Trauma-induced threat-based mechanisms underlying psychosis

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Declaration

I, Paul Gu-Yun Jung, 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 my thesis.

Signature Date 08/08/2022

Abstract

There is growing evidence that developmental trauma is causally associated with an increased risk of psychosis. However, there is a striking lack of understanding of the precise mechanisms that underlie this association. Consistent with biopsychosocial and cognitive theories of psychosis, multiple lines of evidence converge on the role of threat processing in the pathway linking developmental trauma and psychosis. This thesis examined the effect of developmental trauma on threat processing and the neural structures underlying threat processing – the amygdala and ventromedial prefrontal cortex (vmPFC) - and examined their role in the association between developmental trauma and psychotic experiences.

Using data from a systematic review and meta-analysis, three cross-sectional studies and one population-based cohort study, this thesis provides evidence that developmental trauma is associated with lasting alterations in threat processing and the brain structures underlying threat processing. These alterations in threat processing were associated with increased severity of psychotic experiences. Importantly, developmental trauma-associated alterations in threat processing played a mediating role in the relationship between developmental trauma and psychotic experiences.

This thesis presents evidence suggesting neurobiological and cognitive mediators of the trauma-psychotic experience relationship and demonstrate that altered neural processing of threat may be target mechanisms for personalised therapies and for the secondary prevention of psychosis in adult survivors of developmental trauma.

Impact statement

Developmental trauma is associated with an increased risk of psychosis. Adult survivors of developmental trauma with psychosis have more severe illness and poorer treatment outcomes compared to individuals with psychosis who have not experienced developmental trauma. There is therefore a pressing need to develop preventative interventions that reduce the number of adult survivors of developmental trauma who go on to develop psychosis, and to improve treatment outcomes for survivors with psychosis. A significant barrier for the development of preventative interventions for adult survivors of developmental trauma and targeted treatments for survivors with psychosis is the lack of understanding of how developmental trauma gives rise to psychosis.

A common feature of developmental trauma and psychosis is threat: traumatic experiences are by nature threatening, and psychotic experiences are commonly characterised by a sense of threat. This thesis examined how developmental trauma may affect how the brain processes threat, and how these alterations in threat processing may play a role in the mechanistic pathway between developmental trauma and psychosis. In doing so, this thesis contributes to the academic literature in several ways.

Using data from a systematic review and meta-analysis, three cross-sectional studies and one population-based cohort study, this thesis provided evidence that developmental trauma is associated with lasting alterations in threat processing and the underlying brain structures. These alterations in threat processing were associated with increased severity of psychotic experiences. Importantly,

developmental trauma-associated alterations in threat processing played a mediating role in the relationship between developmental trauma and psychotic experiences.

The findings from this thesis also have implications for the treatment and prevention of psychosis in adult survivors of developmental trauma. Developmental trauma-associated alterations in threat processing may be potential targets treating psychosis and preventing psychosis in adult survivors of developmental trauma. Researchers could develop psychological and pharmacological interventions that targets alterations in threat processing, and clinicians could focus specifically on altered threat processing, such as avoidance behaviours, and their relation to psychotic experiences that are threatening. In addition, clinicians should ask patients about experiences of developmental trauma to provide trauma-informed care. Given that alterations in threat processing were observed in adult survivors of developmental trauma prior to the development of clinical levels of psychosis, targeting altered threat processes in these individuals may enable the secondary prevention of psychosis in adult survivors of developmental trauma.

To disseminate findings of this thesis, findings from studies included here have been presented at international conferences including the British Association for Psychopharmacology Summer Meeting (London), the European College of Neuropsychopharmacology Annual Meeting (Lisbon) and the Schizophrenia International Research Society conference (Florence). In addition, six papers are being prepared for publication in high impact peer-reviewed journals.

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Contents

Declaration 2

List of tables 11

List of figures 13

1. Chapter I: Background 15

1.1. Psychosis 16

1.2. Epidemiology 16

1.3. Illness burden of psychosis 18

1.4. Clinical features of psychosis 18

1.5. Psychotic experiences 20

1.6. Psychosis aetiology 25

1.7. Environmental risk factors 29

1.8. Developmental trauma 31

1.9. Mechanisms underlying the association between developmental trauma and psychosis 45

1.10. Threat-based mechanisms underlying the association between developmental trauma and psychosis 46

1.11. Threat processing and its neural basis 47

1.12. Threat-based mechanisms underlying the association between developmental trauma and psychosis 55

1.13. Models of threat-based mechanisms underlying the association between developmental trauma and psychosis 65

1.14. Summary 72

1.15. Aims of this thesis 73

1.16. Hypotheses relating to this thesis 74

1.17. Overview of the thesis 75

2. Chapter II: A systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood 76

2.1. Introduction 77

2.2. Aim 80

2.3. Materials and Methods 81

2.4. Results 83

2.5. Discussion 106

3. Chapter III: The relationship between developmental trauma, threat attention and psychotic experiences 111

3.1. Introduction 112

3.2. Hypotheses 113

3.3. Materials and Methods 114

3.4. Results 119

3.5. Discussion 130

4. Chapter IV: The relationship between developmental trauma, threat recognition and response and psychotic experiences 136

4.1. Introduction 137

4.2. Hypotheses 140

4.3. Materials and Methods 141
4.4. Results 147
4.5. Discussion 160
5. Chapter V: The relationship between developmental trauma, threat learning and psychotic experiences 169
5.1. Introduction 170
5.2. Hypotheses 172
5.3. Materials and Methods 173
5.4. Results 185
5.5. Discussion 190
6. Chapter VI: The effect of developmental trauma on brain structures involved in threat processing and its relation to psychotic experiences in adulthood 197
6.1. Introduction 198
6.2. Hypotheses 200
6.3. Materials and Methods 201
6.4. Results 206
6.5. Discussion 213
7. Chapter VII: Discussion 220
7.1. Introduction 221
7.2. Study I: A systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood 222

7.3. Study II: The relationship between developmental trauma, threat attention and psychotic experiences 223

7.4. Study III: The relationship between developmental trauma, threat recognition and response and psychotic experiences 225

7.5. Study IV: The relationship between developmental trauma, threat learning and psychotic experiences 227

7.6. Study V: The effect of developmental trauma on brain structures involved in threat processing and its relation to psychotic experiences in adulthood 230

7.7. General conclusions 232

7.8. Strengths and limitations 240

7.9. Clinical implications 244

7.10. Directions for future study 249

7.11. Final conclusion 252

8. References 253

9. Appendix 299

Chapter II. A systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood: Full search 299

List of tables

Table 1. Environmental risk factors that have been proposed for psychosis. From (Dean and Murray, 2005) 30

Table 2. Bradford Hill criteria for a causal association between developmental trauma and psychosis. Biological gradient, coherence, analogous evidence and specificity criteria are not necessarily appropriate for causal associations in neuropsychiatry (van Reekum, Streiner and Conn, 2001), but where demonstrable, have been included to add to the argument for causation. 36

Table 3. Commonly used animal paradigms of early adversity. Adapted from McLaughlin et al., (McLaughlin, Sheridan and Lambert, 2014)..... 57

Table 4. Experimental paradigms to assess various domains of threat processing in behavioural and neuroimaging studies in humans. 61

Table 5. Characteristics and main findings of included studies 85

Table 6. Quality and risk of bias assessment results using the Newcastle Ottawa scale 93

Table 7. Participant demographics and CTQ scores 120

Table 8. Participant clinical variables and childhood trauma questionnaire scores 122

Table 9. Emotional dot probe response times and errors by group and congruency 124

Table 10. Reliability estimates for emotional dot probe response times by emotion and congruency. Reliability of dot probe response times separated by groups showed poor to good reliability. 125

Table 11. Reliability estimates for emotional dot probe response times by group, emotion and congruency 125

Table 12. Demographic and clinical characteristics of the sample 148

Table 13. Fit indices of mediation models. All mediation models meet 3 out of 3 fit index criteria. 157

Table 14. Indirect Effect, Total Effect, and R^2 of the mediation models..... 158

Table 15. Model fits to participants' choice behaviour. (A) The full behavioural model (i), that assumes that participants use information about outcome probability and duration when making their choices. (ii) A model that ignores information about the duration of aversive sounds. (iii) A model that uses information about the duration of aversive sounds, but does not update its expected outcome probability on the basis of previous outcomes. (B) A simplified version of the full model that uses 2 learning rate parameters (one for the stable block and one for the volatile block), but only one risk preference and one inverse temperature parameter across the whole task. ... 183

Table 16. Demographic and clinical characteristics..... 186

Table 17. Sample characteristics..... 206

Table 18. Exposure to trauma and psychotic experiences, by type and timing of trauma 207

Table 19. Association between developmental trauma and brain structures involved in threat processing..... 209

Table 20. Association between ROI volumes and psychotic experiences..... 211

List of figures

Figure 1. Pooled incidence of schizophrenia by age and sex in England, 1950-2009 (Jauhar, Johnstone and McKenna, 2022). 17

Figure 2. Models of psychosis distributions, severity of psychotic experiences on the x-axis, and frequency on the y-axis. 23

Figure 3. Genetic architecture of schizophrenia. 27

Figure 4. Aetiological models explaining the association between developmental trauma and psychosis. 41

Figure 5. The neural circuitry underlying threat processing. 51

Figure 6. The sociodevelopmental cognitive model of psychosis. 69

Figure 7. PRISMA flowchart of included studies. The systematic literature search identified a total of 18 behavioural studies that met the inclusion criteria 83

Figure 8. Categorisation of included studied based on threat processing domain ... 84

Figure 9. Meta-analysis of the effect of developmental trauma on threat attention in adulthood.. 99

Figure 10. Meta-analysis of the effect of developmental trauma on threat recognition in adulthood. 101

Figure 11. Meta-analysis of the effect of developmental trauma on threat response in adulthood. 105

Figure 12. Attentional bias for angry faces. 127

Figure 13. Group mean (95% CI) for (A) hits, demonstrating the ability to recognise anger (B) sensitivity, demonstrating the ability to discriminate between anger and other emotions in conditions of uncertainty and (C) response bias, representing how liberal or conservative participants were in recognising anger 150

Figure 14. Group mean (95% CI) for (A) valence and (B) arousal responses on the face ratings task, by facial expression (neutral and anger)..... 154
Figure 15. Mediation analyses. (A) Reduced sensitivity for angry, (B) more negative valence responses for neutral faces and (C) increased arousal responses for neutral faces significantly mediates the association between the severity of developmental trauma and psychotic experiences..... 159
Figure 16. Calibration of aversive sounds. 177
Figure 17. Learning curves illustrating participant and model choice during the aversive learning task.. 181
Figure 18. Group means (95% CI) for delta learning rates, calculated as the difference in learning rates between volatile and stable blocks of the task..... 188
Figure 19. Reduced adjustment of learning rates to volatility did not mediate the association between developmental trauma and psychotic experiences..... 189
Figure 20. Left amygdala volume mediates the association between exposure to developmental trauma and psychotic experiences 212

Chapter I: Background

1.1. Psychosis

Psychosis is a severe and potentially extremely distressing clinical syndrome associated with high morbidity and mortality worldwide (Charlson *et al.*, 2018). Psychosis has been proposed to exist as a continuum of experiences and symptoms, varying in the type, number, complexity, severity and duration of psychotic experiences, ranging from subclinical psychotic experiences in the general population to schizophrenia spectrum disorders in clinical populations (Os *et al.*, 2009).

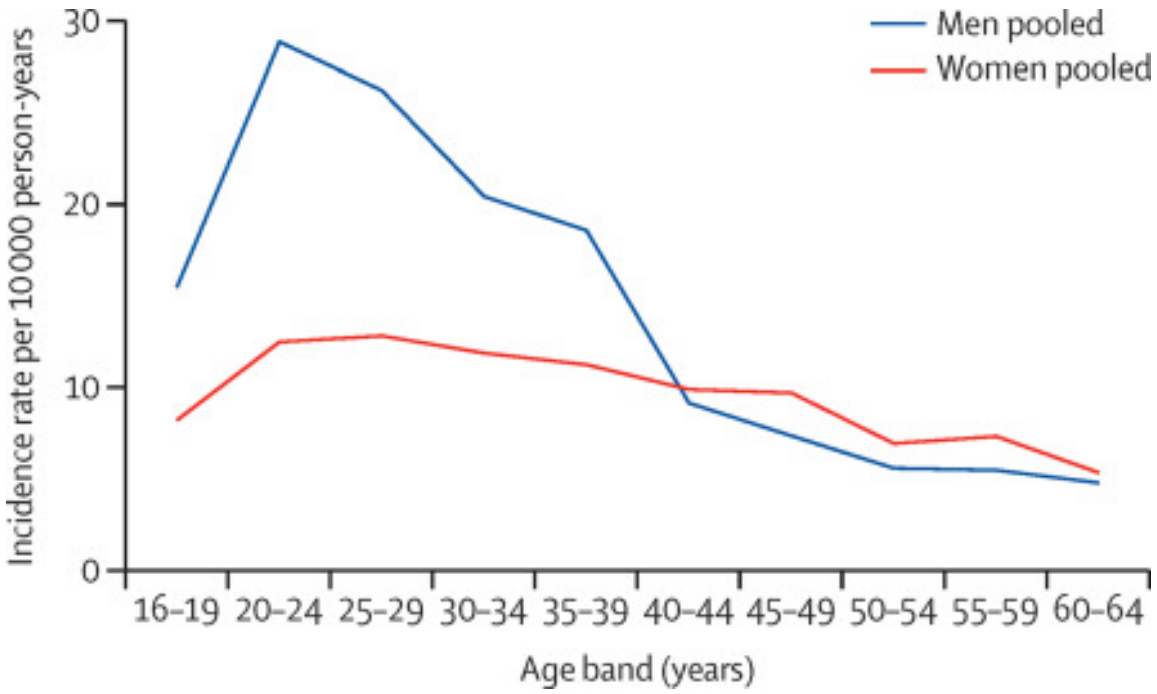
1.2. Epidemiology

At the extreme of the continuum of psychosis is schizophrenia, a clinical syndrome characterised by chronic psychosis. Schizophrenia has an estimated lifetime prevalence of 7.49 per 1000 individuals and an estimated point prevalence of 3.89 per 1000 individuals (Moreno-Küstner, Martín and Pastor, 2018). The annual incidence of schizophrenia has been estimated to be 2.8 per 1000 persons (Charlson *et al.*, 2018). Evidence from a large meta-analysis suggests that there is a modestly higher frequency of schizophrenia in men, with a male-to-female incidence rate ratio of 1.7 (Jongsma *et al.*, 2019).

Psychosis can occur throughout the lifespan, although the majority of onsets fall within the 15-54 years of age interval. The onset of psychosis in men peaks in the early twenties and declines steadily thereafter. In women, this peak is less sharp and less steep (**Figure 1**). A widely held view is that there is a second peak of onset in women in later life (Ochoa *et al.*, 2012), though a pooled analysis of 15 studies found only limited support for this (**Figure 1**)(Kirkbride *et al.*, 2012). However, given evidence that within families carrying a high genetic risk of schizophrenia, there are

no significant differences in age at onset between male and female siblings (Albus and Maier, 1995), and evidence that the male predominance in the frequency of onsets in younger age groups is attenuated or even inverted in some populations (Murthy *et al.*, 1998; Phillips *et al.*, 2004), suggests that there are similar pathogenic mechanisms underlying psychosis in males and females.

Figure 1. Pooled incidence of schizophrenia by age and sex in England, 1950-2009 (Jauhar, Johnstone and McKenna, 2022).



1.3. Illness burden of psychosis

Schizophrenia (i.e. chronic psychosis) is a leading cause of disability, and is estimated to have a standardised mortality ratio of 2.6, with suicide being the main contributor early in the course of the illness (McGrath *et al.*, 2008). The global health burden of schizophrenia is high, given the high levels of distress experienced by individuals, the burden of care on caregivers (Lauber *et al.*, 2005), as well as treatment side-effects, cognitive impairment and stigmatisation, which overall contribute to a reduced quality of life in people experiencing psychosis (Millier *et al.*, 2014).

1.4. Clinical features of psychosis

Central to the diagnostic construct of psychosis are 'positive symptoms', including paranoia, hallucinations and delusions and 'negative symptoms', including anhedonia, avolition, impaired social functioning, blunted affect and alogia. This thesis is primarily concerned with the neurobiology underlying positive symptoms, and for the purposes of this thesis, the term psychosis refers to positive symptoms, unless otherwise stated.

Paranoia is a common feature of psychosis and involves unfounded, or at least highly exaggerated, beliefs that others intend to harm the individual (Freeman and Garety, 2014). Persecutory delusions are a severe form of paranoia characterised by the belief that harm is going to occur and that others intend it, and are a common and clinically important feature of psychosis, experienced by an estimated 70-80% of patients with first episode of psychosis (Andreasen, 1987; Coid *et al.*, 2013).

Delusions are firmly held false beliefs, which are based on incorrect (false) inferences about the world, the self and others, and maintained firmly despite the presence of contradictory evidence. Delusions occurring in patients with schizophrenia may have persecutory, grandiose, nihilistic, somatic, sexual and religious themes, which can differ according to the individual's cultural background (Andreasen, 2020).

Hallucinations are abnormal sensory perceptions that occur in the absence of a corresponding external or somatic stimulus, and with a quality similar to real and regular perceptual experiences. Though hallucinations can occur in any sensory modality (auditory, visual, tactile, gustatory or olfactory), they are most commonly auditory in people experiencing psychosis, with an estimated 60-80% of all patients diagnosed with a schizophrenia spectrum disorder experiencing auditory hallucinations (Waters *et al.*, 2014). Of note, approximately two-thirds of auditory hallucinations are experienced as threatening voices (Nayani and David, 1996; McCarthy-Jones *et al.*, 2014), whereby individual experiences the voice of a perpetrator intending to cause harm to the individual or those around them (McCarthy-Jones *et al.*, 2014; Sheaves *et al.*, 2020).

1.5. Psychotic experiences

Psychotic experiences can occur in the general population without psychiatric illness. Though the estimated prevalence and incidence of psychotic experiences in the general population varies considerably across studies, meta-analyses report an estimated lifetime risk of approximately 5-10% and a median incidence rate of approximately 2.5-3% (Os *et al.*, 2009; Linscott and van Os, 2013).

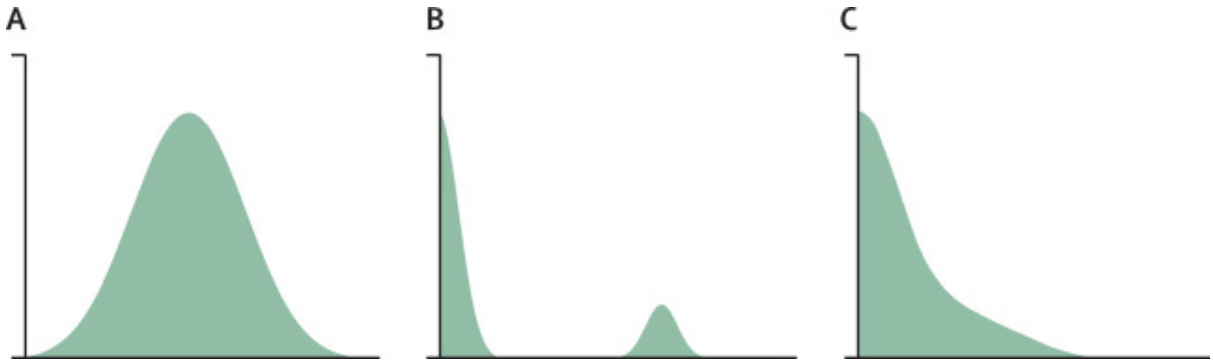
These observations have been interpreted as evidence of a continuum model of psychosis, whereby psychosis exists as a continuum that varies in severity and persistence from infrequent psychotic experiences in the general population to more persistent, distressing and functionally impairing experiences in a clinical population (Os *et al.*, 2009). Consistent with this, epidemiological evidence suggests that paranoia also exists on a spectrum, ranging from mild social concerns, in the general population, to persecutory delusions, in clinical populations (Freeman *et al.*, 2005; Bebbington *et al.*, 2011; Bell and O'Driscoll, 2018).

Studies have yet to show the pattern of distribution of the psychosis continuum. However, given that the majority of the population experience very low levels of psychotic experiences, and a non-trivial proportion of the population experience some greater degree of psychotic experiences, it is thought the psychosis continuum can be described as a half-normal distribution (

Figure 2C) that lies between that of a continuous and dichotomous distribution (

Figure 2A, 2B) (Johns and van Os, 2001).

Figure 2. Models of psychosis distributions, severity of psychotic experiences on the x-axis, and frequency on the y-axis. (A) A continuous and normal distribution of psychotic experiences in the general population (B) A bimodal distribution, with most of the population having no psychotic experiences, whereas a very small proportion have severe psychotic experiences (C) a continuous, but only half-normal distribution, with the majority of population having very low levels of psychotic experiences, but also a non-trivial population having some degree of psychotic experiences (Jauhar, Johnstone and McKenna, 2022)



As will be discussed in more detail in the subsequent sections, there is mounting evidence of shared risk factors across the psychosis continuum, which give rise to the suggestion that the mechanisms underlying clinical and subclinical psychotic experiences may overlap.

This model of continuity between psychotic experiences in the general population to psychotic disorder in clinical populations has two important implications. Firstly, given the overlapping mechanisms underlying clinical and subclinical psychotic experiences, psychotic experiences in the general population can be used to address questions relating to the aetiological, biological or psychosocial mechanisms underlying the psychosis continuum. Secondly, given that subclinical psychotic experiences occur early in the sequence that results in the onset of psychotic disorder, subclinical psychotic experiences can be interpreted as an index and marker of psychosis risk (Linscott and van Os, 2013).

1.6. Psychosis aetiology

1.6.1. The genetic architecture of psychosis

Psychosis is a highly heritable disorder. Estimates of the heritability of psychosis, the proportion of phenotypic variation that is attributable to genetic inheritance based on twin studies is 81% (Lichtenstein *et al.*, 2009).

As both the genetic and environmental backgrounds of twins are correlated, it is difficult to separate the contribution of genetic and environmental factors through twin studies alone. Adoption studies, given the premise that adoptees should show evidence for phenotypic correlation with their biological relatives despite their removal from a correlated environment, are instead able to separate environmental from genetic effects. Adoption studies have confirmed the heritability of psychosis, with adopted-away children of individuals with psychosis having higher rates of psychosis than adoptees of controls (Gottesman and Shields, 1976).

Since these earlier studies, genome-wide association studies (GWAS) have provided increasing and now unequivocal evidence that the genetic risk for psychosis arise from different forms of DNA sequence variation: the best established are single nucleotide polymorphisms (SNPs) and copy number variants (CNVs) (Harrison, 2015).

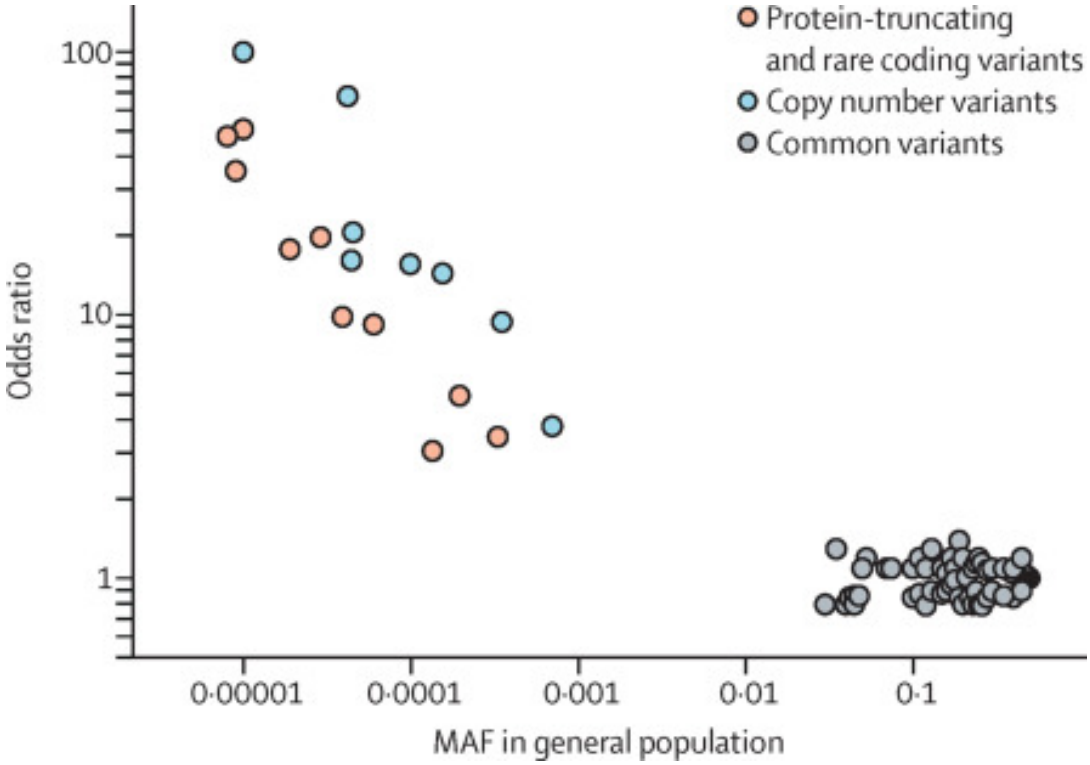
In the largest and most recent GWAS study to date by the Schizophrenia Working Group of the Psychiatric Genomics Consortium, 287 distinct genomic loci were identified which contain SNP(s) significant for the association to schizophrenia at genome-wide level (Trubetskoy *et al.*, 2022). These findings are consistent with the

theory that the genetic risk contribution for schizophrenia is polygenic, representing the cumulative effects of hundreds or possibly thousands of genes, each with small effects, contributing to elevated risk (Jauhar, Johnstone and McKenna, 2022).

In addition to SNPs, a small number of rare copy number variants (J. 5 *et al.*, 2008; Pocklington *et al.*, 2015), gene-disrupting variants including rare-coding variants (Genovese *et al.*, 2016; Singh *et al.*, 2017; Rees *et al.*, 2020), and protein-truncating variants have been identified. Though these variants have moderate to large effect sizes and are the strongest individual risk factors identified to date, they are so rare and often occur *de novo* that they do not explain much of the genetic heritability of psychosis (Malhotra and Sebat, 2012; Singh, Neale and Daly, 2020).

Notably, the genetic risk factors for psychosis converge on the same underlying neuronal genes that have been implicated on the pathophysiology of psychosis. These genes are important to synaptic organisation, differentiation and transmission relevant to schizophrenia pathogenesis (Trubetskoy *et al.*, 2022) and include the dopamine D_2 receptor and NMDA receptor signalling (Harrison, 2015).

Figure 3. Genetic architecture of schizophrenia. Odds ratios (y-axis, -log10) and minor allele frequency (MAF, x-axis, -log10), for protein-truncating and rare coding variants, copy number variants and common variants (single-nucleotide polymorphisms). MAF= minor allele frequency. From (Jauhar, Johnstone and McKenna, 2022)



These existing studies, however, account for only a minority of the heritability of psychosis; the remainder likely results from many more SNPs, CNVs and rare variants, from gene-gene interactions and epigenetic factors that contribute to gene-environment interactions (Harrison, 2015).

Importantly, evidence that the probandwise concordance rates in monozygotic twins is low (33%; (Hilker *et al.*, 2018) demonstrates the importance of shared and non-shared, environmental (i.e. non-genetic) risk factors involved in the aetiology of schizophrenia. Indeed, whilst a history of schizophrenia in a first-degree relative is associated with the highest relative risk of schizophrenia at the individual level, environmental risk factors account for far more cases on a population level (Mortensen *et al.*, 1999). Moreover, there is evidence to suggest that environmental factors may be necessary for schizophrenia to manifest in individuals with a genetic risk for schizophrenia (Sham, 1996; van Os and Marcelis, 1998). Taken together, and considering that environmental risk factors are by their very nature modifiable, this provides a strong rationale for understanding the environmental risks for schizophrenia and their underlying biological mechanisms that give rise to symptoms.

1.7. Environmental risk factors

Accumulating evidence from epidemiologic, clinical and neuroscience research suggest that psychosis is primarily a neurodevelopmental disorder, whereby alterations in brain development during early life underlie the later emergence of psychosis during adulthood (Nasrallah and Weinberger, 1986; Murray and Lewis, 1987).

Initial evidence in support of this hypothesis was observed in studies that found associations between psychosis and risk factors occurring before and shortly after birth, including prenatal exposure to viral infection (Brown, 2006), obstetric complications (Lewis and Murray, 1987), and nutritional deficiencies (Susser and Lin, 1992).

The neurodevelopmental model of psychosis has subsequently been expanded to include the exposure to other environmental factors and drug use over the life course (Murray *et al.*, 2017). These risk factors include childhood and adolescent psychological trauma, adverse child-rearing experiences, including early parental loss, adverse parenting and drug use, particularly heavy cannabis use (Myers *et al.*, 2014).

Table 1. Environmental risk factors that have been proposed for psychosis. From (Dean and Murray, 2005)

Foetal, perinatal and early infant period	**Childhood and adolescence**	**Adolescence and adulthood life**
Obstetric complications Season of birth Maternal infection Maternal malnutrition Maternal stress	Adverse child rearing Childhood and adolescent abuse Head injury	Drug use Migration Ethnic minority status Urbanisation Social adversity Life events

An umbrella meta-analysis analysing 41 meta-analyses of environmental risk factors for schizophrenia found that exposure to childhood adversity, including physical and psychological trauma, and cannabis use were most robustly associated with an increased risk of psychosis (Belbasis *et al.*, 2018). . Exposure to childhood adversity has been linked with later drug use disorders, indicating a possible correlation between these two risk factors (Myers *et al.*, 2014) and demonstrates the complexity of the causative pathways underlying psychosis, whereby risk factors increase the risk of exposure to other risk factors and the disorder itself.

This thesis is concerned with investigating how childhood and adolescent trauma, including physical and psychological trauma, increase the risk of psychosis, as this represents one of the largest and most robust modifiable risk factors for psychosis.

1.8. Developmental trauma

Throughout this thesis, the term developmental trauma refers to exposure to very stressful events or situations of an exceptionally threatening or catastrophic nature, likely to cause pervasive distress in almost anyone, most commonly inter-personal and prolonged or repetitive, before the age of 18 years. Developmental trauma here includes experiences such as childhood and adolescent abuse (i.e. physical abuse, emotional abuse, sexual abuse) and neglect (i.e. physical neglect, emotional neglect), but does not include instances of adversity such as household dysfunction (substance abuse, parental mental illness, parental absence) or economic adversity which are typically included in measures of childhood and adolescent adversity, such as in the adverse childhood experiences (ACE) study (Felitti *et al.*, 1998).

1.8.1. Epidemiology of developmental trauma

Developmental trauma is highly prevalent; in a large meta-analysis of 244 studies, the estimated prevalence of sexual abuse ranged from 4%-22%, physical abuse 14%-24%, emotional abuse 11-47%, physical neglect 7%-19% and emotional neglect 15%-40% (Stoltenborgh *et al.*, 2015). Estimates of exposure to multiple types of trauma range between 20% to 50% (Finkelhor *et al.*, 2009; Saunders and Adams, 2014). There are differences in prevalence estimates according to sex, with

a meta-analysis of 65 studies from 22 countries reporting a higher prevalence of sexual abuse in women (19.2%) compared to men (7.9%) (Pereda *et al.*, 2009b).

The wide variance in prevalence rates of developmental trauma is likely to reflect methodological differences between studies, including how developmental trauma is defined and on the method of data collection. Studies vary on how developmental trauma is defined including the severity of exposure, the number of types of trauma and the timing of trauma that is asked about (i.e. lifetime or past year). Face-to-face interviews have been found to result in higher reporting rates compared to self-completed questionnaires (Pereda *et al.*, 2009a), and prevalence estimates based on informants of trauma (child protection services staff, general practitioners, teachers, staff, etc) are lower than estimates based on self-reports (Stoltenborgh *et al.*, 2015). The timing of trauma assessment also plays an important role. A meta-analysis of 16 studies examining the agreement between prospective and retrospective measures of developmental trauma found substantial differences, suggesting differences in reporting attributable to non-disclosure (i.e. feeling uncomfortable with interview or self-report questions, reluctance to discuss upsetting events or fear of referral to the authorities), false-disclosure (e.g. in the context of family disputes, harassment or revenge) and memory biases (Baldwin *et al.*, 2019).

1.8.2. Developmental trauma and mental health outcomes

It is important to consider that developmental trauma increases the risk for all psychiatric illnesses (Kessler et al., 2018), and given its high prevalence, is an important determinant of psychiatric illness on a population-level. Furthermore, there is little evidence of specificity between developmental trauma and psychiatric illness

(Kessler et al., 2018), indicating that causal pathways linking developmental trauma and psychiatric illnesses may also be non-specific and disorder agnostic.

This thesis is concerned with investigating the mechanisms underlying the association between developmental trauma and psychosis, a severe and potentially extremely distressing clinical syndrome associated with high morbidity and mortality worldwide (Charlson *et al.*, 2018), of which developmental trauma represents one of the largest and robust modifiable risk factors (Belbasis *et al.*, 2018).

However, in accordance with the dominant framework of developmental psychopathology and resilience research and the National Institute of Mental Health's Research Domain Criteria (Cicchetti and Toth, 2009; Insel *et al.*, 2010), and given that psychotic experiences commonly occur in several psychiatric disorders, such as psychotic depression and type I bipolar disorder, it is important to note that the mechanisms underlying the developmental trauma-psychosis association, which is the focus of this thesis, may still reveal neurobiological insights that may translate to other psychiatric disorders, and uncover potential avenues for further investigation.

1.8.3. Developmental trauma and psychosis

Meta-analysis of case-control, prospective and population-based cross-sectional studies indicate that the odds of psychosis are 2.78-fold higher in adult survivors of developmental trauma, compared to those who have not experienced developmental trauma (OR: 2.78, 95% CI: 2.34-3.31) (Varese *et al.*, 2012). Overall, the population attributable risk (PAR) of exposure to developmental trauma on psychosis is estimated to be 33% (95% CI = 0.16-0.47) (Varese *et al.*, 2012).

There is evidence that this association between developmental trauma and psychosis exists throughout the psychosis continuum, from subclinical psychotic experiences in the general population (Addington *et al.*, 2013; DeRosse *et al.*, 2014; Alemany *et al.*, 2015; Kraan *et al.*, 2015) to psychotic symptoms in clinical populations (Larsson *et al.*, 2013; DeRosse *et al.*, 2014; Alemany *et al.*, 2015). In line with this, developmental trauma is associated with elevated psychotic symptom severity in clinical populations (Dam *et al.*, 2012; Mansueto *et al.*, 2019), and also with an increased risk of psychotic experiences in general population samples (Varese *et al.*, 2012; Trotta, Murray and Fisher, 2015; Cunningham, Hoy and Shannon, 2016).

Clinically, adult survivors of developmental trauma with psychosis have more severe illness, are more likely to be hospitalised than individuals with psychosis who have not experienced developmental trauma and have poorer response to treatment (Aas *et al.*, 2016). Adult survivors of developmental trauma therefore represent a particularly vulnerable group, and it is therefore important to elucidate the mechanisms underlying psychosis in these individuals.

1.8.4. Evidence of a causal association between developmental trauma and psychosis

That developmental trauma may be causally associated with psychosis was first suggested by Ferenczi, elaborating on earlier work by Breuer and Freud in the 19th century (Breuer and Freud, 1957; Ferenczi, 1988). Following these early theories, evidence fulfilling the Bradford Hill criteria including strong, consistent, temporal, dose-response relationships provide evidence in support of a causal association between developmental trauma and psychosis (Hill, 1965).

Table 2. Bradford Hill criteria for a causal association between developmental trauma and psychosis. Biological gradient, coherence, analogous evidence and specificity criteria are not necessarily appropriate for causal associations in neuropsychiatry (van Reekum, Streiner and Conn, 2001), but where demonstrable, have been included to add to the argument for causation.

Bradford Hill criteria supporting a causal association	**Key findings**
Strength of association	Odds of psychosis is 2.78-fold higher in adult survivors of developmental trauma compared to those without experiences of developmental trauma (Varese *et al.*, 2012)
Consistency of the evidence	A meta-analysis of 36 case-control, prospective cohort and cross-sectional studies, conducted in 13 countries, report a consistent association between developmental trauma and psychosis (Varese *et al.*, 2012)
Temporal sequence	Evidence from prospective cohort studies report that exposure to developmental trauma increases the likelihood of psychosis (Varese *et al.*, 2012)
Biological gradient	Evidence from meta-analysis of dose-response associations between developmental trauma and psychosis (Varese *et al.*, 2012) Evidence from a population-based prospective study of dose-response associations between developmental and psychosis, robust to the

	effects of confounding and reverse-causality (Croft *et al.*, 2019)
Biological rationale and coherence	Cognitive and neurodevelopmental theories of psychosis propose the association between exposure to developmental trauma and later emergence of psychosis (Nasrallah and Weinberger, 1986; Murray and Lewis, 1987; Garety and Freeman, 1999; Freeman *et al.*, 2002).
Experimental evidence	Not ethically possible in humans Evidence that early life adversity results in psychosis-like phenotypes in rodent models (Hall *et al.*, 1998, 1999)

As illustrated by Varese and colleagues' meta-analysis of 36 observational studies, there is evidence of a strong (OR: 2.78, 95% CI: 2.34-3.31), consistent relationship between developmental trauma and psychosis (Varese *et al.*, 2012).

Cross-sectional and case-control designs limit the inferences that can be made about the temporal association between developmental trauma and psychosis due to the possibility of reverse causality. Longitudinal studies are more informative about the temporal association between exposure to developmental trauma and subsequent psychotic experiences. A pooled analysis of 8 prospective cohort studies estimated that exposure to developmental trauma was associated with a 2.75-fold increase in the likelihood of psychosis (Varese *et al.*, 2012). More recently, using data from a large population-based birth cohort in the United Kingdom, Croft and colleagues found that developmental trauma was associated with a 2.91-fold increase in the odds of psychotic experiences at 18 years (Croft *et al.*, 2019).

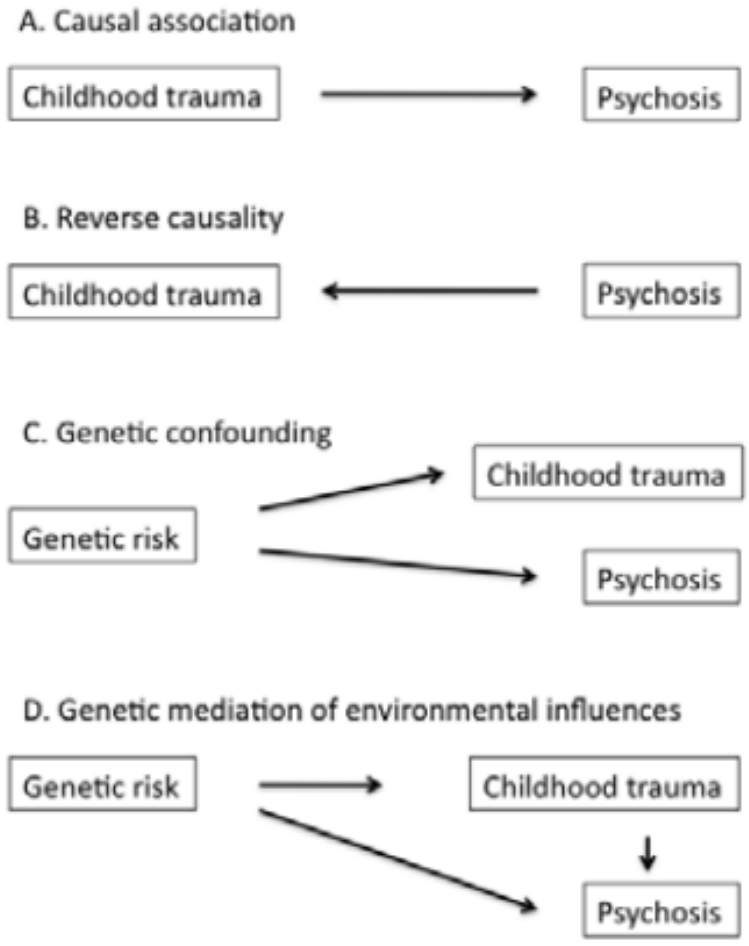
There is evidence of dose-response associations between developmental trauma and psychosis. In Varese and colleagues' meta-analysis, dose-response associations were observed in 9 out of 10 studies which tested for these associations (Varese *et al.*, 2012). Consistent with this, Croft and colleagues also found evidence supporting dose-response associations for exposure to multiple types of developmental trauma and at multiple age periods, robust to the effects of confounding and reverse-causality (Croft *et al.*, 2019). Moreover, these dose-response associations have been observed across the entire psychosis continuum, ranging from psychotic experiences in the general population to psychotic symptoms in clinical populations (Shevlin *et al.*, 2012; Mackie *et al.*, 2013; Muenzenmaier *et al.*, 2015; Trauelsen *et al.*, 2015; Longden, Sampson and Read, 2016).

It is important to consider alternative explanations of association between developmental trauma and psychosis. These are reverse causation and gene-environment correlation. Reverse causation is the theory that early symptoms of psychosis arising in childhood and adolescence increase the risk of exposure to developmental trauma, rather than the other way around (**Figure 4A, B**). Evidence of a temporal association between developmental trauma and psychosis suggest that reverse causation is unlikely (Varese *et al.*, 2012; Croft *et al.*, 2019).

A second explanation is a gene-environment correlation. Children with genetic predispositions may have traits associated with psychosis such as cognitive impairment and impaired social function that place them at greater risk of victimisation (van Winkel *et al.*, 2013). This results in a gene-environment correlation, whereby a genetic predisposition to psychosis results in an increased likelihood of exposure to developmental trauma and later expression of psychosis (**Figure 4C**). There is indeed evidence of this from a study of patients with psychosis, their unaffected siblings and healthy controls, whereby unaffected siblings were more likely to have experienced developmental trauma than healthy control subjects (Heins *et al.*, 2011). However, given that many experiences of developmental trauma pertain to the family environment, the increased prevalence of trauma in siblings in this study may also represent familial clustering of traumatic experiences, rather than a true gene-environment correlation (van Winkel *et al.*, 2013). Other studies that have not investigated gene-environment correlations directly, have instead controlled for genetic risk in their analyses. These studies report strong and significant associations between developmental trauma and psychosis after controlling for genetic risk (Husted *et al.*, 2010; Arseneault *et al.*, 2011; Heins *et al.*, 2011; Alemany *et al.*, 2013), providing evidence. In summary,

these findings suggest that there are gene-environment correlations, though the actual exposure of developmental trauma in itself further increases the risk of psychosis, resulting in a partial genetic mediation of the effects of developmental trauma on psychosis (**Figure 4D**).

Figure 4. Aetiological models explaining the association between developmental trauma and psychosis. A. Exposure to developmental trauma causes psychosis. B. Psychotic symptoms increase the likelihood of victimisation and developmental trauma. C. Genetic risk simultaneously increases the risk for psychosis and developmental trauma. D. Genetic risk factors directly increase the risk of psychosis and increases the risk of developmental trauma, which has an additional effect on the expression of psychosis. From (van Winkel *et al.*, 2013).



1.8.5. The type and timing of developmental trauma and psychosis

It is currently unclear the extent to which the type and timing of developmental trauma is involved in increasing the risk of psychosis and particular psychotic symptoms.

Given that exposure to different types of developmental trauma frequently co-occurs (Dong *et al.*, 2004; Finkelhor *et al.*, 2009; McLaughlin *et al.*, 2012), and given high rates of revictimization (Lurie, Boaz and Golan, 2013; Radford *et al.*, 2013; Fisher *et al.*, 2015), collinearities between the type and timing of trauma make it difficult to determine the specific effects of the type and timing of trauma on psychosis and findings should be interpreted with caution. Moreover, psychotic symptoms frequently occur together than in isolation (van Nierop *et al.*, 2014) making inferences about associations between particular trauma types and particular psychotic symptoms difficult.

There is evidence to suggest that specific types of developmental trauma are each associated with an increased risk of psychosis (Schreier *et al.*, 2009; Bebbington *et al.*, 2011; Wolke *et al.*, 2014). These studies each examine only a single type of trauma, which precludes comparison of the effects of individual trauma types on psychosis. Instead, studies analysing multiple types of trauma, adjusting for collinearity between trauma types through multivariable regression modelling or penalised regression modelling, comparing the effects of trauma type on psychosis find limited evidence of differential effects of trauma type (Fisher *et al.*, 2010; McGrath *et al.*, 2017; Schalinski *et al.*, 2019).

Cross-sectional and longitudinal studies investigating whether different types of developmental trauma are differentially associated with specific psychotic symptoms, though reporting strong associations between developmental trauma and psychosis across the entire range of psychotic symptoms, do not find evidence for specificity in the relationship between particular trauma types and particular psychotic experiences (Bentall *et al.*, 2012; van Nierop *et al.*, 2014; Abajobir *et al.*, 2017).

Few studies have investigated the effect of different age-periods (Spauwen *et al.*, 2006; Arseneault *et al.*, 2011; Croft *et al.*, 2019; Schalinski *et al.*, 2019), providing limited evidence for the suggestion that the timing of developmental trauma has dissociable effects on psychosis.

Overall, there is inconsistent evidence to suggest that (1) specific types of developmental trauma are differentially associated with specific psychotic symptoms and overall psychosis outcomes and (2) that the timing of trauma is differentially associated with psychosis. Taken together with evidence that specific types of developmental trauma are each associated with an increased risk of psychosis gives rise to the suggestion of a shared etiological pathway between developmental trauma and psychosis, irrespective of trauma type and timing.

1.8.6. Summary

In summary, there is clear and compelling evidence that developmental trauma is causally associated with an increased risk of psychosis, throughout the psychosis continuum, from subclinical psychotic experiences in the general population to psychotic symptoms in clinical populations.

Importantly, developmental trauma contributes to approximately one third of the population attributable risk fraction for psychosis (Varese *et al.*, 2012) and adult

survivors of developmental trauma with psychosis have more severe illness and poorer prognostic outcomes compared to individuals with psychosis who have not experienced developmental trauma.

There is therefore a pressing need to develop preventative interventions that reduce the number of adult survivors of developmental trauma who go on to develop subsequent psychosis and improve prognostic outcomes of individuals with psychosis attributable to developmental trauma.

A significant barrier for the development of preventative interventions for adult survivors of developmental trauma and targeted treatments for survivors with psychosis is the striking lack of understanding of the precise mechanisms that underlie the association between developmental trauma and psychosis. Understanding these underlying mechanisms therefore has the potential to lead to the development of new treatments and secondary preventive interventions.

There is mounting evidence of overlapping pathogenic mechanisms that underlie the psychosis continuum, from subclinical psychotic experiences in the general population to psychotic symptoms in clinical populations. There is also evidence that the association between developmental trauma and psychosis occurs throughout the psychosis continuum. Taken together, this provides the theoretical basis for this thesis, in addressing questions relating to the mechanisms underlying the developmental trauma-psychosis relationship through the study of psychotic experiences in the general population.

1.9. Mechanisms underlying the association between developmental trauma and psychosis

In general terms, a leading view of the mechanism underlying the association between environmental factors, including developmental trauma, and psychosis is that childhood and adolescence are sensitive periods of brain development, through developmental processes including myelination, synaptogenesis and synaptic pruning (Hensch, 2005; McLaughlin, Sheridan and Lambert, 2014). Environmental factors, acting on pre-existing vulnerabilities, are likely to have pronounced effects on brain development that give rise to psychosis (Walker and Diforio, 1997).

A general principle of this theory is that developmental trauma-associated alterations in the brain reflect changes in response to malevolent environments characterised by threat, deprivation or unpredictability, that may become maladaptive or less well optimised for more normative environments contributing to the development of psychosis (McCrory and Viding, 2015; McCrory, Gerin and Viding, 2017).

Developmental trauma-associated alterations in the brain and neural processes may occur in multiple functional systems, including threat processing, reward processing and cognitive control, and across various hierarchical levels of processing from biological, cognitive and psychological levels. In accordance with the dominant framework of developmental psychopathology and resilience research and the National Institute of Mental Health's Research Domain Criteria (Cicchetti and Toth, 2009; Insel *et al.*, 2010), the mechanisms underlying the developmental trauma-psychosis association are thought to be best indexed by a systems-level approach, considering the various hierarchical levels of processing.

This systems-level approach offers several advantages. Firstly, a systems-level approach, by integrating each level of neural processing in relation to a functional neural system or circuit helps in elucidating and inferring causal mechanisms. One of the difficulties of linking various hierarchical levels of processing is that the mapping between these levels is not one-to-one – the same biological disturbance may affect several neural systems (Huys, Maia and Frank, 2016). By focussing on a particular neural system and considering how each level of neural processing gives rise to alterations in a particular neural system better enables the elucidation of specific causal mechanisms underlying specific psychotic symptoms. Secondly, a systems-level approach may help patients understand their experiences better given that it becomes easier to conceptualise how, for instance, a biological alteration relates to a neural system that in turn relates to the phenomenology of a patient's symptom. A better understanding of a patient's own experiences may aid in the development of psychotherapies. Taken together, a systems-level approach is therefore likely to also have more immediate translational relevance.

1.10. Threat-based mechanisms underlying the association between developmental trauma and psychosis

Given that a common feature of developmental trauma and psychosis is threat: traumatic experiences are threatening to one's survival, physical integrity, or sense of self (McLaughlin, Sheridan and Lambert, 2014) and, as described above, psychotic experiences, such as paranoia, persecutory delusions and threatening auditory hallucinations, are commonly characterised by a sense of threat, that is predictive of higher levels of distress (Brett *et al.*, 2014), this thesis will focus on

threat-based mechanisms underlying the association between developmental trauma.

This idea that threat processing – the ability to detect and learn from stimuli associated with danger and respond in ways that aim to mitigate against such threats – is affected by exposure to overwhelming threat during development, and is implicated in the pathogenesis of psychosis is consistent with the theory of latent vulnerability (McCrory and Viding, 2015; McCrory, Gerin and Viding, 2017). Under this framework, developmental trauma results in measurable changes in threat processing that reflect calibration to an early malevolent environment. These alterations that have been adaptive during childhood and adolescence can become maladaptive when the environment is no longer threatening, leading to psychosis.

As will be discussed in the Section 1.12, there are several lines of evidence that support this theory, which contribute to a unified model of psychosis that describe the mechanisms that underlie the pathogenesis of psychotic experiences on biological, psychological and cognitive levels of explanation.

1.11. Threat processing and its neural basis

1.11.1. Threat and fear

Historically, ‘fear’ was used as a term relating to processes involving the detection and response to threats, such as ‘fear conditioning’ and ‘fear system’. However, as described by LeDoux, the term ‘fear’ blurs the distinction between processes that give rise to conscious, subjective experiences of feeling afraid, and non-conscious processes that control defence responses to threats (LeDoux, 2014).

In this thesis, ‘threat’ refers to the presence of experiences that are actual or perceived threats to one’s survival, physical integrity, or sense of self (McLaughlin, Sheridan and Lambert, 2014). The term ‘threat processing’ will be used to refer to the processes that operate non-consciously in learning, detecting and responding to threat, and ‘fear’ will be used to refer to the conscious subjective experience of feeling afraid (LeDoux, 2014).

1.11.2. The components of threat processing

Threat processing can be separated into the dissociable components: (1) threat learning (2) attention (3) recognition and (4) response (LeDoux 2014).

Threat learning refers to processes in which stimuli and situations are associated with threat, endowing stimuli with the ability to elicit a threat response, or safety. Threat learning within the neuroscience literature has been extensively studied through Pavlovian threat conditioning and extinction. Threat conditioning is an example of associative learning whereby an initially neutral stimulus (conditioned stimulus, CS) comes to elicit threat responses after being associated with an aversive stimulus (unconditioned stimulus, US). Threat extinction occurs when, following threat conditioning, subsequent and repeated presentations of the CS in the absence of the aversive US result in a gradual reduction in conditioned threat responses. Threat-associated stimuli are likely to be of multiple sensory modalities, as well as depend on the environmental context, the set of circumstances around the threat-associated stimulus. Therefore, successful threat learning is predicated on context encoding – encoding of the context in which a threat occurs, as well as

context conditioning – associative learning of the encoded context in which threat occurs (Maren, Phan and Liberzon, 2013).

Threat recognition is the ability to identify and recognise threat and threat-associated stimuli that have been learned to be associated with threats. Threatening stimuli are never completely identical hence, threat generalisation enables detection of stimuli that have a sufficient degree of similarity to threat-associated stimuli (Asok, Kandel and Rayman, 2019).

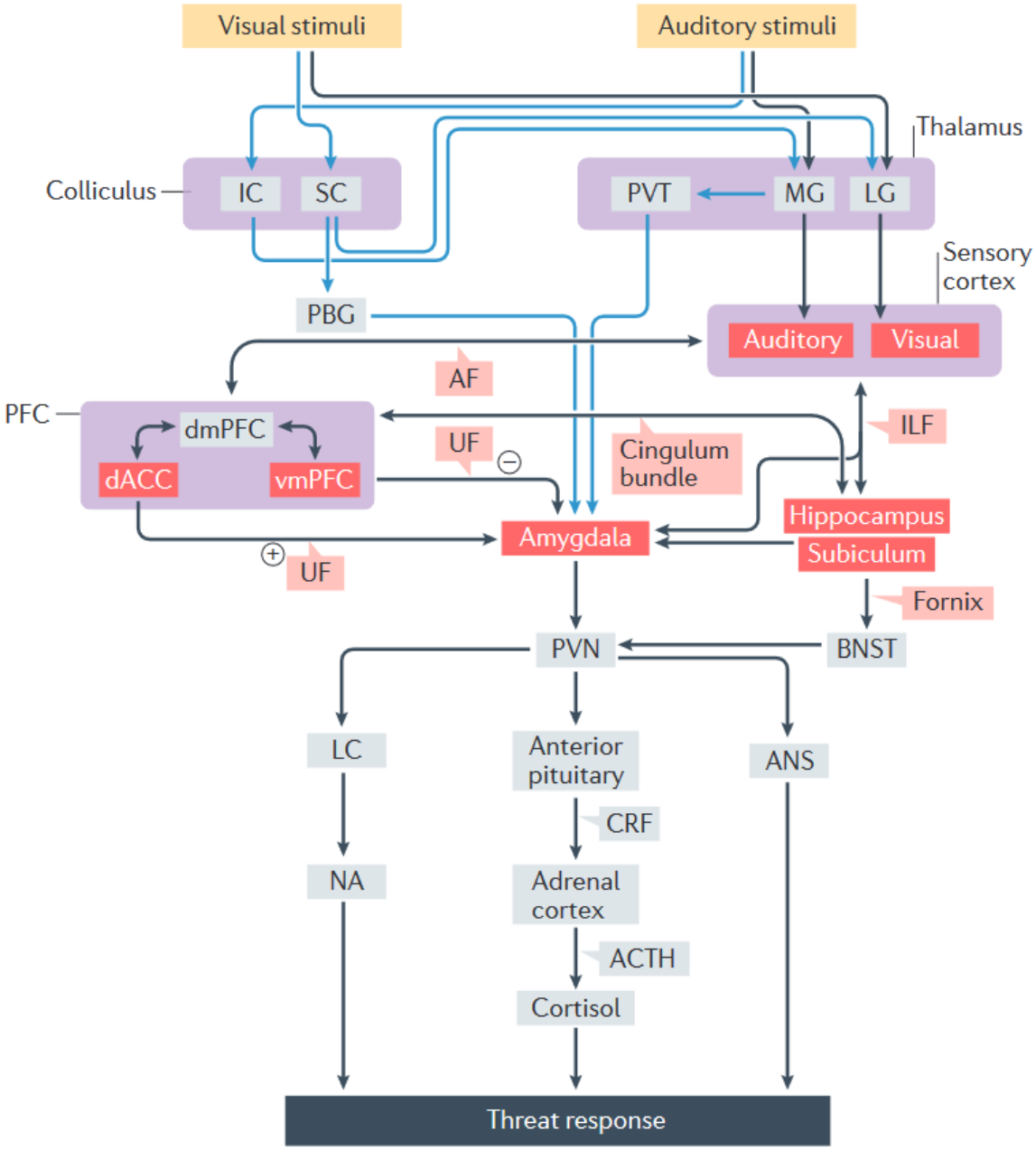
Threat attention refers to the preferential allocation of attention or perception to threats or threat-associated stimuli.

Threat responses are behavioural (e.g., fight, flight, freeze), autonomic (e.g., raised heart rate, blood pressure, respiration), endocrine (e.g., adrenocorticotropic hormone) and conscious subjective (e.g., feeling of being scared) responses that aim to mitigate threat (LeDoux, 2014).

1.11.3. The neural basis of threat processing

The neural circuitry underlying threat processing is illustrated in Figure 5. The neural circuitry underlying threat processing is hierarchically organised, with the amygdala, a heterogenous medial temporal lobe structure, composed of a collection of interconnected subnuclei, playing a central role in this circuit.

Figure 5. The neural circuitry underlying threat processing/ From (Teicher *et al.*, 2016). Visual information from the eyes is relayed to the superior colliculus (SC) and lateral geniculate nucleus (LG). From the SC, information is relayed to the LG or to the parabigeminal nucleus (PBG) and then to the amygdala. From the LG, information is projected to the visual cortex. Auditory information from the ears is relayd to the inferior colliculus (IC) Or the medial geniculate nucleus (MG). Outcome from the IC projects to the MG. From the MG, information can go to the auditory cortex or paraventricular thalamus (PVT) and then to the amygdala. Blue arrows delineate pathway through which information about threatening visual or auditory stimuli can rapidly reach the amygdala without conscious awareness. Sensory cortical regions project to the amygdala, prefrontal cortex (PFC) and hippocampus. The PFC modulates the amygdala response, with the dorsal anterior cingulate cortex (dACC) amplifying this response, and the ventromedial PFC (vmPFC) attenuating it. The dorsomedial PFC (dmPFC) regulates the degree of dACC and vmPFC involvement. The hippocampus provides contextual information to the amygdala. The amygdala projects to the paraventricular nucleus of the hypothalamus (PVN), that helps regulate autonomic responses as well as pituitary adrenal and locus coeruleus (LC) responses. The PVN is also regulated by projections from the hippocampus. ACTH, adrenocorticotropic hormone; AF, arcuate fasciculus; ANS, autonomic nervous system; CRF, corticotropin-releasing factor; ILF, inferior longitudinal fasciculus; NA, noradrenaline; UF, uncinate fasciculus.


Visual stimuli
Auditory stimuli
Thalamus
Colliculus
IC
SC
PVT
MG
LG
Sensory cortex
PBG
Auditory
Visual
AF
PFC
dmPFC
dACC
vmPFC
UF
Cingulum bundle
ILF
Hippocampus
Amygdala
Subiculum
UF
Fornix
PVN
BNST
LC
Anterior pituitary
ANS
CRF
NA
Adrenal cortex
ACTH
Cortisol
Threat response

Anatomically, the most clearly defined amygdala subnuclei are the central (CeA), the basal (BA) and lateral (LA) nuclei (Ressler, 2010; Johansen *et al.*, 2011). The basolateral group of nuclei (BA and LA) are involved in associative learning processes, whereby the LA is a key area where associative learning between the CS and US occur, and the BA is a target area for further processing of information from the LA prior to sending CS-US information to the CeA. The CeA is thought to be the primary effector region, that regulates the threat response including the release of cortisol through the paraventricular nucleus of the hypothalamus, increase in startle responses via the midbrain, and modulation of the autonomic nervous system via the lateral hypothalamus (Ressler, 2010).

The amygdala receives extensive bottom-up projections from lower-order regions such as the thalamus and sensory cortices, which relay sensory information that is typically visual or auditory, as well as contextual information from the hippocampus (LeDoux, 2003). The amygdala in turn projects to a widespread set of efferents, including the paraventricular nucleus of the hypothalamus, the pituitary adrenal and locus coeruleus responses, which give rise to responses to threat. The amygdala also receives top-down modulation, with the dorsal anterior cingulate cortex (dACC) amplifying the amygdala response, and the ventromedial prefrontal cortex (vmPFC) attenuating it. The dorsomedial prefrontal cortex (dmPFC) regulates the degree of dACC and vmPFC involvement (Teicher *et al.*, 2016).

1.11.4. Dopamine and threat processing

Given that developmental trauma has been found to alter dopaminergic signalling (Pruessner, Champagne et al., 2004; Taurisano, Blasi et al., 2013) and given the central role of dopamine in models of psychosis (Kapur, 2003; Howes and Kapur, 2009), the role of dopamine in threat processing should also be considered.

Several lines of evidence converge on the role of dopamine in threat processing. Firstly, dopaminergic neurons in the ventral tegmental area (VTA) and substantia nigra (SN) project to brain structures underlying threat processing including the amygdala, prefrontal cortex and hippocampus (Stubbendorff and Stevenson, 2021). Secondly, dopaminergic signalling is mediated by D_1-type (D_1 and D_5) and D_2-type receptors (D_2, D_3, D_4), which are expressed in these brain regions underlying threat processing (Stubbendorff and Stevenson, 2021). That dopamine in these target regions modulates acute physiology and synaptic plasticity, implicates dopamine as playing a key role in the threat processing (Wise, 2004). Indeed, the excitation or inhibition of dopamine receptor signalling in the CeA has been found to promote or diminish threat conditioning and extinction (De Bundel *et al.*, 2016) and amygdalar responses have been shown to be altered by administration of dopaminergic drugs (Sprengelmeyer *et al.*, 2003). Dopamine is also thought to play an important role in threat extinction via modulation of synaptic plasticity in the medial prefrontal cortex (Salinas-Hernández and Duvarci, 2021).

1.12. Threat-based mechanisms underlying the association between developmental trauma and psychosis

1.12.1. Susceptibility of the threat processing neurocircuitry to the effects of developmental trauma

The brain, and the neurocircuitry underlying threat processing is susceptible to the long-term effects of developmental trauma. Two non-mutually exclusive perspectives for the neural mechanisms underlying the brain's susceptibility to the effects of developmental trauma have been proposed.

The first perspective is the concept of developmental plasticity: the idea that experiences early in development have preferentially permanent impacts on neural structure; childhood and adolescence are sensitive periods of brain development through developmental processes including myelination, synaptogenesis and synaptic pruning, in which neural plasticity is enhanced, meaning that environmental stimuli are likely to have a more pronounced effect on neural structure and function (Hensch, 2005; McLaughlin, Sheridan and Lambert, 2014). Traumatic experiences during these sensitive periods may therefore have long-term impacts on the neural structures underlying threat processing.

The second perspective account is that traumatic experiences, which are inherently stressful and elicit physiological stress responses, induce a cascade of stress-mediated effects on hormones and neurotransmitters that affect the development of vulnerable brain regions (Teicher and Samson, 2016). Activation of the hypothalamic-pituitary-adrenal (HPA) axis results in the release of glucocorticoids, which affect basic developmental processes including neurogenesis, synaptic production and pruning and myelination, of brain regions that have high

concentrations of glucocorticoid receptors. Given that the neural structures underlying threat processing, such as the amygdala, hippocampus and vmPFC have high concentrations of glucocorticoid receptors, they are likely to be susceptible to the long-term effects of developmental trauma (McEwen, 2012)

1.12.2. The association between developmental trauma and alterations in threat processing

There is a substantial body of evidence that developmental trauma is associated with long-term alterations in threat processing and its underlying neural circuitry.

1.12.2.1. Preclinical studies

Given that the neural circuitry underlying threat processing is highly conserved across specific, animal studies have investigated the effects of a variety of early life stress paradigms that parallel the experiences of developmental trauma in humans, whilst controlling for genetic and environmental confounds inherent in human studies. The vast majority of animal studies use rodent models of early adversity, which include repetitive foot shock, chronic restraint, predator odour and minimal bedding (**Table 3**).

Table 3. Commonly used animal paradigms of early adversity. Adapted from McLaughlin et al., (McLaughlin, Sheridan and Lambert, 2014).

Paradigm	Description
Repetitive foot shock	Rodents are administered a series of aversive foot shocks in a closed chamber. The series of shocks is repeated daily for a specified number of days consecutively.
Chronic restraint	Rodents are restrained physically for a specified number of hours. Restraint is repeated daily for a specified number of days consecutively
Predator odour	Rodents are exposed to a natural predator odour in a closed chamber for a specified number of hours. Exposure is repeated daily for a specified number of days consecutively.
Minimal bedding	Rodent dam and litter are housed with a minimal amount of nesting and bedding materials for a specified number of days prior to weaning. Minimal bedding is associated with rough handling of and stepping on pups.
Chronic maternal separation	Litter is removed from rodent dam and placed in an incubator for a specified number of hours. Maternal separation is repeated daily

	for a number of consecutive days prior to weaning.

These preclinical studies provide evidence of long-term structural and functional alterations in the neurocircuitry underlying threat processing, including the amygdala, hippocampus and ventromedial prefrontal cortex (vmPFC) following early-life stressors.

Early exposure to threatening stimuli leads to long-term structural and functional alterations in the amygdala. Chronic stress during early life is associated with amygdalar hypertrophy and atypical dendritic morphology of the amygdala, including increased dendritic spines (Vyas *et al.*, 2002; Vyas, Jadhav and Chattarji, 2006; Eiland *et al.*, 2012). Amygdala reactivity, measured with c-Fos immunohistochemistry, is also enhanced following exposure to chronic stress during early life and adolescence (Raineki *et al.*, 2012; Malter Cohen *et al.*, 2013; Rau *et al.*, 2015).

Early exposure to chronic stress is also associated with structural and functional alterations in the adult hippocampus, including dendritic atrophy and reduced long-term potentiation (Brunson *et al.*, 2005; Rice *et al.*, 2008; Ivy *et al.*, 2010). Notably, there is some evidence that suggests that the effects of early exposure to threat on hippocampal morphology and cellular function do not emerge until adulthood (Isgor *et al.*, 2004; Tsoory, Guterman and Richter-Levin, 2008).

Structural and functional alterations in the ventromedial prefrontal cortex have also been observed. These include reduced apical dendritic length and reduced branching of pyramidal neurons in the ventromedial prefrontal cortex following early

exposure to chronic restraint stress (Eiland *et al.*, 2012). There is also evidence of disrupted synaptic between the vmPFC and hippocampus following early threat, resulting in impaired extinction recall of context-dependent fear extinction (Toledo-Rodriguez and Sandi, 2007).

Beyond effects on neurocircuitry, there is evidence that developmental trauma alters neurochemical systems underlying threat processing, including the dopamine system. Studies in mice have found that developmental trauma potentiates ventral striatal dopamine release in response to aversive stimuli (Fulford and Marsden 1998, Fulford and Marsden 2007).

Taken together, the rodent literature provides evidence that early exposure to threatening stimuli result in long-term changes in the structure and function of brain regions involved in threat processing, including the amygdala, vmPFC and hippocampus, and changes in the underlying neurochemistry, including the dopaminergic system. Notably, these effects last into adulthood, are persistent, and not reversed when the stressor is removed nor diminished (Malter Cohen *et al.*, 2013).

1.12.2.2. Clinical studies

Consistent with preclinical studies, there is a substantial body of evidence that developmental trauma in humans is associated with long-term alterations in threat processing and its underlying neural basis.

1.12.2.2.1. Threatening stimuli used in behavioural and neuroimaging studies

Aversive stimuli that are commonly used in studies in humans include mild electric shocks, air puffs, aversive sounds, including scream stimuli and white-noise stimuli, and threatening facial expressions, such as facial expressions of anger.

Facial expressions are highly salient social cues (Arioli, Crespi and Canessa, 2018) that convey information about others' emotional states, and engage brain circuits involved in social cognition that have considerable overlap with the brain's threat system, most notably the amygdala (Phillips *et al.*, 2003). There are reliable findings that facial expressions, particularly those that are seen as threatening, increase amygdalar responses (Winston *et al.*, 2002), providing the rationale for using facial expressions of anger as threatening stimuli in a substantial number of behavioural studies.

Table 4. Experimental paradigms to assess various domains of threat processing in behavioural and neuroimaging studies in humans.

Threat processing domain	Behavioural paradigm	Description
Learning	Threat conditioning and threat extinction task	Analogous to threat conditioning and extinction paradigms used in animals
Recognition	Emotional recognition task	Assesses the ability to recognise threatening facial expression (anger, fear)
Attention	Emotional dot probe	Assesses attentional bias towards or away from threatening emotional expressions
	Emotional Stroop task	Assesses the ability to allocate attention away from threatening emotional expressions to non-threatening expressions
Response	Fear potentiated startle	Assesses the subjective, autonomic and behavioural responses to aversive stimuli
	Face ratings task	Assesses the subjective arousal and valence responses to threatening facial expressions

The majority of functional neuroimaging studies, with one exception (Taylor *et al.*, 2006), reliably show that developmental trauma is associated with increased amygdala response to emotional faces, particularly those that are seen as threatening (Grant *et al.*, 2011; Bogdan, Williamson and Hariri, 2012; van Harmelen *et al.*, 2013; Teicher *et al.*, 2016). In contrast to the consistent findings of increased amygdalar response to emotional faces observed in the majority of functional neuroimaging studies, studies investigating the effect of developmental trauma on amygdalar volumes are inconsistent (Teicher and Samson, 2016). Most studies report a non-significant decrease (Teicher and Samson, 2016), but some studies report increased amygdalar volumes (Mehta *et al.*, 2009; Tottenham *et al.*, 2010; Pechtel *et al.*, 2014). In line with findings from a large sample longitudinal neuroimaging study in individuals with experiences of developmental trauma, whereby developmental trauma was associated with a non-significant increase in left amygdalar volume at baseline, followed by a more reliable reduction in amygdalar volumes associated with later exposure to trauma (Whittle *et al.*, 2013), it has been hypothesised that developmental trauma produces a small enlargement of the amygdala, but also sensitises it to subsequent stressors, resulting in a graded reduction in volume (Whittle *et al.*, 2013; Teicher and Samson, 2016; Teicher *et al.*, 2016). Additionally, inconsistencies in the relationship between developmental trauma and amygdalar volumes may be affected by the presence or absence of psychopathology (Kuo, Kaloupek and Woodward, 2012; Whittle *et al.*, 2013).

In line with the animal literature demonstrating differences in the development of the hippocampus and vmPFC following early exposure to stress, there is evidence that developmental trauma is associated with reduced hippocampal volumes and

reduced volume and/or thickness of the vmPFC in adulthood (Teicher and Samson, 2016; Teicher *et al.*, 2016).

There is also evidence that developmental trauma alters neurochemical systems involved in threat processing, particularly the dopamine system. In line with findings from animal studies, low maternal care, a type of developmental trauma, is associated with increased ventral striatal dopamine release following acute psychosocial stress and aversive stimuli (Pruessner, Champagne et al., 2004; Taurisano, Blasi et al., 2013). Developmental trauma has also been associated with elevated dopaminergic response to amphetamine administration (Oswald *et al.*, 2014).

Consistent with findings from functional neuroimaging studies of increased amygdalar response to threatening emotional faces, evidence from behavioural studies demonstrate that developmental trauma is associated with atypical processing of threat cues, particularly facial expressions of anger (McCrory, Gerin and Viding, 2017). These include attentional biases towards angry facial expressions (Gibb, Schofield and Coles, 2009; Caldwell *et al.*, 2014; Herzog *et al.*, 2018), enhanced recognition (Gibb, Schofield and Coles, 2009; Tognin *et al.*, 2020) of angry facial expressions and hyperresponsiveness to threat (Pole *et al.*, 2007; Jovanovic *et al.*, 2009; Young *et al.*, 2019).

In summary, evidence from a range of methodologies suggest that developmental trauma is associated with long-term alterations in various domains of threat processing, including increased attentional allocation, enhanced recognition and hyperresponsiveness towards threat, as well as structural alterations in brain regions underlying these threat processes.

1.12.3. The association between altered threat processing and psychosis

Multiple lines of evidence also implicate the role of altered threat processing in psychosis, its development and persistence.

As outlined above, psychotic experiences such as hallucinations and delusions are most commonly threatening in content. Persecutory delusions, which are unfounded beliefs that harm is going to occur, and that others intend it, are present in 70-80% of patients with first episode psychosis (Andreasen, 1987; Coid *et al.*, 2013). In addition, approximately two-thirds of auditory hallucinations are experienced as threatening voices (Nayani and David, 1996; McCarthy-Jones *et al.*, 2014),

Clinically, experiencing threatening psychotic symptoms is predictive of higher levels of distress and increased need-for-care (Lovatt *et al.*, 2010; Brett *et al.*, 2014, 2014; Ward *et al.*, 2014; Underwood, Kumari and Peters, 2016; Peters *et al.*, 2017). In addition, there is evidence that paranoia, unfounded beliefs that others intend harm (Freeman and Garety, 2014), is predictive of transition to psychosis and poor functional outcomes in ultra-high-risk individuals (Demjaha *et al.*, 2012; Valmaggia *et al.*, 2013; Peters *et al.*, 2017) .

There is evidence from human neuroimaging studies of structural alterations in brain regions involved in threat processing in psychosis, with meta-analyses reporting reduced amygdalar, hippocampal, and ventromedial prefrontal cortex (vmPFC) volumes in individuals with schizophrenia (Honea *et al.*, 2005; Glahn *et al.*, 2008; Bora *et al.*, 2011; Haijma *et al.*, 2013; Satterthwaite *et al.*, 2016). Meta-analyses of functional neuroimaging studies have reported reduced amygdala activation in response to aversive stimuli relative to neutral stimuli in individuals with psychosis

compared to healthy controls (Li *et al.*, 2010; Anticevic *et al.*, 2012; Taylor *et al.*, 2012). Taken together with findings of elevated amygdala responses to neutral stimuli (Aleman and Kahn, 2005; Holt *et al.*, 2006), suggest that the apparent reduction in amygdala activation in response to aversive stimuli relative to neutral stimuli may be due to elevated amygdala responses to emotionally neutral stimuli.

There is also consistent evidence from behavioural studies of alterations in threat processing, including threat learning and recognition, in individuals with psychosis compared to healthy controls. In line with neuroimaging findings, meta-analysis of studies of threat learning demonstrate that psychosis is associated with impaired threat learning, due to an increased response to neutral stimulus (Tuominen *et al.*, 2022). Deficits in facial emotion recognition, particularly for negative emotions is a well-replicated finding in psychosis, which is detected at psychosis onset as well as during advanced stages of illness (Tripoli *et al.*, 2022).

In summary, there is a substantial body of evidence that suggest that altered threat processing may contribute to the pathogenesis of psychosis, particularly threatening psychotic experiences.

1.13. Models of threat-based mechanisms underlying the association between developmental trauma and psychosis

Taken together, that developmental trauma alters threat processing and its underlying neural basis, and that altered threat processing is implicated in the pathogenesis of psychosis provides the rationale for the hypothesis that developmental trauma result in long-term alterations in threat processing that contributes to the development of psychosis. This hypothesis is supported by

theoretical models of psychosis that provide mechanistic accounts of how these developmental trauma-associated alterations in threat processing across various levels of neural processes may contribute to the development of psychosis.

1.13.1. The dopamine model of psychosis

The dopamine hypothesis is the longest standing theory of psychosis. The dopamine hypothesis was built on findings that antipsychotic drugs work by blocking dopamine receptors, and that drugs that induce dopamine, such as amphetamine can induce psychotic symptoms (Connell, 1957; Angrist and Gershon, 1970). Subsequent research has demonstrated the relationship between psychosis and striatal hyperdopaminergia, including increased dopamine synthesis capacity, dopamine release and baseline synaptic dopamine concentration (Howes *et al.*, 2012). This relationship with striatal hyperdopaminergia has been found to exist across the psychosis continuum, on the basis of evidence that dopamine synthesis capacity is raised in individuals with clinical high risk of psychosis, which is associated with the severity of prodromal symptoms (Howes *et al.*, 2009) and is specific to individuals who progress to psychosis (Howes *et al.*, 2011).

Based on the evidence that developmental trauma is associated with alterations in dopaminergic signalling (Pruessner, Champagne et al., 2004; Taurisano, Blasi et al., 2013), and that dopamine plays a key role in threat processing (Wise, 2004), the dopamine hypothesis of psychosis provides a mechanism by which developmental trauma alters the dopaminergic system, that underpins alterations in threat processing, which gives rise to psychosis that are likely to be threatening.

Though the dopamine hypothesis explains how developmental trauma-associated alterations in the dopaminergic system, underpinning alterations in threat processing,

may give rise to psychosis, it has been limited in explaining how these molecular abnormalities relate to the phenomenology of symptoms that individuals with psychosis experience.

1.13.2. Cognitive models of psychosis

These neurobiological levels of explanations can be linked with the phenomenological experiences of individuals with psychosis via cognitive models of psychosis that attempt to bridge this explanatory gap.

An influential theory is that dopamine dysregulation results in the aberrant assignment of salience to stimuli that result in anomalies of conscious experience, that trigger a search for meaning (Kapur, 2003; Howes and Kapur, 2009). According to these cognitive models of psychosis, a key influence in the development of psychosis and in the distress experienced by individuals with psychosis is the threat-based nature of the cognitive interpretations of these anomalous experiences, that result in erroneous judgements that these anomalous experiences are externally generated, threatening and uncontrollable – in this way, paranoid delusions are likely to develop (Garety and Freeman, 1999; Garety *et al.*, 2001; Freeman *et al.*, 2002). Under these accounts, developmental trauma may give rise to psychosis by altering cognitive processes that increase the likelihood of threat-based interpretations of uncertain, ambiguous or anomalous experiences (Garety and Freeman, 1999; Garety *et al.*, 2001; Freeman *et al.*, 2002).

The factors that are shaped by developmental trauma, that contribute to these threat-based interpretations may exist across multiple levels of brain function, and include developmental trauma-associated alterations in threat processing, including

attention, perception and response, changes in emotions, and the formation of cognitive schema (i.e. mental constructs of meanings). For instance, attentional biases towards threats and increased perception of threatening stimuli, and the appraisal that ambiguous stimuli are threatening may contribute to interpretations that anomalous experiences are threatening, giving rise to paranoia and persecutory delusions.

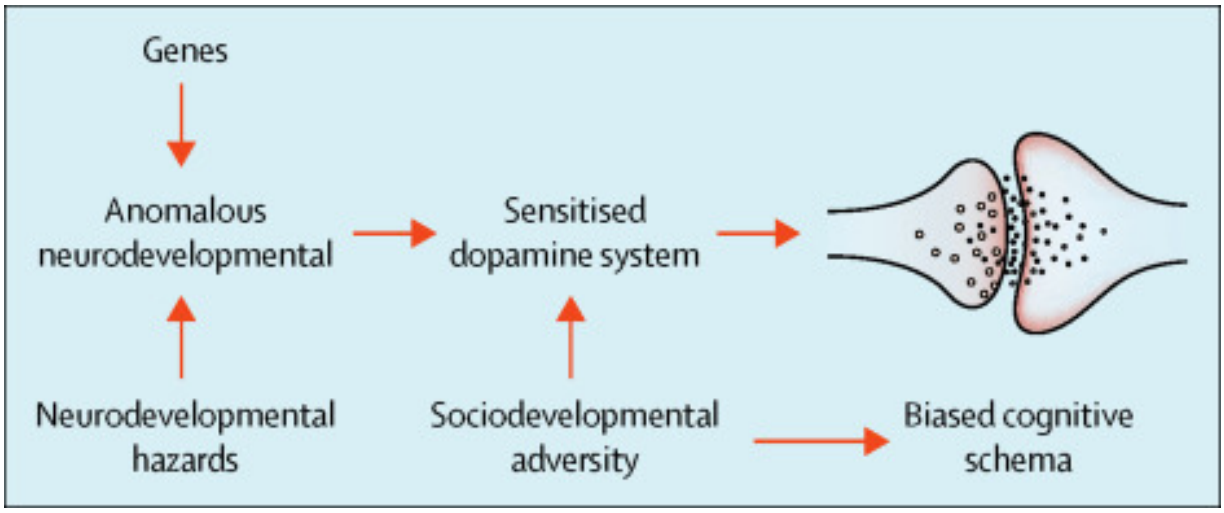
Cognitive models of psychosis also implicate in the pathogenesis of psychosis, cognitive schemata, which are mental constructs of meanings, or pre-existing beliefs that view the world and others are threatening and to attributing negative events and experiences to external factors, such as other people. These cognitive schemata shaped by experiences of developmental trauma have been proposed to bias interpretations to give rise to persecutory beliefs, paranoid delusions and psychotic experiences (Garety and Freeman, 1999; Garety *et al.*, 2001; Freeman *et al.*, 2002).

1.13.3. Integrated models of psychosis

Combining understanding of biological and cognitive theories underlying psychosis, integrated models of psychosis have been proposed (**Figure 6**) (Howes and Murray, 2014). The sociodevelopmental hypothesis posit that neurodevelopmental alterations that arise secondary to variant genes, early brain hazards and social adversities, including developmental trauma disrupt neural development and sensitises the dopamine system that result in excessive dopamine synthesis and release. Social adversities also give rise to cognitive schema that bias an individuals' computations about the world, including in how individuals interpret experiences. A dysregulated dopamine system that results in the aberrant assignment of salience, when

interpreted in the context of cognitive schema about a threatening world, shaped by an individuals' past experiences of trauma, result in paranoid interpretations and psychotic experiences such as paranoia and persecutory delusions.

Figure 6. The sociodevelopmental cognitive model of psychosis. Neurodevelopmental hazards, variant genes and sociodevelopmental adversity sensitise the dopamine system. Sociodevelopmental adversity also bias cognitive schema. A sensitised dopamine system resulting in aberrant salience, which is interpreted in the context of biased cognitive schema give rise to psychotic experiences (Howes and Murray, 2014)



These integrated models of psychosis, though they combine understanding of biological and cognitive theories of psychosis, are limited in their ability to mechanistically link and unify various levels of brain processing.

1.13.4. A unified predictive coding account of psychosis

The predictive coding model conceives the brain as a computational organ that constantly generates and updates its internal model of the world (Friston, 2010; Sterzer *et al.*, 2018). Under this account, the brain, rather than simply passively receiving and detecting sensory information, uses its internal model of the world to predict incoming sensory stimuli to infer their likely causes (Friston, 2009).

This process of inference has recently been formalised computationally through Bayesian inference, where predictions about the environment made prior to observing sensory inputs are updated on the basis of sensory evidence into 'posterior beliefs'. Mismatches between prior beliefs and sensory inputs, result in prediction errors that update the internal model to inform future predictions. (Friston, 2010).

In predictive coding accounts, the degree to which inferences are influenced by prior beliefs and sensory inputs is determined by their relative 'precision', or reliabilities – when the precision of sensory inputs is higher than the precision of prior beliefs, the brain relies more on sensory inputs to make inferences and vice versa.

In terms of the neural basis of hierarchical predictive coding, prediction error signals are thought to be propagated to higher hierarchical levels via glutamatergic alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (Bastos et al., 2012, Shipp et al., 2016). Top-down predictions from higher hierarchical levels are thought to be sent to lower levels via a mixture of AMPA and glutamatergic N-methyl-D-aspartate receptor (NMDAR) signalling and local inhibition (Bastos et al., 2012, Shipp et al., 2016). The relative precision of prior beliefs and sensory inputs is thought to be encoded by various neuromodulators, such as dopamine, as these

receptors can adjust the ‘gain’ of neural messages (Corlett, Frith and Fletcher, 2009; Sterzer *et al.*, 2018).

Under predictive coding accounts, psychotic symptoms are thought to arise from an imbalance of precision, caused by an underlying perturbation of dopaminergic signalling, at various hierarchical levels of the brain’s internal model. Lower levels in the internal model encode highly variable sensory phenomena at limited temporal and spatial scales, whereas higher levels in the internal model encode relatively invariant and abstract representations of environmental phenomena, such as stable beliefs about the world, the self and others (Clark et al., 2013; Hirsh et al., 2013), at larger temporal and spatial scales (Williams, 2018). Given this hierarchy, alterations in predictive coding may have different effects on perceptual (lower levels in the hierarchy) and cognitive domains (higher levels in the hierarchy) (Sterzer *et al.*, 2018). It is thought that an increase in precision of sensory inputs at lower levels of the internal model give rise to experiences of aberrant salience of sensory stimuli, whereas increased precision of prior beliefs at higher levels of the internal model give rise to delusions (Sterzer *et al.*, 2018; Corlett *et al.*, 2019).

Under this account, psychotic symptoms in adult survivors of developmental trauma may arise from an underlying perturbation of dopaminergic signalling that alters the precision of prior beliefs, which have been shaped by past experiences of developmental trauma. These prior beliefs of a threatening world dominate inferences about the causes of incoming sensory experiences, resulting in anomalous experiences that may be interpreted as threatening hallucinations when the cause of sensory inputs are false misattributed to be the voice of a malevolent perpetrator, and the formation of paranoia and persecutory delusions, which result from false inferences about the harmful intentions of others.

In summary, the predictive coding account provides a mechanistically account of the developmental trauma-psychosis relationship, unifying and bridging the gap between neurobiology, threat processing and the phenomenology of psychotic experiences.

1.14. Summary

In contrast to compelling evidence of a causal association between developmental trauma and psychotic experiences across the psychosis continuum, there is a striking lack of understanding of the precise mechanisms that lie on the pathway from developmental trauma to psychosis.

Traumatic experiences are threatening to one's survival, physical integrity, or sense of self and engage neural circuits that aim to mitigate such threats (McLaughlin, Sheridan and Lambert, 2014). The brain's circuits underlying threat processing are susceptible to the effects of developmental trauma, with evidence from behavioural and neuroimaging studies that developmental trauma is associated with long-term alterations in each domain of threat processing, including (1) attentional bias towards threat, (2) enhanced threat recognition, (3) exaggerated threat responses, and (4) impaired threat learning processes, and (5) the neural structures underlying threat processing, including the amygdala and ventromedial prefrontal cortex.

In parallel, alterations in these domains of threat processing and their underlying neural structures, have also been implicated in the pathogenesis of psychosis on the basis of behavioural and neuroimaging studies, as well as in cognitive theories of psychosis.

Taken together, that developmental trauma alters threat processing, and that altered threat processing is implicated in the pathogenesis of psychosis provides the theoretical rationale for the hypothesis that developmental trauma result in long-term alterations in threat processing that contributes to the development of psychosis. This is consistent with existing models of psychosis that implicate the role of altered threat processing in the pathogenesis of psychosis.

As outlined in section, given evidence of overlapping pathogenic mechanisms underlying the psychosis continuum, from subclinical psychotic experiences in the general population to psychotic symptoms in clinical populations, and given evidence of the association between developmental trauma and the psychosis continuum, this thesis addresses questions relating to the threat-based mechanisms underlying the developmental trauma-psychosis relationship through the study of developmental trauma, the associated alterations in threat processing and psychotic experiences, in a general population sample.

1.15. Aims of this thesis

The aim of this thesis, therefore, is to investigate alterations in the various domains of threat processing: (1) threat attention, (2) threat recognition, (3) threat response, and (4) threat learning, and (5) alterations in the neural structures underlying threat processing that are associated with developmental trauma and examine their role in the association between developmental trauma and psychotic experiences.

1.16. Hypotheses relating to this thesis

1. Developmental trauma is associated with increased severity of psychotic experiences
2. Developmental trauma is associated with alterations in threat processing and in the neural structures underlying threat processing
    a. Developmental trauma is associated with an attentional bias towards threat
    b. Developmental trauma is associated with enhanced threat recognition
    c. Developmental trauma is associated with exaggerated threat response
    d. Developmental trauma is associated with increased threat learning and impaired extinction learning
3. Developmental trauma is associated with reduced amygdalar and ventromedial prefrontal cortex volumes
4. These alterations are more pronounced in individuals with psychotic experiences compared to individuals without psychotic experiences
5. Alterations in threat processing mediate the association between developmental trauma severity and psychotic experiences

1.17. Overview of the thesis

The hypotheses relating to this thesis will be tested in chapters II to VI, beginning with a systematic review and meta-analysis (study I), summarising prior literature and characterising the effects of developmental trauma on threat processing in adulthood (chapter II). This is followed by three behavioural studies (study II-IV) examining the effects of developmental trauma on threat attention (chapter III), threat recognition and response (chapter IV) and threat learning (chapter V) and their relation to psychotic experiences, testing each hypothesis. An MRI (magnetic resonance imaging) neuroimaging study (study V) examining the effect of developmental trauma on brain regions involved in threat processing, using data from a large population-based study is presented in chapter VI, again testing each hypothesis. In chapter VII, the results of these studies will be discussed, with a discussion of the clinical implications and future directions for research.

Chapter II: A systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood

2.1. Introduction

As summarised in chapter I, developmental trauma, including physical, sexual, emotional abuse and neglect in childhood and adolescence increases the risk for psychiatric illness in adulthood (Varese et al., 2012). Adult survivors are at a higher risk of adverse prognostic outcomes, including more severe illness, poorer response to treatment, with increased morbidity and mortality (McLaughlin et al., 2017). Despite the compelling association between developmental trauma and psychopathology, the precise neurobiological mechanisms underlying this association are less clear.

A common feature of developmental trauma and psychosis is threat: traumatic experiences are threatening in nature and psychotic experiences are commonly characterised by an exaggerated sense of threat, that is predictive of higher levels of distress. This idea that threat processing – the ability to detect and learn from stimuli associated with danger and respond in ways that aim to mitigate against such threats – is affected by exposure to overwhelming threat during development, and is implicated in the pathogenesis of psychosis is in keeping with the theory of latent vulnerability (McCrory and Viding 2015). Under this framework, developmental trauma results in measurable alterations in threat processing that reflect calibration to an early malevolent environment. These alterations that may have been adaptive during childhood and adolescence in malevolent environments can become maladaptive when the environment is no longer threatening, giving rise to psychotic experiences.

Several lines of evidence that support this theory. Firstly, there is evidence in both humans and animals that the threat processing neurocircuitry is susceptible to the

effects of psychological trauma. By definition, psychological trauma is threatening in nature and engages the organism's threat processing system (McLaughlin, Sheridan and Lambert, 2014). Given that the structure and function of brain regions involved in threat processing undergo significant remodeling and refinement across infancy, childhood and adolescence (Tottenham and Sheridan, 2010), the occurrence of traumatic experiences during these sensitive periods can disrupt neural development and synaptic plasticity that extend into adulthood (Tsoory, Guterman and Richter-Levin, 2008), leading to long-term alterations in the neural systems of threat processing. Traumatic experiences are also inherently stressful and activate the hypothalamic-pituitary-adrenal (HPA) axis to elicit a physiological stress response (de Kloet, Joëls and Holsboer, 2005; Ulrich-Lai and Herman, 2009; Godoy *et al.*, 2018, 2018). The HPA axis interacts with key brain regions that are involved in threat processing via type 1 and type 2 corticotrophin-releasing factor receptors (CRF_1R and CRF_2R), that are highly expressed in the amygdala, hippocampus and hypothalamus (Binder and Nemeroff, 2010). In animal models, acute and chronic exposure to CRF enhances threat-related behaviours, such as enhanced learning and memory of contextual fear conditioning, and enhanced startle responses (Lee and Davis, 1997; Thompson *et al.*, 2004). In line with this, there is also evidence in humans that developmental trauma is associated with changes in the structure of brain regions involved in threat processing as well as their functional connectivity, with marked differences in the amygdala, hippocampus, ventromedial prefrontal cortex and the anterior cingulate cortex (Teicher et al., 2016).

Secondly, aberrant threat processing is strongly implicated in psychosis in terms of phenomenology, neurobiology and aetiology. Phenomenologically, aberrant threat processing is implicated in psychotic experiences that commonly involve threatening

symptoms such as persecutory delusions and threatening auditory verbal hallucinations (Nayani and David, 1996; McCarthy-Jones *et al.*, 2014). Neurobiologically, alterations in the structure and function of brain regions involved in threat processing are consistently observed in psychosis (McCrory, Gerin and Viding 2017). Finally, aberrant threat processing is thought to have aetiological relevance. In cognitive models of psychosis, it has been proposed that anomalous experiences, in the presence of altered threat processing and attentional bias towards threat-related stimuli give rise to threatening interpretations which in turn contribute to the development of paranoid delusions (Garety and Freeman, 1999; Garety *et al.*, 2001; Freeman *et al.*, 2002). In light of this, threat processing is a candidate system to uncover the neurobiological mechanisms underlying the pathogenesis of psychopathology associated with developmental trauma.

As summarised in chapter 1, threat processing can be broadly categorised into four dissociable components: (1) threat learning, (2) threat recognition, (3) threat attention and (4) threat response. Threat learning refers to the process of learning about the stimuli, actions and contexts that predict aversive outcomes, and encompasses subconstructs such as learning, generalisation, the process of generalising threat learning to stimuli that resemble threat-associated stimuli, and extinction, the process of learning about stimuli that are no longer predictive of threat. Threat attention refers to the process of allocating attention to threats. Threat recognition refers to the process of recognising a stimulus' aversive properties. Finally threat response refers to behavioural (e.g. fight, flight, freeze), autonomic (e.g. raised heart rate, blood pressure), endocrine (e.g. adrenocorticotropic hormone) and conscious subjective (e.g. feeling of being scared) responses elicited by aversive stimuli.

Given that some domains of threat processing may be more susceptible to the effects of trauma than others, and that distinct pathways from altered threat processes to psychosis may exist, there is a need to develop current knowledge and summarise the effects of development trauma on threat processing and its various components.

We therefore aimed to synthesise the literature by conducting systematic review and meta-analysis of the effect of developmental trauma on threat processing in adults. Taken together with the fact that threat processing and its separate domains can be measured relatively easily, reliably, and in ecologically valid ways with behavioural tasks (Browning et al., 2019), this systematic review forms an important step in determining the lasting effects of developmental trauma and understanding the threat-based mechanisms underlying psychosis associated with developmental trauma.

2.2. Aim

To synthesise the literature by conducting systematic review and meta-analysis of the effects of developmental trauma on threat processing in adulthood

2.3. Materials and Methods

2.3.1. Pre-registration

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement. The protocol for the study was pre-registered on PROSPERO with the ID: RD42019157311.

2.3.2. Inclusion criteria and search strategies

Studies were eligible for inclusion if they met the following criteria: (1) investigated the effects of developmental trauma exposure in humans under the age of 18, where developmental trauma was identified using structured assessment tools or through being described as trauma in the report; (2) measured threat processing in humans over the age of 18; (3) published in a peer-reviewed journal written in English.

Studies were identified through electronic searches in the MEDLINE, PsycINFO and Embase databases using the OVID interface. Identified studies were written in English and published before 1 November 2019. Four subordinate concepts were combined: 'childhood' terms, 'trauma' terms, 'adult' terms and 'threat processing' terms. The general search string was as follows: (('childhood' AND 'trauma') AND ('adult' AND 'threat processing')). A combination of free text terms, which were kept consistent across databases, and indexed terms were used, which varied by database. The full search string can be found in the Supplementary materials.

Searches were conducted on 1 November 2019 using the search strategy and terms on the specified databases. Duplicates were cross-checked and removed. Two authors individually screened titles and abstracts of all articles retrieved from the search and the full text of potentially eligible articles were screened. Any

disagreements over study inclusion were resolved in consensus meetings. The titles of references in included studies were also screened to identify further relevant studies. Data were extracted by no fewer than two separate authors for accuracy.

2.3.3. Quality assessment

The risk of bias was assessed using the Newcastle-Ottawa quality assessment scale. Eligible studies were assessed against the following criteria: 1) representativeness of sample; 2) sample size; 3) non-respondents; 4) ascertainment of the exposure; 5) comparability; 6) assessment of outcome; 7) statistical test.

2.3.4. Meta-analysis

Relevant behavioural measures from each study were categorised as measuring threat learning, attention, recognition or response. Where there were three or more studies measuring the same threat processing domain, findings were combined using meta-analytic techniques. The effect size for each study was estimated by calculating Cohen's d and 95% confidence intervals (CIs), using the statistical package 'calculate-es' (R Statistical Programming). Studies reporting effect sizes that could not be converted to Cohen's d were excluded from the meta-analysis.

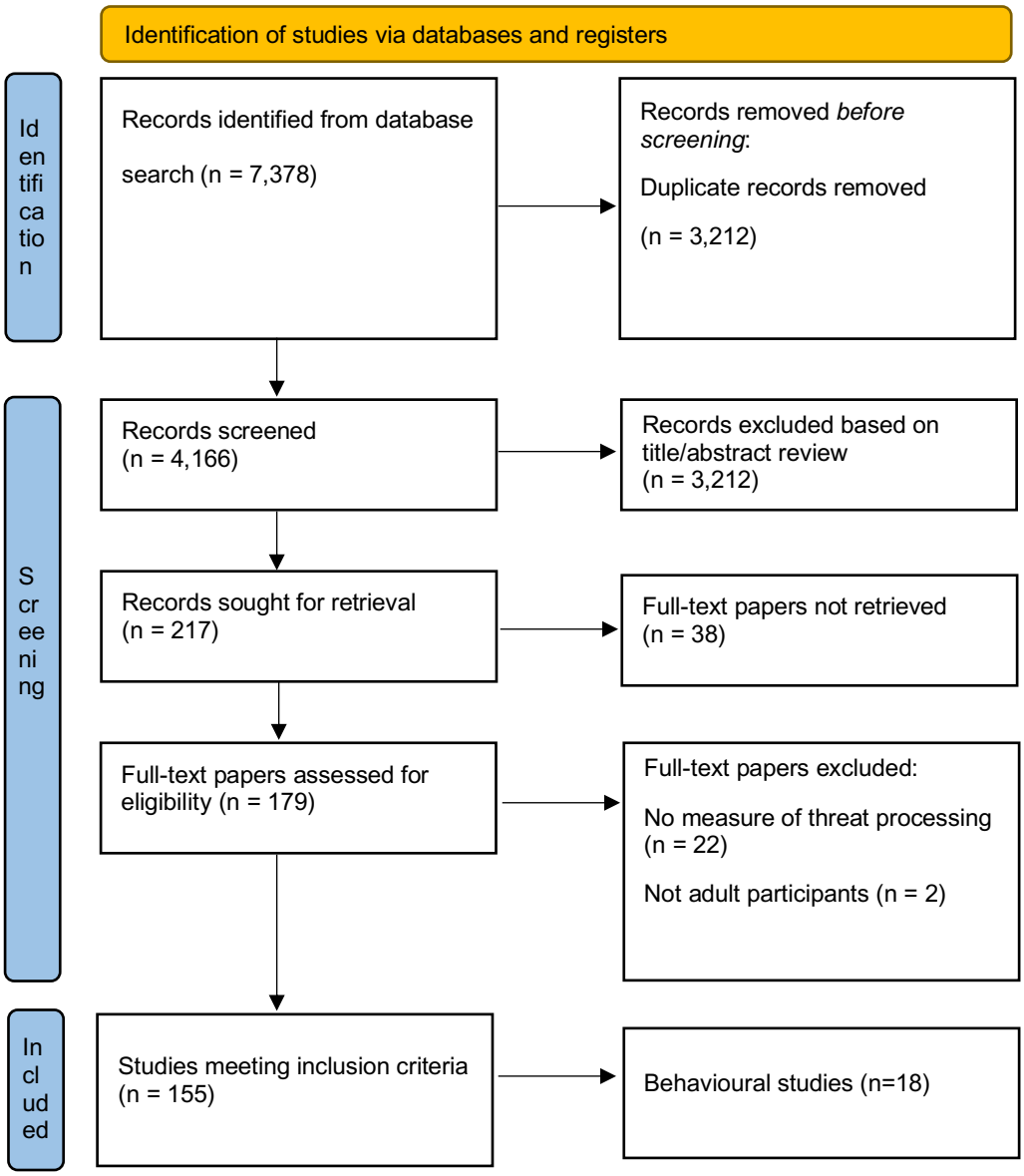
The meta-analysis was performed using the 'metafor' (R Statistical Programming) using a random effects model. Pooled effect sizes were weighted based on the sizes of confidence intervals (Cis). Heterogeneity was assessed by examining X^2 and I^2 statistics.

2.4. Results

2.4.1. Study characteristics

Out of 7,378 studies identified, 18 behavioural studies investigating the effect of developmental trauma on threat processing in adulthood were included. Details of the selection process are presented in a PRISMA flowchart in **Figure 7**.

Figure 7. PRISMA flowchart of included studies. The systematic literature search identified a total of 18 behavioural studies that met the inclusion criteria



Behavioural studies were categorised according to the domain of threat processing investigated (**Figure 8**). Across the studies included, 4 studies examined threat learning, extinction and generalisation, 6 studies examined threat attention, 4 studies examined threat recognition and 5 studies examined threat responses. Sample sizes ranged from 19 to 360 individuals with a median size of 92 individuals. 9 studies consisted of both male and female participants, 7 included exclusively women and 2 exclusively men. 6 studies included both healthy individuals and individuals with psychiatric disorders, 12 included healthy individuals only.

Figure 8. Categorisation of included studied based on threat processing domain

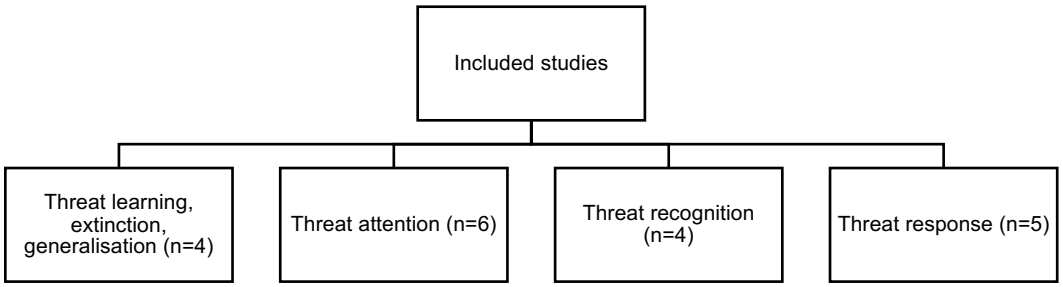


Table 5. Characteristics and main findings of included studies

Study	Sample	DT measure	DT subtype	Domain of threat processing assessed	Main finding, compared to DT-, DT+ demonstrated
Thome et al.,	30 female individuals meeting criteria for PTSD related to repeated childhood abuse, 30 mentally healthy individuals with a history of repeated childhood abuse, 30 healthy, non-trauma exposed controls	CTQ - emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Threat learning (threat conditioning and generalisation)	Impaired response times to safety cues but no threat cues during threat learning Higher expectation of risk of aversive events irrespective of stimulus type Higher subjective ratings of fear Increased fear potentiated startle reflexes non-specific to stimulus type Slowing of response times to safety cues
Bremner et al.,	8 female individuals with a history of childhood sexual abuse and diagnosis of PTSD,	Early Trauma Inventory-Self Report Version - physical abuse, emotional abuse, sexual	Sexual abuse	Threat learning (threat conditioning and extinction)	Potentiated SCR to threat cues in early stages of threat learning SCR responses non-specific to

	11 women without childhood abuse or PTSD	abuse, general traumatic events			stimulus type during threat extinction
Lange et al.,	58 individuals with high levels of childhood maltreatment, 55 participants with no/low levels of childhood maltreatment	CTQ - emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Threat learning (threat generalisation)	No difference in threat discrimination between groups Threat discrimination moderated the association between DT severity and subclinical psychiatric symptoms Elevated clinical symptom load only in adult survivors of developmental trauma who also demonstrated impaired threat discrimination
Lis et al.,	64 female individuals meeting the criteria for PTSD related to repeated physical and/or sexual childhood abuse, 30 non trauma-exposed, mentally healthy control participants	CTQ - emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Physical abuse, sexual abuse	Threat generalisation	Higher expectation of risk of aversive events Higher subjective ratings of fear and fear potentiated startle reflexes that are non-specific to stimulus type

					Slowing of response time to safety cues
Johnson et al.,	48 female individuals meeting criteria for at least one DSM-IV major depressive disorder, 40 individuals with no lifetime history of any DSM-IV mood disorder with varying levels of developmental trauma	CTQ	physical abuse	Threat attention - emotional dot probe	Attention bias for angry faces, but not happy or sad faces
Caldwell et al.,	44 female individuals with high levels of childhood abuse, 45 female individuals with low levels of childhood abuse	CTQ	physical abuse, sexual abuse, emotional abuse	Threat attention - emotional dot probe	Attention bias towards fearful faces
Fani et al.,	129 individuals with varying histories of childhood maltreatment with and without current PTSD symptoms	CTQ, Traumatic Events Interview	emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Threat attention - emotional dot probe	No relationship between DT and attentional bias for angry faces

Davis et al.,	72 individuals with high levels of childhood abuse, 68 individuals with low levels of childhood abuse	CTQ	physical abuse, sexual abuse, emotional abuse	Threat attention - emotional dot probe	No relationship between DT and attentional bias for angry faces Attachment anxiety moderated the association between developmental trauma and attentional bias for happy faces
Herzog et al.,	13 individuals reporting three categories of abuse, 16 participants reporting two categories of abuse, 15 individuals reporting 1 category of abuse, 31 individuals reporting no categories of abuse	Traumatic events screening inventory-brief report form, CTQ	physical , sexual and emotional abuse on either the TESI or CTQ	Threat attention - visual dot-probe task	attentional bias towards highly threatening stimuli in individuals with a single category of trauma exposure attentional bias away from highly threatening stimuli in individuals with three categories of trauma exposure
Gibb et al.,	47 individuals with experiences of DT, 170 healthy controls	CTQ	emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Threat attention - emotional dot probe task Threat recognition - facial affect recognition task	Better recognition of angry faces Attentional bias towards angry faces

Schwaiger et al.,	40 healthy individuals with experiences of DT, 40 healthy controls	CTQ	emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Threat recognition - reading the mind in the eyes test Threat recognition - emotion recognition task	No difference in emotional recognition A single dose of oxytocin increased recognition of fearful and angry faces only in DT+
Tognin et al.,	58 individuals with clinical high risk of psychosis with experiences of developmental trauma, 251 clinical high risk of psychosis without experiences of developmental trauma, 51 healthy controls	Childhood Experience of Care and Abuse, CTQ-B, Bullying questionnaire	Traumatic experiences such as death of a parent, separation from parents, parental discordance, lack of adult support, poverty, cruelty, violence, emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, Bullying	Threat recognition - facial affect recognition task	No evidence of association between DT and recognition of angry faces. Emotional abuse in childhood associated with reduced total facial emotion recognition scores and reduced recognition of neutral stimuli but not angry stimuli in clinical high risk group In individuals with clinical high risk of psychosis, increasing mistakes in emotional recognition from happy to angry associated with a modest increase in transition risk to psychosis

English et al.,	126 healthy university students	CTQ	emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Threat attention - emotional faces task	Emotional maltreatment and total maltreatment associated with better recognition of fearful faces under high cognitive load, but not low cognitive load
Pole et al.,	25 police cadets with experiences of childhood trauma, 65 police cadets with no experiences of childhood trauma	Life stressor Checklist - Revised - e.g. serious accidents, disasters, physical and/or sexual assault	emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect	Threat response to startling sounds	Increased acoustic startle responses No difference in heart rate responses
Young et al.,	45 veterans with experiences of child abuse, 102 veterans without experiences of child abuse	Trauma history questionnaire	Physical and sexual abuse	Threat response to startling sounds	Increased acoustic startle responses No difference in heart rate responses
Jovanovic et al.,	60 African-American individuals from a highly traumatised civilian population	CTQ	Physical abuse, sexual abuse, emotional abuse	Threat response to air blast	Increased startle responses associated with childhood physical and sexual abuse but not emotional abuse

Voellmin et al.,	104 mentally healthy female individuals	Early trauma inventory - Self Report - general trauma, physical abuse, emotional abuse, sexual abuse	Abuse	Threat response - Montreal Imaging Stress Task	Blunted endocrine stress response
Kaiser et al.,	70 healthy female individuals	Traumatic Antecedents Questionnaire - Peer aggression, parental conflict, parental verbal or physical abuse, sexual abuse	Threat-related early life stressors	Threat response - Maastricht Acute Stress Test	Blunted endocrine stress response

Abbreviations: CTQ; Childhood Trauma Questionnaire, DT; developmental trauma, PTSD; Post-traumatic stress disorder,

2.4.2. Quality and strength of evidence appraisal

The methodological quality of included studies as measured by the Newcastle Ottawa scale are displayed in **Table 6**. The quality of evidence of the included studies ranged from levels 6 to 7 on the Newcastle Ottawa scale.

Table 6. Quality and risk of bias assessment results using the Newcastle Ottawa scale

	Selection			Comparability		Outcome		
Study	Representativeness of the sample	Non-response rate	Ascertainment of the exposure	Subjects in different outcome groups are comparable, based on study design or analysis; confounding factors are controlled		Assessment of the outcome blinded	Statistical test	Total score
Thome et al.,	0	1	1	1	1	1	1	6
Bremner et al.,	0	1	1	1	1	1	1	6
Lange et al.,	1	1	1	1	1	1	1	7
Lis et al.,	0	1	1	1	1	1	1	6
Johnson et al.,	0	1	1	1	1	1	1	6
Caldwell et al.,	0	1	1	1	1	1	1	6
Fani et al.,	0	1	1	1	1	1	1	6
Davis et al.,	0	1	1	1	1	1	1	6

Herzog et al.,	1	1	1	1	1	1	1	7
Gibb et al.,	1	1	1	1	1	1	1	7
Schwaiger et al.,	1	1	1	1	1	1	1	7
Tognin et al.,	1	1	1	1	1	1	1	7
English et al.,	0	1	1	1	1	1	1	6
Pole et al.,	0	1	1	1	1	1	1	6
Young et al.,	0	1	1	1	1	1	1	6
Jovanovic et al.,	0	1	1	1	1	1	1	6
Voellmin et al.,	0	1	1	1	1	1	1	6
Kaiser et al.,	0	1	1	1	1	1	1	6

2.4.3. Threat learning, extinction and discrimination

Four studies investigated the effects of developmental trauma on threat learning in adulthood (Bremner *et al.*, 2005; Thome *et al.*, 2018; Lange *et al.*, 2019; Lis *et al.*, 2020). There was evidence from one study of increased threat learning in adult survivors of developmental trauma, where individuals demonstrated potentiated skin conductance responses to threat cues in the early stages of threat learning (Bremner *et al.*, 2005) compared to individuals without experiences of developmental trauma. There was also evidence from two studies of impaired safety learning, where adult survivors of developmental trauma had increased response times to safety cues, but not threat cues, during threat learning (Thome *et al.*, 2018; Lis *et al.*, 2020).

There was also evidence of impaired threat extinction in adult survivors of developmental trauma, where during threat extinction, individuals displayed skin conductance responses that were non-specific to stimulus type (Bremner et al., 2005).

In line with these findings, there was consistent evidence of impaired threat discrimination in adult survivors of developmental trauma. Adult survivors of developmental trauma expected higher risk of aversive events, reported higher subjective ratings of fear and fear potentiated startle reflexes that were non-specific to the stimulus type (Thome *et al.*, 2018; Lis *et al.*, 2020). Adult survivors of developmental trauma also demonstrated a slowing of response time to safety cues (Thome *et al.*, 2018; Lis *et al.*, 2020).

Furthermore, though one study did not observe a difference in threat discrimination in adult survivors of developmental trauma, they found that threat discrimination

moderated the association between developmental trauma severity and subclinical psychiatric symptoms (Lange *et al.*, 2019). Specifically, they found elevated clinical symptom load only in adult survivors of developmental trauma who also demonstrated impaired threat discrimination (Lange *et al.*, 2019).

Although there were four studies investigating the effect of developmental trauma on threat learning, effect sizes could not be extracted from all studies.

In summary, developmental trauma was associated with elevated threat responses during the early stages of threat learning, impaired safety learning, and impaired threat discrimination.

2.4.4. Threat attention

Studies investigating threat attention in adult survivors of developmental trauma report mixed findings, with including an attentional bias towards or away from negative stimuli, or no attentional bias at all.

Three studies have found attention bias towards angry faces. Gibb et al., found that young adults with exposure to developmental trauma was associated with attentional bias towards angry faces, in contrast to controls, who did not demonstrate an attentional bias for angry faces (Gibb, Schofield and Coles, 2009). Johnson et al., also found attention bias for angry faces, but not happy or sad faces in women reporting developmental trauma (Johnson, Gibb and McGeary, 2010). Another study by Caldwell et al., using an emotional Stroop task, found attention bias towards fearful faces in women reporting histories of developmental trauma, but not in women who did not report histories of developmental trauma (Caldwell *et al.*, 2014).

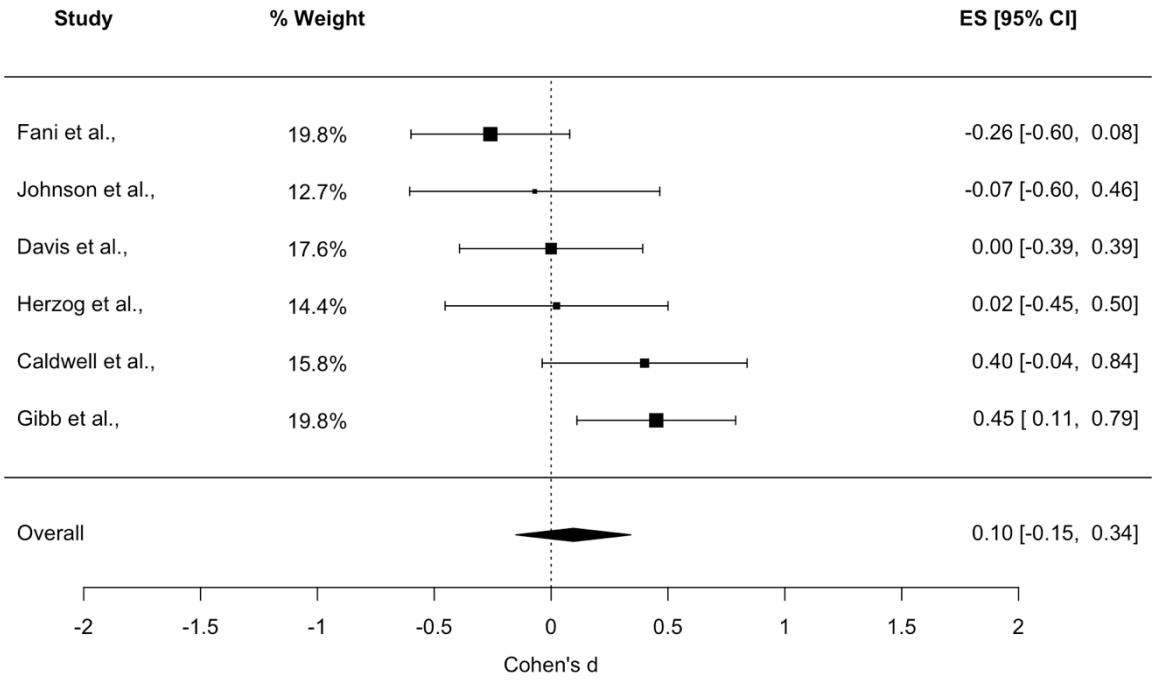
Two studies investigating threat attention using an emotional dot probe with emotional facial stimuli (Fani *et al.*, 2011; Davis *et al.*, 2014) found no relationship between developmental trauma and attentional bias for angry faces. Davis et al., investigated the effect of developmental trauma and attachment style on attentional bias for angry and happy faces in a low-income population. Though they did not find an association between developmental trauma and attentional bias for angry faces, they found that attachment anxiety was associated with an attentional bias away from angry faces. Attachment anxiety moderated the association between developmental trauma and attentional bias for happy faces. Notably, the only individuals to show attentional bias away from positive stimuli were those with high levels of abuse and high attachment anxiety (Davis *et al.*, 2014). Fani et al., in a highly traumatised, low socioeconomic status population, found no associations between developmental trauma and attentional bias for angry faces. However, they found that developmental trauma was associated with attentional bias towards happy faces, mediating the association between trauma and PTSD avoidance and numbing symptoms (Fani *et al.*, 2011).

One study investigated threat attention with respect to attentional bias for mildly and highly threatening stimuli from the international affective pictures system (IAPS) (Herzog *et al.*, 2018). Herzog et al., in women grouped based on exposure to multiple types of childhood interpersonal victimisation, found that there was no evidence of attentional bias for mildly threatening stimuli. However, for highly threatening stimuli, they found that individuals who reported a single category of trauma demonstrated attentional bias towards highly threatening stimuli, whereas individuals who reported three categories of trauma demonstrated attentional bias away from threatening stimuli. Herzog et al., also examined relationships between

physiology and attention biases. Baseline parasympathetic nervous system activity, as measured by respiratory sinus arrhythmia, moderated the association between trauma and attentional bias for mildly threatening stimuli in all groups as lower parasympathetic nervous system activity was associated with hypervigilance. However, parasympathetic nervous system activity differentially moderated the relationship between trauma and attentional bias for highly threatening stimuli between groups. In individuals reporting one or two categories of trauma, lower parasympathetic nervous system activity was associated with hypervigilance, whereas in individuals reporting three categories of trauma, lower parasympathetic nervous system activity was associated with avoidance. Higher task-related sympathetic activity, as indexed by heart rate reactivity, was associated with increased avoidance of highly threatening stimuli, only in individuals reporting three categories of trauma.

Meta-analysis indicated that developmental trauma did not significantly affect threat attention (pooled Cohen's *d*=0.10; pooled 95% CI: -0.15-0.34, **Figure 9**), with moderate heterogeneity between studies (I^2 = 53.3).

Figure 9. Meta-analysis of the effect of developmental trauma on threat attention in adulthood. Sizes of black squares represent weights of Cohen's *d* effect size (ES) according to sample size; horizontal lines indicate 95% CIs; the diamond represents the overall ES and 95% CIs.



In summary, studies investigating the effect of developmental trauma on threat attention report mixed findings, as illustrated in the meta-analysis of these studies, including attentional bias towards or away from angry faces.

2.4.5. Threat recognition

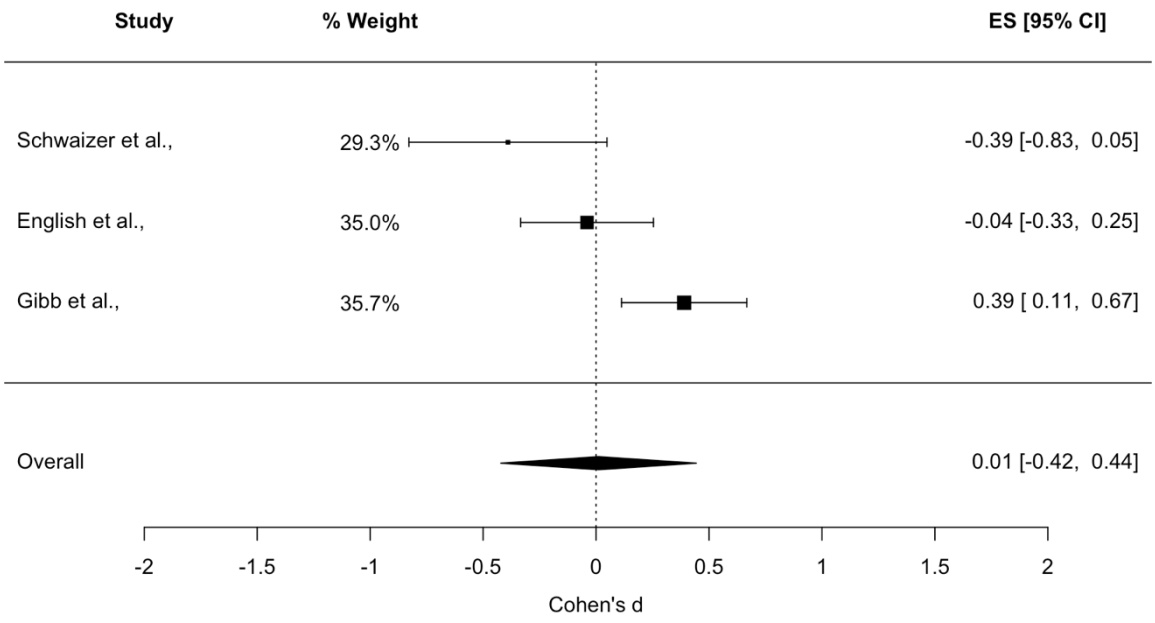
Four studies investigating the effect of developmental trauma on threat recognition found mixed results.

Gibb et al., found that a history of developmental trauma was associated with increased recognition of angry faces, driven by an increased sensitivity to detect anger at lower levels of emotional intensity (Gibb, Schofield and Coles, 2009). Consistent with this, English et al., found, in a sample of female university students, emotional maltreatment and total maltreatment were associated with better recognition of fearful faces under high cognitive load, though not under low cognitive load (English, Wisener and Bailey, 2018). Schwaiger et al., found that following administration of oxytocin, only adult survivors of developmental trauma demonstrated a significant increased in recognition of angry and fearful faces (Schwaiger, Heinrichs and Kumsta, 2019). Tognin et al., found that childhood emotional abuse was associated with poorer recognition of neutral faces in individuals at clinical high risk of psychosis, a pattern of behaviour not observed in healthy individuals (Tognin *et al.*, 2020). Notably, in individuals with clinical high risk of psychosis, increasing mistakes in emotional recognition from happy to angry faces was associated with a modest increase of transition risk to psychosis.

In contrast to these studies, Schwaiger et al., found that healthy adults exposed to developmental trauma did not differ in facial emotion recognition to those who had not been exposed to trauma.

Meta-analysis indicated that developmental trauma did not significantly affect threat recognition (pooled Cohen's d=0.01; pooled 95% CI: -0.42-0.44, **Figure 10**)., with high heterogeneity between studies (I^2 = 80.7).

Figure 10. Meta-analysis of the effect of developmental trauma on threat recognition in adulthood. One study was excluded because the effect size could not be extracted (Tognin *et al.*, 2020). Sizes of black squares represent weights of Cohen's d effect size (ES) according to sample size; horizontal lines indicate 95% CIs; the diamond represents the overall ES and 95% CIs.



In summary, there is evidence from some, but not all, studies of enhanced threat recognition associated with developmental trauma.

2.4.6. Threat response

Six studies examined the effects of developmental trauma on threat responses, three of which investigated defensive responses to startling sounds (Pole *et al.*, 2007; Jovanovic *et al.*, 2009; Young *et al.*, 2019), and three of which investigated responses to acute psychosocial stress (Banihashemi *et al.*, 2015; Voellmin *et al.*, 2015; Kaiser *et al.*, 2018). There were converging findings of exaggerated startle reflexes and skin conductance responses to threat, but mixed findings on physiological responses to threat in individuals exposed to developmental trauma.

There was converging evidence from studies investigating responses to startling sounds of exaggerated threat responses, in particular startle reflexes. Two studies (Pole *et al.*, 2007; Young *et al.*, 2019) in psychiatrically healthy police cadets, and veterans respectively, both observed increased acoustic startle reflexes and increased skin conductance responses in individuals exposed to developmental trauma, but no differences in heart rate responses. In another study, Jovanovic et al., found that increased startle responses were associated with childhood physical and sexual abuse, but not emotional abuse (Jovanovic *et al.*, 2009).

Consistent with studies investigating responses to startling sounds, one study investigating responses to acute psychosocial stress found that childhood physical abuse, but not emotional abuse, was associated with increased mean arterial pressure responses, but not heart rate responses (Banihashemi *et al.*, 2015).

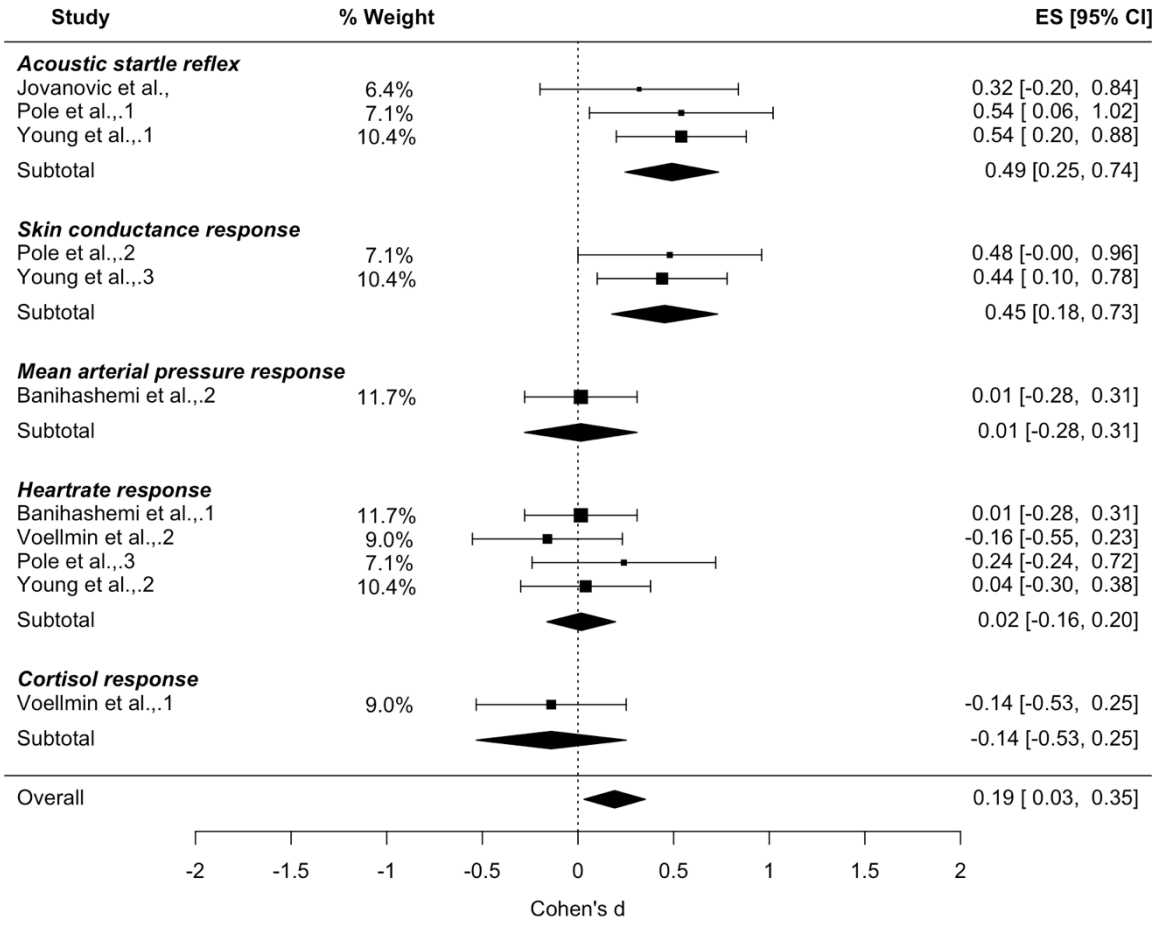
In contrast to this, two studies in women found that acute psychosocial stress was associated with blunted endocrine stress responses, as measured by cortisol responses (Voellmin *et al.*, 2015; Kaiser *et al.*, 2018).

Effect sizes extracted from five studies were included in the meta-analysis. One study was excluded because effect sizes could not be extracted (Kaiser *et al.*, 2018). Meta-analysis indicated that developmental trauma potentiates threat responses in adulthood (pooled Cohen's d=0.19; pooled 95% CI: 0.03-0.35,

Figure 11. There was moderate heterogeneity between studies (I^2 = 48.4%) and between subgroups.

In summary, evidence from studies investigating the effect of developmental trauma on threat responses demonstrate that that developmental trauma is associated with potentiated startle reflexes and skin conductance responses, a mixed pattern of autonomic responses and blunted endocrine responses to threat.

Figure 11. Meta-analysis of the effect of developmental trauma on threat response in adulthood. One study was excluded because effect sizes could not be extracted (Kaiser et al.,). Sizes of black squares represent weights of Cohen's d effect size (ES) according to sample size; horizontal lines indicate 95% Cis; the diamond represents the overall ES and 95% Cis.



2.5. Discussion

2.5.1. Summary

Across 18 studies included in this systematic review and meta-analysis, though results differed substantially across studies, most studies provided evidence in support of the hypothesis that developmental trauma is associated with alterations in threat processing in adulthood, within all domains of threat processing including (1) enhanced threat learning and impaired safety learning resulting in impaired threat discrimination, (2) enhanced threat recognition, (3) a complex pattern of attentional bias towards or away from threatening stimuli, and (4) a complex pattern of threat responses.

2.5.2. Interpretation of findings of the systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood

The effects of developmental trauma on each domain of threat processing differed substantially across studies. The inconsistencies across these studies may result from differences in study methodologies, such as differences in behavioural paradigms used to assess threat processing and in the operationalisation of developmental trauma, and differences in study samples, such as size, sociodemographic background and the type of developmental trauma experienced, which are likely to have influenced the results of included studies, as well as the results of meta-analyses conducted in this study. These will be discussed in detail in Section 7.2.3

Though the specific pattern or direction of alteration in threat processing differed across studies, most studies in this review reported some form of alteration in each domain of threat processing in adult survivors of developmental trauma, which contributes to our understanding of potential threat-based mechanisms that may lie in the pathway between developmental trauma and psychosis.

The complex pattern of the effects of developmental trauma on threat learning, attention and recognition, and to an extent, threat responses, and the heterogeneity detected in the pooled analyses should be discussed. One interpretation, that will be discussed in detail in Section 7.2.3, is that the observed differences in the patterns of alterations in threat processing arise from methodological differences between studies. However, given that mixed patterns of developmental trauma-associated alterations in threat processing have been observed *within* both human and animal studies, whereby the pattern of alteration is influenced by the context of developmental trauma (e.g. type, timing and duration) and the individual or animal exposed to trauma (e.g. sex), another plausible interpretation is these complex patterns of alterations in threat processing reflect experience-dependent modifications that reflect the context of developmental trauma and the individual (McCrory and Viding, 2015; Teicher and Samson, 2016; Teicher *et al.*, 2016). It is also possible that multiple patterns of threat processing may exist in an individual (McCrory and Viding, 2015).

The specific pattern of alteration In threat processing domains may depend on the type, timing and onset of trauma, as well as on the genetic and environmental context of the individual. Though there were not enough studies included in this study to examine the specific effect of type, timing and onset of trauma on threat processing across studies, there was evidence that the number of types of

developmental trauma experienced differentially affected threat processing, whereby single experiences of developmental trauma was found to result in hypervigilant patterns of threat attention, whereas experiencing multiple traumas resulted in avoidant patterns of attention (Herzog *et al.*, 2018). This interpretation that complex patterns of alterations in threat processing arise following developmental trauma is supported by the wider literature, including neuroimaging studies, where there is evidence of opposing effects of trauma on amygdalar activation in response to threat, depending on the timing of trauma, where pre-pubertal trauma is associated with attenuated amygdalar activation whereas post-pubertal trauma is associated with potentiated amygdalar activation (Zhu *et al.*, 2019).

These experience-dependent alterations in threat processing are thought to reflect adaptive changes in response to developmental trauma (McCrory and Viding, 2015; Teicher and Samson, 2016; Teicher *et al.*, 2016). For instance, within the domain of threat attention, it has been proposed that avoidant patterns of attentional allocation may be a (mal)adaptive coping strategy that reduces the subjective distress associated with identifying threat (Heuer, Rinck and Becker, 2007). In contrast, hyper-vigilant patterns of attention may enable individuals to rapidly identify and respond to threat (Zhu *et al.*, 2019).

2.5.3. Strengths and limitations of the systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood

Strengths and limitations specific to this study will be discussed below, and general strengths and limitations of all data included in this thesis will be discussed in detail in the general discussion (Section 7.9).

This study has several strengths. A broad range of studies investigating behavioural measures of threat processing, with broad search terms were used to assess key domains of threat processing separately. Given that alterations in threat processing are likely to be present prior to the onset of psychotic experiences (McCrory and Viding, 2015), that this systematic review and meta-analysis did not limit studies to individuals with psychotic experiences enables the identification of alterations in threat processing that may contribute to increased psychosis risk, rather than alterations that are associated with psychosis.

There were considerable methodological differences between studies. These included differences in the operationalisation of developmental trauma and the ways in which each threat processing domain was measured. The majority of studies used the Childhood Trauma Questionnaire (Bernstein *et al.*, 2003), though studies differed on whether they used the entire scale or a particular subscale indexing a particular type of developmental trauma. Other self-reported assessments of developmental trauma were also used, which may include experiences that are not assessed in the Childhood Trauma Questionnaire. These include experiences such as household dysfunction (domestic violence, substance abuse, parental mental illness, parental absence) or economic adversity. These experiences may differ in the degree to which they engage threat processing (McLaughlin, Sheridan and Lambert, 2014), and the degree to which they affect the neural circuitry underlying threat processing, which may have contributed to the heterogeneity of findings reported in this study. An assessment of the differential effects of trauma type on threat processing was not possible due to the insufficient number of studies and resultant lack of statistical power for detailed analyses.

Studies also varied on how each threat processing domain was measured, and the meta-analysis combines different behavioural measures of threat processing in its summary statistics. For example, some studies assessing threat attention use an emotional dot probe task, whereas others use an emotional Stroop task. Furthermore, there was heterogeneity in the type of aversive stimulus used. For example, some studies use an electric shock, whereas others have used distress screams. Though there is evidence that the types of stimuli used in these studies are aversive irrespective of modality (Beaurenaut *et al.*, 2020), there are likely to be subtle individual differences in responses depending on the type of threat used.

Studies varied in study populations. Several studies included individuals with diagnoses of psychopathology, in particular post-traumatic stress disorder (PTSD) associated with developmental trauma, which were not controlled for. Furthermore, there were also differences in the gender balance of some studies, some only including male participants, and others, female participants. Effect size estimates were unadjusted for covariates and so may be susceptible to the effect of confounds, such as age, sex, medication use, sociodemographic factors, family history of psychosis and genetic risk for psychosis.

An assessment of publication bias was not possible due to an insufficient number of studies available.

Chapter III: The relationship between developmental trauma, threat attention and psychotic experiences

3.1. Introduction

As summarised in chapter I, developmental trauma increases the risk for psychiatric illness in adulthood (Varese et al., 2012). Adult survivors are at a higher risk of adverse prognostic outcomes, including more severe illness, poorer response to treatment, with increased morbidity and mortality (McLaughlin et al., 2017). Despite this compelling association between developmental trauma and psychopathology, the precise neurobiological mechanisms underlying this association are less clear.

Recent work suggests that processes involved in post-traumatic stress disorder may mediate the relationship between developmental trauma and psychotic experiences in adulthood (Bloomfield *et al.*, 2021). Given that elevated subjective threat is both a cardinal feature of post-traumatic stress disorder and implicated in the development of psychotic experiences (ICD 11, Ehlers and Clark 2000, Freeman et al., 2007), aberrant threat processing represents a plausible candidate vulnerability mechanism underlying the relationship between developmental trauma and psychosis (McCrory and Viding, 2015).

Several cognitive theories implicate a role for threat attention, the process of attentional allocation towards threatening stimuli, in the development of psychotic experiences that are threatening in nature, such as hallucinations (e.g. threatening voices) and paranoid delusions. For instance, attentional bias towards threatening stimuli may lead to maladaptive appraisals of safe environments as being threatening, resulting in paranoia. Similarly, maladaptive threat appraisals prompting a search for meaning or explanation, when attributed to external agents, may result in paranoid beliefs (Freeman, 2007). More recently, computational accounts of these theories have been conceptualised, whereby a disruption in how the brain's

predictions about the world and incoming sensory information are processed result in false, and threatening, inferences about the world (Linson and Friston, 2019; Linson, Parr and Friston, 2020).

Though there is evidence from behavioural studies of attentional bias for threat, as measured by attentional bias towards or away from facial expressions of anger, in adult survivors of developmental trauma (towards angry faces: (Gibb, Schofield and Coles, 2009; Johnson, Gibb and McGeary, 2010; Caldwell *et al.*, 2014), away from angry faces:(Herzog *et al.*, 2018)), there is a lack of knowledge on how these alterations in threat attention relate to psychotic experiences in adult survivors of developmental trauma.

Given mounting evidence of an aetiological continuity between clinical and subclinical psychotic experiences (Os *et al.*, 2009; Ettinger *et al.*, 2014; Barrantes-Vidal, Grant and Kwapil, 2015), we recruited a sample of non-clinical adults with varying degrees of subclinical psychotic experiences to investigate the threat-attention based processes underlying psychotic experiences in adult survivors of developmental while avoiding the potential confounds that complicate the study of clinical samples.

3.2. Hypotheses

1. Adult survivors of developmental trauma have elevated psychotic experiences compared to adults who have not experienced developmental trauma
2. Adult survivors of developmental trauma exhibit attentional bias towards threat, as measured by an attentional bias towards angry faces, compared to adults who have not experienced developmental trauma

3. As an exploratory hypothesis, attentional bias for angry faces mediates the relationship between developmental trauma and psychotic experiences

3.3. Materials and Methods

3.3.1. Ethics

This study received ethical approval from the University College London (UCL) Research Ethics Committee (14317/001). All participants provided written informed consent prior to participation.

3.3.2. Participants and procedure

Participants were recruited via online and social media advertising. Participant inclusion criteria were: (1) good physical health; (2) UK-based, (3) fluent in English; (4) of working age (aged 18-65); (5) access to a computer to undertake the study; (6) capacity to give written informed consent. Exclusion criteria were: (1) Currently receiving treatment from a mental health care provider, (2) current use of psychiatric medicines; (3) any past or current major medical condition.

Participants completed a battery of questionnaires and an emotional dot probe task through an online web-based experimental platform, gorilla.sc (Anwyl-Irvine *et al.*, 2020). Potential confounds were examined including demographic variable (age, sex, ethnicity, educational attainment, smoking history, prior use of secondary care mental health services, and psychiatric medication) and childhood socioeconomic status, as well as measures of depression, anxiety, drug abuse and alcoholism.

3.3.3. Assessment of developmental trauma

Self-reported exposure to developmental trauma was assessed using the 28-item Childhood Trauma Questionnaire (CTQ; (Bernstein *et al.*, 2003). The CTQ has shown acceptable reliability and validity in community populations and in patients with psychosis (Bernstein *et al.*, 1994, 2003; Kim *et al.*, 2013). The CTQ retrospectively measures the frequency of childhood traumatic experiences classified into five subtypes: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Pre-defined cut-off scores were used such that each participant was classified as having experienced no abuse, mild, moderate, or severe levels of abuse for each of the five trauma subtypes ((Bernstein *et al.*, 2003) . The cut-offs to score 'mild', 'moderate' or 'severe' were 9, 13 and 16 respectively for emotional abuse, 8, 10 and 13 for physical abuse, 6, 8 and 13 for sexual abuse, 10, 15 and 18 for emotional neglect and 8, 10 and 13 for physical neglect (Bernstein *et al.*, 1994). Individuals reporting at least 'moderate' exposure to more than one type of trauma were assigned to the developmental trauma (DT+) group, and individuals reporting below 'moderate' self-reported exposure to all five types of trauma were assigned to the control (DT-) group. Individuals who were not assigned to either group (individuals reporting moderate exposure to one type of trauma) were excluded from group analyses.

3.3.4. Assessment of clinical variables

Subclinical psychotic symptoms were assessed using the 15-item Community Assessment of Psychic Experiences (CAPE-P15; Capra *et al.*, 2013). The Oxford-Live(Spielberger, 1983)rpool Inventory of Feelings and Experiences (sO-LIFE; Mason, Linney and Claridge, 2005) was used to measure positive schizotypy.

Depressive symptoms and anxiety were assessed using the Quick Inventory of Depressive Symptomatology (QIDS; Rush *et al.*, 2003) and Spielberger State-Trait Anxiety Inventory (STAI; Spielberger, 1983) respectively. Drug abuse and alcoholism was assessed using the Drug Abuse Screening Test (DAST-10; Skinner, 1982) and the Short Michigan Alcoholism Screening Test (SMAST; Selzer, Vinokur and van Rooijen, 1975), respectively.

3.3.5. Assessment of threat attention

Each trial started with a fixation cross that was presented for 500 ms. Following presentation of the fixation cross, a pair of face photographs were presented for 500 ms; in each pair, an angry, happy or neutral face was paired with a neutral face. The faces used in this task were selected from the Karolinska Directed Emotional Faces stimulus set, a facial picture database with good validity (KDEF; Lundqvist, Flykt and Öhman, 1998; Goeleven *et al.*, 2008). After the presentation of the face pair, a dot appeared in place of one of the faces. If the dot appeared in place of the emotional face, this was defined as a ‘congruent’ trial, and if the dot appeared in place of the neutral face, this was defined as an ‘incongruent’ trial. Participants indicated as quickly as possible whether the dot appeared on the left- or right-hand side of the

screen using a forced-choice button press response ('F' for left and 'R' for right). The task consisted of 80 trials (32 positive-neutral, 32 threat-neutral, 16 neutral-neutral face pairs) presented in random order. The probe appeared on the left- or right-hand side of the screen an equal number of times.

Response time (RTs) analysis for the emotional dot probe task was performed for trials on which a correct response was given. The internal reliabilities of emotional dot probe response times were computed using Cronbach's alpha, treating each trial as an item. RTs shorter than the ^{5t}h percentile or longer than the 9^{5t}h percentiles for each participant and condition (emotion, congruency) were identified as outliers, and excluded from the RT analyses. Attentional bias scores for each emotion (happy, threat) were calculated by subtracting mean RTs in congruent trials from mean RTs in incongruent trials stimuli (MacLeod, Mathews and Tata, 1986). Positive scores indicate attentional bias towards the selected emotion, and negative scores indicate attentional bias away from the emotion.

3.3.6. Statistical analyses

Associations between developmental trauma and degree of subclinical psychotic symptoms were assessed using the independent samples *t*-tests and Pearson's correlation coefficients. To examine whether exposure to developmental trauma was a significantly predictor associated of with psychotic-like symptoms and psychosis proneness after adjusting for confounds, multiple regression analyses were performed using CAPE-P15 and sO-LIFE scores as dependent measures, and total CTQ score as the predictor variable.

To investigate differences in threat attention between groups, independent samples *t*-test were conducted on attentional bias scores for angry faces. To determine whether attentional bias scores for angry faces differed from zero, one-sample t-tests were conducted on mean attentional bias scores.

Mediation analyses were used to investigate whether attentional bias to threatening stimuli mediated the effect of developmental trauma on subclinical psychotic symptoms using the Hayes PROCESS macro for SPSS (version 3.2; Hayes, 2018). Effect sizes were computed using 5000 bootstrap samples, and mediation was deemed as significant if 0 was not contained within the 95% bootstrap confidence interval for an indirect effect.

3.3.7. Sample size and power

A priori power calculations were conducted using G*Power. To compare differences in attentional bias scores between DT+ and DT-, based on an alpha level of 0.05 and an estimated effect size, Cohen's *d*=.56, previously observed in a similar study (Gibb, Schofield and Coles, 2009), a minimum sample size of 52 participants per group was required to achieve 80% power.

3.4. Results

3.4.1. Participant characteristics and clinical scores

The total sample included 258 participants; 84 were included in the DT- group and 174 in the DT+ group. Participant demographics and CTQ scores are displayed in **Table 7**. DT- and DT+ did not differ significantly in age, sex and ethnicity. DT+ had lower levels of educational attainment (<0.001) and childhood socioeconomic status (<0.001) and higher levels of eligibility for free school meals (<0.001), prior access to mental health services (<0.001) and tobacco smoking (p<0.036).

DT+, compared to DT-, scored significantly higher on measures of drug abuse (DAST-10), alcoholism (SMAST), anxiety (STAI) and depressive symptoms (QIDS) (**Table 7.** Participant demographics and CTQ scores).

Table 7. Participant demographics and CTQ scores

Sample characteristic	DT- (n=84)	DT+ (n=174)	*p*
Age (years), mean (SD)	36.8 (13.4)	38.1 (13.7)	0.48[a]
Sex (F), %	59.5	52.3	0.28[b]
Ethnicity, %			0.66[b]
White British	76.2	81.6	
Asian	8.3	5.2	
Mixed	1.2	1.7	
Other	14.3	11.5	
Educational attainment, %			<0.001[b]
Degree-level or above	76.2	54.6	
Without degree	23.8	45.4	
Childhood SES			<0.001[b]
High	17.9	37.4	
Intermediate	15.5	17.2	
Low	66.7	45.4	
Childhood eFSM, % eligible	14.3	37.9	<0.001[b]
Prior access to mental health services, %	48.8	78.3	<0.001[b]
Past psychiatric medication use, %	26.2	50	<0.001[b]
Tobacco use, %	27.4	40.8	0.036[b]
CTQ score, mean (SD)	31.6 (5.0)	65.3 (18.6)	<.001[a]

Abbreviations: CTQ, Childhood Trauma Questionnaire, Childhood SES, Childhood socioeconomic status, eFSM, eligibility for free school meals

a Independent samples t-test

b χ^2 test

3.4.2. Relationship between developmental trauma and psychotic experiences

Adult survivors of developmental trauma (DT+) scored higher on measures of psychosis-like experiences (t_{256}=6.404, p<.001, d=.80) and positive schizotypy (t_{256}=7.075, p<.001, d=.88), compared to adults who had not experienced significant developmental trauma (DT-), with large effect sizes. After controlling for educational attainment, childhood socioeconomic status, childhood eligibility to free school meals, prior access to mental health services, past psychiatric medication use and tobacco use, total CTQ score predicted CAPE scores (adjusted R^2 change=.032, $F_{1,244}$ change=14.52, p<.001), driven by persecutory ideation (p<.001) and perceptual abnormalities (p=.042). Whilst CTQ scores were not associated with total O-LIFE scores, CTQ scores were associated with unusual experiences (adjusted R^2 change=.030, $F_{10,247}$=11.43, p=0.001).

Table 8. Participant clinical variables and childhood trauma questionnaire scores

Clinical variable	DT- (n=84) Mean (SD)	DT+ (n=174) Mean (SD)	Effect size *d*	*p*
CAPE-P15				
Persecutory ideation	8.9 (2.0)	11.7 (3.1)	0.930	<0.001
Bizarre experiences	8.3 (2.0)	9.9 (3.3)	0.526	<0.001
Perceptual abnormalities	3.4 (0.7)	3.9 (1.4)	0.395	0.002
Total	20.5 (4.1)	25.5 (6.6)	0.801	<0.001
sO-LIFE				
Unusual experiences	2.1 (2.2)	4.7 (3.2)	0.837	<0.001
Cognitive dissociation	3.9 (3.2)	7.1 (3.3)	0.908	<0.001
Introvertive anhedonia	4.7 (1.4)	5.1 (1.5)	0.279	0.026
Impulsive nonconformity	4.4 (1.8)	5.2 (1.9)	0.430	0.001
Total	15.0 (6.1)	22.1 (7.3)	0.963	<0.001
DAST-10	0.74 (0.95)	1.18 (1.91)	0.253	0.044
SMAST	0.58 (1.03)	1.33 (2.13)	0.383	0.002
QIDS	6.48 (4.69)	13.1 (5.94)	1.12	<0.001
STAI				
State	35.7 (11.8)	48.9 (13.4)	0.959	<0.001
Trait	41.5 (12.9)	56.0 (12.2)	1.10	<0.01

Abbreviations: CAPE-P15, Community Assessment of Psychic Experiences-Positive Scale; DAST-10, Drug Abuse Screening Test; QIDS, Quick Inventory of Depressive Symptomology; SD, standard deviation; SHAPS, Snaith-Hamilton Pleasure Scale; sO-LIFE, Oxford-Liverpool Inventory of Feelings and Experiences short version; SMAST, Short Michigan Alcoholism Screening Test; STAI, State-Trait Anxiety Inventory

3.4.3. Relationship between developmental trauma and threat attention

The mean response times, standard deviation, and percent error by group are presented in **Table 9**.

Table 9. Emotional dot probe response times and errors by group and congruency

	DT- (*n*=84)			DT+ (*n*=174)		
	Mean RT	SD	Error (%)	Mean RT	SD	Error (%)
Angry124ncongruentt	387.087	61.929	6.40	409.154	94.111	6.11
Angry congruent	387.589	62.058	5.58	403.198	89.85	7.69
Neutral	384.706	62.920	6.18	409.109	94.194	7.54

3.4.3.1. Emotional dot probe reliability

Dot probe response times across groups showed moderate-to-good internal reliability (Cronbach's alpha between 0.678 and 0.826) (**Table 10**, **Table 11**). The DT+ and DT- groups did not in differ significantly in average reliability ($X^2_{1, 258}$=.182, *p*=.67).

Table 10. Reliability estimates for emotional dot probe response times by emotion and congruency. Reliability of dot probe response times separated by groups showed poor to good reliability.

Trial type	**Cronbac''s α**
Negative congruent	0.726
Negative incongruent	0.736
Neutral	0.769

Table 11. Reliability estimates for emotional dot probe response times by group, emotion and congruency

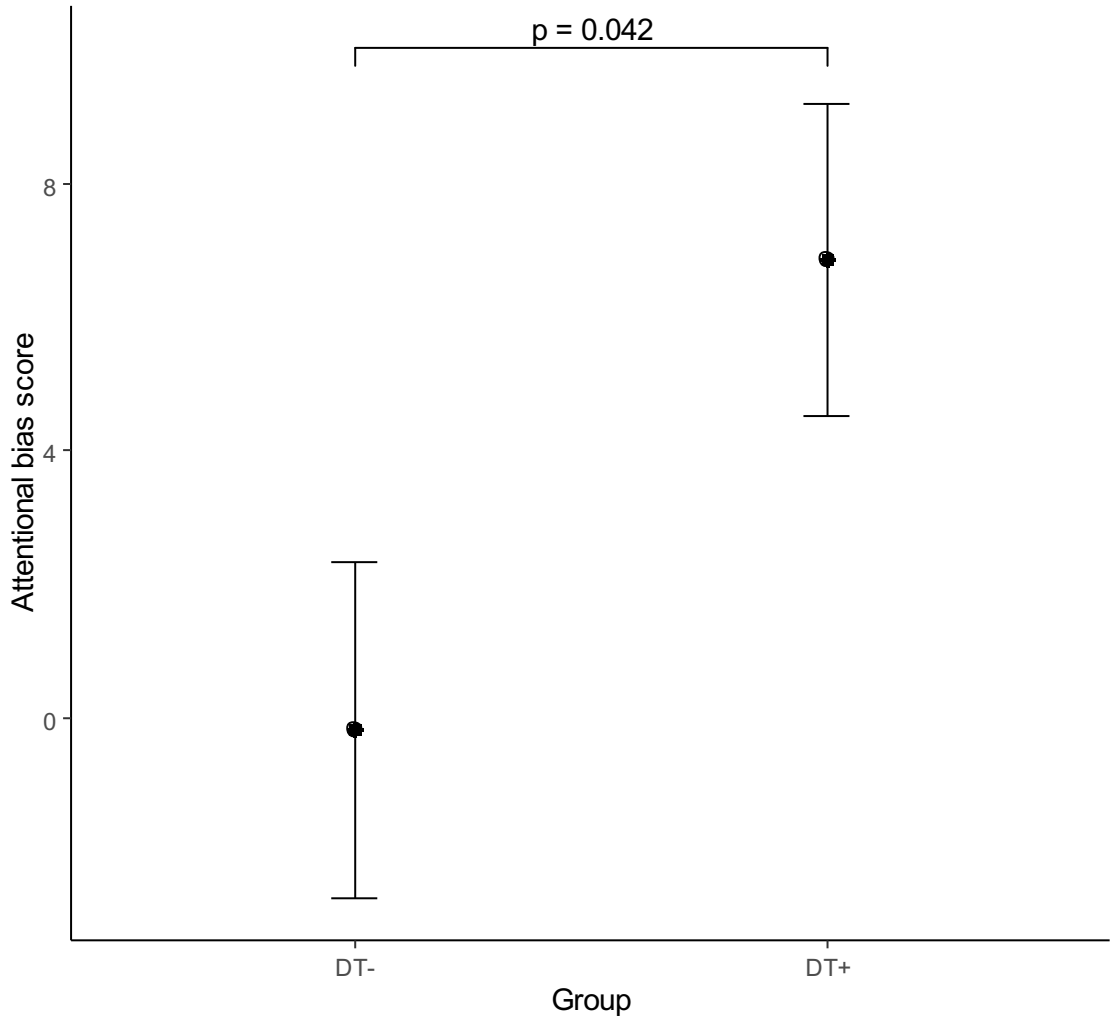
	Cronbach's α	
Trial type	**DT- (*n*=84)**	**DT+ (*n*=174)**
Negative congruent	0.846	0.699
Negative incongruent	0.632	0.795
Neutral	0.528	0.800

3.4.3.2. Attentional bias for angry faces

There was a significant difference between DT+ and DT- on attentional bias scores (t_{199}=2.05, p=.042, d=.26).

In the DT+ group there was a significant attentional bias towards angry faces (one-sample t-test against 0: t_{159}=2.92, p=0.004, d=0.45). There was no evidence for an attentional bias towards angry faces in the DT- group (t_{78}=.077, p=.939, d=.009).

Figure 12. Attentional bias for angry faces. Scores greater than zero indicate attentional bias towards emotional stimuli, whereas scores less than zero indicate attentional bias away from emotion stimuli. DT+ demonstrate a significant increase in attentional bias for angry compared to DT-. DT+ have an attentional bias towards angry faces, whereas DT- do not. Error bars indicate 95% confidence intervals

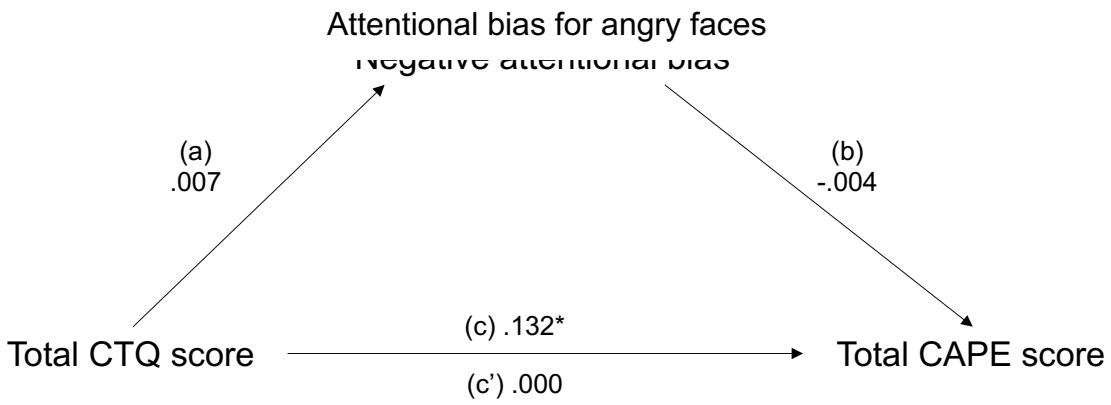


3.4.4. Mediating effect of attentional bias for angry faces on the relation between developmental trauma and psychotic experiences

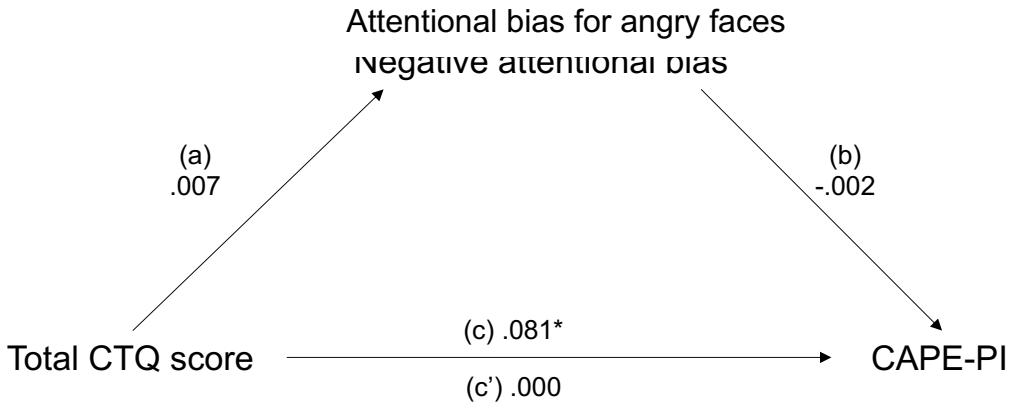
In adult survivors of developmental trauma, there were no significant associations between attentional bias for angry faces and psychotic-like experiences (*B*=-.022, *p*=.770), positive schizotypy (*B*=-.041 , *p*=.591) or anxiety (*B*=-.030, *p*=.696). Mediation analyses to test whether attentional bias towards angry faces mediated the relationship between developmental trauma and subclinical psychotic symptoms were performed (Figure 2). Attentional bias scores for angry faces did not significantly mediate the association between CTQ scores and total CAPE-P15 scores (indirect effect β=.000, 95% CI= -.0031 to .0024), or the association between CTQ scores and the persecutory ideations subscale of the CAPE-P15 (indirect effect β=.000, 95% CI= -.0019 to .0015).

Figure 2. Attentional bias scores for angry faces was examined as a mediator between total CTQ score and (A) total CAPE-P15 score or (B) Persecutory ideation subscale of the CAPE-P15. (A) Attentional bias for angry faces did not significantly mediate the association between developmental trauma and CAPE-P15 score (B) Attentional bias for angry faces did not significantly mediate the association between developmental trauma and the persecutory ideations subscale of the CAPE-P15 scale. *p<.001, unstandardised beta regression coefficients displayed.

A



B



3.5. Discussion

3.5.1. Summary

Adult survivors of developmental trauma exhibited elevated psychotic experiences compared to individuals who have not experienced developmental trauma. Adult survivors of developmental trauma also demonstrated attentional bias towards angry faces, a pattern that was not observed in individuals without experiences of developmental trauma. However, attentional bias for angry faces did not mediate play a mediating role in the relationship between developmental trauma severity and psychotic experiences.

3.5.2. Interpretation of findings of the study on the relationship between developmental trauma, threat attention and psychotic experiences

Consistent with existing literature, adult survivors of developmental trauma exhibited increased levels of subclinical psychotic symptoms (Varese *et al.*, 2012; Velikonja *et al.*, 2015). These findings remained statistically significant after controlling for demographic factors that are known to be associated with trauma providing support to traumagenic neurodevelopmental models of psychosis that propose that trauma-induced changes in the brain during developmental periods increase vulnerability to psychotic disorders (Read et al., 2014). Moreover, these findings of higher levels of psychotic symptoms within a healthy, subclinical population confirm that developmental trauma is positively associated with psychotic symptoms across the psychosis continuum (van Os et al., 2009).

Adult survivors of developmental trauma demonstrated an attentional bias towards threatening stimuli, which can be interpreted as either hypervigilance or difficulty disengaging from threatening stimuli. These findings are consistent with previous literature reporting attentional bias towards threat-associated cues in adult survivors of developmental trauma. Furthermore, though causal inferences cannot be made due to the study's cross-sectional design, given findings from behavioural studies in children who have experienced developmental trauma of difficulties in disengaging from angry faces (McCrory, Gerin and Viding, 2017; Curtis and Cicchetti, 2013; Pollak and Sinha, 2002; Pollak and Tolley-Schell, 2003; Pollak, Vardi, Putzer Bechner, and Curtin, 2005, Shackman and Pollak, 2007; Pine et al., 2005), these findings provide support to the hypothesis that developmental trauma induces long-term changes in threat attention that extend from childhood through to adulthood (Pollak, 2003).

Consistent with traumagenic neurodevelopmental models of psychosis, evidence from previous studies suggest the role of aberrant threat processing associated with developmental trauma in increasing vulnerability to psychiatric disorders (McCrory and Viding, 2015). Furthermore, a recent meta-analysis has found that post-traumatic stress disorder symptoms and emotional dysregulation played a mediating role in the relationship between developmental trauma hallucinations (Bloomfield *et al.*, 2021). Emotional dysregulation involves a reduction in the ability to produce changes in elicited emotions, including the modification of valence, intensity or duration (McCrory et al., 2017; Cole et al., 2004; Eisenberg et al., 2004; Ochsner et al., 2004). Alterations in attentional allocation to, or difficulties in disengaging from emotional stimuli that manifest as changes in attentional bias may reflect emotional dysregulation in adult survivors of developmental trauma. Mediation analyses were

therefore conducted to explore the potential mediating role of attentional bias towards angry faces in the relationship between developmental trauma and psychotic symptoms. However, attentional bias towards threatening stimuli was not a significant mediator between developmental trauma and subclinical psychotic symptoms, reflecting non-significant associations between developmental trauma and attentional bias towards angry faces, as well as between attentional bias and psychotic symptoms (Baron and Kenny, 1986).

Given evidence that developmental trauma may have opposing effects on amygdala response to angry faces depending on the timing of trauma, with early exposure associated with a blunted response, and later exposure associated with an increased response (Zhu et al., 2019), it is possible that adult survivors of developmental trauma have differing attentional bias towards or away from emotional stimuli depending on the type and timing of trauma. Indeed, a prior study found a pattern of threat hypervigilance in individuals exposed to a single type of trauma, compared to a pattern of avoidance in individuals exposed to multiple types of trauma (Herzog et al., 2018). The heterogeneity of attentional bias among adult survivors of developmental trauma may therefore have diminished associations between attentional bias for angry faces and psychotic symptoms**.** Due to high rates of co-occurrence of multiple types of trauma, further investigation of the effects of specific trauma types as well as their timings on emotional attentional bias are warranted.

Furthermore, it is conceivable that factors that promote resilience against psychosis may be at play, given that a mediating role for threat attention in the relationship between developmental trauma and psychotic symptoms was not identified. Although the criteria for developmental trauma used in this study were fairly liberal, participants with active psychiatric diagnoses were excluded, which may have

resulted in the recruitment of participants with a degree of resilience to frank psychosis. These individuals may have ‘recalibrated’ threat processing systems, whereby adaptation towards more normative emotional attention processing confers a resilience to psychosis (McCrory and Viding, 2017). In addition, in light of previous findings that baseline amygdala activity measured prior to stressful life events predict the emergence of psychiatric symptoms post-stress (McCrory and Viding 2017, Hariri et al., 2015, Admon et al., 2013), it is conceivable that developmental trauma induces small-to-modest changes in threat attention that are compounded following later experiences of stressful life events. Hence, the use of a cross-sectional study design within a healthy population, where adult survivors of developmental trauma with increased resilience, whose normative threat processing systems may protect against severe psychotic symptoms even after later stressors, are grouped with adult survivors of developmental trauma who have not experienced later stressors, and have not been subject to its compounding effects, may likely have further ambiguated group differences. Further investigation of the interaction between developmental trauma, later stressful life events and threat processing are therefore indicated to uncover more nuanced resilience and risk factors that may underlie developmental trajectories of psychosis. Consistent with existing literature, adult survivors of developmental trauma also demonstrated increased symptoms of depression and anxiety suggesting that developmental trauma is associated with an increased transdiagnostic risk for multiple forms of psychopathology (McLaughlin and Lambert, 2017; McLaughlin et al., 2020). Therefore, further research is required to identify specific risk and resilience phenotypes that may underlie shifts and/or accelerations in developmental trajectories of multiple psychopathologies.

These findings of attentional bias towards negative emotional stimuli give indirect support for hierarchical predictive coding accounts of psychosis. Attentional bias towards negative emotional stimuli that indicate either hypervigilance (inappropriate threat attention) or difficulties in disengaging from threatening stimuli (inappropriate threat response), can jointly arise from aberrantly strong prior beliefs for threat that will bias threat attention, learning and responses. This is in line with evidence that individuals with psychosis have increased precision of prior beliefs (Haarsma et al., 2020, Adams et al., 2016) and highlights the need for further direct investigation of prior beliefs for threat.

3.5.3. Strengths and limitations of the study on the relationship between developmental trauma, threat attention and psychotic experiences

Strengths and limitations specific to this study will be discussed below, and general strengths and limitations of all data included in this thesis will be discussed in detail in the general discussion (Section 7.9).

This is the first study to experimentally investigate the threat-based mechanisms underlying increased vulnerability to psychosis in adult survivors of developmental trauma, using a validated and well-established attentional-bias task.

Methodological limitations should be discussed. A stimulus onset asynchrony (SOA) of 500ms was used in this emotional dot probe paradigm. With long SOAs (i.e. >300ms), RTs may reflect either enhanced vigilance or impaired disengagement from stimuli meaning that it was not possible to identify the underlying cause of the findings of attentional bias towards negative stimuli. Future studies should therefore compare short SOAs (<300ms), which may reveal differences in initial attention

stages of threat processing, and long SOAs that may demonstrate differences in later, response stages of threat processing (Matthews et al., 1990).

Chapter IV: The relationship between developmental trauma, threat recognition and response and psychotic experiences

4.1. Introduction

As summarized in chapter I, there is growing evidence that developmental trauma – psychologically traumatic events experienced during childhood and/or adolescence – is causally associated with increased psychotic experiences in adulthood (Varese et al., 2012). Despite this, there is a lack of understanding of the precise neurobiological mechanisms that underlie this association.

Multiple lines of evidence converge on the role of altered threat processing as a potential mediating mechanism in the association between developmental trauma and psychosis. Traumatic experiences during development are commonly interpersonal events that are threatening to one's survival, physical integrity, or sense of self (McLaughlin et al., 2014); experiences of abuse and neglect, which commonly occur together, either involve the presence of a perpetrator with harmful intentions, or primary caregiver(s) who fail to provide adequate care. Traumatic experiences therefore engage neural circuits underlying threat processing and social cognition, which comprise highly conserved and overlapping brain regions such as the amygdala, hippocampus and ventral prefrontal cortex, and are involved jointly in accurately detecting and responding to social cues signalling others' emotional states, particularly those that are threatening or potentially so (McLaughlen et al., 2014; Johansen et al., 2011; Ledoux, 2003). The brain's circuits underlying threat processing are susceptible to the effects of developmental trauma (Tottenham and Sheridan 2010, Tsoorey et al., 2008, Binder and Nemeroff, 2010), with consistent evidence from behavioural and neuroimaging studies in animals and humans that developmental trauma is associated with long-term changes in threat processing and its underlying neural circuitry (Teicher et al., 2016).

Facial expressions are highly salient social cues (Kato and Konishi from Arioli et al., 2018), that convey information about others' emotional states, and engage brain circuits involved in social cognition that have considerable overlap with the brain's threat processing system, most notably the amygdala (Phillips et al., 2003). There is substantial evidence that developmental trauma is associated with long-term changes in the processing of negative facial expressions including anger, disgust and fear (Amminger et al., 2012), with reliable findings of increased amygdala response to emotional faces, particularly those that are seen as threatening, in adult survivors of developmental trauma (Teicher et al., 2016). These are also consistent with findings from behavioural studies of lasting effects of developmental trauma on the emotional processing of facial expressions of anger (McCrory et al., 2014).

In parallel, these alterations in the processing of threatening social cues are also present in individuals with psychosis, across the psychosis spectrum. Evidence from meta-analyses and from the largest studies to date (Tripoli et al., 2022), have found evidence of impairments in interpreting facial emotional expressions, particularly anger, in people with schizophrenia at early stages of illness and throughout the course of disorder, as well as in individuals at-risk for psychosis (Tripoli et al. ,2022). These alterations are particularly of interest given their possible relationship with increased risk of psychosis (Tognin et al., 2020), which is in line with cognitive theories of psychosis whereby altered processing of threat-related stimuli can give rise to threatening interpretations in response to anomalous experiences (Freeman et al., 2002), and in line with the neurodevelopmental model of schizophrenia, whereby deficits in cognitive domains may occur prior to the onset of illness (Murray et al., 2017).

Taken together, that altered processing of threatening social cues, particularly facial expressions of anger, are implicated in developmental trauma, and are a relevant factor in the pathogenesis of psychosis, provides a theoretical rationale for the hypothesis that developmental trauma exposure results in altered processing of threatening social cues that increase the risk of future psychosis. Given that existing studies have implicated altered processing of non-angry facial expressions, including disgust (Seo et al., 2020; Kohler et al., 2003), which are thought to signal social rejection, a type of social threat (Reicher *et al.*, 2016), and neutral facial expressions, in individuals with schizophrenia (Kohler et al., 2003), we also explored the relationships between developmental trauma and facial expressions of disgust and neutral faces and their associations with psychotic experiences.

Given that the association between developmental trauma and psychosis have been observed across various populations (Varese et al., 2012), and in consideration of the bias of existing behavioural studies in recruiting participants from Western, Educated, Industrialized, Rich, and Democratic (WEIRD) societies (Henrich, Heine and Norenzayan, 2010), extending this work to other population groups may yield cross-cultural and cross-population, neurobiological insights about the mechanisms underlying the association between developmental trauma and psychosis. Therefore, to test the hypothesis that developmental trauma exposure results in altered processing of threatening social cues that increase the risk of future psychosis, we recruited participants into a large, international study, to assess three distinct components of threat processing – attention, recognition and response – and examined their association with developmental trauma and psychotic experiences.

4.2. Hypotheses

1. Developmental trauma is associated with enhanced threat recognition, measured by the ability to recognise facial expressions of anger, and elevated threat response, measured by subjective valence and arousal ratings to facial expressions of anger
2. The These alterations in threat recognition and response are more pronounced in individuals with at risk mental states for psychosis compared to individuals without psychotic experiences
3. Alterations in threat recognition and response mediate the association between the severity of developmental trauma and psychotic experiences

4.3. Materials and Methods

4.3.1. Ethics

The study received ethical approval from the UCL Research Ethics Committee (reference 17495/001) and Seoul National University Bundang Hospital Research Ethics Committee (reference B-2011-648-306). All participants provided informed consent to participate.

4.3.2. Participants and procedure

Participants were recruited from the United Kingdom and Republic of Korea using social media platforms including Facebook, Twitter and Reddit. Eligibility criteria were: (1) good physical health; (2) aged 18-40; (3) capacity to give written informed consent. Exclusion criteria were: (1) Currently receiving treatment from a mental health care provider, (2) current use of psychiatric medicine

Participants were allocated to one of four groups based on their developmental trauma, as measured by the Childhood Trauma Questionnaire (Bernstein and Fink, 1997), and psychotic symptom status, as measured by the Community Assessment of Psychic Experiences (CAPE, Stefanis *et al.*, 2002): healthy individuals with (Psy-DT+) or without (Psy-DT-) experiences of developmental trauma, and participants with at risk mental states for psychosis with (Psy+DT+) or without experiences of developmental trauma (Psy+DT-). Participants reporting ‘moderate’ exposure to more than two types of trauma, or ‘severe’ to at least one type of trauma were assigned to the developmental trauma (DT+) groups, and participants reporting ‘none’ or ‘low’ on self-reported exposure to all five types of trauma were assigned to

the DT- groups. Participants were assigned to ‘Psy+’ groups using a mean cut-off score of 1.5 on both the frequency and distress of the positive items of the CAPE based on previous research showing that this cut-off identified individuals with an at-risk mental state (Bukenaite *et al.*, 2017). Participants scoring less this cut-off were assigned to the ‘Psy-’ group. Participants who were not assigned to any groups were assigned to a fifth exclusion group.

Participants completed a battery of questionnaires, an emotional dot probe, an emotional recognition task and a face ratings task on an online web-based experimental platform, gorilla.sc (Anwyl-Irvine et al., 2020). Potential confounds were examined including demographic information (age, sex, ethnicity, educational attainment, smoking history, prior use of secondary care mental health services, and psychiatric medication), childhood socioeconomic status, as well as measures of depression and anxiety.

4.3.3. Assessment of developmental trauma

Self-reported exposure to developmental trauma was assessed using the 28-item Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). The CTQ has shown acceptable reliability and validity in community populations and in patients with psychosis (Bernstein *et al.*, 2003; Kim *et al.*, 2013). The CTQ retrospectively measures the frequency of childhood traumatic experiences classified into five subtypes: emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect. Pre-defined cut-off scores were used such that each participant was classified as having experienced no abuse, mild, moderate, or severe levels of abuse for each of the five trauma subtypes (Bernstein *et al.*, 2003) . The cut-offs for

‘mild’, ‘moderate’ and ‘severe’ levels of abuse for emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect were 9/13/16, 8/10/13, 6/8/13, 10/15/18 and 8/10/13 respectively.

4.3.4. Assessment of clinical variables

Psychotic experiences were assessed using the Community Assessment of Psychic Experiences (CAPE; Stefanis *et al.*, 2002) This is a 40 item self-report measure that assesses the frequency and associated distress of three symptom domains: positive, negative and depressive symptoms.

Depressive symptoms and anxiety were assessed using the Patient Health Questionnaire (PHQ-9; Kroenke, Spitzer and Williams, 2001) and the Generalised Anxiety Disorder Questionnaire (GAD-7; Spitzer *et al.*, 2006).

4.3.5. Measures of threat processing

4.3.5.1. Threat recognition

Emotional recognition task (Hindocha *et al.*, 2014). In this task, participants were shown a series of faces that varied on valence (happy, sad, angry, fearful, surprise, disgust and neutral), and intensity (20%, 40%, 60%, 80%, 100%). Participants recruited from the United Kingdom and Republic of Korea were presented with stimuli from the NimStim set of facial expression set (Tottenham *et al.*, 2009) or Korean Facial Emotion stimuli set (Kim *et al.*, 2017), respectively. Participants indicated the emotion that most closely matched the facial expression. There were

no time limits. Outcome variables were hit rates, sensitivity and response bias. Hit rates were scored as the number of correctly-identified emotions divided by the total number of possible hits. Sensitivity was calculated by subtracting the number of false alarms (FA), which constitute selecting an emotion when the stimulus is not that emotion, from the number of hits. Sensitivity (Pr) measures the probability that a stimulus crosses a recognition threshold (Kamboj et al., 2012), and represents the participants' perceptual sensitivity to differences in emotions under conditions of uncertainty. Response bias (Rb) were calculated as p(FA)/(1-Pr). Higher response bias represents a liberal bias and lower values represent a more conservative approach for selecting an emotional expression. A correction was applied to correct for zero, as per Snodgrass and Corwin, 1988 (Snodgrass and Corwin, 1988).

4.3.5.2. Threat response

Face ratings task (Hindocha *et al.*, 2014; Bloomfield *et al.*, 2022). In this task, participants recruited from the United Kingdom and Republic of Korea were shown a series of emotional expressions from the NimStim set of facial expression set (Tottenham *et al.*, 2009) or Korean Facial Emotion stimuli set (Kim *et al.*, 2017). Stimuli were male and female adults with open-mouth happy, angry or neutral expressions. Participants viewed the faces in randomised order and indicated on a likert scale the subjective valance and their emotional arousal in response to the facial expression. The valence rating was described through the question: 'How positive or negative does this image look to you?', and rated along a 7-point visual analogue scale (VAS) from '-3: very negative' to '3: very positive'. The arousal rating was described through the question: 'How emotionally aroused does the image

make you feel?', and rated along a 7-point visual analogue scale (VAS) from '0: not at all aroused' to '+6: extremely aroused'. Faces remained on the screen until both rating judgements were made. Participants were instructed to respond as quickly and accurately as possible, and there were no time limits. Participants were also informed that arousal referred to an emotional reaction rather than sexual arousal.

4.3.6. Statistical analyses

Analyses were performed using R (version 4.1.2). Sociodemographic and clinical data were analysed using means and standard deviations for continuous data and frequencies for categorical data.

For the emotional recognition task, separate analysis of covariance (ANCOVAs) on hit rate, sensitivity and response bias for each facial expression (neutrality, anger, disgust, fear, happiness, sadness and surprise) were applied with adjustments for covariates including age, gender, ethnicity and recruitment site, to compare scores between groups (Psy-DT-, Psy-DT+, Psy+DT-, Psy+DT+). Results for emotional recognition of anger are presented below, and results for the other emotional conditions are presented in the appendix (Appendix 1.1).

For the face ratings task, separate ANCOVAs adjusting for covariates were conducted on valence and arousal ratings for each expression (neutral, anger, happiness) to assess differences between groups. Results for face ratings for neutral and anger are presented below, whilst results for the 'happy' condition are presented in the appendix (Appendix 2.1).

Where main effects were identified, post hoc tests, using Bonferroni corrections where applicable, were used to examine differences in outcome variables. In each ANCOVA model, participants who scored >3 standard deviations (SDs) away from the mean for that particular measure were excluded.

To assess the association between the severity of developmental trauma and severity of psychotic experiences, after adjusting for age, gender, ethnicity and recruitment site, multiple regression analyses were performed using CAPE scores as dependent measures and total CTQ scores as the predictor variable, controlling for covariates.

Mediation analyses were conducted using the 'lavaan' package, with bootstrapping with 5000 resampling to calculate 95% confidence intervals for the indirect effect. The Comparative Fit Index (CFI) > 0.95, root mean square error of approximation (RMSEA) < 0.06, and standardized root mean square residual (SRMR) < 0.0858 along with the proposed cut-off criteria were used to assess the fit between the hypothesized models and the data (Hu and Bentler, 1999).

4.4. Results

4.4.1. Participant characteristics and clinical scores

The final sample consisted of 1592 participants: 364 Psy-DT-, 410 Psy-DT+, 119 Psy+DT- and 699 Psy+DT+.

Table 12 provides demographic information and data on the levels of psychotic experiences, depression and anxiety. There were statistically significant, but small differences in age ($F_{3,1588}$=9, p<.001, η_p^2=.017). There were no differences between ethnicity and the proportion of individuals recruited from each site between groups *(p*>.078*).* Though groups did not differ on sex (p=.255), all groups had a higher proportion of female participants.

There was a significant difference in psychotic experiences between groups ($F_{3,1588}$=661, p<.001, η_p^2=.56). *Post hoc* tests with Bonferroni corrections revealed significant differences between each group, with a graded increase in psychotic experience from HDT-, HDT+, SDT- to SDT+ (adjusted p<.001).

Groups also differed significantly on levels of anxiety ($F_{3,1588}$=275, p<.001, η_p^2=.34) and depressive symptoms ($F_{3,1588}$=283, p<.001, η_p^2=.35).

Table 12. Demographic and clinical characteristics of the sample

Sample characteristics	**Psy-DT (n=364)**	**Psy-DT+ (n=410)**	**Psy+DT- (n=119)**	**Psy+DT+ (n=699)**	***p***
Age, Mean (SD)	26.5 (5.70)	28.1 (5.64)	26.1 (6.05)	26.4 (5.95)	<.001
Sex, %F	61.50%	38.50%	67.10%	32.90%	0.255
Site					0.078
United Kingdom	42.03%	37.80%	42.00%	45.78%	
Republic of Korea	57.97%	62.20%	57.98%	54.22%	
Ethnicity					0.125
White British	26.40%	27.08%	36.14%	31.04%	
Black	0.82%	0.24%	0.84%	0.29%	
Mixed	1.10%	1.22%	2.52%	1.43%	
Asian	1.92%	1.22%	2.52%	2.15%	
Other	11.80%	8.05%	14.29%	10.44%	
Korean (Republic of Korea)	58.00%	62.20%	57.98%	54.65%	
Socioeconomic status (FAS)	5.10 (1.75)	4.45 (1.77)	5.07 (1.73)	4.39 (1.76)	<.001
Past psychiatric history, %	14.30%	32.00%	30.30%	50.50%	<.001
Drug history, %	10.70%	24.40%	21.80%	41.10%	<.001
Tobacco use, %	28%	48.80%	42.00%	52.90%	<.001
CTQ	32.1 (5.04)	59.5 (14.3)	35.9 (4.83)	66.7 (15.2)	<.001
CAPE	64.3 (9.10)	69.7 (9.72)	85.1 (10.4)	93.8 (13.9)	<.001
PHQ	4.67 (3.93)	7.13 (4.89)	10.4 (5.07)	13.5 (5.83)	<.001
GAD	3.42 (3.44)	5.02 (4.18)	8.57 (4.77)	11.4 (5.59)	<.001

Abbreviations: FAS; Family Affluence Scale, CTQ; childhood trauma questionnaire, PHQ; Patient Health Questionnaire, GAD; Generalised Anxiety Disorder Questionnaire

4.4.2. Relationship between developmental trauma and threat recognition

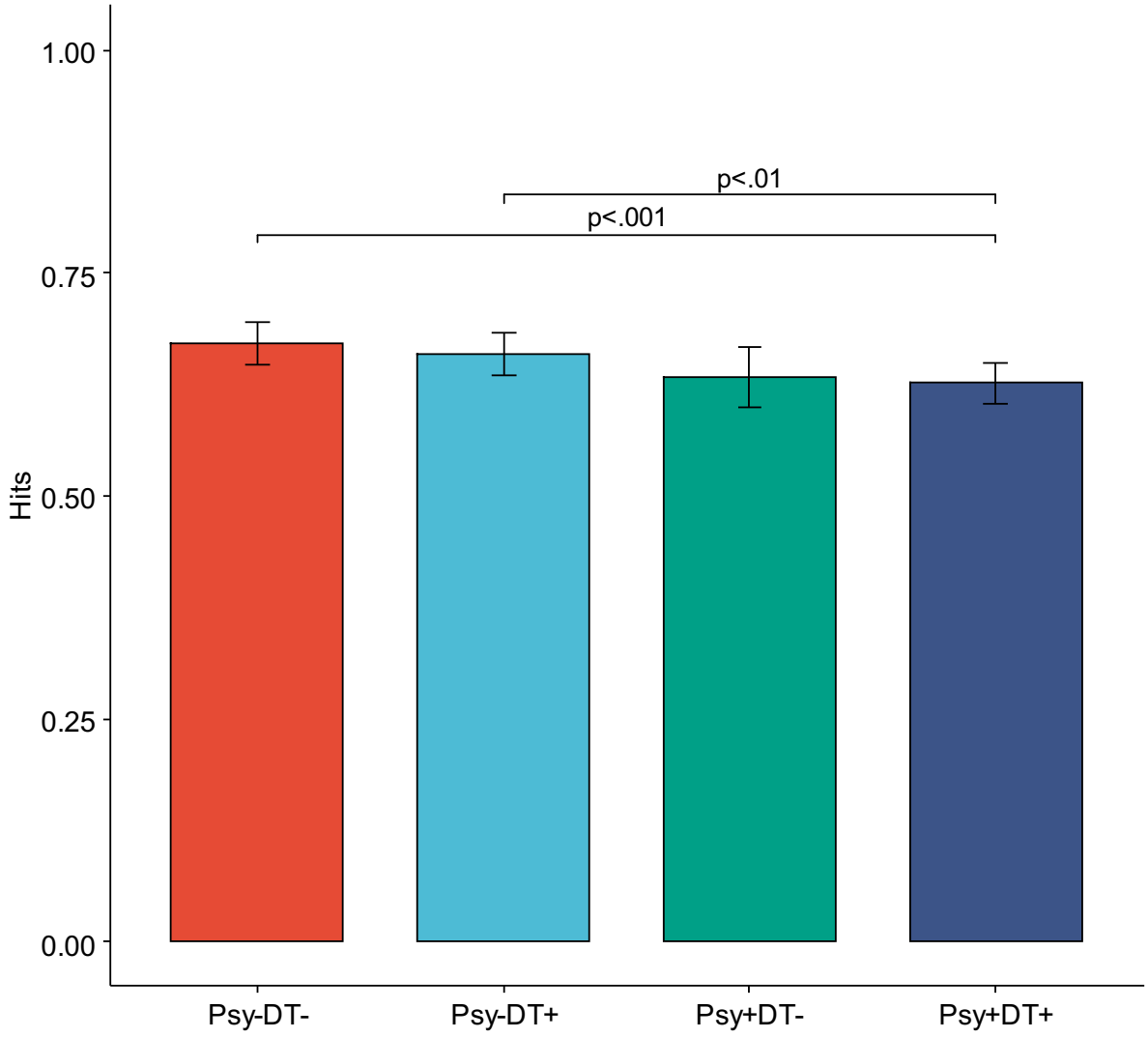
Groups differed significantly on accuracy for identifying anger ($F_{3,1527}$=8.68, p<.001). Post hoc tests revealed poorer recognition accuracy in Psy+DT+ compared to Psy- groups (Psy+DT+ vs Psy-DT- adjusted *p<.001,* Psy+DT+ vs Psy-DT+ adjusted *p=.003)* (**Figure 13A**).

Groups differed significantly in sensitivity to differences between emotional expressions of anger and other emotional expressions ($F_{3,1527}$=9.17, p<.001). *Post hoc* tests indicated reduced sensitivity in Psy+DT+ compared to Psy- groups (Psy+DT+ vs Psy-DT- adjusted *p<.001,* Psy+DT+ vs Psy-DT+ adjusted *p=.004)* and reduced sensitivity in Psy+DT- compared to Psy-DT- (adjusted *p=.03)* (**Figure 13B**).

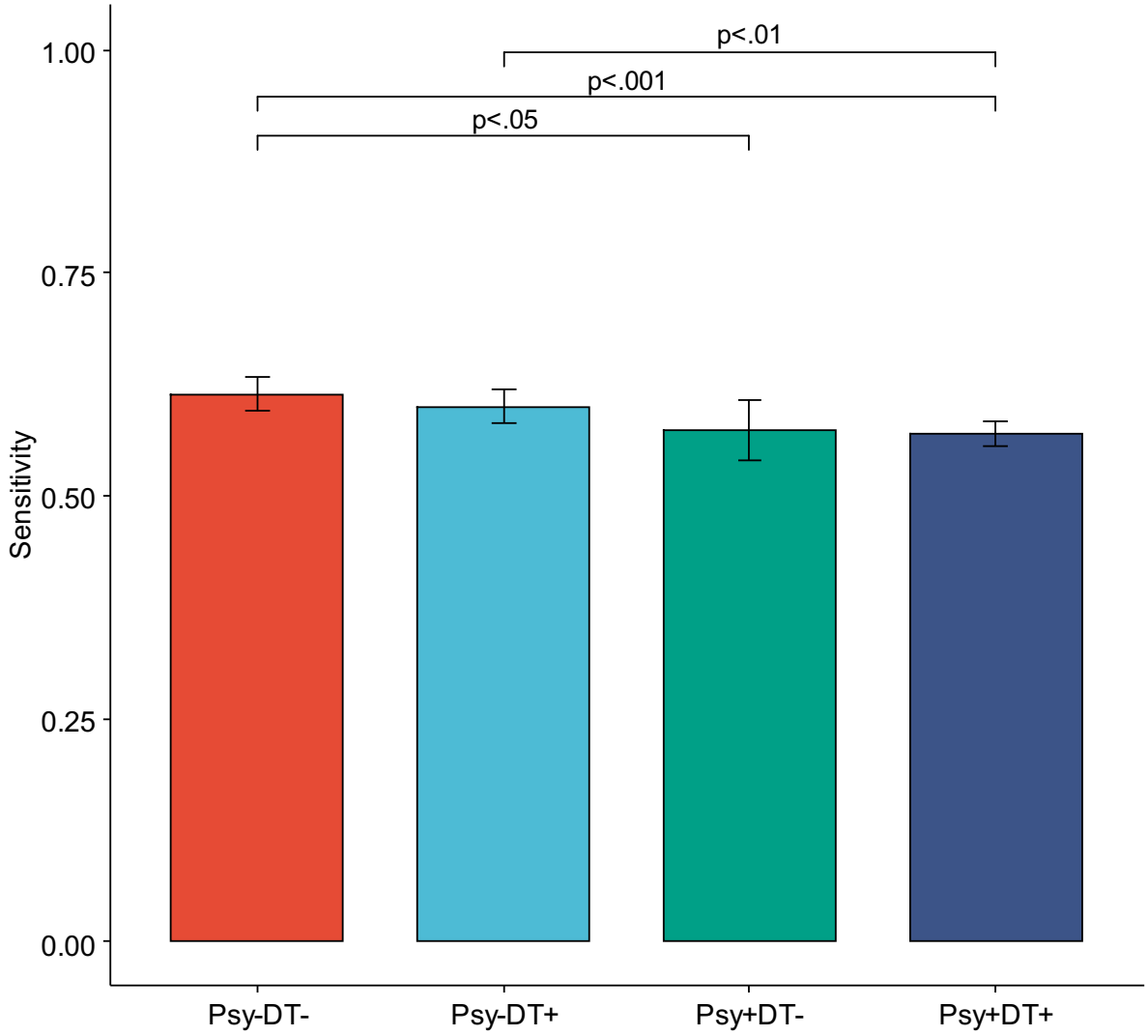
No group differences were observed in response bias for selecting facial expressions of anger (p>.11) (**Figure 13C**).

Figure 13. Group mean (95% CI) for (A) hits, demonstrating the ability to recognise anger (B) sensitivity, demonstrating the ability to discriminate between anger and other emotions in conditions of uncertainty and (C) response bias, representing how liberal or conservative participants were in recognising anger

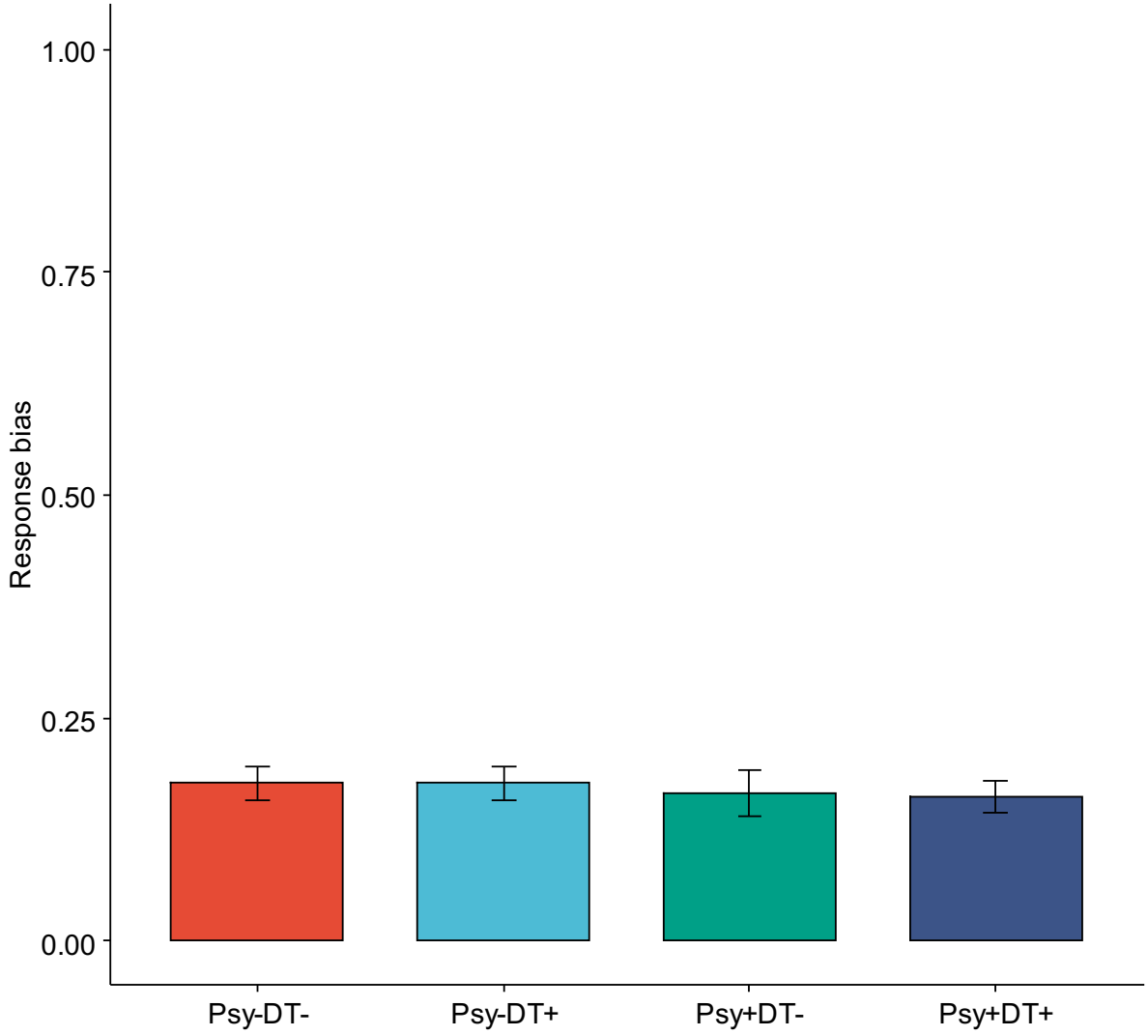
(A)



(B)


p<.01
p<.001
p<.05
1.00
0.75
0.50
0.25
0.00
Sensitivity
Psy-DT-
Psy-DT+
Psy+DT-
Psy+DT+

(C)



4.4.3. Relationship between developmental trauma and threat response

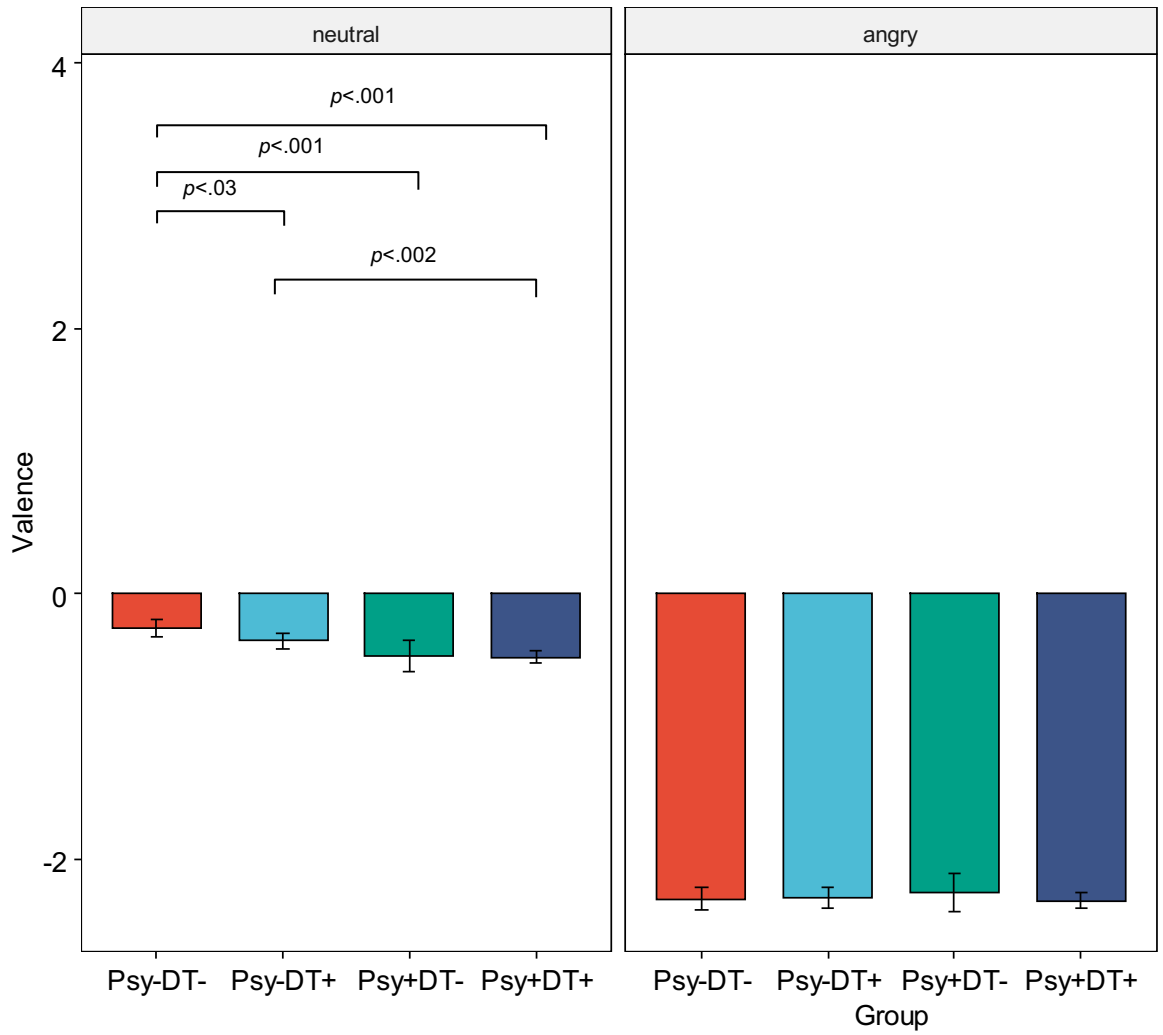
No group differences were observed in valence and arousal responses for facial expressions of anger (p>.71) (**Figure 14A, B**).

However, significant group differences in valence responses for neutral facial expressions were observed ($F_{3,1527}$=16.1, p<.001). Psy-DT+ (adjusted p=.03), Psy+DT- (Bonferroni corrected p<.001), Psy+DT+ (adjusted p<.001) all demonstrated more negative valence responses for neutral faces compared to Psy-DT-. Psy+DT+ also demonstrated more negative valence responses for neutral faces than Psy-DT+ (adjusted p=.002).

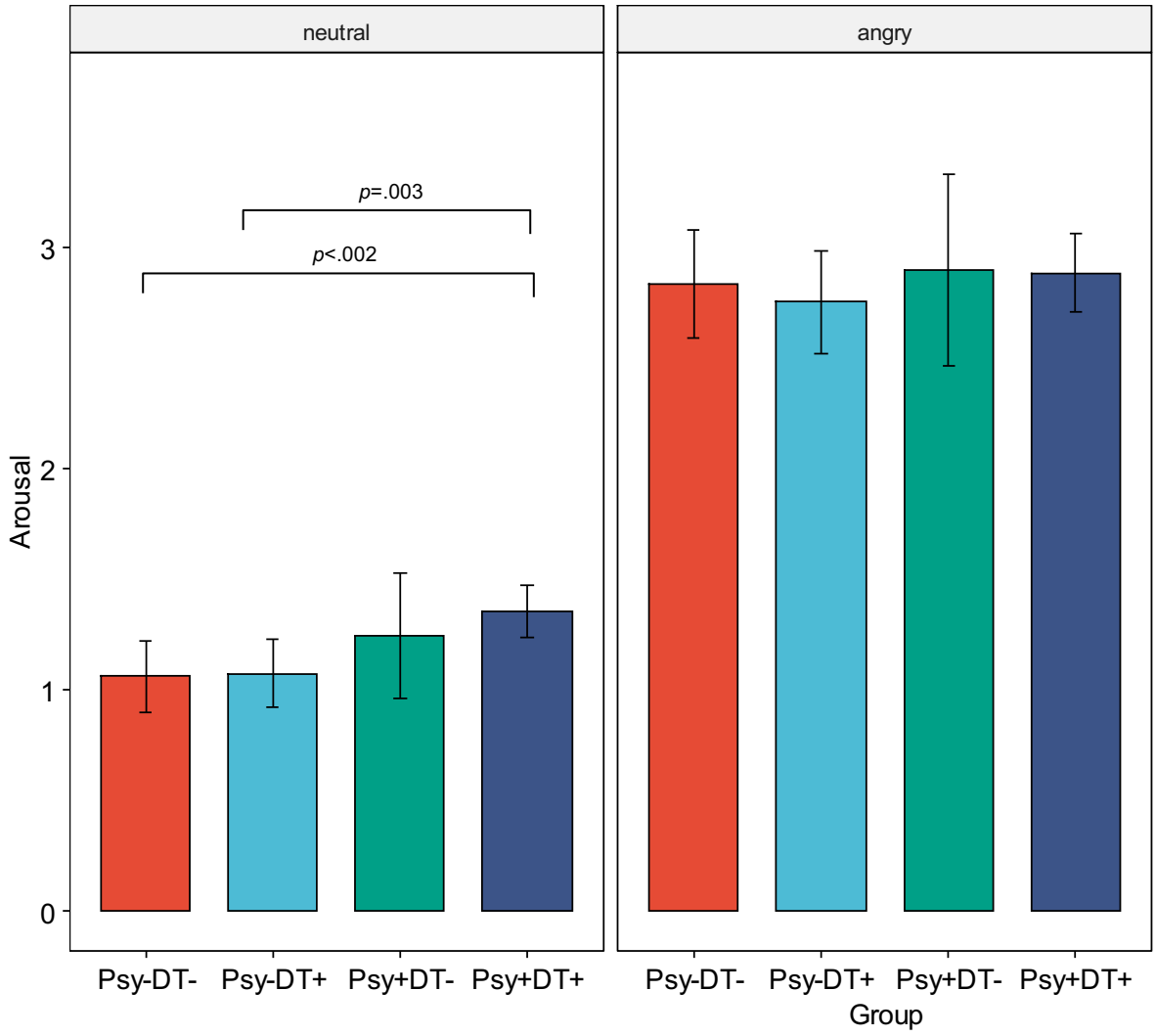
Groups also differed significantly in arousal responses for neutral faces ($F_{3,1527}$=6.42, p<.001), whereby Psy+DT+ reported increased arousal for neutral faces compared to Psy-DT- (Bonferroni corrected p<.001) and Psy-DT+ (adjusted p=.003).

Figure 14. Group mean (95% CI) for (A) valence and (B) arousal responses on the face ratings task, by facial expression (neutral and anger)

(A)



(B)


neutral
angry
p=.003
p<.002
Arousal
0
1
2
3
Psy-DT-
Psy-DT+
Psy+DT-
Psy+DT+
Group

4.4.4. Role of threat recognition and response in the association between severity of developmental trauma and severity of psychotic experiences

Consistent with findings from grouped analyses, across the whole sample, the severity of developmental trauma was significantly associated with reduced sensitivity for angry faces (B=-0.001, p<.001) more negative valence responses for neutral faces (B=-.004, p<.001), and increased arousal responses for neutral faces (B=.004, p=.009).

Reduced sensitivity for angry faces (B=-10.95, p=.001), more negative valence responses for neutral faces (B=-3.28, p<.001) and increased arousal responses for neutral faces (B=1.338, p<.001) were also significantly associated with increased severity of psychotic experiences, when controlling for the severity of developmental trauma.

Given that developmental trauma was associated with altered threat processes, and these altered threat processes were associated with increased psychotic experiences, mediation analyses were conducted examining the role of valence and arousal responses for neutral faces and sensitivity for angry faces on the association between developmental trauma and psychotic experiences.

The fit indices of the tested models were satisfactory meeting 3 out of 3 fit index criteria (detailed fit indices are reported in **Table 13**).

Detailed path coefficients of the models are presented in **Table 14**, and the direct effect, indirect effect, total effect and R^2 are reported in **Figure 15**.

Reduced sensitivity for angry faces (indirect, mediating effect, *B*=.008, *p*=.016, direct effect, *B*=.470, *p*<.001), more negative valence responses for neutral faces (indirect mediating effect, *B*=.012, *p<.001,* direct effect, *B*=.470, *p*<.001) and increased arousal responses for neutral faces (direct effect, *B*=.470, *p*<.001, indirect effect, *B*=.006, *p=.036*), adjusted for correlations between threat processing measures significantly, mediated the association between developmental trauma and psychotic experiences.

Table 13. Fit indices of mediation models. All mediation models meet 3 out of 3 fit index criteria.

Model	RMSEA (90% CI)	SRMR	CFI
Direct effect	0.000	0.000	1.000
Mediation models			
Sensitivity for angry faces	0.000	0.000	1.000
Valence responses for neutral faces	0.000	0.000	1.000
Arousal responses for neutral faces	0. 000	0. 000	1.000

Abbreviations: CFI, comparative fit index; CI, confidence interval; RMSEA, root mean square error of approximation; SRMR, standardized root mean square residual.

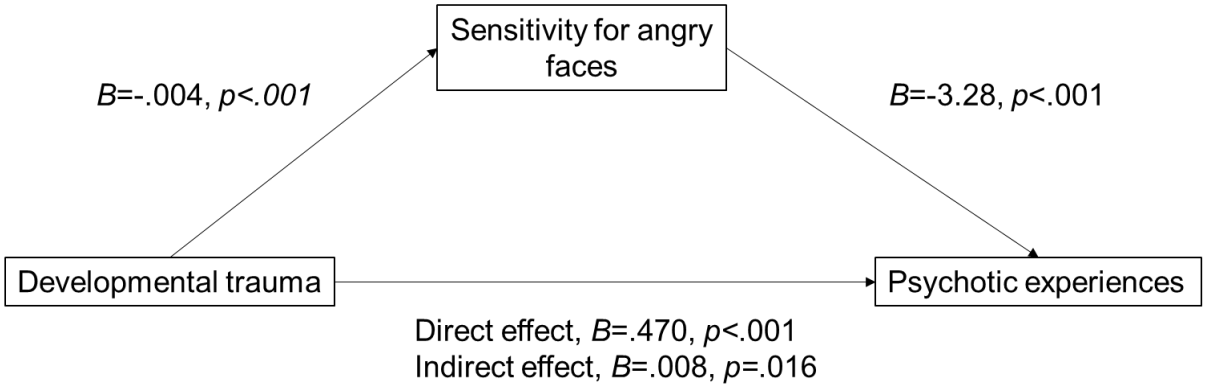
Table 14. Indirect Effect, Total Effect, and R^2 of the mediation models

Model	Indirect effect (95% CI)	Total effect	R^2
Direct effect		0.471	0.283
Mediation models			
Sensitivity for angry faces	0.008 (0.003-0.016)	0.470	0.022
Valence responses for neutral faces	0.012 (0.005-0.019)	0.470	0.045
Arousal responses for neutral faces	0.006 (0.001-0.012)	0.470	0.032

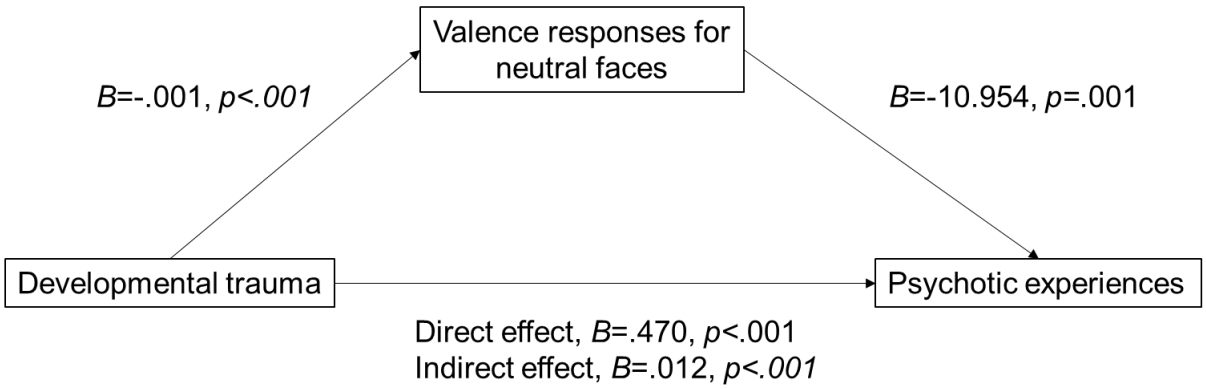
Abbreviations: CI; confidence intervals

Figure 15. Mediation analyses. (A) Reduced sensitivity for angry, (B) more negative valence responses for neutral faces and (C) increased arousal responses for neutral faces significantly mediates the association between the severity of developmental trauma and psychotic experiences.

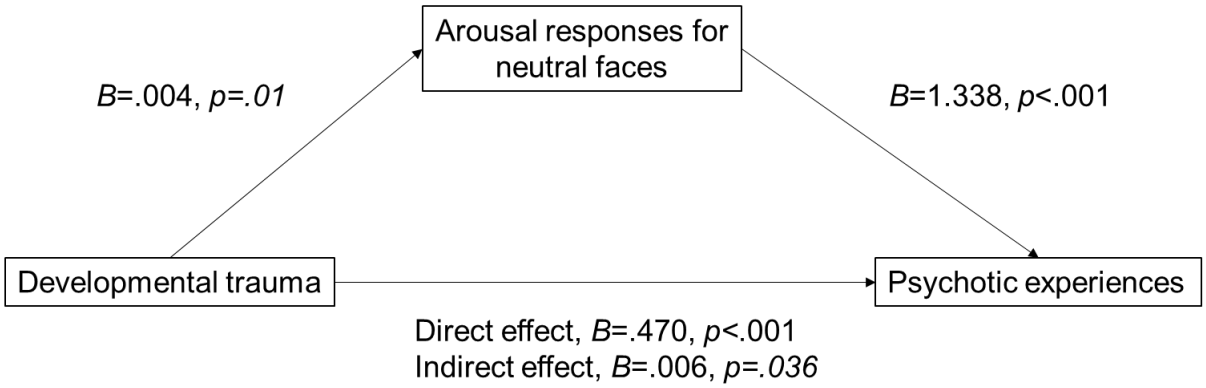
(A)



(B)



(C)



4.5. Discussion

4.5.1. Summary

Compared to healthy individuals without experiences of developmental trauma, adult survivors of developmental trauma with psychotic experiences demonstrated poorer recognition of facial expressions of anger, which was attributable to reduced perceptual sensitivity. Adult survivors of developmental trauma with psychotic experiences also exhibited more negative valence responses and elevated arousal responses for neutral faces. These alterations in threat recognition and response played a small, but statistically significant role in mediating the relationship between developmental trauma and psychotic experiences.

4.5.2. Interpretation of findings of the study on the relationship between developmental trauma, threat recognition and response and psychotic experiences

4.5.2.1. Developmental trauma, threat recognition and psychotic experiences

Adult survivors of developmental trauma with at risk mental states for psychosis demonstrated poorer recognition of facial expressions of anger compared to healthy individuals without experiences of developmental trauma. Moreover, there was evidence of a dose-response association between the severity of developmental trauma and poorer recognition of facial expressions of anger.

Though there is a paucity of studies investigating threat recognition in adult survivors of developmental trauma, the finding that developmental trauma was associated with poorer recognition of anger is inconsistent with existing literature observing enhanced recognition of angry faces associated with developmental trauma (Gibb, Schofield and Coles, 2009; Schwaiger, Heinrichs and Kumsta, 2019). Poorer recognition of angry faces associated with developmental trauma observed in this study could be attributed to reduced perceptual sensitivity to differences between facial expressions of anger and other emotional expressions, indicating a reduced ability to discriminate facial expressions of anger from other expressions. Though causal inferences cannot be made due to the study's cross-sectional design, given findings in children that trauma is associated with reductions in the perceptual sensitivity to angry faces (Pollak *et al.*, 2000), similar findings in adult populations recruited in this study suggest that developmental trauma-induced changes in perceptual sensitivity to angry faces persists from childhood through adulthood.

Alterations in threat processing have been proposed to initially arise as phenotypic adaptations to a malevolent environment (McCrory and Viding, 2015; Teicher *et al.*, 2016). In line with this hypothesis, it is conceivable that different patterns of alterations may arise depending on the nature of the traumatic experience, such as the type, timing and duration of trauma, as well on individual factors, such as an individual's genetic susceptibility to the effects of trauma or the presence of social support from other caregivers. In line with the findings from behavioural studies in adult survivors of developmental trauma demonstrating opposing patterns of threat attention based on the number of types of trauma (Herzog *et al.*, 2018), and findings from neuroimaging studies demonstrating opposing patterns of amygdalar responses to threatening faces dependent on the timing of trauma (Zhu *et al.*, 2019), it is possible that both patterns of threat recognition, either enhanced or impaired, may exist in different individuals.

The finding that poorer recognitio" of 'ngry faces was associated with elevated psychotic experiences is in line with evidence from meta-analyses and large studies suggesting that the most prominent deficits in emotion recognition associated with psychosis are in anger and/or fear (Kohler *et al.*, 2014; Tripoli *et al.*, 2022). Moreover, these deficits are detected in individuals with clinical high risk of psychosis prior to the full expression of psychotic illness (Amminger *et al.*, 2012), suggesting that poorer threat recognition may be implicated in the pathogenesis of psychosis. This is consistent with findings from neuroimaging studies that suggest that alterations in the amygdala, which plays an important role in the recognition of threatening stimuli (Winston *et al.*, 2002), is a relevant factor in the pathogenesis of psychosis (Fudge *et al.*, 1998; Nelson *et al.*, 1998; Aleman and Kahn, 2005).

Two unpredicted findings warrant discussion, though these results should be interpreted with caution given no formal hypotheses were made. Firstly, adult survivors with developmental trauma with at risk mental states demonstrated global impairments in the emotion recognition, compared to healthy controls without experiences of developmental trauma. These findings are consistent with findings of general impairments in emotional recognition in individuals with clinical high risk of psychosis (Tognin *et al.*, 2020; Tripoli *et al.*, 2022). Impairments in global emotional recognition and the inability to discriminate between threatening and non-threatening facial expressions may render the facial expressions of others to be unpredictable and ambiguous. In line with cognitive theories of psychosis, under such circumstances of uncertainty, individuals may interpret facial expressions and others' emotional states based on biased cognitive schema that have been shaped by their experiences of developmental trauma, giving rise to threatening interpretations and paranoia (Freeman *et al.*, 2002).

Secondly, developmental trauma was associated with a response bias towards facial expressions of disgust. Facial expressions of disgust are thought to signal social rejection, a type of social threat (Reicher *et al.*, 2016). Given the relevance of social threat in psychosis, in particular in the phenomenology of threatening auditory hallucinations or persecutory delusions that are characterised by the presence of a perpetrator who intends to cause harm, the finding of response bias towards disgust provides indirect support to the hypothesis that altered recognition of threats are involved in the pathway from developmental trauma to psychosis. Given evidence that self-disgust mediates the relationship between developmental trauma and psychosis (Simpson *et al.*, 2020) further investigation of these underlying mechanisms should be investigated.

4.5.2.2. Developmental trauma, threat response and psychotic experiences

No group differences in valence and arousal responses to facial expressions of anger were observed. These findings are inconsistent with the hypothesis that developmental trauma is associated with elevated threat responses, and inconsistent with the pattern of hyperresponsiveness to threat observed in neuroimaging studies observing increased amygdala responses faces that are seen as threatening (Grant *et al.*, 2011; Bogdan, Williamson and Hariri, 2012; van Harmelen *et al.*, 2013; Teicher *et al.*, 2016) and behavioural studies finding increased defensive responses, including exaggerated startle reflexes and skin conductance responses to threat (Pole *et al.*, 2007; Young *et al.*, 2019). There are several possible explanations for this. Firstly, facial expressions of anger may not be as salient or threatening as aversive stimuli used in prior studies, such as acute psychosocial stress or startling sounds. Moreover, there may have been ceiling effects, given that the tasks were conducted online, limiting the degree to which facial expressions of anger are threatening, and their ability to evoke emotional responses. Secondly, inconsistencies in findings may arise given existing studies examined autonomous, non-conscious responses to threat whereas this study examined conscious and subjective responses to threat. Conscious responses to threat may be influenced by multiple factors including an individuals' appraisal or interpretation of facial expressions, differences in how individuals understood the prompts, and how engaged individuals were during the task.

However, there is some evidence to suggest that developmental trauma may have opposing effects on threat responses. For instance, behavioural studies have observed that developmental trauma is associated with blunted endocrine stress responses, as measured by cortisol responses (Voellmin *et al.*, 2015; Kaiser *et al.*, 2018), and neuroimaging studies have found opposing effects of trauma on amygdalar activation in response to threat, including attenuated and potentiated amygdalar activation, depending on the timing of trauma (Zhu *et al.*, 2019). It is therefore possible that the heterogeneity of effects of developmental trauma on threat responses may have attenuated group differences in valence and arousal responses to angry faces within this study.

Developmental trauma was associated with more negative valence and elevated arousal responses to neutral faces, which is consistent with findings from behavioural studies that adult survivors of developmental trauma demonstrate increased skin conductance responses to neutral stimuli that are not associated with threat during threat conditioning (Bremner *et al.*, 2005). Taken together, these findings suggest that under conditions of emotional uncertainty, whereby neutral facial expressions are uninformative of others' underlying emotional states, developmental trauma is associated with more negative appraisals and increased arousal to neutral and ambiguous facial expressions.

Taken together with findings that developmental trauma was associated with reduced perceptual sensitivity to detect differences between facial expressions of anger and other facial expressions, indicating a reduced ability to discriminate facial expressions of anger from other expressions, suggests that adult survivors of developmental trauma are less able to recognise angry faces, and more likely to

interpret ambiguous facial expressions as being more negative and more emotionally arousing.

The finding that psychotic les were associated with more negative valence responses and elevated arousal responses to neutral faces, but not angry faces is consistent with evidence from a meta-analysis of behavioural studies that report elevated skin conductance responses to neutral stimuli but not aversive stimuli in individuals with psychosis, which correlates with the severity of delusional ideation (Tuominen *et al.*, 2022). Moreover, these findings are broadly consistent with cognitive models of psychosis, whereby under conditions of uncertainty, biased cognitive schema result in ambiguous stimuli being interpreted as threatening (Freeman *et al.*, 2002).

In line with this cognitive theory of psychosis, given findings here that demonstrated that reduced sensitivity to anger, more negative responses to neutral faces and elevated arousal responses to neutral faces played a mediating role in the association between developmental trauma and psychosis suggests that impaired threat recognition and altered threat responses may lie on the pathway between developmental trauma and psychosis.

4.5.3. Strengths and limitations of the study on the relationship between developmental trauma, threat attention and psychotic experiences

Strengths and limitations specific to this study will be discussed below, and general strengths and limitations of all data included in this thesis will be discussed in detail in the general discussion (Section 7.9).

This study has several strengths. Firstly, its use of a large, international community-based sample increases the statistical power to detect associations and increases the generalisability of these findings. Given that these findings were significant even when controlling for recruitment site and ethnicity, provides strong evidence of a shared etiological pathway from developmental trauma and psychosis that is independent of social and cultural differences between individuals. Secondly, all participants were free of psychiatric medication, removing the confounding effects of medication. Thirdly, given that face processing is affected by the race or ethnicity (Elfenbein and Ambady, 2002; Herrmann *et al.*, 2007), well-documented, reliable and validated facial expression stimuli from databases that were similar in ethnicity to the recruitment site were used to increase ecological validity of the findings; the NimStim set of facial expressions developed in the United States (Harmer *et al.*, 2003; Tottenham *et al.*, 2009) for participants recruited in the United Kingdom, and the Korean Facial Emotional Stimuli set (Kim *et al.*, 2017) for participants recruited in the Republic of Korea.

This study had several limitations. Threat recognition and responses were measured using a static task that may not capture the complexity of facial expressions in the real-world (Adolphs, 2002). Nonetheless, studies comparing emotional recognition of

static photographs and dynamic videos of facial expressions in individuals with psychosis have observed similar findings irrespective stimulus type (Johnston *et al.*, 2010; Hargreaves *et al.*, 2016). Given that the study was completed on an online experimental platform, physiological threat responses could not be measured, which limits the inferences that can be made about how the degree to which facial expressions were threatening and their effects on autonomic threat responses.

Chapter V: The relationship between developmental trauma, threat learning and psychotic experiences

5.1. Introduction

As summarized in chapter I, there is growing evidence that developmental trauma – psychologically traumatic events experienced during childhood and/or adolescence – is causally associated with increased psychotic experiences in adulthood (Varese et al., 2012). Despite this, there is a lack of understanding of the precise neurobiological mechanisms that underlie this association.

Multiple lines of evidence converge on the role of altered threat learning, more specifically, an impairment in the ability to appropriately use contextual information under conditions of uncertainty to learn about threats, as a potential mediating mechanism in the association between developmental trauma and psychosis. Firstly, evidence from behavioural and neuroimaging studies suggest that developmental trauma is associated with lasting alterations in threat learning, which may reflect an impaired ability to use contextual information to differentially learn about threats (McLaughlin *et al.*, 2016). Secondly, cognitive theories of psychosis also implicate the role of altered threat learning in conditions of ambiguity or uncertainty in the emergence and persistence psychotic experiences, particularly those that are threatening in nature (Garety *et al.*, 2001; Freeman, 2016). Thirdly, this is supported by behavioural and neuroimaging studies reporting associations between psychosis with altered neural threat learning processes and structural and functional alterations in brain regions involved in threat learning, including the amygdala, hippocampus and ventromedial prefrontal cortex (vmPFC) (Teicher *et al.*, 2016; Tuominen *et al.*, 2022).

Within the computational literature, in the context of decision-making models, threat learning has been formalised as the process of forming and updating expectancies,

or ‘beliefs’, about action-outcome contingencies in response to the environment. According to models of reinforcement learning, beliefs are updated to reflect new information from the environment in proportion to the prediction error, the difference between expected and actual outcomes.

An important aspect of threat learning is the ability to adapt threat learning in response to changes in the underlying causal structure of the environment. One aspect of the underlying causal structure of the environment that can be experimentally manipulated within behavioural tasks is environmental volatility, the extent to which action-outcome contingencies within the environment are stable or volatile. Depending on the stability or volatility of the environment, the learning rate, which is the degree by which beliefs are updated, should be adjusted. In a stable environment, prediction errors arising from unexpected, or ‘surprising’ outcomes are likely caused by noise, and beliefs about action-outcome contingencies should be updated to a lesser degree. However, if prediction errors arise from a change in action-outcome contingencies in a volatile environment, beliefs should be updated to a greater degree. This adjustment in learning rates in response to the volatility of the environment has indeed been demonstrated in computational studies of decision-making (Behrens *et al.*, 2007, 2008; Browning *et al.*, 2015).

Taken together, cognitive theories of psychosis and findings from behavioural and neuroimaging studies provide a theoretical rationale for the hypothesis that developmental trauma-associated impairments in adapting threat learning rates in response to the higher order structure of the environment increases the risk of future psychotic experiences.

5.2. Hypotheses

1. During threat learning, developmental trauma is associated with a reduced ability to adapt learning rates, defined as the extent to which expectations or ‘beliefs’ about action-outcome contingencies are updated, in response to changes in the higher order structure of the environment, defined by environmental volatility, the extent to which action-outcome contingencies in the environment are stable or volatile
2. Reductions in the ability to adapt learning rates in response to changes in environmental volatility are more pronounced in individuals with at risk mental states for psychosis compared to healthy individuals
3. Reductions in the ability to adapt learning rates in response to changes in environmental volatility mediate the association between the severity of developmental trauma and psychotic experiences

5.3. Materials and Methods

5.3.1. Ethics

This study received ethical approval from the University College London (UCL) Research Ethics Committee (14317/001). All participants provided written informed consent prior to participation.

5.3.2. Participants and procedure

A sub-sample of participants were recruited from participants who completed Study III in the United Kingdom described in chapter IV. Eligibility criteria and participant group allocation from Study III, as described in chapter IV, were used.

Participants completed an aversive learning task (Behrens *et al.*, 2007; Browning *et al.*, 2015) in which outcomes were aversive sounds, on an online web-based experimental platform, gorilla.sc (Anwyl-Irvine *et al.*, 2020). Before participants completed the task, the duration of aversive sounds were calibrated such that the maximum duration administered had a subjective unpleasantness level of 7 on a scale of 1 (not at all unpleasant) to 10 (extremely unpleasant).

5.3.3. Assessment of threat learning

5.3.3.1. The aversive learning task

The aversive learning task comprised two blocks of 90 trials in which participants chose between two stimuli that were probabilistically associated with an aversive sound. In one block, the choice-outcome contingencies were stable (shape A resulted in an aversive sound 75% of the time and shape B 25% of the time). In the

other block, the choice-outcome contingencies were volatile and switched every 20 trials. The duration of aversive sound delivered if the shape associated with the aversive sound was chosen is specified separately for each shape and varied from trial to trial. The two blocks were completed sequentially with no break. Participants were not explicitly cued as to the division of the task into two distinct blocks. Participants were randomly assigned to complete either the stable or volatile block first.

5.3.3.2. Task details

On each trial, participants were presented with a fixation cross flanked by two shapes. Participants were asked to choose one of the two shapes, one of which would result in the delivery of an aversive sound. During the stable block, choosing one of the two shapes resulted in the delivery of an aversive sound with a probability of 75%, whereas the other shape resulted in the delivery on the remaining trials. During the volatile block, the choice-outcome contingencies switched every 20 trials, with one shape resulting in the delivery of an aversive sound with a probability of 80% and the other with a probability of 20%. The duration of aversive sound delivered if the chosen shape was associated with an aversive sound was specific to each shape and displayed as a two digit number (between 01 and 99) in the centre of the shape. The duration value for each shape was chosen from two random distributions. Participants had up to 4s to choose one of the two shapes. Once the participant made a choice of one of the two shapes, the chosen shape was highlighted in yellow. Following a jittered interval (min 2s, mean 4s), the outcome (aversive sound or no sound) was presented. If participants chose the shape associated with the aversive sound, the aversive sound was delivered, the duration

of which was determined by the duration value associated with the chosen shape. Following this, a single fixation cross was displayed for 500ms before the next trial began.

5.3.3.3. Aversive sounds

Aversive sounds were created using human scream sound stimuli from the International Affective Digital Sounds (IADS) (Yang *et al.*, 2018). Each aversive sound stimulus from IADS were trimmed generating stimuli with shorter durations, determined using a random distribution (min 1s, mean: 1.5s), These shorter stimuli of variable lengths were used to create two aversive sound stimuli lasting 20s by appending the sounds in a random sequence. These two longer aversive sound stimuli were then superimposed to generate a single 20s aversive sound stimulus (master sound stimulus). During the task, the aversive sound stimulus delivered, which varied in duration, were sampled with a random starting timepoint from the master sound stimulus.

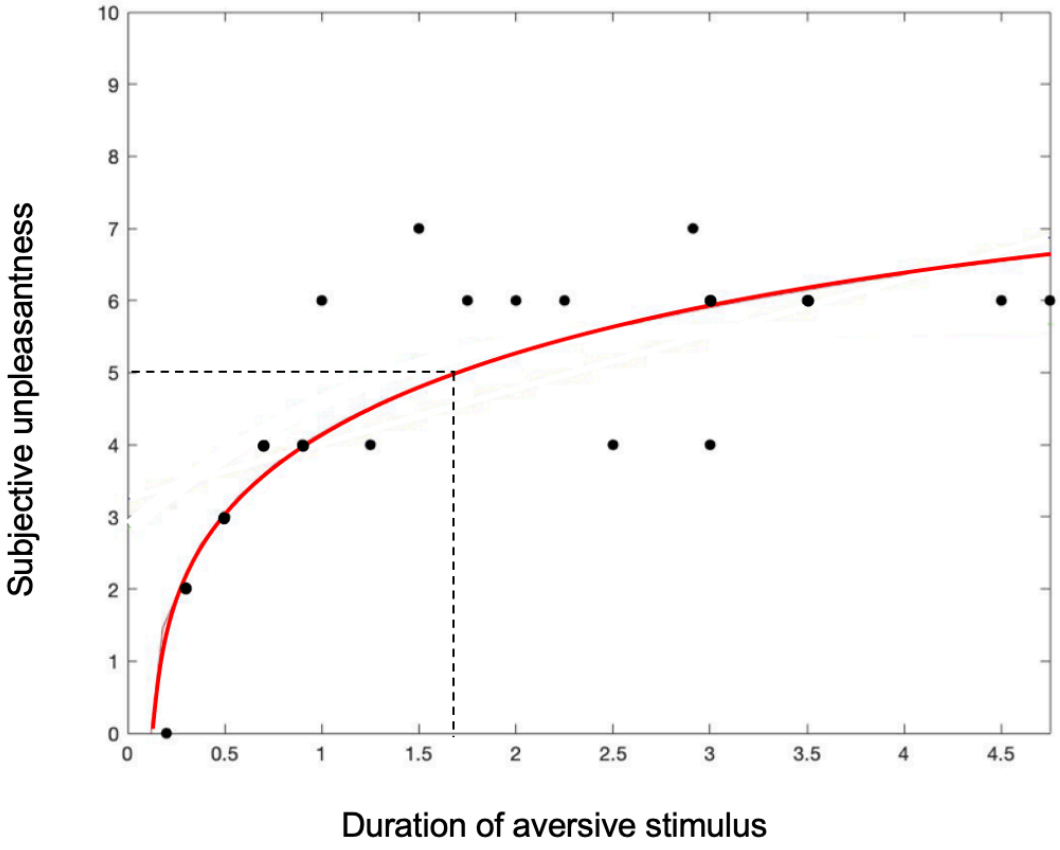
5.3.3.4. Calibration of aversive sounds

Participants completed a calibration procedure prior to completing the aversive learning task. During the calibration procedure, participants rated the unpleasantness of the sound ("On a scale of 0-10, how unpleasant was the sound? 0 being not unpleasant at all and 10 being very unpleasant"). The duration of the aversive sound was increased from 100ms by 100ms increments until participants rated the sound as 1/10 unpleasant. The duration of the aversive sound was then increased in 2500ms increments until participants rated the sound as 7/10 unpleasant, which was used as the maximum duration of aversive sound. Across

participants, the maximum duration of aversive sound ranged from 5000ms to 20000ms, with no differences in maximum duration between groups (ps>.1).

Participants then completed 14 trials during which the duration of aversive sounds were randomly varied between the duration that elicited an unpleasantness rating of 1/10 and 7/10. Participants' subjective unpleasantness ratings to these different durations of aversive sounds were fitted to a logarithmic curve. This curve was used to determine the duration of aversive sound delivered for each duration value (1-99) during the task. That is, a duration value of '1' resulted in the delivery of an aversive sound with a duration that elicited an unpleasantness rating of 1/10, and a duration value of '99' resulted in the delivery of an aversive sound with a duration that was rated as 7/10. All other durations were interpolated using the logarithmic curve.

Figure 16. Example calibration of aversive sounds during a single trial for one participant. During the calibration procedure, various durations of aversive sounds were presented to the participant, following which, the participant reported a subjective unpleasantness rating (0=not unpleasant at all, 10=very unpleasant). No durations exceeding a subjective unpleasantness rating of 7 were delivered. The graph demonstrates this calibration procedure, showing data points (dots) and a fitted logarithmic curve (red line) for a single, characteristic participant. For each participant, the duration of aversive sounds was interpolated using the fitted logarithmic curve. This is illustrated here by a dashed line, showing the duration of aversive sound (x-axis) corresponding to the desired subjective unpleasantness rating of 5/10 that would be calculated for this participant.



5.3.3.5. Computational model

A simple learning model consisting of a Rescorla-Wagner predictor (Rescorla, 1971) coupled to a softmax based action selector were fitted to participant choice data.

The Rescorla-Wagner predictor updated its estimate of outcome probabilities using the following Equation.

$$r_{(i+1)} = r_{(i)} + \alpha\varepsilon_{(i)}$$

Here, $r_{(i+1)}$ is the estimated outcome probability for the i+1st trial, $r_{(i)}$ is the estimated outcome probability for the i^{th} trial, α is the learning rate and $\varepsilon_{(i)}$ is the prediction error on the i^{th} trial.

The softmax based action selector transforms these predictions into action probabilities as follows. First, the 'aversiveness' or negative value of the two options is estimated. Here, a high probability high duration aversive sound is of high 'negative' value, and a low probability, low duration aversive sound is of a low 'negative' value. The equation assumes, for ease of reference, that blue and green stimuli were used in The task.

$$g_{blue\ (i+1)} = F(r_{i+1}, \gamma) f_{blue\ (i+1)}$$

$$g_{green\ (i+1)} = F(1 - r_{i+1}, \gamma) f_{green\ (i+1)}$$

Here, $g_{blue\ (i+1)}$ and $g_{green\ (i+1)}$ are the estimated negative values of the stimuli on the i+1st trial, $f_{blue\ (i+1)}$ and $f_{green\ (i+1)}$ are the known shock durations for the two stimuli, and $F(r, \gamma)$ is a linear transform within the bounds of 0 and 1:

$$F(r, \gamma) = \max\left[\min[(\gamma(r - 0.5) + 0.5), 1], 0\right]$$

Here, γ is the risk preference parameter that allows the model to place greater weight on outcome duration $(\gamma < 1)$ or outcome probability $(\gamma > 1)$ when calculating the expected value. This effectively allows the model to flexibly capture the extent to which a given participant prefers to minimise the probability or the duration of potential aversive sounds.

Given that the estimated values are negative, the final action probabilities were generated using the following probability distribution:

$$P_{(choice=blue)} = \frac{1}{1 + exp^{(-\beta(g_{(green)} - g_{(blue)})}}$$

Here, $\beta$is the inverse decision temperature and influences the degree to which the expected values are used in determining the shape chosen.

In summary, the combined predictor and selector model has 3 free parameters (α, β, γ). These parameters were estimated separately for each participant, for the stable and volatile blocks. Parameter estimates were obtained by maximum likelihood estimation, generating the best set of parameters that would maximise the likelihood of predicting each participant's choices. The ability of the model to recapitulate participant choice is displayed in

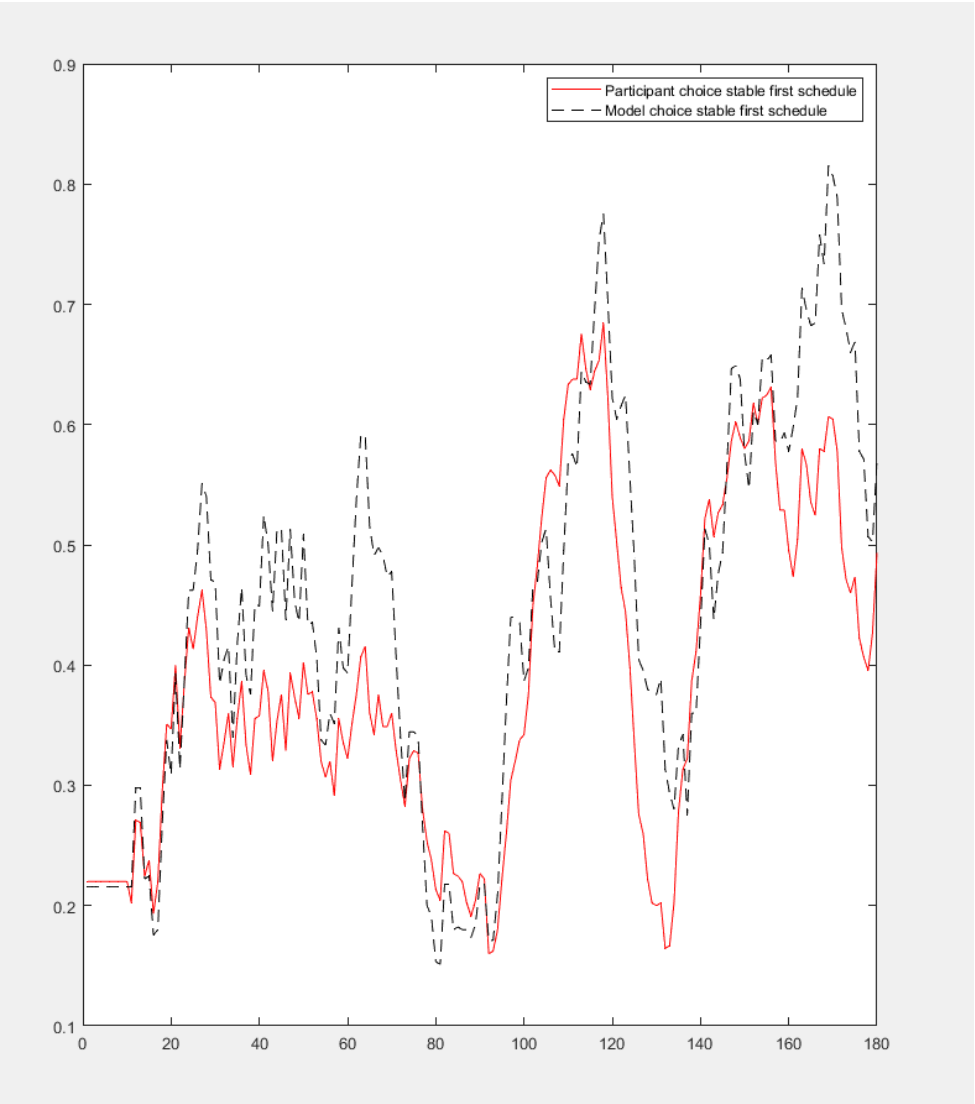
Figure 17.

This model was compared against alternative models, including two simplified models that only use information about the outcome probability, not duration, and vice versa, and one model that assumes that participants keep β and γ fixed across blocks. The fit of each model to the observed data was compared using negative log likelihood, a measure of model fit, as well as the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC), two model fit statistics which penalise additional parameters (**Table 15**).

To formally test the model's predictions of participants' choices, the model's predictions were discretised such that on a given trial, if the model predicted the likelihood that a participant would choose option A as >50%, this was labelled as a correct prediction of choice if the participant chose option A. This provides a coarse measure of model performance, given that a 99% likelihood of option A being chosen and 51% likelihood of option A being chosen are treated the same (**Table 15**). There were no difference in model accuracy between groups (p=.48).

As demonstrated in **Table 15**, though the full behavioural model outperformed alternative models on overall model performance and based on the negative log likelihood, but the model did not outperform alternative models on model fit statistics that penalised additional parameters.

Figure 17. Learning curves illustrating participant and model choice during the aversive learning task. The model output was generated by running the behavioural model on the task trial sequences for each participant using the individually fitted parameter values. Participant choices and model predictions were then smoothed using a running average of 10 trials to more clearly illustrate the effects of learning on participant choice and model output. **(A)** The plot shows an overlay of choice behaviour of participants who completed the stable block first or **(B)** the volatile block first with the output of the behavioural model (dotted line).



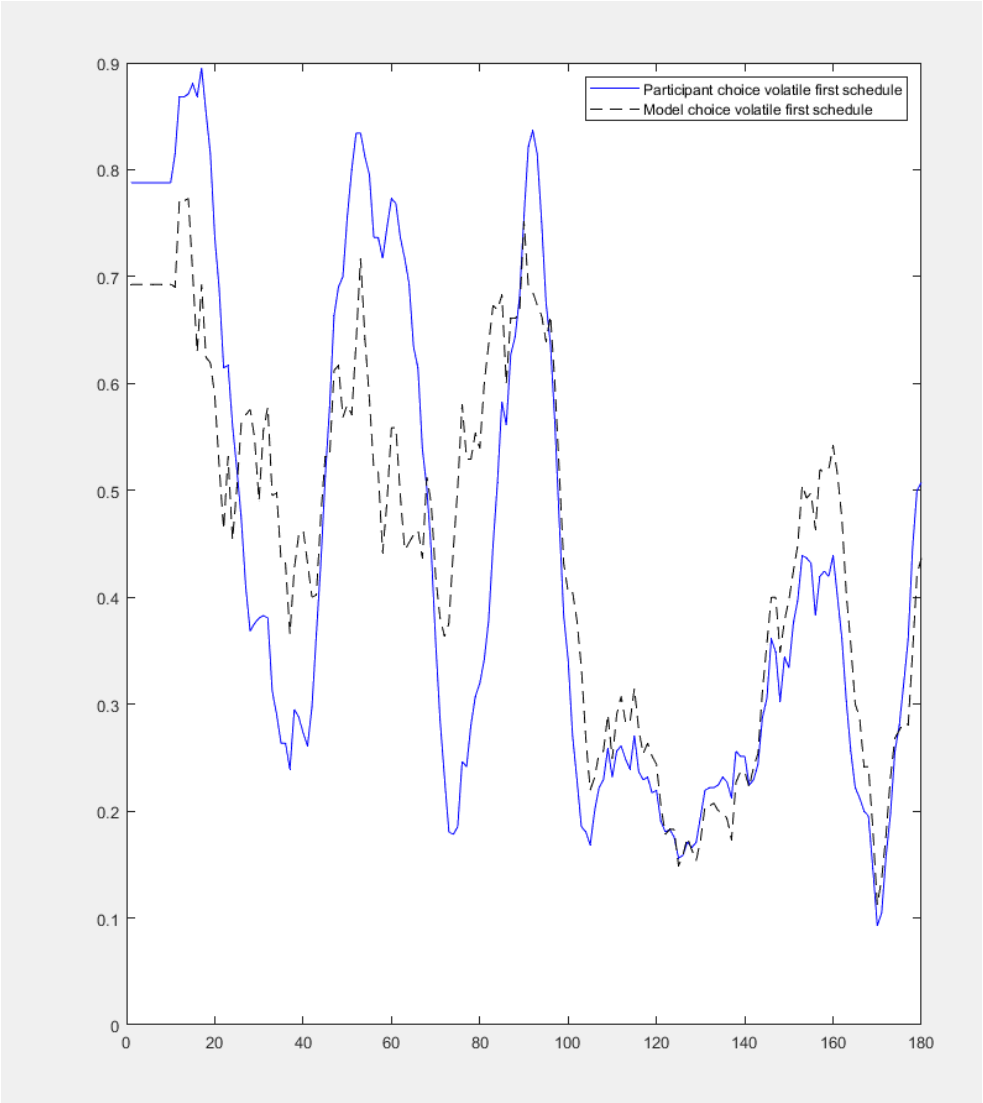

Participant choice volatile first schedule
Model choice volatile first schedule
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
20
40
60
80
100
120
140
160
180

Table 15. Model fits to participants' choice behaviour. (A) The full behavioural model (i), that assumes that participants use information about outcome probability and duration when making their choices. (ii) A model that ignores information about the duration of aversive sounds. (iii) A model that uses information about the duration of aversive sounds, but does not update its expected outcome probability on the basis of previous outcomes. (B) A simplified version of the full model that uses 2 learning rate parameters (one for the stable block and one for the volatile block), but only one risk preference and one inverse temperature parameter across the whole task.

Model	**Number of parameters**	**Negative Log Likelihood (lower is better)**	**AIC (lower is better)**	**BIC (lower is better)**	**Model performance (higher is better)**
A					
(i) Full model	6 (α, β, γ per block)	7667	13.27	-5.89	74.6%
(ii) Prior outcome history model	4 (α, β per block)	9633	2.43	-10.35	61.5%
(iii) Outcome value model	2 (β per block)	8621	-7.74	-14.12	54.5%
B					
Full model with single risk preference (β) and inverse temperature	4 (α per block, single β, γ across blocks)	16244	1.38	-11.39	64.5%

(γ) across blocks

5.3.4. Assessment of clinical variables

Assessment of clinical variables including subclinical psychotic experiences, depressive symptoms, and anxiety have been outlined in chapter 4.

5.3.5. Statistical analyses

Analyses were performed using R (version 4.1.2). Sociodemographic and clinical data were analysed using means and standard deviations for continuous data and frequencies for categorical data. Analysis of variance (ANOVAs) with Bonferroni correction for multiple comparisons was used to examine group differences in continuous variables.

For the aversive learning task, separate 2x4 mixed model repeated measures ANOVA were conducted on learning rates, risk preference and inverse decision temperature, with block (stable, volatile) as a within-subjects factor and group (Psy-DT-, Psy-DT+, Psy+DT-, Psy+DT+) as a between-subject factor. Age, gender and ethnicity were entered as covariates.

Mediation analyses were conducted using the 'Mediation' package, with bootstrapping with 20,000 resampling to calculate 95% Cis for the indirect effect.

5.4. Results

5.4.1. Participant characteristics and clinical scores

The sample comprised of 67 participants: 18 Psy-DT-, 19 Psy-DT+, 10 Psy+DT- and 20 Psy+DT+.

Table 16 provides demographic information and data on the levels of psychotic experiences, depression and anxiety. There were no significant group differences in age, sex, ethnicity and socioeconomic status (*ps*>.057).

Groups also differed significantly on levels of anxiety ($F_{3,63}$=13.3, p<.001, η_p^2=.39) and depressive symptoms ($F_{3,63}$=10.2, p<.001, η_p^2=.33) with a graded increase in psychotic experiences from Psy-DT-, Psy-DT+, Psy+DT- to Psy+DT+ (adjusted *ps*<.05).

Table 16. Demographic and clinical characteristics

Sample characteristics	**Psy-DT (n=18)**	**Psy-DT+ (n=19)**	**Psy+DT- (n=10)**	**Psy+DT+ (n=20)**	***p***
Age, Mean (SD)	28.8 (6.67)	31.2 (4.89)	29.2 (6.91)	27.1 (5.41)	.190
Sex, n, %F	9 (50.0%)	12 (63.2%)	10 (100%)	14 (70.0%)	0.057
Ethnicity					0.770
White British	10	**13**	**5**	**10**	
Black	1	0	0	1	
Mixed	1	1	0	1	
Asian	1	0	2	1	
Other	5	5	3	7	
Socioeconomic status (FAS)	5.00 (1.82)	4.16 (1.71)	4.60 (1.27)	3.80 (1.58)	.150
Past psychiatric history, %	0.28 (0.46)	0.32 (0.48)	0.30 (0.48)	0.75 (0.44)	.007
Drug history, %	0.11 (0.32)	0.32 (0.48)	0.20 (0.42)	0.55 (0.51)	.024
Tobacco use, %	0.22 (0.43)	0.74 (0.45)	0.30 (0.48)	0.65 (0.49)	.004
CTQ	32.5 (5.18)	58.0 (14.6)	34.1 (4.53)	66.1 (14.4)	<.001
CAPE	61.6 (13.0)	74.1 (10.3)	82.4 (9.90)	95.6 (18.7)	<.001
PHQ	4.44 (3.80)	7.63 (5.16	9.30 (5.31)	13.35 (5.80)	<.001
GAD	2.78 (2.88)	6.42 (5.00)	7.40 (4.35)	12.1 (5.43)	<.001

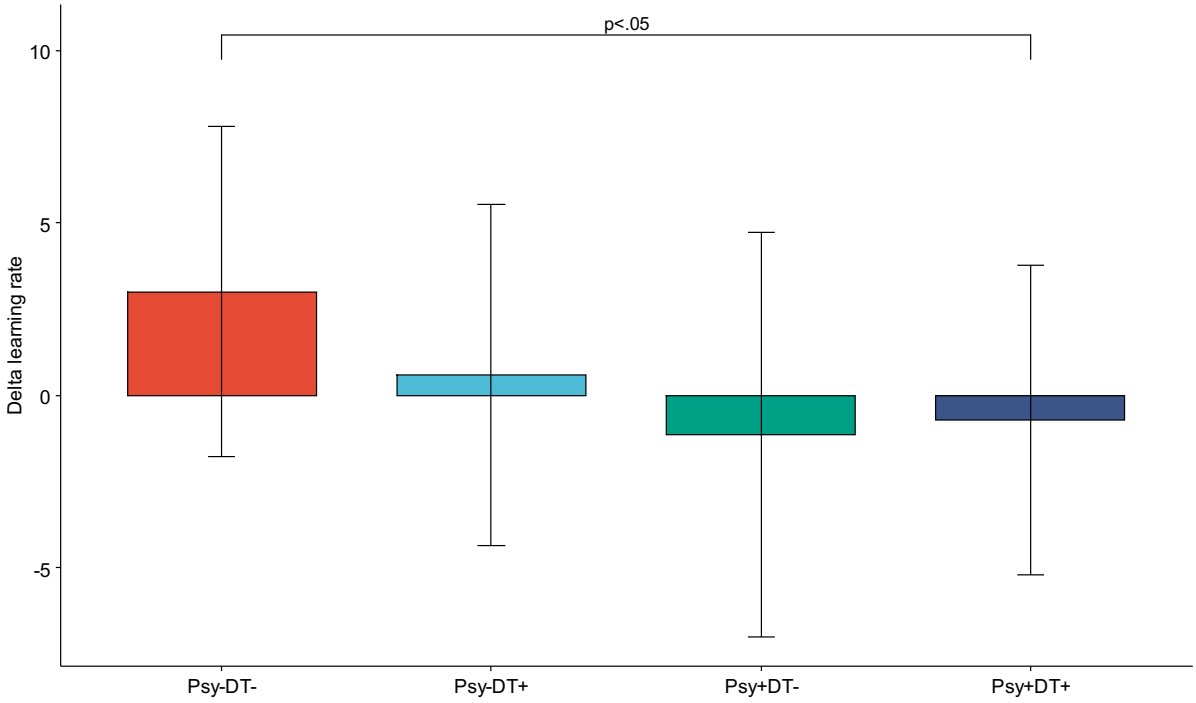
Abbreviations: FAS; Family Affluence Scale, CTQ; childhood trauma questionnaire, PHQ; Patient Health Questionnaire, GAD; Generalised Anxiety Disorder Questionnaire

5.4.2. Relationship between developmental trauma and threat learning

Compared to Psy-DT-, Psy+DT+ demonstrated a diminished change in learning rates between blocks, indicating a reduced ability to adapt their learning rates between the volatile and stable blocks of the task (t_{37}=-2.63, p=.049, Cohen's d=.086) (**Figure 18**). There were no other significant differences between groups (ps>.1).

There were no differences between groups in risk preference (that is, whether a participant prefers low-probability, high-duration aversive sounds over high-probability, low-duration sounds) or decision temperatures (that is, how much a participant's calculations of the expected value of their actions influence choice) in the stable and volatile task blocks (ps>.1), across blocks, or in the change in risk preference and decision temperatures between blocks (ps>.1).

Figure 18. Group means (95% CI) for delta learning rates, calculated as the difference in learning rates between volatile and stable blocks of the task.



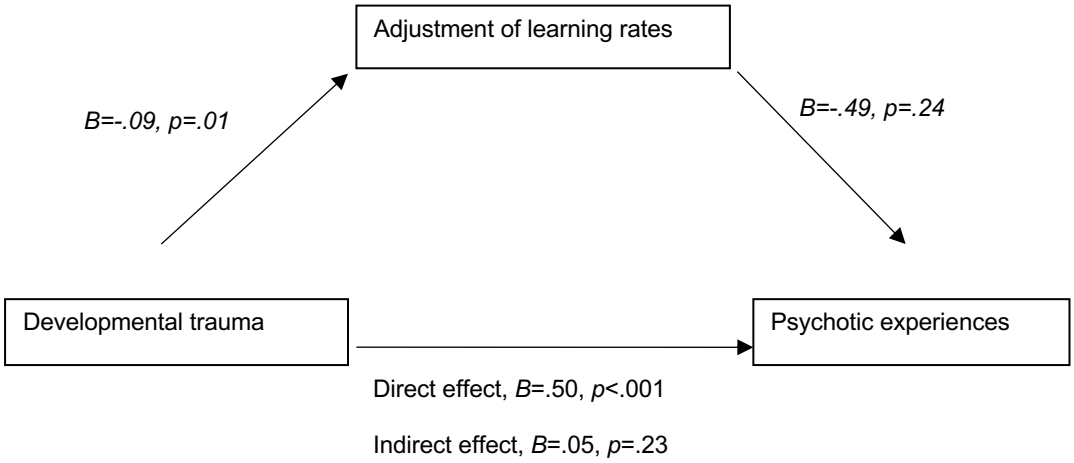
5.4.2.1. Role of threat learning in the association between severity of developmental trauma and severity of psychotic experiences

The severity of developmental trauma was significantly associated with a reduced adjustment of learning rates to volatility (*B*=.09, R^2=.09, *p*=.011).

Reduced adjustment of learning rates to volatility were not significantly associated increased severity of psychotic experiences, when controlling for the severity of developmental trauma (B=-.49, R^2=.015, *p*=.24).

Reduced adjustment of learning rates to volatility did not mediate the association between developmental trauma and psychotic experiences (mediation effect: .05, 95% CI=-.03-.15, *p*=.23), reflecting non-significant associations in adjustment of learning rates to volatility and severity of psychotic experiences **Figure 19**.

Figure 19. Reduced adjustment of learning rates to volatility did not mediate the association between developmental trauma and psychotic experiences



Post hoc power analysis revealed that given a sample size of 67 participants, and an alpha of 0.05, the study was underpowered (power=.22) to detect a mediating effect of adjustment of learning rates to volatility on the relationship between developmental trauma and psychotic experiences.

5.5. Discussion

5.5.1. Summary

In this threat learning task, compared to healthy individuals without experiences of developmental trauma, adult survivors of developmental trauma with at risk mental states for psychosis demonstrated a reduced ability to adjust their learning about aversive outcomes, based on whether the action-outcome contingencies of the environment were stable or volatile. The severity of developmental trauma was associated with a poorer ability to adjust learning rates to volatility. Reduced ability to adjust learning rates was not associated with the severity of psychotic experiences, and did not mediate the association between the severity of developmental trauma and psychotic experiences.

5.5.2. Interpretation of findings from the study on the relationship between developmental trauma, threat learning and psychotic experiences

Adult survivors of developmental trauma with at risk mental states for psychosis demonstrated a reduction in the ability to adjust learning rates to environmental volatility compared to healthy individuals without experiences of developmental trauma. Moreover, there was evidence of a dose-response association between the severity of developmental trauma and reduced ability to adjust learning rates to

environmental volatility. Reduced ability to adjust learning rates to volatility was associated with the severity of psychotic experiences, but not after controlling for the severity of developmental trauma, and did not play a mediating role in the relationship between the severity of developmental trauma and psychotic experiences.

The theory of latent vulnerability, which states that alterations in threat processing reflect adaptations to an early malevolent environment that can become maladaptive in contexts which are no longer threatening (McCrory and Viding, 2015; McCrory, Gerin and Viding, 2017), suggests an important role of adapting threat processes appropriately to reflect the nature of the environment. The observation that developmental trauma was associated with a reduction in the ability to adjust learning rates to environmental volatility, indicating a difficulty in adapting learning about aversive outcomes in response to changes in the higher order structure of the environment, is in keeping with this theory.

These findings are broadly in line with existing literature. Behavioural studies find that developmental trauma is associated with lasting alterations in threat learning that are consistent with a pattern of enhanced threat generalisation, an impaired ability to use contextual information to adaptively learn about threats (Bremner *et al.*, 2005; McLaughlin *et al.*, 2016; Thome *et al.*, 2018; Lis *et al.*, 2020). An alternative interpretation that cannot be excluded based on these findings alone is that developmental trauma is associated with a generalised impairment of associative learning, consistent with findings of reduced IQ in individuals who have experienced developmental trauma (Koenen *et al.*, 2003). However, these deficits in associative learning nevertheless affect threat learning processes, including those observed in this study, and can give rise to symptoms characterised by enhanced threat

processes such as heightened anxiety and avoidance behaviours (Grillon, 2002), demonstrating the importance of future research on not only understanding the precise mechanisms underlying these findings but also the implications of these findings within the context of threat processes.

Given that threat learning is formalised within the computational literature as the process of forming and updating of 'beliefs', or expectancies, about threat in response to the environment, these findings suggest potential mechanisms that may underlie the association between developmental trauma and psychotic experiences, particularly delusions, which are irrational and maladaptive beliefs that persist despite evidence to the contrary. Under predictive coding accounts of brain function, developmental trauma shapes prior beliefs about the world that are aberrantly maintained and exert inordinate influence on neurocognitive processes of perception, learning and action. The findings of developmental trauma-associated reductions in the ability to adjust learning about threats based on changes in the environment may arise from aberrantly strong prior beliefs about threat. These strong prior beliefs about threat that are given undue influence, or precision, on learning processes, may result in learning that is biased by prior beliefs rather than incoming sensory inputs that convey information about the environment. Aberrantly strong prior beliefs for threat may result in aberrant threat learning in 'safe' environments, whereby strong prior beliefs for threat dominate learning processes, resulting in false beliefs that neutral cues are threatening. When neutral social cues are aberrantly learned to be threatening, this may give rise to paranoia, a common feature of psychosis, that involves unfounded belief that others intend harm. A deficit in appropriately learning about threats is also likely to result in threats being experienced as unpredictable and less avoidable.

In line with predictive coding account for how developmental trauma may result in psychotic experiences, and on the basis of evidence from behavioural and neuroimaging studies demonstrating impaired threat learning in individuals with psychosis (Tuominen *et al.*, 2022), which may reflect poorer ability to differentially learn about and discriminate between cues associated with threats and cues not associated with threats, developmental trauma-associated deficits in adapting threat learning to environmental volatility was hypothesised to be associated with an increased severity of psychotic experiences. This study found that the association between reduced adjustment of learning rates to environmental volatility was significantly associated with increased severity of psychotic experiences, though these associations did not remain significant when controlling for the severity of developmental trauma. Given the finding that developmental trauma-associated reductions in the ability to adjust learning rates to environmental volatility was not significantly associated with the severity of psychotic experiences, mediation analyses also indicated that these alterations in threat learning did not play a mediating role in the association between the severity of developmental trauma and psychotic experiences.

There are several possible interpretations for these findings, including the null hypothesis that developmental trauma-associated alterations in threat learning are not related to psychotic experiences. A more plausible possibility is that the study's small sample size resulted in a lack of power to detect significant associations and mediation effects. Another consideration is that prior studies observe impaired differential threat learning in individuals with clinical levels of psychosis, as opposed to individuals with subclinical levels of psychotic experiences from the general population, as recruited in this study. This means that although associations between

altered threat learning and frank psychotic symptoms such as delusion have been observed in prior studies (Tuominen *et al.*, 2022), the associations between altered threat learning and subclinical psychotic experiences, such as those examined in this study, may be weaker.

5.5.3. Strengths and limitations of the study on the relationship between developmental trauma, threat learning and psychotic experiences

Strengths and limitations specific to this study will be discussed below, and general strengths and limitations of all data included in this thesis will be discussed in detail in the general discussion (Section 7.9).

Though traditional threat learning tasks are unable to capture the neural processes underlying threat learning, for instance, in this study groups did not differ on overall task performance, as measured by the total number of aversive sounds received, computational modelling of this threat learning task enabled the underlying processes to be examined.

There were several limitations to this study. Firstly, it is unclear whether the relationships between developmental trauma and altered threat learning are specific to learning about threats or whether they reflect global deficits in associative learning, given that this study did not examine learning about different outcomes other than aversive sounds, such as learning about reward gains or losses. For instance, this interpretation would be consistent with evidence documenting reduced IQ in individuals who have been maltreated (Koenen *et al.*, 2003). Future research is needed to distinguish the exact mechanisms underlying these findings.

Secondly, methodological issues should be discussed. In contrast to existing studies that use varying intensities of electrical stimulation (shocks) as aversive stimuli, this

study used varying durations of aversive sounds. In line with existing studies using electrical stimulation (Browning *et al.*, 2015) calibration procedure ensured that the duration of aversive sounds evoked an unpleasantness rating of 7/10, but given that the study was conducted online and used aversive sounds instead of electrical stimulation, it is possible that the aversive stimuli used in this study were not as unpleasant or aversive as those used in prior studies. It is also important to consider the face validity of the threat learning task. Though it can be argued that this threat reversal task, modelled using simple reinforcement learning models, is suitable to estimate and parameterise neurocognitive processes involved in threat processing, how well this captures neurocognitive processes underlying the processing of threats in the real world, which are more likely to be aversive social cues rather than aversive sounds or electrical stimulation, is less clear.

Several computational models were used to fit participants' choices. Contrary to previous literature (Browning *et al.*, 2015), though the full computational model outperformed alternative models in predicting participants' choices and based on the negative log likelihood, the model did not outperform alternative models on model fit statistics that penalised additional parameters. Given the use of this model in previous literature, and that this model outperformed alternative models in predicting participants' choices this model was used in analyses, but it possible that the model was susceptible to the effects of overfitting, meaning results should be replicated to ensure the generalisability of findings.

There is evidence that anxiety and internalising psychopathology are also associated with reduced adjustment of learning rates to volatility (Browning *et al.*, 2015; Gagne *et al.*, 2020). Given associations between developmental trauma with anxiety and depressive symptomatologies in this study, it is possible that the observed

associations between developmental trauma and reduced adjustment of learning rates to volatility may be due to underlying differences in anxiety and depressive symptomatology. This study did not, however, control for anxiety and depressive symptoms given evidence that developmental trauma increases the risk of both anxiety and depression (Kuzminskaite *et al.*, 2021). This means that anxiety and depressive symptoms may lie within the causal pathway between developmental trauma and reduced adjustment of learning rates to volatility, and controlling for these variables would diminish the observable associations between developmental trauma and reduced adjustment of learning rates. Instead, further research should be conducted to understand the exact pathways and causal relationships linking developmental trauma, anxiety and depressive symptomatology and reduced adjustment of learning rates to volatility.

Finally, the cross-sectional nature of this study precludes inferences about causal associations between developmental trauma and reduced adjustment of learning rates to volatility.

Chapter VI: The effect of developmental trauma on brain structures involved in threat processing and its relation to psychotic experiences in adulthood

6.1. Introduction

As summarised in chapter I, developmental trauma increases the risk for psychiatric illness in adulthood (Varese et al., 2012). Adult survivors are at a higher risk of adverse prognostic outcomes, including more severe illness, poorer response to treatment, with increased morbidity and mortality (McLaughlin et al., 2017). Despite this compelling association between developmental trauma and psychopathology, the precise neurobiological mechanisms underlying this association are less clear.

Traumatic experiences are by nature threatening, and engage neural circuits that aim to mitigate such threats. Crucial in this process is the brain's threat system that enables organisms to appropriately detect, learn and respond to threats (LeDoux 2013). Two important regions underlying this are the amygdala and ventromedial prefrontal cortex (vmPFC). The amygdala is a crucial region involved in the detection of potential threats (Isenberg et al., 1999, Ohman et al., 2015), and necessary for threat learning and response (Johansen et al., 2011; LeDoux, 2003). The vmPFC down-regulates the amygdala response and is involved in safety learning and threat extinction (Phelps et al., 2014, Quirk et al., 2000). The amygdala and vmPFC are susceptible to the effects of developmental trauma (Tottenham and Sheridan 2010, Tsoorey et al., 2008, Binder and Nemeroff, 2010) and exposure to developmental trauma has consistently been shown to structurally and functionally alter the amygdala and vmPFC (Teicher et al., 2016).

In parallel, evidence from human neuroimaging studies implicate the role of structural alterations of the amygdala and vmPFC in psychosis, with meta-analyses reporting reductions in amygdalar and vmPFC volumes in individuals with

schizophrenia (Satterthwaite et al., 2016, Lawrie et al., 2018, Bora et al., 2011, Glahn et al., 2008, Hajima et al., 2013, Honea et al., 2005).

These findings are in line with cognitive theories of psychosis that highlight the roles of altered threat and memory processing in underpinning psychotic symptoms. For example, altered attentional processing of threat-related stimuli leads to threatening interpretations in response to anomalous experiences, contributing to the development of paranoid delusions (Freeman et al., 2007)

Taken together, it is proposed that developmental trauma may increase the risk of psychotic experiences by structurally altering the amygdala and vmPFC. To test this hypothesis, we investigated in a well-characterised birth cohort, the effect of developmental trauma, assessed prospectively, on amygdalar and vmPFC volumes– and examined their potential role in the association between developmental trauma and psychotic experiences in adulthood. Given that psychotic experiences occurring during childhood may confound the association between developmental trauma and alterations in amygdalar and vmPFC volumes in adulthood, we repeated analyses in a subgroup of individuals who did not report psychotic experiences at age 12. In addition, we also explored whether these associations were confounded by genetic risk for psychosis, by repeating analyses, whilst controlling for schizophrenia Polygenic Risk Scores.

6.2. Hypotheses

1. Developmental trauma is associated with reductions in amygdala and vmPFC volumes
2. Reduced amygdala and vmPFC volumes mediate the relationship between developmental trauma and psychotic experiences

6.3. Materials and Methods

6.3.1. Ethics

This study received ethical approval provided by the Cardiff University School of Psychology Ethics Committee and the ALSPAC Ethics and Law Committee (IRB00003312).

6.3.2. Participants and procedure

All participants were recruited as part of the Avon Longitudinal Study of Parents and Children (ALSPAC; http://www.bristol.ac.uk/alspac/). All pregnant women residing in the county of Avon, in the Southwest of England with an expected delivery from 1st April, 1991, to 31st December, 1992 were invited to participate. Out of 14,000 births, 418 participants completed assessment of traumatic experiences between 0-17 years, the Psychosis-Like Symptom interview (PLIKSi) at age 12 and 18, and underwent structural MRI between the ages of 19-24 years.

6.3.3. Assessment of psychotic experiences

Psychotic experiences were assessed at age 12 and 18, using the psychotic-like symptoms semi-structured interview (PLIKSi) (Zammit et al. 2013). The PLIKSi comprises 12 core questions that assess delusions (grandiose ability, control, reference, thoughts being read, being spied on, persecution and unspecified delusions), auditory hallucinations, visual hallucinations and thought inference (thought withdrawal, broadcasting, and insertion). The interviews were conducted by

trained psychologists who rated responses in accordance with the Schedules for Clinical Assessment in Neuropsychiatry guidelines, using probing and cross-questioning to establish the presence or absence of psychotic experiences. Interviewers rated experiences as absent, suspected to be present, definitely present or as meeting a clinical diagnosis of psychosis. Experiences were classified as suspected to be present if individuals did not provide a credible example of an experience that would meet a clinical diagnosis. Psychotic experiences in suspected, definitely present and clinical groups were not attributable to the effects of substance use, sleep or fever.

6.3.4. Assessment of developmental trauma

Developmental trauma variables were derived from assessments completed through self-report by participants or by the participant's parents at three separate time points (0-4.9 years, 5-10.9 years, and 11-17 years). Trauma types included emotional, physical and sexual abuse, emotional neglect, domestic violence and bullying. There was no self-report assessment of emotional neglect between 0-4.9 years, so only data from 5-10.9 years was used. This study included two trauma variables that were 1) exposure to any trauma type between 0 and 17 years as a binary variable, and 2) the number of types of traumas experienced, ranging from 0-6 types of trauma.

6.3.5. Confounding variables

Data on sex, age at scanning and total intracranial volume (TIV) were also collected. Given the narrow range of participants' ages at the timing of scans (ages 19-24), only sex and TIV were controlled for during analysis.

6.3.6. MRI acquisition, preprocessing and volumetric measures

All imaging data was acquired at the Cardiff University Brain Imaging Centre (CUBRIC) on a 3-T General Electric SIGNA HDx (GE Medical Systems, Milwaukee, WI, USA) using an 8-channel head coil for radiofrequency reception. Gray matter volume was acquired from high-resolution, fast-spoiled gradient-echo T1-weighted isotropic images acquired with slices parallel to the AC–PC line (TR = 7808 ms, TE = 2988 ms, inversion time = 450 ms, flip angle = 20°, field of view = 256 × 256 mm, resolution = 1 mm3).

Structural magnetic resonance imaging (sMRI) data was collected using the Computation Anatomy Toolbox (CAT12) on Statistical parametric mapping (SPM version 8; www.fil.ion.ucl.ac.uk/spm) and pre-processed by Dr Kate Merritt. T1-weighted images were segmented using default tissue probability maps of white and grey matter, and segmentation parameters were then imported into DARTEL (Ashburner 2007), producing rigidly aligned grey matter images. A mean image template of all participants was reiteratively created, which was then normalised to the template defined by the Montreal Neurological Institute (MNI). Resulting deformations were applied to transform the segmented grey matter images and smoothed with a Gaussian filter of 8-mm full-width half-maximum.

Brain volumes of interest included total intracranial volume in addition to left and right amygdala and the ventromedial prefrontal cortex (vmPFC). Total volumes for all structures were extracted using the MarsBar (v.0.44) (Brett *et al.*, 2002) toolbox on SPM, using ROI masks that were created from the AAL Atlas in WFU Pickatlas (Maldjian *et al.*, 2003).

6.3.7. Statistical analyses

Statistical were conducted using R (version 4.1.2). Ordinal logistic regression was used to calculate odds ratios (Ors) and 95% Cis for psychotic experiences associated with exposure to developmental trauma before and after adjusting for confounding. Hierarchical linear regression was used to examine the associations between exposure to developmental trauma, ROI volumes and psychotic experiences, modelled as linear terms. To examine the role of altered ROI volumes in the association between exposure to developmental trauma and psychotic experiences, mediation analyses were conducted when both paths of the indirect effect (path 1: exposure to developmental trauma to ROI volume, and path 2: ROI volume to psychotic experiences) were significant. For the mediation analyses, bootstrapping with 5000 resampling was used to calculate the 95% Cis for the indirect effect.

Dose-response associations between number of trauma types experienced were examined, modelled as linear terms, with ROI volumes and psychotic experiences modelled as linear terms, whilst adjusting for confounding.

To minimise the effect of reverse causation, analyses were repeated in a subgroup of individuals who did not report psychotic experiences at age 12 years. To minimise

the effect of genetic confounding caused by gene-environment correlations, analyses were repeated, adjusting for schizophrenia Polygenic Risk Scores.

6.4. Results

6.4.1. Participant characteristics

The sample of 418 participants included 248 (59.2%) females and 171 (40.3%) males with a mean age at scan of 21.2 (1.45) years. Demographic data are presented in **Table 17**.

As summarised in **Table 18**, 277 (66.1%) participants reported exposure to developmental trauma. 152 (36.4%) participants were rated as having suspected (n=47, 11.2%), definite (n=71, 17.2%) or clinical (n=34, 8.1%) levels of psychotic experiences at 18 years.

Table 17. Sample characteristics

	PLIKSi				
	All (419)	None (267)	Suspected (47)	Definite (71)	Clinical (34)
Age at scan, mean (SD)	21.2 (1.5)	21.5 (1.4)	20.8 (1.1)	20.9 (1.6)	20.1 (0.9)
Sex, % Female	59.2	56.6	66.0	56.3	76.5

Abbreviations: PLIKSi, Psychotic-like symptoms semi-structured interview

Table 18. Exposure to trauma and psychotic experiences, by type and timing of trauma

		PLIKSi				Adjusted [a]	
	All (n=419)	**None (n=266)**	**Suspected (n=47)**	**Definite (n=71)**	**Clinical (n=34)**	**OR (95% CI)**	***P* Value**
Trauma exposure (n, %)	277 (66.1)	163 (61)	40 (85.1)	48 (67.6)	26 (76.5)	1.77 (1.15-2.75)	0.01
Physical abuse	112 (26.7)	61 (22.8)	13 (27.7)	24 (33.8)	14 (41.2)	1.77 (1.15-2.71)	<.01
Emotional abuse	106 (25.3)	57 (21.3)	19 (40.4)	19 (26.8)	11 (32.4)	1.59 (1.03-2.43)	0.03
Bullying	139 (33.2)	69 (25.8)	26 (55.3)	30 (42.3)	14 (41.2)	2.06 (1.38-3.09)	<.001
Sexual abuse	56 (13.4)	26 (9.7)	7 (14.9)	13 (18.3)	10 (29.4)	2.25 (1.28-3.9)	<.01
Domestic violence	91 (21.7)	51 (19.1)	10 (21.3)	21 (29.6)	9 (26.5)	1.53 (0.97-2.4)	0.07
Emotional neglect	39 (9.3)	17 (6.4)	8 (17)	6 (8.5)	8 (23.5)	1.94 (0.98-3.78)	0.05
Trauma types							
0	142 (33.9)	104 (39)	7 (14.9)	23 (32.4)	8 (23.5)	0 (0-0)	
1	125 (29.8)	82 (30.7)	16 (34)	19 (26.8)	8 (23.5)	0.85 (0.55-1.29)	0.45
2	83 (19.8)	53 (19.9)	13 (27.7)	9 (12.7)	8 (23.5)	0.95 (0.58-1.53)	0.84
≥3	69 (16.5)	28 (10.5)	11 (23.4)	20 (28.2)	10 (29.4)	2.9 (1.79-4.7)	<.001
Linear trend							

[a] Adjusted for confounders: sex

6.4.2. Developmental trauma exposure and psychotic experiences

Exposure to developmental trauma was associated with increased odds of psychotic experiences at age 18 (OR=1.80; 95% CI=1.17-2.81, *p*<.001), with evidence supporting dose-response effects of developmental trauma on psychotic experiences. Experiencing three or more types of developmental trauma significantly increased psychotic experiences (OR=2.90, 95% CI=1.79-4.70, p<.001), and experiencing trauma during both childhood and adolescence were associated with increased psychotic experiences (OR=2.26, 95% CI=1.49-3.42, p<.001) whereas experiencing trauma during only childhood (OR=0.68, 95% CI=0.43-1.07, p=.10) or adolescence (OR=1.18, 95% CI=0.67-2.05, p=.56) was not.

6.4.3. Developmental trauma exposure and brain structures involved in threat processing

Developmental trauma was associated with reduced left amygdala volume in adulthood (*B*=-.01, *p*=.014). Moreover, there was evidence supporting a dose-response effect, whereby increased number of trauma types experienced were associated with greater reductions in left amygdala volumes (*B*=-.004, *p*=.047).

No associations between developmental trauma and vmPFC were observed (p>.22).

Table 19. Association between developmental trauma and brain structures involved in threat processing

		Amygdala						vmPFC					
		Both		Left		Right		Both		Left		Right	
Trauma measure	Trauma exposure (*n*, %)	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*	*B*	*p*
Trauma exposure	276 (66.03)	-0.007	0.058	-0.011	0.014	-0.003	0.389	0.001	0.616	0.002	0.563	0.001	0.713
Trauma types	276 (66.03)	-0.001	0.304	-0.003	0.047	0.000	0.803	0.001	0.215	0.001	0.226	0.001	0.241

6.4.4. Brain structures involved in threat and memory processing and psychotic experiences

Reduced left (OR=.0007, 95% CI=0-.03, p<.01) and right (OR=.0006, 95% CI=0-.19, p=.01) amygdala volume was associated with increased odds of psychotic experiences at age 18 years (**Table 20**).

Reduced total vmPFC volume was significantly associated with increased odds of psychotic experiences (OR=.0005, 95% CI=0-0.85), p<.05).

Table 20. Association between ROI volumes and psychotic experiences

		PLIKSi		
		OR	95% CI	p Value
Amygdala	Both	0.0001	0-0.03	<.01
	Left	0.0007	0-0.06	<.01
	Right	0.0006	0-0.19	0.01
vmPFC	Both	0.0005	0-0.85	<0.05
	Left	0.0010	0-1.16	0.06
	Right	0.0008	0-1.09	0.05

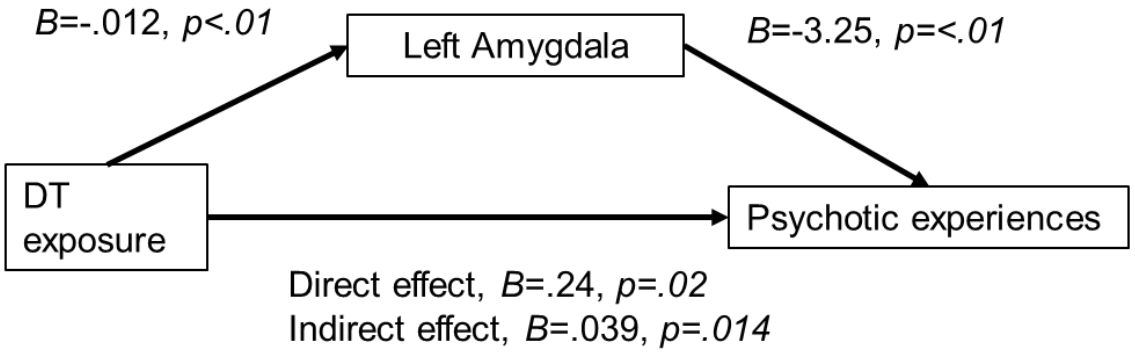
6.4.5. The role of the amygdala and vmPFC in the association between trauma and psychotic experiences

Given that exposure to developmental trauma was significantly associated with reduced left amygdala volume, and that reduced left amygdala volume was significantly associated with increased psychotic experiences, mediation analyses were conducted to examine the role of reduced left amygdala volume on the association between developmental trauma exposure and psychotic experiences.

Reduced left amygdala volume mediated 16% (95% CI=2%-80%, *p*=.03) of the association between developmental trauma and psychotic experiences (mediation effect: 0.04, 95% CI=0.01-0.08, *p*=.015) (**Figure 20**).

No mediation analyses were conducted for the vmPFC due to the lack of significant association with exposure to developmental trauma.

Figure 20. Left amygdala volume mediates the association between exposure to developmental trauma and psychotic experiences. DT; Developmental trauma



6.4.6. Sensitivity analyses

To minimise the effect of reverse causation, analyses were repeated in a subgroup of individuals who did not report psychotic experiences at age 12. To minimise the effect of genetic confounding caused by gene-environment correlations, analyses were repeated, adjusting for schizophrenia Polygenic Risk Scores.

6.4.6.1. Reverse causation

Analyses were repeated in a subgroup of individuals who did not report psychotic experiences at age 12. Exposure to developmental trauma was significantly associated with reduced left amygdala volume (p=.006) and reduced left amygdala volume was significantly associated with increased psychotic experiences (p=.02).

Left amygdalar volumes significantly mediated the relationship between developmental trauma exposure and psychotic experiences (mediation effect: 0.04, 95% CI=0.01-0.08, *p*=.04).

6.4.6.1.1. Polygenic risk score

Analyses were also repeated adjusting for schizophrenia Polygenic Risk Scores. Exposure to developmental trauma was associated with reduced left amygdala volume at a marginal significant level (*p*=.072) and reduced left amygdala volume was significantly associated with increased psychotic experiences (*p*=.006). Left amygdalar volumes mediated the relationship between developmental trauma exposure and psychotic experiences at a marginal significance level (mediation effect: 0.03, 95% CI=-0.003-0.08, *p*=.094).

6.5. Discussion

6.5.1. Summary

These results using data from a large, well-characterised birth cohort demonstrate that developmental trauma was associated with increased psychotic experiences in adulthood and reduced left amygdala volumes, with evidence supporting dose-response relationships. Reductions in both the left amygdala and total vmPFC were associated with increased psychotic experiences. Reduced left amygdala volumes mediated 16% of the association between developmental trauma and psychotic experiences.

6.5.2. Interpretation of findings from the study on the effect of developmental trauma on brain structures involved in threat processing and its relation to psychotic experiences in adulthood

As previously reported (Croft *et al.*, 2019), in this subsample of the ALSPAC birth cohort with neuroimaging data we found that exposure to developmental trauma was associated with increased psychotic experiences in adulthood, with evidence supporting a dose-response relationship.

The finding that developmental trauma was associated with reductions in left amygdalar volumes with evidence supporting a dose-response relationships is partially consistent with findings of non-significant decrease in amygdalar volumes from existing literature (Whittle *et al.*, 2013; Teicher and Samson, 2016; Teicher *et al.*, 2016). These associations were not explained by sensitivity analyses aimed at minimising the effect of reverse causation or genetic confounding. Taken together, alongside evidence that the association between developmental trauma and left amygdalar volumes is temporal, consistent and biologically plausible, these findings support the hypothesis that a causal association exists between developmental trauma and left amygdalar volumes.

Given that developmental trauma was associated with left but not right amygdalar volumes suggests that the left amygdala may be more sensitive to the effects of developmental trauma than the right amygdala. It has been hypothesised that the left

amygdala may be particularly vulnerable to early abandonment or disrupted attachment, whereas the right amygdala may be more vulnerable to physical, sexual or emotional abuse (Teicher and Samson, 2016; Teicher *et al.*, 2016). Though the present study was not able to examine this directly as developmental trauma was defined as exposure to emotional, physical and sexual abuse, emotional neglect, domestic violence and bullying, given the findings that increased number of types of trauma, including physical, sexual and emotional abuse was associated with further reductions in left amygdalar volumes suggests evidence contrary to this hypothesis.

Given the central role of the amygdala in detecting and responding to threat and evidence of an inverse association between amygdala volume and activation (Siegle *et al.*, 2003; Kalmar *et al.*, 2009), the present findings suggest that developmental trauma is associated with heightened left amygdalar activation resulting in vigilance and hyperresponsiveness to threat. Studies investigating the lateralisation of amygdala activation suggest that the left amygdala is predominantly involved in emotional processing, in particular negative emotions (Wager *et al.*, 2003; Baas, Aleman and Kahn, 2004) and in the processing of detailed, perceptual and emotional information (Cahill, 2003; Gläscher and Adolphs, 2003), as well as hypervigilance (Fetterman, Ode and Robinson, 2013). Taken together, in line with the theory of latent vulnerability (McCrory and Viding, 2015), alterations in left amygdalar volume, indicating alterations in the emotional processing of threat including hypervigilance and hyperresponsiveness may contribute to increased psychotic experiences in adult survivors of developmental trauma.

Importantly, that grey matter reductions of the left amygdala, but not the right amygdala have been reported in patients with psychosis (Pol *et al.*, 2001), and for

unaffected relatives of psychosis patients (Lawrie *et al.*, 1999), this suggests the specificity in the role of the left amygdala in the association between developmental trauma and psychosis.

Indeed, this study found that reductions in left amygdalar volumes played a mediating role in the association between developmental trauma and psychosis, providing evidence in support of the hypothesis that altered threat processing contributes to increased psychotic experiences in adult survivors of developmental trauma. These findings are in line with evidence from meta-analyses that symptoms of post-traumatic stress disorder, such as hyperarousal, mediate the association between developmental trauma and psychotic experiences (Bloomfield *et al.*, 2021), and provide empirical support for cognitive theories of psychosis such as the threat anticipation model (Freeman *et al.*, 2002), which implicate heightened anticipation of threat in the development of paranoia and persecutory delusions.

Though reduced total vmPFC volumes was associated with increased psychotic experiences, vmPFC volumes were not significantly associated with exposure to developmental trauma. Given that the vmPFC plays a central role in down-regulating the amygdala and is essential for safety learning and inhibition of threat fear (Quirk *et al.*, 2000, 2003), the finding that reduced total vmPFC volumes were associated with increased psychotic experiences is in keeping with the existing literature demonstrating impaired safety learning and threat discrimination in individuals with schizophrenia (Tuominen *et al.*, 2022).

The finding that developmental trauma was not associated with total vmPFC volumes is inconsistent with existing literature reporting reduced vmPFC volumes in

adult survivors of developmental trauma (Andersen *et al.*, 2008; Dannlowski *et al.*, 2012; van Harmelen *et al.*, 2013; Morey *et al.*, 2016). It is possible that the lack of association may be due to a lack of statistical power, though this is unlikely given the large sample size. Potential alternative explanations for these findings are that the vmPFC function may be more susceptible to the effects of developmental trauma than vmPFC structure (van Harmelen *et al.*, 2014).

6.5.3. Strengths and limitations of the study on the effect of developmental trauma on brain structures involved in threat processing and its relation to psychotic experiences in adulthood

This is the largest study to date examining the effect of developmental trauma on brain structures involved in threat processing, and the first study to examine their role in the association between developmental trauma and psychotic experiences in adulthood.

This study has many strengths, including its use of a large population-based birth cohort, with multiple measures of trauma at different stages of childhood to minimise recall bias. The use of clinically rated semi-structured interviews to assess psychotic experiences increased the validity of the outcome, as well as confidence in the general inferences made.

Some limitations in this study should be acknowledged. First, though sensitivity analyses were conducted to reduce reverse causality and the confounding effect of pre-existing psychotic experiences on the association between developmental trauma and brain structures involved in threat processing, the cross-sectional nature

of neuroimaging data limits making inferences about the causal relationships between developmental trauma, alterations in brain structures involved in threat processing and subsequent psychotic experiences. Moreover, though this study controlled for demographic confounders including age and sex, as will be discussed in Section 7.9, this study may be affected by other confounding factors, such as the presence of other psychiatric conditions, drug use and sociodemographic factors.

Second, given that this study recruited a subsample of individuals from a birth cohort, where, as with most cohort studies, there was substantial attribution over time, the study is susceptible to the effects of selection bias, as will be discussed in Section 7.9.

Third, psychotic experiences were assessed at age 18, and it is possible that some participants without psychotic experiences at age 18 may go on to develop psychosis later in life. Longitudinal studies are needed to determine whether alterations in brain structure identified here predict the onset of psychotic experiences in later life.

Fourth, these findings of alterations in left amygdalar volumes provide indirect evidence for the hypothesis that developmental trauma alters the function of the left amygdala and alters threat processing on a behavioural level. These findings should be supplemented with functional magnetic resonance imaging (fMRI) studies and behavioural studies to directly examine the effect of developmental trauma on brain function and behaviour, and their associations with psychotic experiences. Moreover functional connectivity studies should examine how developmental trauma affects

the neurocircuitry underlying threat processing as a system, and how these relate to psychotic experiences.

Fifth, it has been hypothesised that developmental trauma produces a small enlargement of the amygdala, but sensitises it to subsequent experiences of trauma, resulting in a graded reduction in volume (Teicher and Samson, 2016; Teicher *et al.*, 2016). Given that developmental trauma was only measured at three timepoints in this population-based study, the study lacked the temporal resolution of traumatic experiences to explore single versus multiple incidences of developmental trauma and their effects on brain structures involved in threat processing.

Chapter VII: Discussion

7.1. Introduction

The aim of the thesis was to examine threat-based mechanisms underlying the association between developmental trauma and psychosis. I have addressed this by conducting a systematic review and meta-analysis, which summarises prior literature and characterises the effects of developmental trauma on threat processing in adulthood (Study I; Chapter II), three behavioural studies, which examine the relationship between developmental trauma and various domains of threat processing, including threat attention (Study II), recognition and response (Study III; Chapter IV) and learning (Study IV; Chapter V) and their relations with psychotic experiences, and by analysing data from the ALSPAC cohort, which examines the relationship between developmental trauma and brain regions involved in threat processing (Study V; Chapter VI).

The next section summarises the results from each study and their main findings, which is followed by a discussion of the general conclusions, strengths and limitations, clinical implications and future directions for research.

7.2. Study I: A systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood

7.2.1. Main findings

To synthesise the existing literature and characterise the effects of developmental trauma on threat processing in adulthood, a systematic review and meta-analysis of previous studies was conducted.

Across 18 studies included in this systematic review and meta-analysis, though results differed substantially across studies, most studies provided evidence in support of the hypothesis that developmental trauma is associated with alterations in threat processing in adulthood, within all domains of threat processing including (1) enhanced threat learning and impaired safety learning resulting in impaired threat discrimination, (2) enhanced threat recognition, (3) a complex pattern of attentional bias towards or away from threatening stimuli, and (4) a complex pattern of threat responses.

7.2.2. Summary of interpretations of findings from the systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood

There is evidence that developmental trauma is associated with long-term alterations in threat processing that persist to adulthood. Adult survivors of developmental trauma have a tendency for potentiated threat responses in adult survivors of

developmental trauma, and exhibit a complex pattern of effects on threat learning, attention and recognition. These findings extend previous models of the mechanisms that underlie vulnerability to psychopathology across of range of disorders following developmental trauma.

7.3. Study II: The relationship between developmental trauma, threat attention and psychotic experiences

7.3.1. Main findings

Adult survivors of developmental trauma exhibited elevated psychotic experiences compared to individuals who have not experienced developmental trauma. Adult survivors of developmental trauma also demonstrated attentional bias towards angry faces, a pattern that was not observed in individuals without experiences of developmental trauma. However, attentional bias for angry faces did not mediate the relationship between developmental trauma severity and psychotic experiences.

7.3.2. Hypothesis I: Adult survivors of developmental trauma have elevated psychotic experiences compared to adults who have not experienced developmental trauma

Consistent with the first hypothesis, adult survivors of developmental trauma exhibited greater subclinical psychotic symptoms than individuals who have not experienced developmental trauma.

7.3.3. Hypothesis II: Adult survivors of developmental trauma exhibit attentional bias towards threatening stimuli compared to adults who have not experienced developmental trauma

Providing support for the second hypothesis, adult survivors of developmental trauma demonstrated attentional bias towards angry faces, which was not observed in individuals without experiences of developmental trauma.

7.3.4. Exploratory hypothesis: Attentional bias for threatening stimuli mediates the relationship between developmental trauma and psychotic experiences

Attentional bias for angry faces did not play a mediating role in the relationship between developmental trauma and psychotic experiences.

7.3.5. Summary of findings of the study on the relationship between developmental trauma, threat attention and psychotic experiences

Developmental trauma was associated with greater subclinical psychotic symptoms and attentional bias towards angry faces. These findings provide evidence in partial support of the hypothesis that threat-attention based mechanisms may underlie increased vulnerability to psychosis in adult survivors of developmental trauma.

7.4. Study III: The relationship between developmental trauma, threat recognition and response and psychotic experiences

7.4.1. Main findings

Compared to healthy individuals without experiences of developmental trauma, adult survivors of developmental trauma with at risk mental states for psychosis demonstrated poorer recognition of facial expressions of anger, which was attributable to reduced perceptual sensitivity to differences between anger and other emotional expressions under conditions of uncertainty. Adult survivors of developmental trauma with psychotic experiences also exhibited more negative valence responses and elevated arousal responses for neutral faces. These alterations in threat recognition and response each played a small, but statistically significant role in mediating the relationship between developmental trauma and psychotic experiences.

7.4.2. Hypothesis I: Developmental trauma is associated with enhanced threat recognition and elevated threat response

The finding of poorer threat recognition in adult survivors of developmental trauma with at risk mental states for psychosis compared to healthy individuals without experiences of developmental trauma is inconsistent with the hypothesis that developmental trauma is associated with enhanced threat recognition.

The finding of more negative valence responses and elevated arousal responses for neutral faces in adult survivors of developmental trauma with at risk mental states for psychosis compared to healthy individuals without experiences of developmental

trauma provides partial support to the hypothesis that developmental trauma is associated with elevated threat responses.

7.4.3. Hypothesis II: These alterations in threat recognition and response are more pronounced in individuals with at risk mental states for psychosis compared to healthy controls

The finding of poorer threat recognition in adult survivors of developmental trauma with at risk mental states for psychosis compared to healthy individuals without experiences of developmental trauma provides partial support to this hypothesis.

The finding of more negative valence responses and elevated arousal responses for neutral faces in adult survivors of developmental trauma with at risk mental states for psychosis compared to healthy individuals without experiences of developmental trauma provides partial support to this hypothesis.

7.4.4. Hypothesis III: Alterations in threat recognition and response mediate the association between developmental trauma and psychotic experiences

The findings of mediating roles of these alterations in threat recognition and responses in the association between the severity of developmental trauma and psychotic experiences is consistent with this hypothesis.

7.4.5. Summary of findings of the study on the relationship between developmental trauma, threat recognition and response and psychotic experiences

These findings suggest that developmental trauma is associated with impaired threat recognition, attributed to a reduced perceptual sensitivity to detect differences between facial expressions of anger from other expressions, more negative subjective valence responses and elevated arousal responses to neutral facial expressions, which mediate the association between developmental trauma and psychosis. Developmental trauma may increase the risk of psychosis through alterations in threat recognition and responses to neutral emotional stimuli.

7.5. Study IV: The relationship between developmental trauma, threat learning and psychotic experiences

7.5.1. Main findings

In this threat learning task, compared to healthy individuals without experiences of developmental trauma, adult survivors of developmental trauma with at risk mental states for psychosis demonstrated a reduced ability to adjust their learning about aversive outcomes, based on whether the action-outcome contingencies of the environment were stable or volatile. Reduced ability to adjust learning rates to

volatility did not mediate the association between developmental trauma and psychotic experiences.

7.5.2. Hypothesis I: Developmental trauma is associated with a reduction in the ability to adapt learning about aversive outcomes based on the higher order structure of the environment

The finding of a reduced ability to adjust learning rates to environmental volatility in adult survivors of developmental trauma with at risk mental states for psychosis compared to healthy individuals without experiences of developmental trauma provides partial support to this hypothesis.

The finding that the severity of developmental trauma was significantly associated with a reduced adjustment of learning rates to volatility provides support to this hypothesis.

7.5.3. Hypothesis II: Alterations in the ability to adapt threat learning are more pronounced in individuals with at risk mental states for psychosis compared to healthy controls

The finding of a reduced ability to adjust learning rates to environmental volatility in adult survivors of developmental trauma with at risk mental states for psychosis compared to healthy individuals without experiences of developmental trauma provides partial support to this hypothesis.

The finding that the association between reduced adjustment of learning rates to volatility and increased severity of psychotic experiences became non-significant

when controlling for the severity of developmental trauma provides evidence that is inconsistent with this hypothesis.

7.5.4. Hypothesis III: Alterations in the ability to adapt threat learning mediate the association between developmental trauma and psychotic experiences

The finding that reduced ability to adjust learning rates to volatility did not mediate the association between developmental trauma and psychotic experiences provides evidence that is inconsistent with this hypothesis. Post hoc power analyses revealed that the study was underpowered to detect a mediating effect of adjustment of learning rates to volatility on the relationship between developmental trauma and psychotic experiences.

7.5.5. Summary of findings of the study on the relationship between developmental trauma, threat learning and psychotic experiences

These findings suggest that developmental trauma is associated with altered threat learning, attributed to a difficulty in adapting threat learning in response to changes in the higher order structure of the environment. These findings also suggest one potential mechanistic pathway between developmental trauma and psychotic experiences via developmental trauma-associated alterations in predictive processing of threat.

7.6. Study V: The effect of developmental trauma on brain structures involved in threat processing and its relation to psychotic experiences in adulthood

7.6.1. Main findings

This study examined the effect of developmental trauma on brain structures involved in threat processing, in a large, well-characterised birth cohort, and their role in the association between developmental trauma and psychotic experiences in adulthood. Developmental trauma was associated with increased psychotic experiences in adulthood and reduced left amygdala volumes, with evidence supporting dose-response relationships. Reductions in both the left amygdala and vmPFC were associated with increased psychotic experiences. Reduced left amygdala volumes mediated 16% of the association between developmental trauma and psychotic experiences.

7.6.2. Hypothesis I: Developmental trauma is associated with reductions in amygdala and vmPFC volumes

The finding that developmental trauma was associated with reduced left amygdala volume in adulthood, with evidence supporting a dose-response effect, whereby increased number of trauma types experienced were associated with greater reductions in left amygdala volumes is consistent with hypothesis I.

The finding that there were no associations between developmental trauma and vmPFC is inconsistent with this hypothesis.

7.6.3. Hypothesis II: Reductions in amygdala and vmPFC volumes are associated with increased odds of psychotic experiences

Consistent with hypothesis II, reduced left and right amygdala and reduced total vmPFC volumes were associated with increased odds of psychotic experiences at age 18.

7.6.4. Hypothesis III: Reduced amygdala and vmPFC volumes mediate the relationship between developmental trauma and psychotic experiences

Consistent with hypothesis III, reduced left amygdala volume significantly mediated 16% of the association between developmental trauma and psychotic experiences. The finding that reduced vmPFC volumes did not mediate the relationship between

developmental trauma and psychotic experiences is inconsistent with this hypothesis.

7.6.5. Summary of findings of the study on the effect of developmental trauma on brain structures involved in threat processing and its relation to psychotic experiences in adulthood

These results using neuroimaging data from a large, well-characterised birth cohort suggest that developmental trauma is associated with reduced left amygdalar volumes, a key neural structure underlying threat processing, which mediates the association between developmental trauma and psychosis. Developmental trauma may therefore increase the risk of psychotic experiences through alterations in brain structures involve in threat processing.

7.7. General conclusions

The studies detailed above indicate that developmental trauma is associated with lasting alterations in the various domains of threat processing. A systematic review on the effects of developmental trauma on threat processing in adulthood (study I) found evidence of (1) attentional bias towards or away from threatening stimuli, (2) enhanced threat recognition, (3) enhanced or blunted responses to threatening stimuli and (4) altered threat learning processes resulting in poor threat discrimination.

In keeping with these findings, behavioural studies II, III and IV demonstrated that developmental trauma was associated with (1) attentional bias towards threatening stimuli, and (2) altered threat learning processes, attributed to a difficulty in adapting threat learning in response to changes in the higher order structure of the environment. In addition, behavioural study III demonstrated that developmental trauma was associated with (3) impaired recognition of threatening emotional stimuli, attributable to reduced perceptual sensitivity to detect differences between facial expressions of anger from other expressions and (4) more negative valence and enhanced arousal responses to neutral emotional stimuli but not threatening emotional stimuli. Neuroimaging study V found that developmental trauma was associated with (5) reduced left amygdalar volumes.

Finally, Studies III and V demonstrated that developmental trauma-associated impairments in threat recognition, hyperresponsiveness towards neutral emotional stimuli and reductions in left amygdalar volumes played a mediating role in the relationship between the severity of developmental trauma and psychotic experiences.

7.7.1. Developmental trauma-associated alterations in threat processing

Multiple lines of evidence from this thesis support the hypothesis that developmental trauma is associated with alterations in threat processing and the neural structures underlying threat processing.

Firstly, findings from study V demonstrated that developmental trauma was associated with reduced left amygdalar volumes, providing direct evidence in support of the hypothesis that developmental trauma results in long-term effects on brain

structure. This finding is consistent with the developmental plasticity and diathesis-stress models of neural susceptibility to the effects of developmental trauma. In line with the developmental plasticity model, experiences of developmental trauma are threatening to one's survival and engage neural circuits underlying threat processing. When trauma occurs in sensitive periods of early brain development, in which neural plasticity is enhanced, traumatic experiences have a more pronounced effect on neural structure and function (Hensch, 2005; McLaughlin, Sheridan and Lambert, 2014). In line with diathesis-stress models, traumatic experiences are inherently stressful and activates the HPA axis that affect developmental processes of vulnerable brain regions, including the amygdala, which contains high concentrations of glucocorticoid receptors. Taken together, these models produce biological plausibility to the findings that developmental trauma is associated with reduced left amygdalar volumes. In addition, alongside evidence that the association between developmental trauma and left amygdalar volumes was temporal, consistent with animal and human studies, and had a dose-response relationship provides support for the hypothesis that developmental trauma causes reduced left amygdala volumes.

Findings from study I-IV also provide evidence in support of developmental trauma-associated alterations in threat processing that may be related to developmental trauma-associated changes in neural structures underlying threat processing. These studies demonstrated that developmental trauma was associated with alterations in every domain of threat processing including (1) attentional bias towards or away from threatening stimuli in study I and II, (2) enhanced or poorer recognition of threat and (3) a complex pattern of threat responses in study I and III, and (4) impaired

learning processes in study I and IV. These findings are in line with findings from study V of reduced left amygdalar volumes associated with developmental trauma, given the central role of the amygdala in threat processing.

These findings also provide indirect evidence that developmental trauma may alter the dopaminergic system. As illustrated in chapter I, the dopaminergic system is thought to play an important role in threat processing (Wise, 2004), including threat learning (De Bundel *et al.*, 2016), and threat recognition (Sprengelmeyer *et al.*, 2003). The involvement of dopamine in threat processes therefore provides an important link between altered threat processing and an altered dopaminergic system.

7.7.2. Developmental trauma-associated alterations in threat processing and their relation to psychosis

These findings provide support to cognitive theories of psychosis that explain how alterations in threat processing may give rise to psychotic experiences. Under these accounts, in conditions of uncertainty or following dopaminergic dysfunction resulting in aberrant assignment of salience to stimuli, cognitive processes that bias interpretations towards threatening interpretations contribute to the development of paranoid delusions and psychotic experiences (Garety and Freeman, 1999; Garety *et al.*, 2001; Freeman *et al.*, 2002).

Firstly, findings from study II this thesis provide empirical evidence for cognitive accounts of the developmental trauma-psychosis relationship. Developmental trauma was associated with poorer recognition of facial expressions of anger, which was attributed to reduced perceptual sensitivity to detect differences between facial

expressions of anger from other expressions. These may arise from developmental trauma-induced perturbations to the dopaminergic system, which is involved in emotion recognition (Sprengelmeyer *et al.*, 2003), or, given similar findings from behavioural studies that demonstrate poorer ability to discriminate between threatening and neutral cues in adult survivors of developmental trauma (Bremner *et al.*, 2005; Thome *et al.*, 2018; Lis *et al.*, 2020) may arise from alterations in the common neural structures underlying these threat processes, such as the amygdala and vmPFC. Reduced perceptual sensitivity to discriminate between facial expressions of anger from other expressions is likely to result in uncertainty and ambiguity surrounding the emotional expressions, and the underlying emotional states of others. Taken together with the finding from study III that developmental trauma is associated with more negative subjective valence responses and enhanced arousal responses to neutral facial expressions provides support to cognitive models of the developmental trauma-psychosis relationship, of resultant threatening interpretations of ambiguous or excessively salient stimuli. Consistent with the view that these threatening interpretations give rise to psychotic experiences, reduced perceptual sensitivity for angry faces, more negative subjective valence responses and enhanced arousal responses to neutral faces were associated with increased severity of psychotic experiences, and played a mediating role in the association between the severity of developmental trauma and psychotic experiences.

Under cognitive and predictive coding models of psychosis, cognitive schema or pre-existing beliefs that view the world and others are threatening, shaped by experiences of developmental trauma may bias interpretations of ambiguous or

excessively salient stimuli to give rise to paranoia and persecutory delusions (Garety and Freeman, 1999; Garety *et al.*, 2001; Freeman *et al.*, 2002). Findings from study IV provide indirect support to the hypothesis that developmental trauma shape cognitive schemas and the degree to which they bias interpretations. The findings of developmental trauma-associated reductions in the ability to adjust learning about threats based on changes in the environment provide indirect evidence of developmental trauma-associated prior beliefs about threat. These strong prior beliefs about threat that are given undue precision on learning processes, may result in learning that is biased by prior beliefs rather than incoming sensory inputs that convey information about the environment.

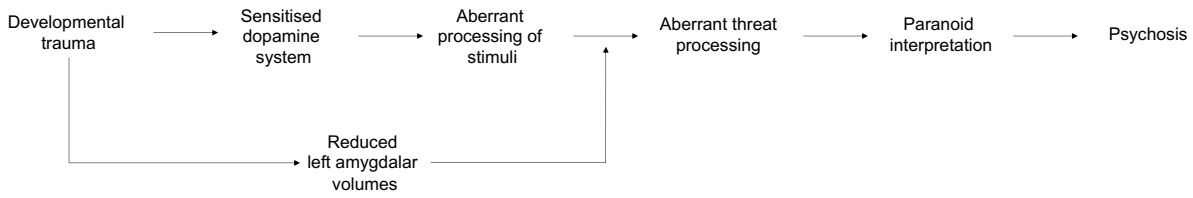
In support of the hypothesis based on cognitive and computational models of psychosis, that developmental trauma-associated alterations in threat processing give rise to psychotic experiences, studies from the thesis demonstrated that impaired threat recognition, attributable to a reduced perceptual sensitivity to detect differences between facial expressions of anger and other expressions, hyperresponsiveness to neutral facial expressions and reduced left amygdalar volumes played a significant mediating role in the association between developmental trauma and psychosis.

7.7.3. An integrated model of trauma-induced, threat-based mechanisms underlying psychosis

Taken together, an integrated, putative model of a developmental trauma-induced threat-based mechanism underlying psychosis can be proposed (**Figure 21**). Firstly, developmental trauma disrupts brain development and sensitises the dopamine system that results in excessive dopamine synthesis and release (Pruessner, Champagne et al., 2004; Taurisano, Blasi et al., 2013). At the same time, developmental trauma results in lasting alterations in brain regions involved in threat processing, such as the left amygdala, as observed in Study V, giving rise to alterations in threat processing as observed in Studies I, II, III and IV. These include altered threat learning, whereby individuals demonstrate a difficulty in adapting threat learning in response to changes in the higher order structure of the environment, and impaired recognition of threatening emotional stimuli, attributable to a reduced perceptual sensitivity to discriminate threatening emotional stimuli from non-threatening emotional stimuli. A sensitised dopamine system resulting in anomalous perceptual processing, in tandem with a sensitised neural threat circuitry, may give rise to aberrant perceptual processing, whereby neutral or ambiguous stimuli are falsely inferred to be threatening, which is consistent with findings from Study III, where developmental trauma was associated with more negative valence and enhanced arousal responses to neutral emotional stimuli. Ultimately, this gives rise to paranoid interpretations of the world, where non-threatening, neutral or ambiguous stimuli are perceived as current threats, giving rise to threatening auditory

hallucinations, in the case of false inferences about incoming auditory stimuli, or persecutory delusions, when the intent of other people are falsely inferred to be malevolent and harmful. These experiences may ultimately give rise to psychosis.

Figure 21. An overall model of trauma-induced, threat-based mechanisms underlying psychosis.



7.8. Strengths and limitations

Findings from this thesis present the first evidence suggesting neurobiological and cognitive mediators underlying the trauma-psychotic experience relationship. Strengths of this thesis include, firstly, the use of large community-based samples that increase statistical power to detect associations between developmental trauma, threat processing and psychotic experiences, and increases the generalisability of these findings. Secondly, given that Study III, as outlined in Chapter IV recruited individuals internationally, from the United Kingdom and the Republic of Korea, provides evidence of a common etiological pathway from developmental trauma to psychosis that is independent of social and cultural differences between individuals. Thirdly, all participants were free of psychiatric medication, removing the confounding effects of medication. Fourth, the use of a large population-based cohort study in Study V, as outlined in Chapter VI enabled the study of prospective measures of developmental trauma that occurred prior to the onset of psychotic experiences, and the measurement of neuroimaging data. Fifth, sensitivity analyses were conducted in this study to minimise the effect of reverse causation and the confounding effect of polygenic risk scores for psychosis were conducted.

7.8.1. Causality

Cross-sectional study designs were used in Studies I-IV as described in Chapters II-V, precluding inferences about causal associations between developmental trauma, alterations in threat processing and psychotic experiences. Reverse causality therefore cannot be excluded in these studies. Study V, as described in Chapter IV,

used data from a prospective population-based cohort, whereby exposure to developmental trauma were measured prospectively, measures of psychotic experiences were measured at age 12 and age 18, and neuroimaging data were collected in adulthood. Sensitivity analyses aimed at minimising the effects of reverse causality between developmental trauma, structural changes in the brain and psychotic experiences were conducted, by repeating analyses in a subsample of individuals who had not experienced psychotic experiences at age 12. These sensitivity analyses minimise the effect of reverse causal associations between psychotic experiences and developmental trauma, whereby individuals with psychotic experiences may be more likely to be exposed to developmental trauma, and the effect of reverse causal associations between psychotic experiences at age 12 and altered brain volumes, whereby psychotic experiences occurring earlier in life are associated with resultant changes in brain volumes. However, two limitations should be acknowledged. Firstly, given that psychotic experiences were measured at age 18 but not at the age at which neuroimaging data were collected, temporal associations between brain volumes and psychotic experiences cannot be inferred, given that individuals may have gone on to develop psychotic experiences after age 18, but prior to neuroimaging data collection. Secondly, given that neuroimaging data were only collected at adulthood, reverse causal associations between brain volumes, developmental trauma and psychotic experiences cannot be ruled out. For instance, it is possible that certain differences in brain volumes may be associated with increased likelihoods of exposure to developmental trauma which in turn subsequently increases the risk of psychotic experiences.

In addition, as described in chapter I, though psychotic experiences in a subclinical population have overlapping etiological and pathophysiological mechanisms, and are informative in investigating the mechanisms underlying the associations between developmental trauma and psychosis, not all individuals with subclinical psychotic experiences go on to develop psychosis (Os *et al.*, 2009). The cross-sectional study design therefore limits inferences about the associations between developmental trauma, altered threat processing and the development of clinical levels of psychosis.

Given these limitations of cross-sectional study designs, longitudinal studies should investigate the temporal relationships between alterations in threat processing that mediate the association between developmental trauma and psychotic experiences, both subclinical and clinical, identified in this thesis.

7.8.2. Selection bias

It is possible that the studies described within this thesis may have been affected by selection bias. Given that in studies II-IV, participants were mainly recruited from social media this may have resulted in selection bias, limiting the generalisability of these findings. Study V is likely to have been affected by, as is the case will all cohort studies, the problem of attrition. Given that lower socioeconomic status and poorer educational attainment are associated with greater attrition (Howe *et al.*, 2013), and that trauma is associated with lower socioeconomic statuses (Assari, 2020), selection biases may have been introduced.

Though psychosis is more common in men than women (Jongsma *et al.*, 2019), more participants were female in studies II-IV, limiting the generalisability of these findings. In addition, given that there are gender differences in developmental

trauma, whereby males report higher rates of emotional or physical neglect and females report higher levels of emotional abuse (Pruessner *et al.*, 2019) and evidence that developmental trauma may affect males and females differentially (Abrams, Milisavljević and Šoškić, 2019) further research should investigate the role of gender in the association between developmental trauma and psychosis.

In studies II-IV, participants with active psychiatric diagnoses were excluded. This may have resulted in the recruitment of participants who had past experiences of developmental trauma who have not gone on to develop psychiatric conditions, suggesting they these recruited individuals may have had a degree of resilience to the effects of developmental trauma, and resilience to the development of psychiatric conditions including psychosis. This limits the generalisability of these findings.

7.8.3. Measurement error

Sources of potential measurement error, including in the assessment of developmental trauma and psychotic experiences should be considered. Developmental trauma was assessed retrospectively via self-reported questionnaires, and hence recall bias may have affected these results. Clinical variables including psychotic experiences and sociodemographic variables were also assessed using validated self-report questionnaires, which could have influenced reporting.

7.8.4. Confounding

In each chapter, demographic variables including age, sex and ethnicity were accounted for. Given that developmental trauma is associated with a range of adverse psychiatric outcomes, including depression and anxiety (McKay *et al.*, 2021), given the collinearity between these measures and severity of psychotic symptoms, these confounders were not accounted for, in order to minimise the likelihood of collider bias and type II errors. Moreover, these psychiatric conditions may also be associated with altered threat processing, particularly conditions that are characterised by an excessive sense of threat such as anxiety, which could not be controlled for in this thesis. Genetic confounding may have occurred, whereby genetic factors increase the risk of psychosis and also the risk of developmental trauma, introducing gene-environment correlations (van Winkel *et al.*, 2013). Genetic confounding and gene-environment correlations cannot be ruled out in this thesis.

7.9. Clinical implications

Though causal inferences about the mechanisms underlying the association between developmental trauma and psychosis cannot be made, by advancing knowledge on the effects of developmental trauma on threat processing, and their relation to psychotic experiences, these findings have important clinical implications in the development of treatments and preventative interventions for psychosis in adult survivors of developmental trauma.

Firstly, altered threat processing may be potential targets for personalised therapies and secondary prevention of psychosis in adult survivors of developmental trauma. Particularly, given findings that impaired recognition of threatening emotional stimuli,

hyperresponsiveness to neutral emotional stimuli and reduced amygdalar volumes particularly mediated the relationship between the severity of developmental trauma and psychotic experiences, they may be initial mechanistic targets. There are already several psychological and pharmacological that target these alterations in threat processing. One example are selective serotonin reuptake inhibitors (SSRIs), on the basis of behavioural and neuroimaging studies that show that SSRI administration increases the recognition of happy facial expressions (Harmer *et al.*, 2003), increases attention to positive socially relevant stimuli (Browning *et al.*, 2007) and reduces amygdalar activation to threat and other aversive stimuli (Del-Ben *et al.*, 2005; Anderson *et al.*, 2007; Murphy *et al.*, 2009). In keeping with cognitive models of psychosis, it can be theorised that SSRI administration, by increased emotional recognition and attention for positive facial expressions, and reducing amygdalar activation to threats may reduce the likelihood of threatening interpretations of ambiguous facial expressions, and prevent the development of psychotic experiences. Future studies should examine whether pharmacological interventions in fact correct or attenuate developmental trauma-associated alterations in threat processing.

An important caveat to the findings of alterations in threat processing identified in this thesis is that they relate to the processing of neutral, uncertain or ambiguous conditions and stimuli rather than alterations in the processing of actually threatening stimuli per se. An implication of this is that further work should not just focus on targeting the neural processing of threatening stimuli, but also the processing of neutral and ambiguous stimuli.

One potential target arising from findings from this thesis are threat beliefs, which bias an individuals' neural computations and interpretation of neutral and ambiguous stimuli towards threatening interpretations. Maladaptive threat beliefs, or cognitive schema, are already the target of cognitive-behavioural therapies (CBT) and cognitive treatments for individuals with positive symptoms of psychosis, such as the Feeling Safe Programme (Freeman *et al.*, 2021), which is theoretically based on cognitive models of persecutory delusions (Freeman, 2016). These have been found to significantly reduce persistent persecutory delusions, with the largest treatment effects seen for patients with persistent delusions (Freeman *et al.*, 2021). Given that maladaptive threat beliefs may exist prior to the development of psychotic disorder, it should be investigated whether these therapies administered to adult survivors of developmental trauma with maladaptive threat beliefs may be targets for secondary prevention of psychosis in survivors.

Given that altered threat processes that were measured via behavioural tasks were associated with developmental trauma and were predictive of increased psychotic risk, they may represent latent markers of vulnerability associated with developmental trauma. The case for using behavioural tasks to measure altered neural processes to identify individuals at risk of psychiatric illness arises from the idea that neurocognitive processes, including threat processing, can be measured relatively easily, reliably and in ecologically valid ways (Browning *et al.*, 2019) and that alterations in neurocognitive processes may arise prior to the onset of psychiatric disorder (McCrory and Viding, 2015). In studies outlined in this thesis, whilst the former was true, given the small effect sizes of the associations between developmental trauma, altered threat processing and psychotic experiences

observed in this thesis, though useful for identifying potential neural processes on a group level and elucidating possible causal mechanisms, these measures of threat processes would be less suitable as markers of psychotic risk on an individual level.

The small effect sizes observed in the mediating role of impaired recognition of threatening emotional stimuli and hyperresponsiveness to neutral emotional stimuli in the association between developmental trauma and psychotic experiences are in line with existing studies, particularly in large population-representative samples investigating associations between biological variables and clinical symptoms (Paulus and Thompson, 2019). This provides strong support for the hypothesis that psychiatric disorders cannot be explained by unicausal or oligocausal theories. In keeping with this, though it is beyond the scope of this thesis, it is not unreasonable to suggest that there are several mechanisms underlying the pathogenesis psychosis in adult survivors of developmental trauma. For instance, given that traumatic environments may also be characterised by deprivation, including emotional and physical neglect (McLaughlin, Sheridan and Lambert, 2014), trauma may alter neural processing of rewards, which may be relevant in the pathogenesis of negative symptoms of psychosis, which include symptoms of anhedonia and blunted affect. As such, small effect sizes of the associations observed in studies in this thesis, rather than representing a small, but generalised effect across the population, could represent effects within a smaller subgroup of individuals in whom developmental trauma-associated alterations in threat processing play a more substantial role in the developmental trauma-psychosis relationship. Future research should be conducted to further elucidate this possibility.

Though not examined directly, and beyond the scope of this thesis, given findings that adult survivors with developmental trauma had elevated levels of depressive and anxious symptomatology, implicates that altered threat processing may also be important in the development and maintenance of general psychopathology. Indeed, altered threat processing is not just implicated in psychosis, but in a variety of psychiatric disorders in terms of phenomenology, neurobiology and aetiology. Phenomenologically, aberrant threat processing is implicated in many psychiatric disorders. For instance, anxiety disorders are characterised by excessive feelings of fear, which are conscious emotional responses to threat (Britton *et al.*, 2011) and post-traumatic disorders are characterised by ongoing excessive threat responses (Gonzalez and Martinez, 2014). Neurobiologically, alterations in the structure and function of brain regions involved in threat processing have also been observed consistently in psychiatric disorders, with alterations of amygdala and insular cortex activation observed in disorders such as post-traumatic stress disorder (PTSD), anxiety and mood disorders (McCrory and Viding, 2015). Finally, altered threat processing has aetiological relevance to other psychiatric conditions, including anxiety, whereby altered threat processing leading to attentional and cognitive biases towards threat-related information give rise to negative thought and images, contributing to the experience of anxiety (Mogg and Bradley, 2016). Taken together, findings from this thesis may be relevant in the pathogenesis of a variety of psychiatric conditions, not just psychosis, which requires further investigation. In accordance with the National Institute of Mental Health's Research Domain Criteria (Cicchetti and Toth, 2009; Insel *et al.*, 2010), investigation of threat-based mechanisms underlying symptom dimensions, rather than diagnostic criteria may be

helpful in elucidating biological, cognitive and computational mechanisms underlying the distressing symptoms characterised by threat that individuals across many diagnostic categories experience. Given that developmental trauma is associated with a range of psychiatric conditions (McKay *et al.*, 2021), and that alterations in threat processing are thought to arise prior to the onset of disorder, this has important implications on the development of effective secondary prevention strategies for a variety of adverse psychiatric outcomes.

7.10. Directions for future study

Several directions for future study have emerged from the findings in this thesis, many of which have been discussed already.

Firstly, of the Bradford Hill criteria for causal associations, evidence is more sparse for a temporal sequence between developmental trauma, altered threat processing and psychotic experiences. Therefore, prospective studies investigating longitudinal associations between developmental trauma, altered threat processing and psychotic experiences are required to make causal inferences. Longitudinal evidence is needed to test temporal associations between developmental trauma, altered threat processing and subsequent psychotic experiences. Given that the cognitive tasks used in studies outlined in this thesis were delivered online, similar tasks assessing various domains of threat processing could be used in larger, longitudinal samples. Given complex interactions between developmental trauma, psychotic experiences and genetics, these studies should be genetically informed, collecting data on polygenic risk scores for psychosis.

This thesis identified that developmental trauma may be associated with complex patterns of threat processing, which represent experience-dependent modification of threat processes in response to the nature of developmental trauma. Studies in the literature have begun to do so, with some studies demonstrating opposing effects of the timing of developmental trauma on amygdalar activation to threat (Zhu *et al.*, 2019). Other factors related to developmental trauma that may modulate its effects on threat processing include the type of trauma, the duration of trauma, the response of primary caregivers to an individual's traumatic experience and an individual's appraisal of experiences of developmental trauma. Future studies should further characterise the effects of developmental trauma on the directionality of alterations in threat processing.

Several aspects of threat processing were not assessed in this thesis. These include autonomic responses to threat and functional magnetic resonance imaging (fMRI) to elucidate alterations in the function of brain regions involved in threat processing. Future research should therefore supplement findings from this thesis with functional magnetic resonance imaging (fMRI) and behavioural studies to directly examine the effect of developmental trauma on brain function and behaviour, and their associations with psychotic experiences. Moreover, functional connectivity studies should examine how developmental trauma affects the neurocircuitry underlying threat processing as a system, and how these relate to psychotic experiences.

This thesis identified potential neurobiological and neurocognitive mediators of the developmental trauma-psychosis relationship suggesting that altered threat processing may be potential targets for personalised therapies and secondary prevention of psychosis in adult survivors of developmental trauma. Future studies

should examine psychological or pharmacological interventions that correct or attenuate developmental trauma-associated alterations in threat processing, and assess whether 'recalibration' of threat processing help prevent the development of psychotic experiences in adult survivors of developmental trauma. Furthermore, future studies should examine whether 'recalibration' of threat processing in individuals with psychosis reduce the severity of psychotic symptoms, or prevent relapse of psychotic symptoms.

Given small effect sizes observed in this study, particularly in the partial mediation of the relationship between developmental trauma and psychosis by impaired recognition of threatening emotional stimuli and hyperresponsiveness to neutral emotional stimuli in the relationship between, future studies should investigate whether there are certain individuals in whom threat-based mechanisms may play a greater role. For instance, future studies may examine specific psychotic experiences, such as threatening auditory hallucinations or persecutory delusions, and elucidate whether developmental trauma-associated alterations in threat processing play a greater role in mediating the relationship between developmental trauma and specific psychotic experiences that are characterised by threat.

Moreover, it was beyond the scope of this thesis to examine the association between developmental trauma and negative psychotic symptoms. Negative symptoms are important given that they contribute to long-term disability and poor functional outcomes in individuals with psychosis, and given that there are no validated treatments for primary negative symptoms in clinical use (Aleman *et al.*, 2017; Galderisi *et al.*, 2018). Given that there is some evidence of an association between altered threat learning, particularly impaired threat generalisation, with negative

symptom severity (Tuominen *et al.*, 2021), and a phenomenological overlap between negative symptoms and avoidance behaviours future studies should elucidate whether threat-based mechanisms are specific to positive dimensions of psychosis or whether they also extend to negative symptoms.

An unanswered question arising from findings from this thesis is on the specificity of the relationship between developmental trauma-associated alterations in threat processing and psychotic experiences, given that developmental trauma is also associated with an increased risk of other psychiatric conditions. In line with the National Institute of Mental Health's Research Domain Criteria (Cicchetti and Toth, 2009; Insel *et al.*, 2010), it is likely that similar threat-based mechanisms may also underlie other psychiatric conditions. If so, future research should determine the factors that contribute specifically to the pathogenesis of psychotic experiences in adult survivors of developmental trauma.

7.11. Final conclusion

This thesis examined threat-based mechanisms underlying the association between developmental trauma and psychotic experiences. This thesis included a varied body of work examining the hypothesis that developmental trauma, through its effects on threat processing and its underlying neural structures, gives rise to psychotic experiences. Data from a systematic review, three cross-sectional studies and a population-based cohort study were used to test this hypothesis using performance on cognitive tasks, computational modelling and structural neuroimaging.

Key findings were that developmental trauma was associated with lasting alterations in various domains of threat processing, including threat learning, attention, recognition and response, as well as in the amygdala, a key neural structure underlying threat processing. Importantly, in line with cognitive and computational accounts of psychosis, there was evidence that impaired threat recognition, attributable to a reduced sensitivity for threatening emotional stimuli, hyperresponsiveness for neutral emotional stimuli, and reductions in left amygdalar volumes played a mediating role in the relationship between the severity of developmental trauma and psychotic experiences.

These findings therefore present the first evidence suggesting neurobiological and cognitive mediators of the trauma-psychotic experience relationship. Though future research using longitudinal data are required to infer whether these developmental trauma-associated alterations in threat processing precede the development of psychosis, these findings demonstrate that altered neural processing of threat may be target mechanisms for personalised therapies and for the secondary prevention of psychosis in adult survivors of developmental trauma.

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Appendix

Appendix Supplementary Information

Chapter II. A systematic review and meta-analysis of the effect of developmental trauma on threat processing in adulthood**:** Full search

1. (child* or young or adolescen* or infant* or juvenile or early-life).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
2. child/ or child development/ or childhood/
3. adolescent/ or adolescent development/
4. infant/ or juvenile/
5. 1 or 2 or 3 or 4
6. (trauma* or abus* or maltreat* or neglect* or bully* or violen* or advers* or stress* or depriv*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. emotional deprivation/ or parental deprivation/ or stress/ or acute stress/ or maternal stress/ or social stress/ or sexual abuse/ or emotional abuse/ or physical abuse/ or abuse/ or neglect/ or bullying/ or family violence/ or

physical violence/ or sexual violence/ or violence/ or exposure to violence/ or emotional stress/ or family stress/ or home stress/ or food deprivation/

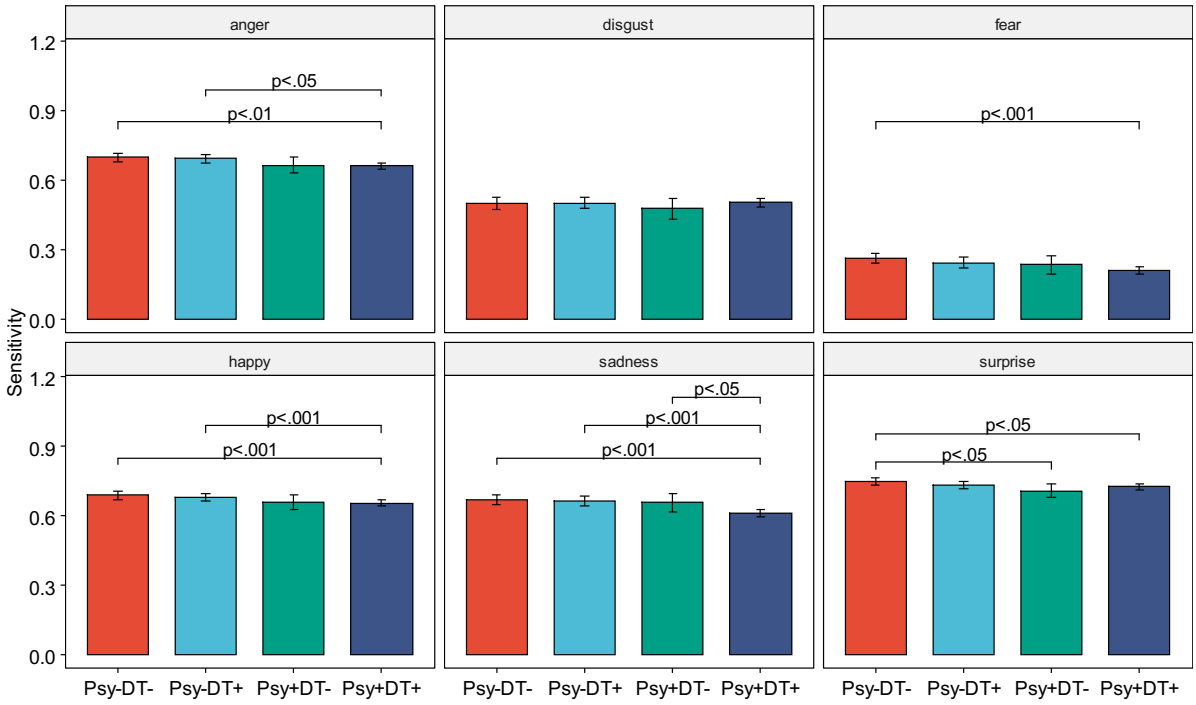
8. 6 or 7
9. 5 and 8
10. child abuse/ or child abuse survivor/ or childhood sexual abuse survivor/ or child sexual abuse/ or child neglect/ or early life stress/
11. 9 or 10
12. (threat processing or threat learning or fear processing or fear learning or fear extinction or fear conditioning or fear generali#ation or fear acquisition or safety learning or threat avoidance or threat hypervigilance or threat detection or emotion* processing or punishment processing).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
13. Adult*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. (anterior cingulate cortex or prefrontal cortex or orbitofrontal cortex or hippocampus or subiculum or thalamus or sensory cortex or amygdala or paraventricular nucleus or locus coeruleus or hypothalamus).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept

word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

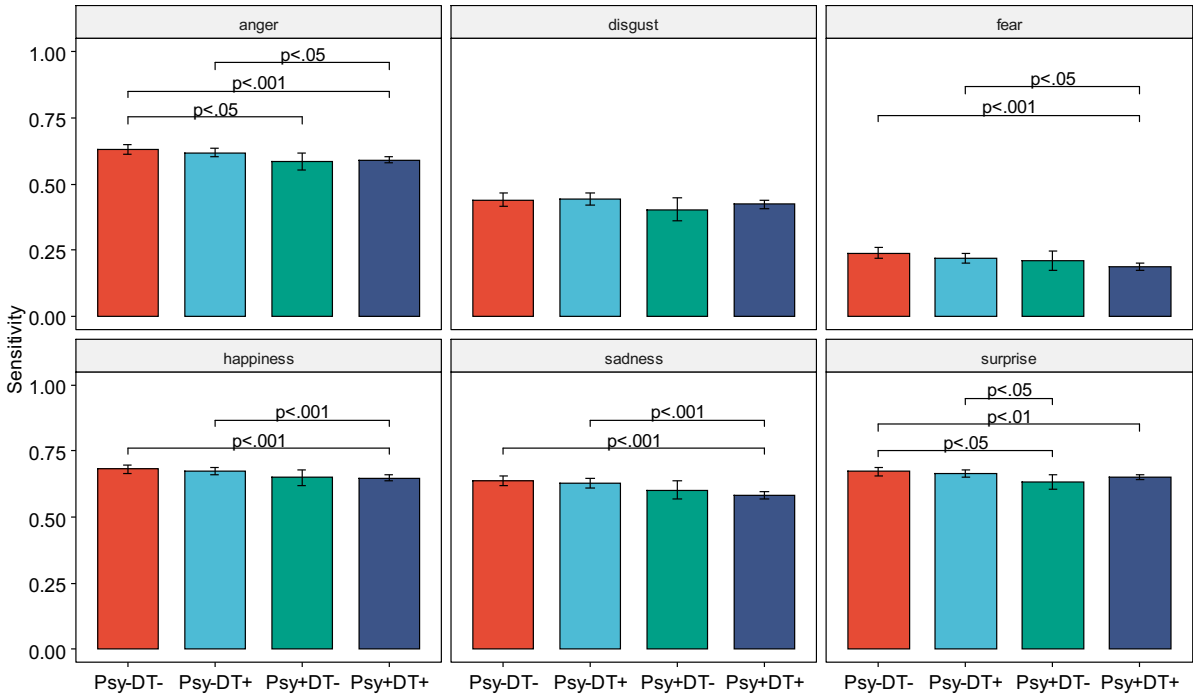
15. 14 and imaging.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
16. 15 or 12
17. 16 and 13
18. 17 and 11

Appendix Figure 1. Group mean (95% CI) for (A) hits, (B) sensitivity and (C) response bias (D) emotional misattributions of facial expression as anger (e.g. neutral as anger) on the emotional recognition task

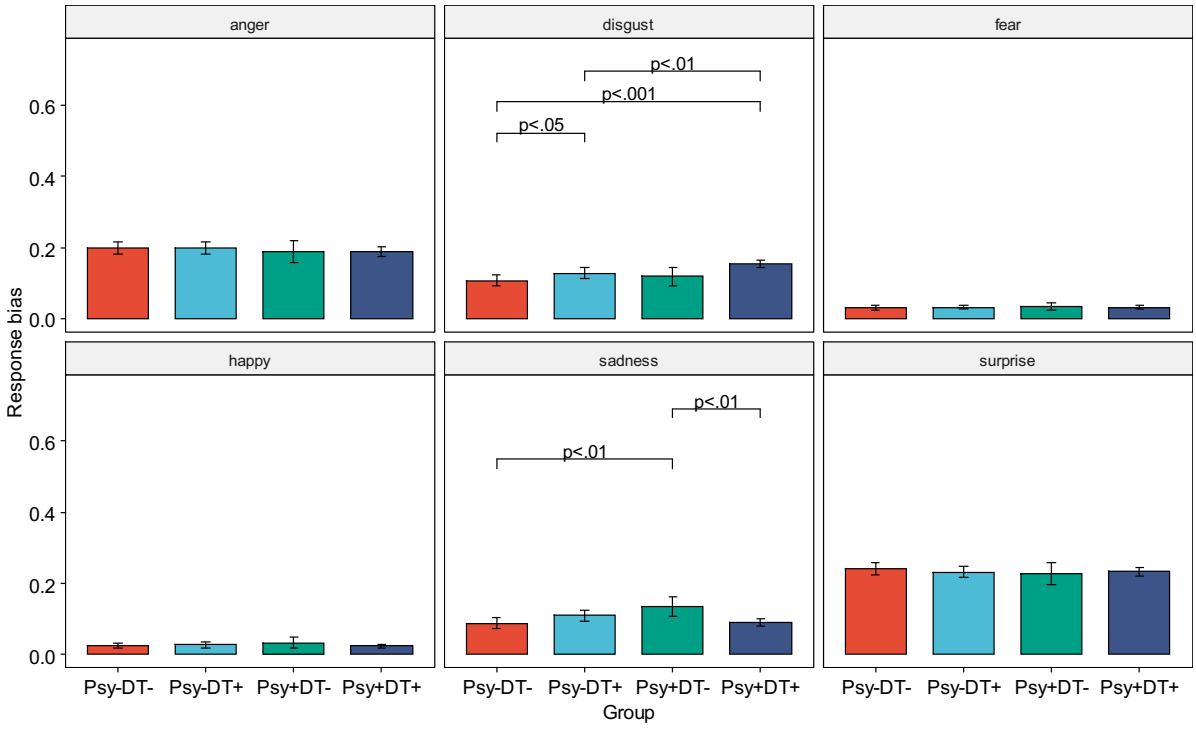
(A)



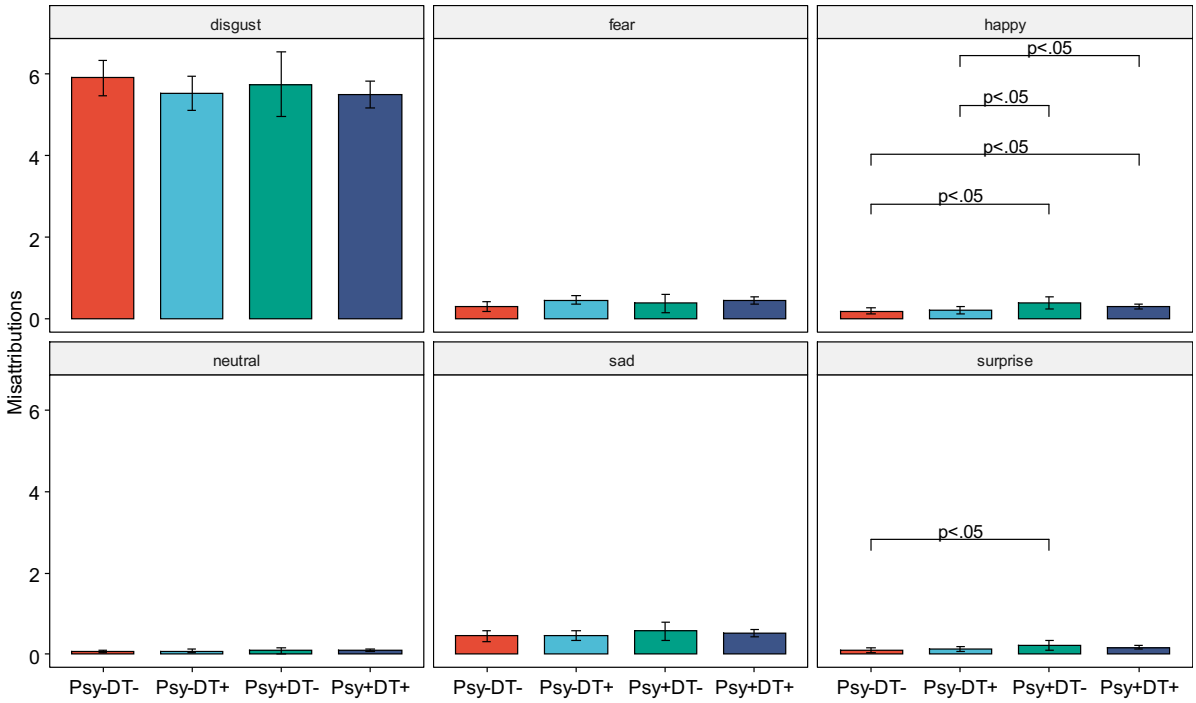
(B)


anger
disgust
fear
happiness
sadness
surprise
Sensitivity
1.00
0.75
0.50
0.25
0.00
p<.05
p<.001
p<.01
Psy-DT-
Psy-DT+
Psy+DT-
Psy+DT+

(C)

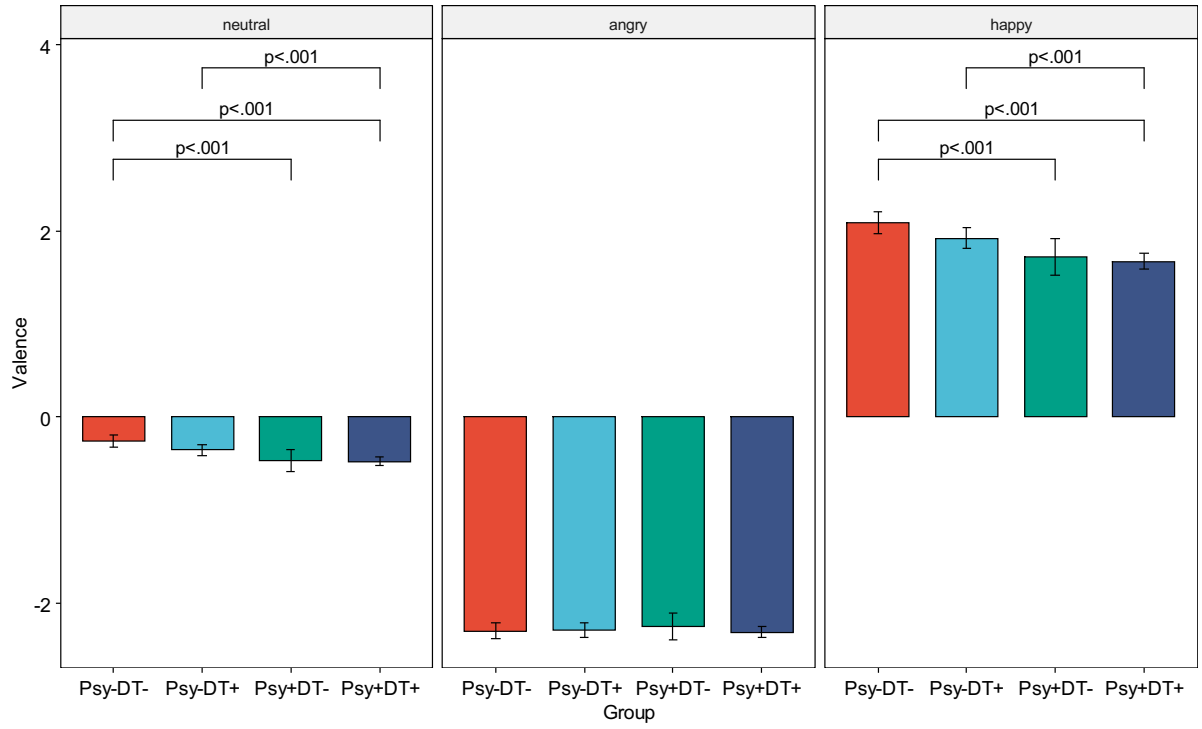

anger
disgust
fear
happy
sadness
surprise
Response bias
0.6
0.4
0.2
0.0
p<.05
p<.001
p<.01
Psy-DT-
Psy-DT+
Psy+DT-
Psy+DT+
Group

(D)

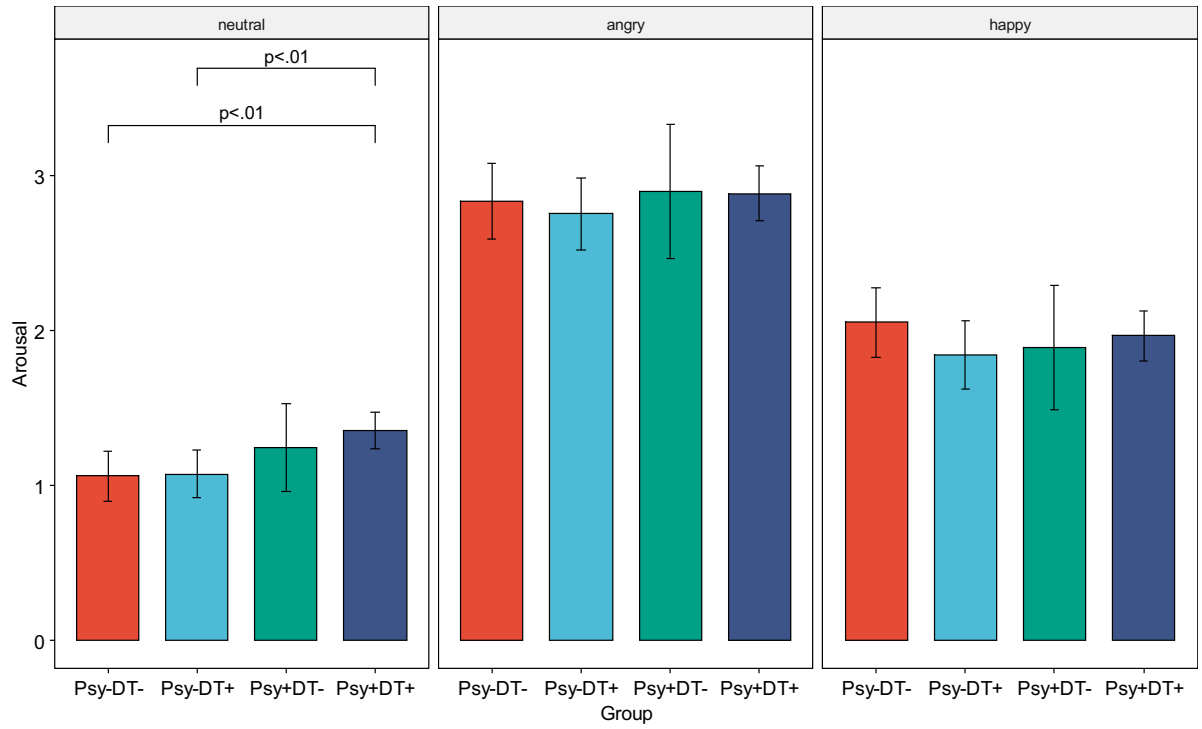


Appendix Figure 2. Group mean (95% CI) for (A) valence and (B) arousal responses on the face ratings task, by facial expression

(A)


neutral
angry
happy
p<.001
p<.001
p<.001
Valence
4
2
0
-2
Psy-DT-
Psy-DT+
Psy+DT-
Psy+DT+
Group

(B)


neutral
angry
happy
p<.01
p<.01
Arousal
3
2
1
0
Psy-DT-
Psy-DT+
Psy+DT-
Psy+DT+
Group