals from ALSPAC, found that individuals reporting persistent PLEs at ages 12, 18 and 24 consistently performed scored on their vocabulary task. Once again, this was not explored in relation to paranoia.

However, the present findings may reflect the fact that PLEs in late childhood are not inherently pathological, as they appear to spontaneously remit in most individuals (Linscott & Os, 2013). This may also explain the lack of centrality of the cortical thickness measures, despite there being some evidence of global cortical thickness reductions in psychosis (Jung et al., 2011; Crespo-Facorro et al., 2011). It also remains a possibility that there is a reverse causal pathway, whereby children and young people who exhibit deficits in cognitive functions such as language experience more victimisation, which may not initiate or have an important effect on psychopathology until later in development. Not only has victimisation been associated with risk of developing psychosis, but it has also been found to predict PLEs in late childhood (Arseneault et al., 2011) and adolescence (Catone et al., 2017). Moreover it has been reported that young people with developmental impairments are more likely to be exposed to trauma, and the association between neurodevelopmental impairments and PLEs has been found to be partially mediated by victimisation (Liu et al., 2021).

As stated earlier, whilst there has been a substantial increase in studies taking a network perspective (Contreras et al., 2019), only a few studies have attempted

to integrate variables from different levels of explanation (Isvoranu et al., 2020; Gaweda et al., 2021; Isvoranu et al., 2016; Fonseca-Pedrero et al., 2020). To our knowledge, the present study is the first to examine PLEs in late childhood. The ABCD study provides a unique opportunity to elucidate the mechanisms underlying the emergence of psychosis as it recruited participants aged 9 at baseline (Volkow et al., 2018), several years before the typical age of onset, and the present findings indicate that the syndromal relationship between common components and correlates of psychosis in adults does not appear to replicate in children aged 9-10. One explanation for this is that the unhelpful relationship between these components is likely to develop over time and that childhood PLEs do not just appear as a 'mini psychosis syndrome'. Other potential explanations will be explored below.

One of the main strengths of the present study is the large sample, which consisted of over 10,000 children. The ABCD study sought to recruit a diverse sample that is as representative of the socio-demographic variation of the US population as possible (Garavan et al., 2018), in line with a population neuroscience approach (Falk et al., 2013). Having a diverse sample is important as unfavourable socio-environmental conditions, such as holding an ethnic minority position has been reported as a risk factor for both psychotic symptoms and PLEs (Leaune et al., 2019). Future research can examine whether these networks are different in individuals who are in an ethnic minority position.

However, some limitations are important to bear in mind. Firstly, some of the centrality metrics were not stable. Moreover, whilst central nodes have been suggested to be particularly important in sustaining networks, implying that they may represent important treatment targets, provided edges reflect potential causal connections between nodes (McNally et al., 2015). Moreover, some simulation studies have argued that centrality may not necessarily identify the most important nodes in a network and are poor substitutes for causal inference (Dablander & Hinne, 2019). It has also been stated that they may not identify the most viable targets for intervention. (Fried et al., 2018). For instance, while PLE distress may represent a target for psychological interventions, we were unable to include this in the network due

to non-independence. Another noteworthy limitation is that between-domain links tends to be weaker and may be underestimated due to a lack of statistical power, when compared to variables from the same domain (Isvoranu et al., 2016). Whilst an unregularised network was performed in order to combat this, this may be a potential explanation for why the present study failed to replicate the relationship between common correlates and components which have been observed in adult psychosis. Moreover, as networks represent conditional independence relations, it is possible that the omission of variables may have impacted upon the results. It also remains possible that the networks may vary in different populations, thus future research should examine how demographic factors may affect the configuration of the networks.

Furthermore, the data used in the present study was cross-sectional as it was based on the data collected at baseline, which makes it difficult to draw causal inferences. Longitudinal analysis is required to characterise the developmental trajectories of PLEs and to examine the temporal stability of the networks. Nevertheless, the ABCD study is longitudinal, and all of the measures included in the network are obtained on an annual basis-with the exception of neuroimaging data, which is acquired biennially. Further research can therefore examine these networks over time, through performing the same analysis over subsequent time points and comparing the network structure between pairs of waves, as in Pappa et al. (2020). Alternatively, the network models can be generated from time-series data provided there are at least three waves of data available (Epskamp, 2020).

Another limitation is that the analysis did not include the amount of distress associated with the PLEs. The PQ-BC includes a second component in which respondents are asked about how much they are bothered by the experience. Although the prevalence of PLEs reduce with age, they remain relatively common in the adults (Linscott & Os, 2013), and not all individuals who experience persistent PLEs are distressed by them or have a "need for care" (van Os et al., 2009). Further research could incorporate distress into the networks, or examine whether the networks differ in individuals who feel distressed.

To conclude, the present study is the first to take a network approach towards PLEs in childhood and it found that the relationship between common correlates of psychosis in adults is absent at age 9-10. Only depressive symptoms were strongly associated with PLEs at this age, suggesting that the relationship with neurocognition and trauma develops over time. This in turn poses the question of whether the existence of a psychosis continuum can be applied to childhood and early adolescence, as PLEs at this developmental stage may be caused by different mechanisms.

Chapter 3

Study 2: Reward Processing and Psychotic-like Experiences in childhood

Study 2 in abridged form has been published as Harju-Seppänen, J., Irizar, H., Bramon, E., Blakemore, S.-J., Mason, L., Bell, V. (2021, December). Reward Processing in Children with Psychotic-like Experiences. Schizophrenia Bulletin Open, sgab054.

It can be accessed at: https://academic.oup.com/schizbullopen/article/3/1/sgab054/6451174

3.1 Abstract

Alterations to striatal reward pathways have been proposed as the final common pathway that generates psychotic symptoms and experiences through aberrant attribution of motivational salience, with both accumulated genetic risk and childhood adversity increasing the impact of stress on this reward pathway. Despite this, surprisingly few studies have examined whether children with psychotic-like experiences (PLEs) also exhibit these alterations, limiting our understanding of how differences in reward processing relate to hallucinations and delusional ideation in childhood, as well as providing little empirical data to substantiate the current developmental models of psychosis. Consequently, we examined whether PLEs and PLE-related distress were associated with reward-related activation in the striatum in 9-10 year olds. This included the ventral striatum (nucleus accumbens, NAcc) and dorsal striatum (caudate and putamen), regions which have consistently been implicated in reward processing, along with the emergence of psychosis. The sample consisted of children (N = 6,718) from the Adolescent Brain Cognitive Development (ABCD) study aged 9-10 years who completed the Monetary Incentive Delay (MID) task with functional MRI. We used robust mixed-effects linear regression models to investigate the relationship between PLEs (non-distressing and distressing versus control) and activation during the reward anticipation and reward outcome stages of the MID task. Analyses were adjusted for gender, household income, ethnicity, depressive symptoms, movement in the scanner, pubertal development, scanner ID, subject and family ID. We performed several additional analyses to investigate the association between PLEs and reward processing: firstly, we used a quantitative measure of PLEs and associated distress as a predictor (rather than PLEs as a categorical variable), secondly, we performed a series of sensitivity analyses where we examined the association between PLEs and reward processing in all individuals, and also only in individuals with a psychiatric diagnosis. There was no reliable association between PLEs and alterations to anticipation-related or outcome-related striatal reward processing in the NAcc, caudate or putamen. We discuss the implications for developmental models of psychosis and suggest an al-

ternative “developmental delay” model of how PLEs may arise at this early stage of development.

3.2 Introduction

Psychotic-like experiences (PLEs) include delusion-like beliefs and hallucinations that remain below the threshold for psychotic disorder. PLEs are relatively common in childhood (Linscott & Os, 2013) with a median prevalence of 17% among children aged 9–12 years and 7.5% among those aged 13–18 years (Kelleher, Connor, et al., 2012). Even during childhood, however, they are a predictor of later transition to psychosis (Fisher et al., 2013; Healy et al., 2019; Poulton et al., 2000) and poor physical and mental health outcomes across the lifespan (Davies et al., 2018; Healy et al., 2019; Trotta et al., 2020; Kelleher, Connor, et al., 2012). Nonetheless, it is unclear how childhood PLEs relate to established neurocognitive mechanisms for adult psychosis.

One hypothesis is that both adult and childhood PLEs are associated with altered striatal dopamine (Macmanus et al., 2012). The importance of dopamine in the pathophysiology of psychosis was first proposed five decades ago, based on multiple indirect lines of evidence. Note, this theory has also been referred to as the "mesolimbic theory" in the literature (McCutcheon, Beck, Jauhar, & Howes, 2018), and in its first iteration, it proposed that schizophrenia develops due to overactive striatal dopamine systems (van Rossum, 1966). Meltzer and Stahl (1976) conducted one of the early reviews on the dopamine hypothesis. Even then, it was known that dopamine is not present uniformly across the brain, and that there are a number of pathways. Meltzer and Stahl (1976) stated that the dopamine hypothesis was supported by the following observations: 1) lesions to the limbic system in animals was found to lead to an impairment of their ability to filter out stimuli and was also associated with disturbances in behaviour (Smythies & Adey, 1966) 2) electrical stimulation of the dorsal hippocampus (which forms part of the outflow of the limbic striatum) has been associated with disruptions to thinking, as well as hallucinations (Horowitz & Adams, 1970) and 3) stimulation or ablation of the limbic system in humans had been shown to induce paranoia, perceptual distortion and impact mood (Torrey & Peterson, 1974). It was also based on amphetamine models, as these pharmacological agents primarily impact dopamine. Amphetamine-induced psy-

chosis was first described in Young and Scoville (1938), and a 42-case monograph was subsequently published by Connell (1958) in which amphetamine-induced psychosis was recognised as a potential consequence of chronic amphetamine use.

The dopamine hypothesis has since been revised. Howes and Kapur (2009) provided a summary of the evolution of the dopamine hypothesis, which they describe as having two main prior incarnations. Howes and Kapur (2009) then proposed "The Dopamine Hypothesis of Schizophrenia: Version III and this has been the predominant framework since. The second version of the hypothesis was described in a landmark paper by Davis, Kahn, Ko, and Davidson (1991). This paper argued that the existing findings were not compatible with the simple excess dopaminergic neurotransmission proposal of Version I. Rather, they argued that the negative symptoms of schizophrenia occurred due to frontal hypodopaminergia, whilst positive symptoms were hypothesised to be the result of striatal hyperdopaminergia. Version III of the dopamine hypothesis (Howes & Kapur, 2009) attempted to integrate the concept of aberrant salience– a process where typically innocuous experiences are assigned heightened motivational significance – with the dopaminergic abnormalities observed in schizophrenia, along with its clinical presentation for the first time (Howes & Kapur, 2009; Howes & Murray, 2014). They referred to literature indicating that dopamine plays a role in motivational incentive salience. One extension of the dopamine hypothesis (Kapur, 2003; Kapur, Mizrahi, & Li, 2005) argues that the abnormal firing of dopamine neurons and the abnormal release of dopamine causes an aberrant assignment of salience to innocuous stimuli. Based on this, they argue that psychotic symptoms, particularly delusions and hallucinations, appear over time as the individual's attempt to explain the experience of aberrant salience.

The dopamine hypothesis has subsequently been referred to as the Developmental Risk Factor Model (Murray et al., 2017), recognising the impact of environmental and neurodevelopmental risk on the development of psychosis. In this current model, dysregulated striatal dopamine is proposed as a final common pathway where genetic risk and developmental adversity converge and lead to psychosis

via the generation of aberrant salience (Howes & Kapur, 2009; Murray et al., 2017). Indeed, neuroimaging studies on reward processing in psychosis risk states and prodromal periods indicate that dysregulation of striatal dopamine is detectable before the onset of frank psychotic disorder (reviewed in Howes, Hird, Adams, Corlett, & McGuire, 2020). Whilst there is a substantial amount of literature exploring reward processing in individuals deemed "ultra-high risk", there is a paucity of studies examining reward processing in those earlier on in development. Examining reward processing in individuals with PLEs provides an opportunity to study larger samples without confounds introduced by anti-psychotic medication.

Initial evidence suggests that there is an earlier association between dysregulated striatal reward processing and psychotic-like experiences in 14-19 year-old adolescents (Papanastasiou et al., 2018). However, it is still not clear if the same mechanism of altered striatal reward processing that predicts psychosis and psychosis-risk in older individuals would necessarily explain the presentation of PLEs at a younger age. This is important because childhood is a crucial point of risk divergence for PLEs. An estimated 75–90% of psychotic experiences during childhood and adolescence are transitory (Rubio, Sanjuán, Flórez-Salamanca, & Cuesta, 2012; van Os et al., 2009) but those whose PLEs do not resolve have particularly poor outcomes (Calkins et al., 2017; Downs et al., 2013) with distress related to PLEs at age 12 adding predictive value for poor outcome later in life (Sullivan et al., 2020). However, PLEs at ages 8-15 years show a weaker relationship with later poor outcome than PLEs at ages 16 and over, despite a greater prevalence at this earlier age (Schimmelmann, Michel, Martz-Irngartinger, Linder, & Schultze-Lutter, 2015), suggesting that they may emerge due to a different mechanism from PLEs in later adolescence. Consequently, understanding whether dysregulated reward processing is associated with PLEs and PLE-related distress during earlier childhood could provide important evidence to understand to what extent these experiences reflect an early disruption to a key causal mechanism present in later psychosis. The aim of the current study was therefore to examine whether PLEs and PLE-related distress in childhood is associated with alterations to striatal reward processing.

Reward processing is multifaceted, consisting of two separate functions of the reward system which dissociate, namely reward anticipation and reward outcome (Schultz, 2002). The Monetary Incentive Delay (MID) task was designed to distinguish these functions when used in functional magnetic imaging studies (fMRI) studies (Knutson, Westdorp, Kaiser, & Hommer, 2000). It has been used extensively in psychosis research and a meta-analysis of relevant fMRI studies provide strong evidence for ventral striatal reward system dysregulation in adults with psychosis (Radua et al., 2015). Additional studies have also found evidence for these alterations in antipsychotic naive patients with schizophrenia (Nielsen et al., 2012), and in adults with PLEs (Wotruba et al., 2014). Evidence from concurrent fMRI and positron emission tomography (PET) indicates that changes to dopamine transport underlie changes in fMRI reward system-related activation during the MID task (Dubol et al., 2018), suggesting that fMRI studies of the MID task are a reliable proxy for alterations to reward-related dopamine function. Studies with children indicate that the paradigm is valid for measuring reward processing in this age group (Dougherty et al., 2018). The majority of the literature on reward processing in individuals with psychosis or PLEs focuses on the ventral striatum (and specifically the nucleus accumbens, NAcc) as there is evidence that they are the principal targets of dopamine neurons (Ikemoto & Panksepp, 1999). However, a recent meta-analysis of imaging studies suggested that the dorsal, rather than ventral striatum may be the most common site of atypical activation in studies of the reward system in psychosis (McCutcheon et al., 2018).

A major limitation of existing fMRI studies has been small sample sizes and lack of representative sampling, especially in children and young adolescents (Turner, Paul, Miller, & Barbey, 2018) and this has been cited as a particular issue for neuroimaging studies of children (Herting, Gautam, Chen, Mezher, & Vetter, 2018). Here, we availed of a very large representative sample (N= 6,900+) of 9-10 year olds from the Adolescent Brain Cognitive (ABCD) study (Garavan et al., 2018), to test whether PLEs or PLE-related distress was associated with dysregulated reward-processing in the left and right NAcc, caudate and putamen during

childhood by examining the association between activation during the fMRI MID task in a large (N=6,900+) sample of 9–10-year-olds, who were part of the ABCD study (Garavan et al., 2018).

Specifically, we tested whether PLEs or PLE-related distress could be explained by dysregulated ventral and dorsal striatal reward processing during the fMRI Monetary Incentive Delay Task. We tested for associations of PLEs, both with anticipation-related and with outcome-related reward processing, while controlling for potential confounders. Analyses were first performed in the left and right NAcc (to examine ventral striatal reward processing) and were then repeated for the caudate and putamen (to examine dorsal striatal reward processing).

3.3 Methods

3.3.1 Sample

The ABCD dataset (release 3.0; https://abcdstudy.org/) includes 11,878 children aged 9-10 years (Volkow et al., 2018). This is a longitudinal dataset being collected at 21 sites across the US. Full details of recruitment are described in (Garavan et al., 2018). Institutional review board approval was obtained for each site before data collection and all parents provided written informed consent in addition to assent from the participants (Clark et al., 2018). See the supplement for a detailed description of the full sample (Appendix A).

Data from participants was excluded based on the following criteria: having a psychiatric diagnosis (N = 1973), not completing the Prodromal Questionnaire (N = 12), taking psychotropic medication (N = 1032), not completing the MID task in the scanner (N = 1030), insufficient performance on the task (N= 573), missing motion data (N = 455), missing fMRI data (N = 27). Individuals whose reward-related activation was more than three standard deviations from the mean in the relevant region were then excluded on the basis of being identified as outliers. This left N = 6,718 who contributed to either the final anticipation or outcome analysis for the NAcc analysis (N = 223 were excluded for reward anticipation; N = 123 for reward outcome). For the caudate analysis, 6686 contributed to either the final anticipation

or outcome analysis (outliers were N = 384 for reward anticipation and N = 230 for reward outcome). 6683 contributed to either the final anticipation or outcome analysis for the putamen (outliers were N = 398 for reward anticipation and N = 237 for reward outcome). The ABCD data repository grows and changes over time. The ABCD data used in this report came from doi: 10.15154/1521353. DOIs can be found at https://doi.org.

3.3.2 Measures

3.3.2.1 Psychotic-like experiences

Psychotic-like experiences (PLEs) were measured using the Prodromal Questionnaire – Brief Child Version (PQ-BC), a modified version of the Prodromal Questionnaire Brief Version (PQ-B) (Loewy et al., 2011) – a self-report measure for psychosis risk syndromes that has been validated in nine to ten year olds (Karcher et al., 2018). Unlike the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-5), also available in the ABCD dataset, the PQ-BC allows for measurement of PLEs alongside a measure of distress for the same items. The PQ-BC is a 21-item questionnaire that measures unusual perceptions and sensations, ideas of reference, affective changes, unusual beliefs, or abnormally suspicious thoughts, along with associated distress. The PQ-BC consists of two parts: the first asks whether the individual has had any of the listed psychotic-like thoughts, feelings and experiences, with an overall score ranging from 0-21. If they answer yes, participants also indicate how distressing the experience was in the second part of the questionnaire (from 1-5).

A subset of six items were selected to identify young people with PLEs. These were *"Did you hear strange sounds that you never noticed before like banging, clicking, hissing, clapping, or ringing in your ears?"* (auditory hallucination), *"Did you feel that someone else, who is not you, has taken control over the private, personal, thoughts or ideas inside your head?"* (thought insertion), *"Did you suddenly feel that you could not trust other people because they seemed to be watching you or talking about you in an unfriendly way?"* (paranoia), *"Did you honestly believe in things that other people would say are unusual or weird?"* (bizarre beliefs), *"Did*

you feel that other people might want something bad to happen to you or that you could not trust other people?" (paranoia) and *"Did you suddenly start to be able to see things that other people could not see or they did not seem to see?"* (visual hallucination). PLE types were derived from this variable, where participants were categorised as having no PLEs, non-distressing PLEs, or distressing PLEs. This was based on a) endorsement of the PLE item and b) if the young person reported whether there was any distress associated with the PLE. Additional analyses used total sum of PLEs and PLE-related distress. See Appendix B for a full list of the items in the PQ-BC.

3.3.2.2 Demographic characteristics

The following demographic characteristics of the sample are reported in Section 3.4 below: age, gender, ethnicity and household income and parental education. This has been reported for the overall sample as well as separately for the different PLE groups (no PLEs, distressing PLEs and non-distressing PLEs). The demographic items are from the ABCD Parent Demographics Survey. Age at time of interview was collected in months and this was transformed to years. Carers were also asked about the sex of the young person at the young person, and were asked to check all of the races that they considered the young person to be. Additionally, carers were asked about the total combined family income for the past 12 months and the highest educational qualification they had received.

Household income and parental education were transformed using code provided by the NDA https://github.com/ABCD-STUDY/analysis-nda/blob/master/notebooks/general/core_demographics3.0.R

Similarly, ethnicity was transformed using code provided by the NDA https://github.com/ABCD-STUDY/analysis-nda/blob/master/notebooks/general/categorical_extension3.0.R.

3.3.2.3 Monetary Incentive Delay task

The Monetary Incentive Delay (MID) task (Knutson et al., 2000) measures the anticipation and receipt of rewards and losses. Participants are presented with an in-

centive cue (2000ms) at the beginning of each trial (Win $5, Win $0.20, Lose $0.20, Lose $5 or $0-no money at stake), followed by a jittered anticipation event (lasting 1500- 4000ms). Participants then need to respond to a variable target (150-500ms), in order to either win or avoid losing money. In the ABCD study, participants are presented with 40 reward (20 small reward, 20 large reward) and 40 loss anticipation trials (20 small loss, 20 large loss), 20 no money anticipation trials, and feedback trials (Casey et al., 2018). The task was individualised with the initial duration of the response target drawn from a practice session completed by the participant prior to entering the scanner. In order to reach a 60% accuracy rate, task difficulty was adjusted during the task after every third incentivised trial based on the overall accuracy rate of the previous six trials. The target duration was shortened if the individual's accuracy falls below the target accuracy level. Participants who did not reach acceptable performance in the task were excluded from analysis (indexed by whether all trial types resulted in more than three events for both positive and negative feedback), as well as those whose regional activity was above or below three standard deviations. The MID task has been previously validated in typically developing children during fMRI (Cao et al., 2019) and validation studies for the paradigm and data used in this study have been previously conducted by Casey et al. (2018) and Chaarani et al. (2021). Casey et al. (2018) reported that the experimental manipulation was successful in maintaining hit rates at close to 60%, and that reaction times and payoff amounts were consistent across experimental runs. Chaarani et al. (2021) reported that the task is associated with robust brain activations which are consistent with the extant literature.

3.3.2.4 Imaging acquisition

The first outcome was reward-related activation during the MID task from the left and right NAcc. The second outcome was reward-related activation in the left and right caudate and putamen. Full details on imaging acquisition are provided in Casey et al. (2018). Imaging data was collected across sites using 3 Tesla systems and multi-channel coils and multiband echo planar imaging acquisition. Scanning

included a fixed order of localiser, T1- and T2-weighted images, resting state, and diffusion-weighted imaging. Three tasks (MID task, stop signal, and emotional n-back) were completed in an order randomised across participants. Blood-oxygen-level-dependent (BOLD) images were acquired using gradient EPI with standardised acquisition parameters.

3.3.2.5 Imaging processing and analysis

The ABCD Data Analysis and Informatics Center performed centralised processing and analysis of the imaging data. Full information regarding this is detailed in Hagler et al. (2019), and is summarised here. Left and right NAcc, caudate and putamen regions of interest were derived from subcortical segmentation using FreeSurfer 5.3.0 (Fischl, 2012). Estimated task-related activation were computed for individual subjects using the general linear model in AFNI 3dDeconvolve and were available as contrast beta weights. The contrasts used in this study were "large reward vs. no money" and "small reward vs. no money" for reward anticipation activity, and "all reward positive vs. negative feedback" for reward outcome activity. For these contrasts, region of interest average beta coefficients were computed for each of the two runs and then averaged. The average for the relevant ROI was used as the outcome for all analyses.

3.3.3 Statistical analysis

We conducted analyses to investigate the association between PLEs, presence of non-distressing PLEs, presence of distressing PLEs, and reward-related activation using multi-level regression analyses. Each analysis was conducted and reported separately for two outcomes: left and right hemisphere activation during the reward anticipation stage of the MID task, and left and right hemisphere activation during the reward outcome stage of the MID task. We tested for evidence of heteroscedasticity in the data, and due to its presence, estimated the effects of the predictor variables using robust mixed effects linear regression models (Koller, 2016).

For the main analyses, we initially tested for a minimally adjusted association

between PLE type and reward-related activation, adjusted only for the random effects covariates (scanner ID, and subject ID nested within family ID) and motion in scanner. We then subsequently updated the model to include additional fixed effect covariates to test the association after adjustment for potential confounders. These included sex, household income, parental education, ethnicity, depressive symptoms and pubertal development. Only the minimally adjusted analyses were performed in the subset analysis of individuals with a psychiatric diagnosis.

Sex, household income, parental education, and ethnicity were included as covariates in all models owing to their association with psychosis risk (Jongsma et al., 2021; D. Murphy, Vallières, Murphy, McElroy, & Hyland, 2020). Depression was included as a potential confounder due to its association with alterations in reward processing (Keren et al., 2018). Pubertal development was included as a potential confounder due to associations between reward processing and puberty (Ladouceur et al., 2019). Motion in scanner was included due to its known role as a confounder in fMRI activation studies.

Missing data for the covariates was imputed through multiple imputation using the *Mice* package in R (Buuren & Groothuis-Oudshoorn, 2011). This was done separately for females and males, due to sex-specific items in the PDS. Polytomous regression was used for unordered factor variables. Proportional odds model was used for ordered factor variables. Logistic regression imputation was used for binary variables.

We subsequently repeated the main analyses but included all individuals with psychiatric diagnoses and medication known to have significant impact on reward processing (stimulants and anti-psychotics). We also completed alternative analyses where PLEs were included as sum total, along with their associated distress. Finally, we performed analyses only in individuals with a psychiatric diagnosis or who indicated they were taking psychiatric medication, and also repeated the main analyses in the dorsal striatum for reward anticipation and reward outcome. Separate analyses were conducted for NAcc, caudate and putamen.

All analyses were conducted in R (version 3.6.2) using the *robustlmm* pack-

age (Koller, 2016). The data was transformed into long format using *reshape* (Wickham, 2007) to allow us to test for multivariate outcomes. All analysis code and analysis output for this study has been made freely available on an Open Science Framework archive:

https://osf.io/vqzhu/

3.4 Results

After applying our exclusion criteria, comparable numbers of participants remained for the NAcc analyses (N = 6553 for reward anticipation and N = 6654 for reward outcome), caudate analysis (N = 6392 for reward anticipation and N = 6546 for reward outcome) and putamen analyses (N = 6378 for reward anticipation and N = 6539 for reward outcome). The demographic characteristics of the sample are shown in Table 3.1 and describes the individuals who contributed to either the NAcc, caudate or putamen analysis (N = 6718).

	Total (*N = 6718*)	*No PLEs* (*N = 4025*)	*Non-distressing PLEs* (*N = 833*)	*Distressing PLEs* (*N = 1860*)
Age (SD)	9.9 (0.62)		9.9 (0.62)	9.9 (0.62)
Gender N (%)				
Female	3494 (52.0%)	2107 (52.3%)	386 (46.3%)	1001 (53.8%)
Household income (USD)				
<50k	1872 (27.9%)	984 (24.4%)	236 (28.3%)	652 (35.1%)
>=50k & <100k	1866 (27.8%)	1090 (27.1%)	237 (28.4%)	539 (29.0%)
>=100k	2980 (44.4%)	1951 (48.5%)	360 (43.2%)	669 (36.0%)
Parental education N (%)				
<HS diploma	398 (5.9%)	181 (4.5%)	49 (5.9%)	168 (9.0%)
HS diploma/ GED	641 (9.5%)	347 (8.6%)	76 (9.1%)	218 (11.7%)
Some college	1847 (27.5%)	989 (24.6%)	262 (31.5%)	596 (32.0%)
Bachelor	2002 (29.8%)	1276 (31.7%)	230 (27.6%)	496 (26.7%)
Postgraduate degree	1830 (27.2%)	1232 (30.6%)	216 (25.9%)	382 (20.5%)
Ethnicity				
Asian	172 (2.6%)	114 (2.8%)	22 (2.6%)	36 (1.9%)
Black	886 (13.2%)	437 (10.9%)	124 (14.9%)	325 (17.5%)
Other/mixed	1193 (17.8%)	647 (16.1%)	166 (19.9%)	380 (20.4%)
White	4467 (66.5%)	2827 (70.2%)	521 (62.5%)	1119 (60.2%)

Table 3.1: Demographic characteristics of participants who contributed to either the reward anticipation or outcome analysis for the NAcc, caudate or putamen (N= 6718)

3.4.1 Ventral Striatum

3.4.1.1 Effect of PLEs and distress on reward anticipation

As can be seen from Table 3.2 and Table 3.3, there were main effects of reward magnitude and laterality on reward anticipation activity, indicating the validity of the paradigm, even after adjustment for potential confounders. However, there was no association with non-distressing or distressing PLEs in either analysis. Effects of PLE type on NAcc activation for reward anticipation are displayed by left and right laterality in Figure 3.1.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.001	-0.015, 0.013	0.923
Distressing PLEs	-0.005	-0.016, 0.005	0.329
Laterality (Right NAcc >Left NAcc)	-0.012	-0.017, -0.008	<0.001
Reward magnitude (Large Reward >Small Reward)	0.072	0.068, 0.077	<0.001
Motion	-0.040	-0.060, -0.020	<0.001

Table 3.2: Minimally adjusted regression model (N = 6553) examining the effect of presence and type of PLEs, reward magnitude and laterality on nucleus accumbens (NAcc) response to reward anticipation

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.0005	-0.014, 0.015	0.949
Distressing PLEs	-0.002	-0.012, 0.009	0.755
Laterality (Right NAcc >Left NAcc)	-0.012	-0.017, -0.008	<0.001
Reward magnitude	-0.072	-0.077, -0.068	<0.001
Gender	0.001	-0.009, 0.010	0.912
Depressive symptoms	-0.005	-0.019, 0.009	0.461
Household income [<50K]	-0.001	-0.015, 0.013	0.856
Household income [>=50K & <100K]	-0.001	-0.013, 0.010	0.798
Parental education - <HS Diploma	-0.023	-0.046, -0.0001	0.049
Parental education - HS Diploma/GED	-0.025	-0.044, -0.007	0.007
Parental education - Post Graduate Degree	-0.007	-0.019, 0.005	0.231
Parental education - Some College	0.002	-0.015, 0.011	0.755
Race - Asian	-0.020	-0.049, 0.008	0.162
Race - Black	-0.003	-0.018, 0.012	0.698
Race - Other	-0.005	-0.017, 0.008	0.464
Motion	-0.036	-0.057, -0.016	<0.001
Pubertal development	-0.005	-0.015, 0.005	0.338

Table 3.3: Fully adjusted regression model (N = 6553) examining the effect of presence and type of PLEs, reward magnitude and laterality on nucleus accumbens (NAcc) response to reward anticipation

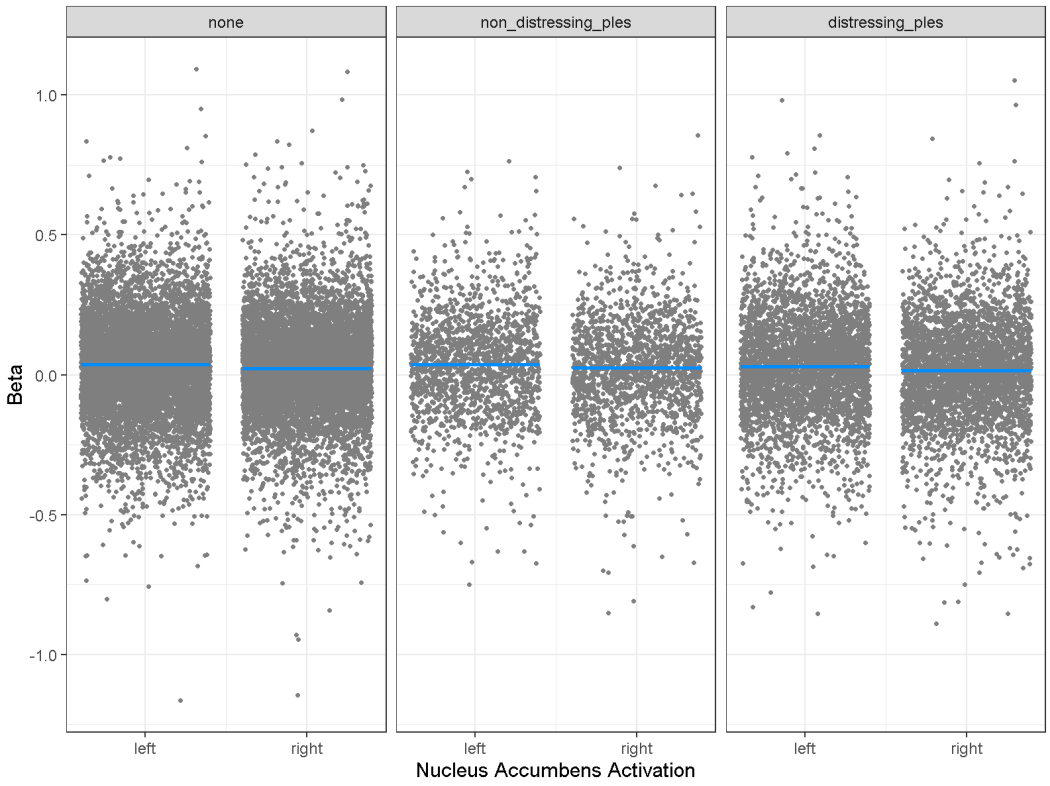


Figure 3.1: Relationship between PLE group status on left and right nucleus accumbens activation in the reward-anticipation component of the Monetary Incentive Delay task

3.4.1.2 Effect of PLEs and distress on reward outcome

As shown in Table 3.4 and Table 3.5, there were main effects of NAcc laterality on reward anticipation activity, even after adjustment for potential confounders, but no association with non-distressing or distressing PLEs in either analysis. Effects of PLE type on NAcc activation for reward outcome are displayed by left and right laterality in Figure 3.2.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.005	-0.022, 0.012	0.571
Distressing PLEs	-0.009	-0.021, 0.004	0.183
Laterality (Right NAcc >Left Nacc)	-0.025	-0.030, -0.021	<0.001
Motion	0.075	0.052, 0.097	<0.001

Table 3.4: Minimally adjusted regression model (N = 6654) on association between types of PLEs, distress, laterality on nucleus accumbens (NAcc) response to reward outcome.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.005	-0.022, 0.012	0.553
Distressing PLEs	-0.008	-0.021, 0.005	0.213
Laterality (Right NAcc >Left NAcc)	-0.025	-0.030, -0.021	<0.001
Gender	0.008	-0.003, 0.019	0.132
Depressive symptoms	0.009	-0.007, 0.026	0.265
Household income [<50K]	0.002	-0.015, 0.019	0.812
Household income [>=50K & <100K]	-0.00002	-0.013, 0.014	0.981
Parental education - <HS Diploma	-0.009	-0.037, 0.018	0.512
Parental education - HS Diploma/GED	-0.006	-0.029, 0.016	0.569
Parental education - Post Graduate Degree	-0.006	-0.021, 0.008	0.415
Parental education - Some College	-0.002	-0.017, 0.014	0.831
Race - Asian	0.022	-0.013, 0.058	0.212
Race - Black	-0.025	-0.044, -0.007	0.007
Race - Other	-0.012	-0.027, 0.003	0.127
Motion	0.075	0.052, 0.098	<0.001
Pubertal development	0.002	-0.011, 0.014	0.806

Table 3.5: Fully adjusted regression model (N = 6654) on association between types of PLEs, distress, laterality on nucleus accumbens (NAcc) response to reward outcome.

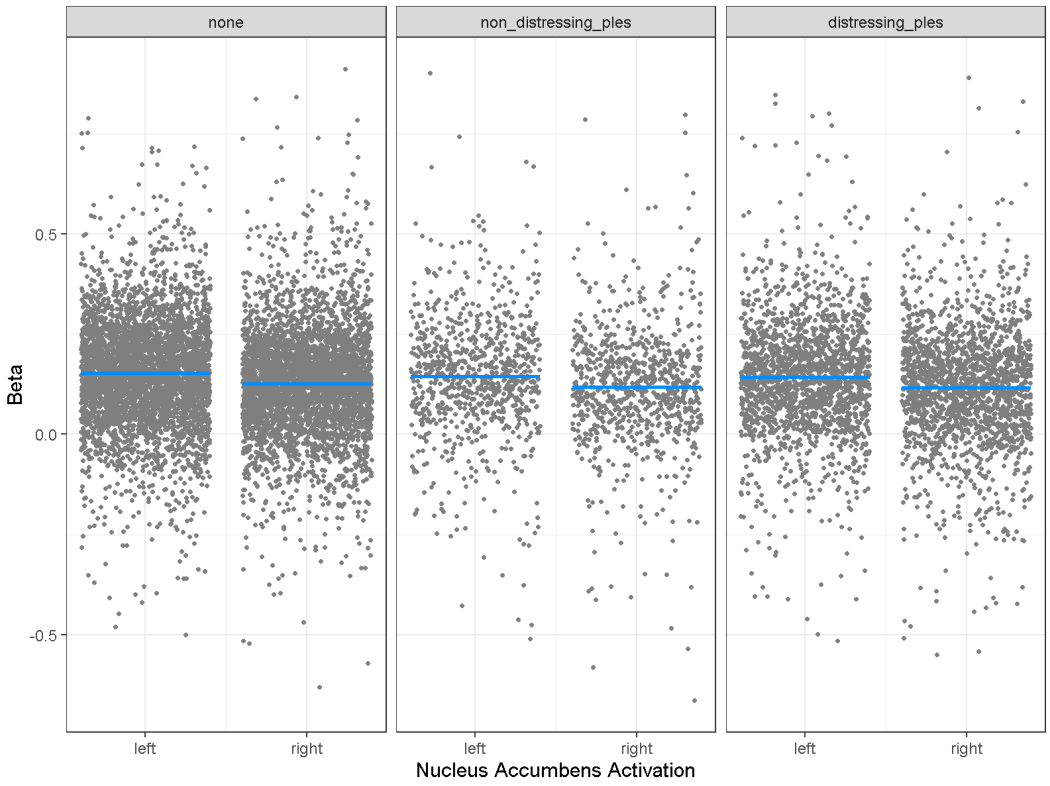


Figure 3.2: Relationship between PLE group status on left and right nucleus accumbens activation in the reward-outcome component of the MID task

3.4.1.3 Effect of total number of PLEs and PLE-related distress on reward anticipation and outcome

We also completed additional analysis examining the effect of PLEs and PLE-related distress by coding them as sum total variables: total number of PLEs and total levels of PLE-related distress. Total number of PLEs was not related to anticipation-related reward activation (β = 0.001, 95% CI = -0.006, 0.007, p = 0.825, see Table 3.6) or reward outcome-related reward activation (β <0.001, 95% CI = -0.008, 0.008, p = 0.973, see Table 3.7) in minimally adjusted analyses. This pattern of relationships remained unchanged in the fully adjusted analyses (see Table 3.8 and Table 3.9).

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	0.001	-0.006, 0.007	0.825
Laterality (Right NAcc >Left NAcc)	-0.012	-0.017, -0.008	<0.001
Total distress	-0.002	-0.005, 0.0002	0.075
Reward magnitude (Large Reward >Small Reward)	0.072	0.068, 0.077	<0.001
Motion	-0.039	-0.059, -0.019	<0.001

Table 3.6: Minimally adjusted regression model (N = 6553) on association between number of PLEs and total distress, reward magnitude and laterality on nucleus accumbens (NAcc) response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	0.001	-0.005, 0.008	0.718
Laterality (Right NAcc >Left NAcc)	-0.012	-0.017, -0.008	<0.001
Total distress	-0.002	-0.005, 0.001	0.119
Reward magnitude (Large Reward >Small Reward)	-0.072	-0.077, -0.068	<0.001
Gender	0.0001	-0.009, 0.009	0.977
Depressive symptoms	-0.003	-0.017, 0.012	0.727
Household income [<50K]	-0.001	-0.015, 0.013	0.882
Household income [>=50K & <100K]	-0.001	-0.012, 0.010	0.842
Parental education - <HS Diploma	-0.022	-0.045, 0.001	0.056
Parental education - HS Diploma/GED	-0.025	-0.043, -0.007	0.008
Parental education - Post Graduate Degree	-0.008	-0.020, 0.004	0.212
Parental education - Some College	-0.002	-0.015, 0.011	0.777
Race - Asian	-0.021	-0.049, 0.008	0.153
Race - Black	-0.002	-0.017, 0.013	0.775
Race - Other/Mixed	-0.004	-0.017, 0.008	0.499
Motion	-0.036	-0.056, -0.016	<0.001
Pubertal development	-0.004	-0.015, 0.006	0.404

Table 3.7: Fully adjusted regression model (N = 6553) on association between number of PLEs and total distress, reward magnitude and laterality on nucleus accumbens (NAcc) response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	0.0001	-0.008, 0.008	0.973
Laterality (Right NAcc >Left NAcc)	-0.025	-0.030, -0.021	<0.001
Total distress	-0.001	-0.005, 0.002	0.421
Motion	0.074	0.052, 0.097	<0.001

Table 3.8: Minimally adjusted regression model (N = 6554) on association between number of PLEs, total distress and laterality on nucleus accumbens (NAcc) response to reward outcome.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	-0.0005	-0.008, 0.007	0.908
Laterality (Right NAcc >Left NAcc)	-0.025	-0.030, -0.021	<0.001
Total distress	-0.001	-0.004, 0.002	0.546
Gender	0.008	-0.003, 0.019	0.143
Depressive symptoms	0.010	-0.007, 0.026	0.255
Household income [<50K]	0.002	-0.015, 0.019	0.806
Household income [>=50K & <100K]	0.0002	-0.013, 0.014	0.976
Parental education-<HS Diploma	-0.010	-0.037, 0.018	0.492
Parental education-HS Diploma/GED	-0.006	-0.029, 0.016	0.569
Parental education - Post Graduate Degree	-0.006	-0.020, 0.009	0.423
Parental education - Some College	-0.002	-0.017, 0.013	0.803
Race - Asian	0.022	-0.013, 0.058	0.214
Race - Black	-0.025	-0.043, -0.007	0.008
Race - Other/Mixed	-0.012	-0.027, 0.003	0.127
Motion	0.075	0.052, 0.098	<0.001
Pubertal development	0.002	-0.011, 0.014	0.808

Table 3.9: Fully adjusted regression model (N = 6554) on association between number of PLEs, total distress and laterality on nucleus accumbens (NAcc) response to reward outcome.

3.4.1.4 Effect of PLEs on reward processing when including individuals with a psychiatric diagnosis or psychiatric medication use

In addition, we completed sensitivity analyses that included all individuals, including those with a psychiatric diagnosis or medication use. The pattern of results was similar across analyses with regard to PLEs. The only exception was that non-distressing PLEs were significantly associated with striatal activation in the minimally adjusted reward anticipation analysis (β = -0.011, 95% CI = -0.020, -0.002, p = 0.013). However, this relationship became non-significant in the fully adjusted analysis (β = -0.010, 95% CI = 0.0184, 0.0001, p = 0.053). See Tables 6.7-6.10 in Appendix E.

3.4.1.5 Effect of PLEs on reward anticipation and outcome including only individuals with a psychiatric diagnosis

We also performed additional analyses including only the subset of individuals with a psychiatric diagnosis. These analyses indicated that there was no reliable association between PLEs and reward outcome. In this same subset of participants, distressing PLEs (but not non-distressing PLEs) were associated with reward anticipation activation, showing an association with a small reduction in reward anticipation related activity (β= -0.032, 95% CI = -0.054, -0.010, p = 0.005). See Tables 6.11-6.12 in Appendix E.

3.4.1.6 Effect of PLEs on reward anticipation and outcome including only healthy controls and individuals with a psychiatric diagnosis

A final sensitivity analysis was performed for the NAcc, which included healthy controls and individuals with a psychiatric diagnosis. As seen in the tables below, there was no evidence that reward anticipation or outcome activity in the NAcc was associated with PLEs. It was not possible to run a fully adjusted anticipation analysis with this sample as this resulted in a singular fit.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.0001	-0.013, 0.013	0.990
Distressing PLEs	-0.008	-0.018, 0.002	0.106
Laterality (Right NAcc >Left NAcc)	-0.013	-0.017, -0.009	<0.001
Reward magntiude (Large >Small)	0.070	0.066, 0.074	<0.001
Motion	-0.050	-0.068, -0.031	<0.001

Table 3.10: Minimally adjusted regression model (N = 7316) examining the effect of presence and type of PLEs, reward magnitude and laterality on NAcc to reward anticipation, in healthy controls and individuals with a psychiatric diagnosis

Predictor	Estimate	95% CIs	p value
Non-distressing PLEs	-0.004	-0.020, 0.012	0.607
Distressing PLEs	-0.007	-0.019, 0.005	0.242
Laterality (Right NAcc >Left NAcc)	-0.026	-0.031, -0.022	<0.001
Motion	0.073	0.052, 0.094	<0.001

Table 3.11: Minimally adjusted regression model (N = 7417) examining the effect of presence and type of PLEs and laterality on NAcc to reward outcome, in healthy controls and individuals with a psychiatric diagnosis

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.004	-0.021, 0.012	0.590
Distressing PLEs	-0.007	-0.019, 0.005	0.276
Laterality (Right NAcc >Left NAcc)	-0.026	-0.031, -0.022	<0.001
Gender	0.006	-0.004, 0.017	0.227
Depressive symptoms	0.008	-0.007, 0.024	0.288
Household income [<50K]	0.003	-0.013, 0.019	0.708
Household income [>=50K & <100K]	0.000	-0.013, 0.013	0.949
Parental education-<HS Diploma	-0.010	-0.035, 0.016	0.453
Parental education-HS Diploma/GED	-0.008	-0.029, 0.013	0.466
Parental education - Post Graduate Degree	-0.004	-0.018, 0.010	0.577
Parental education - Some College	0.000	-0.015, 0.014	0.985
Race - Asian	0.020	-0.014, 0.055	0.249
Race - Black	-0.022	-0.040, -0.005	0.011
Race - Other/Mixed	-0.009	-0.023, 0.006	0.232
Motion	0.074	0.053, 0.095	<0.001
Pubertal developmen	0.001	-0.011, 0.012	0.911
Diagnosis- schizophrenia	-0.419	-0.731, -0.108	0.008

Table 3.12: Fully adjusted regression model (N = 7417) examining the effect of presence and type of PLEs and laterality on NAcc to reward outcome, in healthy controls and individuals with a psychiatric diagnosis

3.4.2 Dorsal Striatum

3.4.2.1 Effect of PLEs and distress on reward anticipation

We then performed additional analyses to examine reward anticipation activity in the dorsal striatum. This was done through performing separate analyses for the caudate (see Table 3.13 - Table 3.14) and putamen (see Table 3.15 - Table 3.16. We did not find evidence of a reliable association with PLEs - whilst distressing PLEs were a significant predictor of caudate activity in the minimally adjusted anticipation analysis (β= -0.010, 95% CI = -0.021, -0.0001, p = 0.049), this was no longer

the case in the fully adjusted analysis. There was no evidence that activity in the putamen during reward anticipation was associated with PLEs.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.007	-0.021, 0.008	0.363
Distressing PLEs	-0.010	-0.021, -0.0001	0.049
Laterality (Right caudate >Left caudate)	0.011	0.008, 0.014	<0.001
Reward magnitude (Large Reward > Small Reward)	0.076	0.073, 0.080	<0.001
Motion	-0.082	-0.103, -0.061	<0.001

Table 3.13: Minimally adjusted regression model (N = 6392) examining the effect of presence and type of PLEs, reward magnitude and laterality on caudate response to reward anticipation

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.005	-0.019, 0.010	0.524
Distressing PLEs	-0.006	-0.016, 0.005	0.306
Laterality (Right Caudate >Left Caudate)	0.011	0.008, 0.014	<0.001
Reward Magnitude (Large Reward >Small Reward)	0.076	0.073, 0.080	<0.001
Gender	0.010	0.001, 0.019	0.029
Depressive symptoms	-0.006	-0.020, 0.009	0.439
Household income [<50K]	-0.006	-0.020, 0.008	0.404
Household income [>=50K & <100K]	-0.006	-0.017, 0.006	0.324
Parental education - <HS Diploma	-0.032	-0.054, -0.009	0.007
Parental education - HS Diploma/GED	-0.024	-0.042, -0.006	0.011
Parental education - Post Graduate Degree	-0.009	-0.021, 0.003	0.157
Parental education - Some College	-0.014	-0.027, -0.001	0.031
Race - Asian	-0.025	-0.054, 0.003	0.079
Race - Black	-0.009	-0.024, 0.006	0.245
Race - Other	-0.010	-0.023, 0.002	0.101
Motion	-0.077	-0.098, -0.055	<0.001
Pubertal development	0.003	-0.007, 0.013	0.553

Table 3.14: Fully adjusted regression model (N = 6392) examining the effect of presence and type of PLEs, reward magnitude and laterality on caudate response to reward anticipation

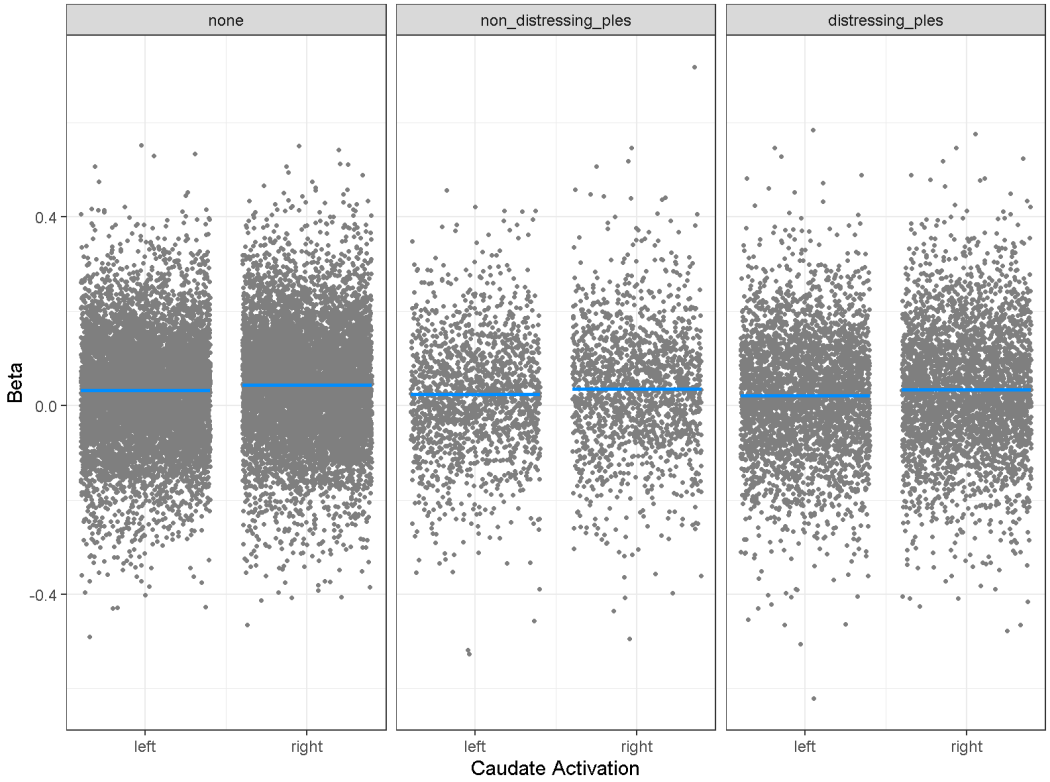


Figure 3.3: Relationship between PLE group status on left and right caudate activation in the reward-anticipation component of the Monetary Incentive Delay task

Predictor	*Estimate*	*95% CIs*	*pvalue*
Non-distressing PLEs	0.0004	-0.011, 0.012	0.944
Distressing PLEs	-0.004	-0.012, 0.005	0.415
Laterality (Right putamen >Left putamen)	0.005	0.003, 0.008	<0.001
Reward magnitude (Large Reward >Small Reward)	0.056	0.053, 0.058	<0.001
Motion	-0.072	-0.089, -0.055	<0.001

Table 3.15: Minimally adjusted regression model (N = 6378) examining the effect of presence and type of PLEs, reward magnitude and laterality on putamen response to reward anticipation

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.002	-0.010, 0.013	0.798
Distressing PLEs	0.0002	-0.009, 0.009	0.969
Laterality (Right Putamen >Left Putamen)	0.005	0.003, 0.008	<0.001
Reward Magnitude (Large Reward >Small Reward)	0.056	0.053, 0.058	<0.001
Gender	0.011	0.004, 0.018	0.004
Depressive symptoms	-0.005	-0.016, 0.006	0.388
Household income [<50K]	-0.014	-0.026, -0.003	0.015
Household income [>=50K & <100K]	-0.009	-0.018, 0.001	0.068
Parental education - <HS Diploma	-0.015	-0.034, 0.004	0.117
Parental education - HS Diploma/GED	-0.014	-0.029 0.001	0.071
Parental education - Post Graduate Degree	-0.008	-0.017, 0.002	0.123
Parental education - Some College	-0.006	-0.017, 0.004	0.237
Race - Asian	-0.008	-0.031, 0.015	0.496
Race - Black	-0.003	-0.016, 0.009	0.608
Race - Other	-0.007	-0.017, 0.004	0.203
Motion	-0.069	-0.087, -0.052	<0.001
Pubertal development	-0.001	-0.010, 0.007	0.728

Table 3.16: Fully adjusted regression model (N = 6378) examining the effect of presence and type of PLEs, reward magnitude and laterality on putamen response to reward anticipation

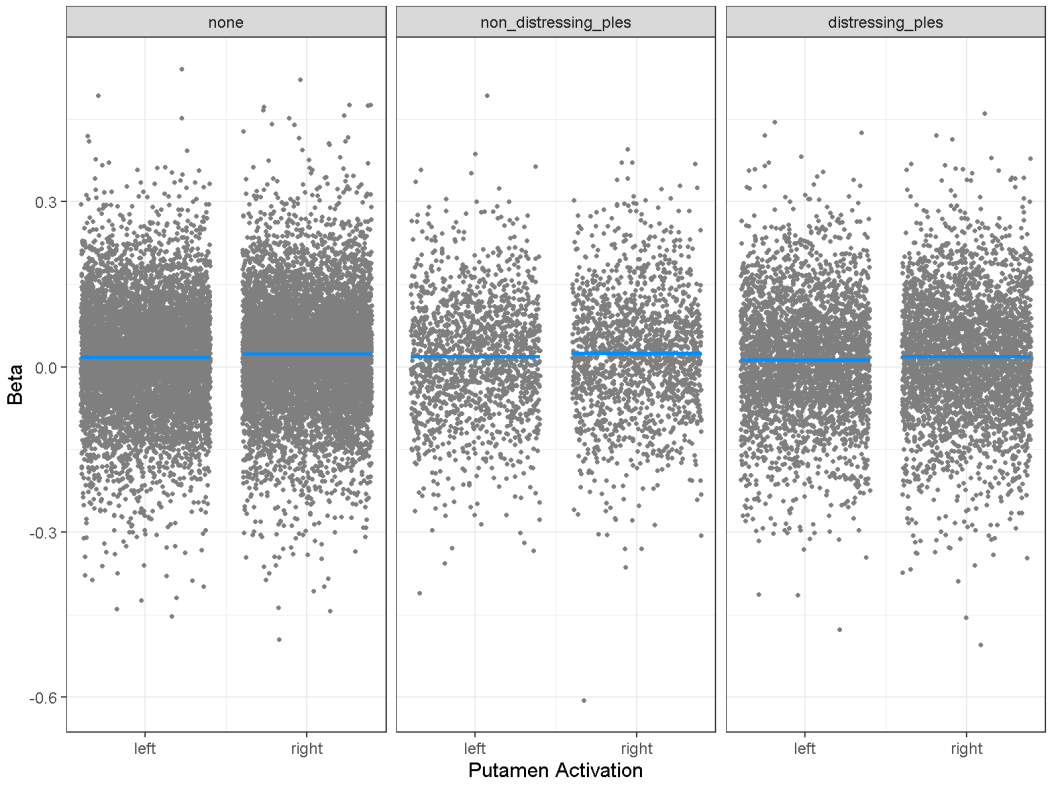


Figure 3.4: Relationship between PLE group status on left and right putamen activation in the reward-anticipation component of the Monetary Incentive Delay task

3.4.2.2 Effect of PLEs and distress on reward outcome

We performed additional analyses to examine reward outcome activity in the dorsal striatum. This was done through performing separate analyses for the caudate (see Table 3.17 - Table 3.18) and putamen (see Table 3.19 - Table 3.20). We found no evidence of an association between PLEs and reward outcome activity in the caudate or putamen.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.002	-0.015, 0.020	0.792
Distressing PLEs	0.001	-0.012, 0.013	0.911
Laterality (Right Caudate >Left Caudate)	-0.002	-0.004, 0.001	0.185
Motion	0.076	0.052, 0.100	<0.001

Table 3.17: Minimally adjusted regression model (N = 6546) on association between types of PLEs, distress, laterality on caudate response to reward outcome

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.003	-0.014, 0.021	0.698
Distressing PLEs	0.004	-0.009, 0.017	0.590
Laterality (Right Caudate >Left Caudate)	-0.002	-0.004, 0.001	0.187
Gender	0.002	-0.009, 0.013	0.719
Depressive symptoms	-0.009	-0.026, 0.008	0.289
Household income [<50K]	-0.006	-0.023, 0.012	0.527
Household income [>=50K & <100K]	-0.001	-0.014, 0.013	0.935
Parental education - <HS Diploma	0.018	-0.009, 0.046	0.195
Parental education - HS Diploma/GED	0.011	-0.012, 0.033	0.345
Parental education - Post Graduate Degree	-0.001	-0.016, 0.013	0.851
Parental education - Some College	0.006	-0.009, 0.022	0.419
Race - Asian	0.018	-0.017, 0.053	0.319
Race - Black	-0.033	-0.051, -0.014	0.000
Race - Other	-0.014	-0.029, 0.001	0.075
Motion	0.079	0.054, 0.104	0.000
Pubertal development	-0.003	-0.016, 0.009	0.616

Table 3.18: Fully adjusted regression model (N = 6546) on association between types of PLEs, distress, laterality on caudate response to reward outcome

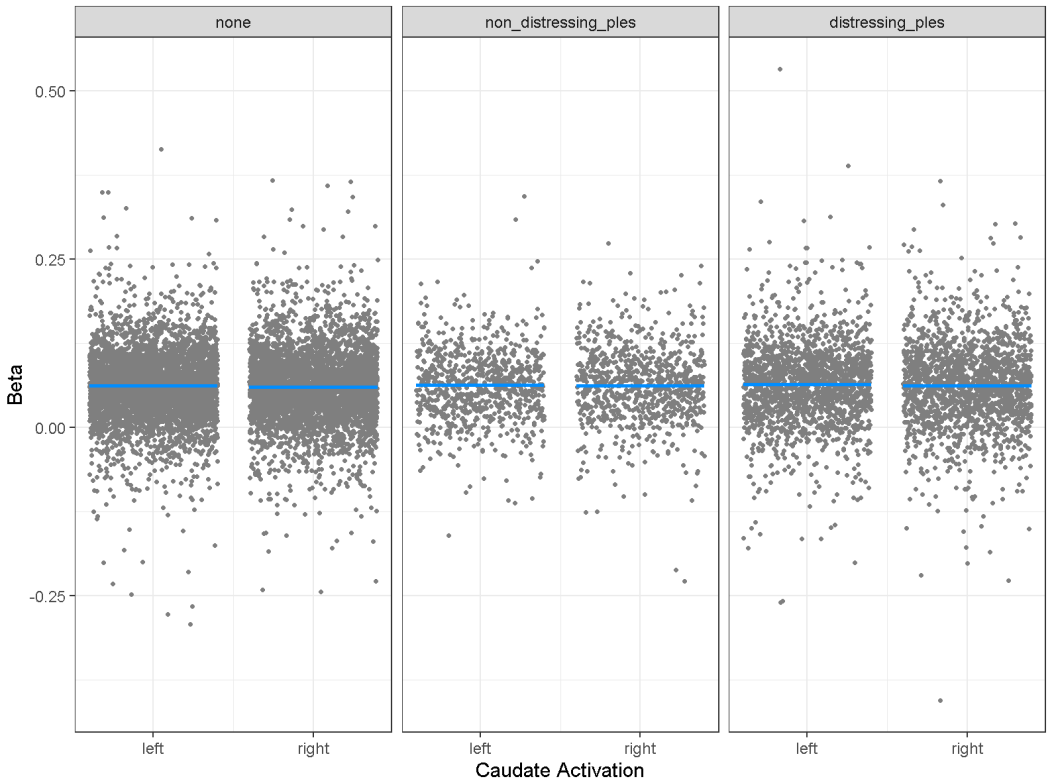


Figure 3.5: Relationship between PLE group status on left and right caudate activation in the reward-outcome component of the Monetary Incentive Delay task

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.003	-0.011, 0.017	0.672
Distressing PLEs	-0.001	-0.011, 0.010	0.892
Laterality (Right Putamen >Left Putamen)	0.001	-0.001, 0.003	0.252
Motion	0.055	0.035, 0.075	<0.001

Table 3.19: Minimally adjusted regression model (N = 6539) on association between types of PLEs, distress, laterality on putamen response to reward outcome

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.003	-0.011, 0.017	0.687
Distressing PLEs	0.001	-0.010, 0.012	0.898
Laterality (Right Putamen >Left Putamen)	0.001	-0.001, 0.003	0.253
Gender	0.015	0.006, 0.024	0.001
Depressive symptoms	-0.010	-0.024, 0.004	0.174
Household income [<50K]	-0.006	-0.020, 0.009	0.439
Household income [>=50K & <100K]	-0.002	-0.013, 0.010	0.771
Parental education - <HS Diploma	0.008	-0.015, 0.031	0.511
Parental education - HS Diploma/GED	0.000	-0.019, 0.019	0.992
Parental education - Post Graduate Degree	-0.004	-0.016, 0.008	0.547
Parental education - Some College	0.010	-0.002, 0.023	0.113
Race - Asian	0.028	-0.003, 0.058	0.073
Race - Black	-0.011	-0.027, 0.004	0.153
Race - Other	-0.015	-0.027, -0.002	0.023
Motion	0.053	0.032, 0.073	0.000
Pubertal development	0.005	-0.006, 0.015	0.393

Table 3.20: Fully adjusted regression model (N = 6539) on association between types of PLEs, distress, laterality on putamen response to reward outcome

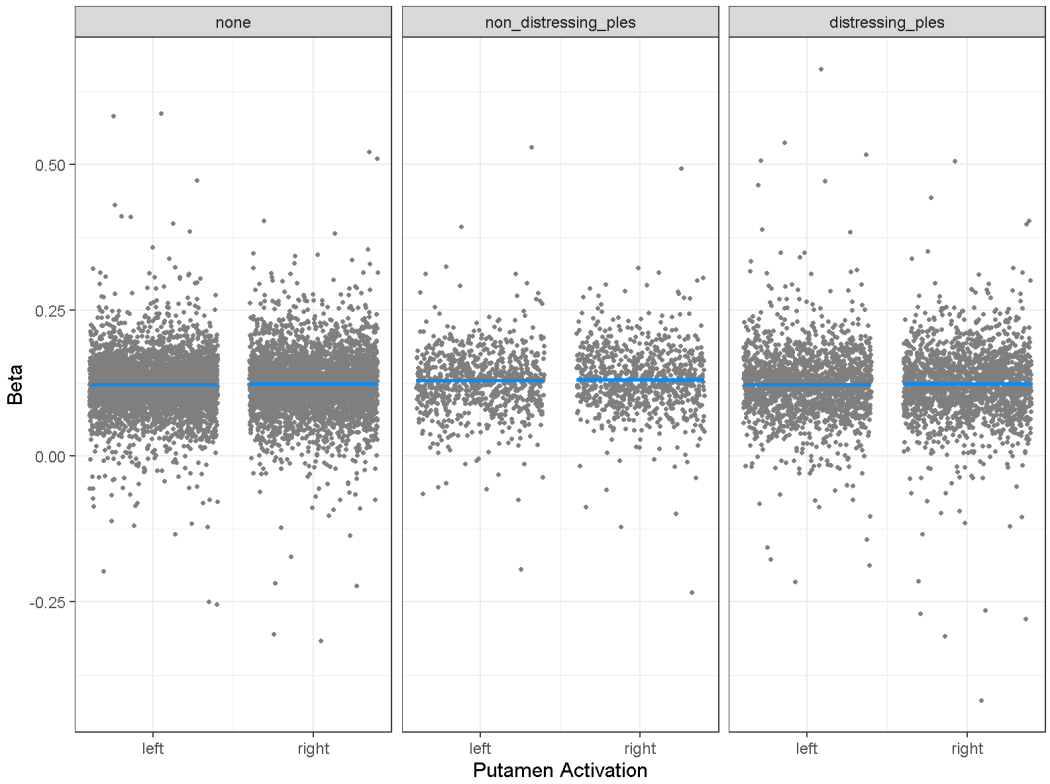


Figure 3.6: Relationship between PLE group status on left and right putamen activation in the reward-outcome component of the Monetary Incentive Delay task

3.4.2.3 Effect of total number of PLEs and PLE-related distress on reward anticipation and outcome

There was no evidence that total number of PLEs or PLE-related distress is associated with caudate (see Table 3.21 and Table 3.22) or putamen response (Table 3.23 and Table 3.24) to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	-0.001	-0.007, 0.006	0.835
Total distress	-0.001	-0.004, 0.001	0.305
Laterality (Right Caudate >Left Caudate)	0.011	0.008, 0.014	<0.001
Reward magnitude (Large Reward >Small Reward)	0.076	0.073, 0.080	<0.001
Motion	-0.082	-0.103, -0.061	<0.001

Table 3.21: Minimally adjusted regression model (N = 6392) on association between number of PLEs, total distress and laterality on caudate response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	-0.0003	-0.007, 0.006	0.920
Total Distress	-0.001	-0.003, 0.002	0.618
Laterality (Right Caudate >Left Caudate)	0.011	0.008, 0.014	<0.001
Reward magnitude	0.076	0.073, 0.080	<0.001
Gender	0.010	0.001, 0.019	0.032
Depressive symptoms	-0.005	-0.019, 0.009	0.467
Household income [<50K]	-0.006	-0.020, 0.008	0.413
Household income [>=50K & <100K]	-0.006	-0.017, 0.006	0.327
Parental education - <HS Diploma	-0.032	-0.055, -0.009	0.007
Parental education - HS Diploma/GED	-0.024	-0.042, -0.006	0.011
Parental education - Post Graduate Degree	-0.009	-0.021, 0.003	0.159
Parental education - Some College	-0.014	-0.027, -0.002	0.028
Race - Asian	-0.026	-0.050, 0.003	0.077
Race - Black	-0.009	-0.024, 0.006	0.246
Race - Other	-0.011	-0.023, 0.002	0.097
Motion	-0.077	-0.099, -0.055	<0.001
Pubertal development	0.003	-0.007, 0.014	0.553

Table 3.22: Fully adjusted regression model (N = 6392) on association between number of PLEs, total distress and laterality on caudate response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	0.001	-0.005,0.006	0.850
Total distress	-0.001	-0.003, 0.001	0.289
Laterality (Right putamen >left putamen)	0.005	0.003, 0.008	<0.001
Reward magnitude (Large Reward >Small Reward)	0.056	0.053, 0.058	<0.001
Motion	-0.072	-0.089, -0.055	<0.001

Table 3.23: Minimally adjusted regression model (N = 6378) on association between number of PLEs, total distress and laterality on putamen response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	0.001	-0.005, 0.006	0.778
Total Distress	-0.001	-0.003, 0.002	0.597
Laterality (Right Putamen >Left Putamen)	0.005	0.003, 0.008	<0.001
Reward magnitude	0.056	0.053, 0.058	<0.001
Gender	0.011	0.004, 0.018	0.004
Depressive symptoms	-0.004	-0.016, 0.007	0.452
Household income [<50K]	-0.014	-0.026,-0.003	0.015
Household income [>=50K & <100K]	-0.008	-0.018, 0.001	0.070
Parental education - <HS Diploma	-0.015	-0.033, 0.004	0.120
Parental education - HS Diploma/GED	-0.014	-0.029, 0.001	0.074
Parental education - Post Graduate Degree	-0.008	-0.018, 0.002	0.118
Parental education - Some College	-0.006	-0.017, 0.004	0.242
Race - Asian	-0.008	-0.031, 0.015	0.493
Race - Black	-0.003	-0.015, 0.009	0.627
Race - Other	-0.006	-0.017, 0.004	0.210
Motion	-0.069	-0.086, -0.052	<0.001
Pubertal development	-0.001	-0.010, 0.007	0.753

Table 3.24: Fully adjusted regression model (N = 6378) on association between number of PLEs, total distress and laterality on putamen response to reward anticipation.

Similarly, there was no evidence to indicate that total number of PLEs or PLE-related distress is associated with caudate (see table 3.25 and table 3.26) or putamen (see table 3.27 and table 3.28) response to reward outcome.

Predictor	Estimate	95% CIs	p value
Number of PLEs	-0.001	-0.009, 0.007	0.732
Total distress	0.000	-0.004, 0.003	0.837
Laterality (Right Caudate >Left Caudate)	-0.002	-0.004, 0.001	0.184
Motion	0.075	0.051, 0.099	<0.001

Table 3.25: Minimally adjusted regression model (N = 6546) on association between number of PLEs, total distress and laterality on caudate response to reward outcome.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	-0.001	-0.009, 0.007	0.810
Total Distress	0.0002	-0.003, 0.003	0.908
Laterality (Right Caudate >Left Caudate)	-0.002	-0.004, 0.001	0.187
Gender	0.002	-0.009, 0.013	0.707
Depressive symptoms	-0.008	-0.025, 0.009	0.364
Household income [<50K]	-0.005	-0.023, 0.012	0.532
Household income [>=50K & <100K]	-0.0004	-0.014, 0.013	0.953
Parental education - <HS Diploma	0.019	-0.009, 0.046	0.179
Parental education - HS Diploma/GED	0.011	-0.012, 0.034	0.340
Parental education - Post Graduate Degree	-0.001	-0.016, 0.013	0.843
Parental education - Some College	0.007	-0.009, 0.022	0.400
Race - Asian	0.018	-0.017, 0.053	0.319
Race - Black	-0.032	-0.051, -0.014	0.001
Race - Other	-0.013	-0.029, 0.002	0.081
Motion	0.079	0.054, 0.104	<0.001
Pubertal development	-0.003	-0.015, 0.010	0.673

Table 3.26: Fully adjusted regression model (N = 6546) on association between number of PLEs, total distress and laterality on caudate response to reward outcome.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	0.001	-0.006, 0.007	0.803
Total distress	-0.001	-0.004, 0.002	0.488
Laterality (Right Putamen >Left Putamen)	0.001	-0.001, 0.003	0.252
Motion	0.055	0.035, 0.075	<0.001

Table 3.27: Minimally adjusted regression model (N = 6539) on association between number of PLEs, total distress and laterality on putamen response to reward outcome.

Predictor	*Estimate*	*95% CIs*	*p value*
Number of PLEs	0.0004	-0.006, 0.007	0.917
Total Distress	-0.0004	-0.003, 0.002	0.779
Laterality (Right Putamen >Left Putamen)	0.001	-0.001, 0.003	0.254
Gender	0.015	0.006, 0.024	0.001
Depressive symptoms	-0.009	-0.023, 0.005	0.209
Household income [<50K]	-0.006	-0.020, 0.009	0.448
Household income [>=50K & <100K]	-0.002	-0.013, 0.010	0.788
Parental education - <HS Diploma	0.008	-0.015, 0.031	0.499
Parental education - HS Diploma/GED	0.0002	-0.019, 0.019	0.985
Parental education - Post Graduate Degree	-0.004	-0.016, 0.008	0.535
Parental education - Some College	0.011	-0.002, 0.023	0.109
Race - Asian	0.027	-0.003, 0.058	0.074
Race - Black	-0.011	-0.027, 0.004	0.159
Race - Other	-0.015	-0.027, -0.002	0.024
Motion	0.053	0.032, 0.073	<0.001
Pubertal development	0.005	-0.006, 0.015	0.375

Table 3.28: Fully adjusted regression model (N = 6539) on association between number of PLEs, total distress and laterality on putamen response to reward outcome.

3.4.2.4 Effect of PLEs on reward processing when including individuals with a psychiatric diagnosis or psychiatric medication use

There was no evidence that caudate or putamen activity was associated with PLE status in the anticipation or outcome analyses. See Tables 6.13-6.20 in Appendix E. Additional analysis including only healthy controls and individuals with a psychiatric diagnosis can also be found in the appendix. See Tables 6.21-6.24 in Appendix E.

3.4.2.5 Effect of PLEs on reward anticipation and outcome including only individuals with a psychiatric diagnosis

The final set of dorsal striatum analyses were conducted only in individuals with a psychiatric diagnosis. There was no evidence of an association between dorsal or caudate reward anticipation-related activity and PLEs. See Tables 6.21-6.24 in Appendix E.

3.5 Discussion

In this large study of over 6,500 9-10-year-old children, we find no association between PLEs and fMRI striatal activation during either the reward anticipation or reward outcome stages of the Monetary Incentive Delay task. This was the case regardless of whether PLEs were included as a categorical or continuous variable. Further exploratory analyses that also included participants with a psychiatric diagnosis revealed only two weak positive associations: distressing PLEs (but not non-distressing PLEs) were associated with greater NAcc activation during reward anticipation (but not reward outcome), in the analysis including all of the individuals and in the analysis consisting only of individuals with a diagnosis. However given that this effect was small, resulted from a large number of tests, was not present for PLEs without distress in the same analysis, we suggest it is unlikely to be strong evidence for the presence of this mechanism.

The findings have several implications for developmental models of psychosis risk and our understanding of explanatory mechanisms for psychosis-spectrum experiences more broadly. In terms of psychosis risk, the developmental risk factor model (Murray et al., 2017) suggests that accumulated childhood and social adversity combined with genetic risk makes the striatal dopamine system hyper-responsive to stress. According to the model, these alterations generate the symptoms of psychosis through a process of aberrant assignment of salience to stimuli that would normally appear to have low levels of motivational significance (Howes & Kapur, 2009; Kapur, 2003). These findings have been supported by fMRI studies reporting dysregulated reward processing in the MID task in adults with psychosis (Juckel et al., 2006; Kirschner et al., 2018) and in adolescents with PLEs (Papanastasiou et al., 2018). However, it is noteworthy that the developmental risk factor does not predict at what age alterations to the striatal dopamine system lead to aberrant salience.

This study found no evidence for the presence of this mechanism at a peak age for PLEs in 9-10-year-old children despite a very large sample and validated measures that have produced reliable evidence for this association in older age groups.

This is despite the fact that PLEs in children of this age predict poor outcome over the lifespan (Calkins et al., 2017; Downs et al., 2013), poorer cognitive abilities (Reichenberg et al., 2010) and greater levels of adversity (Trotta, Murray, & Fisher, 2015). This suggests whilst PLEs at this age may be markers of adverse development and / or psychopathology, they are potentially not associated with alterations to striatal activation, raising doubts over whether they share a mechanism proposed for psychotic-spectrum experiences later in life. As such, further longitudinal research is needed to investigate whether alterations in reward processing emerge later on in development. This might particularly be the case as most PLEs typically spontaneously remit, with some studies estimating that they are transient in 75-90% of young people (Calkins et al., 2017). However, whilst some studies have argued that PLEs prior to age 16 bear low predictive power (Schimmelmann et al., 2015), this is at odds with the existing view of psychosis continuum, which does not specify an age at which PLEs suddenly become clinically relevant and potentially pathological. Additionally, we attempted to examine PLEs that are more likely to be clinically relevant, through including PLE-related distress. To our knowledge, this has not been examined previously and ought to be investigated in further longitudinal neuroimaging studies.

Notably, pre-adolescents have been shown to have several perceptual and reasoning differences that alter and stabilise during adolescence, potentially suggesting other mechanisms that might generate PLEs. For example, there is evidence that pre-adolescent children may perform auditory functions more unreliably than adults, tending to rely more heavily on top-down interpretation of sounds (Moore, 2012). Similarly, in the visual domain, pre-adolescent children tend to rely more on high spatial frequencies to extract local facial features to perceive fearful facial expressions whereas adolescent children use rapid decoding of global features using in the low spatial frequency ranges (Peters & Kemner, 2017). Additionally- and relevant to the measurement of unusual beliefs- magical thinking is common in childhood, although it typically declines into adolescence. This is largely understood in terms of the under-development of causal reasoning (Muentener & Bonawitz, 2018)

involving the understanding of transfer of physical force between objects, the outcomes of goal-directed actions produced by dispositional agents, and the ability to track co-variation relations between events. Development in each of these domains may additionally be affected by developmental adversities, potentially giving rise to PLEs during preadolescence that are generated by distinct mechanisms from PLEs reported later in life.

Based on current findings, we suggest that PLEs during preadolescence in the general population may be largely generated by processes of delayed development in perception and causal reasoning. Psychosis is a multi-dimensional and heterogeneous construct and it is likely that there are different mechanisms underlying the emergence of PLEs. Here, the presence of childhood adversity could impact the typical developmental trajectory of these systems, meaning that greater numbers of PLEs largely reflect developmental delay in these systems rather than dysregulation of striatal dopamine at this age. This view has been supported by studies such as Carey et al. (2021), which reported that early poorer development in domains such as motor and cognitive function is associated with hallucinatory experiences. Nevertheless, accumulation of pre-existing and environmental risk factors, particularly those that have a broader impact on development (M.-d.-G. Dominguez et al., 2010), will make later hyper-responsiveness of the striatal dopamine system more likely. This interactive developmental model might account for the contrasting trajectories of PLEs from childhood to adolescence where the majority of children show resolving or attenuated PLEs and only a small high-risk minority show persistent or intermittent PLEs (Thapar et al., 2012).

However, this study presents several limitations that warrant caution when interpreting its results. One limitation is the extent to which blood-oxygen-level-dependent (BOLD) signal in the ventral striatum allows accurate localisation of dysregulated subcortical dopamine. Meta-analytic evidence from PET studies suggests that it may be the dorsal rather than ventral striatum where dopamine dysregulation may be most apparent in adult psychosis (McCutcheon et al., 2018). As such, we also performed analyses in the caudate and putamen, and found no evi-

dence that children with PLEs displayed dysregulated reward processing in these regions. Additionally, activation in the ventral striatum during the MID task has been reliably associated with psychosis. As stated previously, a meta-analysis of multiple studies conducted by Radua et al. (2015) found evidence that individuals with psychosis display reduced activation in response to reward. This meta-analysis included 23 studies (involving 917 patients) in the reward anticipation analysis and found evidence of significant bilateral ventral striatal hypoactivation. No residual heterogeneity or potential reporting bias was observed (p =.12-.92), and they found no evidence for an effect of age, sex, antipsychotic medication use, publication year, or quality score (p = .14 to >.99). Therefore, it is likely that BOLD signal response reliably reflects altered dopamine-mediated reward processing. Nevertheless it is possible that it may not accurately localise it. Indeed, a prior multi-modal PET-fMRI study of the MID task (Dubol et al., 2018) reported that reward anticipation was reliably associated with BOLD signal in the NAcc, with PET imaging showing it was associated with dopamine transporter availability in the midbrain. This was confirmed by our analyses on the dorsal striatum that found no evidence of an association between PLEs and reward processing in any bar one of the sensitivity analyses. However, given these validation studies were conducted in adults, we also note the limitations of generalising this assumption to 9-10-year-old children. Whilst PET studies may provide a direct measure of dopaminergic transmission, they are typically used to cross-validate the role of dopamine in regional fMRI activation. However, PET studies are not routinely conducted on children except for clinical reasons, as they are generally contraindicated in this age group.

Although the ABCD is one of the largest and most representative samples, children from higher income families were still over-represented (Heeringa & Berglund, 2020). We attempted to address this by including family and site as random effects as suggested by Heeringa and Berglund (2020). Another potential limitation is that PLEs were measured with the Prodromal Questionnaire – Brief Child Version. This is a self-report questionnaire and although it has been well validated in this sample (Karcher et al., 2018), it may not have had the same sensitivity as structured

interview assessments.

We note there were only two positive significant statistical associations in this study. The first was between reward anticipation and distressing PLEs in the subgroup of children who had a psychiatric diagnosis. We also note that this finding was small and seemingly very selective – it was present in a minimally adjusted analysis, absent for reward outcome and was not associated with non-distressing PLEs in the same analysis. However, it is possible that this group represents a subgroup where the earliest effects of dopamine system dysregulation may be found, potentially related more broadly to psychopathology, and this may be worth noting as a hypothesis for future investigation. The second statistical association was between distressing PLEs and reward anticipation activity in the caudate and emerged when including individuals with a psychiatric diagnosis. However, neither of these associations survived adjustment for covariates. In conclusion, we found no reliable evidence that the presence of PLEs in a large and well-powered sample predicted dysregulated reward processing in children from the general population. It is likely that there are numerous mechanisms underlying the emergence of psychosis. As the ABCD study is an ongoing cohort study, future research should focus on explore PLE-related differences in reward processing further, examining whether they arise during development, and if this occurs at different times for different groups of young people.

Chapter 4

Study 3: Social, cognitive and affective predictors of the Persistence, Remission and New Incidence of Psychotic-like Experiences

4.1 Abstract

Psychotic-like experiences (PLEs) are common in childhood. It has been proposed that PLEs that are persistent are more pathological and likely to become clinically relevant. However, whilst there is some research examining the predictors of PLEs, there is a paucity of studies examining this earlier on in development, in childhood and adolescence. Additionally, limited research has investigated the factors associated with the persistence of PLEs, including neural markers of persistence. The findings outlined in previous chapters of this thesis indicated that the mere presence of distressing PLEs in late childhood may be of limited clinical relevance. As such, this chapter sought to examine the predictors of the persistence, remission and new incidence of PLEs. This was done using data from the Adolescent Brain Cognitive Development (ABCD) study, a large ongoing longitudinal cohort study in the US. This chapter consists of two studies; Study 1 sought to investigate the social, cognitive and affective predictors of PLEs at age 9-10, along with the predictors of persistence, remission and new incidence of PLEs at one-year follow-up. Specifically, Study 1 explored whether depressive symptoms, cognition and trauma predicted PLEs both cross-sectionally and longitudinally, whilst controlling for sociodemographic factors. Study 2 aimed to examine whether reward processing at age 9-10 is associated with persistence, remission and new incidence of PLEs at one-year follow-up. The results of Study 1 indicated that depressive symptoms are a strong predictor PLEs as they were associated with PLEs at baseline, as well as persistence and new incidence of PLEs. This contrasts from cognition, which predicted the presence of PLEs at baseline in both the minimally and fully-adjusted analysis, but was only significantly associated with persistence and new incidence of PLEs at one year follow-up in the minimally adjusted analysis. Similarly, there was limited evidence that trauma is associated with PLEs during late childhood, as it was only a predictor of PLEs at baseline and persistence in the minimally adjusted analysis, and was not found to be associated with the new incidence of PLEs at follow-up. Study 2 did not find any evidence that reward processing activity predicts PLE status at one-year follow up. These findings indicate that depressive symptoms are of

particular clinical relevance when it comes to predicting individuals who may be more likely to experience persistent PLEs.

4.2 Introduction

Psychotic-like experiences (PLEs) are common in childhood (Linscott & Os, 2013), and whilst there is evidence that PLEs are associated with an increased likelihood of developing psychosis (Poulton et al., 2000) or other psychiatric disorders later in life (Dhossche et al., 2002), these experiences are transient for most. Thus, they have been argued to be a behavioural expression of normative neurodevelopmental processes (Linscott & Os, 2013). As such, it is vital to identify which individuals are experiencing pathological, rather than benign, PLEs. However, our ability to do so remains poor (Yung et al., 2009).

It has been argued that persistent PLEs might be of particular clinical relevance. This is based on two lines of evidence. Firstly, the observation that persistence is associated with poorer outcome. As noted previously in Subsection 1.6.5, a psychotic disorder is by definition a PLE that persists for a particular length of time, one month in the case of the DSM-5 (American Psychiatric Association, 2013). Severe episodes are characterised by higher levels of persistence and thus persistence is central to what makes PLEs of clinical concern, and it represents one of the most relevant mechanisms for psychotic disorders. Individuals with persistent PLEs have been found to have higher odds of displaying a need for care (Hanssen et al., 2005; Dominguez et al., 2011), and some studies have indicated that there is a dose-response relationship between persistence of PLEs and risk of transition to frank psychosis (Kaymaz et al., 2012). Additionally, those with persisting PLEs report higher levels of overall distress, as well as PLE-related distress (Wigman, van Winkel, et al., 2011).

Secondly, almost all models of psychotic symptoms require an explanation of persistence (often referred to as maintenance), and therefore predicting persistence is to a great degree understanding what makes a symptom a symptom. In Coltheart, Langdon, and McKay (2011)'s two factor model of delusions, they propose two components necessary for the formation of delusions: a first factor, which is responsible for the content of the unusual belief, and a second factor, which is responsible for the failure to reject the belief. Garety et al. (2001)'s cognitive model of the

positive symptoms of psychosis and Freeman et al. (2002)'s model of persecutory delusions also attempt to explain the maintenance of psychotic experiences. Both of these models are underpinned by a stress-vulnerability framework, in which the emergence of the psychotic symptoms relies on an interaction between vulnerability (due to genetic, biological, psychological and social risk factors) and stress (which might also be biological, psychological or social). They also both emphasise the role of negative affect in the maintenance (i.e., persistence) of PLEs.

One influential model is the Developmental Risk Factor Model (Murray et al., 2017) that cites deficits in cognition (due to subtle differences in their neural networks), as reflecting an altered developmental trajectory. This trajectory consists of increasing difficulties in functioning (both academically and socially), which in turn leads to exposure to other environmental stressors such as substance use or victimisation. This exposure to adverse life experiences causes dysregulation in dopamine release, which in turn causes the aberrant assignment of salience to otherwise innocuous experiences. Murray et al. (2017) argue that a vicious cycle is formed as a result, whereby stress increases dopamine dysregulation, which causes more stress due to the emergence of anomalous experiences, followed by more dopamine release, and this "eventually hard-wires the psychotic interpretation". Murray et al. (2017) use hypertension and obesity as an analogy for psychosis, stating that similarly to how when an individual's blood pressure is persistently above a level they are considered hypertensive, if psychotic experiences pass a certain level and persist, they qualify for a clinical diagnosis. However, whilst the Developmental Risk Factor Model cites development as key, it does not actually take a developmental perspective as the majority of the evidence is based on adults, rather than children and adolescents.

In contrast, Cougnard et al. (2007)'s psychosis-proneness persistence impairment model is, as far as the author is aware, the only model to explicitly acknowledge that PLEs are a common and transient developmental phenomenon in childhood but that they may become persistent and therefore pathological. It proposes that PLEs may become abnormally persistent and clinically relevant if the individ-

ual is exposed to environmental risk, such as cannabis use and childhood trauma. Cougnard et al. (2007) based their model on the following lines of evidence: firstly, the observation that PLEs are more common earlier on in development, and decreases over age. Secondly, the finding that whilst PLEs are a risk factor, most young people with PLEs do not actually transition to frank psychosis. Thirdly, Cougnard et al. (2007) noted that PLEs clusters in families and some evidence suggests it may be impacted by genetic factors. Finally, they argue that as most PLEs are transient, the outcome is "generally good", but that these experiences may be persistent, and an individual may display a clinical need if they are exposed to additional environmental risk factors such as trauma and urbanicity. Cougnard et al. (2007) illustrated their model, which is depicted in Figure 4.1.

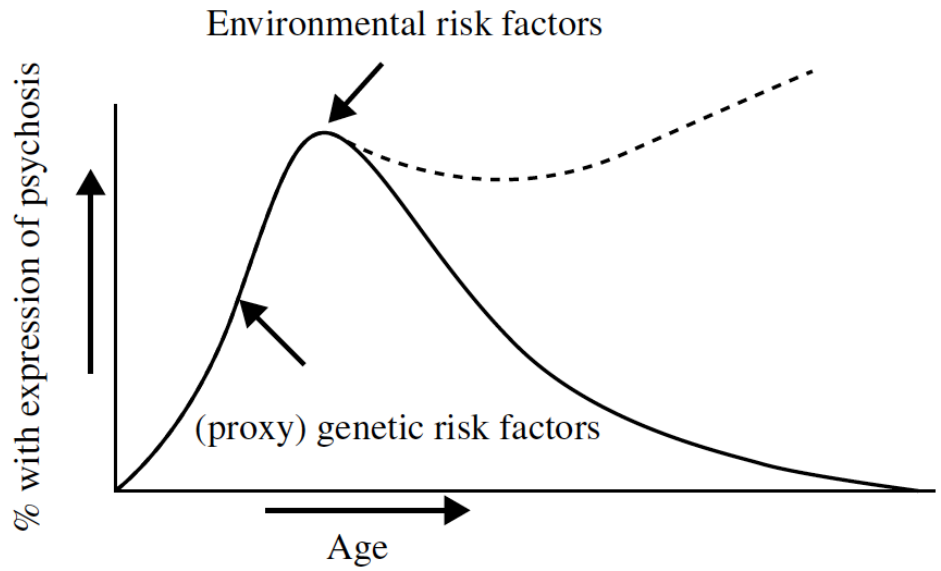


FIG. 1. Development of psychotic disorder: abnormal persistence (- - -) of developmental expression of psychosis.

Figure 4.1: Psychosis-proneness-persistence model from Cougnard, A., Marcelis, M., Myin-Germeys, I., Graaf, R. D., Vollebergh, W.,Krabbendam, L., [...] Os, J. V. Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness–persistence model. Psychological Medicine, 37(4), 513–527

van Os et al. (2009) also make reference to this model, in their systematic re-

view and meta-analysis of the psychosis continuum. More recently, the psychosis-proneness-persistence-impairment model has been supported by studies such as Downs et al. (2013) indicating that persisting PLEs in children as young as nine years old might contribute to the development of internalising and externalising psychopathology, and Mackie et al. (2011), which found that adolescents with persistent PLEs report more frequent victimisation and higher scores in depression and anxiety. Similarly, Wigman, van Winkel, et al. (2011)'s findings indicated that a persistent trajectory of PLEs was related to cannabis use, ethnic minority status, childhood trauma and developmental problems. This indicates that environmental stressors are not just predictors of PLEs at baseline, but also act as predictors of the persistence of these experiences.

Nevertheless, our understanding of the causal mechanisms for persistence in children is limited. Cognitive models have argued that trauma, cognition and affect are involved in the causation of psychosis more generally (Garety et al., 2001; Murray et al., 2017), but this has not been as extensively investigated in children. Trauma has been proposed to act as both a risk factor for onset as well as through leading to the emergence of maintaining factors. It has been hypothesised that PTSD and psychosis may interact with each other to exacerbate symptoms. PTSD may directly influence psychosis through avoidance, overarousal and re-experiencing the traumatic event, and it may have an indirect impact through causing difficulties with interpersonal relationships, or substance abuse (Mueser et al., 2002). Moreover, problematic, culturally unacceptable interpretations of the unusual experiences may be triggered by adult memories of childhood trauma, in addition to current trauma (Morrison et al., 2003; Hardy, van de Giessen, & van den Berg, 2020). Whilst the role of negative affect has been supported by studies such as Bird et al. (2017) for childhood paranoia, there is comparatively limited empirical research examining the predictors of the presence and persistence before adulthood. This was illustrated in a recent scoping review by Kalman et al. (2019), which identified only a few studies exploring predictors of PLEs in childhood and adolescence, and found that none had adequately replicated. Additionally, few studies have ade-

quately controlled for other variables which have been shown to impact persistence, including sex, ethnicity, socioeconomic status, neighbourhood deprivation and urbanicity (Kalman et al., 2019).

Consequently, this chapter consists of two studies. Study 1 examined whether PLEs are predicted by depressive symptoms, cognition and trauma. Each of these have been evidenced as maintaining factors for psychotic experiences in adults and have been hypothesised as candidates for symptom maintenance in children. Thus, their relationship to PLEs in late childhood was tested both cross-sectionally and longitudinally, to examine their relationship with:

1. PLEs at baseline
2. Remission of PLEs versus persistence
3. New incidence of PLEs versus control

Following evidence for the central role of reward-related dopamine dysregulation in psychosis, Study 2 tested whether reward processing in the ventral and dorsal striatum measured with fMRI during the Monetary Incentive Delay task predicted the persistence, remission and new incidence of PLEs at one year follow-up. These had to be tested separately as it was not possible to conduct a single analysis exploring the neurocognitive and social predictors of PLE status due to convergence issues.

4.3 Methods

Study 1 was pre-registered on OSF https://osf.io/cd96r/

4.3.1 Sample

The ABCD cohort (release 3.0; https://abcdstudy.org/) includes 11,878 children aged 9-10 years at baseline (Volkow et al., 2018). This is a longitudinal dataset being collected at 21 sites across the US. Detailed information regarding the recruitment strategy is described in Garavan et al. (2018) and is summarised here. Institutional review board approval was obtained for each site prior to data collection and all carers provided written informed consent. Additionally, assent was

obtained from the participants (Clark et al., 2018). See the supplement for a more comprehensive description of the full sample (Appendix A). In both studies, data from participants was excluded based on the following criteria: having a psychiatric diagnosis at baseline (N = 1973), taking psychotropic medication at baseline (N = 83), not completing the psychosis questionnaire at baseline (N = 12). For Study 1, this left N = 9810 who contributed to the baseline analysis, and N = 9237 who had completed the psychosis questionnaire at baseline and follow-up and contributed to the longitudinal analyses.

For Study 2, additional exclusion criteria were implemented. This included excluding individuals based on the following: not completing the MID task in the scanner (N = 1030), insufficient performance on the task (N= 573), missing motion data (N = 455), missing fMRI data (N = 27). Additionally, individuals whose reward-related activation was more than three standard deviations from the mean were then excluded on the basis of being identified as outliers (N = 223 were excluded for reward anticipation; N = 123 for reward outcome). Finally, those who had not completed the PC-BQ at one year follow-up were excluded (N = 402). This left N = 6,308 who contributed to either the final anticipation or outcome analysis .

4.3.2 Measures

4.3.2.1 Psychotic-like experiences

Psychotic-like experiences (PLEs) were measured using the Prodromal Questionnaire – Brief Child Version, a modified version of the Prodromal Questionnaire Brief Version (PQ-B; (Loewy et al., 2011) – a self-report measure for psychosis risk syndromes that has been validated in nine to ten year olds (Karcher et al., 2018). Unlike the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-5), also available in the ABCD dataset, the PQ-BC allows for measurement of PLEs alongside a measure of distress for the same items. The PQ-BC is a 21-item questionnaire that measures unusual perceptions and sensations, ideas of reference, affective changes, unusual beliefs, or abnormally suspicious thoughts, along with associated distress. The PQ-BC consists of two parts: the first asks whether the individual has had any of the listed psychotic-like thoughts, feelings, and experi-

ences, with an overall score ranging from 0-21. If they answer yes, participants also indicate how related distressing in the second part (from 1-5).

As in Harju-Seppänen et al. (2021) a subset of six items were selected to identify young people with PLEs. These were *"Did you hear strange sounds that you never noticed before like banging, clicking, hissing, clapping, or ringing in your ears?"* (auditory hallucination), *"Did you feel that someone else, who is not you, has taken control over the private, personal, thoughts or ideas inside your head?"* (thought insertion), *"Did you suddenly feel that you could not trust other people because they seemed to be watching you or talking about you in an unfriendly way?"* (paranoia), *"Did you honestly believe in things that other people would say are unusual or weird?"* (bizarre beliefs), *"Did you feel that other people might want something bad to happen to you or that you could not trust other people?"* (paranoia) and *"Did you suddenly start to be able to see things that other people could not see or they did not seem to see?"* (visual hallucination). PLE types were derived from this variable, where participants were categorised as having no PLEs (based on young people not reporting PLEs at baseline or follow-up), persistent PLEs (PLEs at both time points), new incidence (PLEs at follow-up but not baseline) and remission (PLEs at baseline but not follow-up).

4.3.2.2 Demographic characteristics

The following demographic characteristics of the sample are reported in Section 4.4.1 below: age, gender, ethnicity and household income and parental education. These items are from the ABCD Parent Demographics Survey. Age at time of interview was collected in months and this was transformed to years. Carers were also asked about the sex of the young person at the young person, and were asked to check all of the races that they considered the young person to be. Additionally, carers were asked about the total combined family income for the past 12 months and the highest educational qualification they had received.

Household income and parental education were transformed using code provided by the NDA https://github.com/ABCD-STUDY/analysis-nda/blob/master/notebooks/general/core_demographics3.0.R

Similarly, ethnicity was transformed using code provided by the NDA https://github.com/ABCD-STUDY/analysis-nda/blob/master/notebooks/general/categorical_extension3.0.R.

4.3.2.3 Depressive symptoms

Depressive symptoms were measured using the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS-5). The ABCD study used a recently validated and computerised version of the KSADS-5 (Townsend et al., 2020). The following depressive symptoms were added to create a depression score: depressed mood, anhedonia, and irritability. Depressive symptoms were included as a predictor in Study 1 and as a covariate in Study 2.

4.3.2.4 Monetary Incentive Delay task

Detailed information Data from the Monetary Incentive Delay (MID) task (Knutson et al., 2000) was included as the predictor for Study 2. This task measures the anticipation and receipt of rewards and losses. Participants are presented with an incentive cue (2000ms) at the beginning of each trial (Win $5, Win $0.20, Lose $0.20, Lose $5 or $0-no money at stake), followed by a jittered anticipation event (lasting 1500- 4000ms). Participants then need to respond to a variable target (150-500ms), in order to either win or avoid losing money. In the ABCD study, participants are presented with 40 reward (20 small reward, 20 large reward) and 40 loss anticipation trials (20 small loss, 20 large loss), 20 no money anticipation trials, and feedback trials (Casey et al., 2018). The task was individualised with the initial duration of the response target drawn from a practice session completed by the participant prior to entering the scanner. In order to reach a 60% accuracy rate, task difficulty was adjusted during the task after every third incentivised trial based on the overall accuracy rate of the previous six trials. The target duration was shortened if the individual's accuracy falls below the target accuracy level. Participants who did not reach acceptable performance in the task were excluded from analysis (indexed by whether all trial types resulted in more than three events for both positive and negative feedback), as well as those whose regional activity was above or below

three standard deviations. The MID task has been previously validated in typically developing children during fMRI (Cao et al., 2019) and validation studies for the paradigm and data used in this study have been previous by (Casey et al., 2018) and (Chaarani et al., 2021). Casey et al. (2018) reported that the experimental manipulation was successful in maintaining hit rates at close to 60%, and that reaction times and pay-off amounts were consistent across experimental runs. Chaarani et al. (2021) reported that the task is associated with robust brain activations which are consistent with the extant literature.

4.3.2.5 Imaging acquisition

The imaging acquisition for the ABCD study is described in Casey et al. (2018). In Study 2, the outcome was reward-related activation during the MID task from the left and right NAcc. Each site collected imaging data using 3 Tesla systems and multi-channel coils and multiband echo planar imaging acquisition. Scanning included a fixed order of localiser, T1- and T2-weighted images, resting state, and diffusion-weighted imaging. The MID task, stop signal, and emotional n-back were all completed in the scanner, in a randomised order for each participant. Blood-oxygen-level-dependent (BOLD) images were acquired using gradient EPI with standardised acquisition parameters.

4.3.2.6 Imaging processing and analysis

The imaging processing and analysis is available in Hagler et al. (2019), and is summarised briefly here. Centralised processing and analysis of the imaging data was conducted at the ABCD Data Analysis and Informatics Center. Subcortical segmentation using FreeSurfer 5.3.0 (Fischl, 2012) was used to derive left and right regions of interest. AFNI 3dDeconvolve was used to compute estimated task-related activation were computed for each participant, using the general linear model. This was available as contrast beta weights. As in Harju-Seppänen et al. (2021), the following contrasts were used: “large reward vs. no money” and “small reward vs. no money” for reward anticipation activity, and “all reward positive vs. negative

feedback" for reward outcome activity. Region of interest average beta coefficients were calculated for each of the two runs of the task and subsequently averaged. The average for the relevant ROI was used as the predictor for the neuroimaging analysis (study 2).

4.3.2.7 Covariates

Study 1

Sex, household income, parental education, and ethnicity were included as covariates owing to their association with psychosis risk (Jongsma et al., 2021; Morgan et al., 2009; D. Murphy et al., 2020). Neighbourhood Deprivation was measured using the Area Deprivation Index (ADI; (Kind et al., 2014), and urbanicity was measured by the Residential History Derived Scores (UN adjusted population density). Quintiles were then created based on the ADI scores, where the first quintile represents the lowest degree of deprivation (Vargas, Damme, & Mittal, 2020) and UN adjusted population density. Trauma was measured using the ABCD Parent Diagnostic Interview for DSM-5 (KSADS) Traumatic events. Each item was coded as 0= no and 1 = yes. A total trauma score was derived through summing the amount of traumatic experience for each individual. A full list of the items included in this measure can be found in Appendix C. Matrix reasoning was measured by the Wechsler Intelligence Scale for Children, 5th Edition (WISC-V) Matrix Reasoning Total Raw Score (Wechsler, 2014). See Chapter 2 for a full description of the matrix reasoning task. Total distress elicited by the PLEs was included as a covariate in the persistence versus no PLEs analysis, as some studies have suggested that it may be associated with higher odds of persistence (Wigman, van Winkel, et al., 2011).

Site ID were included as random-effects covariates. Subject ID was nested within family ID (Heeringa & Berglund, 2020).

Study 2

Sex, household income, parental education, and ethnicity were included as potential confounders owing to their association with psychosis risk (Jongsma et al., 2021; D. Murphy et al., 2020). Depression was included as a potential confounder

due to its association with alterations in reward processing (Keren et al., 2018). Motion in scanner was included due known role as a confounder in fMRI activation studies.

Missing data for the covariates in Study 1 and Study 2 were imputed through multiple imputation using the Mice package in R (Buuren & Groothuis-Oudshoorn, 2011). Polytomous regression was used for unordered factor variables. Proportional odds model was used for ordered factor variables. Logistic regression imputation was used for binary variables.

4.3.3 Statistical Analyses

Study 1

We conducted three main analyses to investigate predictors of the persistence of PLEs.

1. Presence of PLEs at baseline
2. Remission / Persistence: Individuals with PLEs at baseline but not follow-up, versus individuals with PLEs at baseline and follow-up
3. New incidence: Individuals who have no PLEs at baseline and have PLEs at follow-up, versus control.

This was done using multi-level logistic regression analyses. All analyses included sex, household income, parental education, ethnicity, depressive symptoms, neighbourhood deprivation, urbanicity, total trauma and matrix reasoning as fixed effects in all analyses. Site ID and family ID were included as random effects in all analyses. The analysis comparing individuals with persistent PLEs versus those whose PLEs remitted also included PLE-related distress as a covariate.

The following deviations from the pre-registered analysis occurred: 1) it was decided to correct for the number of tests and 2) the pre-registered analysis erroneously failed to mention controlling for total distress in the persistence versus control analysis.

The significance threshold was adjusted for multiple testing. As three tests were conducted, the significance threshold was set at 0.017 (0.05/3).

Study 2

Similarly to Study 1, we conducted the following analyses to investigate predictors of the persistence of PLEs.

1. Remission / Persistence: Individuals with PLEs at baseline but not follow-up, versus individuals with PLEs at baseline and follow-up

2. New incidence: Individuals who have no PLEs at baseline and have PLEs at follow-up, versus control.

However, in this case multi-level logistic regression analyses were conducted to investigate the association between reward processing at age 9-10 and persistence of PLEs at one year follow-up. Each analysis was conducted and reported separately for two outcomes: left and right activation during the reward anticipation stage of the MID task, and left and right activation during reward outcome stage of the MID task. These analyses were conducted separately for the NAcc, caudate and putamen.

For the majority of the analyses, we initially tested for a minimally adjusted association between reward-related activation and PLE persistence, adjusted only for the random effects covariates (subject ID, nested within family ID, and scanner ID). We then subsequently updated the model to include additional fixed effect covariates to test the association after adjustment for potential confounders. These included sex, household income, parental education, ethnicity and depressive symptoms.

4.4 Results

4.4.1 Study 1

After applying our exclusion criteria, 9810 individuals remained for the first analysis, which examined the predictors of PLEs at baseline (age 9-10). The demographic characteristics of the sample are shown in Table 4.1. As seen in the table below, 9245 individuals had completed the PQ-BC at baseline and one year follow up. 4396 (47.6%) were identified as not having PLEs at either time point. 1065 (11.5%) were categorised as belonging to the new incidence group, as they endorsed

one or more of the relevant PC-BQ items at one year follow-up, but not baseline. 1957 (21.2%) had remitting PLEs, as they had reported PLEs at baseline and not follow-up. Finally, 1827 (19.8%) were identified as having persistent PLEs (i.e., PLEs at both baseline and one year follow-up).

	Baseline (N = 9810)		*One year follow-up (N = 9245)*			
	No PLEs	*PLEs*	*No PLEs*	*Persistence*	*Remission*	*Incidence*
	N = 5762	*N = 4048*	*N = 4396*	*N = 1827*	*N = 1957*	*N = 1065*
Age (SD)	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)
Gender N (%)						
Female	2952 (51.2%)	2045 (50.5%)	2241 (60.0%)	902 (49.4%)	999 (51.0%)	546 (51.3%)
Household income (USD)						
<50k	1507 (26.2%)	1455 (35.9%)	968 (22.0%)	712 (39.0%)	589 (30.1%)	392 (36.8%)
>=50k & <100k	1612 (28.0%)	1151 (28.4%)	1216 (27.7%)	543 (29.7%)	551 (28.2%)	317 (29.8%)
>=100k	2643 (45.9%)	1442 (35.6%)	2212 (50.3%)	572 (31.3%)	817 (41.7%)	356 (33.4%)
Parental education N (%)						
<HS diploma	288 (5.0%)	350 (8.6%)	168 (3.8%)	166 (9.1%)	139 (7.1%)	80 (7.5%)
HS diploma/ GED	531 (9.2%)	481 (11.9%)	354 (8.1%)	234 (12.8%)	199 (10.2%)	115 (10.8%)
Some college	1483 (25.7%)	1314 (32.5%)	1038 (23.6%)	618 (33.8%)	586 (29.9%)	350 (32.9%)
Bachelor	1767 (30.7%)	1045 (25.8%)	1433 (32.6%)	454 (24.8%)	554 (28.3%)	275 (25.8%)
Postgraduate degree	1693 (29.4%)	858 (21.2%)	1403 (31.9%)	356 (19.5%)	479 (24.5%)	245 (23.0%)
Ethnicity						
White	3946 (68.4%)	2357 (58.2%)	3173 (72.2%)	993 (54.3%)	1262 (64.5%)	628 (59.0%)
BAME	1816 (31.5%)	1691 (41.8%)	1223 (27.8)	834 (45.6%)	695 (35.5%)	437 (41.0%)

Table 4.1: Demographics table: characteristics of sample who contributed to analyses

4.4.1.1 Predictors of the presence of PLEs at baseline

Depressive symptoms predicted the presence of PLEs at baseline in both the minimally adjusted (OR= 3.56, 95% CI = 3.40, 4.18, p <0.001) and fully adjusted analyses (OR= 3.21, 95% CI = 2.74, 3.77, p <0.001). Similarly, cognition predicted the presence of PLEs in the minimally adjusted (OR = 0.95, 95% CI = 0.94, 0.96, p <0.001) and fully adjusted analysis (OR = 0.98, 95% CI = 0.97, 0.99, p = 0.001). However, whilst total trauma was a significant predictor of PLEs at baseline in the minimally adjusted analysis, OR = 1.09, 95% CI = 1.04, 1.14, p <0.001), this association did not remain in the fully adjusted analysis (OR = 1.06, 95% CI = 1.01, 1.11, p = 0.013).

Additionally, the results of the fully adjusted analyses indicated that the presence of PLEs was predicted by a number of other factors. See tables 6.25-6.27 in Appendix F) for the full details of the fully adjusted analyses.

	Minimally adjusted			Adjusted for confounders		
	OR	95% CIs	p value	OR	95% CIs	p value
Depressive symptoms	3.56	3.04, 4.18	<0.001	3.21	2.74, 3.77	<0.001
Cognition	0.95	0.94, 0.96	<0.001	0.98	0.97, 0.99	0.001
Total trauma	1.09	1.04, 1.14	<0.001	1.06	1.01, 1.11	0.013

Table 4.2: Predictors of PLEs at baseline (N= 9810)

4.4.1.2 Predictors of persistence versus remission

The second analysis sought to investigate the predictors of persistence of PLEs at one-year follow-up, in the subset- of individuals who had reported PLEs at baseline. Depressive symptoms at baseline were associated with a higher odds of experiencing persistence of PLEs rather than remission (OR= 1.48, 95% CI = 1.28, 1.71, p <0.001), however, these odds were somewhat reduced in the fully adjusted analysis (OR= 1.40, 95% CI = 1.21, 1.61, p <0.001). Cognition at baseline predicted the persistence of PLEs at one-year follow-up in the minimally adjusted analysis (OR = 0.96, 95% CIs = 0.95, 0.98, p < 0.001), but not the fully adjusted analysis (OR = 0.98, 95% CIs 0.96, 1.00, p = 0.059). Trauma was a significant predictor in the minimally adjusted (OR = 1.13, 95% CIs 1.05, 1.22, p = 0.001), as well as the fully

adjusted analysis (OR = 1.10, 95% CIs 1.02, 1.18, p = 0.011). See Tables 6.28-6.30 in Appendix F for the full details of the fully adjusted analyses.

	Minimally adjusted			Adjusted for confounders		
	OR	95% CIs	p value	OR	95% CIs	p value
Depressive symptoms	1.48	1.28, 1.71	<0.001	1.40	1.21, 1.61	<0.001
Cognition	0.96	0.95, 0.98	<0.001	0.98	0.96, 1.00	0.059
Total trauma	1.13	1.05, 1.22	0.001	1.10	1.02, 1.18	0.011

Table 4.3: Predictors of persistence of PLEs (N=3784)

4.4.1.3 Predictors of new incidence of PLEs at follow-up, versus control

The third and final analysis investigated the predictors of new incidence of PLEs at follow-up (when aged 10-11) versus controls, who did not report PLEs at either time point. Depressive symptoms at baseline were associated with higher odds of new incidence of PLEs at follow-up in both the minimally- (OR= 2.22, 95% CI = 1.69, 2.90, p <0.001) and fully-adjusted analyses (OR= 1.92, 95% CI = 1.46, 2.52, p <0.001). Cognition at baseline, on the other hand, predicted the new incidence of PLEs in the minimally adjusted (OR = 0.95, 95% CI 0.93, 0.97, $p < 0.001$). This contrasts from total trauma, which was not a significant predictor in the minimally adjusted (OR = 1.07, 95% CI = 1.00, 1.13, $p = 0.035$) or fully adjusted analysis (OR = 1.04, 95% CI =0.98, 1.11, $p = 0.206$).

Tables 6.31-6.32 in Appendix F for the full details of the fully adjusted analyses. *Note, it was not possible to run a fully adjusted analysis for cognition due to convergence issues.*

	Minimally adjusted			Adjusted for confounders		
	OR	95% CIs	p value	OR	95% CIs	p value
Depressive symptoms	2.22	1.69, 2.90	<0.001	1.92	1.46, 2.52	<0.001
Cognition	0.95	0.93, 0.97	<0.001		-	
Total trauma	1.07	1.00, 1.13	0.035	1.04	0.98, 1.11	0.206

Table 4.4: New Incidence versus control (N = 5461)

See Tables 6.33-6.325 in Appendix F for a sensitivity analysis in which the analyses from study 1 were repeated in the whole sample, including individuals who

had a psychiatric diagnosis at baseline or who reported taking psychiatric medication.

4.4.2 Study 2

The second study sought to examine whether reward processing activity in the NAcc predicts whether the trajectory of PLEs at one year-follow up. After applying exclusion criteria, 6,308 individuals remained who contributed to either the final anticipation or outcome analysis. The demographic characteristics of the sample are shown in Table 4.5.

	Total (N = 6308)	*No PLEs (N = 3113)*	*Persistence (N = 1174)*	*Remission (N = 1325)*	*New incidence (N = 696)*
Age (SD)	9.9 (0.62)	9.9 (0.62)	9.9 (0.62)	9.9 (0.63)	9.9 (0.61)
Gender N (%)					
Female	3271 (51.9%)	1641 (52.7%)	593 (50.5%)	687 (51.8%)	350 (50.3%)
Household income (USD)					
<50k	1685 (26.7%)	651 (20.9%)	422 (35.9%)	378 (28.5%)	234 (33.6%)
>=50k & <100k	1800 (28.5%)	835 (26.8%)	383 (32.6%)	371 (28.0%)	211 (30.3%)
>=100k	2823 (44.8%)	1627 (52.3%)	369 (31.4%)	576 (43.5%)	251 (36.0%)
Parental education N (%)					
<HS diploma	346 (5.5%)	104 (3.3%)	98 (8.3%)	91 (6.9%)	53 (7.6%)
HS diploma/ GED	577 (9.1%)	243 (7.8%)	145 (12.4%)	121 (9.1%)	68 (9.8%)
Some college	1697 (26.9%)	699 (22.4%)	393 (33.5%)	385 (29.1%)	220 (31.6%)
Bachelor	1925 (30.5%)	1044 (33.5%)	312 (26.6%)	381 (28.8%)	188 (27.0%)
Postgraduate degree	1763 (27.9%)	1023 (32.9%)	226 (19.3%)	347 (26.2%)	167 (24.0%)
Ethnicity					
BAME	2037 (32.3)%	828 (26.6%)	518 (44.1%)	424 (32.0%)	267 (38.3%)

Table 4.5: Demographics table: characteristics of sample who contributed to study 2

4.4.2.1 Ventral Striatum

Persisting versus remitting PLEs

There was no evidence that anticipation-related activity in the NAcc predicted if someone had persistent versus remitting PLEs at one-year follow-up in either the minimally or fully adjusted analysis (see Table 4.6 below). Similarly, there was no evidence that outcome-related activity in the NAcc predicted if someone experiencing persistent, rather than remitting PLEs at one-year follow-up. This was the case in both the minimally- and fully- adjusted analyses. A full description of the NAcc analyses can be seen in Table 6.36 and Table 6.37 in Appendix F.

	Minimally adjusted			Adjusted for confounders		
	OR	*95% CIs*	*p value*	*OR*	*95% CIs*	*p value*
Anticipation-related activity	1.01	0.75, 1.37	0.954	1.03	0.75, 1.41	0.861
Outcome-related activity	0.94	0.64, 1.38	0.743	0.94	0.75, 1.37	0.743

Table 4.6: Persistence versus remission analysis for NAcc (N = 2547 for anticipation and N = 2561 for outcome)

New incidence versus control

The minimally adjusted analysis did not find any evidence that anticipation-related activity predicts the new incidence of PLEs one year later (see Table 4.7 below). We were unable to run a fully adjusted analyses to see whether anticipation- or outcome-related activity predicted new incidence versus control due to convergence and singularity issues. However, this was not pursued further due to the observed lack of association in the minimally adjusted analysis.

	Minimally adjusted			Adjusted for confounders		
	OR	*95% CIs*	*p value*	*OR*	*95% CIs*	*p value*
Anticipation-related activity	1.02	0.70, 1.48	0.932	Failed to converge		
Outcome-related activity	1.01	0.67, 1.53	0.95	Singular fit		

Table 4.7: New incidence versus control analysis for NAcc (N = 3789 for anticipation and N = 3809 for outcome)

4.4.2.2 Dorsal Striatum

Persisting versus remitting PLEs

These analyses were also repeated using dorsal striatum activity (with the caudate and putamen as predictors), and similarly, there was no evidence that reward anticipation in these regions predict PLEs at one-year follow-up. Additionally, there was no evidence that reward outcome activity in the caudate or putamen predicts PLEs at one-year follow-up.

	Minimally Adjusted			Adjusted for confounders		
	OR	95% CIs	p value	OR	95% CIs	p value
Anticipation-related activity						
Caudate	0.9604	0.2449, 3.767	0.954	1.028	0.218, 4.852	0.972
Putamen	0.9557	0.1805, 5.0611	0.9575	1.099	0.168, 7.179	0.921
Outcome-related activity						
Caudate	1.204	0.226, 6.407	0.798	1.936	0.169, 22.209	0.596
Putamen	0.8304	0.156, 4.415	0.8274	1.144	0.080, 16.307	0.921

Table 4.8: Persistence versus remission analysis for dorsal striatum (N = 2446 for caudate anticipation, N = 2492 for caudate outcome, N = 2429 for putamen anticipation and N = 2483 for putamen outcome)

The full results of the fully adjusted analyses for the caudate can be seen in tables 6.38-6.41, and detailed results for the putamen can be seen in tables 6.42-6.45. We were unable to perform the new incidence versus control analyses using dorsal striatal activity as a predictor.

4.5 Discussion

The first study explored whether depressive symptoms, cognition and trauma are predictors of PLEs, all of which have been evidenced as factors involved in the maintenance of psychotic experiences in adults. The study found that depression was a significant and substantial predictor of PLEs at baseline, and was also found to predict the persistence and new incidence of PLEs at follow-up in study one. This remained the case even after controlling for confounding variables, providing additional evidence that this may be an important causal factor. Cognition was weakly associated with PLEs cross-sectionally, including after adjustment for confounders. Cognition was also weakly associated in unadjusted analyses with PLE

persistence and new incidence but these associations did not survive adjustment for confounders. Moreover, it is notable that the effect size for any of the reported associations between cognition and PLEs was very small, indicating that evidence for a meaningful association remains weak. Traumatic events were weakly associated with PLEs and PLE persistence but the effect was largely accounted for by confounders as the association did not survive adjustment in the baseline analysis. Additionally, there was no association with new incidence of PLEs, raising the question of whether trauma is a meaningfully associated with PLEs at this age. These findings were replicated in the sensitivity analysis, with exception to the fact that trauma remained a significant predictor even after adjustment when including individuals with a psychiatric diagnosis at baseline along with those who reported taking psychiatric medication. The second study explored whether reward processing activity in the NAcc, caudate and putamen predict the persistence, remission or new incidence of PLEs at one-year follow-up. There was no evidence of a reliable association between reward processing and PLEs in any analysis.

The results indicated that PLEs were persistent in 21.2% of the sample. This is similar to the figure reported in the seminal review by Linscott and Os (2013) (which included data from 61 cohorts) estimated that PLEs were persistent in 20% of young people. It is also similar to the persistence rate in a recent population-based cohort study, which reported that hallucinatory experiences persisted in 20.5% of the participants (n = 3473) (Steenkamp et al., 2021).

In this study individuals with depressive symptoms displayed three times as high odds of reporting PLEs at baseline, as well as almost twice as high odds of experiencing new incidence of PLEs at one-year follow-up. Not only is this consistent with theoretical accounts of psychosis, which postulate that the disorder often emerges in individuals with long-standing depression and anxiety (Garety et al., 2001; Freeman et al., 2002), but it is also supported by more recent empirical studies. van Rossum et al. (2011) reported a cohort study of over 2000 young people who were followed-up at two time points (3.5 and up to 10 years later). The findings indicated that most PLEs occurred in the presence of affective dysregulation;

not only were PLEs that met a clinically relevant threshold more likely to occur with higher levels of depressive symptoms (OR = 1.28), they were also more likely to persist (OR = 1.15). The authors subsequently argued that this affective dysregulation may facilitate the mechanism of aberrant salience attribution. However, some studies suggest that whilst PLEs and depressive symptoms are co-occurring phenomena, they do not predict each other over time (Wigman, Lin, et al., 2011). Interestingly, depressive symptoms were not associated with PLE status at one year follow-up in study 2, which explored whether reward processing activity predicted PLEs one year later.

Cognition emerged as a weak but significant predictor in the cross-sectional analysis, indicating there is a contemporaneous relationship between cognition and PLEs. However, there was limited evidence that cognition predicts PLEs at one year follow-up, as this relationship did not survive adjustment for confounders. At first, this may appear to be inconsistent with existing literature, as childhood PLEs have been associated with cognitive under-performance in several longitudinal studies Hameed et al. (2013); Barnes et al. (2021). Data from the ALSPAC study has suggested that young people reporting PLEs at age 12 display reduced attention at age 11, as well as reduced performance in processing speed at age 8, compared to their peers without PLEs. There is also some evidence for an associated decline in age-matched cognitive performance between the ages of 8-11 (Niarchou et al., 2013). Gur et al. (2014) reported found that individuals with PLEs were neurocognitively behind their chronological age, and that this delay ranged between 6-18. As such, there is evidence that childhood PLEs are associated with reduced cognitive performance on a range of tasks. However, a limitation of existing findings is that they are drawn from cohort studies that were not designed to be representative of the wider population. As a result, it is possible that some of the association is accounted for by population stratification, whereby individuals who share risk factors for PLEs also share risk factors for poor cognition. Moreover, the present findings may be due to the cognitive measure used, and it is possible that performance on a extensive cognitive battery may predict PLE status at follow-up.

The association between total trauma and PLEs was less consistent. It was included as a predictor in study one and it was only a significant predictor of persistence in both the minimally and fully adjusted analyses. It was only a significant predictor of baseline PLEs in the minimally adjusted analysis, and it was not found to be associated with new incidence of PLEs. Trauma in particular has been argued to be a significant risk factor for the development of psychosis (Varese et al., 2012). However, there are multiple potential explanations of the observed lack of association. Firstly, it could be a result of the fact that only a minority of the children in the ABCD study were reported to have experienced traumatic events. Secondly, it is possible that the measure used in this study (K-SADS traumatic events) may not capture the full range of traumatic events, as it has been found that relying on a single method to identify adverse life events such as maltreatment often results in an underestimate of the frequency of these experiences (Shaffer et al., 2008). Thirdly, it is possible that trauma is not a predictor of PLEs at age 9-10, but that it may emerge as a significant predictor at a later age as the experience of trauma accumulates over childhood. Finally, there are multiple life course theoretical models which have been used to explain the relationship between childhood adversity and psychopathology, namely: recency, accumulation, or sensitive periods. It is unclear how the characteristics of adversity impacts mental health outcomes, for instance the timing of exposure to the trauma, or the duration of the experience (Dunn et al., 2018). It is likely that the children in the study varied in terms of these characteristics in ways that were not adequately captured, and indeed, on other unmeasured protective factors.

For Study 2, there was no evidence that reward processing at baseline predicted the persistence, remittance or new incidence of PLEs at one-year follow-up. Upon first observation this is not consistent with existing developmental models of psychosis risk such as the developmental risk factor model (Murray et al., 2017). This model proposes that the alterations in striatal dopamine are the final step underlying the emergence of psychotic symptoms. Indeed, there are numerous fMRI studies indicating that there are alterations in reward processing tasks as measured

by the MID task. However, these have been conducted in adults with a diagnosis of psychosis (Juckel et al., 2006; Kirschner et al., 2018) with the earliest association found in adolescents aged 14 with PLEs (Papanastasiou et al., 2018).

Nonetheless, the observed lack of association between reward anticipation activity and PLE persistence is not necessarily inconsistent with the developmental risk factor model, because it does not explicitly predict the age at which striatal dopamine dysregulation leads to aberrant salience. In fact, the model alludes to there being a cumulative impact of PLEs and stress, as it refers to a "vicious cycle", which eventually "hardwires" (Murray et al., 2017). This has also been referred to as "sensitisation" in the literature, whereby repeated exposure to an environmental risk factor results in an increased response over time. The final step of this is a lasting change in response amplitude, which has been termed to as lasting sensitisation (i.e., persistence) (Collip, Myin-Germeys, & Van Os, 2007).

Nevertheless, the present findings highlight a need for existing models to integrate findings regarding the developmental nature of PLEs. As there is currently no evidence that these alterations in reward processing are presenting in children aged 9-10 who experience distressing or non-distressing PLEs, as seen in Chapter 3, it is possible that there is another mechanism underlying PLEs in childhood and early adolescence. Future research should examine at what age PLEs being to predict aberrations in reward processing begin to emerge, in order to both aid early identification and refine our existing models of psychosis. Future research should also seek to elucidate the neurobiological mechanisms underlying PLEs in late childhood and early adolescence.

One of the main strengths of the ABCD study is its large and diverse sample, which aims to reflect the demographic make up of the US (Garavan et al., 2018). However, whilst the ABCD endeavoured to obtain a nationally representative sample, children from higher income families were over-represented. We attempted to address this by including family and site as random effects as suggested by Heeringa and Berglund (2020). Nevertheless, it is possible that this did not fully eliminate sampling biases. Additionally, PLEs were measured with the Prodromal Question-

naire – Brief Child Version (Loewy et al., 2011). This is a self-report questionnaire and although it has been well validated in this sample (Karcher et al., 2018), it may not have had the same sensitivity as structured interview assessments. However, the semi-structured assessment used in the ABCD study (KSADS-5) does not address the distress associated with PLEs.

We note here that although only included as a covariate and not the main focus of the study, study one reported that occupying a minority ethnic position was associated with having PLEs at baseline and new incidence of PLEs. Given recent meta-analytic evidence for increased risk in non-white groups (Selten, van der Ven, & Termorshuizen, 2020) this should be investigated further. Future research should also examine the developmental mechanisms through which occupying an ethnic minority position might lead to an increased risk of developing PLEs (Fung, Bhugra, & Jones, 2009).

Urban density was not a significant predictor in any of the models in study one. Not only is this contrary to theoretical accounts such as Cougnard et al. (2007) and Garety et al. (2001), but it has long been hypothesised that urbanicity may increase the risk for developing psychosis. This was first suggested by Ødegaard (1932). However, the findings in the literature are mixed. Whilst some studies report that urbanicity is associated with an increased risk of developing psychosis, other studies have found the contrary. Empson et al. (2020) highlight that the mixed findings could arise as urbanicity is a generic term, which refers to a range of known and unknown interconnected environmental and social risk factors. Similarly, parental education and sex were not significant in any of the models in either study. There was some evidence that household income is associated with new incidence of PLEs at one-year follow-up, however, this is regarded as weak as it only emerged as significant in one of the analyses conducted.

In conclusion, the results of study one found that depressive symptoms are associated with not only the presence of PLEs at baseline, but also the persistence and new incidence of PLEs one year later, even after adjusting for confounding factors. As such, this implies that distressing PLEs and PLEs accompanied by affective

symptoms warrant intervention. Study two did not find that reward processing activity in the ventral or dorsal striatum predict the presence of PLEs at one-year follow up. The mechanisms underlying PLEs in late childhood and early adolescence remain unclear and warrant further investigation. Future studies with longer periods of follow-up are required in order to characterise the developmental trajectory of PLEs and to further our understanding of the individuals who will later transition to frank psychosis.

Chapter 5

General Discussion and Synthesis

5.1 General Discussion

5.1.1 Summary of existing literature and present findings

In this thesis, I sought to examine whether potential mechanisms underlying psychotic-like experiences (PLEs) in late childhood and early adolescence are similar to those underlying PLEs and psychosis in adults. PLEs are anomalous perceptual experiences and delusion-like beliefs which occur in the absence of a clinical diagnosis (Hinterbuchinger & Mossaheb, 2021). However, existing models of psychosis fail to consider the developmental nature of PLEs, namely, the fact that they are significantly more common in childhood and appear to spontaneously remit in early adolescence (Linscott & Os, 2013). It has often been assumed that PLEs emerge due to similar mechanisms as in clinical psychosis, but it remains unclear whether the risk factors that have been reliably associated with psychosis and PLEs in adults, namely affective dysregulation, cognitive deficits, change to structural brain changes, and adverse experiences, are present in children. Additionally, existing neurocognitive models of psychosis in adults typically cite the causal role of early life experiences, affect, and cognition during development, however, these are often inferred from retrospective studies and little evidence has been drawn from contemporaneous studies particularly of pre-adolescent children. The Developmental Risk Factor Model (Murray et al., 2017) makes specific reference to the role of dopamine as a 'final common pathway' where these factors converge to gen-

erate psychotic experiences, but this is based on evidence from adults and makes the assumption that the same mechanism applies to all PLEs, regardless of when they occur in development. This too has remained untested in childhood. Finally, another significant gap in the literature was the fact that whilst persistence and distress of PLEs in children have been found to be a risk factor for poor psychiatric outcomes and increased risk of psychosis in later life, there was little evidence that tested whether established causal mechanisms for psychotic symptoms in adults were relevant earlier for PLEs earlier in development.

In my first empirical chapter, I used network analysis to explore how established environmental, neurocognitive and affective factors associated with psychotic symptoms in adults relate to the presence of PLEs in a sample of approximately 8000 children. The findings indicated that PLEs were strongly associated with depressive symptoms, but not with cognition, cortical thickness or trauma, implying that the syndromal relationship between common components and correlates of psychosis in adults were largely absent at this younger age. As such, this suggests that the relationship between these risk factors develops over time and that PLEs in childhood are not simply manifestations of a 'mini psychosis syndrome'.

In my second empirical chapter, I investigated whether reward processing, a purported mechanism for psychotic symptoms in adults is associated with the presence of PLEs in children aged 9-10. I did so whilst also controlling for a range of confounders as well as the impact of distress caused by PLEs, as distress has been shown to be of clinical relevance. This study found no evidence that PLEs (both non-distressing and distressing) are associated with alterations to reward anticipation or reward outcome in the ventral striatum (nucleus accumbens) or dorsal striatum (caudate and putamen). This indicates that whilst PLEs at this age are a potential marker of adverse development or psychopathology, they are unlikely to be generated by reward system dysregulation and may in fact be caused by a different mechanism from psychotic-spectrum experiences later in life. Hence, this first part of my thesis, which explores the presence of PLEs in late childhood, failed to find support for the view that a key purported mechanism of psychosis in adults is

replicated in late childhood.

My third and final empirical chapter focused on persistence. This was due to two reasons. Firstly, the persistence of PLEs is an important risk factor for future psychopathology and psychosis later in life (Downs et al., 2013). Secondly, persistence has been considered as a marker of psychotic disorder, as opposed to a psychotic experience, as conceptualised in neurocognitive models of psychotic symptoms (Freeman et al., 2002; Garety et al., 2001). Specifically, I explored predictors of the persistence of PLEs. This was done through conducting two studies, the first of which explored whether social, cognitive and affective predictors of adult psychosis predict the persistence, remission and incidence of PLEs in children. The second study built upon the previous chapter through investigating whether reward processing at age 9-10 predicts the persistence, remission and incidence of PLEs at one-year follow-up. The results of the first study indicated that depressive symptoms are important predictors of the presence and persistence of PLEs. Conversely, there was little to no evidence that trauma and cognition was associated with the presence or persistence of PLEs in this age group. I also attempted to explore the neurobiological basis of persistence, and found no evidence that reward processing at aged 9-10 is associated with PLE status at one-year follow-up.

5.1.2 Primary interpretation of findings

The findings of this doctoral research indicate that we need a model of psychotic experiences that is specific to this developmental stage. Depressive symptoms emerged as the strongest predictor of PLEs in late childhood and early adolescence. This was initially illustrated in the network analysis in Chapter 2. However, this was a cross-sectional analysis, and the findings could be accounted for by causality, unmeasured confounding, or shared risk factors. As such, this association was tested in a series of longitudinal models in Chapter 4, and the depressive symptoms remained a significant predictor of PLE persistence even after controlling for confounders. Reward processing, one of the key proposed mechanisms underlying the generation of psychotic experiences was tested in Chapter 3, was not found to be associated with PLEs in the general population at age 9-10. Therefore, the present

findings indicate that depressive symptoms may play a key causal role in the development of psychosis in this age group, and the mere presence of the examined PLEs, in the absence of affective dysregulation and help-seeking behaviour, may be of limited clinical significance.

5.1.2.1 Interpretation of null findings

Cognition

As outlined previously in the thesis (see Chapter 1 for a summary), numerous studies have reported that PLEs in young people are associated with cognitive deficits. This includes reduced literacy (Hameed et al., 2013), as well as other cognitive processes such as executive functioning and episodic memory (Gur et al., 2014). The findings in Chapter 4 indicated that cognition was weakly associated with PLEs cross-sectionally, as well as longitudinally, predicting both persistence and new incidence, only when not adjusted for relevant covariates. It is possible that this is a reflection of the non-pathological nature of PLEs at this developmental stages. Nonetheless, it also remains a possibility that the absence of a consistent association between cognition and PLEs is due to the subset of PLEs examined, a consideration which is discussed further in the limitations section of this chapter. Additionally, it is possible that a more extensive cognitive battery is required, or one which contains tasks assessing proposed cognitive mechanisms for psychosis.

Neuroimaging

Compared to cognition, the relationship between PLEs in young people and brain structure and functional activity is less extensive. This contrasts from the adult literature where there is significant evidence of ventral striatal reward system dysregulation in adults with psychosis, as seen in the meta-analysis by Radua et al. (2015). The lack of association between PLEs and reward processing in the present thesis suggests that while PLEs may act as markers of altered development, they are potentially not associated with alterations to striatal activation, raising doubts over whether they share a mechanism proposed for psychotic-spectrum experiences later in life. Similarly to functional neuroimaging studies, structural imaging studies report mixed findings, with some observing that young people at clinical high

risk for psychosis display atypical cortical thinning (Jung et al., 2011; Kwak et al., 2019), others do not (Hong et al., 2013). Unlike the ABCD study, many existing neuroimaging studies are limited by small sample sizes and this may explain the mixed findings in the existing literature.

Trauma

As discussed previously in the thesis (see Chapter 1), trauma has been cited in existing models of psychosis, and has been proposed to act as both a risk factor for onset as well as through leading to the emergence of maintaining factors. Study one in Chapter 4 indicated that whilst traumatic events were weakly associated with PLEs and PLE persistence, the effect was largely accounted for by confounders, and there was no association with new incidence of PLEs. These findings were replicated in the sensitivity analyses, which were performed in the whole sample, including those with psychiatric diagnosis and those who had indicated they were taking psychiatric medication at baseline. The only difference in the findings is that trauma remained a significant predictor of the presence of PLEs at baseline, even after adjustment in the sensitivity analysis. This could be due to a higher prevalence of exposure to traumatic events in the clinical group, or a reflection of the fact that young people who are receiving mental health support at age 9-10 represent a different group from the general population (Lång et al., 2022). Additionally, the network analysis in Chapter 2 indicated that trauma was one of the less central nodes, raising the question of whether trauma is meaningfully associated with PLEs at this age. Nevertheless, it is possible that this finding is due to the fact that only a small minority of the participants from the general population were reported to have experienced traumatic events and it may be that traumatic events later in development are more significant, or that there is a cumulative effect of trauma which is expressed later on in life.

5.1.2.2 Evidence for depression as an important causal factor in childhood PLEs

As stated earlier, the present findings indicate that depressive symptoms may play an important causal role in the formation and maintenance of psychotic experiences

during childhood and early adolescence. This is consistent with existing theoretical models of adult psychosis (Garety et al., 2001; Morrison, 2001; Beck & Rector, 2003; Bentall, Kinderman, & Kaney, 1994; Kesting & Lincoln, 2013; Yao & Thakkar, 2022). Whilst these models differ in terms of their emphasis, they all propose that negative affect and negative self-beliefs play a role in maintaining unusual experiences.

Whilst more research has examined the role of affective symptoms in the prodromal phase of psychosis (Freeman & Garety, 2003), the role of negative affect in maintaining PLEs also been supported by numerous studies. The first epidemiological study to demonstrate this is Jones (1994), which analysed data from over 5000 individuals in the British 1946 birth cohort and concluded that anxiety at age 13 was associated with higher odds of developing schizophrenia. This study did not examine depressive symptoms although considering the well-established comorbidity between anxiety and depression, it is plausible that both were important predictors. More recently, Escher, Romme, Buiks, Delespaul, and Van Os (2002) followed up 80 children who heard voices (mean age 12.9 years at baseline) for three years and found that affective symptoms and negative appraisals of the voices were predictors of persistence. Moreover, they were superior at predicting persistence than global functioning and more traditional measures of psychotic symptomatology such as frequency. Furthermore, there are also studies which have failed to find a longitudinal bi-directional relationship between PLEs and depressive symptoms. This includes Wigman, van Winkel, et al. (2011), who performed a cross-lagged panel analysis and suggested that PLEs and depressive symptoms are interwoven but do not predict each other over time, indicating that they may emerge due to a common cause. This contrasts slightly from Sullivan et al. (2014)'s findings, which found that depressive symptoms at age 12 are not associated with an elevated risk of developing PLEs at age 18, once the co-occurrence of depression and PLEs is accounted for. They did, however, find evidence that PLEs are associated with slightly higher odds of developing depression. Nevertheless, it is worth noting that these studies are limited by their sample size (N= 138 for Wigman, van Winkel, et al. (2011), the

fact that the participants were help-seeking and their age (15-24 for Wigman, van Winkel, et al. (2011), 12 for Sullivan et al. (2014).

The last two characteristics of these studies in particular limit the authors' ability to draw inferences regarding the causal role of depressive symptoms in the development of psychosis. Overall, Hartley, Barrowclough, and Haddock (2013)'s review concluded that there is evidence from longitudinal studies that depression and anxiety predate the first episode of psychosis, as well as acute relapses, lending support to the notion that they play a causal role in triggering psychotic experiences. However, Hartley et al. (2013) has noted important limitations to the existing evidence. Firstly, it is possible that anxiety and depression are identified more easily than PLEs. Secondly, they acknowledge that temporal precedence is not necessarily equivalent to causality, as psychosis, anxiety and depression may emerge by a common cause.

The notion that psychosis, anxiety and depression exist as comorbid phenomena, rather than being causally linked was first proposed by Verdoux et al. (1998). This was based on the observation that psychosis proneness was associated with a greater risk of depression, which led the authors to propose that the two may emerge due to a common liability. It has also been argued that psychosis and depression share common risk factors. This view has been supported by factor analyses based on both self-report (Stefanis et al., 2002) and clinical interview data (Krabbendam et al., 2004) which have found that PLEs and depression are separate but correlated dimensions. Not only is there a paucity of studies which have investigated the risk factors for depression and PLEs within the same study (Breetvelt et al., 2010; Krabbendam et al., 2004), few have explicitly tested whether risk factors are shared between PLEs and depression, while jointly modelling both outcomes. Additionally, both studies that have examined this used data from the ALSPAC study (Davies et al., 2018; Kounali et al., 2014). Kounali et al. (2014) used data from ALSPAC and examined the association with 19 risk factors and found that most of the established risk factors for psychosis were associated with both PLEs and depressive symptoms. As such, the authors suggested that the argument that PLEs

present as valid markers to study the aetiology of psychosis as they share risk factors is questionable, as PLEs also share many risk factors with depression. In fact, the only risk factors that appeared to discriminate between the two outcomes was female sex, and to a weaker extent, family history of depression. Both of these were more common in individuals with depressive symptoms, whilst markers of delayed neurodevelopment were more strongly associated with PLEs. The fact that neurodevelopmental impairments were more pervasive in those with PLEs suggests that PLEs and depression are not solely expressions of a common underlying cause. However, this study examined PLEs and depressive symptoms at age 18, which limits our understanding of the causal role of depression.

Moreover, it remains a possibility that anxiety and depression act as a mediator. For instance, a study analysing data from the 2007 Adult Psychiatric Morbidity Survey (Marwaha & Bebbington, 2015) found affect mediated the link between childhood sexual abuse and psychosis. The results also indicated that depression may be of more significance than anxiety. This is consistent with studies such as Alameda, Conus, Ramain, Solida, and Golay (2021), which followed up 330 individuals with early psychosis at six time points (up to 36 months after treatment). Approximately one third of the participants had been exposed to abuse before the age of 16, and in these individuals it was found that depression and anxiety partially mediated over a quarter of the association between abuse and positive symptoms. However, only depression appear to mediate these symptoms over time, while anxiety was only a mediator at baseline. Nevertheless, it is worth noting that affect was measured essentially contemporaneously with PLEs in Marwaha and Bebbington (2015), as respondents were asked about their anxiety and depressive symptoms in relation to the preceding week. Additionally, subsequent studies have failed to find evidence that depressive or anxiety symptoms mediate the association between sexual trauma and transition to psychosis (A. Thompson et al., 2016). Most importantly, these studies do not examine affective dysregulation in childhood. Other potential pathways involving anxiety and depression have been proposed, such as in Francesconi et al. (2020), which used data from the ALSPAC study and found

that internalising symptoms mediated the relationship between inflammation at age 9 and PLEs at age 18. Nevertheless, a recent review of the mediators and moderators of the association between childhood adversity and psychosis reported that the evidence for the mediating role of mood was not robust (Sideli et al., 2020). It is worth noting that strong proponents of the Developmental Risk Factor Model may argue that the present findings are not necessarily in conflict with the predictions of this model. This argument may take several forms. Firstly, one may state that the participants in this cohort study may not have accumulated enough risk to display signs of psychopathology (Dunn et al., 2018). Nonetheless, if this is the case, it is unclear why PLEs are associated with depressive symptoms at this age.

As stated in the introduction, it has been argued that PLEs may be present for one of three reasons (Nelson & Yung, 2009), and that they may represent:

1. An expression of underlying and more fundamental disturbance (including self- or ipseity disturbance)

2. Clinical "noise" around a non-psychotic disorder

3. Present in non-clinical individuals, not associated with distress or reduced functioning

The present thesis attempted to focus on hypotheses relating to the first category as this is the most clinically significant category in terms of psychosis risk. In order to do this, it examined clinically relevant PLEs, through addressing both distress and persistence and focusing on a specific subset of PLEs, in order to understand the development of psychosis. The findings of the present thesis do not support the existence of a fully dimensional continuum in childhood and early adolescence, as the key purported mechanism of psychotic symptoms was not replicated. However, it remains unclear whether a diagnostic discontinuous model or quasi-dimensional model best explains PLEs in childhood. The present thesis indicates that depressive symptoms appear to play a causal role in the development of psychosis. Moreover, it is likely that there are multiple routes into psychosis, as PLEs are complex and multi-dimensional phenomena. As highlighted by Bentall et

al. (2014), psychosis is a heterogeneous phenomenon and it is unlikely that there is one single pathway leading to its onset, even if we are looking at one specific cause. Therefore, a number of possible pathways have been proposed below, based on the present doctoral thesis as well as the existing body of research.

1. Direct impact of affective dysregulation on cognitive biases via anxiety, hyper-vigilance or mood
2. Developmental delay leading to impeded cognitive and perceptual trajectory
3. Genetic risk
4. Accumulative latent risk via adverse life events

In order to test the routes outlined above, longitudinal studies need to have multiple data collection points in childhood and early adolescence -ideally annually- where PLEs and affective symptoms are measured. Additionally, exposure to adverse life events and cognition should be examined regularly.

5.1.3 Implications for the continuum model of psychosis

These findings also raise the question of whether the continuum of psychosis model, drawn from adult studies, can be conceptualised as extending into late childhood and early adolescence with unmodified assumptions about its causal mechanisms and taxometric continuity across all age groups. In this case, a taxon refers to the existence of a separate latent population which underlies PLEs in adolescence (Bentall et al., 2014). Typically, evidence for the existence of the continuum is considered in a cross-sectional manner, as it is based on epidemiological or population based studies which report a high level of PLEs in the general population (van Os & Kapur, 2009). However, there is an implicit assumption of the existence of a temporal continuum as well, one which extends across development. Consequently, existing accounts also make an assumption that the same mechanisms are underlying these experiences across the population (Murray et al., 2017). Whilst some may argue that this is the case in adults, the findings of this thesis strongly suggest that a

concept of a unitary psychosis continuum does not easily extend into earlier development. This is evidenced by the fact that established risk factors for psychosis did not appear to cluster together with PLEs in children aged 9-10, as well as the fact that we found no evidence that PLEs were associated with reward processing at this age either, even when the distress induced by PLEs was accounted for.

Nevertheless, it is worth noting that even the concept of a psychosis continuum in adults is not without controversy. For instance, David (2010) states that even proponents of a continuum set a threshold in order to define unusual experiences. This results in a prevalence rate of PLEs that varies substantially (van Os & Kapur, 2009). It has also been argued that some the items in PLE measures may encourage false positives (David, 2010), such as the item 'Some people believe in mind reading or being psychic. Have other people ever read your mind?' which is used in the Dundein interview for children (Poulton et al., 2000). In David (2010)'s editorial, the author refers to type I and type II continua. Type I refers to the population level, whereby each individual is regarded to exhibit a trait which may assume a normal distribution when plotted. This approach is taken in epidemiological studies of PLEs (van Os & Kapur, 2009). Type II is the phenomenological approach and refers to a continuum of experience. Strauss (1969)'s seminal paper implements this approach, as it focused on definite delusions and hallucinations as well as those that could not as easily be classified, arguing that delusions and hallucinations themselves form a continuum. More recent research which take a type II continuum approach include studies which examine hallucinations (Sommer et al., 2010) and delusions (E. Peters, Joseph, & Garety, 1999; E. Peters et al., 2016) in non-clinical and clinical populations. The different continuum approaches can be seen in Figure 5.1 below.

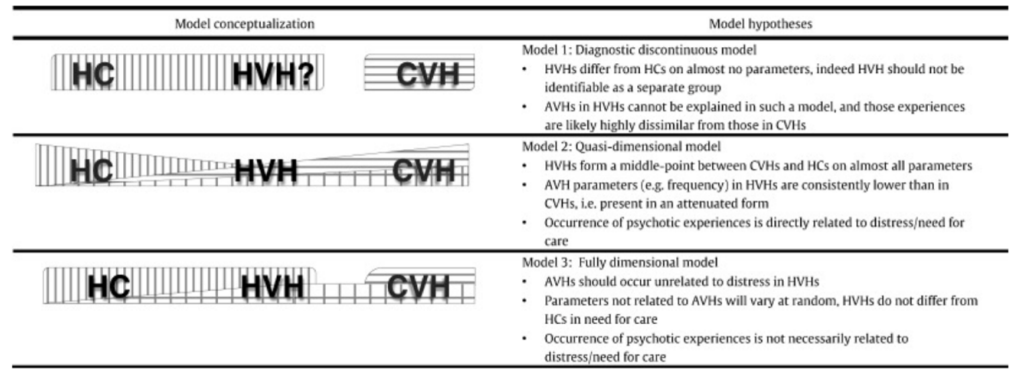


Figure 5.1: Existing psychosis continuum conceptualisations, from Baumeister, D., Sedgwick, O., Howes, O., Peters, E. (2017, February). Auditory verbal hallucinations and continuum models of psychosis: A systematic review of the healthy voice-hearer literature. Clinical Psychology Review, 51, 125–141

David (2010)'s editorial also argues we ought to question whether the concept of a continuum can be applied to psychological phenomena such as psychosis, which is multi-dimensional, suggests that we may instead "micro-dissect phenomena" in order to identify the specific mechanisms underlying them.

Conversely, it has subsequently been argued that psychosis continuum models enable us to establish the extent to which healthy voice hearers (HVHs) are actually "healthy" and the likelihood of them remaining so (Baumeister, Sedgwick, Howes, & Peters, 2017). If one takes the view of the diagnostic models, benign auditory verbal hallucinations (AVHs) should be very different from AVHs in clinical voice hearers, and HVHs and healthy controls should show a significant difference in risk exposure. A quasi-dimensional model purports that HVHs are in the middle of CVHs and HCs on all parameters, and so an increase in the frequency of PLEs ought to be associated with an increased need for care. Finally, according to the fully dimensional model, AVHs should not be associated with a need for care, and HVHs should not be at elevated risk of distress when compared to healthy controls (Baumeister et al., 2017). Overall, this review concluded that the existing evidence is inconsistent with categorical models of PLEs, and that there is an equal level of support for quasi- and fully dimensional models. Indeed, it appears that whilst PLEs

are continuous with psychotic disorders, they can present independently. According to the transdiagnostic extended phenotype model (van Os & Reininghaus, 2016), PLEs are a reflection of two underlying constructs 1) firstly, the existence of a specific phenotypic expression of sub-clinical psychosis (hallucinatory experiences and delusional ideation) and 2) transphenotypic expressions of psychopathology (negative symptoms, disorganisation, affective symptoms). Therefore, the authors are essentially arguing for a bi-modal model of psychosis, which consists of a general transdiagnostic psychosis factor and specific psychosis factors. It is the combination of positive symptoms and non-specific psychotic factors such as affective dysregulation which is critical for causing an individual to display a need for care.

Up until now, it has been assumed that adult psychosis continuum models apply to children. The existence of a single continuum appears unlikely given 1) the significantly higher prevalence of PLEs in childhood and 2) the observation that these PLEs spontaneously remit in the majority of individuals. As such, it is likely that there are multiple psychosis continua, with multiple different mechanism underlying these experiences. This is particularly the case as the present research failed to find evidence that alterations in reward processing, a key purported mechanism for the development of psychosis, is associated with PLEs in late childhood. Further consideration needs to be given to the conceptualisation of the continuum in childhood, as it predates the typical onset of psychosis and can thus inform our understanding of the development of psychotic disorders.

5.1.4 Strengths and Limitations

5.1.4.1 Strengths

One of the main strengths of the ABCD study is its sample size and diversity. As mentioned earlier, this study implemented a "population neuroscience" approach, and as such, aimed to recruit a sample that is representative of the US population (Volkow et al., 2018). This is of importance because occupying an ethnic minority position has been found to be associated with an increased risk of developing psychosis (Jongsma et al., 2021), and some research has found that this elevated risk may be observed in childhood (Adriaanse et al., 2015). Additionally, the young peo-

ple participating in the ABCD study are age 9 at the time of the baseline assessment, which allows for the examination of premorbid markers of mental health difficulties (Karcher & Barch, 2021). However, there is a possibility that there was an over-representation of children from higher income families. Heeringa and Berglund (2020) recommend a three-level multi-level specification (site, family, individual) when using regression modelling, which is an approach that has been implemented wherever possible in this thesis.

Another strength of this doctoral research is that it examined the role of PLE-induced distress. This was only possible through using the PQ-BC (Karcher et al., 2018), rather than the KSADS-5. The PQ-BC asks the respondent both about whether they had a certain experience and if so, how much distress it caused them. The PQ-BC has been validated in children aged 9 to 10 (Karcher et al., 2018). Nonetheless, studies have found highlighted potential discrepancies between self-reported and interviewed PLEs, and it has been suggested that specific experiences such as auditory hallucinations may be more reliably reported (Granö et al., 2016). Gundersen et al. (2019) analysed data from children aged 11-12 from the Copenhagen Child Cohort 2000 (N= 1571) and found that the PLEs elicited by the self-report DAWBA has high specificity and it can be used to screen for PLEs in the general population. However, this has not been explored specifically in relation to the PQ-BC.

5.1.4.2 Limitations

This thesis focused on a specific subset of PLEs, rather than all the items available in the PQ-BC. This was a theoretically driven approach, as the items included in the present analyses were selected as they map onto the first-rank symptoms proposed by Schneider (Schneider, 1959). Schneider argued that specific symptoms are indicative of schizophrenia and should therefore be given "first-rank" status within the diagnostic hierarchy. First rank symptoms (FRS) include auditory hallucinations, somatic hallucinations, delusional perception and passivity symptoms (which includes thought insertion, thought withdrawal and thought broadcasting). The DSM-5 treats FRS in the same manner as other Criterion A symptoms. As

summarised in Heinz et al. (2016), there are three lines of argument that have been used against first-rank symptoms, firstly, that they are not exclusive to schizophrenia. Secondly, that they appear in individuals without a clinical disorder, and finally that the impairments in FRS reflect European traditions regarding self-reflection. Whilst FRS are no longer part of the diagnostic criteria in the DSM-5 (American Psychiatric Association, 2013), there has been a renewed interest in their clinical utility, due to reviews indicating that FRS have a high specificity (Soares-Weiser et al., 2015).

The majority of existing research has measured PLEs in a single scale, in which the scores are summed together in order to calculate a total score. Nevertheless, it has been argued that psychotic experiences such as paranoia and hearing voices are qualitatively distinct and may vary in terms of their aetiology (Zavos et al., 2014). Thus, summing the scores may result in imprecision in the estimation of PLEs, as the items in the measure may be weighted differently or differ in terms of the severity they represent (Gibbons, Weiss, Frank, & Kupfer, 2016). As such, some suggested that research examining PLEs in adolescence should focus on specific symptoms. This includes paranoia, which Bird et al. (2021) has argued may exert a particular influence on daily life, through impacting social relationships, especially as adolescence may be a sensitive time for social interaction (Orben, Tomova, & Blakemore, 2020).

Another limitation of this thesis is that symptoms of anxiety were not included, due to high levels of missingness in the ABCD cohort at baseline. As seen previously in Evidence for depression as an important causal factor in childhood PLEs, both depressive and anxiety symptoms have been implicated in the development of psychosis. Nonetheless, there appears to be a stronger evidence that depressive symptoms are of particular relevance (Hartley et al., 2013). Future studies should examine whether specific symptoms of depression are more heavily implicated in the development of psychosis, as research has highlighted that depression is heterogeneous and different scales address different aspects of the syndrome (Fried, 2017).

Another limitation of the present thesis is the absence of a chapter examining the association between resting-state functional MRI activity and PLEs. This was not possible due to the impact of Covid-19, which meant that a planned research visit was unable to go ahead. Future research should explore this further. Other avenues for future research using this dataset include: investigating whether specific PLEs are more likely to be distressing and persistent and therefore of potential clinical relevance, exploring the longitudinal trajectories of PLEs in the ABCD dataset and conducting longitudinal network analyses as this was not possible due to time constraints.

5.1.5 General conclusion

In conclusion, it appears that current adult models of psychosis, and the existence of a single psychosis continuum, cannot be easily applied developmentally to childhood PLEs. This is as childhood PLEs are benign experiences for most, and the likely causal factors underlying them appears to differ from the mechanisms underlying adult PLEs. As such, future research research should consider whether there are multiple continua underlying PLEs in young people. Moreover, affective dysregulation appears to be a key factor when considering the potential clinical relevance of childhood PLEs. As such, models need to incorporate the key role of negative affect in the causal developmental of psychosis.

Chapter 6

Appendices

6.1 Appendix A: Description of ABCD study sample

Sampling and Recruitment Procedure

A summary of the sampling and recruitment procedure in the ABCD study is provided below. See Garavan et al. (2018) for a full description.

A baseline cohort of 11,500 individuals aged nine and ten (as well as their parents/guardians) was recruited and will be followed up for ten years. The final cohort is planned to include 9780 single births and 1720 twins. The sample size includes an anticipated 10% attrition rate. See Iacono et al. (2018) for a detailed account of how the twin recruitment was conducted. The recruitment method was developed in order to obtain a sample that reflects the demographic characteristics of the US population.

This was done using multi-stage probability sampling, which theoretically speaking provides all those eligible inclusion a known, non-zero probability of inclusion in the cohort. This approach has previously been used in studies such as the National Health and Nutrition Examination Survey (Heeringa, West, & Berglund, 2017). This type of design allows researchers to implement design-based statistical methods that result in unbiased or nearly unbiased inferences to the larger population from which the sample was selected. The recruitment for the ABCD cohort adopts a multi-stage probability sample of eligible participants, with 21 primary stage sites located across the US, probability sampling of schools within the catch-

ment area for each of these sites, and finally, recruitment of children and young people in each school. The only instance in which the ABCD deviates from probability sampling is in terms of the selection of the neuroimaging sites. Whilst the sites are distributed well on a national level (see Table 6.1), the selection of collaborating sites was influenced by the grant review selection process and the requirement to have both the required research expertise and neuroimaging equipment needed to implement the study protocol. As such, the neuroimaging research centres are more likely to be located in urban areas. This in turn may lead to an under-representation of young people living in rural areas.

Census Region of ABCD Study Site	Total Study Sites	Single Birth Baseline Cohort[c]	Race/Ethnicity of Child[a]					Rural School Students
			White	African-American	Hispanic	Asian	All Other[b]	
Northeast	4	1900	1252	315	207	68	58	358
Midwest	4	1385	795	321	124	94	49	210
South	6	2710	1114	694	596	85	221	310
West	7	3520	1546	251	1284	257	195	320
Total ABCD Baseline	21	9515	4707	1581	2211	504	512	1198
% of ABCD Single Birth Total in Target Sample	NA	100.0%	49.5%	16.6%	23.2%	5.3%	5.4%	12.3%
%Total ABCD 21 Site Age 9–10 Children in Public and Private Schools	NA	100.0%	51.3%	14.9%	23.4%	5.6%	4.9%	12.3%
%Total U.S. Population Age 9–10 Children in Public and Private Schools	NA	100.0%	50.7%	14.5%	25.1%	5.0%	4.7%	17.5%

Table 6.1: ABCD Single Birth Expected Demographic Targets for the Nation and by U.S. Census Region. From Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R. Z., Heeringa, S., . . . Zahs, D. (2018, August). Recruiting the ABCD sample: Design considerations and procedures. Developmental Cognitive Neuroscience, 32, 16–22. doi: 10.1016/j.dcn.2018.04.004

a Assumes a 50:50 female to male allocation for each race/ethnicity category.

b Includes children of Native Hawaiian, Pacific Islander, Alaskan Native, American Indian and multiple races.

c An additional 265 subjects, which will bring the single birth total to 9780, are not yet allocated. Their allocation will be made to ensure that the final sample

matches the target demographics.

6.2 Appendix B: Prodromal Questionnaire-Brief Child Version (PQ-BC)

6.2.1 Description of PQ-BC

Full details regarding the measure is available in Karcher et al. (2018)

1. Did places that you know well, such as your bedroom, or other rooms in your home, your classroom or school yard, suddenly seem weird, strange or confusing to you; like not the real world?

2. **Did you hear strange sounds that you never noticed before like banging, clicking, hissing, clapping, or ringing in your ears?**

3. Did things you looked at seem different than they usually do; like did they seem shinier or darker, larger or smaller or changed in some other way?

4. Did you feel like you had special, unusual powers like you could make things happen by magic, or that you could magically know what was inside another person's mind, or magically know what was going to happen in the future when other people could not?

5. **Did you feel that someone else, who is not you, has taken control over the private, personal, thoughts or ideas inside your head?**

6. Did you suddenly find it hard to figure out how to say something quickly and easily so that other people would understand what you meant?

7. Did you ever feel very certain that you have very special abilities or magical talents that other people do not have?

8. **Did you suddenly feel that you could not trust other people because they seemed to be watching you or talking about you in an unfriendly way?**

9. Did your skin or just beneath your skin suddenly start feeling strange, like bugs crawling?

10. Did you lose concentration because you noticed sounds in the distance that you usually don't hear?

11. Although you could not see anything or anyone, did you suddenly start to feel that an invisible energy, creature, or some person was around you?

12. Did you start to worry at times that your mind was trying to trick you or was not working right?

13. Did you feel that the world is not real, you are not real, or that you are dead?

14. Did you feel confused because something you experienced didn't seem real or it seemed imaginary to you?

15. **Did you honestly believe in things that other people would say are unusual or weird?**

16. Did you feel that parts of your body had suddenly changed or worked differently than before; like your legs had suddenly turned to something else or your nose could suddenly smell things you'd never actually smelled before?

17. Did you feel that sometimes your thoughts were so strong you could almost hear them, as if another person, NOT you, spoke them?

18. **Did you feel that other people might want something bad to happen to you or that you could not trust other people?**

19. Did you suddenly start to see unusual things that you never saw before like flashes, flames, blinding light, or shapes floating in front of you?

20. **Did you suddenly start to be able to see things that other people could not see or they did not seem to see?**

21. Did you suddenly start to notice that people sometimes had a hard time understanding what you were saying, even though they used to understand you well?

6.3 Appendix C: Parent Diagnostic Interview for DSM-5 (KSADS) Traumatic Events

Carers are asked to indicate whether the young person has experiencing the following events *(yes/no)*:

1. A car accident in which your child or another person in the car was hurt bad enough to require medical attention
2. Another significant accident for which your child needed specialized and intensive medical treatment
3. Witnessed or caught in a fire that caused significant property damage or personal injury
4. Witnessed or caught in a natural disaster that caused significant property damage or personal injury
5. Witnessed or present during an act of terrorism (e.g., Boston marathon bombing)
6. Witnessed death or mass destruction in a war zone
7. Witnessed someone shot or stabbed in the community
8. Shot, stabbed, or beaten brutally by a non-family member
9. Shot, stabbed, or beaten brutally by a grown up in the home
10. Beaten to the point of having bruises by a grown up in the home
11. A non-family member threatened to kill your child
12. A family member threatened to kill your child
13. Witness the grownups in the home push, shove or hit one another
14. A grown up in the home touched your child in their privates, had your child touch their privates, or did other sexual things to your child

15. An adult outside your family touched your child in their privates, had your child touch their privates or did other sexual things to your child
16. A peer forced your child to do something sexually
17. Learned about the sudden unexpected death of a loved one

6.4 Appendix D: Supplementary Analyses for Chapter 2

6.4.1 Endorsement of PLE items at baseline

	Healthy controls (N = 8460)	Clinical sample (N = 3404)
AVH (PQ-BC Item 2)		
Endorsement	1587 (18.8%)	738 (21.7%)
Distress	1010 (63.6%)	477 (64.6%)
TI (PQ-BC Item 5)		
Endorsement	383 (4.5%)	209 (6.1%)
Distress	299 (78.1%)	149 (71.3%)
Paranoia 1 (PQ-BC Item 8)		
Endorsement	1773 (21.0%)	805 (23.7%)
Distress	1425 (80.4%)	632 (78.5%)
Bizarre Beliefs (PQ-BC Item 15)		
Endorsement	936 (11.1%)	392 (11.5%)
Distress	339 (36.2%)	142 (36.2%)
Paranoia 2 (PQ-BC Item 18)		
Endorsement	1150 (13.6%)	580 (17.0%)
Distress	768 (66.8%)	387 (66.7%)
VH (PQ-BC Item 20)		
Endorsement	756 (8.9%)	445 (13.1%)
Distress	292 (38.6%)	166 (37.3%)

Table 6.2: Endorsement of individual PLEs from PQ-BC and proportion of distress for healthy controls and clinical sample (individuals with a psychiatric medication or who are taking psychiatric medication)

Number of PLEs (N / %)	Healthy controls (N = 8460)	Clinical sample (N = 3404)
0	4976 (58.8%)	1809 (53.1%)
1	1752 (20.7%)	758 (22.3%)
2	894 (10.6%)	406 (11.9%)
3	465 (5.5%)	223 (6.6%)
4	235 (2.8%)	127 (3.7%)
5	118 (1.4%)	64 (1.9%)
6	20 (0.2%)	17 (0.5%)

Table 6.3: Distribution of number of PLEs for healthy controls and clinical sample (individuals with a psychiatric medication or who are taking psychiatric medication)

6.4.2 Correlation matrix

Variable	Trauma	Frontal lobe	Occipital lobe	Parietal lobe	Temporal lobe	WM	Vocabulary	FI
Trauma	1.00	-0.03	-0.04	-0.04	-0.03	-0.02	-0.02	-0.03
Frontal lobe	-0.03	1.00	0.53	0.80	0.75	0.00	0.02	0.01
Occipital lobe	-0.04	0.53	1.00	0.62	0.55	0.09	0.05	0.06
Parietal lobe	-0.04	0.80	0.62	1.00	0.73	0.04	0.03	0.02
Temporal lobe	-0.03	0.75	0.55	0.73	1.00	0.05	0.07	0.07
WM	-0.02	0.00	0.09	0.04	0.05	1.00	0.34	0.65
Vocabulary	-0.02	0.02	0.05	0.03	0.07	0.34	1.00	0.62
FI	-0.03	0.01	0.06	0.02	0.07	0.65	0.62	1.00

Table 6.4: Correlation matrix for continuous variables included in network

6.4.3 Accuracy of networks

Edge-weights and their bootstrapped confidence intervals

Edge	*Mean edge-weight*	*CIs*
Auditory Hallucination–Anhedonia	0.19	0.04, 0.28
Auditory Hallucination–Bizarre Beliefs	0.22	0.14, 0.29
Auditory Hallucination–Depressed Bood	0.14	-0.03, 0.30
Auditory Hallucination–Frontal Lobe	0 (no edge)	-0.001, 0.001
Auditory Hallucination– Irritability	0.05	-0.12, 0.12
Auditory Hallucination– Fluid Intelligence	0 (no edge)	-0.01, 0.01
Auditory Hallucination– Working Memory	0 (no edge)	-0.003, 0.003
Auditory Hallucination– Receptive Vocabulary	0 (no edge)	-0.004, 0.004
Auditory Hallucination– Occipital Lobe	0 (no edge)	0.0, 0.0
Auditory Hallucination– Paranoia	0.31	0.27, 0.35
Auditory Hallucination– Parietal Lobe	0 (no edge)	0.0, 0.0
Auditory Hallucination– Temporal Lobe	0 (no edge)	0.0, 0.0
Auditory Hallucination–Thought Insertion	0.50	0.40, 0.61
Auditory Hallucination– Total Trauma	0 (no edge)	-0.02, 0.02
Auditory Hallucination–Visual Hallucination	0.43	0.35, 0.50
Bizarre Beliefs–Anhedonia	0.01	-0.07, 0.07
Bizarre Beliefs– Depressed mood	0 (no edge)	-0.03, 0.03
Bizarre Beliefs–Frontal lobe	0 (no edge)	-0.002, 0.002
Bizarre Beliefs–Irritability	0.13	-0.07, 0.30
Bizarre Beliefs– Fluid Intelligence	0 (no edge)	0.0, 0.0
Bizarre Beliefs–Working Memory	0 (no edge)	-0.02, 0.02
Bizarre Beliefs–Receptive Vocabulary	0 (no edge)	-0.002, 0.002
Bizarre Beliefs–Occipital Lobe	0 (no edge)	0.0, 0.0
Bizarre Beliefs–Parietal Lobe	0 (no edge)	0.0, 0.0
Bizarre Beliefs–Temporal Lobe	0 (no edge)	0.0, 0.0
Bizarre Beliefs–Total Trauma	0 (no edge)	-0.004, 0.004
Paranoia–Anhedonia	0.21	0.12, 0.27
Paranoia–Bizarre Beliefs	0.32	0.27, 0.37
Paranoia–Depressed mood	0.24	0.12, 0.33
Paranoia–Frontal Lobe	0 (no edge)	-0.005, 0.005
Paranoia–Irritability	0.23	0.12, 0.32
Paranoia–Fluid Intelligence	0 (no edge)	-0.01, 0.01

Table 6.5: Edge-weights and their bootstrapped confidence intervals (part 1)

Edge	*Mean edge-weight*	*CIs*
Paranoia–Working Memory	-0.05	-0.07, -0.03
Paranoia–Receptive Vocabulary	0 (no edge)	-0.004, 0.004
Paranoia–Occipital Lobe	0 (no edge)	0.0, 0.0
Paranoia–Parietal Lobe	0 (no edge)	0.0, 0.0
Paranoia–Temporal Lobe	0 (no edge)	-0.01, 0.01
Paranoia–Total Trauma	0 (no edge)	-0.004, 0.0
Paranoia–Visual Hallucination	0.34	0.28, 0.39
Thought Insertion–Anhedonia	0.07	-0.15, 0.15
Thought Insertion–Bizarre Beliefs	0.16	0.03, 0.28
Thought Insertion–Depressed Mood	0.12	-0.09, 0.32
Thought Insertion–Frontal Lobe	0 (no edge)	0.0, 0.0
Thought Insertion–Irritability	0.05	-0.15, 0.15
Thought Insertion–Fluid Intelligence	0	-0.01, 0.01
Thought Insertion–Working Memory	-0.01	-0.03, 0.03
Thought Insertion–Receptive Vocabulary	0 (no edge)	-0.01, 0.01
Thought Insertion–Occipital Lobe	0 (no edge)	0.0, 0.0
Thought Insertion–Paranoia	0.5	0.41, 0.56
Thought Insertion–Parietal Lobe	0 (no edge)	0.0, 0.0
Thought Insertion–Temporal Lobe	0 (no edge)	-0.02, 0.02
Thought Insertion–Total Trauma	0 (no edge)	-0.03, 0.03
Thought Insertion–Visual Hallucination	0.35	0.23, 0.47
Visual Hallucination–Anhedonia	0.28	0.14, 0.40
Visual Hallucination–Bizarre Beliefs	0.43	0.34, 0.52
Visual Hallucination–Depressed Mood	0.23	0.05, 0.40
Visual Hallucination–Frontal Lobe	0 (no edge)	-0.003, 0.003
Visual Hallucination–Irritability	0.12	-0.06, 0.28
Visual Hallucination–Fluid Intelligence	-0.02	-0.06, 0.06
Visual Hallucination–Working Memory	-0.01	-0.04, 0.04
Visual Hallucination–Receptive Vocabulary	0 (no edge)	-0.02, 0.02
Visual Hallucination–Occipital Lobe	0 (no edge)	0.0, 0.0
Visual Hallucination–Parietal Lobe	0 (no edge)	0.0, 0.0
Visual Hallucination–Temporal Lobe	0 (no edge)	-0.005, 0.005
Visual Hallucination–Total Trauma	0.01	-0.03, 0.03

Table 6.6: Edge-weights and their bootstrapped confidence intervals (part 2)

Differences between non-zero edge-weights Figure 6.1. Differences between edge-weights: statistically significant differences indicated by a black square, non-significant differences by a grey square.

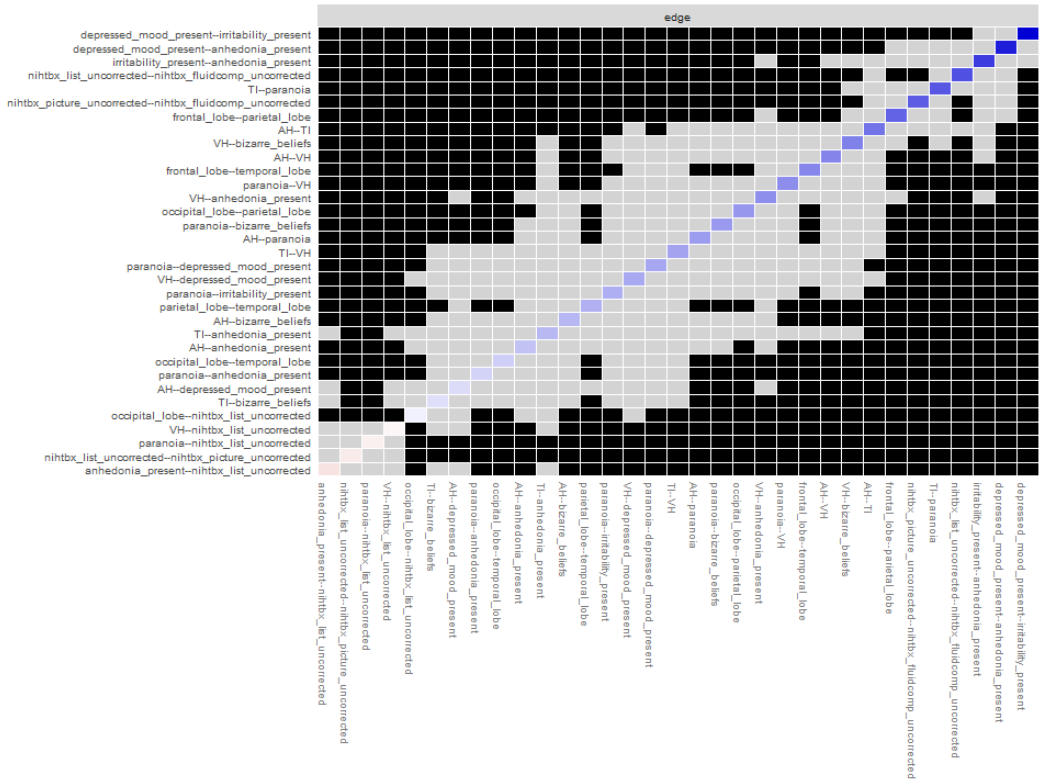


Figure 6.1: Differences between edge-weights

6.4.4 Sensitivity analysis

As seen below, the sensitivity analysis indicated that the estimated network was similar to the network in the main sample (i.e., individuals without a diagnosis and who are not taking psychiatric medication).

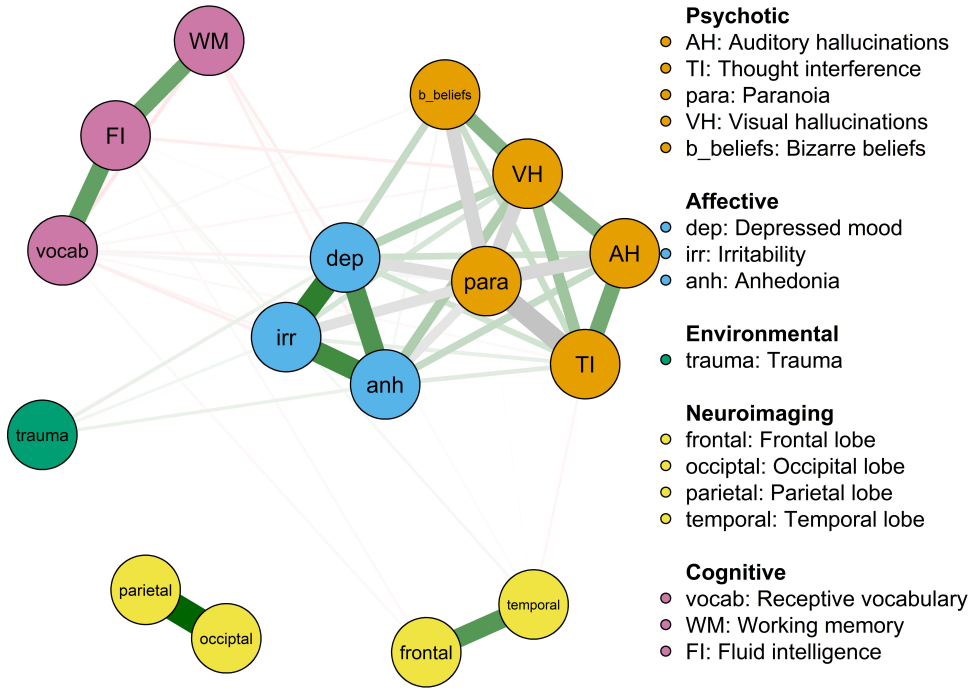


Figure 6.2: Estimated network when including all participants

6.5 Appendix E: Supplementary Analyses for Chapter 3

6.5.1 Ventral striatum: Effect of PLEs on reward processing when including individuals with a psychiatric diagnosis or psychiatric medication use

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.002	-0.014, 0.011	0.796
Distressing PLEs	-0.011	-0.020, -0.002	0.013
Laterality (Right NAcc >Left NAcc)	-0.012	-0.015, -0.008	<0.001
Reward magnitude (Large Reward >Small Reward)	0.070	0.066, 0.074	<0.001
Motion	-0.050	-0.067, -0.034	<0.001

Table 6.7: Sensitivity analysis – Minimally adjusted regression model including all individuals (N = 8808) examining the effect of presence and type of PLEs, reward magnitude and laterality on nucleus accumbens (NAcc) response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.001	-0.013, 0.011	0.840
Distressing PLEs	-0.010	-0.0184, 0.0001	0.053
Laterality (Right NAcc >Left NAcc)	-0.012	-0.0155, -0.0080	<0.001
Reward magnitude (Small Reward >Large Reward)	-0.070	-0.0737, -0.0663	<0.001
Gender	0.002	-0.0057, 0.0100	0.589
Depressive symptoms	-0.003	-0.0144, 0.0087	0.631
Household income [<50K]	0.003	-0.0092, 0.0150	0.639
Household income [>=50K & <100K]	0.005	-0.0047, 0.0151	0.305
Parental education - <HS Diploma	-0.020	-0.0396, -0.0004	0.046
Parental education - HS Diploma/GED	-0.023	-0.0389, -0.0072	0.004
Parental education - Post Graduate Degree	-0.006	-0.0169, 0.0042	0.237
Parental education - Some College	-0.005	-0.0163, 0.0057	0.343
Race - Asian	-0.005	-0.0313, 0.0217	0.723
Race - Black	0.0001	-0.0128, 0.0130	0.989
Race - Other/Mixed	-0.004	-0.0150, 0.0065	0.440
Motion	-0.047	-0.0638, -0.0307	<0.001
Pubertal development	-0.009	-0.0177, 0.0001	0.052
Diagnosis - schizophrenia	-0.139	-0.3491, 0.0720	0.197

Table 6.8: Sensitivity analysis – Fully adjusted regression model including all individuals (N = 8808) examining the effect of presence and type of PLEs, reward magnitude and laterality on nucleus accumbens (NAcc) response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.002	-0.017, 0.013	0.791
Distressing PLEs	-0.007	-0.018, 0.004	0.221
Laterality (Right NAcc >Left NAcc)	-0.027	-0.031, -0.023	<0.001
Motion	0.067	0.048, 0.085	<0.001

Table 6.9: Sensitivity analysis – Minimally adjusted regression model including all individuals (N = 8939) on association between types of PLEs, distress and laterality on nucleus accumbens (NAcc) response to reward outcome.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.002	-0.016, 0.013	0.840
Distressing PLEs	-0.007	-0.018, 0.004	0.230
Laterality (Right NAcc >Left NAcc)	-0.027	-0.031, -0.023	<0.001
Gender	0.007	-0.003, 0.016	0.175
Depressive symptoms	0.015	0.001, 0.029	0.030
Household income [<50K]	-0.001	-0.016, 0.014	0.890
Household income [>=50K & <100K]	-0.001	-0.012, 0.011	0.928
Parental education - <HS Diploma	-0.007	-0.031, 0.016	0.544
Parental education - HS Diploma/GED	-0.007	-0.026, 0.012	0.449
Parental education - Post Graduate Degree	-0.001	-0.014, 0.012	0.893
Parental education - Some College	-0.001	-0.014, 0.013	0.928
Race - Asian	0.015	-0.018, 0.048	0.368
Race - Black	-0.027	-0.042, -0.011	<0.001
Race - Other/Mixed	-0.006	-0.019, 0.007	0.330
Motion	0.068	0.050, 0.087	<0.001
Pubertal development	-0.0002	-0.011, 0.010	0.972
Diagnosis - schizophrenia	-0.480	-0.734, -0.225	<0.001

Table 6.10: Sensitivity analysis – Fully adjusted regression model including all individuals (N = 8939) on association between types of PLEs, distress and laterality on nucleus accumbens (NAcc) response to reward outcome.

6.5.2 Ventral striatum: Effect of PLEs on reward anticipation and outcome including only individuals with a psychiatric diagnosis

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.010	-0.041, 0.021	0.532
Distressing PLEs	-0.032	-0.054, -0.010	0.005
Laterality (Right NAcc >Left NAcc)	-0.010	-0.020, - 0.00001	0.050
Reward magnitude (Large Reward >Small Reward)	0.054	0.044, 0.064	<0.001
Motion	-0.080	-0.116, -0.044	<0.001

Table 6.11: Minimally adjusted regression model including only individuals with a psychiatric diagnosis (N = 1325) examining the effect of presence and type of PLEs, reward magnitude and laterality on nucleus accumbens (NAcc) response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.020	-0.019, 0.059	0.306
Distressing PLEs	0.000	-0.027, 0.027	0.995
Laterality (Right NAcc >Left NAcc)	-0.026	-0.037, -0.015	<0.001
Motion	0.055	0.012, 0.099	0.013

Table 6.12: Minimally adjusted regression model including only individuals with a psychiatric diagnosis (N = 1311) examining the effect of presence and type of PLEs, and laterality on nucleus accumbens (NAcc) response to reward outcome.

6.5.3 Dorsal Striatum: Effect of PLEs on reward processing when including individuals with a psychiatric diagnosis or psychiatric medication use

We were unable to run a robust version of the caudate reward anticipation analysis in this sample. Thus, the table below is reporting the results of a a non-robust logistic mixed effects regression.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	-0.003	-0.02, 0.01	0.628
Distressing PLEs	-0.01	-0.02, 0.001	0.094
Laterality (Right >Left Caudate)	0.01	0.008, 0.014	<0.001
Reward magnitude (Large >Small)	0.07	0.07, 0.08	<0.001
Motion	-0.07	-0.08, -0.05	<0.001

Table 6.13: Sensitivity analysis – Minimally adjusted regression model including all individuals (N = 8594) on association between types of PLEs, distress, laterality on caudate response to reward anticipation

Predictor	*Estimate*	*95% CIs*	*p value*
Distressing PLEs	-0.003	-0.015, 0.009	0.596
Non-distressing PLEs	-0.008	-0.017, 0.002	0.106
Laterality (Right Caudate >Left Caudate)	0.011	0.008, 0.014	0.000
Reward magnitude (Large Reward>Small Reward)	0.075	0.072, 0.077	0.000
Gender	0.008	-0.0003, 0.015	0.060
Depressive symptoms	-0.002	-0.013, 0.010	0.747
Household income [<50K]	-0.011	-0.023, 0.0004	0.059
Household income [>=50K & <100K]	-0.004	-0.014, 0.006	0.397
Parental education - <HS Diploma	-0.025	-0.045, -0.006	0.010
Parental education - HS Diploma/GED	-0.022	-0.038, -0.006	0.006
Parental education - Post Graduate Degree	-0.010	-0.021, 0.0003	0.058
Parental education - Some College	-0.013	-0.024, -0.002	0.021
Race - Asian	-0.007	-0.033, 0.019	0.582
Race - Black	-0.009	-0.022, 0.003	0.155
Race - Other	-0.004	-0.015, 0.006	0.424
Motion	-0.065	-0.083, -0.047	0.000
Pubertal development	-0.002	-0.011, 0.007	0.683
Diagnosis - schizophrenia	-0.077	-0.284, 0.129	0.463

Table 6.14: Sensitivity analysis – Fully adjusted regression model including all individuals (N = 8594) on association between types of PLEs, distress, laterality on caudate response to reward anticipation

Similarly, We were unable to run a robust version of the putamen reward anticipation analysis in this sample. Thus, the table below is reporting the results of a a non-robust logistic mixed effects regression.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.005	-0.01, 0.02	0.365
Distressing PLEs	-0.003	-0.01, 0.005	0.478
Laterality (right putamen >left putamen)	0.007	0.004, 0.01	<0.001
Motion	-0.058	-0.07, -0.04	<0.001

Table 6.15: Sensitivity analysis – Minimally adjusted regression model including all individuals (N = 8561) on association between types of PLEs, distress, laterality on putamen response to reward anticipation

Predictor	Estimate	95% CIs	p value
Distressing PLEs	0.004	-0.006, 0.014	0.388
Non-distressing PLEs	0.000	-0.008, 0.007	0.928
Laterality (Right Putamen >Left Putamen)	0.006	0.004, 0.009	<0.001
Reward magnitude (Large Reward >Small Reward)	0.054	0.052, 0.056	<0.001
Gender	0.008	0.002, 0.015	0.011
Depressive symptoms	-0.006	-0.015, 0.004	0.224
Household income [<50K]	-0.013	-0.023, -0.003	0.008
Household income [>=50K & <100K]	-0.003	-0.011, 0.005	0.408
Parental education - <HS Diploma	-0.013	-0.028, 0.003	0.111
Parental education - HS Diploma/GED	-0.012	-0.025, 0.001	0.063
Parental education - Post Graduate Degree	-0.006	-0.015, 0.002	0.159
Parental education - Some College	-0.005	-0.013, 0.004	0.313
Race - Asian	0.007	-0.014, 0.028	0.533
Race - Black	-0.005	-0.015, 0.006	0.374
Race - Other	-0.003	-0.012, 0.006	0.482
Motion	-0.059	-0.073, -0.045	0.000
Pubertal development	-0.002	-0.009, 0.006	0.661

Table 6.16: Sensitivity analysis – Fully adjusted regression model including all individuals (N = 8561) examining the effect of presence and type of PLEs, reward magnitude and laterality on putamen response to reward anticipation.

Predictor	*Estimate*	*95% CIs*	p value
Non-distressing PLEs	0.002	-0.01, 0.02	0.815
Distressing PLEs	0.002	-0.01, 0.01	0.716
Laterality (Right Caudate >Left Caudate)	-0.002	-0.005, 0.0002	0.067
Motion	0.060	0.04, 0.08	<0.001

Table 6.17: Sensitivity analysis – Minimally adjusted regression model including all individuals (N = 8797) on association between types of PLEs, distress, laterality on caudate response to reward outcome

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.004	-0.011, 0.019	0.643
Distressing PLEs	0.003	-0.008, 0.014	0.594
Laterality (Right Caudate >Left Caudate)	-0.002	-0.004, <0.001	0.054
Gender	0.000	-0.009, 0.010	0.923
Depressive symptoms	0.001	-0.013, 0.016	0.844
Household income [<50K]	-0.005	-0.020, 0.010	0.489
Household income [>=50K & <100K]	-0.005	-0.018, 0.007	0.383
Parental education - <HS Diploma	0.013	-0.010, 0.037	0.270
Parental education - HS Diploma/GED	0.004	-0.016, 0.023	0.722
Parental education - Post Graduate Degree	-0.005	-0.018, 0.008	0.442
Parental education - Some College	0.004	-0.009, 0.018	0.531
Race - Asian	0.021	-0.012, 0.054	0.215
Race - Black	-0.021	-0.037, -0.005	0.009
Race - Other	-0.008	-0.022, 0.005	0.211
Motion	0.076	0.055, 0.096	<0.001
Pubertal development	-0.006	-0.017, 0.005	0.296
Diagnosis - schizophrenia	-0.305	-0.622, 0.011	0.059

Table 6.18: Sensitivity analysis – Fully adjusted regression model including all individuals (N = 8797) on association between types of PLEs, distress, laterality on caudate response to reward outcome

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.006	-0.007, 0.018	0.355
Distressing PLEs	0.003	-0.006, 0.012	0.503
Laterality (Right Putamen >Left Putamen)	0.001	-0.001, 0.003	0.398
Motion	0.048	0.032, 0.065	<0.001

Table 6.19: Sensitivity analysis – Minimally adjusted regression model including all individuals (N = 8782) on association between types of PLEs, distress, laterality on putamen response to reward outcome

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.005	-0.007, 0.017	0.431
Distressing PLEs	0.003	-0.007, 0.012	0.544
Laterality (Right Putamen >Left Putamen)	0.001	-0.001, 0.003	0.381
Gender	0.017	0.009, 0.025	<0.001
Depressive symptoms	0.002	-0.010, 0.013	0.774
Household income [<50K]	-0.006	-0.018, 0.006	0.338
Household income [>=50K & <100K]	-0.003	-0.013, 0.007	0.595
Parental education - <HS Diploma	0.001	-0.019, 0.021	0.904
Parental education - HS Diploma/GED	-0.007	-0.023, 0.010	0.427
Parental education - Post Graduate Degree	-0.007	-0.018, 0.004	0.200
Parental education - Some College	0.006	-0.006, 0.017	0.324
Race - Asian	0.022	-0.006, 0.050	0.125
Race - Black	-0.008	-0.022, 0.005	0.213
Race - Other	-0.010	-0.021, 0.001	0.063
Motion	0.046	0.029, 0.062	0.000
Pubertal development	0.004	-0.005, 0.013	0.339
Schizophrenia diagnosis	-0.109	-0.370, 0.151	0.411

Table 6.20: Sensitivity analysis – Fully adjusted regression model including all individuals (N = 8782) on association between types of PLEs, distress, laterality on putamen response to reward outcome

6.5.4 Dorsal striatum: Effect of PLEs on reward anticipation and outcome including only individuals with a psychiatric diagnosis

Predictor	Estimate	95% CIs	p value
Non-distressing PLEs	0.0002	-0.030, 0.03	0.988
Distressing PLEs	-0.005	-0.026, 0.016	0.627
Laterality (Right caudate >left caudate)	0.013	0.006, 0.021	0.001
Reward magnitude (Large Reward >Small Reward)	0.059	0.052, 0.067	<0.001
Motion	-0.065	-0.104, -0.027	0.001

Table 6.21: Minimally adjusted regression model including only individuals with a psychiatric diagnosis (N = 1300) examining the effect of presence and type of PLEs, reward magnitude and laterality on caudate response to reward anticipation.

We were unable to adjust for motion in the putamen reward anticipation for the subset analysis including only individuals with a psychiatric diagnosis, as this resulted in a singular fit.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.004	-0.020, 0.028	0.736
Distressing PLEs	-0.001	-0.018, 0.016	0.888
Laterality (Right Putamen >Left Putamen)	0.007	0.001, 0.014	0.019
Reward magnitude (Large Reward >Small Reward)	0.045	0.038, 0.051	<0.001

Table 6.22: Minimally adjusted regression model including only individuals with a psychiatric diagnosis (N = 1288) examining the effect of presence and type of PLEs, reward magnitude and laterality on putamen response to reward anticipation.

Predictor	Estimate	95% CIs	p value
Non-distressing PLEs	0.003	-0.035, 0.041	0.877
Distressing PLEs	0.011	-0.016, 0.038	0.421
Laterality (Right caudate >Left Caudate)	-0.008	-0.014, -0.003	0.003
Motion	0.026	-0.019, 0.070	0.254

Table 6.23: Minimally adjusted regression model including only individuals with a psychiatric diagnosis (N = 1324) examining the effect of presence and type of PLEs, and laterality on caudate response to reward outcome.

Predictor	*Estimate*	*95% CIs*	*p value*
Non-distressing PLEs	0.016	-0.016, 0.049	0.315
Distressing PLEs	0.015	-0.008, 0.037	0.197
Laterality (Right Putamen >Left Putamen)	-0.001	-0.006, 0.003	0.571
Motion	0.040	0.002, 0.078	0.040

Table 6.24: Minimally adjusted regression model including only individuals with a psychiatric diagnosis (N = 1320) examining the effect of presence and type of PLEs, and laterality on putamen response to reward outcome

6.6 Appendix F: Analyses for Chapter 4

6.6.1 Supplementary analyses for study 1

6.6.1.1 Predictors of PLEs at baseline

	Odds Ratio	95% CIs	P value
Cognition	0.98	0.97, 0.99	0.001
Race	1.24	1.12, 1.38	<0.001
Household income	0.99	0.96, 1.01	0.299
Parental education	0.94	0.92, 0.96	<0.001
Neighborhood deprivation	1.14	1.09, 1.19	<0.001
Urban density	1.01	0.97, 1.05	0.651
Gender	1.07	0.98, 1.17	0.133

Table 6.25: Fully adjusted analysis to examine whether cognition predicts PLEs at baseline (N = 9810)

	Odds Ratio	95% CIs	P value
Depressive Symptoms	3.21	2.74, 3.77	<0.001
Race	1.24	1.12, 1.37	<0.001
Household income	0.99	0.97, 1.02	0.54
Parental education	0.94	0.92, 0.96	<0.001
Neighborhood deprivation	1.13	1.08,1.18	<0.001
Urban density	1.01	0.97, 1.05	0.582
Gender	1.07	0.98, 1.17	0.153

Table 6.26: Fully adjusted analysis to examine whether depressive symptoms predicts PLEs at baseline (N = 9810)

	Odds Ratio	95% CIs	P value
Trauma	1.06	1.01, 1.11	0.013
Race	1.26	1.13, 1.39	<0.001
Household income	0.98	0.96, 1.01	0.184
Parental education	0.94	0.92, 0.96	<0.001
Neighborhood deprivation	1.14	1.09, 1.19	<0.001
Urban density	1.01	0.97, 1.05	0.671
Gender	1.08	0.99, 1.18	0.083

Table 6.27: Fully adjusted analysis to examine whether trauma predicts PLEs at baseline (N = 9810)

6.6.1.2 Predictors of persistence of PLEs

	Odds Ratio	95% CIs	P value
Cognition	0.98	0.96, 1.00	0.059
Gender	1.11	0.97, 1.27	0.125
Race	1.22	1.05, 1.42	0.009
Household income	0.98	0.94, 1.02	0.282
Parental education	0.99	0.96, 1.02	0.51
Neighborhood Deprivation	1.14	1.07, 1.21	<0.001
Urban density	1.04	0.98, 1.09	0.229

Table 6.28: Fully adjusted analysis to examine whether cognition predicts persistence of PLEs (N=3784)

	Odds Ratio	95% CIs	P value
Depressive symptoms	1.4	1.21, 1.61	<0.001
Gender	1.11	0.97, 1.27	0.122
Race	1.22	1.05, 1.42	0.009
Household income	0.98	0.94, 1.02	0.27
Parental education	0.99	0.96, 1.02	0.498
Neighborhood deprivation	1.14	1.07, 1.21	<0.001
Urban density	1.04	0.98, 1.10	0.216

Table 6.29: Fully adjusted analysis to examine whether depressive symptoms predict persistence of PLEs (N=3784)

	Odds Ratio	95% CIs	P value
Trauma	1.1	1.02, 1.18	0.011
Gender	1.12	0.98, 1.28	0.098
Race	1.22	1.05, 1.41	0.01
Household income	0.98	0.94, 1.02	0.257
Parental income	0.99	0.96, 1.02	0.34
Neighborhood deprivation	1.14	1.07, 1.21	<0.001
Urban density	1.04	0.98,1.10	0.224

Table 6.30: Fully adjusted analysis to examine whether trauma predicts persistence of PLEs (N=3784)

6.6.1.3 Predictors of new incidence of PLEs

	Odds Ratio	95% CIs	P value
Depressive symptoms	1.92	1.46, 2.52	<0.001
Gender	1.04	0.90, 1.19	0.611
Race	1.38	1.18, 1.61	<0.001
Household income	0.92	0.89, 0.96	<0.001
Parental Education	0.97	0.94, 1.00	0.095
Neigborhood Deprivation	1.08	1.02, 1.15	0.01
Urban density	0.98	0.93, 1.04	0.535

Table 6.31: Fully adjusted analysis to examine whether depressive symptoms predict new incidence of PLEs (N = 5461)

	Odds Ratio	95% CIs	P Value
Trauma	1.04	0.98, 1.11	0.206
Gender	1.04	0.91, 1.19	0.591
Race	1.38	1.18, 1.62	<0.001
Household income	0.92	0.88, 0.95	<0.001
Parental education	0.97	0.94, 1.00	0.091
Neighborhood Deprivation	1.08	1.02, 1.15	0.009
Urban density	0.98	0.93, 1.04	0.482

Table 6.32: Fully adjusted analysis to examine whether trauma predicts new incidence of PLEs (N = 5461)

6.6.1.4 Sensitivity analysis for study 1

	Minimally adjusted			Adjusted for confounders		
Predictor	OR	95% CIs	p value	OR	95% CIs	p value
Depressive symptoms	3.56	3.10, 4.09	<0.001	3.23	2.82, 3.71	<0.001
Cognition	0.95	0.94, 0.96	<0.001	0.98	0.97, 0.99	<0.001
Total trauma	1.10	1.06, 1.14	<0.001	1.07	1.03, 1.11	0.001
N = 11864						

Table 6.33: Baseline analysis with all individuals

	Minimally adjusted			Adjusted for confounders		
Predictor	OR	95% CIs	p value	OR	95% CIs	p value
Depressive symptoms	1.55	1.36, 1.76	<0.001	1.46	1.28, 1.66	<0.001
Cognition	0.96	0.95, 0.98	<0.001	0.99	0.97, 1.00	0.162
Total trauma	1.14	1.07, 1.21	<0.001	1.09	1.03, 1.16	0.005
N = 4750						

Table 6.34: Persistence analysis with all individuals

	Minimally adjusted			Adjusted for confounders		
Predictor	OR	95% CIs	p value	OR	95% CIs	p value
Depressive symptoms	2.18	1.73, 2.76	<0.001	1.96	1.55, 2.49	<0.001
Cognition	0.95	0.93, 0.96	<0.001	Failed to converge		
Total trauma	1.04	0.99, 1.10	0.144	1.02	0.96, 1.08	0.567
N = 6433						

Table 6.35: New incidence analysis with all individuals

6.6.2 Supplementary analyses for study 2

6.6.2.1 NAcc analyses

Predictor	Odds Ratio	95% CIs	P Value
Anticipation-related activity	1.08	0.41, 2.84	0.868
Depressive symptoms	0.90	0.06, 14.18	0.943
Total distress	24.19	15.50, 37.76	<0.001
Gender (Male >Female)	5.16	0.76, 34.94	0.093
Race (BAME >White)	29.04	3.41, 247.09	0.002
Household income	0.60	0.37, 0.97	0.038
Parental education	1.06	0.78, 1.45	0.709

Table 6.36: Fully adjusted persistence versus remission analysis: reward anticipation (N = 2547) in Nucleus accumbens (NAcc)

Predictor	Odds Ratio	95% CIs %	p value
Outcome-related activity	0.83	0.23, 3.02	0.775
Depressive symptoms	1.71	0.18, 16.48	0.644
Total distress	14.29	9.79, 20.84	<0.001
Gender (Male >Female)	3.97	0.78, 20.19	0.097
Race (BAME >White)	34.69	3.29, 365.69	0.003
Household income	0.75	0.46, 1.22	0.243
Parental education	0.93	0.63, 1.35	0.691

Table 6.37: Fully adjusted persistence versus remission analysis: reward outcome (N= 2561) in Nucleus accumbens (NAcc)

6.6.2.2 Caudate analyses

Predictor	Odds Ratio	95% CIs	p value
Anticipation-related activity	0.9604	0.2449, 3.7673	0.954

Table 6.38: Minimally adjusted persistence versus remission analysis: reward anticipation in caudate (N = 2446)

Predictor	Odds Ratio	95% CIs	p value
Anticipation-related activity	1.028	0.218, 4.852	0.972
Total distress	26.227	16.381, 41.993	<0.001
Gender (Male >Female)	7.456	1.008, 55.172	0.049
Race (BAME >White)	63.207	6.123, 652.44	<0.001
Depressive symptoms	0.541	0.057, 5.142	0.593
Household income	0.558	0.333, 0.935	0.027
Parental education	1.089	0.777, 1.527	0.621

Table 6.39: Fully adjusted persistence versus remission analysis: reward anticipation in caudate (N = 2446)

Predictor	Odds Ratio	95% CIs	p value
Outcome-related activity	1.204	0.226, 6.407	0.798

Table 6.40: Minimally adjusted persistence versus remission analysis: reward outcome in caudate (N = 2492)

Predictor	Odds Ratio	95% CIs	p value
Outcome-related activity	1.936	0.169, 22.209	0.596
Total distress	0.069	0.046, 0.104	<0.001
Gender (Male >Female)	0.236	0.044, 1.261	0.091
Race (BAME >White)	0.043	0.005, 0.368	0.004
Depressive symptoms	1.232	0.088, 17.320	0.877
Household income	1.526	0.929, 2.507	0.095
Parental education	0.970	0.697, 1.352	0.859

Table 6.41: Fully adjusted persistence versus remission analysis: reward outcome in caudate (N = 2492)

6.6.2.3 Putamen analyses

Predictor	Odds Ratio	95% CIs	p value
Anticipation-related activity	0.9557	0.1805, 5.0611	0.9575

Table 6.42: Minimally adjusted persistence versus remission analysis: reward anticipation in putamen (N = 2429)

Predictor	Odds Ratio	95% CIs	p value
Anticipation-related activity	1.099	0.168, 7.179	0.921
Total distress	27.188	17.084, 43.267	<0.001
Gender (Male >Female)	9.398	1.288, 68.557	0.027
Race (BAME >White)	57.048	5.943, 547.627	<0.001
Depressive symptoms	0.592	0.069, 5.115	0.634
Household income	0.596	0.358, 0.992	0.046
Parental education	1.057	0.760, 1.470	0.742

Table 6.43: Fully adjusted persistence versus remission analysis: reward anticipation in putamen (N = 2429)

Predictor	Odds Ratio	95% CIs	p value
Outcome-related activity	0.8304	0.156, 4.415	0.8274

Table 6.44: Minimally adjusted persistence versus remission analysis: reward outcome in putamen (N = 2483)

Predictor	Odds Ratio	95% CIs	p value
Outcome-related activity	1.144	0.080, 16.307	0.921
Total distress	15.388	10.372, 22.829	<0.001
Gender (Male >Female)	4.380	0.791, 24.254	0.091
Race (BAME >White)	31.375	3.024, 325.555	0.004
Depressive symptoms	0.998	0.032, 30.697	0.999
Household income	0.627	0.371, 1.062	0.082
Parental education	1.044	0.742, 1.469	0.803

Table 6.45: Fully adjusted persistence versus remission analysis: reward outcome in putamen (N = 2483)

6.7 Colophon

This document was set in the Times Roman typeface using the LaTeX document processing system originally developed by Leslie Lamport, based on TeX typesetting system created by Donald Knuth and BibTeX, and was composed in Overleaf.

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