Are Maternal Symptoms of Depression/PTSD and Child Genetic Risk Scores for Depression/PTSD Associated with Childhood Subcortical Brain Volumes?

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The Almighty God.

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Abbreviations

ANOVA	Analysis of Variance
BDI-II	Beck Depression Inventory
CAPS	Clinician-Administered PTSD Scale
DCHS	Drakenstein Child Health Study
EPDS	Edinburgh Postnatal Depression Scale
GSA	Global Screening Array
GWAS	Genome-Wide Association Study
HWE	Hardy-Weinberg Equilibrium
IBD	Identical-by-descent
ICV	Intracranial volume
LD	Linkage disequilibrium
LMIC	Low- and middle-income country
MAF	Minor allele frequency
MDD	Major depressive disorder
MINI	Mini International Neuropsychiatric Interview
mPSS	Modified PTSD Symptom Scale
MRI	Magnetic Resonance Imaging
PC	Principal component
PGC	Psychiatric Genomics Consortium
PRS	Polygenic Risk Score
PsychChip	PsychArray BeadChip
PTSD	Post-traumatic stress disorder
SES	Socio-economic status
SNP	Single nucleotide polymorphism
SRQ-20	Self-Report Questionnaire

Abstract

The antenatal period is a critical window for genetic and environmental factors to influence a child's brain development. While previous research in East Asian and European populations has linked child polygenic risk scores (PRSs) for depression and maternal antenatal symptoms (E) to child caudate, amygdala, and hippocampal volumes, these associations remain unexplored in African populations. Moreover, in children, PRSs for post-traumatic stress disorder (PTSD) have not been investigated in relation to subcortical brain volumes. This study examined: 1) the associations between child genetic risk for depression or PTSD (G), including the interaction with maternal antenatal symptoms of depression or PTSD (G+E or GxE), on child subcortical brain volumes at two years of age; and 2) the genetic loci associated with child subcortical brain volumes.

Using PRS-CSx, PRSs for depression and PTSD were derived from Psychiatric Genomics Consortium (PGC) summary statistics, with the Drakenstein Child Health Study (DCHS; N = 128) as the target dataset. Associations between child genetic risk, maternal antenatal symptoms and child subcortical brain volumes were tested using linear regression. In addition, a genome-wide association study (GWAS; N = 163) was used to investigate genetic associations with child subcortical brain volumes.

For depression, 1) model G was associated with larger total thalamus, left thalamus, and left hippocampus volumes, and smaller right thalamus, bilateral putamen and total pallidum volumes, and 2) model GxE was associated with larger bilateral caudate volume. For PTSD, 1) model G was associated with larger total and right putamen and right pallidum volumes, and with smaller left putamen and left hippocampus volumes, and 2) model G+E was associated with larger total thalamus and right thalamus volumes, and 3) model GxE was associated with larger bilateral caudate volumes. In the GWAS, no SNPs reached genome-wide significance, but three SNPs showed trending associations: rs6052713 (left caudate), rs11771415, and rs7317597 (right hippocampus).

This study provides preliminary evidence of depression and PTSD-related gene-environment interactions associated with larger bilateral caudate volumes, larger total thalamus and right thalamus volumes in a South African population. Findings partially align with prior research

and highlight the need for larger studies to clarify the mechanisms linking maternal mental health, child genetics, and brain development.

1. Introduction

1.1. Background summary

Psychiatric disorders such as major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) place a significant burden on individuals and communities worldwide, with the impact being especially severe in low- and middle-income countries (LMICs) (Yatham et al., 2018). Despite their high global prevalence, there remain research gaps in understanding the mechanisms driving these disorders (Wang et al., 2023).

Both genetic predispositions and environmental factors are known to increase the risk of developing these psychiatric conditions (Schmitt et al., 2014). These may be particularly relevant during the antenatal period (Jagtap et al., 2023) and in subcortical brain regions, given their role in emotional regulation and stress responses (Martin & Ochsner, 2016).

Recent studies have begun to explore how genetic predispositions for MDD and the association with maternal antenatal depression may influence subcortical brain volumes in children (Alex et al., 2023). However, such research is still lacking for PTSD. In addition, understanding how genetic variation contributes to alterations in subcortical brain regions may improve the understanding of the genetic and neurobiological underpinnings of depression and PTSD (Ohi et al., 2020).

This study aims to 1) investigate the association of child genetic risk for depression and PTSD and the association with maternal antenatal symptoms of depression and PTSD on subcortical brain volumes in children at two years of age and 2) to explore genetic loci associated with child subcortical brain volumes in the DCHS.

The introduction begins with a description of depression and PTSD, focusing on their epidemiology and prevalence, followed by an exploration of the genetic predisposition and environmental factors associated with these conditions. The study emphasizes how maternal depression and PTSD influence child health, particularly regarding subcortical brain structures and genetic variation, forming the study's rationale.

1.2.Depression and PTSD symptomology

1.2.1. Depression symptomology

Depression ranges from mild, temporary episodes of sadness to severe, persistent conditions, with clinical levels of depression referred to as MDD (American Psychiatric Association, 2022a). While initial depressive episodes are often triggered by psychosocial stressors – such as relationship issues, work stress, or major life changes – subsequent episodes may arise without any clear external cause, particularly after multiple episodes. Symptoms include sadness, loss of interest, fatigue, and feelings of worthlessness, which disrupt daily functioning. These symptoms may require long-term treatment, typically involving medication, psychotherapy, or both (American Psychiatric Association, 2022a).

1.2.2. PTSD symptomology

PTSD is a trauma- and stress-related psychiatric disorder that can arise after an individual has encountered a traumatic event, a series of events, or prolonged traumatic circumstances (American Psychiatric Association, 2022b). Symptoms include the manifestation of fear or anxiety (fight-or-flight response), which is evident through reliving the traumatic event (memories, flashbacks, or nightmares), avoidance of reminders of the trauma, persistent negative thoughts about oneself, distress upon encountering trauma reminders (unpleasant emotions, feelings, thoughts, conditions, or behaviours), and hyperarousal (paranoia, insomnia, irritability, or inability to concentrate), which continue for more than a month (American Psychiatric Association, 2022b).

1.2.3. Insights into the co-occurrence of depression and PTSD

Both depression and PTSD are complex, often debilitating psychiatric disorders that can co-occur, particularly following exposure to trauma (Flory & Yehuda, 2015). Approximately 52% of individuals with current PTSD also have co-occurring MDD (Rytwinski et al., 2013). While they share overlapping features, such as their influence on biological systems, including cellular, immunological, endocrine, and metabolic functions (Yehuda et al., 2015), important distinctions exist in their underlying mechanisms. Both conditions affect brain circuitry and neurochemistry but differ in the specifics of these alterations (Ploski & Vaidya, 2021). For

example, the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is a common feature in both disorders (Herman et al., 2016). However, the nature of this dysregulation may vary between MDD and PTSD (Negriff et al., 2023). Likewise, changes in neurotransmitter systems, such as serotonin and dopamine, are implicated in both, though the patterns of disruption may differ (Du et al., 2016). Brain regions such as the hippocampus, amygdala, and prefrontal cortex are involved in both disorders, but the extent and nature of their involvement may be context-dependent (Jiang et al., 2024).

1.3. Epidemiology and prevalence of depression and PTSD

1.3.1. Epidemiology of depression

Depression is one of the key contributors to the global burden of disease. Globally, an estimated 3.8% of the population – between 280 to 350 million people – experience depression at some point in their lives (World Health Organization, 2017). Mental disorders account for 4.9% (95% confidence interval; 3.9% – 6.1%) disability-adjusted life years (DALYs), equivalent to losing one year of full health. Specifically, depressive disorders account for the highest proportion of mental health DALYs (37.3%) (Global Burden of Disease Study, 2022). South Africa is among the top five countries in sub-Saharan Africa with the highest lifetime prevalence (4.6%), with other sub-Saharan African countries having similarly high rates: Botswana (4.7%), Lesotho (4.8%), Mozambique (4.1%), Namibia (4.4%) and Zimbabwe (4.0%) (Gbadamosi et al., 2022). These statistics underscore the profound impact of depression on global health, particularly in LMICs, where the burden remains high.

1.3.2. Epidemiology of PTSD

PTSD affects millions of individuals worldwide (estimated 3.9% lifetime prevalence) (Koenen et al., 2017), with higher prevalence rates in LMICs, where trauma exposure is more frequent (Asnaani & Hall-Clark, 2017). As noted earlier, mental health disorders contribute significantly to the global burden of disease, with anxiety- and trauma-related disorders making up 22.9% of mental health DALYs (Global Burden of Disease Study, 2022). A meta-analysis including 58,887 individuals from 10 countries in sub-Saharan Africa found the lifetime prevalence of PTSD to be 22% (Ng et al., 2020). Amongst the countries with the highest one-month prevalence are the Democratic Republic of Congo (50.1%), Ethiopia (37.3%), Liberia (12.6%

– 44.0%), Rwanda (13.6% – 26,1%), South Africa (10.8%), and Uganda (11.8% – 74.3%) (Ng et al., 2020). Notably, there is a significant overlap in genetic load between PTSD and individuals with MDD (Odds ratio: 1.04 (95% confidence interval; 1.01–1.07)) (Mundy et al., 2022).

1.3.3. Prevalence of depression and PTSD in women

Research indicates that globally, women are approximately twice as likely as men to experience depression (Kuehner, 2017). However, this is not universally true, as these statistics vary greatly among different countries and populations. Further, the prevalence in women becomes especially concerning during pregnancy (Salk et al., 2017), where depression can have profound associations with both maternal and child health (Glover, 2020). In a systematic review of 589 studies, encompassing data from 616,708 women across 51 countries, the prevalence of perinatal depression was 24.7% (95% confidence interval, 23.7% – 25.6%). Notably, prevalence varied by country income, with lower-middle-income countries reporting the highest rates at 25.5% (95% confidence interval, 23.8% – 27.1%) from 197 studies involving 212,103 individuals (Mitchell et al., 2023).

Similarly, PTSD is two to three times more prevalent in women (Kessler et al., 2017), with hormonal influences and higher exposure to traumatic events (e.g., sexual violence and domestic abuse) being significant contributing factors (Garza & Jovanovic, 2017). In addition to biological factors, women are more likely than men to experience trauma in their lifetimes, such as sexual assault, domestic violence, and childhood abuse (Olff, 2017). Following this premise, depression and PTSD are prevalent worldwide and common among expectant women (Falah-Hassani et al., 2017), which is a significant public health concern, as maternal mental health has important implications for both the mother and her child (Satyanarayana et al., 2011).

1.4. Familial and genetic risk of depression and PTSD

Depression and PTSD have a heritable component and exhibit familial patterns (Smoller, 2016a). Genome-wide association studies (GWASs) identify common genetic variants associated with these disorders by scanning the entire genome (Uffelmann et al., 2021). These studies have uncovered risk loci linked to depression and PTSD, providing insight into their

biological mechanisms, including pathways related to neurotransmission, stress regulation, and immune function (Flint, 2023).

However, GWASs have primarily focused on European ancestry populations, resulting in diverse populations being underrepresented (Sirugo et al., 2019). Initially, performing GWAS in individuals of European ancestry was a practical choice due to the accessibility of samples, constrained funding, genotyping technologies, and analytical approaches. However, there is widespread recognition of the necessity for greater sample diversity and enhanced analytical techniques (Peterson et al., 2019). Recent advancements in genomic tools enable meaningful comparisons of genetic architecture across ancestries, uncovering population-specific variants, improving disease risk predictions, and promoting health equity (Peterson et al., 2019). In addition, African populations have the highest genetic diversity of any human population (Campbell & Tishkoff, 2008). This diversity can lead to the discovery of novel genetic variants that might not be present in other populations (Didion et al., 2012). Thus, expanding the range of populations studied will not only potentially contribute to health equity, but may also enhance the efficacy of genomic medicine by improving our comprehension of disease origins (Green et al., 2020).

Investigating the cross-generational influences of depression and PTSD is crucial, as these patterns often exacerbate vulnerability within families. The genetic variations that increase the risk of these disorders are passed down from parents to children, and shared environmental exposures, such as trauma or adverse childhood experiences, compound these risks (Kardia et al., 2003). Without intervention, this dynamic can perpetuate cycles of mental health challenges, leaving subsequent generations at increased risk (Institute of Medicine (US) Committee on Assessing Interactions Among Social, 2006). Studying the children of depressed or traumatised mothers is particularly meaningful because maternal mental health has a profound influence on child development (Kinsella & Monk, 2009). This research can provide insights into how maternal health influences child outcomes through various mechanisms, including genetic factors (Armstrong-Carter et al., 2020), epigenetic modifications (Dieckmann & Czamara, 2024), and environmental factors (Groenewold et al., 2022). Furthermore, longitudinal studies facilitate the monitoring of these influences over time, offering crucial insights into the emergence of risks throughout childhood and into later life (Sutter-Dallay et al., 2011).

1.4.1. Heritability and genetic predisposition of depression

As mentioned, twin studies offer valuable insights by showing early familial influences and the genetic heritability of depression (Wium-Andersen et al., 2020). For severe depression, heritability estimates from twin studies are approximately 35% (Pettersson et al., 2019). The largest GWAS of MDD to date has identified 178 genomic risk loci and proposed more than 200 candidate genes associated with depression (Levey et al., 2021). Notably, significant genes involved in the risk for depression include *NR3C1*, which regulates the HPA-axis by controlling cortisol levels. Additionally, *SLC6A4*, coding for a serotonin transporter responsible for serotonin reuptake into a presynaptic neuron, has been implicated in the pathogenesis of depression. Furthermore, *BDNF*, which provides instructions for making brain-derived neurotrophic factors found in the brain and spinal cord, has also been linked to depressive disorders (Park et al., 2019).

1.4.2. Heritability and genetic predisposition of PTSD

Similar to depression, PTSD also has a strong genetic component. The heritability of PTSD varies greatly depending on individual and environmental factors. Family and twin studies have indicated the heritability of PTSD ranges from 24% – 72% (Duncan et al., 2018). Additionally, PTSD heritability estimates based on single nucleotide polymorphisms (SNPs) in females are approximately 29%, almost three times higher than in males (Duncan et al., 2018; Nievergelt et al., 2018). As mentioned previously, findings indicate that psychiatric disorders have a varied polygenic architecture that requires well-powered investigations to identify the significant causal variants (Duncan et al., 2018; Sartor et al., 2011). The genome-wide significant loci implicated numerous associations between PTSD and variants in genes. These include *FKBP5*, which encodes for a co-chaperone that regulates glucocorticoid receptor activity in stress response; *ADCYAP1R1*, which codes for a pituitary adenylate cyclase-activating polypeptide type I receptor that binds pituitary adenylate cyclase-activating peptide; *CRP*, which codes for a protein that binds damaged tissue to nuclear antigens in a calcium-dependent manner (Swart et al., 2021); rs72657988 on chromosome one, intronic region of the *GABBR1* gene, which provides instructions for a subunit of the Gamma-Aminobutyric Acid (GABA) receptor protein on chromosome six; *DFNA5*, which involved in apoptosis pathways, on chromosome seven; an intron of *FOXP2,* which provides instructions for making the protein forkhead box P2 on

chromosome seven; and the intronic region of *FAM120A*, which codes for constitutive coactivator of PPAR-gamma-like protein one on chromosome nine (Maihofer et al., 2022).

1.5.Polygenic Risk Scores (PRS) for psychiatric disorders

While individual genes contribute to the risk of developing depression or PTSD, more recent polygenic methods, such as PRSs are often used. PRSs are a method used to quantify genetic predisposition to complex traits, such as psychiatric disorders, by aggregating the effects of multiple genetic variants (Choi et al., 2020). These scores are calculated for individuals using their individual-level genotype data, which is compared against the results of large-scale GWASs (Lewis & Vassos, 2020). These studies identify SNPs associated with specific disorders, and the effect sizes from GWAS are used as weights in the PRS calculation (Wray et al., 2021). By summing the weighted contributions of multiple SNPs, PRS captures the cumulative, small effects of many genetic factors, offering a more comprehensive view of genetic risk than focusing on individual genes (Choi et al., 2020).

Recent studies indicate that PRS captures some degree of variability in psychiatric disorders, including depression and PTSD (Lambert et al., 2019). Studies have shown that individuals with higher PRS for depression or PTSD may have an elevated likelihood of developing these conditions (Thorp et al., 2023). Currently, PRSs for MDD only explains approximately 3.6% of the variance (Ni et al., 2021) and 4.7% for PTSD (Misganaw et al., 2019). However, there is variability between studies depending on the ancestry, sample size and the differences in statistical methods used (Bigdeli et al., 2022). Given the genetic diversity of populations, the effectiveness of PRS may vary across different ancestral backgrounds (Riefski & Terry, 2023). While ancestry-matched PRS may offer a more accurate prediction for individuals within a specific population, cross-ancestry PRS could potentially extend the applicability of these models across diverse groups (Wang et al., 2023b). Although PRS shows promise, its predictive power remains moderate and currently does not exceed the clinical relevance of traditional familial risk factors (Cross et al., 2022). Thus, while PRSs hold promise for future advancements in predictive ability, they should be considered a complementary tool rather than a standalone clinical measure (Lewis & Vassos, 2020). The onset and severity of these disorders are shaped by a complex interplay of genetic and environmental factors, underscoring the need to study their interactions to better understand individual risks (Marchese & Huckins, 2022).

1.6.Maternal mental health and the interplay of genetics and the environment

Several environmental factors have been strongly linked to the risk of depression and PTSD. Low socio-economic status (SES) correlates with both poor physical health and a higher prevalence of mental health disorders (van der Wal et al., 2020). Chronic stress and trauma, frequently associated with low SES, can lead to long-term mental health issues, including depression and PTSD (Swain et al., 2017). The interaction between an individual's genetic predisposition and their environmental exposures is crucial in shaping their mental health outcomes. Evidence from research highlights that environmental moderators, such as trauma, influence the degree to which genetic susceptibility leads to mental health outcomes (Musci et al., 2019). Maternal mental health, specifically depression and PTSD, is a significant environmental factor with considerable intergenerational implications (Roubinov et al., 2022). The emphasis on maternal mental health as a moderator arises from its potential to either amplify or mitigate the influence of a child's genetic predisposition on developmental outcomes. Maternal symptoms of mental health disorders can affect child development through both direct mechanisms, such as caregiving behaviours, and indirect mechanisms, such as stress during pregnancy influencing foetal development (Kingston et al., 2012). This is especially pertinent when considering the association between PRSs and subcortical brain volumes in children, where maternal mental health may serve as a key environmental factor shaping these associations (Qiu et al., 2017). Thus, understanding the moderating role of maternal mental health offers a more nuanced perspective on how genetic and environmental factors interact to influence child brain development and mental health risk.

1.7.The influence of maternal depression and PTSD on child health

Navigating the challenges faced by expectant mothers experiencing symptoms of depression or PTSD and the potential influence on their children is an intricate and multifaceted concern (Gentile, 2017; Satyanarayana et al., 2011). Maternal antenatal depression or PTSD can negatively affect the physical health of the child, as these conditions may hinder mothers from reaching their full potential (Nolvi et al., 2023). Children born to these mothers may face an elevated risk of psychological difficulties due to early environmental stress and instability (McLaughlin & Sheridan, 2016), the high genetic heritability of these disorders, as well as shared environmental stressors such as low SES (M. K. Kim et al., 2018). Notably, maternal mental health has been linked to changes in the brain development of children, particularly in

the subcortical brain regions, which are key areas involved in emotion regulation and stress response (Jagtap et al., 2023; Manning et al., 2024). Recent studies have started to explore the associations of maternal antenatal symptoms of depression with the subcortical brain volume of children (Alex et al., 2023).

1.8.Subcortical brain regions associated with depression and PTSD

The subcortical brain regions, including the amygdala, hippocampus, thalamus, caudate nucleus, globus pallidum, nucleus accumbens, and putamen, play a crucial role in regulating emotions, motivation, and reward processing (Ji et al., 2019). Variations in the volume of these regions have been associated with several depressive and anxiety disorders, highlighting the importance of understanding their structural differences in relation to mental health (Ohi et al., 2020). Disruptions in brain circuits involving these subcortical structures, which are critical for movement, learning, memory, and motivation, can contribute to abnormal behavior and psychiatric conditions (Hibar et al., 2015). Moreover, the genetic influences on subcortical brain volumes show significant overlap with the genetic risk for psychiatric disorders (Eggins et al., 2018; Ohi et al., 2020).

1.8.1. Subcortical brain regions associated with depression

Depression affects several subcortical brain regions (Zhang et al., 2018). Studies have shown that areas including the amygdala, hippocampus and basal ganglia are of interest when researching symptoms of depression (Drevets et al., 2008; Wu et al., 2024). A meta-analysis study of three-dimensional (3D) brain magnetic resonance imaging (MRI) from the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium's MDD working group, included data from 45 MDD studies from 14 countries across six continents (healthy individuals: N = 9,788 and individuals with MDD: N = 4,372) (Schmaal et al., 2020). This meta-analysis study consistently found hippocampal volumes in patients with MDD to be smaller than in control patients. Interestingly, previous reports on volume abnormalities in other subcortical regions, including the amygdala, have been non-significant or inconsistent (Schmaal et al., 2020).

1.8.2. Subcortical brain regions associated with PTSD

Several meta-analysis studies using MRI have identified subcortical brain regions to be associated with PTSD. The hippocampus, the corpus callosum, the caudate, the putamen, and the amygdala have reportedly had different volumes in patients with PTSD than in control cases (Landré et al., 2010; O'Doherty et al., 2017; Skórzewska et al., 2020). An ENIGMA-PTSD study in 2018 included neuroimaging and clinical data from 1,868 participants (PTSD cases: N = 794; controls: N = 1,074) from 16 cohorts. This study found a significantly smaller hippocampus in patients who had PTSD compared to trauma-exposed control subjects. The study also found smaller amygdala volumes, although the amygdala findings did not survive correction for multiple testing (Logue et al., 2018).

1.8.3. Heritability and genetic architecture of subcortical brain regions

Understanding the genetic influences on subcortical brain regions provides insight into how these areas may be affected by maternal mental health, as well as their potential role in psychiatric disorders. Additionally, research revealed levels of SNP-based heritability for the amygdala (9% – 17%), thalamus (18% – 47%), globus pallidum (17% – 40%), nucleus accumbens (19 – 22%) putamen (26% – 41%), caudate nucleus (26% – 36%) (Satizabal et al., 2019) and hippocampus (21 – 27%) (Elliott et al., 2018).

Family-based heritability for the different subcortical brain regions was higher than SNP-based heritability: amygdala (34% – 59%), thalamus (47% – 54%), globus pallidum (55% – 60%), nucleus accumbens (66%) putamen (71% – 79%), caudate nucleus (71% – 85%) (Satizabal et al., 2019) and hippocampus (78%) (Rentería et al., 2014). A high heritability value (> 50%), for example, what is seen in the globus pallidus, nucleus accumbens, putamen, and caudate nucleus, indicates that genetic factors are playing a larger role in determining the variation in the trait, while the lower heritability values (< 50%) that is seen in the amygdala and thalamus suggests that environmental factors are more important (Cullen et al., 2022).

Furthermore, in the same study by Satizibal *et al.* (2019), a GWAS was conducted (N = 37,741) that identified 48 independent genome-wide SNPs across the subcortical brain volumes. These SNPs were associated with regions involved in pathways related to neurodevelopment, synaptic signalling, axonal transport, apoptosis, inflammation and susceptibility to

neurological disorders (Satizabal et al., 2019). Genetic variations and environmental factors, including age, can influence gene expression (Harris et al., 2017). Specific genes associated with psychiatric disorders may influence brain development and function through changes in gene expression, particularly in brain cells and subcortical tissues (Naumova et al., 2013). Studying gene expression patterns and their timing at different developmental stages can help identify SNPs that influence brain development and mental health outcomes (Abdellaoui et al., 2022).

1.8.4. Genetic overlap between depression, PTSD, and subcortical brain regions

The complex genetic architecture of subcortical brain regions is further implicated in the structural brain abnormalities observed in individuals with depression and PTSD. Both psychiatric disorders and subcortical brain regions are polygenic and heterogeneous in their genetic architecture (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). A recent study investigated the extent of polygenic overlap using the bivariate causal mixture model (MiXeR), using summary statistics from the largest GWAS for depression (N = 674,452) and 14 subcortical volumetric phenotypes (N = 33,224) (Liu et al., 2024). This study revealed that subcortical volumes share between 23.4% and 83.3% of their trait-influencing variants with depression. Another study investigated the concordance of genetic variation that increases the risk for anxiety disorders and PTSD and that influences their underlying neurocircuitry (van der Merwe et al., 2019). This study included GWAS summary statistics of subcortical brain regions (N = 13,171), PTSD (N = 2,424) and anxiety (N = 7,016). The results demonstrated a significant concordance between risk variants for anxiety disorders and those associated with decreased amygdala volume. However, after applying multiple corrections, the concordance between PTSD-related variants and decreased putamen volume was found to be non-significant (van der Merwe et al., 2019).

The emerging nature of research and the variability in findings regarding the genetic overlap between psychiatric disorders and subcortical brain volumes highlight that neither can serve as a reliable proxy for the other, emphasising the need to include both in studies.

1.8.5. The interplay between genetic risk and maternal environment on subcortical brain volumes

In 2020, Acosta *et al.* conducted a study investigating the interaction between a PRS-MDD, based on European ancestry, and antenatal MDD symptoms in infant right amygdala and hippocampal volumes. The study included 105 Finnish mother-infant dyads from the FinnBrain birth cohort. The results showed a significant gene-environment interaction (GxE) association with larger right amygdalar volumes, but this result was non-significant after correction for multiple comparisons. Additional exploratory studies showed a sex-specific GxE association with larger right hippocampus volumes (Acosta, Kantojärvi, Tuulari, et al., 2020). Another study by Acosta *et al.* in 2021, using the same FinnBrain cohort, indicated that smaller brain volume in the left putamen and smaller right caudate volume in children are associated with their sex and maternal depressive symptoms (Acosta et al., 2021). In 2017, a study used the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) birth cohort to investigate the associations of antenatal maternal depressive symptoms on neonatal brain development and the modulation of these by PRS-MDD (Qiu et al., 2017). The study followed 1,163 expectant Southeast Asian mothers from their first trimester until birth, and the mother-child dyads had routine check-ups until the child was three years of age. The results showed that maternal depressive symptoms positively influence amygdala and hippocampus volumes in neonates (Qiu et al., 2017).

It is important to note that, to date, no studies have investigated the association between PRS-PTSD and maternal antenatal symptoms of PTSD on child subcortical brain volumes (Alex et al., 2023).

1.9.Rationale

Depression and PTSD place a significant burden on individuals, especially in LMICs (Meyer et al., 2004). Despite the high global prevalence of depression and PTSD, there remains a gap in research concerning the underlying mechanisms driving these disorders (Charlson et al., 2016). Both genetic predispositions and environmental factors are known to increase the risk of developing these disorders (Marchese & Huckins, 2022; Northoff, 2013). This is reflected in the significant overlap in structural brain abnormalities observed between individuals with these two conditions (Kroes et al., 2011). The antenatal period represents a heightened

vulnerability (Kanai & Rees, 2011), during which the interplay between genetic risk and environmental stressors can affect the child's subcortical brain volumes (Martin & Ochsner, 2016).

To date, only seven studies have investigated the interaction between the mother's symptoms of depression and PTSD and the outcome of the child's subcortical brain volume, with many null findings (Alex et al., 2023). Of the seven studies, three focused on individuals of European ancestry, three on Asian ancestry, and only one on Mixed ancestry, resulting in a significant underrepresentation of children from other ancestral backgrounds. Among these, only three studies have considered the genetic risk for MDD, while none have accounted for genetic risk related to PTSD (Alex et al., 2023). Acosta *et al.* (2020) found that maternal antenatal symptoms of depression were linked to smaller left putamen and right caudate volumes(Acosta, Kantojärvi, Tuulari, et al., 2020). Additionally, in a subsequent study using the same FinnBrain cohort, Acosta *et al.* (2020) found that PRS-MDD was linked to smaller right amygdalar volumes in infants, though this association became non-significant after correction for multiple testing (Acosta H et al., 2020). Finally, Qiu *et al.* (2017) found that maternal antenatal symptoms of depression interacted with a PRS-MDD to influence the right hippocampus and amygdala; however, direction was not investigated (Qiu et al., 2017). Furthermore, the limited and often contradictory findings may stem from variations in ancestry, geographical locations, socioeconomic status, sample sizes, the age of the children, and sex of the cohorts (Landré et al., 2010).

In conclusion, little is known about child genetic risk for depression and PTSD and its association with maternal antenatal symptoms of depression and PTSD on subcortical brain volumes in African and Mixed ancestry populations. This study aims to utilise a South African birth cohort to investigate: 1) the associations of child genetic risk for depression and PTSD (G), including the interaction with maternal antenatal symptoms of depression and PTSD (G+E or GxE), on child subcortical brain volumes at two years of age; and 2) explore genetic loci associated with child subcortical brain volumes.

2. Aims and Objectives

This research study has two aims:

1. To explore the associations of children's genetic risk for depression and PTSD and the association with maternal antenatal symptoms of depression and PTSD on child subcortical brain volumes at two years of age.
2. To explore genetic loci associated with child subcortical brain volumes.

To achieve the aims, the following objectives have been identified:

1. To explore the associations of children's genetic risk for depression and PTSD, and the association with maternal antenatal symptoms of depression and PTSD on child subcortical brain volumes at two years of age.
    1.1. Determine the suitability of ancestry-matched or cross-ancestry discovery cohorts for PRS generation in this population.
    1.2. Estimate children's PRS for depression and PTSD using the best algorithm as determined in 1.1.
    1.3. Assess associations between children's PRS and subcortical brain volumes.
    1.4. Assess the combined associations of the children's PRS and maternal antenatal symptoms of depression and PTSD with subcortical brain volumes.

2. To explore genetic loci associated with child subcortical brain volumes
    2.1. Examine genome-wide associations with child subcortical brain volumes at two years of age.
    2.2. Assess whether identified genetic associations are consistent with those reported in a European cohort (Satizabal et al., 2019).

3. Methods

3.1. Description of the Drakenstein Child Health Study (DCHS) cohort

3.1.1. Ethical approval

The DCHS study obtained ethical approval from the Faculty of Health Sciences Research Ethics Committee, University of Cape Town (401/2009) and the Provincial Research Committee to perform recruitment. The follow-up study investigating the association between child subcortical brain regions, genetic risk for depression and PTSD and the association with maternal antenatal symptoms of depression and PTSD, received ethics approval in 2023 (483/2023) (Appendix 1) and was renewed in 2024 (Appendix 2).

3.1.2. DCHS population and broader Drakenstein community

The DCHS enrolled 1,225 expectant women in the peri-urban Drakenstein district, Western Cape, South Africa (Figure 1) between March 2012 and March 2015 (Zar et al., 2015). The women attended routine antenatal check-ups at either the Mbekweni clinic or the TC Newman clinic. These two clinics are located in racially, culturally, and linguistically diverse neighbourhoods and serve distinct populations of the broader Drakenstein community (Zar et al., 2015). The Mbekweni clinic serves a predominantly Xhosa-speaking Black African population (hereafter referred to as African ancestry), whilst TC Newman serves a predominantly Afrikaans-speaking mixed ancestry population (Zar et al., 2015). These communities are located in a low socioeconomic area characterised by a high prevalence of psychological risk factors, including low education levels, high rates of single parenthood, and large household sizes (Stein et al., 2015). Such challenges are commonly seen in peri-urban regions of South Africa (Mabizela & Van Wyk, 2022).

3.1.3. Eligibility of and participation in the DCHS

To be eligible for the study, the women had to be at least 18 years old, visit one of the two aforementioned clinics, plan to reside in the district for at least a year after the child's birth, and provide written informed consent (Stein et al., 2015). The study's purpose, along with the

potential benefits and risks, were explained to participants in their preferred language before obtaining consent (Donald et al., 2018). In total, 1,225 pregnant women met the inclusion criteria and were enrolled (Zar et al., 2019).

Figure 1: Map of the Western Cape Province with the Drakenstein district highlighted

Figure 1 shows a map of the Western Cape Province in South Africa, reflecting the municipal boundaries as of the 2011 elections, with the Drakenstein Local Municipality indicated in red. The district covers 1,537 km², including the Gouda, Paarl, Saron, and Wellington areas. Image retrieved from Wikimedia Commons.

3.2.Characterisation of socioeconomic status, substance use and child physical health

A questionnaire incorporating selected items from the South African Stress and Health (SASH) study was used to collect data on sociodemographic variables such as household income, employment status, and education (Myer et al., 2008; Stein et al., 2015). The questionnaire was administered by trained study staff in an interview format antenatally at 28 – 32 weeks of gestation and during annual study visits. In addition to sociodemographic data, maternal substance use, including alcohol and tobacco use, was assessed using the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) (Stein et al., 2015; WHO ASSIST Working Group, 2002; Zar et al., 2015).

Of the initial DCHS study cohort consisting of a total of 1,225 enrolled pregnant mothers, 1,137 mothers gave birth to 1,143 live infants, including six sets of twins, over three years. Upon

birth, professional personnel documented the delivery manner, the baby's weight, length, and head circumference. Additionally, the baby's in-utero exposure to HIV, if applicable, was documented. One of three methods was used to determine gestational age: either self-reported dates of the last known menstrual period, maternal fundal height at enrolment, or early ultrasound measures taken during the second trimester (Zar et al., 2015).

3.3. Measurements of maternal symptoms of depression and PTSD

To comprehensively evaluate maternal mental health, the women were asked to complete a series of mental health measures, some of which were administered by clinicians. Of the 1,225 women initially enrolled, 1,189 completed the mental health measures. Since the focus is on symptoms of depression or PTSD during pregnancy, tools that serve as either diagnostic assessments or measures of symptom severity were utilised in this study. Maternal symptoms of depression were assessed using the Beck Depression Inventory (BDI-II) (Beck et al., 1961), the Edinburgh Postnatal Depression Scale (EPDS) (Cox et al., 1987), the Self Reporting Questionnaire (SRQ-20) (Beusenberg et al., 1994), and the Mini International Neuropsychiatric Interview (MINI) (Lecrubier et al., 1997). Maternal symptoms of PTSD were evaluated using the modified PTSD Symptom Scale (mPSS) (Falsetti et al., 1993), the Clinician-Administered PTSD Scale for DSM-V (CAPS) (Blake et al., 1995), and the MINI (Lecrubier et al., 1997). The trauma that led to the PTSD symptoms could have occurred any time before the assessment. The measures were completed between 28 and 32 weeks of gestation and at either six months, 18 months, or two years after birth (Table 1). However, not all women completed every available measure across all time points; thus, the congruency between the measures was investigated. All time points were included in the calculation of PRS; however, only antenatal measures were incorporated into the linear regression models, as the antenatal period plays a crucial role in shaping child neurodevelopment. For this study, case status was determined if a mother was classified as a case using a diagnostic tool or met the threshold symptom criteria on at least two of the relevant mental health measures, described in more detail below. This approach was adopted to ensure the inclusion of individuals with sub-diagnostic threshold symptoms, in line with the conceptualisation of mental disorders existing on a broad spectrum, ranging from healthy to pathological. Additionally, it may more accurately capture individuals who may have a genetic predisposition to either disorder.

It is important to note that many of the measures, such as the BDI-II, EPDS, and SRQ-20, assess similar constructs related to both depression and PTSD symptoms (Beusenberg et al., 1994; Hubley, 2022; Lecrubier et al., 1997; Levis et al., 2020). Although each tool may have a different format or scoring system, they often target overlapping symptom domains, such as mood disturbances, anxiety, and cognitive patterns associated with depression and PTSD. This common focus naturally leads to congruence in identifying cases and controls across these measures.

Table 1: Mental health measures completed at different time points during the study

Measure	**Antenatally (28-32 weeks)**	**Six months after birth**	**Eighteen months after birth**	**Two years after birth**
BDI-II	✓	✗	✗	✓
EPDS	✓	✗	✗	✗
SRQ-20	✓	✗	✗	✓
MINI	✓	✓	✓	✓
mPSS	✓	✗	✗	✗
CAPS	✓	✓	✓	✓

Table 1 shows the time points at which various psychological measures – used for measuring symptoms of depression and PTSD – were completed. A check mark (✓) indicates that the measure was completed at the indicated time point, while a cross (✗) signifies that it was not completed. BDI-II: Beck Depression Inventory; EDPS: Edinburgh Postnatal Depression Scale; SRQ-20: Self-Report Questionnaire; MINI: Mini International Neuropsychiatric Interview; mPSS: modified PTSD Symptom Scale; CAPS: Clinician-Administered PTSD Scale for DSM-V.

3.3.1. Measures used to assess maternal symptoms of depression

Four tools that consider either symptom severity or diagnostic criteria were used to assess maternal symptoms of depression. The BDI-II is a self-report questionnaire designed to assess the presence and severity of depressive symptoms (Beck et al., 1961, 1988). It consists of 21 items, each measured on a four-point scale ranging from zero (no symptoms) to three (severe symptoms). While the BDI-II is not specifically designed for pregnancy, its flexibility in administration enables a comprehensive assessment of depressive symptoms both during pregnancy and at subsequent time points. The BDI-II items probe various symptoms of

depression, including sadness, loss of interest, and feelings of guilt. For instance, participants might rate their feelings of sadness from "I do not feel sad" to "I am so sad or unhappy that I can't stand it". The overall score, which can range from 0 to 63, is calculated by summing the highest scores from each of the 21 questions. Scores between 0 – 13 indicate little depression, 14 – 19 indicate mild depression, 20 – 28 indicate moderate depression, and 29 – 63 indicate severe depression. (Beck et al., 1988). The BDI-II has demonstrated strong validity and internal consistency when applied to both psychiatric and non-psychiatric groups (García-Batista et al., 2018). In the DCHS, a cut-off score of 20 or more was implemented to identify participants who had moderate to severe depression (Stein et al., 2015).

The EPDS is a ten-item self-report questionnaire specifically designed for screening postnatal depression (Cox et al., 1987). Each question is scored between zero and three, allowing individuals to select responses that best reflect their feelings. The EPDS addresses key emotional states related to postnatal depression. For example, one item asks, “I have been able to laugh and see the fun side of things,” with responses ranging from “as much as I always could” to “not at all” (Cox et al., 1987). Although this questionnaire was designed for screening postnatal depression, it has been validated for use in pregnant mothers, making it applicable to the mothers in the cohort (Murray & Cox, 1990). The EPDS demonstrates strong validity as a screening tool throughout the perinatal period (Levis et al., 2020). In the DCHS, a threshold score of 13 has been used to indicate probable depression, in line with the scale's initial development and South African guidelines (Hartley et al., 2011; Murray & Cox, 1990).

The SRQ-20 is a 20-item self-report questionnaire designed to measure psychological distress, including depression and anxiety (Beusenberg et al., 1994). Responses are recorded in a yes-or-no format, with symptoms scored as either zero (no symptoms) or one (symptoms are present). The items reflect a range of common symptoms experienced in mental disorders, such as fatigue, anxiety, and sadness (Beusenberg et al., 1994). This tool has demonstrated strong reliability and validity and has been extensively used in South African settings (Rumble et al., 1996), making it fitting for the cohort. For the DCHS, a threshold score of eight or above was chosen, which indicates that a woman is at high risk for depression (Stein et al., 2015).

The MINI is an abridged version of the Structured Clinical Interview for DSM-IV (Lecrubier et al., 1997). The MINI is a clinician-administered diagnostic interview to assess a wide range of major psychiatric disorders, including depression and PTSD. Although it covers various

psychiatric conditions, in this study, the MINI was used to measure symptoms of both depression and PTSD. Mothers were asked yes-or-no questions, and these responses were subsequently categorised into quantitative levels: none, mild, moderate, very severe, and extreme, based on the frequency and severity of reported symptoms (Lecrubier et al., 1997; Sheehan et al., 1998). The MINI has shown high levels of concordance with longer diagnostic interviews, such as the Structured Clinical Interview for DSM Disorders (SCID), which is considered a gold standard (Sheehan et al., 1997). In the DCHS cohort, trained staff administered the MINI to mothers, assessing symptoms of depression (Bromet et al., 2011) and PTSD according to DSM-IV criteria (Friedman et al., 2011).

3.3.2. Measures used to assess maternal symptoms of PTSD

Three interviews that consider either diagnostic or measures of symptom severity were used to assess maternal symptoms of PTSD (the MINI is explained above). Each of these measures offers valuable insights into symptoms of PTSD, allowing for a comprehensive evaluation of maternal mental health.

The mPSS is a 17-item clinician-administered interview designed to assess the presence and severity of PTSD symptoms based on DSM-IV criteria (Falsetti et al., 1993). The mPSS assesses three key symptom clusters: re-experiencing, avoidance, and increased arousal. Each item is rated on a frequency scale from zero (no symptoms) to three (symptoms occurring frequently). Since the mPSS does not explicitly ask whether an individual was exposed to trauma, an independent “exposure to trauma” question was asked. To suggest a PTSD diagnosis, specific scoring criteria are employed: a minimum of one symptom from re-experiencing, at least three symptoms from avoidance/emotional numbing, two symptoms from increased arousal, and a duration of symptoms lasting at least one month (Falsetti et al., 1993) and exposure to trauma as per the additional question. The validity of the mPSS has been supported by its consistent use in clinical and research settings, demonstrating high reliability in measuring PTSD symptoms across different populations (Santiago Papini, 2014).

The CAPS-IV is a clinician-administered interview consisting of 30 questions aimed at establishing current or lifetime diagnoses and severity of PTSD based on 20 symptoms (Blake et al., 1995). The CAPS items evaluate a range of PTSD symptoms, such as re-experiencing trauma, emotional numbing, and hyperarousal. For example, questions may ask how often the

mother experiences flashbacks or nightmares related to the trauma. The scoring is based on a four-point severity rating, ranging from zero (absent) to four (incapacitating). The total symptom severity score is obtained by summing the severity scores for all 20 symptoms, with a cutoff score above 40 indicating moderate to severe symptomology. (Blake et al., 1995). The CAPS has been known to have excellent psychometric properties with high reliability (Weathers et al., 2001).

3.4.Drakenstein Child Health Study (DCHS) neuroimaging sub-study

Mother-child pairs were invited to participate in the neuroimaging sub-study when the child turned two years old (Wedderburn et al., 2020). To be included, participants had to meet the following criteria: remained in the research region, were actively participating in the cohort, had no medical comorbidity (specifically: genetic syndrome, neurological illness, or congenital deformity), gestation at birth was more than 36 weeks, had an Apgar score of more than seven at five minutes; were not admitted to the neonatal intensive care unit; no illegal drug use by the mother during pregnancy; and no HIV infection in the child (Wedderburn et al., 2020). A total of 239 met the inclusion criteria and were enrolled in the neuroimaging sub-study.

3.4.1. Structural MRI data acquisition and preprocessing

Structural MRI with T1-weighting was used to examine the subcortical brain volumes in the children at two years old (N = 239) (Donald et al., 2018). The scans were performed on a Siemens Tesla 3 Magnetom Allegra MRI scanner at the Cape University Brain Imaging Centre (CUBIC) in Cape Town (Wedderburn et al., 2020). Sagittal 3D T1-weighted images in two-year-old children were acquired with scan parameters: TR = 3200 ms; TE = 409 ms; FOV = 230 × 230 mm; 160 slices; voxel size = 0.9 x 0.9 x 1.0 mm. The sequence took three minutes and seven seconds to acquire. The brain images were then processed using FreeSurfer version 6 [http://surfer.nmr.mgh.harvard.edu/] on the local supercomputing cluster at the Centre for High Performance Computing (CHPC, Cape Town) [https://www.chpc.ac.za] (Wedderburn et al., 2020). The mean and standard deviation for each brain region is shown in Appendix 3.

3.4.2. Quality control of subcortical volumes

Of the 239 children selected for neuroimaging, 49 were excluded due to unsuccessful scans (e.g., failure to sleep during the procedure), and 23 were included in the pilot study (Pellowski et al., 2023; Wedderburn et al., 2020). Further, 21 children were excluded due to the following: two failed data processing, one had a history of illicit substance use, two had abnormal clinical reports, and 16 were identified as outliers according to the ENIGMA protocol if segmentation was incorrect. This was done through visual quality control procedures (Pellowski et al., 2023; Wedderburn et al., 2020). As reported by Pellowski *et al.* (2023) (Figure 2), the final neuroimaging sub-study sample size was N = 147. Since these exclusions were conducted in prior research, the details are described in the methods section rather than the results.

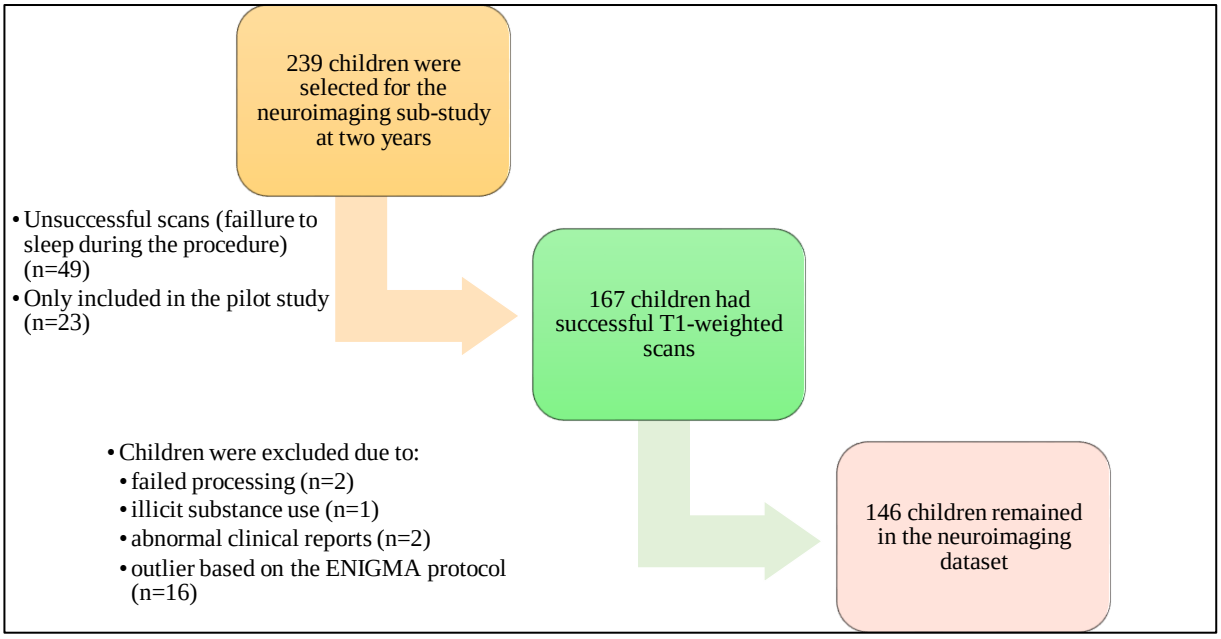


Figure 2: DCHS neuroimaging sub-study consort diagram, adapted from Pellowski et al. (2023)

Figure 2 shows the flow of the study design and analytic samples in the present sub-study. ENIGMA: Enhancing Neuro Imaging Genetics Through Meta-analysis.

3.5.Genotyping

3.5.1. DNA extraction and genotyping in the DCHS cohort

For the DCHS cohort, DNA was isolated from blood samples collected at the time of delivery from the children and either antenatally or postnatally from the mothers. Genotyping was performed using either the Illumina Infinium PsychArray BeadChip (PsychChip) or the Illumina Infinium Global Screening Array (GSA) at the University of British Columbia (UBC) or Life and Brain Institute (LB) (Table 2). Notably, out of the 239 children initially selected for the neuroimaging sub-study described above, 167 had successful T1-weighted scans. These children were included for the genetics analysis but excluded four children who did not have genetic data available. This resulted in a final sample size of N = 163 children for the genetic analysis.

Table 2: Description of genotyping performed for the DCHS cohort

Genotyping microarray	**Full maternal cohort N = 1,189**	**Neuroimaging sub-study N = 163**	**Institution**
PsychChip	678	35	UBC
GSA	511	11	UBC
GSA	432	117	LB

Table 2 summarises the genotyping platforms used, along with the number of participants in both the full maternal cohort and the neuroimaging sub-study, specifying the institutions where the genotyping was performed. PsychChip: PsychArray BeadChip; GSA: Global Screening Array; UBC: The University of British Columbia; LB: Life and Brain Institute.

3.5.2. Pre-imputation quality control

Pre-GWAS quality control procedures were conducted on the mothers (N = 1,189) and children (N = 163) using PLINK version 1.90 [https://zzz.bwh.harvard.edu/plink/]. Quality control methods are required to lessen the burden of erroneous positive and negative correlations, which are unrelated to the trait of interest (Laurie et al., 2010). Studies of complex traits have found that associations with small-effect variants, especially in large datasets, are vulnerable to errors introduced during the study (Turner et al., 2011). Various factors, including processing and collecting samples independently (batch effects), especially when comparing cases and

controls, variations in DNA quality among samples, errors in genotyping, incorrectly labelled samples, and variations in ancestry and hidden relatedness among samples, can introduce bias (Laurie et al., 2010).

Quality control measures, including minor allele frequency (MAF), missingness rate, Hardy-Weinberg Equilibrium (HWE) in control samples, a sex check, and relatedness, were applied (Figure 3), as per Turner *et al.*, 2011. Variants with a MAF of less than 1% were excluded, as rare variants often lack statistical power, which can result in unreliable findings (Skol et al., 2006). Variants with a missingness rate greater than 1% were also filtered out to prevent bias from incomplete genotyping, which could distort results, particularly if missingness differs between cases and controls (Turner et al., 2011). Additionally, variants that deviated from HWE in the control group ($p < 1x10^{-8}$) were excluded, as HWE deviations may indicate genotyping errors, poor DNA quality, or selective pressures that could confound the results (Ryckman & Williams, 2008; Turner et al., 2011). A sex check was used to identify discrepancies between reported and genotypic sex, and samples with sex discrepancies were removed (Anderson et al., 2010). Lastly, duplicate and related samples were identified and excluded if their Identical-by-descent (IBD) value was greater than 0.125 to prevent confounding due to familial relationships (Weale, 2010).

Principal components (PCs) were calculated using principal component analysis (PCA) in PLINK version 1.90 to correct for population stratification and relatedness (Zhang et al., 2008). The PCs are linear combinations of the original variables, designed to capture the maximum variance in the data within a reduced-dimensional space (Elhaik, 2022). This helps account for population structure (Maćkiewicz & Ratajczak, 1993). While PCs often reflect differences due to ancestry, they also capture cryptic genetic differences between individuals (Price et al., 2006) and are commonly used with PRS to improve model fit (Chen et al., 2015).

3.5.3. Imputation

Genotype imputation is a powerful statistical technique that uses data from reference genomes to anticipate genotypes in loci that have not been genotyped. This is essential for fine mapping of loci associated with a phenotype of interest, increasing the power of GWAS due to the linkage disequilibrium (LD) between SNPs (Li *et al.*, 2009). This technique relies on the concept of LD, where variants close to each other in the genome tend to be inherited together,

forming haplotypes (Slatkin, 2008). These haplotypes can then be predicted based on their frequencies in the population. Haplotype phasing groups SNPs by parental inheritance, improving imputation accuracy by identifying which variants co-localize on the same chromosome (Browning & Browning, 2011). Computational algorithms have been developed to estimate the most likely haplotype combinations based on the frequencies observed in a reference genome. These algorithms, such as those used by the Michigan Imputation Server, enhance the accuracy of imputation by leveraging large and diverse reference panels, which provide better predictions across various populations (Hancock et al., 2012). The reference panels that are currently available for African samples are limited, and they do not include the African population that is the focus of this study. Therefore, SNPs were imputed on the 1,000 Genomes Phase III reference panel (2,504 samples from 26 populations) (Auton et al., 2015) using the Michigan Imputation Server. Since this reference panel only comprises genotyping data for autosomal chromosomes, chromosome 23 was excluded from the analysis (Auton et al., 2015).

3.5.4. Post-imputation quality control

Only SNPs imputed with a r^2 value of at least 0.5 were kept after imputation. The r^2 value serves as a post-imputation quality metric, indicating the correlation between the observed and expected allele frequencies of the imputed SNPs (Liu et al., 2012). Additionally, individuals who did not have accompanying subcortical brain volume data were excluded. Finally, as with the pre-imputation quality control steps previously described, SNPs were excluded if they had an MAF of less than 1% and were not present in at least 95% of the samples (Turner et al., 2011).

3.6.Polygenic Risk Score (PRS)

3.6.1. Polygenic Risk Score (PRS) and the PRS-CSx method

PRS is a mathematical aggregate of risk-associated SNPs identified from a GWAS of the trait of interest (discovery dataset) weighted by the relevant effect size and used to predict the likelihood of the disorder in independent individuals (target dataset) (Choi et al., 2020; Lewis & Vassos, 2020; Wand et al., 2021). Most GWASs have been conducted in populations of European descent and, given the differences in genetic architecture between populations, the

PRS derived from this data does not adequately account for the variation in African ancestries (Janssens, 2019).

Polygenic Risk Score Continuous Shrinkage across ancestries (PRS-CSx) is an extension of Polygenic Risk Score Continuous Shrinkage (PRS-CS), which is a Bayesian modelling and prediction method. It has the potential to enhance the cross-population polygenic prediction of common disorders (Choi et al., 2020). PRS-CSx estimates the effect sizes of SNPs across diverse populations by integrating GWAS summary statistics from multiple ancestry groups. This method requires the 1,000 Genomes Project Phase III's LD reference panels and SNP information from the ancestries represented in the discovery cohort [http://www.internationalgenome.org] (Ruan et al., 2022). Since PRS-CSx stems from PRS-CS, it also has the computational advantages of CS priors, and the efficient and robust posterior inference algorithm, known as Gibbs sampling (Ge et al., 2022). This common prior improves computational efficiency by considering correlations between populations and allowing for different effect size estimates across ancestries, thereby maintaining the flexibility of the modelling framework (Ge et al., 2022). PRS-CSx generates adjusted beta values for SNPs shared between the discovery and target datasets, reflecting the strength and direction of their association (effect size) with the trait of interest (Figure 3) (Ruan et al., 2022). Additionally, PRS-CSx provides the flexibility to explore different models for genetic risk prediction, enabling the selection of the best model fit. Following this, PLINK calculates the PRS for each individual, leveraging the generated SNP weights to assess genetic risk across diverse populations (Chang, 2020; Chang et al., 2015). By integrating these ancestry-specific GWAS data, PRS-CSx provides a comprehensive approach to understanding genetic risk, ultimately enhancing the accuracy of effect size estimates and allowing for flexible modelling of genetic associations (Ruan et al., 2022).

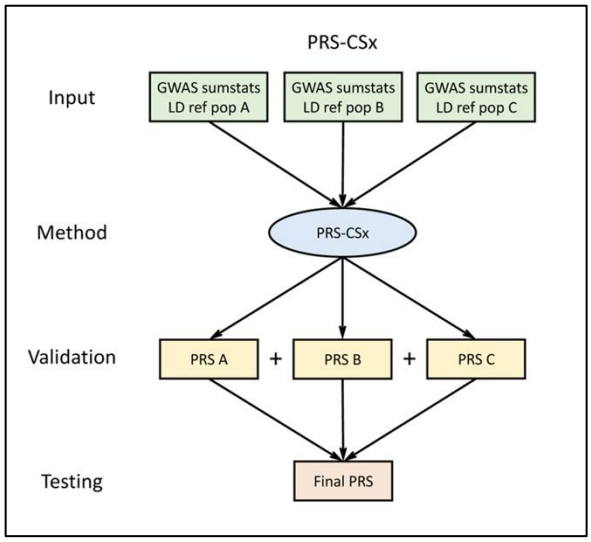


Figure 3: Overview of the PRS-CSx method, adapted from Ruan et al., 2022

Figure 3 shows the steps in the PRS-CSx method. The discovery samples (to generate GWAS summary statistics), validation samples (to tune hyper-parameters in PRS construction methods), and testing samples (to assess prediction accuracy) are non-overlapping. LD ref: LD reference panel; pop A/B/C: Population A/B/C.

3.6.2. Discovery dataset

This study used the latest GWAS summary statistics from the Psychiatric Genomics Consortium (PGC)-MDD and PGC-PTSD working groups as the discovery cohorts for each of the available ancestry subsets (Giannakopoulou et al., 2021; Maihofer et al., 2022). The PGC-MDD GWAS (N = 694,747) consists of 72% European participants (170,756 cases and 329,443 controls; N = 500,199; N(SNPs) = 8,483,302) and 28% African participants (36,818 cases and 161,679 controls; N = 198,497; N(SNPs) = 14,384,782) (Giannakopoulou et al., 2021; Meng et al., 2024). The PGC-PTSD GWAS (N = 1,273,916) consists of 96% European participants (137,136 cases and 1,085,746 controls; N = 1,222,882; N(SNPs) = 7,193,586) and 4% African participants (11,560 cases and 39,474 controls; N = 51,034; N(SNPs) = 11,726,202) (Maihofer et al., 2022).

3.6.3. Target dataset, PRS-CSx model generation, and evaluating the model fit

Since the two-year-olds do not yet exhibit symptoms of depression or PTSD, and phenotypic information is required to determine which PRS model accounts for the most variance, the expectant mothers were initially used as the target dataset. This approach leverages the shared genetic architecture and ancestry between mothers and children in the DCHS cohort to enhance

the reliability of the children's PRS, which cannot be independently assessed. The mothers completed mental health measures that were used to assess the presence of lifetime and antenatal symptoms of depression and PTSD (as described in section 3.3), which served as the case/control phenotype for each disorder. In addition to the previously mentioned discovery cohorts, the PRS-CSx tool generated a meta-analysed population, combining individuals of African and European ancestries. This allowed me to determine which discovery dataset and which combination of target datasets is most appropriate for the DCHS populations, i.e. accounts for the most variance in each phenotype. Due to the nature of PRS, it is important to identify whether the PRS adds explained variance beyond accounting for the genetic PCs alone. Thus, the analysis includes two models: model zero, where the mother's symptoms of depression or PTSD were explained by the PCs (Model 0: Phenotype ~ PCs), and model one, where the mother's symptoms of depression or PTSD were explained by the PCs and the addition of PRS (Model 1: Phenotype ~ PCs + PRS). Further, given that the DCHS consists of two ancestry groups (African and Mixed ancestry) and genotyping was performed on two different microarrays (GSA and PsychChip), the target dataset was investigated in the following combinations: 1) as the full combined cohort: both microarrays and ancestries analysed together, 2) subset by ancestry, and 3) subset by microarray. This approach addresses platform-specific biases and confounding due to differences in ancestry (Ruan et al., 2022)

3.6.4. PRS-CSx model generation and evaluating model fit

PRS models were generated using PRS-CSx for depression (PRS-MDD) and PTSD (PRS-PTSD) using the discovery cohorts and three target cohort combinations described above. Thereafter, the individual PRS scores for each mother were calculated using PLINK version 2 [https://www.cog-genomics.org/plink/2.0/]. To assess shared genetic liability, the correlation between PRS-MDD and PRS-PTSD was calculated using linear regression models implemented in R Statistical Software version 4.0.2 (R Core Team, 2023). Nagelkerke's R^2 was used to evaluate the proportion of variance explained by models 0 and 1. Nagelkerke's R^2 scales the Cox & Snell R^2 to ensure that it can reach a maximum value of one, providing a more interpretable measure of model fit (Cox & Snell, 1989; Nagelkerke, 1991). It is commonly used to assess the explanatory power of a model, with values closer to one indicating a better fit (Hosmer et al., 2013). Additionally, the deviance between models 0 and 1 was investigated; when comparing two nested models, a significantly lower deviance for the more complex model suggests that the additional parameters improve the model's explanatory power (Song,

2007). To determine which algorithm was best suited to the DCHS dataset, the R^2 value, the model's p-value, the deviance explained by model 1 over model 0, and the Chi-squared test p-value between the models, as determined by ANOVA, were evaluated.

3.6.5. PRS generation in the children

To calculate the children's PRS, the best-fitting model from the maternal cohort analysis was applied, as described previously in section 3.6.3. The children's PRS-MDD and PRS-PTSD were calculated using PLINK version 2, based on the same discovery cohorts and scoring parameters optimised for the maternal cohort.

3.7. Statistical analyses: Testing the association between child genetic risk, maternal symptoms of depression and PTSD, and child subcortical brain volumes

Multiple linear regression analyses were used to examine whether there is an association between the seven subcortical brain volumes and their lateral regions (N = 21) in children at two years of age, the child's genetic risk, and the antenatal environment. In total, five models were applied to each subcortical brain volume for each disorder of interest (Table 3). Regression analyses were performed using R Statistical Software version 4.0.2 (R Core Team, 2023). To minimise the likelihood of false positives, model p-values for the subcortical brain regions were adjusted for 21 comparisons (the left, right, and total volumes of the seven subcortical brain regions) using false-discovery rate (FDR) correction (Weller et al., 1998).

Table 3: Models used to investigate the association between genetics and/or environment and subcortical brain volume

Model name (symbol)	Model description
Base (B)	Subcortical brain volume ~ covariates
Genetic (G)	Subcortical brain volume ~ PRS + PCs + covariates
Environmental (E)	Subcortical brain volume ~ maternal symptoms + covariates
Additive (G+E)	Subcortical brain volume ~ (maternal symptoms + PRS) + PCs + covariates
Interaction (GxE)	Subcortical brain volume ~ (maternal symptoms x PRS) + PCs + covariates

Table 3 shows the description of the five statistical models used to examine the associations between subcortical brain volume and genetic and environmental predictors. PRS: polygenic risk score, PCs: principal components..

All numeric covariates and predictors (PRS, maternal age, child age at the time of the scan, Birth weight, ICV, and SES) were standardised. In regression, numeric variables often have different scales, which can lead to numerical instability within the model. Standardising these variables helps minimise these disparities, ensuring that each variable contributes proportionally during model fitting (Neter et al., 1996). For example, the standardisation of PRSs to a normal distribution allows the effect in the model to be expressed in units of one standard deviation of the PRS (Collister et al., 2022).

Covariates were included in the linear regression models to account for potential confounding factors that could influence the relationship between exposures and child subcortical brain volumes. The covariates include five maternal factors (ancestry, zSES: the sum of standardised SES components – education, income, assets, and employment – maternal age, smoking, and alcohol use) and five child factors (child age at scan, sex, intracranial volume (ICV), zBirth weight: weight-for-age z-score, and HIV exposure). These covariates were carefully chosen to align closely with previous research studies with similar aims (Acosta H et al., 2020; Pellowski et al., 2023; Qiu et al., 2017). Analysis was conducted using minimally and fully adjusted models to assess the influence of the additional covariates on the results. The minimally adjusted models included ancestry, child age at the time of the scan, sex, ICV, and zBirth weight as covariates. Fully adjusted models included all covariates from the minimally adjusted models and additionally included zSES, maternal age, smoking, alcohol use, and HIV exposure.

The models that included PRS (Models G, G+E, and GxE) were run with and without the first ten PCs. PCs were included in the genetic linear regression models to further account for the relative genetic variation between the children, which may not be fully captured in the PRS. Including PCs may also reduce potential confounding due to ancestry differences, which ensures that the observed associations are not driven by underlying genetic variation related to population stratification (Abegaz et al., 2019).

3.7.1. Determining the best-fit models for each subcortical brain region

3.7.1.1. Introduction to analysis of variance (ANOVA)

Analysis of variance (ANOVA) is a statistical method used to evaluate whether the variance between group means (represented by the F-statistic) is significantly greater than the variance within groups (Sthle & Wold, 1989). This method is grounded in the law of total variance, which partitions the total observed variance into components attributable to different sources, such as between-group variance and within-group variance. ANOVA generalises the t-test by allowing comparisons of multiple means, making it particularly useful for analysing groups. The null hypothesis of ANOVA posits that all group means are equal, while the alternative hypothesis suggests that at least one mean differs (Sthle & Wold, 1989).

3.7.1.2. Application of ANOVA as used in this study

ANOVA was used in this study to assess whether the inclusion of PRS and PCs provided additional explanatory power over PCs only. Furthermore, minimally and fully adjusted linear regression were compared using ANOVA to determine whether the fully adjusted models added explanatory value over the minimally adjusted models. Thereafter, ANOVA was used to determine if models G or E added significant explanatory value over model B. If Models G or E were a better fit than model B, they were also compared to models G+E and GxE. Finally, if models G+E and GxE were a better fit than models G or E, they were compared to each other to identify the best-fit model for explaining subcortical brain volumes.

3.8. Genome-Wide Association Study (GWAS) of child subcortical brain volumes

3.8.1. The concept of a Genome-Wide Association Study (GWAS)

A GWAS compares SNPs across the genome to test for an association with traits through a case-control design (Visscher et al., 2012). Due to the extensive multiple testing involved in analysing the SNPs, the threshold for statistical significance in GWAS is very stringent, with a p-value of $5x10^{-8}$ (Smith et al., 2019). The SNPs analysed in GWAS are usually common, with a MAF greater than either 1% or 5% in the population, depending on the sample size. Significant findings in GWAS may not directly identify causal variants for a disease or trait but rather highlight associated SNPs or genes due to LD, where alleles co-occur at high frequencies (Burton et al., 2007). Because of these complexities and the need for extensive replication and functional validation, GWAS results are often considered to generate hypotheses for further research (Cantor et al., 2010). The initial findings from GWASs can be used together with additional research to develop better interventions and move towards more personalised or population-specific medication and treatment (Abdellaoui et al., 2023).

3.8.2. Application of Genome-Wide Association Studies (GWASs) as used in this study

To explore the genetic architecture of child subcortical brain volumes, a GWAS was conducted. The GWAS analysis included individual-level data from 163 children, including ancestry, microarray, sex, zBirth weight, ICV, and HIV exposure as covariates. Additionally, ten PCs were included to account for possible population stratification. The analysis focused on the seven subcortical brain regions, further subdivided into the left and right regions, bringing the total regions investigated to 21. The 1,000 Genomes Phase III (Auton et al., 2015) reference panel was used to clump the target dataset to get an LD-pruned set of SNPs. This eliminates SNPs that are in LD ($r^2 > 0.1$) with these SNPs and keeps the SNPs with the least p-values within a 250 kb frame. SNPs below a threshold of $1x10^{-5}$ in the genomic locus were highlighted as tentative associations.

Following the GWAS, Manhattan plots were generated to visualise the GWAS results, and QQ-plots were generated to assess inflation using Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA GWAS) (Watanabe et al., 2017). Additionally,

functional annotation was performed using the SNP2GENE function on the FUMA website [https://fuma.ctglab.nl]. This tool mapped lead SNPs to candidate genes, prioritised by their biological relevance. FUMA's GENE2FUNC tool was then used to explore gene expression in human brain tissue, providing additional insights into the potential functional consequences of the associated SNPs.

3.9.Comparison of subcortical brain volume GWAS across populations

African genomes are more genetically diverse and complex as compared to European genomes, which have historically been the primary focus of genetic research (Sirugo et al., 2019). This disparity poses challenges in understanding complex traits and diseases in African populations, as differences in genetic architecture and the under-representation of African populations in genetic studies limit the generalisability of findings and hinder advancements in precision medicine (Coram et al., 2015). Developing precise, population-specific risk prediction models advances precision medicine by elucidating genetic connections across diverse groups (Fatumo et al., 2022; Sirugo et al., 2019). This is crucial for studies involving individuals of African and Mixed ancestry to ensure that findings are relevant and beneficial (Popejoy & Fullerton, 2016).

3.9.1. Popcorn software to estimate correlation of causal variant effects

Popcorn is a Python package designed to estimate causal variant effect correlations across populations (Brown et al., 2016). The software operates through two main steps: compute mode and fit mode. In the compute mode, cross-population scores are computed from a reference panel, reflecting LD patterns at each SNP across diverse populations. Then, in the fit mode, the software fits the heritability and transethnic genetic correlation by analysing a pair of summary statistics files against the computed scores. Popcorn outputs include the heritability (h^2) of common SNPs on the observed scale for each population, the genetic impact correlation (rg_i), and the standard error of these estimates. The genetic impact correlation quantifies the shared genetic factors influencing multiple traits, indicating the extent of genetic similarity or divergence across populations. Additionally, Popcorn calculates Z-scores and associated p-values. For heritability, the p-value tests whether heritability exceeds zero, while for genetic correlation, it assesses whether the correlation is less than one, indicating distinct genetic influences across populations (Brown et al., 2016).

3.9.2. Applications of Popcorn as used in the study

This study used Popcorn [https://github.com/brielin/Popcorn] (Brown et al., 2016) to estimate the heritability and genetic correlation of each subcortical brain volume. The 1,000 Genomes reference panels for African (661 individuals from seven countries; hereafter referred to as the African population) and European populations (503 individuals from five countries; hereafter referred to as the European population) were used during the compute mode to generate cross-population scores, reflecting LD patterns at each SNP across these populations. In the fit mode, heritability and genetic correlation estimates were derived by analysing summary statistics from the DCHS African-mixed ancestry cohort (N = 163; 37,016 SNPs) and Satizabal *et al.* (2019)'s European cohort (N = 38,851; 49,999 SNPs) (Satizabal *et al.*, 2019). Individual-level data was used to compute the cross-population scores for the paired populations, with all analyses conducted in Python version 3.7. Subsequently, heritability and transethnic genetic correlation were estimated by fitting the cohort summary statistics files to these computed scores (Brown et al., 2016).

4. Results

4.1. Descriptive characteristics of all the mothers in the Drakenstein Child Health Study (DCHS)

4.1.1. Maternal symptom analysis on case identification and congruency across mental health measures

The case/control criteria from section 3.3 were applied to the 1,189 mothers who completed the mental health measures. Four measures were used to screen for symptoms of depression (SRQ-20: n = 1,093, EPDS: n = 1,013, BDI-II: n = 1069, MINI: n = 872) and three measures were used to screen symptoms of PTSD (mPSS: n = 159, MINI: n = 597, and CAPS: n = 131). Individuals were classified as cases if they met the case criteria on at least two assessment measures. For depression, a total of 493 (41.46%) individuals met the criteria to be categorised as "depression cases" and 696 (58.54%) individuals as "depression controls". After applying the case/control criteria, 206 (17.33%) mothers met the criteria to be categorised as a "PTSD case" and 982 (82.67%) individuals as a "PTSD control". Varying rates of congruency were seen for depression cases (34.72% – 57.82%), depression controls (79.76% – 87.54%), PTSD cases (53.85% – 89.58%), and PTSD controls (28.57% – 53.70%) (Appendices 3 and 4). Furthermore, 129 mothers (11%) had overlapping symptoms of depression and PTSD (Figure 4).

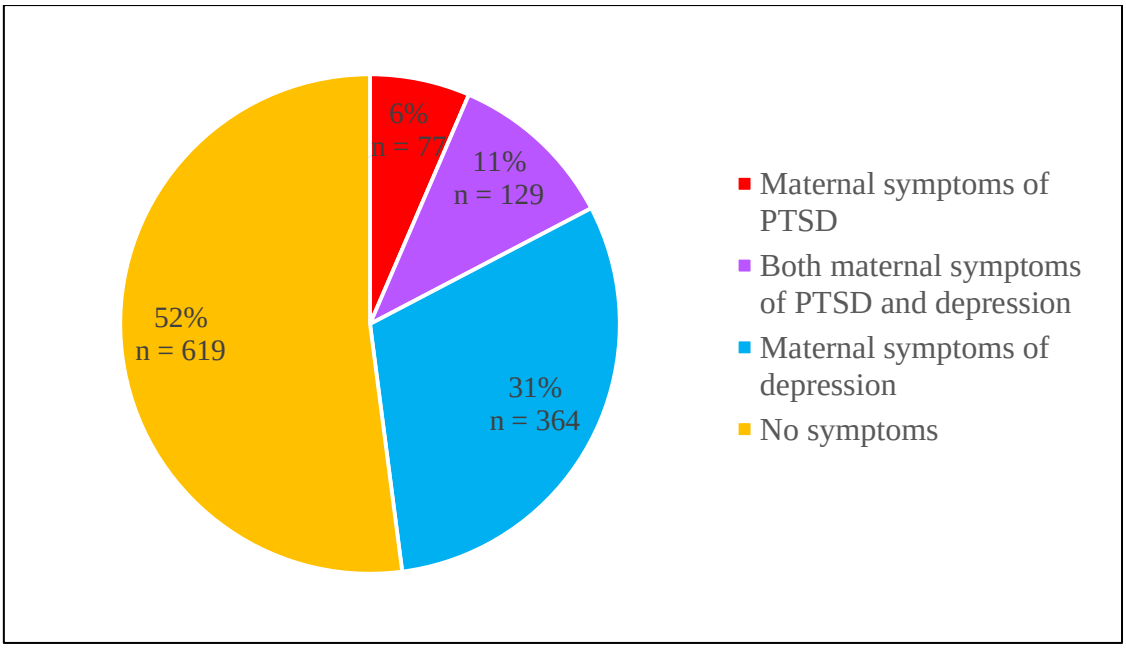


Figure 4: Overlap of maternal symptoms of depression and PTSD

Figure 4 shows the distribution of maternal PTSD- and depressive symptoms. The red segment represents mothers with symptoms of PTSD, the purple segment represents those with symptoms of both depression and PTSD, the blue segment reflects symptoms of depression, and the yellow segment reflects mothers without either depression or PTSD symptoms.

4.2.Descriptive characteristics of the neuroimaging sub-study

The Drakenstein population faces challenges, including poverty, psychological distress, violence, and substance abuse, which are all well-documented contributors to mental health disorders (Meyer et al., 2004). The socioeconomic context of the DCHS cohort underscores the higher prevalence of depression and PTSD in low-income populations, highlighting the need to examine demographics and health characteristics to understand child health outcomes (Table 4). Notably, the PsychChip microarray was excluded from downstream analysis due to the small sample size (N = 18) and associated power limitations, as further discussed in section 4.3. Most children were male (n = 72; 56.25%), HIV unexposed (n = 67; 52.34%), and had a healthy birth weight (zBirth weight (weight-for-age z-score): -0.27 ± 1.09). At the time of the scan, the average child age was 1,058.811 (± 48.194) days, and the average ICV was 1,209,947.90 (± 122,952.32) mm^3. Most of the mothers did not drink (n = 106; 82.82%) or smoke during their pregnancy (n = 95; 74.22%) and did not have symptoms of depression (n = 80; 62.50%) or PTSD (n = 111; 86.72%).

Table 4: Demographic characteristics of the neuroimaging sub-study

		Total	Maternal antenatal symptoms of depression		Maternal antenatal symptoms of PTSD	
			Case	Control	Case	Control
		N = 128	48	80	17	111
Continuous characteristics: mean ±SD						
Child age at scan (in days)		1,058.81 ± 48.19	1,055.19 ± 56.09	1,061.01 ± 42.94	1,039.35 ± 65.22	1,061.82 ±44.63
ICV (in mm^3)		1,209,947.90 ±122,952.32	1,197,333.73 ±126,464.79	1,217,516.40 ± 120,965.86	1,176,822.70 ± 121,077.18	1,215,021.13 ± 122,986.63
SES		0.26 ± 1.89	-0.18 ± 1.76	0.53 ± 1.93	-0.01 ± 2.61	0.31 ± 1.77
zBirth weight		-0.27 ± 1.09	-0.17 ± 1.00	-0.34 ± 1.15	-0.21 ± 1.10	0.67 ± 0.99
Binary characteristics: n (%)						
Child sex	Female	56 (43.75%)	19 (39.58%)	37 (46.25%)	7 (41.18%)	49 (44.14%)
	Male	72 (56.25%)	29 (60.42%)	43 (53.75%)	10 (58.82%)	62 (55.86%)
Child in-utero HIV exposure	Exposed	61 (47.66%)	20 (41.67%)	41 (51.25%)	8 (47.09%)	53 (47.75%)
	Unexposed	67 (52.34%)	28 (58.33%)	39 (48.75%)	9 (52.94%)	58 (52.25%)
Maternal alcohol use	Present	19 (14.84%)	8 (16.67%)	11 (13.75%)	3 (17.65%)	16 (14.42%)
	Absent	106 (82.82%)	40 (83.33%)	69 (86.25%)	14 (82.35%)	92 (82.88%)
	Unavailable	3 (2.34%)	0 (0.00%)	3 (3.75%)	0 (0.00%)	3 (2.70%)
Maternal tobacco/ nicotine use	Present	33 (25.78%)	19 (39.58%)	14 (17.50%)	5 (29.41%)	28 (25.23%)
	Absent	95 (74.22%)	29 (60.42%)	66 (82.5%)	12 (70.59%)	83 (74.77%)

Table 4 shows descriptive characteristics of the neuroimaging sub-study (N = 128). n: number of individuals; SD: standard deviation; ICV: intracranial volume; SES: socio-economic status; zBirth weight: Weight-for-age z-score.

4.3.Genotyping

Before performing genetic analyses, extensive quality control procedures were applied to both maternal (N = 1,151 and 16,693,293 variants) and child genetic data (N = 163 and 281,341 variants) to ensure the reliability and accuracy of the data (Figure 5). These steps were conducted sequentially, starting with the removal of variants with a missingness rate > 5% (mothers: n = 4,611,739; children: n = 243,306). Next, samples with a missing genotype rate exceeding 1% were excluded from further analysis (mothers: n = 2; children: n = 0). Additionally, variants that did not adhere to HWE among controls were filtered out ($p < 1x10^{-8}$.) (mothers: n = 1,272,735; children: n = 0), and duplicate and related samples were identified and excluded if their IBD value was > 0.125 (mothers: n = 30; children: n = 0). Variants with a MAF less than 0.01 were also removed to focus on common variants (mothers: n = 1,542,421; children: n = 1,019). Finally, the first ten PCs were calculated to account for population stratification. 1,119 mothers (9,266,398 variants) and 163 children (37,016 variants) passed genetic quality control and were included for further analysis.

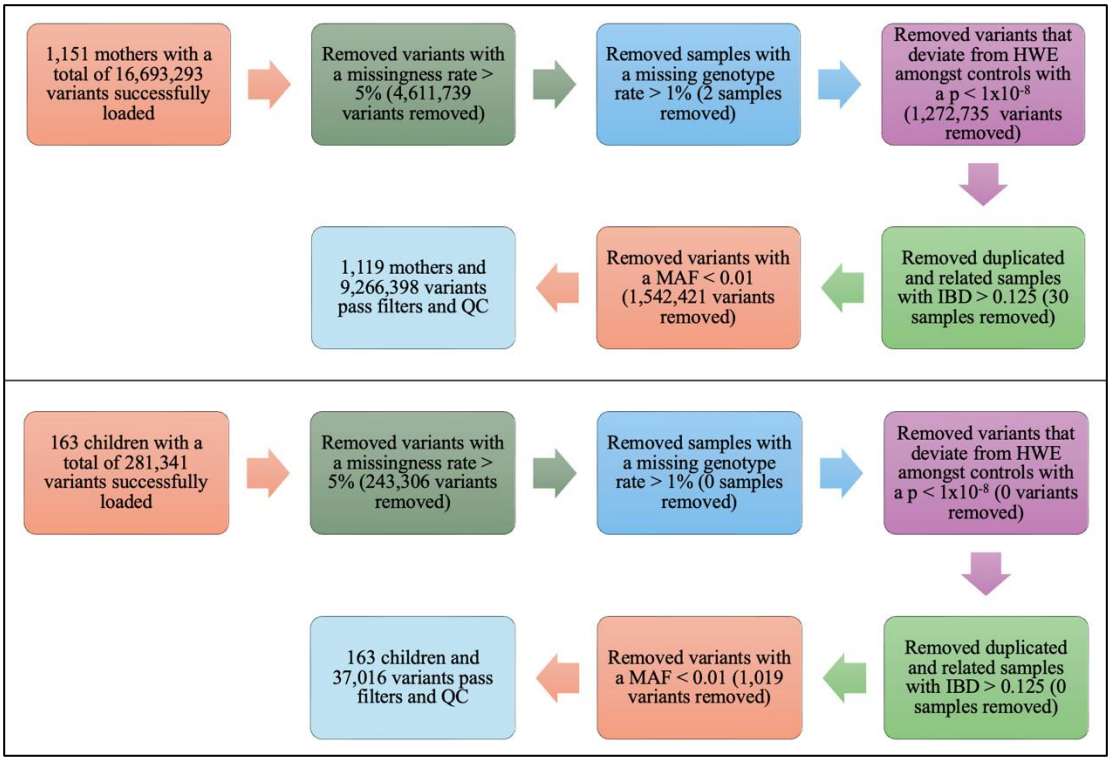


Figure 5: Sequence of genetic pre-imputation quality control procedures

A: sequential steps of quality control procedures applied to maternal genetic data. B: sequential steps of quality control procedures applied to child genetic data. HWE: Hardy-Weinberg Equilibrium, IBD: identical-by-descent; MAF: minor allele frequency, QC: quality control.

4.4.Polygenic Risk Scoring (PRS)

4.4.1. The best-fitting PRS models for the DCHS population

The first step of the statistical analysis involved assessing the maternal PRSs for the full cohort to identify the best-fit PRS algorithm. The best-fitting models in the mothers were then used as a proxy to calculate the children's individual PRS.

4.4.1.1. Best-fitting PRS model for depression

For depression, the DCHS maternal population was compared to three sets of GWAS summary statistics: a European PGC-MDD GWAS (387,707 common variants), an African MDD GWAS (439,086 common variants), and a trans-ancestry meta-analysis (440,048 common variants). All variants reported were the common variants remaining after PRS analysis. Given the known genetic differences between ancestries and the strong effects of the microarray in this cohort (Figure 6), the cohort was subdivided by microarray (PsychChip and GSA) and ancestry (African ancestry and Mixed ancestry), respectively, to test the PRS model fit in each group (Table 5).

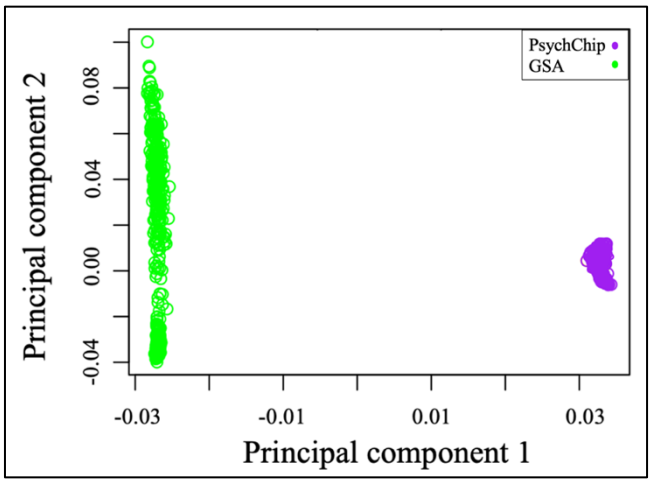


Figure 6: Plot of the first two PCs split by microarray

Figure 6 shows the PCA for the PsychChip microarray (green) (n = 678) and GSA microarray (purple) (n = 512). PsychChip: PsychArray BeadChip; GSA: Global Screening Array; n: number of individuals. The plot was generated using the R package ggplot2. PCs: principal components; PCA: principal component analysis.

The highest R^2 values were observed for model 1 (Phenotype ~ PRS + PCs) in the analysis when the cohort was stratified by microarray. Among individuals genotyped with the

PsychChip microarray, which was included in the PRS analysis but excluded from the linear regression analysis, the African discovery cohort provided the best model fit (R^2 = 19.8%, p-value = 2.2^{-16}, deviance = -98.578, Chi-test p = 2.2^{-16}). Similarly, the African discovery cohort showed the best fit for individuals genotyped using the GSA microarray (R^2 = 9.0%, p-value = 2.2^{-16}, deviance = -4.261, Chi-test p = 0.039). Although the African discovery cohort's model p-value was non-significant (p = 0.997), it was still selected as the best fit due to it having the highest R^2 value (R^2 = 9.0%), the most deviance explained over the null model (deviance = -4.261), and the most significant Chi-test p-value (Chi-test p = 0.039). A negative deviance reflects less unexplained variance in model 1 as opposed to model 0.

Table 5: Identification of the best fit PRS model for maternal symptoms of depression

DCHS target cohort	**PGC Discovery cohort**	**R^2**	**Model p-value**	**Deviance**	**Chi-test p-value**
Full cohort (N = 1,189)	European	5.3%	0.499	-1.171	0.279
	African	5.1%	0.029	-1.145^{-5}	0.997
	Meta-analysis	5.1%	0.082	-0.055	0.815
PsychChip individuals (n = 678)	European	1.3%	0.647	-0.584	0.445
	African	19.8%	2.2^{-16}	-98.578	2.2^{-16}
	Meta-analysis	10.6%	2.2^{-16}	-24.396	4.346^{-12}
GSA individuals (n = 511)	European	8.0%	0.012	-0.534	0.465
	African	9.0%	0.997	-4.261	0.039
	Meta-analysis	8.5%	0.993	-2.938	0.252
African ancestry (n = 667)	European	10.3%	0.829	-0.956	0.328
	African	10.3%	0.548	-0.981	0.322
	Meta-analysis	10.1%	0.392	-0.276	0.599
Mixed ancestry (n = 522)	European	5.1%	0.174	-0.081	0.776
	African	5.6%	0.008	-1.893	0.169
	Meta-analysis	5.4%	0.036	-0.995	0.318

Table 5 shows summary statistics for model 1 (Phenotype ~ principal components + polygenic risk score) for mothers with symptoms of depression in the DCHS cohort. Nagelkerke's R^2-value presented as percentages, model p-value, additional deviance explained of model 1 over model 0, and the Chi-test p-value. The deviance and Chi-test p-value are results derived from an ANOVA. The sample cohort that best fits the target cohort is highlighted in blue. DCHS: Drakenstein Child Health Study; PGC: Psychiatric Genomics Consortium.

4.4.1.2. Best-fitting PRS model for PTSD

For PTSD, the DCHS maternal population was compared against three sets of PGC-PTSD GWAS summary statistics: a European GWAS (673,913 common variants), an African GWAS (758,744 common variants), and a trans-ancestry meta-analysis (792,627 common variants). All variants reported were the common variants remaining after PRS analysis. Similar to the analysis of depression, the cohort was subdivided by microarray (PsychChip, GSA) and ancestry (African ancestry, Mixed ancestry) to test the PRS model fit in each group (Table 6).

Here, the highest R^2 values were also observed for model 1 in the analysis when the cohort was stratified by microarray, similar to my PRS-MDD analysis. Among individuals genotyped with the PsychChip microarray, the European ancestry group provided the best model fit (R^2 = 4.1%, p-value = 0.001, deviance = -4.336, Chi-test p = 0.037). For individuals genotyped with the GSA microarray, the trans-ancestry meta-analysis best fit the model (R^2 = 5.6%, p-value = 2.73^{-6}, deviance = -2.599, Chi-test p = 0.107). Although the Chi-squared test p-value for the trans-ancestry meta-analysis was non-significant, it was still chosen as it had the lowest p-value in the GSA microarray analysis.

The individual-level PRS-MDD and PRS-PTSD, derived from the best-fit models, were weakly but positively correlated (r = 0.177, p = 0.024). This suggests a modest yet statistically significant degree of shared genetic liability between the two traits, consistent with partially overlapping polygenic architectures.

Table 6: Identification of the best fit PRS model for maternal symptoms of PTSD

DCHS target cohort	PGC discovery cohort	R^2	Model p-value	Deviance	Chi-test p-value
Full cohort (N = 1,189)	European	1.9%	0.116	-0.259	0.610
	African	2.0%	0.002	-1.515	0.218
	Meta-analysis	2.0%	0.001	-0.986	0.321
PsychChip individuals (N = 678)	European	4.1%	0.001	-4.336	0.037
	African	3.2%	8.99^{-11}	-0.041	0.839
	Meta-analysis	3.2%	0.023	-0.164	0.685
GSA individuals (N = 511)	European	5.5%	0.005	-2.284	0.131
	African	5.5%	2.79^{-9}	-2.526	0.112
	Meta-analysis	5.6%	2.73^{-6}	-2.599	0.107
African ancestry (N = 667)	European	3.1%	0.646	-0.081	0.776
	African	3.4%	0.089	-1.101	0.294
	Meta-analysis	3.2%	0.021	-0.583	0.445
Mixed ancestry (N = 522)	European	4.4%	0.189	-0.001	0.982
	African	5.0%	2.2^{-16}	-2.279	0.131
	Meta-analysis	4.9%	0.016	-0.199	0.665

Table 6 shows summary statistics for model 1 (Phenotype ~ principal components + polygenic risk score) for mothers with symptoms of PTSD in the DCHS cohort. Nagelkerke's R^2-value presented as percentages, model p-value, additional deviance explained of model 1 over model 0, and the Chi-test p-value. The deviance and Chi-test p-value are results derived from an ANOVA. The sample cohort that best fits the target cohort is highlighted in blue. DCHS: Drakenstein Child Health Study; PGC: Psychiatric Genomics Consortium.

4.4.2. Individual PRS in the DCHS children

The best-fitting models in the mothers were then used as a reference to calculate the children's individual PRS for depression and PTSD. Since splitting the cohort by microarray provided the best model fit for the mothers, the same approach was applied to the children. However, the PsychChip microarray was excluded from the children's analysis due to the small sample size in the neuroimaging study (N = 35). Therefore, PRS for the kids were calculated for the GSA microarray only, using the African PGC-discovery cohort for depression and the Meta-analysed PGC-discovery cohort for PTSD. Distribution plots were used to visualise the

distribution of child PRS (Figures 7 and 8). Across all of the children, the average PRS for depression was -8.63^{-7}, ranging from -2.73^{-6} to 1.39^{-6}. African ancestry was compared to the Mixed Ancestry population, with differences observed in the distribution. An average PRS for depression for the African ancestry (N = 92) of -9.19^{-7} was observed, ranging from -2.48^{-6} to 1.01^{-6}; and for Mixed ancestry (N = 36), an average of -7.20^{-7} was observed, ranging from -2.73^{-6} to 1.39^{-6}. Across all of the children (N = 128), the average PRS for PTSD was 1.21^{-6}, ranging from -5.52^{-7} to 2.14^{-6}. African ancestry was compared to the Mixed Ancestry population, with differences again observed in the distribution. An average PRS for depression for the African ancestry (N = 92) of 1.36^{-6} was observed, ranging from 6.31^{-7} to 2.14^{-6}; and for Mixed ancestry (N = 36), an average of 8.11^{-7} was observed, ranging from -5.52^{-7} to 2.06^{-6}.

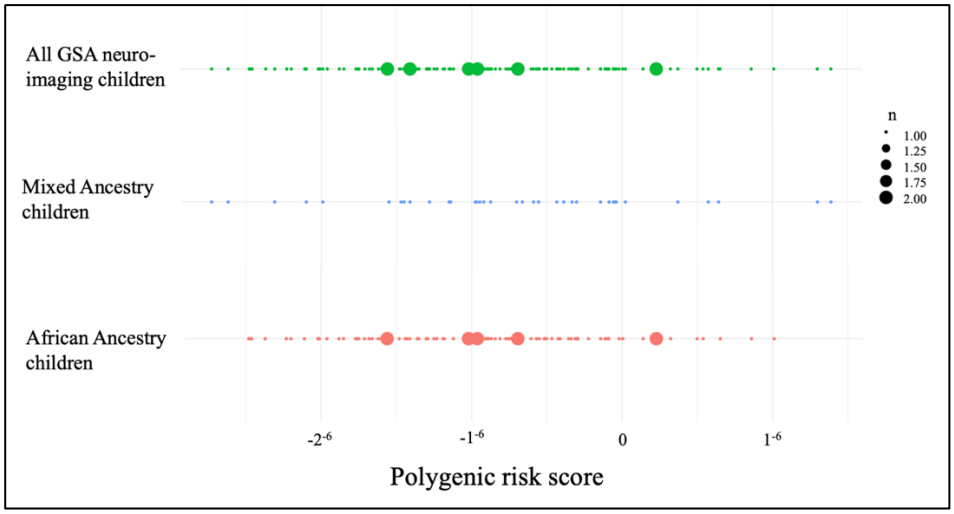


Figure 7: Density plot of child PRS for depression

Figure 7 shows the polygenic risk score distribution for depression in the children in the neuroimaging cohort, split by ancestry. The plot was generated using the R package ggplot2.

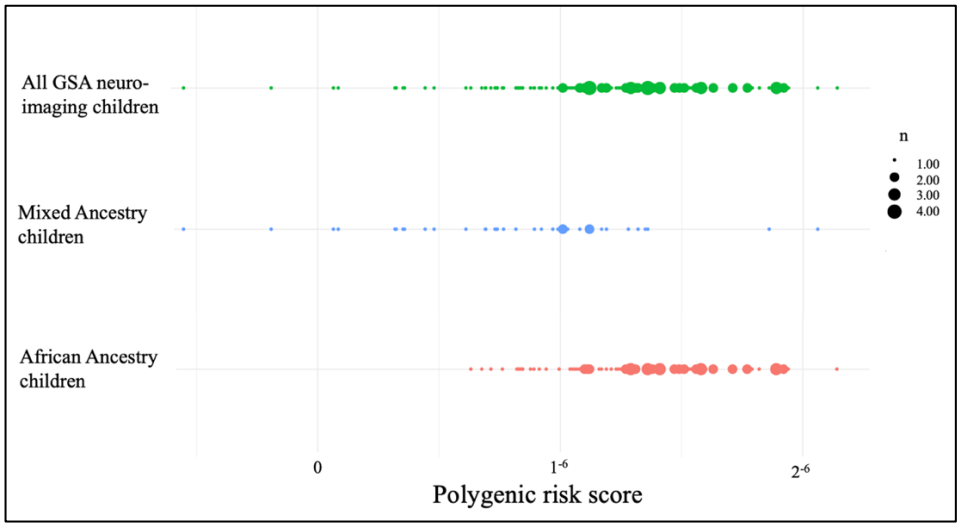


Figure 8: Density plot of child PRS for PTSD

Figure 8 shows the polygenic risk score distribution for PTSD in the children in the neuroimaging cohort, further split by ancestry. The plot was produced using the R package ggplot2.

4.5. Assessing the association between genetic risk, maternal symptoms and child subcortical brain volumes

4.5.1. Assessing covariates

To evaluate the significance of the selected covariates on the analysis of psychiatric phenotypes and brain structures, both minimally and fully adjusted models were initially run in model B (subcortical brain volume ~ covariates). The minimally adjusted models added explanatory power over the fully adjusted models, but this effect was not significant (Appendix 6). Thus, the minimally adjusted models were used in the analyses to avoid redundancy. Additionally, model G (subcortical brain volume ~ PRS + covariates) was run both with and without the first ten PCs, given that PRS + PCs showed better explanatory power than PRS only to assess the contribution to the model. Including the first ten genetic PCs in sensitivity analyses significantly improved the model fit (Appendix 7), and these PCs were included in the models that include genetics (Model G: subcortical brain volume ~ PRS + PCs + covariates, G+E: subcortical brain volume ~ (maternal symptoms + PRS) + PCs + covariates; and GxE: subcortical brain volume ~ (maternal symptoms x PRS) + PCs + covariates).

4.5.2. Analysis of models and main effects

Interestingly, all five linear regression models (B, G, E: subcortical brain volume ~ maternal symptoms + covariates; G+E, and GxE) demonstrated statistical significance across all subcortical brain regions after FDR correction (Appendices 8 and 9). Consequently, ANOVA was used to determine if models G or E added significant explanatory value over model B (BvsG and BvsE). If models G or E were a better fit than model B, they were also compared to models G+E and GxE (GvsG+E, GvsGxE, EvsG+E, and EvsGxE). Finally, if models G+E and GxE were a better fit than models G or E, they were compared to each other (G+EvsGxE). Tables 7 and 8 show the final best-fit model for each subcortical brain region for depression and PTSD, respectively.

4.5.2.1. Depression

For depression, the results show model G is the best fit for the bilateral thalamus (pFDR = 2.20^{-16}, beta = 5.855), left thalamus (pFDR = 2.20^{-16}, beta = 10.683), right thalamus (pFDR = 2.20^{-16}, beta = -4.828), bilateral putamen (pFDR = 1.86^{-8}, beta = -89.210), left putamen (pFDR = 1.25^{-7}, beta = -27.352), right putamen, (pFDR = 4.07^{-8}, beta = -61.858), right pallidum (pFDR = 7.12^{-9}, beta = -18.444), and left hippocampus (pFDR = 4.43^{-13}, beta = 8.975) (Table 7). Model GxE best fits the bilateral caudate (pFDR = 9.94^{-11}, beta = 146.250), left caudate (pFDR = 1.04^{-9}, beta = 66.809), and right caudate (pFDR = 9.94^{-11}, beta = 79.441). Model B was the best fit for the remaining subcortical regions. Appendix 8 shows the reported summary statistics for all models for the 21 brain regions.

For the caudate volumes, it's important to note that both models G+E and GxE were significantly better than models G and E, but when comparing the two models, the differences were non-significant. The summary statistics of model GxE are reported here since model GxE was marginally better in fit (AIC = 2059.480 for the bilateral caudate, AIC = 1888.755 for the left caudate, AIC = 1888.786 for the right caudate) than model G+E (AIC = 2059.991 for the bilateral caudate, AIC = 1888.871 for the left caudate, AIC = 1889.506 for the right caudate).

Table 7: Summary statistics for the best-fit models of depression

Subcortical brain region	**Best-fit model**	**pFDR-value of best fit model**	**Beta coefficient for best fit model**	**SE**	**t-statistic**	**Adjusted R^2**	**Main predictor p-value**
Thalamus	G	2.20^{-16}	5.855	68.385	0.086	0.646	0.932
Left thalamus	G	2.20^{-16}	10.683	36.612	0.292	0.615	0.771
Right thalamus	G	2.20^{-16}	-4.828	34.708	-0.139	0.638	0.890
Caudate	GxE	9.94^{-11}	146.250	105.759	1.383	0.460	0.170
Left caudate	GxE	1.04^{-9}	66.809	54.002	1.237	0.430	0.219
Right caudate	GxE	9.94^{-11}	79.441	54.009	1.471	0.468	0.144
Putamen	G	1.86^{-8}	-89.210	86.974	-1.026	0.371	0.307
Left putamen	G	1.25^{-7}	-27.352	47.840	-0.572	0.341	0.569
Right putamen	G	4.07^{-8}	-61.858	44.972	-1.375	0.358	0.172
Pallidum	B	1.67^{-10}	-25.520	71.674	-0.356	0.342	0.722
Left pallidum	B	5.25^{-9}	-26.796	42.307	-0.633	0.297	0.528
Right pallidum	G	7.12^{-9}	-18.444	15.693	-1.175	0.388	0.242
Hippocampus	B	1.30^{-14}	-62.950	104.559	-0.602	0.453	0.548
Left hippocampus	G	4.43^{-13}	8.975	22.909	0.392	0.518	0.696
Right hippocampus	B	6.20^{-12}	-31.219	59.120	-0.528	0.385	0.598
Amygdala	B	2.39^{-12}	12.806	54.098	0.237	0.398	0.813
Left amygdala	B	6.20^{-12}	-17.874	27.193	-0.657	0.383	0.512
Right amygdala	B	2.52^{-10}	30.679	31.868	0.963	0.336	0.338
Accumbens	B	4.69^{-8}	-3.857	30.162	-0.128	0.266	0.898
Left accumbens	B	4.92^{-7}	-13.294	17.463	-0.761	0.234	0.448
Right accumbens	B	6.08^{-6}	9.437	15.695	0.601	0.230	0.549

Table 7 summarizes the pFDR-value, beta value, SE, t-statistics, adjusted R^2 value and the p-value for the main predictor for each subcortical brain volume's best-fit model in depression. B: Model B: Subcortical brain volume ~ covariates; G: Model G: Subcortical brain volume ~ PRS + principal component + covariates; GxE: Subcortical brain volume ~ (maternal antenatal symptoms of depression x PRS) + principal components + covariates. SE: standard error.

4.5.2.2.PTSD

For PTSD, the results show model G is the best-fit model for the bilateral putamen (pFDR = 2.64^{-8}, beta = 7.461), left putamen (pFDR = 1.32^{-7}, beta = -7.649), right putamen (pFDR = 8.70^{-8}, beta = 15.110), right pallidum (pFDR = 9.27^{-9}, beta = 9.152), and left hippocampus (pFDR = 3.04^{-13}, beta = -27.698). Model E is the best-fit model for the left thalamus (pFDR = 2.20^{-16}, beta = -239.901). Model G+E best fits the bilateral thalamus (pFDR = 2.20^{-16}, beta = 36.463), and right thalamus (pFDR = 2.20^{-16}, beta = 6.470). Model GxE best fits the bilateral caudate (pFDR = 6.85^{-11}, beta = 247.640), left caudate (pFDR = 1.25^{-9}, beta = 117.558), and right caudate (pFDR = 4.05^{-11}, beta = 130.082). Model B was the best fit for the remaining subcortical regions (Table 8). Appendix 9 shows the reported summary statistics for all models for the 21 brain regions.

For the thalamus and caudate volumes, it's important to note that both models G+E and GxE were significantly better than models G and E (except for the left thalamus), but when comparing the two models, the differences were non-significant (except for the right caudate with p = 0.048). The summary statistics of model G+E for the bilateral and right thalamus are reported below since model G+E was marginally better in fit (AIC = 2047.076 for the bilateral thalamus, AIC = 1875.432 for the right thalamus) than model GxE (AIC = 2048.987 for the bilateral thalamus, AIC = 1877.221 for the right thalamus). The summary statistics of model GxE for the caudate volumes are reported below since model GxE was marginally better in fit (AIC = 2058.482 for the bilateral caudate, AIC = 1889.256 for the left caudate) than model G+E (AIC = 2060.688 for the bilateral caudate, AIC = 1890.734 for the left caudate).

Notably, the only main predictor that was significant was in model E for the left caudate in PTSD (p = 0.024). However, the significance of the main predictor diminishes when genetic factors are considered.

Table 8: Summary statistics for the best-fit models of PTSD

Subcortical brain region	Best-fit model	pFDR-value of best fit model	Beta coefficient for best fit model	SE	t-statistic	Adjusted R^2	Main predictor p-value
Thalamus	G+E	2.20^{-16}	36.463	83.837	0.435	0.654	0.664
Left thalamus	E	2.20^{-16}	-239.901	104.861	-2.288	0.598	*0.024
Right thalamus	G+E	2.20^{-16}	6.470	42.653	0.152	0.644	0.880
Caudate	GxE	6.85^{-11}	247.640	172.376	1.437	0.154	0.325
Left caudate	GxE	1.25^{-9}	117.558	88.538	1.328	0.187	0.357
Right caudate	GxE	4.05^{-11}	130.082	87.528	1.486	0.140	0.325
Putamen	G	2.64^{-8}	7.461	106.955	0.070	0.365	0.945
Left putamen	G	1.32^{-7}	-7.649	58.636	-0.130	0.339	0.896
Right putamen	G	8.70^{-8}	15.110	55.495	0.272	0.347	0.786
Pallidum	B	1.67^{-10}	-25.520	71.674	-0.356	0.342	0.722
Left pallidum	B	5.25^{-9}	-26.796	42.307	-0.633	0.297	0.528
Right pallidum	G	9.27^{-9}	9.152	19.307	0.474	0.382	0.636
Hippocampus	B	1.30^{-14}	-62.950	104.559	-0.602	0.453	0.548
Left hippocampus	G	3.04^{-13}	-27.698	27.935	-0.992	0.522	0.324
Right hippocampus	B	6.20^{-12}	-31.219	59.120	-0.528	0.385	0.598
Amygdala	B	2.39^{-12}	12.806	54.098	0.237	0.398	0.813
Left amygdala	B	6.20^{-12}	-17.874	27.193	-0.657	0.383	0.512
Right amygdala	B	2.52^{-10}	30.679	31.868	0.963	0.336	0.338
Accumbens	B	4.69^{-8}	-3.857	30.162	-0.128	0.266	0.898
Left accumbens	B	4.92^{-7}	-13.294	17.463	-0.761	0.234	0.448
Right accumbens	B	6.08^{-7}	9.437	15.695	0.601	0.230	0.549

Table 8 summarises the pFDR-value, beta value, SE, t-statistics, adjusted R^2 value and the p-value for the main predictor for each subcortical brain volume's best-fit model in PTSD. B: Model B: Subcortical brain volume ~ covariates; G: Model G: Subcortical brain volume ~ PRS + principal components + covariates; E: Model E: Subcortical brain volume ~ maternal antenatal symptoms of PTSD + covariates; G+E: Subcortical brain volume ~ maternal antenatal symptoms of PTSD + PRS + principal components + covariates; GxE: Subcortical brain

volume ~ (maternal antenatal symptoms of PTSD x PRS) + principal components + covariates. Significant main predictors are indicated with an asterisk (*). SE: standard error.

4.6.Genome-Wide Association Study (GWAS)

The second aim of this study was to perform a GWAS to investigate the genetic architecture of subcortical brain volumes in all children in the neuroimaging sub-study (N = 163). This analysis focused on the volumes of seven subcortical brain regions, analysed as both combined hemispheres and each hemisphere separately, to identify genetic variants associated with differences in these structures in this ancestry group and at this age.

As expected, due to the small sample size, none of the subcortical regions had genome-wide significance. Analysis with genetic variants below the p-value threshold of $1x10^{-5}$ was conducted, as these are considered lead SNPs in the FUMA pipeline (Watanabe et al., 2017). This included only three SNPs: one from the left caudate and two from the right hippocampus (Table 9). Variant rs6052713 on chromosome 20 was associated with a smaller left caudate volume (p-value = 1.45^{-6}, B = -468.196 ± 82.078), and rs11771415 on chromosome 7 (p = 6.79^{-6}, 314.182 ± 60.255), and rs7317597 on chromosome 13 (p = 2.88^{-6}, 340.853 ± 219.096) were associated with a larger right hippocampus volume. However, as can be seen in the Manhattan plots (Figures 9A and 10A, and Appendix 10), these three standalone SNPs do not have a pattern of trailing genetic markers in LD, and thus, we should be cautious of potential false positives (Bush & Moore, 2012). The λ_{GC} values (left caudate = 1.041, right hippocampus = 0.998) shown in the QQ-plots (Figures 9B and 10B) indicate that the association test statistics closely match the expected distribution, with minimal inflation from confounding. However, a slight leftward deviation at the tail end of the QQ-plot for the left caudate indicates more positive associations compared to what would be expected under the null hypothesis (Figure 9B), whereas a slight rightward deviation at the end tail of the QQ-plot for the right hippocampus indicates negative associations compared to what would be expected under the null hypothesis (Figure 10B) (Huang et al., 2019).

Table 9: Top three GWAS results

	Left Caudate	**Right Hippocampus**	
Unique identifier	20:4624558:A:G	7:48722484:A:G	13:63405083:A:G
Nucleotide change	A > G		
rsID	rs6052713	rs11771415	rs7317597
Beta (± SE)	-468.196 ± 82.078	314.182 ± 60.255	340.853 ± 219.096
Chromosome	20	7	13
Position (bp)	4624558	48722484	63405083
MAF (nucleotide)	0.28 (G)	0.24 (G)	0.24 (A)
p-value	1.45^{-6}	6.79^{-6}	2.88^{-6}
Functional effect	Intergenic variant		
Nearest gene(s)	*RPS4XP2*	*AC091770.3*	*LINC00448*
	PRNP	*AC004899.3*	*LINC00376*

Table 9 summarises important identifiers of the three top variants identified in the GWAS analysis. Bp: base pair. This table was generated using GENE2GENE ANNOVAR and SNP Annotation analysis on the FUMA website [https://fuma.ctglab.nl/gene2func] and ENSEMBL [https://www.ensembl.org/index.html]. rsID: Reference SNP cluster ID; SE: standard error.

The GENE2GENE ANNOVAR and SNP Annotation analysis on FUMA (Watanabe et al., 2017) revealed the three intergenic SNPs closest to two genes each: rs6052713 was closest to *RPS4XP2* and *PRNP* on chromosome 20; rs11771415 was closest to *AC091770.3* and *AC004899.3* on chromosome seven; rs7317597 was closest to *LINC00448* and *LINC00376* on chromosome 13 (Table 9). Notably, *PRNP* and *RPS4XP2* exhibit high expression levels during the prenatal stages (8-26 weeks post-conception) and early infancy (4-10 months post-conception) (Figure 11), suggesting a crucial role in brain development. In contrast, *AC004899.3*, *AC091770.3*, *LINC00376*, and *LINC00448* show low expression across all stages, indicating they may have less involvement in early developmental processes.

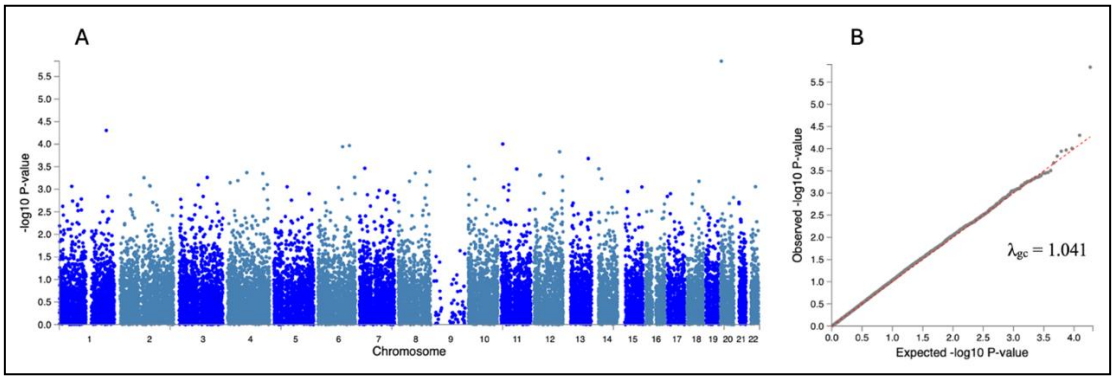


Figure 9: Genome-Wide Association Analysis for the left caudate

A. Manhattan plot: shows the associated SNPs on 22 human chromosomes, indicated on the x-axis, with the -log10 p-value on the y-axis. No significant SNPs were found. B. QQ-plot: shows the normal distribution that fits the theoretical distribution when comparing the expected -log10 p-value, on the x-axis, and the observed -log10 p-value, on the y-axis. This figure has a genomic inflation rate (λ_{GC}) of 1.041, which is indicative of positive associations. These figures were generated using SNP2GENE on the FUMA website [https://fuma.ctglab.nl/snp2gene].

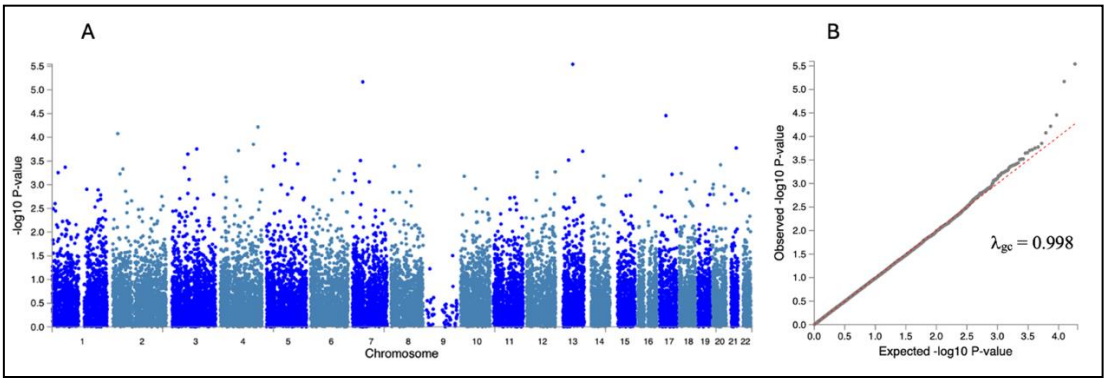


Figure 10: Genome-Wide Association Analysis for the right hippocampus

A. Manhattan plot: shows the associated SNPs on 22 human chromosomes, indicated on the x-axis, with the -log10 p-value on the y-axis. No significant SNPs were found. B. QQ-plot: shows the normal distribution that fits the theoretical distribution when comparing the expected -log10 p-value, on the x-axis, and the observed -log10 p-value, on the y-axis. This figure has a genomic inflation rate (λ_{GC}) of 1.041, which is indicative of positive associations. These figures were generated using SNP2GENE on the FUMA website [https://fuma.ctglab.nl/snp2gene]. GWAS: Genome-Wide Association Study.

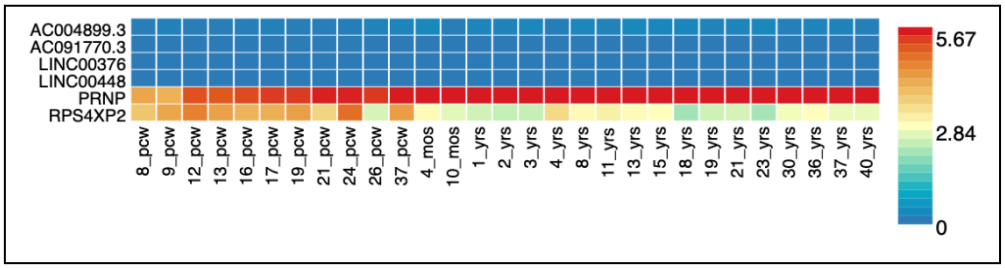


Figure 11: Heatmap of gene expression across various brain development stages

Figure 11 shows a heatmap displaying the expression levels of genes closest to SNPs across different developmental stages. The y-axis lists the genes, and the x-axis denotes various life stages, ranging from eight weeks post-conception (pcw), months (mos) to 40 years (yrs). The colour gradient shown on the right, represents gene expression values as a sliding scale, with blue indicating lower expression, yellow indicating intermediate expression, and red representing high expression levels. The figure was generated using GENE2GENE ANNOVAR on the FUMA website [https://fuma.ctglab.nl/gene2func].

4.7.Popcorn

The frequencies of genetic variants can vary across populations due to evolutionary factors (Choudhury et al., 2014). Popcorn enables the estimation of transethnic genetic correlations. To account for genetic diversity, genetic correlations between the DCHS cohort (hereafter referred to as the African population) and the Satizibal *et al.* (2019) European cohort (hereafter referred to as the European population) was calculated using the Popcorn package (Brown et al., 2016). This quantifies the extent to which the genetic architecture of each subcortical brain volume is similar across different ancestries. Furthermore, these scores provide insights into how population-specific evolutionary forces, such as selection and drift, influence genetic associations on complex traits (Brown et al., 2016).

The initial step of this analysis was to calculate cross-population scores from the 1,000 Genomes Phase III reference panel for the African and European populations (Auton et al., 2015). This score file was compared to the African and European summary statistics. Initially, for the summary statistics, 37,016 SNPs were detected for the African population and 49,999 SNPs for the European population. After both cohorts were integrated with the score file, 1,175 SNPs remained. Finally, after allele frequency check and self-complementary SNP-removal, only 224 SNPs remained for analysis (Figure 12).

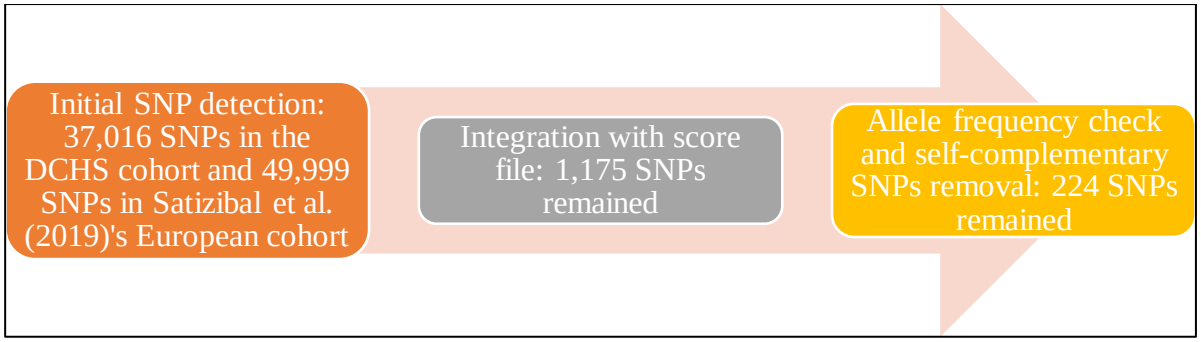


Figure 12: Popcorn pipeline of SNP detection and retention

Figure 12 illustrates the workflow of the Popcorn pipeline used for SNP detection and retention. SNP: single nucleotide polymorphism; DCHS: Drakenstein Child Health Study.

Heritability estimates (h_1^2 and h_2^2) – reflecting genetic contributions to subcortical brain volumes in the DCHS and European cohort, respectively – exhibited high standard errors and non-significant p-values (Table 10). For the DCHS cohort, the highest h_1^2 was observed in the caudate (h_1^2 = 530.406, standard error = 998.011, p = 0.595), and the lowest h_1^2 was observed in the putamen (h_1^2 = -776.088, standard error = 716.549, p = 0.279).

Additionally, Popcorn calculates genetic impact correlation (r_{gi}), which accounts for allele frequency differences and weighs common alleles more heavily than rare ones. The accumbens, caudate, pallidum, and thalamus regions showed no genetic impact correlations. The exceptions, which include the amygdala (rg_i = 3.605, p = 0.517), hippocampus (rg_i = 2.367, p = 0.871), and putamen (0.908, p = 0.966), had measurable but non-significant correlations (Table 10).

Table 10: Statistics for common-SNP heritability and genetic correlation for each subcortical brain region

		Observed values	**Standard Error**	**Z-score**	**P-value**
Accumbens	h_1^2	179.669	1,274.542	0.141	0.888
	h_2^2	-2.194	6.035	-0.364	0.716
	rg_i	No genetic impact			
Amygdala	h_1^2	-542.185	434.086	-1.249	0.212
	h_2^2	-2.194	6.035	-0.364	0.716
	rg_i	3.605	4.024	-0.647	0.517
Caudate	h_1^2	530.406	998.011	0.531	0.595
	h_2^2	-2.194	6.035	-0.364	0.716
	rg_i	No genetic impact			
Hippocampus	h_1^2	-402.575	799.955	-0.503	0.615
	h_2^2	-2.194	6.035	-0.364	0.716
	rg_i	2.367	8.451	-0.162	0.871
Pallidum	h_1^2	292.452	528.299	0.554	0.580
	h_2^2	-2.194	6.035	-0.364	0.716
	rg_i	No genetic impact			
Putamen	h_1^2	-776.088	716.549	-1.083	0.279
	h_2^2	-2.194	6.035	-0.364	0.716
	rg_i	0.908	2.182	0.042	0.966
Thalamus	h_1^2	415.550	533.067	0.780	0.436
	h_2^2	-2.194	6.035	-0.364	0.716
	rg_i	No genetic impact			

Table 10 shows the statistics for common-SNP heritability (h_1^2:Drakenstein Child Health Study; h_2^2:Satizibal et al. (2019)'s European cohort) and genetic impact correlation (rg_i) for the seven subcortical brain regions. "No genetic impact" indicates that there was no significant genetic effect for that specific genetic component in the corresponding brain region. This table was generated using the Popcorn tool [https://github.com/brielin/Popcorn]. SNP: single nucleotide polymorphism.

5. Discussion

In summary, this study investigated how children's genetic risk for MDD and PTSD influences subcortical brain volumes at two years of age, using a South African cohort. As a secondary analysis, it was investigated whether maternal symptoms of depression and PTSD interact with the child's genetic risk to impact the subcortical brain volumes. To the best of my knowledge, this study is the first to explore the association between child genetic risk for MDD and PTSD with maternal antenatal symptoms of depression and PTSD and the impact on child subcortical brain volumes in a South African population.

The findings from this study are partly consistent with prior research while also revealing novel associations. Specifically, for depression, model G (subcortical brain volume ~ PRS + PCs + covariates) was linked to variations in the thalamus, hippocampus, putamen, and pallidum volumes, while model GxE (subcortical brain volume ~ (maternal symptoms x PRS) + PCs + covariates) was associated with larger caudate volumes. This partly aligns with previous studies in European and Southeast Asian populations that reported associations with the caudate (G), amygdala (GxE), and hippocampus (GxE) (Acosta et al., 2021; Acosta, Kantojärvi, Tuulari, et al., 2020; Qiu et al., 2017). Additionally, for PTSD, this study revealed significant associations with model G and the putamen, pallidum, and hippocampus volumes; model E (subcortical brain volume ~ maternal symptoms + covariates) with smaller left thalamus volumes; and models G+E (subcortical brain volume ~ (maternal symptoms + PRS) + PCs + covariates) and GxE with larger thalamus and caudate volumes, respectively. Finally, this study aimed to identify genetic loci associated with subcortical brain volumes in two-year-old South African children. No SNPs reached genome-wide significance, but three top SNPs were identified: rs6052713 was closest to *RPS4XP2* and *PRNP* on chromosome 20; rs11771415 was closest to *AC091770.3* and *AC004899.3* on chromosome seven; rs7317597 was closest to *LINC00448* and *LINC00376* on chromosome 13. However, trans-ancestry genetic correlations were too underpowered to detect shared genetic architecture with European studies.

These findings emphasise the critical role of considering the genetic risk for depression and PTSD, as well as environmental factors (maternal antenatal symptoms of depression and PTSD) in shaping subcortical brain volumes in children. By investigating how these factors impact subcortical brain development, we can gain valuable insights into the mechanisms

underlying the risk for psychopathology in children. Moreover, this underscores the need for further research in diverse populations to uncover novel associations and advance our understanding in this field. I next expand on this summary, covering key findings, insights into existing research, exploratory and null findings, contextualisation of results, and finally, strengths and limitations of the study.

5.1.Key findings

5.1.1. Best-fit models for genetic associations between subcortical brain volumes and depression and PTSD

The analysis of depression revealed model G (subcortical brain volume ~ PRS + PCs + covariates) was significantly associated with larger volumes of the thalamus, left thalamus, and left hippocampus (B = 5.855, p = 2.20^{-16}; B = 10.683, p = 2.20^{-16}; and B = 8.795, p = 4.43^{-13}, respectively). The analysis also revealed negative associations with the right thalamus (B = -4.828, p = 2.20^{-16}), putamen (B = -89.210, p = 1.86^{-8}), and pallidum (B = -18.444, p = 7.12^{-9}), as well as both the left and right putamen (B = -27.352, p = 1.25^{-7}; B = -61.858, p = 4.07^{-8}; respectively). These findings align with previous studies that suggest structural changes in regions involved in emotion, motor control, and reward processing may underlie depressive symptoms (Drevets et al., 2008). Moreover, model GxE (subcortical brain volume ~ (PRS x maternal antenatal symptoms of PTSD) + PCs + covariates) was the best-fit model for the caudate (B = 146.250, p = 9.94^{-11}; B = 66.809, p = 1.04^{-9}; and B = 79.441, p = 9.94^{-11}, for bilateral, left, and right caudate, respectively). This suggests that both genetic and environmental influences on the caudate may be particularly important in understanding depression, especially in the context of prenatal environmental factors (Pradhan et al., 2014).

In the analysis of PTSD, model G was again the best-fit model, associated with observed differences including the larger putamen (B = 7.461, p = 2.64^{-8}), right putamen (B = 15.110, p = 8.70^{-8}) and larger right pallidum (B = 9.152, p = 9.27^{-9}), smaller left putamen (B = -7.649, p = 1.32^{-7}), and left hippocampus (B = -27.698, p = 3.04^{-13}). These findings reflect previous research indicating that structural abnormalities in the basal ganglia and hippocampus are related to PTSD, which is characterised by alterations in emotional regulation and memory processing (Boukezzi et al., 2020). Notably, model G+E (subcortical brain volume ~ (PRS +

maternal antenatal symptoms of PTSD) + PCs + covariates), which incorporated the additive interaction with maternal antenatal depression symptoms, was the best-fit model for the thalamus, showing significant positive associations with thalamic volumes (B = 36.463, p = 2.20^{-16}; and B = 6.470, p = 2.20^{-16}, for bilateral and right thalamus, respectively). This suggests that the thalamus, a region involved in sensory integration and attention regulation, may be sensitive to both genetic and environmental influences in PTSD (Yoshii, 2021). Finally, model GxE was the best fit for the caudate, with significant associations with larger volumes in all regions of the caudate (B = 247.640, p = 6.85^{-11}; B = 117.558, p = 1.25^{-9}; and B = 130.082, p = 4.05^{-11}, for bilateral, left, and right caudate). These findings highlight the caudate's centrality in stress and reward processing, frequently disrupted in PTSD (Boukezzi et al., 2020). Together, these results emphasise the complex interplay between genetic risk and environmental factors in shaping brain volumes and contributing to the risk for psychiatric disorders such as depression and PTSD.

5.1.2. Alterations in subcortical brain volumes and their significance in psychiatric disorders

My findings indicate that smaller putamen and right pallidum volumes are associated with model G in depression, emphasising the significance of genetic risk, including both PRS and genetic PCs. Results in the PTSD analysis showed both larger and smaller putamen and smaller pallidum volumes are associated with model G. A recent study done in the ABCD study has shown smaller putamen and pallidum volumes to be associated with familial depression (van Dijk et al., 2024). This has been supported by previous research (Espinoza Oyarce et al., 2020), often seen in schizophrenia and depression, where it contributes to symptoms including motor slowing and anhedonia, a reduced ability to experience pleasure (Liang et al., 2022). However, research on PTSD has predominantly focused on the hippocampus and amygdala volumes (Logue et al., 2018). In contrast, fewer studies have examined the putamen and pallidum volumes and PTSD.

The putamen, pallidum, caudate (basal ganglia), thalamus and hippocampus are key subcortical structures implicated in various psychiatric disorders due to their roles in emotion regulation, reward processing, and behavioural control (Ji et al., 2019). My results show alterations in these structures, highlighting their relevance. The basal ganglia, comprising the striatum

(caudate, putamen, nucleus accumbens) and pallidum, primarily regulate motor control, learning, and emotions (Lanciego et al., 2012), with additional connectivity to the thalamus and hippocampus (Knierim, 2015).

The caudate is involved in planning movement, learning, memory, reward, and emotion and plays a significant role in habit formation and goal-directed behaviour (Grahn et al., 2008). My findings indicate larger caudate volumes in both depression and PTSD (model GxE), which aligns with a previous study in the same South African cohort revealing enlarged caudate after antenatal maternal depression exposure (Groenewold et al., 2022). In contrast, other studies have shown smaller caudate volumes associated with depression (M. J. Kim et al., 2008), PTSD (Herringa et al., 2012), schizophrenia (Levitt et al., 2002), suicide ideation (Ho et al., 2021), and bipolar disorder (Beyer et al., 2004). This is possibly due to overlapping symptoms linked to cognitive impairments, including difficulties in learning and memory retention (Ho et al., 2021).

The thalamus, a relay station connecting the basal ganglia and cortex (Lanciego et al., 2012), showed both larger and smaller volumes in depression (model G) and larger volumes in PTSD (model G+E). Thalamic responses to fearful stimuli may explain its role in emotional distress in depression and heightened fear responses in PTSD (Burra et al., 2019). However, it has been noted that severe stress can induce lateral brain atrophy (Yoshii et al., 2017), potentially accounting for the laterality in the pathological significance of the thalamus (Yoshii, 2021).

The hippocampus is crucial for memory, learning, and emotion regulation (Lanciego et al., 2012). My results showed model G was associated with larger left hippocampus volumes in depression but smaller left hippocampus volumes in PTSD. Smaller hippocampus volumes have consistently been reported in psychiatric and neurodevelopmental literature (Erickson et al., 2012; Logue et al., 2018; Opel et al., 2014). Additionally, Acosta *et al.* reported smaller hippocampus volumes in children of mothers with prenatal maternal anxiety (Acosta et al., 2021) and sex-specific interaction GxE of prenatal maternal depression (Acosta H et al., 2020).

The beta coefficients in these models, which capture the influence on subcortical brain volumes, vary in both direction and size. This variability underscores the intricate relationship between these factors and subcortical brain volumes, potentially reflecting interactions or

opposing effects. Moreover, the substantial standard errors associated with these beta values may arise from small sample sizes, multicollinearity among predictors, or insufficient statistical power, all of which warrant cautious interpretation of the findings. This is a common challenge in this area of research due to its inherent complexity, underscoring the need to interpret my findings within a similar contextual framework.

5.1.3. Genetic influences on subcortical brain volumes

Subcortical regions are critical for emotional processing, reward systems, and motor control. The high heritability estimates (47% – 85%) underline that genetic factors play a dominant role in determining the size and structure of these regions (Satizabal et al., 2019), suggesting that individual variations are largely inherited. More recently, the polygenic overlap between depression and subcortical brain volumes has been investigated. A 2024 study investigated the extent of polygenic overlap using MiXeR using summary statistics from the largest genome-wide association studies for depression (N = 674,452) and 14 subcortical volumetric phenotypes (N = 33,224) (Liu et al., 2024). The findings from Liu *et al.* (2024) highlight a significant genetic overlap between subcortical brain traits and depressive disorders. The putamen, with its extensive overlap (up to 83.3%), may play a pivotal role in depression, aligning with its known involvement in reward-related processing and motivation (Talati et al., 2022). The lower overlap observed in the pallidum and thalamus (27.7% – 51.7%) suggests that these regions are influenced by other genetic or environmental factors, reflecting a more complex interplay in their relationship with symptoms of depression (Liu et al., 2024). Interestingly, the variation in the ratio of shared to total genetic variants (7.4% – 28.5%) implies that the extent of genetic overlap is not uniform across subcortical regions. This heterogeneity points to region-specific genetic mechanisms driving the observed traits (Liu et al., 2024). For example, regions such as the putamen may have more shared pathways with depression, possibly through dopaminergic systems, while the thalamus may involve additional, non-shared factors (Gong et al., 2017). These findings highlight the importance of considering the genetic factors – genetic risk scores and PCs – underlying both subcortical brain volumes and psychiatric disorders. Additionally, incorporating the interaction with environmental influences that shape their structure and function could deepen our understanding of how specific brain regions contribute to the pathophysiology of psychiatric disorders.

5.2. Insights into existing research

5.2.1. Comparative findings from related research on depression

When comparing this study's findings to previous research, summarised by Alex *et al.* (2023), several important overlaps and distinctions emerge in understanding how genetic and environmental factors shape brain development while considering maternal mental health. The work by Acosta *et al.* (2020) underscores the complexity of these gene-environment interactions. They used a neuroimaging subset of the FinnBrain birth cohort of Finnish mother-infant dyads (N = 105), with infants between the ages of 11 – 54 days. Acosta *et al.* (2020) found that maternal antenatal symptoms of depression were linked to smaller left putamen and right caudate volumes in a Finnish cohort, with associations that varied by sex. Specifically, the study found that the relationship between PRS-MDD and caudate volumes was stronger in boys than girls. Additionally, in a subsequent study using the same FinnBrain cohort, Acosta *et al.* (2020) found that PRS-MDD was linked to right amygdalar volumes in infants, though this association became non-significant after correction. As partial support of these studies, my study also showed that model G was significantly associated with smaller bilateral, left, and right putamen for depression. Additionally, model GxE was significantly associated with larger bilateral, left, and right caudate volumes. As a novel finding, model G was associated with smaller bilateral and right putamen and with larger left putamen volumes for PTSD. Furthermore, model GxE was significantly associated with larger bilateral, left, and right caudate volumes. However, unlike these studies, my study found no significant associations with amygdala volumes.

Acosta *et al.*'s research and my study both highlight the influence of genetic and environmental factors on subcortical brain volumes but reveal distinct patterns of association likely due to differences in methodology, populations, and study focus. Acosta *et al.* emphasised sex-specific associations, which revealed novel insights, an area not explicitly addressed in my analysis. The sample sizes and child ages between the two studies differ with Acosta *et al.*, including 105 mother-infant dyads with infants aged 11 – 54 days, compared to the 128 mother-child dyads aged 924 – 1191 days from DCHS. These variations in age are important because different stages of child development are more or less sensitive to environmental influences (Miguel et al., 2019). Furthermore, Acosta *et al.* focused on specific subcortical regions in their studies, examining the caudate and putamen in the 2020 study and the amygdala and

hippocampus in the 2021 study. In contrast, I analysed all seven subcortical regions, further divided into lateral regions, providing a more comprehensive exploration but requiring more stringent multiple correction thresholds. While this broader approach increases robustness and reduces potential biases, it may explain why my findings extend beyond those reported by Acosta *et al.* Finally, differences in maternal depression assessments further distinguish the studies. Acosta *et al.* used only the EPDS to measure maternal antenatal symptoms of depression, whereas I incorporates four different measures (EPDS, BDI-II, SRQ-20, and MINI). Cases in this study had to have symptoms of depression in at least two of the four measures, providing a more rigorous and multidimensional evaluation of maternal mental health. The methodological and population differences noted here likely contribute to the variation in findings between the two studies.

A study by Qiu *et al.* (2017) focused on a neuroimaging subset of the GUSTO cohort of Southeast Asian mother-neonate dyads (N = 253), with infants aged between 5 – 14 days. They found that maternal antenatal symptoms of depression interacted with a PRS-MDD to influence the right hippocampus and amygdala. Whereas my study revealed a GxE interaction in the bilateral, left, and right caudate volumes. These differences may arise from a combination of environmental, methodological, and population-specific factors. In calculating the PRSs, I analysed European, African, and a meta-analysed population from the PGC to determine the best fit for the cohort, whereas Qiu *et al.* (2017) relied solely on the European PGC cohort. Furthermore, Qiu *et al.* only investigated two subcortical brain regions, the amygdala and hippocampus, whereas my study included all seven subcortical brain regions, further divided into lateral regions. Although this provided a more comprehensive investigation, it required more stringent multiple correction thresholds. Similar to Acosta *et al.*, Qiu *et al.* (2017) used only the EPDS to screen for symptoms of depression. Additionally, Qiu *et al.* (2017) had a sample size (N = 253) that was double that of ours (N = 128), and this difference may have influenced their findings.

Despite these differences, these studies underscore the importance of genetic and environmental influences on brain development, particularly in subcortical regions, and suggest that maternal mental health plays a critical role in shaping these outcomes.

5.2.2. The strong link between depression and PTSD

Depression and PTSD are often comorbid due to overlapping risk factors, including trauma exposure (Ndungu et al., 2020), and genetic predisposition (genetic correlation (r_g) = 0.71–0.08) (Zhang et al., 2022). This means that some of the associations observed with PRS-MDD could also capture shared genetic vulnerabilities linked to PTSD and vice versa (Mundy et al., 2022). Although previous studies with similar aims have not examined PTSD specifically, the genetic links between depression and PTSD suggest that brain volume differences observed in children with a genetic risk for depression could, to some extent, reflect underlying susceptibilities relevant to PTSD as well. Out of the 1,189 mothers, 129 (11%) of the mothers had antenatal symptoms of both depression and PTSD, after applying the stringent criteria of meeting the threshold for at least two measures relevant to each disorder. Of the mothers (N = 128) included in the neuroimaging sub-study, nine mothers (7%) had symptoms of both. Furthermore, the PRSs from the best-fit models for PRS-MDD and PRS-PTSD were positively correlated (r = 0.177, p = 0.024), indicating a degree of shared genetic architecture. However, the presence of distinct associations for each PRS in the study's findings suggests that the tools are effectively distinguishing between the phenotypes, despite some genetic overlap. This is substantiated by the overlapping findings between depression and PTSD in this study.

My results highlight significant associations with the same subcortical brain regions across depression and PTSD. For example, in both depression and PTSD, thalamus volumes were influenced by genetic factors. However, it is important to note the differences in best-fit models: in depression, model G was the best-fit model for the thalamus (bilateral: B = 5.855, $p = 2.20^{-16}$; left: B = 10.683, $p = 2.20^{-16}$, and right: B = -4.828, $p = 2.20^{-16}$); whereas, in PTSD, model G+E was the best-fit model for bilateral (B = 36.463, $p = 2.20^{-16}$) and right thalamus volumes (B = 6.470, $p = 2.20^{-16}$), and model E was the best-fit for left thalamus (B = -239.901, $p = 2.20^{-16}$). Notably, the effect size and direction of lateral volumes vary between disorders, depending on the best-fit model, suggesting that different models do indeed still capture distinct brain volume patterns in depression and PTSD, reflecting the complexity of genetic and environmental interactions. Similar trends regarding the effect sizes and directions are seen in the putamen, left hippocampus, and right pallidum volumes in this study.

For both conditions, model GxE was the best-fit model for the caudate, with this interaction model associated with larger caudate volumes (depression: bilateral: B = 146.250, $p = 9.94^{-11}$; left: B = 66.809, $p = 1.04^{-9}$; right: B = 79.441, $p = 9.94^{-11}$; PTSD: bilateral: B = 247.640, $p = 6.85^{-11}$; left: B = 117.558, $p = 1.25^{-9}$; right: B = 130.082, $p = 4.05^{-11}$). This finding suggests that genetic and environmental interactions play a significant role in shaping caudate volumes. Previous studies have shown that the caudate has a strong heritable component (family-based $h^2 = 71 – 85\%$; SNP-based $h^2 = 26\% – 36\%$) (Satizabal et al., 2019) and is critical for reward processing and habit formation. While this may indicate a shared neurobiological susceptibility to conditions like depression and PTSD, it does not imply that genetic contributions are larger when both conditions are present; rather, overlapping genetic association might explain some common variance (Smoller, 2016). Difficulty managing and regulating emotions, a common feature of both conditions, has been linked to caudate function in previous research (Grahn et al., 2008), suggesting that this brain region could mediate shared vulnerabilities. Finally, these findings may have implications for understanding pathways to risk and resilience in the context of early adversity.

5.3. Exploratory findings

5.3.1. Maternal antenatal symptoms of PTSD improve model fit for the left thalamus

Subcortical brain development is shaped by the interplay between genetic predispositions and environmental influences. Among these, maternal antenatal psychological distress has been linked to structural and functional changes in a child's brain. Studies highlight its associations on regions including the thalamus, hippocampus, and amygdala, which are crucial for cognitive, emotional, and motor processes (Koen et al., 2017). My study found that maternal antenatal symptoms of PTSD, as modelled in model E, were significantly associated with smaller left thalamus volumes (B = -239.901, $p = 2.20^{-16}$). This result underscores the relevance of investigating both genetic and environmental influences and their interaction on subcortical brain development, aligning with growing research on maternal mental health and child brain structure (Bremner, 2006). These findings align with insights from Mandl *et al.* (2024), who conducted a systematic review regarding how maternal antenatal distress affects foetal and infant brains, observing consistent structural and functional alterations in limbic and cortical areas due to elevated prenatal stress exposure (Mandl et al., 2024).

Maternal antenatal symptoms of distress, including depression and PTSD, not only affect the maternal-foetal environment but also influence child brain development (Dufford et al., 2021; Muglia et al., 2022). These can be through mechanisms including HPA-axis dysregulation, epigenetic modifications, and neuroinflammation (Pagliaccio et al., 2015). The left thalamus, known for its role in sensory integration and cognitive processes (Sommer, 2003), is particularly vulnerable to these influences. The review by Mandl *et al.* (2024) highlighted how stress-responsive subcortical regions, such as the thalamus and hippocampus, undergo structural adaptations under prenatal stress exposure. These adaptations may predispose individuals to neuropsychiatric conditions in later life. Another literature review conducted in 2021 specifically revealed smaller thalamus volumes in individuals diagnosed with PTSD (Yoshii, 2021a), suggesting a convergence of evidence linking PTSD to structural alterations in this region. These findings align with the observations of smaller left thalamus volumes in children of mothers with antenatal symptoms of PTSD.

Together, this research underscores the thalamus as a key subcortical region impacted by maternal PTSD, suggesting that disrupted development of the thalamus could lead to widespread dysfunction across neural networks. The integration of maternal PTSD symptoms into predictive models, as done in model E, enhances their explanatory power and supports the growing recognition of maternal mental health as a determinant of neurodevelopmental outcomes.

5.3.2. Polygenic Risk Score (PRS)

Large-scale investigations found that the genetic loci associated with depression and PTSD exhibited variability across different ancestral backgrounds (Meng et al., 2024; Nievergelt et al., 2019), highlighting how genetic information, for example, PRSs, may not be easily transferable across populations (Adam et al., 2022). A critical measure in PRS studies is the percentage of phenotypic variance explained (depicted by the R^2 value), which indicates how well genetic scores predict the trait of interest. For depression, the best-fitting PRS models' R^2 values ranged between 1.3% – 19.8%, while for PTSD, the variance explained was lower, with the R^2 value ranging between 1.9% – 5.6%. The upper bound of 19.8% for depression PRS is notably higher than what is typically reported in the literature, where values usually fall between 1% and 3% (Howard et al., 2019; Kanjira et al., 2024). This discrepancy may be due

to several factors, including differences in the discovery cohorts used to generate the PRS, the specific characteristics and size of the DCHS sample, and how the data were subdivided for analysis. For example, overfitting in smaller subgroups or population-specific genetic architecture could inflate the variance explained (Aw et al., 2024). These factors highlight the importance of cautious interpretation of these estimates, which may not fully generalise beyond the current dataset. Further discussion of these points and their implications is provided below.

In the PGC working groups, PRS models in European ancestries have been shown to explain between 1.5% – 3.2% of the variance in depression risk (Howard et al., 2019) and approximately 5.0% in PTSD (Misganaw et al., 2019). However, when these models are applied to African populations, the variance explained by PRS decreases significantly, likely due to differences in genetic architecture (depression: R^2 = 2.0%, ancestry-matched: 1.8%; and PTSD: R^2 = 1.3%, ancestry-matched: 0.2%) (Kanjira et al., 2024; Swart et al., 2021). My research partially supports this conclusion since within the full maternal cohort (N = 1,189), I observed low R^2 values when using the PGC-European discovery cohort (R^2 = 5.3% for depression and R^2 = 1.9% for PTSD). The predictive accuracy of PRS is also reduced in admixed populations due to differing LD structures, which affect the stability of risk scores (Bitarello & Mathieson, 2020). This finding highlights the low predictive accuracy of PRS for psychiatric conditions in African ancestry populations, which is attributed to their unique genetic architectures, the significant underrepresentation of these populations in GWAS and the limited tools to take these population differences into account in PRS models (Martin et al., 2019).

Dividing the DCHS cohort by microarray revealed a notable impact on PRS performance, with differences in SNP coverage and sensitivity influencing results and leading to higher R^2 values, particularly in depression (Depression: PsychChip: R^2 = 19.8% and GSA: R^2 = 9.0%; PTSD: PsychChip: R^2 = 4.1% and GSA: R^2 = 5.6%). However, this approach did reduce statistical power by subdividing the cohort, which should be considered when interpreting these results. Notably, I observed both positive and negative PRS values in the children for depression and PTSD. The average PRS for depression was -8.63^{-7}, ranging from -2.73^{-6} to 1.39^{-6}; and the average PRS for PTSD was 1.21^{-6}, ranging from -5.52^{-7} to 2.14^{-6}. The negative average PRS values for depression reflect the use of raw, unstandardised scores in the analysis. Unlike standardised scores, which are typically scaled to have a mean of zero and a standard deviation

of one within the target sample, raw PRS values represent the weighted sum of risk alleles based on effect sizes from the discovery GWAS (Choi et al., 2020). Negative PRSs indicate the presence of protective genetic markers (Hou et al., 2022), suggesting they are less likely to develop depression or PTSD compared to those with positive PRS values (Muniz Carvalho et al., 2021). This highlights the variability within the cohort and underscores the importance of accurately capturing genetic diversity to ensure robust and meaningful interpretations.

Microarrays differ in their ability to detect SNPs, particularly those common in non-European ancestries, due to variations in sensitivity to minor allele frequencies and SNP coverage (Kachuri et al., 2024). Arrays designed for European populations often perform less effectively in other populations, potentially underrepresenting variants prevalent in African ancestry and impacting the accuracy of trait-specific studies (Bumgarner, 2013; Wonkam et al., 2022). Among the arrays used in this study, the PsychChip (N = 35) was specifically designed for psychiatric and neurological research (https://www.illumina.com/products/by-type/microarray-kits/infinium-psycharray.html). In contrast, the GSA (N = 128) has been designed for global diversity and offers comprehensive coverage of common variants across multiple populations (https://www.illumina.com/products/by-type/microarray-kits/infinium-global-screening.html). While the larger sample size of incorporating both microarrays could have resulted in more predictive power, the key consideration was that the PsychChip and GSA measure different sets of SNPs. The GSA's optimisation, with its inclusive representation of genetic diversity, made it a more suitable choice for the study, although still not specifically suited to Southern African populations.

5.4. Null findings

5.4.1. GWAS of subcortical brain volumes at two years of age

The secondary aim of this study was to identify associations between SNPs and subcortical brain volumes in children by testing for differences in the allele frequency of genetic variants across the genome. Understanding these associations through GWAS is crucial, as they allow us to uncover genetic factors that may influence brain structure and function, contributing to our knowledge of the underlying mechanisms of psychiatric disorders in diverse populations. The top three SNPs were associated with the left caudate and right hippocampus but did not reach genome-wide significance. Despite the lack of significant findings, this study

underscores the importance of expanding GWAS efforts in African and Mixed ancestry populations, where larger sample sizes may yield more robust insights into genetic contributions to brain structure and psychiatric vulnerability.

The differential expression patterns of six genes nearest to the three identified SNPs suggest roles in brain development. The three identified SNPs include: rs6052713 closest to *RPS4XP2* and *PRNP* on chromosome 20; rs11771415 closest to *AC091770.3* and *AC004899.3* on chromosome seven; rs7317597 closest to *LINC00448* and *LINC00376* on chromosome 13. Among these, *PRNP*, encoding a prion protein, and *RPS4XP2*, encoding ribosomal protein S4 X-linked pseudogene 2, have notable expression during early prenatal stages and late infancy, indicating their potential importance in early development. *PRNP* is implicated in neurodevelopmental functions including memory and spatial learning (Kovač & Čurin Šerbec, 2022). *RPS4XP2* is associated with ribosomal function and protein synthesis (X. Zhou et al., 2015), but its role in psychiatric genetics remains unclear. The other four genes – *AC091770.3*, *AC004899.3*, *LINC00376*, and *LINC00448* – are long intergenic non-coding RNAs (lncRNAs) that exhibit expression across developmental stages. Emerging research suggests that over 50% of lncRNAs are active in the brain (Mercer et al., 2008), where they influence gene expression, synaptic function, and chromatin organisation, all of which are essential for maintaining neural structure and plasticity (Rusconi et al., 2020; Zuo et al., 2016). Particularly, lncRNAs are noted for their role in neurodevelopmental processes, as they contribute to the intricate regulation of genes involved in neuron differentiation, connectivity, and response to environmental stressors (G. Wu et al., 2022). While specific functions of many lncRNAs remain unclear, their precise expression patterns and regulatory potential underline their likely involvement in shaping brain architecture and volume, with implications for neurodevelopmental and psychiatric disorders (Roberts et al., 2014).

While the identified SNPs did not reach genome-wide significance, their association with genes involved in neurodevelopment underscores the potential for further research into genetic contributions to brain structure and psychiatric vulnerability.

5.4.2. Trans-ancestry genetic correlation between subcortical brain volumes

The Popcorn program (Brown et al., 2016) was used to compute cross-population heritability values for the subcortical brain volumes between the DCHS cohort and the Satizibal *et al.*

(2019) European discovery cohort. This Bayesian framework provides robust adjustments for ancestral background, leveraging external LD reference panels to account for differences in allele frequencies and genetic architectures between populations. Popcorn's use of both genetic effect (rg_e) and genetic impact (rg_i) correlations allows for a nuanced interpretation of the relationship between SNP effect sizes and their phenotypic impact, even in ancestrally diverse cohorts. The heritability values (h_1^2 and h_2^2) and genetic impact correlation (r_{gi}) estimates reveal key insights into the genetic architecture of subcortical brain traits across populations.

Despite these methodological strengths, the findings revealed null results for cross-population genetic correlations. In this study, heritability estimates (h_1^2 and h_2^2) exhibited high standard errors, indicating substantial variability and reducing confidence in their precision. The non-significant p-values further suggest that these traits may have minimal detectable genetic components in the populations studied. Furthermore, most brain regions showed non-significant genetic impact correlations, implying limited genetic overlap for these traits across populations. The exceptions, which include the amygdala, hippocampus, and putamen, had measurable but non-significant estimates, indicating that genetic differences in these regions may be subtle. Overall, these findings suggest that genetic contributions to these brain traits are difficult to detect within the study samples, and any potential cross-population genetic correlation remains minimal and statistically insignificant. These results reflect several key challenges in conducting genetic studies across ancestrally diverse populations. With their higher genetic diversity, shorter LD blocks, and greater genetic heterogeneity than European populations, African populations enhance the limitations of genotyping arrays, which often fail to capture the full spectrum of genetic variation unique to these populations (Tan & Atkinson, 2023). This lack of coverage likely contributes to the high standard errors and non-significant heritability estimates observed in my analysis.

Additionally, while Popcorn adjusts for LD and is designed to handle summary-level data, the high genetic diversity in African populations may reduce its efficacy compared to more homogenous populations (Jones, 2015). This aligns with previous findings indicating that current genetic tools and methods often battle to achieve reliable cross-ancestry comparability (Peterson et al., 2019). The methodological challenges are compounded by the limited sample size in the cohort, which reduces statistical power and further impedes the detection of significant genetic associations. This is exacerbated by the larger sample size of the European

summary statistics, which may skew the results toward European ancestry and introduce biases when applied to the cohort (Button et al., 2013).

My findings underscore the necessity of addressing these barriers through improvements in genotyping arrays, which should include African-specific variants, and through the development of computational tools tailored to ancestrally diverse populations. Expanding the representation of non-European populations in genetic research is crucial to improve our understanding of the genetic architecture of complex traits and ensure the equitable translation of genetic insights into clinical applications.

5.5.Contextualisation of results

Interpreting my results in the context of LMICs in South Africa requires an examination of how the characteristics of the mother-child dyads (N = 128) may have influenced the findings. The DCHS neuroimaging cohort comprises children from African and Mixed ancestry. Genetic variations that are ancestry-specific (Suarez-Pajes et al., 2021) may play a role in the risk of depression or PTSD. Alleles that are more frequent in African ancestry might contribute differently to the risk of depression or PTSD compared to alleles prevalent in European ancestry (McClellan et al., 2017). This genetic variability needs to be accounted for since it can lead to differences in the expression of these disorders, influencing both the prevalence and the severity of symptoms (Popejoy & Fullerton, 2016). Thus, the importance of including diverse ancestries in genetic studies cannot be overstated (Martin et al., 2019).

Furthermore, living in a peri-urban, low-income setting, as seen in the DCHS cohort, can exacerbate psychological stress through limited access to mental health resources, poor living conditions, and frequent exposure to trauma (Knifton & Inglis, 2020). In addition, the prevalence of HIV exposure during pregnancy (47.66%) is notably high in this sample, which may further increase the vulnerability to PTSD and depressive symptoms in the community (Waldron et al., 2021). As we know, high rates of violence, whether domestic or community-based, foster an environment conducive to the development of depression and PTSD (Morina et al., 2017).

These contextual factors are particularly relevant when interpreting the findings of my study, as they may help explain the heightened prevalence of symptoms of depression and PTSD in the cohort, and underscore the importance of considering socioeconomic and environmental stressors in understanding the mental health challenges faced by participants.

5.6.Strengths and limitations

The study incorporated a diverse cohort of children and their mothers from African and Mixed Ancestry populations. The study's focus on underrepresented populations, being one of the first longitudinal African cohorts, adds significant value to the field of genetic research. The study's sample size is similar to work that has been done in European and East Asian populations (Acosta H et al., 2020; Acosta, Kantojärvi, Tuulari, et al., 2020; Qiu et al., 2017). In addition, I conducted an exploratory analysis allowing for an unbiased approach in the identification of significant results (Rubin & Donkin, 2022). The study used cutting-edge analysis pipelines, such as PRS-CSx and Popcorn, to account for differences in ancestry and enhance the predictive accuracy of genetic risk across diverse populations (Brown et al., 2016; Choi et al., 2020). Furthermore, using maternal case status to guide the selection of children's PRS models creatively addresses the challenge of assessing phenotypic markers despite their young age. Lastly, the integration of multiple linear regression analysis provides a robust statistical framework for examining complex relationships between predictors and outcomes, enhancing the study's depth and potential impact.

Although this study is unique in several ways, some limitations need to be acknowledged. These include sample size and power, the use of genotyping microarrays that are not ideally suited to African populations, the limitations of PRS-CSx, and other methodological challenges that are particularly pronounced when working with diverse African populations.

The primary limitation of this study is the relatively small sample size (N = 128), which affects statistical power (Biau et al., 2008; Button et al., 2013). However, the sample size is comparable to other studies with similar aims, such as Acosta *et al.*, 2020: N = 105; Qiu *et al.*, 2017: N = 253 (Acosta, Kantojärvi, Hashempour, et al., 2020; Acosta, Kantojärvi, Tuulari, et al., 2020; Qiu et al., 2017; Y. Wu et al., 2021). The GWAS analysis, however, is severely underpowered and serves as a pilot to motivate increasing sample sizes in future

neuropsychiatric genetics and imaging studies. Given how rare studies of this nature are, further investigation with larger, better-powered studies is essential since they provide valuable insights into the genetic factors influencing mental health in underrepresented populations.

Secondly, in my study, the use of genotyping arrays introduces several limitations when working with African populations. Genotyping arrays, such as those used in this research, are often designed based on reference panels from European or other non-African populations, which do not capture the full extent of genetic variation found in African genomes (A. R. Martin et al., 2018; Xu et al., 2022). This lack of specificity reduces the precision and power of genome-wide analyses, a key limitation given the high genetic diversity and distinct LD patterns present in Sub-Saharan African populations (Campbell & Tishkoff, 2008). Consequently, many private haplotypes and unique LD structures that are common in these populations may not be adequately represented. The DCHS used two genomic reference panels, the PsychChip and GSA. Due to design differences between these microarrays, as discussed above, it was necessary to split the data by microarray, which further reduced the statistical power.

Thirdly, imputation further complicates the analysis. Although imputation is commonly used to increase the resolution of genotype data, it relies heavily on reference panels that are predominantly based on non-African ancestries, such as the 1000 Genomes and Haplotype Reference Consortium (HRC) panels (Hancock et al., 2012). This lack of representation reduces the accuracy of imputation, especially when applied to individuals of African descent, who have more complex LD structures and higher genetic diversity (Campbell & Tishkoff, 2008; Tan & Atkinson, 2023). While alternative panels, such as the Consortium on Asthma among African-ancestry Populations in the Americas (CAAPA) (Daya et al., 2019), attempt to address this gap, they remain inadequate in terms of coverage across many African regions, with particular deficiencies noted in Sub-Saharan Africa. In practice, this means that tag-SNPs – selected based on haplotype patterns in non-African populations – may not be appropriate for African genomes, limiting the success of imputation and fine-mapping efforts (Conrad et al., 2006). Despite efforts to overcome these limitations through the use of available reference genomes on platforms such as the Michigan Imputation Server, the underrepresentation of African genomes remains a significant hurdle (Auton et al., 2015). Without large and closely

related reference genomes tailored to African populations, imputation accuracy remains low, reducing the reliability of genetic findings in African cohorts (Button et al., 2013).

Fourth, although the statistical models used in this study are methodologically sound, they could be further optimised. FDR correction is commonly used in studies with multiple comparisons because it effectively controls the expected proportion of false positives among the declared significant results, offering greater statistical power than more conservative methods like Bonferroni correction (Benjamini & Hochberg, 1995). However, it does not guarantee control over the probability of any false positive occurring, and it may be less stringent when tests are highly correlated or when multiple models are involved. In this study, FDR correction was applied across the 21 subcortical brain regions, but not across the five separate models. This approach may underestimate the overall false positive rate, particularly given the multiple iterations of testing (Colquhoun, 2014). Ideally, a permutation-based correction strategy accounting for both brain regions and models would provide more robust control of false discoveries. However, due to the exploratory nature of the study and the limited sample size, we opted for a simplified correction approach. These findings should therefore be interpreted with appropriate caution, and future work with larger samples should adopt more stringent correction methods. Similarly, while PRS is a promising tool for understanding genetic risk, it has notable limitations, especially in diverse populations (Majara et al., 2023). The PRS-CSx approach allows for cross-population polygenic risk scoring, but it still struggles to capture the full genetic architecture of psychiatric disorders, particularly in underrepresented populations (Riefski & Terry, 2023). The scores generated from European-based summary statistics are likely less predictive in African populations due to differences in LD patterns and genetic variation (Majara et al., 2023). While PRS offers insights into disease risk (Lewis & Vassos, 2020), it cannot fully account for genetic loading (Sugrue & Desikan, 2019).

Furthermore, the environmental factors, such as the maternal antenatal psychological symptoms of distress in this LMIC might exert a strong influence (Meyer et al., 2004). Since these associations are very complex, it could be possible that the unique environmental contexts could overwhelm the genetic contribution that PRS is currently able to capture, making it harder for genetic models to outperform environmental or combined models (Schmidt, 2007). Finally, it is also possible that the absence of epigenetic data in the study limited my ability to fully capture gene-environment associations, as epigenetic mechanisms, such as DNA

methylation, may mediate the association of environmental stressors on gene expression, particularly in brain development (Ladd-Acosta & Fallin, 2016).

Fifth, several limitations may explain the lack of significant findings in the amygdala and accumbens. As mentioned previously, the small sample size could reduce the statistical power needed to detect genetic influences, especially in a genetically diverse population (Peterson et al., 2019). This limitation may have led to an underestimation of heritability or gene-environment associations, preventing the genetic model from emerging as a stronger fit. Next, the polygenic nature of depression and PTSD implies that the genetic contributions to these conditions are spread across numerous loci, each with a small effect size, making it harder to capture the genetic and/or environmental contribution with precision (Button et al., 2013; Riley et al., 2020). Furthermore, the focus on SNPs excludes other forms of genetic variation that may account for a significant portion of the heritability of these disorders. For instance, copy number variations (CNVs), which involve larger-scale deletions or duplications of DNA segments, have been implicated in psychiatric phenotypes (Malhotra & Sebat, 2012; Marshall et al., 2017). These structural variations may contribute to genetic risk independently or interactively with SNPs, highlighting the need for broader genomic investigations to fully elucidate the genetic architecture of psychiatric disorders.

Sixth, several limitations may explain the absence of significant main-predictor findings in the study. One key factor could be the inherent complexity of psychiatric and neurodevelopmental disorders, where multiple genes and pathways interact with various environmental stressors (Smoller et al., 2009). Developmental timing may also play a crucial role in how these factors interact (Karmiloff-Smith et al., 2014). It is possible that certain critical periods of brain development were more vulnerable to environmental factors (Volkow et al., 2024), which the study did not fully capture. Gene-environment associations are notoriously difficult to detect without large sample sizes and longitudinal data (Munafò et al., 2014), both of which were limited in this study, given that I focused on a single time point at two years of age and had a final sample size of N = 128. However, it may also be beneficial to analyse all the available time points of the DCHS (neonatal and six years) and include the associations of postnatal maternal symptoms. Additionally, some of the measures used to assess maternal symptoms of depression and PTSD lacked diagnostic precision, focusing on symptoms of depression or PTSD rather than formal diagnoses (BDI-II (Jackson-Koku, 2016), EPDS (Cherry, 2020),

SRQ-20 (Beusenberg et al., 1994), MINI (Lecrubier et al., 1997), mPSS (Falsetti et al., 1993), and a trauma exposure questionnaire (Friedman et al., 2011)). Symptoms of depression and PTSD were prioritised over diagnosis due to the availability of validated measures in this cohort. Various measures were used to assess maternal antenatal symptoms of depression and PTSD.

Finally, there is the potential confounding of direct and indirect genetic effects in the observed associations between child PRSs, maternal antenatal symptoms, and child subcortical brain volumes. Maternal symptoms of depression and PTSD may themselves be partly genetically correlated with the child's PRS, given the shared heritability between mother and child (Smoller, 2016). Consequently, the associations observed with brain volumes may reflect a complex interplay of inherited genetic risk and environmentally mediated maternal influences, rather than purely direct genetic or environmental effects. This interpretive complexity is a common challenge in intergenerational designs and limits the ability to disentangle specific pathways of influence (Branje et al., 2020). Future work could address this by employing family-based or genetically informed study designs, such as comparing maternal versus paternal PRSs, applying transmission disequilibrium tests (TDT), or using polygenic transmission disequilibrium analysis (pTDT), to more robustly parse direct genetic effects from indirect genetic nurture effects. Additionally, incorporating non-transmitted parental alleles or using sibling comparison designs could further help isolate environmentally mediated influences from inherited genetic liability.

In summary, this study's strengths, including its diverse cohort of African and mixed-ancestry populations and the use of state-of-the-art trans-ancestry analyses (e.g. PRS-CSx) need to be considered in light of the limitations. This research, despite its challenges, is essential for advancing our understanding of how children's genetic risk for depression and PTSD and the mother's symptoms of depression and PTSD impact subcortical brain volumes, particularly in underrepresented populations.

5.7.Future directions

Depression and PTSD are complex, polygenic traits with genetic architectures that have yet to be fully accounted for (Duncan et al., 2018; Levey et al., 2020; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Additionally, research on neuropsychiatric genetics

has focused on populations of European ancestry, leading to the underrepresentation of African populations and contributing to healthcare disparities (Sirugo et al., 2019). Given the genetic diversity of African populations – the oldest and most diverse populations (Campbell & Tishkoff, 2008) – they are uniquely positioned to provide insights into the fine-mapping of disease-causing variants (Wonkam et al., 2022).

An expanding amount of software tools and statistical techniques have been created to take admixture into account and make use of it in genomics analysis (Tan & Atkinson, 2023). These include Bridge-PRS, SAIGE, and GMMAT, addressing key challenges including population structure, relatedness, and the accuracy of PRSs across diverse ancestries. BridgePRS focuses on accurately estimating causal effect sizes across ancestries, retaining all variants within loci to better tag shared causal variants (Hoggart et al., 2024). It is particularly suited for integrating well-powered GWAS from diverse populations with smaller target samples. Meanwhile, PRS-CSx uses Bayesian modelling with shrinkage priors to reduce the number of SNPs in a PRS by fine-mapping causal variants (Ruan et al., 2022). BridgePRS outperforms PRS-CSx and other PRS methods, especially in situations with higher uncertainty, such as lower trait heritability, higher polygenicity, and greater genetic diversity. It is also computationally efficient, user-friendly, and particularly effective for PRS analyses in non-European populations (Hoggart et al., 2024). Unfortunately, at the time that the analyses in this study were conducted, Bridge-PRS was not yet publicly available but should be considered for future studies.

Next, Scalable and Accurate Implementation of GEneralized mixed model (SAIGE) has been developed for genome-wide association tests in large-scale data sets and biobanks. It has continuously been updated through 2021 and enhances GWAS by effectively correcting for population stratification and relatedness, which are common in admixed populations (W. Zhou et al., 2020). Generalised Linear Mixed Model Association Tests (GMMAT) uses generalised linear mixed models to perform genetic association tests in GWAS that account for complex population structures and relatedness, ensuring robust results across diverse cohorts (Chang et al., 2015). These tools can enhance genetic studies for future research in multi-ancestry studies by addressing the unique challenges presented by admixed populations. However, a major limitation is that these tools are designed for larger datasets and are less effective or overly complex for small sample sizes, where simpler models may yield more meaningful results (Yang et al., 2023).

Addressing the sample size limitation in genomic reference panels, genomic studies, and neuroimaging studies in African populations is critical to advance our understanding of complex traits. Using genotyping platforms such as the Multi-Ethnic Genotyping Array (MEGA) [https://emea.illumina.com/science/consortia/human-consortia/multi-ethnic-genotyping-consortium.html], in future studies could significantly enhance the resolution of African genetic variation. By increasing the capture of these variants, the accuracy of GWASs and imputation efforts would be substantially improved, allowing for more reliable identification of genetic associations and better insights into African genetic architecture. Additionally, larger initiatives including the African Genome Variation Project (AGVP) (Jones, 2015), the Southern African Human Genome Project (SAHGP) (Choudhury et al., 2017), and the Human Heredity and Health in Africa (H3Africa) consortium (Osafo et al., 2015) are pivotal in improving reference panels and genotyping platforms suited to African genomic diversity. Beyond improving genetic reference panels, these initiatives are also crucial for reaching a larger number of individuals. By enhancing research infrastructure, securing funding, and establishing collaborative networks, they can expand access to research opportunities (Puljak & Vari, 2014). Community engagement efforts, including outreach campaigns that raise awareness and address concerns, further build trust and encourage participation (Bhatia, 2023).

Advancing developmental neuroscience requires robust longitudinal studies with large, diverse samples to ensure the statistical power needed to detect subtle developmental changes (Lane & Kelleher, 2023). Large, multidimensional approaches integrating neuroimaging, genetic, cognitive, and environmental data are essential to unravel the complex factors influencing brain development. Open-access initiatives, such as the ABCD study, promote collaboration, replication, and methodological innovation (Karcher & Barch, 2021). Furthermore, emphasising diversity in sampling not only enhances generalisability but also addresses socioeconomic and demographic disparities that are particularly pronounced in LMICs (Shea et al., 2022). SES significantly influences access to healthcare, education, and other resources, which in turn impacts the availability and quality of data from these populations (McMaughan et al., 2020). By incorporating diverse sampling strategies, researchers can ensure that findings are more representative of underrepresented groups from LMICs.

Ultimately, the use of new and improved technology and larger African ancestry cohorts are essential to comprehensively explore genetic variation and identify potential risk factors for brain-related disorders (Weinberger et al., 2020). While current studies have made strides in understanding the genetic basis of these conditions, the power of research would significantly increase with larger sample sizes, particularly in African-ancestry populations that remain underrepresented in genetic research (Fatumo et al., 2022). Further investigation into gene-gene interactions and gene-environment associations is especially promising (Belsky & Domingue, 2023), but requires much larger sample sizes within African populations (Mulder et al., 2020).

By continuing to expand and build on these initiatives, incorporating larger, more diverse family cohorts, genomic and neuroimaging research can be improved, ultimately leading to more accurate and inclusive models of disease and health in African populations.

6. Concluding remarks

This project is the first exploratory investigation into the impact of genetic risk for depression and PTSD on subcortical brain volumes in children at two years of age in a mixed ancestry longitudinal African birth cohort. By considering both genetic risk factors and maternal perinatal symptoms of depression and PTSD, this study provides a comprehensive approach to understanding the factors influencing subcortical brain development in children. My findings partly support previous associations between caudate and hippocampus volumes and PRS-MDD (Acosta, Kantojärvi, Hashempour, et al., 2020; Acosta, Kantojärvi, Tuulari, et al., 2020; Qiu et al., 2017), while also revealing novel associations with the thalamus, putamen, and right pallidum.

The observed volumetric patterns across subcortical regions highlight both shared and distinct neurobiological underpinnings of depression and PTSD. Larger caudate and thalamus volumes in both conditions suggest potential overlaps in the neural circuits implicated in these disorders, perhaps reflecting common pathways related to stress and emotional regulation. However, the distinct volumetric differences in regions such as the putamen, pallidum, and hippocampus underscore the unique neurobiological signatures that differentiate depression from PTSD. These findings emphasize the importance of considering both shared and condition-specific neural mechanisms when exploring the structural correlates of these mental health conditions, which may have implications for tailored therapeutic strategies. Thus, while some brain regions show overlapping associations between the disorders, others display disorder-specific changes, underscoring the need for a deeper understanding of the neurobiological underpinnings of both depression and PTSD. The associations between genetic factors, environmental influences, and their interactions in shaping subcortical brain volumes are evident in both depression and PTSD. For depression, the genetic model was the best fit, showing significant associations with variations in the thalamus, putamen, pallidum, and hippocampus volumes. The gene-environment interaction model was most relevant for the caudate, with both genetic and environmental factors influencing its volume. In PTSD, the genetic model was also the best fit for the putamen, pallidum, and hippocampus, while the environmental model specifically affected the left thalamus. The additive gene-environment model revealed significant associations with thalamus volumes, and, similar to depression, the gene-environment interaction model was best for the caudate. These findings illustrate the complex interplay of

genetic, environmental, and interactive factors in determining subcortical brain volumes, with differential associations observed across regions for both conditions.

This highlights the importance of considering both genetic risk and environmental stressors in influencing brain structures associated with vulnerability to psychiatric disorders. Future research should aim to unravel these interactions to better understand the neurobiological mechanisms underlying depression and PTSD and their contributions to the development and progression of these conditions.

Finally, this study also fills an important gap in the research by focusing on a genetically diverse cohort from a low-income setting. Much of the existing research has been conducted in high-income countries with predominantly European populations, leaving a gap in understanding brain development and the genetics of psychiatric disorders in LMICs. The results underline the relevance of genetic and environmental interactions – such as depression and PTSD – in LMICs, and suggest that future studies should aim to develop more accessible, ancestry-appropriate diagnostic tools and interventions for these populations. Despite limitations, this project represents an important step toward understanding the unique interaction between genetic risk for depression and PTSD and maternal antenatal symptoms and how it is associated with subcortical brain volumes in African and Mixed ancestry populations.

7. Appendix

Appendix 1: Ethics Approval 2023

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Email: hrec-submissions@uct.ac.za
Website: https://health.uct.ac.za/home/human-research-ethics

27th July 2023

HREC REF: 483/2023

Dr Mary Mufford
Department of Psychiatry & Mental Health
Neuroscience Institute- GSH
Email: mary.mufford@uct.ac.za
Student: Grbanj001@myuct.ac.za

Dear Dr Mufford

PROJECT TITLE : CHILD SUBCORTICAL BRAIN VOLUMES: THE INTERACTION BETWEEN GENETIC RISK AND MATERNAL PSYCHOLOGICAL DISTRESS DURING PREGNANCY-SUB-STUDY LINKED TO 401/2009-MASTERS CANDIDATE-MISS ANJE-GROBLER

Thank you for submitting your PI Response to the Faculty of Health Sciences Human Research Ethics Committee (HREC) dated 23 July 2023.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 July 2024.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: https://health.uct.ac.za/home/human-research-ethics)

The HREC acknowledge that the student: Miss Anje-Lore Grobler will also be involved in this study.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC REF in all your correspondence.

Yours sincerely

PROFESSOR MAR
CHAIRPERSON, FEA CSRE S.I.C ALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurai 6 [illegible] S FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

HREC REF NO. 483/2023

Appendix 2: Ethics Renewal 2024

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.7.2025
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	1/8/24

Note: Please note that incomplete subm cannot be reviewed.
Our website address: https://health.uct.ac.za/home/human-research-ethics

HUMAN RESEARCH ETHICS COMMITTEE
31 JUL 2024
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	31 July 2024		
HREC REF Number	483/2023	Current Ethics Approval was granted until	30 July 2024
Protocol title	CHILD SUBCORTICAL BRAIN VOLUMES: THE INTERACTION BETWEEN GENETIC RISK AND MATERNAL PSYCHOLOGICAL DISTRESS DURING PREGNANCY-SUB- STUDY LINKED TO 401/2009-MASTERS CANDIDATE-MISS ANJE-GROBLER		
Principal Investigator	Dr Mary Mufford		
Department and email address	Department of Psychiatry & Mental Health Neuroscience Institute-GSH Email: mary.mufford@uct.ac.za Student: Grbanj001@myuct.ac.za		
1.1 Does this protocol receive US Federal funding?		☐ Yes	x No

2. Protocol status (tick ✓)

☐	Research-related activities are ongoing
x	Data collection is complete, data analysis only
☐	Publication or thesis submitted and final completion?

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

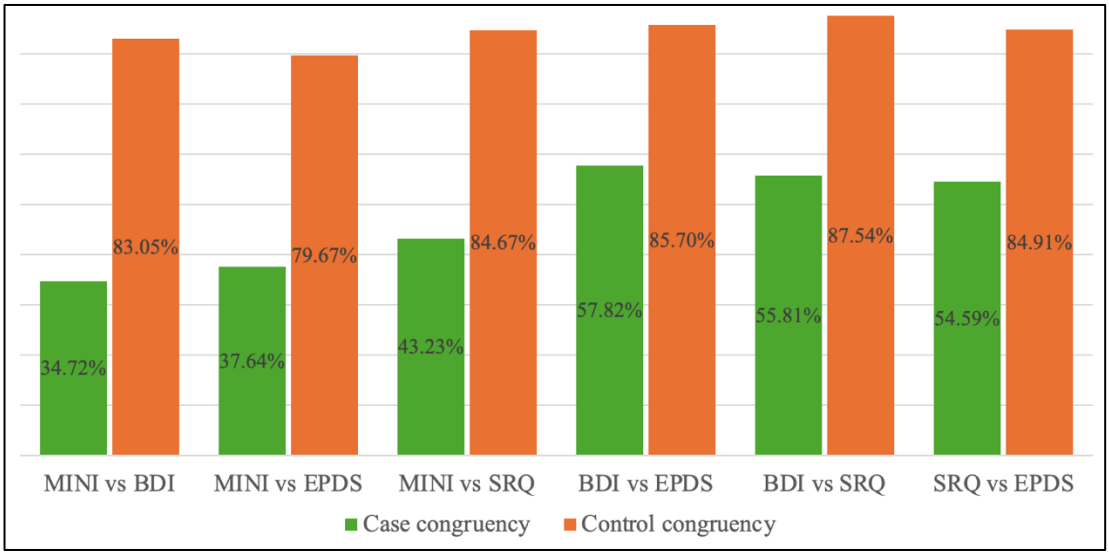
Total number of records or specimens collected, reviewed or stored since the original approval		N/A
Total number of records or specimens collected, reviewed or stored since last progress report		N/A
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	x Yes, Southern African Neuroscience Symposium Poster Presentation	☐ No

Please complete the Closure form (FHS019) if the study is completed within the approval period

4. Signature

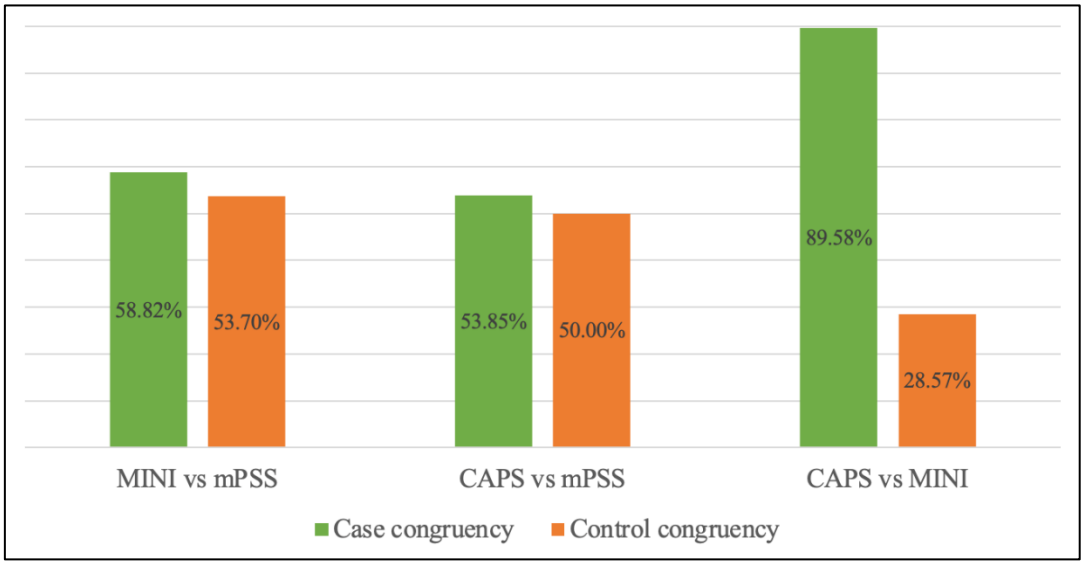
Signature of PI	Date	31 July 2024

Appendix 3: Case and control congruency between depression-symptoms measures



Appendix 3 illustrates the congruency between different pairs of measures used to identify mothers with symptoms of depression. Case congruency stipulates that the mother was classed as a case in both measures. Control congruency stipulates that the mother was classed as a control in both measures. Mothers who did not complete one or both measures were excluded from this figure. SRQ-20: Self-Report Questionnaire; EPDS: Edinburgh Postnatal Depression Scale; MINI: Mini International Neuropsychiatric Interview; BDI-II: Beck Depression Inventory.

Appendix 4: Case and control congruency between PTSD-symptoms measures



Appendix 4 illustrates the congruency between different pairs of measures used to identify mothers with symptoms of PTSD. Case congruency stipulates that the mother was classed as a case in both measures. Control congruency stipulates that the mother was classed as a control in both measures. Mothers who did not complete one or both measures were excluded from this figure. CAPS: Clinician-Administered PTSD Scale for DSM-V; MINI: Mini International Neuropsychiatric Interview; mPSS: modified PTSD Symptom Scale.

Appendix 5: The mean and standard deviation (SD) of subcortical brain volumes of two-year-old children

Subcortical Brain Region	**Mean ± SD (mm^3)**
Left Thalamus	5,898.921 ± 577.825
Right Thalamus	5,821.753 ± 564.933
Bilateral Thalamus	11,709.390 ± 1,129.161
Left Caudate	3,242.372 ± 492.464
Right Caudate	3,341.391 ± 505.122
Bilateral Caudate	6,612.411 ± 993.574
Left Putamen	4,438.479 ± 597.111
Right Putamen	4,505.600 ± 565.077
Bilateral Putamen	8,987.985 ± 1,132.183
Left Pallidum	1,581.810 ± 232.186
Right Pallidum	1,509.180 ± 202.504
Bilateral Pallidum	3,107.302 ± 414.384
Left Hippocampus	3,062.048 ± 334.363
Right Hippocampus	3,149.926 ± 358.574
Bilateral Hippocampus	6,201.767 ± 676.071
Left Amygdala	1,196.164 ± 164.977
Right Amygdala	1,326.490 ± 187.879
Bilateral Amygdala	2,520.817 ± 331.296
Left Accumbens	575.555 ± 96.888
Right Accumbens	578.396 ± 86.671
Bilateral Accumbens	1,158.927 ± 174.961
ICV	1,206,396.362 ± 115,651.024

This table provides descriptive statistics for subcortical brain region volumes measured in cubic millimetres (mm^3) in a cohort of approximately 128 two-year-old children. For each brain region, the mean volume and standard deviation (Mean ± SD) are reported for both the left and right hemispheres, as well as the bilateral volume.

Appendix 6: AIC-values for fully and minimally adjusted base models in the depression and PTSD cohorts

	Region	p-value	Fully adjusted AIC	Minimally adjusted AIC
Depression	Thalamus	0.367	2,059.100	2,054.961
	Left Thalamus	0.374	1,894.467	1,890.257
	Right Thalamus	0.409	1,890.450	1,885.919
	Caudate	0.355	2,073.788	2,069.761
	Left Caudate	0.446	1,903.463	1,898.611
	Right Caudate	0.278	1,900.469	1,897.277
	Putamen	0.284	2,120.993	2,117.731
	Left Putamen	0.292	1,969.521	1,966.171
	Right Putamen	0.354	1,952.966	1,948.947
	Pallidum	0.376	1,862.203	1,857.971
	Left Pallidum	0.169	1,725.667	1,724.067
	Right Pallidum	0.792	1,684.695	1,677.287
	Hippocampus	0.261	1,956.867	1,953.887
	Left Hippocampus	0.232	1,777.071	1,774.471
	Right Hippocampus	0.375	1,813.284	1,809.062
	Amygdala	0.023	1,782.428	1,786.515
	Left Amygdala	0.012	1,605.879	1,611.805
	Right Amygdala	0.076	1,651.304	1,652.100
	Accumbens	0.982	1,647.353	1,638.127
	Left Accumbens	0.991	1,508.742	1,499.310
	Right Accumbens	0.691	1,478.903	1,472.207
PTSD	Thalamus	0.367	2,059.100	2,054.961
	Left Thalamus	0.374	1,894.467	1,890.257
	Right Thalamus	0.409	1,890.450	1,885.919
	Caudate	0.355	2,073.788	2,069.761
	Left Caudate	0.446	1,903.463	1,898.611
	Right Caudate	0.278	1,900.469	1,897.277
	Putamen	0.284	2,120.993	2,117.731
	Left Putamen	0.292	1,969.521	1,966.171

	Right Putamen	0.354	1,952.966	1,948.947
	Pallidum	0.376	1,862.203	1,857.971
	Left Pallidum	0.169	1,725.667	1,724.067
	Right Pallidum	0.792	1,684.695	1,677.287
	Hippocampus	0.261	1,956.867	1,953.887
	Left Hippocampus	0.232	1,777.071	1,774.471
	Right Hippocampus	0.375	1,813.284	1,809.062
	Amygdala	0.023	1,782.428	1,786.515
	Left Amygdala	0.012	1,605.879	1,611.805
	Right Amygdala	0.076	1,651.304	1,652.100
	Accumbens	0.982	1,647.353	1,638.127
	Left Accumbens	0.991	1,508.742	1,499.310
	Right Accumbens	0.691	1,478.903	1,472.207

Appendix 6 shows the p-values and AIC values for the fully and minimally adjusted base model for both depression and PTSD. Fully adjusted: subcortical brain volume ~ ancestry + child age at time of the scan + sex + ICV + zBirth weight + zSES + maternal age + smoking + alcohol use + HIV exposure. Minimally adjusted: subcortical brain volume ~ ancestry + child age at time of the scan + sex + ICV + zBirth weight. AIC: Akaike information criterion.

Appendix 7: AIC-values for model G including and excluding principal components in the depression and PTSD cohorts

	Region	p-value	AIC for model G without PCs	AIC for model G with PCs
Depression	Thalamus	0.006	2,056.588	2,048.970
	Left Thalamus	0.033	1,892.163	1,890.281
	Right Thalamus	0.002	1,887.147	1,876.711
	Caudate	0.016	2,071.707	2,067.324
	Left Caudate	0.005	1,900.565	1,896.449
	Right Caudate	0.013	1,899.219	1,895.884
	Putamen	0.005	2,118.417	2,110.046
	Left Putamen	0.003	1,967.584	1,958.221
	Right Putamen	0.008	1,948.960	1,942.515
	Pallidum	0.060	1,858.937	1,859.213
	Left Pallidum	0.164	1,725.729	1,729.899
	Right Pallidum	0.029	1,677.401	1,675.096
	Hippocampus	0.216	1,955.559	1,960.908
	Left Hippocampus	0.012	1,776.387	1,771.196
	Right Hippocampus	0.753	1,810.485	1,823.007
	Amygdala	0.227	1,788.310	1,793.886
	Left Amygdala	0.186	1,612.479	1,617.186
	Right Amygdala	0.445	1,654.055	1,662.966
	Accumbens	0.403	1,640.112	1,648.483
	Left Accumbens	0.531	1,501.124	1,511.084
	Right Accumbens	0.450	1,473.698	1,482.666
PTSD	Thalamus	0.006	2,056.682	2,048.954
	Left Thalamus	0.032	1,892.175	1,890.210
	Right Thalamus	0.002	1,887.375	1,876.719
	Caudate	0.014	2,071.628	2,066.778
	Left Caudate	0.005	1,900.528	1,896.007
	Right Caudate	0.011	1,899.093	1,895.271
	Putamen	0.005	2,119.633	2,111.249

	Left Putamen	0.004	1,967.708	1,958.579
	Right Putamen	0.009	1,950.933	1,944.595
	Pallidum	0.054	1,859.737	1,859.573
	Left Pallidum	0.150	1,725.962	1,729.750
	Right Pallidum	0.028	1,678.932	1,676.422
	Hippocampus	0.242	1,954.333	1,960.196
	Left Hippocampus	0.017	1,774.351	1,770.243
	Right Hippocampus	0.773	1,810.189	1,822.956
	Amygdala	0.286	1,785.953	1,792.586
	Left Amygdala	0.188	1,612.708	1,617.461
	Right Amygdala	0.573	1,650.776	1,661.220
	Accumbens	0.376	1,639.360	1,647.358
	Left Accumbens	0.485	1,500.055	1,509.462
	Right Accumbens	0.418	1,474.015	1,482.582

Appendix 7 shows the p-values and AIC values for the genetic model without and with principal components, for both depression and PTSD. Model G without PCs: subcortical brain volume ~ PRS + covariates. Model G with PCs: subcortical brain volume ~ PRS + principal components + covariates. AIC: Akaike information criterion; PCs: principal components; PRS: polygenic risk score.

Appendix 8: Summary statistics for all models for depression

	Subcortical brain region	Beta	SE	t-statistic	Adjusted R^2	Model p-value FDR
Model B	Thalamus	-104.144	155.660	-0.669	0.599	2.20^{-16}
	Left Thalamus	-68.525	81.389	-0.842	0.584	2.20^{-16}
	Right Thalamus	-35.620	80.010	-0.445	0.579	2.20^{-16}
	Caudate	57.395	165.000	0.348	0.359	4.08^{-11}
	Left Caudate	9.132	84.110	0.109	0.325	5.09^{-10}
	Right Caudate	48.263	83.669	0.577	0.377	9.15^{-12}
	Putamen	170.026	199.299	0.853	0.278	2.19^{-8}
	Left Putamen	29.597	109.740	0.270	0.242	2.86^{-7}
	Right Putamen	140.429	102.545	1.369	0.270	3.77^{-8}
	Pallidum	-25.520	71.674	-0.356	0.342	1.67^{-10}
	Left Pallidum	-26.796	42.307	-0.633	0.297	5.25^{-9}
	Right Pallidum	1.275	35.190	0.036	0.327	4.82^{-10}
	Hippocampus	-62.950	104.559	-0.602	0.453	1.30^{-14}
	Left Hippocampus	-31.730	51.593	-0.615	0.465	6.90^{-15}
	Right Hippocampus	-31.219	59.120	-0.528	0.385	6.20^{-12}
	Amygdala	12.806	54.098	0.237	0.398	2.39^{-12}
	Left Amygdala	-17.874	27.193	-0.657	0.383	6.20^{-12}
	Right Amygdala	30.679	31.868	0.963	0.336	2.52^{-10}
	Accumbens	-3.857	30.162	-0.128	0.266	4.69^{-8}
	Left Accumbens	-13.294	17.463	-0.761	0.234	4.92^{-7}
	Right Accumbens	9.437	15.695	0.601	0.230	6.08^{-7}
Model G	Thalamus	5.855	68.385	0.086	0.646	2.20^{-16}
	Left Thalamus	10.683	36.612	0.292	0.615	2.20^{-16}
	Right Thalamus	-4.828	34.708	-0.139	0.638	2.20^{-16}
	Caudate	31.455	73.509	0.428	0.418	1.14^{-9}
	Left Caudate	13.081	37.512	0.349	0.387	7.12^{-9}
	Right Caudate	18.374	37.429	0.491	0.430	5.77^{-10}
	Putamen	-89.210	86.974	-1.026	0.371	1.86^{-8}
	Left Putamen	-27.352	47.840	-0.572	0.341	1.25^{-7}

	Right Putamen	-61.858	44.972	-1.375	0.358	4.07^{-8}
	Pallidum	-24.775	32.397	-0.765	0.385	7.12^{-9}
	Left Pallidum	-6.331	19.472	-0.325	0.319	5.00^{-7}
	Right Pallidum	-18.444	15.693	-1.175	0.388	7.12^{-9}
	Hippocampus	-5.574	48.349	-0.115	0.466	3.78^{-11}
	Left Hippocampus	8.975	22.909	0.392	0.518	4.43^{-13}
	Right Hippocampus	-14.549	28.093	-0.518	0.365	2.59^{-8}
	Amygdala	-2.237	25.050	-0.089	0.410	1.79^{-9}
	Left Amygdala	8.218	12.494	0.658	0.405	2.34^{-9}
	Right Amygdala	-10.455	14.961	-0.699	0.331	2.38^{-7}
	Accumbens	0.435	14.132	0.031	0.264	1.46^{-5}
	Left Accumbens	-2.816	8.228	-0.342	0.222	1.30^{-4}
	Right Accumbens	3.251	7.357	0.442	0.227	1.10^{-4}
Model E	Thalamus	-92.094	146.483	-0.629	0.597	2.20^{-16}
	Left Thalamus	-33.437	76.655	-0.436	0.581	2.20^{-16}
	Right Thalamus	-58.656	75.227	-0.780	0.578	2.20^{-16}
	Caudate	-421.687	150.688	-2.798	0.393	6.40^{-12}
	Left Caudate	-214.490	76.825	-2.792	0.361	7.63^{-11}
	Right Caudate	-207.197	76.564	-2.706	0.408	2.64^{-12}
	Putamen	-18.243	187.849	-0.097	0.272	7.65^{-8}
	Left Putamen	20.660	103.422	0.200	0.236	9.09^{-7}
	Right Putamen	-38.903	96.592	-0.403	0.265	1.21^{-7}
	Pallidum	2.011	67.559	0.030	0.336	5.94^{-10}
	Left Pallidum	2.294	39.877	0.058	0.291	1.91^{-8}
	Right Pallidum	-0.283	33.170	-0.009	0.322	1.71^{-9}
	Hippocampus	82.524	98.267	0.840	0.452	4.61^{-14}
	Left Hippocampus	27.197	48.568	0.560	0.462	3.02^{-14}
	Right Hippocampus	55.326	55.497	0.997	0.385	1.13^{-11}
	Amygdala	20.278	50.959	0.398	0.394	6.40^{-12}
	Left Amygdala	10.462	25.614	0.408	0.379	1.78^{-11}
	Right Amygdala	9.815	30.025	0.327	0.331	8.56^{-10}
	Accumbens	-8.667	28.420	-0.305	0.261	1.54^{-7}

	Left Accumbens	-4.091	16.456	-0.249	0.228	1.52^{-6}
	Right Accumbens	-4.576	14.788	-0.309	0.224	1.84^{-6}
Model G+E	Thalamus	5.839	68.696	0.085	0.643	2.20^{-16}
	Left Thalamus	10.693	36.779	0.291	0.611	2.20^{-16}
	Right Thalamus	-4.854	34.856	-0.139	0.635	2.20^{-16}
	Caudate	30.875	71.182	0.434	0.455	9.19^{-11}
	Left Caudate	12.781	36.290	0.352	0.426	8.59^{-10}
	Right Caudate	18.094	36.381	0.497	0.462	6.69^{-11}
	Putamen	-89.154	87.352	-1.021	0.366	4.07^{-8}
	Left Putamen	-27.264	47.968	-0.568	0.338	2.45^{-7}
	Right Putamen	-61.890	45.165	-1.370	0.353	9.53^{-8}
	Pallidum	-24.744	32.529	-0.761	0.380	1.71^{-8}
	Left Pallidum	-6.305	19.541	-0.323	0.314	1.02^{-6}
	Right Pallidum	-18.439	15.764	-1.170	0.383	1.60^{-8}
	Hippocampus	-5.417	48.280	-0.112	0.467	6.10^{-11}
	Left Hippocampus	9.044	22.896	0.395	0.519	8.42^{-13}
	Right Hippocampus	-14.461	28.065	-0.515	0.367	4.07^{-8}
	Amygdala	-2.198	25.130	-0.087	0.406	3.44^{-9}
	Left Amygdala	8.236	12.535	0.657	0.401	4.64^{-9}
	Right Amygdala	-10.434	15.013	-0.695	0.326	4.92^{-7}
	Accumbens	0.433	14.196	0.030	0.257	2.97^{-5}
	Left Accumbens	-2.818	8.265	-0.341	0.215	2.45^{-4}
	Right Accumbens	3.251	7.390	0.440	0.220	2.08^{-4}
Model GxE	Thalamus	123.883	101.940	1.215	0.648	2.20^{-16}
	Left Thalamus	53.846	54.904	0.981	0.612	2.20^{-16}
	Right Thalamus	70.037	51.395	1.363	0.644	2.20^{-16}
	Caudate	146.250	105.759	1.383	0.460	9.94^{-11}
	Left Caudate	66.809	54.002	1.237	0.430	1.04^{-9}
	Right Caudate	79.441	54.009	1.471	0.468	9.94^{-11}
	Putamen	-231.591	129.769	-1.785	0.373	4.32^{-8}
	Left Putamen	-111.997	71.135	-1.574	0.347	1.96^{-7}
	Right Putamen	-119.594	67.358	-1.775	0.355	1.28^{-7}

	Pallidum	-59.111	48.607	-1.216	0.380	3.20^{-8}
	Left Pallidum	-43.778	28.917	-1.514	0.327	7.15^{-7}
	Right Pallidum	-15.333	23.651	-0.648	0.377	3.43^{-8}
	Hippocampus	11.353	72.413	0.157	0.463	9.94^{-11}
	Left Hippocampus	26.199	34.285	0.764	0.516	2.11^{-12}
	Right Hippocampus	-14.847	42.112	-0.353	0.361	8.96^{-8}
	Amygdala	-46.143	37.276	-1.238	0.415	2.59^{-9}
	Left Amygdala	-20.874	18.428	-1.133	0.419	2.06^{-9}
	Right Amygdala	-25.268	22.445	-1.126	0.325	7.41^{-7}
	Accumbens	7.318	21.283	0.344	0.251	5.43^{-5}
	Left Accumbens	1.785	12.387	0.144	0.210	4.08^{-4}
	Right Accumbens	5.533	11.085	0.499	0.213	3.72^{-4}

Appendix 8 shows all the models run across all subcortical brain regions. SE: standard error; FDR: false-discovery rate.

Appendix 9: Summary statistics for all models for PTSD

	Subcortical brain region	Beta	SE	t-statistic	Adjusted R^2	Model p-value FDR
Model B	Thalamus	-104.144	155.660	-0.669	0.599	2.20^{-16}
	Left Thalamus	-68.525	81.389	-0.842	0.584	2.20^{-16}
	Right Thalamus	-35.620	80.010	-0.445	0.579	2.20^{-16}
	Caudate	57.395	165.000	0.348	0.359	4.08^{-11}
	Left Caudate	9.132	84.110	0.109	0.325	5.09^{-10}
	Right Caudate	48.263	83.669	0.577	0.377	9.15^{-12}
	Putamen	170.026	199.299	0.853	0.278	2.19^{-8}
	Left Putamen	29.597	109.740	0.270	0.242	2.86^{-7}
	Right Putamen	140.429	102.545	1.369	0.270	3.77^{-8}
	Pallidum	-25.520	71.674	-0.356	0.342	1.67^{-10}
	Left Pallidum	-26.796	42.307	-0.633	0.297	5.25^{-9}
	Right Pallidum	1.275	35.190	0.036	0.327	4.82^{-10}
	Hippocampus	-62.950	104.559	-0.602	0.453	1.30^{-14}
	Left Hippocampus	-31.730	51.593	-0.615	0.465	6.90^{-15}
	Right Hippocampus	-31.219	59.120	-0.528	0.385	6.20^{-12}
	Amygdala	12.806	54.098	0.237	0.398	2.39^{-12}
	Left Amygdala	-17.874	27.193	-0.657	0.383	6.20^{-12}
	Right Amygdala	30.679	31.868	0.963	0.336	2.52^{-10}
	Accumbens	-3.857	30.162	-0.128	0.266	4.69^{-8}
	Left Accumbens	-13.294	17.463	-0.761	0.234	4.92^{-7}
	Right Accumbens	9.437	15.695	0.601	0.230	6.08^{-7}
Model G	Thalamus	12.322	83.693	0.147	0.646	2.20^{-16}
	Left Thalamus	17.146	44.799	0.383	0.615	2.20^{-16}
	Right Thalamus	-4.825	42.481	-0.114	0.638	2.20^{-16}
	Caudate	-72.794	89.777	-0.811	0.421	9.27^{-10}
	Left Caudate	-32.584	45.833	-0.711	0.389	7.06^{-9}
	Right Caudate	-40.209	45.700	-0.880	0.433	4.57^{-10}
	Putamen	7.461	106.955	0.070	0.365	2.64^{-8}
	Left Putamen	-7.649	58.636	-0.130	0.339	1.32^{-7}

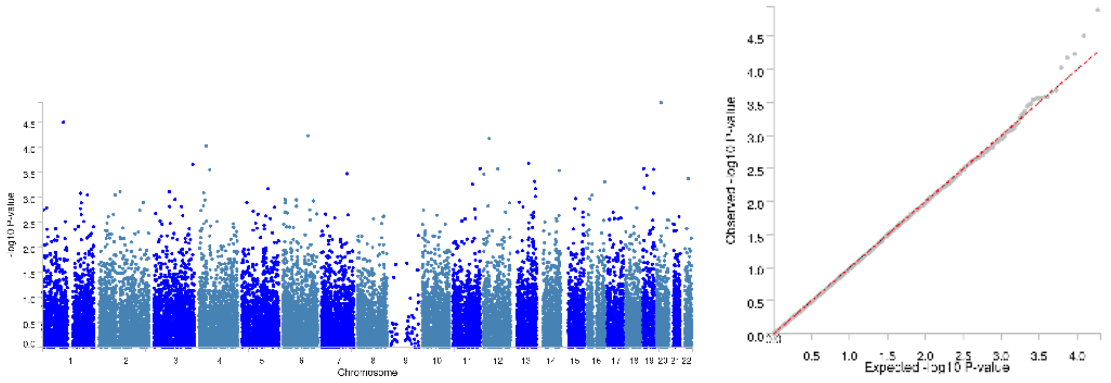
	Right Putamen	15.110	55.495	0.272	0.347	8.70^{-8}
	Pallidum	20.693	39.708	0.521	0.384	9.16^{-9}
	Left Pallidum	11.541	23.818	0.485	0.320	4.74^{-7}
	Right Pallidum	9.152	19.307	0.474	0.382	9.27^{-9}
	Hippocampus	-46.921	59.010	-0.795	0.469	2.87^{-11}
	Left Hippocampus	-27.698	27.935	-0.992	0.522	3.04^{-13}
	Right Hippocampus	-19.224	34.377	-0.559	0.366	2.64^{-8}
	Amygdala	32.571	30.503	1.068	0.416	1.10^{-9}
	Left Amygdala	6.736	15.308	0.440	0.403	2.59^{-9}
	Right Amygdala	25.835	18.186	1.421	0.340	1.32^{-7}
	Accumbens	-17.049	17.220	-0.990	0.270	9.95^{-6}
	Left Accumbens	-12.386	10.006	-1.238	0.232	8.13^{-5}
	Right Accumbens	-4.663	9.001	-0.518	0.227	1.01^{-4}
Model E	Thalamus	-466.856	200.399	-2.330	0.613	2.20^{-16}
	Left Thalamus	-239.901	104.861	-2.288	0.598	2.20^{-16}
	Right Thalamus	-226.955	103.251	-2.198	0.592	2.20^{-16}
	Caudate	-564.277	210.975	-2.675	0.390	7.23^{-12}
	Left Caudate	-271.027	107.906	-2.512	0.354	1.49^{-10}
	Right Caudate	-293.251	106.823	-2.745	0.409	2.40^{-12}
	Putamen	-68.359	262.243	-0.261	0.272	6.92^{-8}
	Left Putamen	18.800	144.429	0.130	0.236	8.65^{-7}
	Right Putamen	-87.158	134.734	-0.647	0.266	9.38^{-8}
	Pallidum	30.071	94.297	0.319	0.337	5.10^{-10}
	Left Pallidum	45.783	55.527	0.825	0.295	1.40^{-8}
	Right Pallidum	-15.712	46.295	-0.339	0.322	1.62^{-9}
	Hippocampus	-220.231	136.144	-1.618	0.460	1.85^{-14}
	Left Hippocampus	-105.989	67.214	-1.577	0.472	1.07^{-14}
	Right Hippocampus	-114.241	77.112	-1.482	0.391	7.23^{-12}
	Amygdala	92.494	70.702	1.308	0.402	3.57^{-12}
	Left Amygdala	46.218	35.542	1.300	0.387	8.65^{-12}
	Right Amygdala	46.276	41.732	1.109	0.337	5.10^{-10}
	Accumbens	-79.812	39.026	-2.045	0.285	2.75^{-8}

	Left Accumbens	-57.696	22.373	-2.579	0.268	9.01^{-8}
	Right Accumbens	-22.116	20.559	-1.076	0.231	1.13^{-6}
Model G+E	Thalamus	36.463	83.837	0.435	0.654	2.20^{-16}
	Left Thalamus	29.993	44.884	0.668	0.623	2.20^{-16}
	Right Thalamus	6.470	42.653	0.152	0.644	2.20^{-16}
	Caudate	-35.696	88.452	-0.404	0.452	1.20^{-10}
	Left Caudate	-14.599	45.302	-0.322	0.417	1.51^{-9}
	Right Caudate	-21.097	44.990	-0.469	0.464	5.47^{-11}
	Putamen	4.788	108.775	0.044	0.360	6.35^{-8}
	Left Putamen	-13.693	59.526	-0.230	0.336	2.58^{-7}
	Right Putamen	18.481	56.408	0.328	0.342	1.93^{-7}
	Pallidum	17.812	40.350	0.441	0.379	2.10^{-8}
	Left Pallidum	7.767	24.116	0.322	0.320	7.11^{-7}
	Right Pallidum	10.045	19.631	0.512	0.377	2.24^{-8}
	Hippocampus	-34.283	59.522	-0.576	0.473	3.70^{-11}
	Left Hippocampus	-21.951	28.195	-0.779	0.525	4.51^{-13}
	Right Hippocampus	-12.332	34.711	-0.355	0.369	3.48^{-8}
	Amygdala	27.507	30.871	0.891	0.417	1.51^{-9}
	Left Amygdala	3.928	15.475	0.254	0.405	3.25^{-9}
	Right Amygdala	23.579	18.446	1.278	0.338	2.47^{-7}
	Accumbens	-12.118	17.253	-0.702	0.285	5.69^{-6}
	Left Accumbens	-8.738	9.930	-0.880	0.262	2.06^{-5}
	Right Accumbens	-3.380	9.122	-0.371	0.226	1.43^{-4}
Model GxE	Thalamus	75.840	166.051	0.457	0.651	2.20^{-16}
	Left Thalamus	38.580	88.925	0.434	0.620	2.20^{-16}
	Right Thalamus	37.259	84.441	0.441	0.641	2.20^{-16}
	Caudate	247.640	172.376	1.437	0.465	6.85^{-11}
	Left Caudate	117.558	88.538	1.328	0.428	1.25^{-9}
	Right Caudate	130.082	87.528	1.486	0.478	4.05^{-11}
	Putamen	399.939	210.958	1.896	0.381	2.39^{-8}
	Left Putamen	187.636	115.779	1.621	0.354	1.22^{-7}
	Right Putamen	212.303	109.649	1.936	0.361	8.07^{-8}

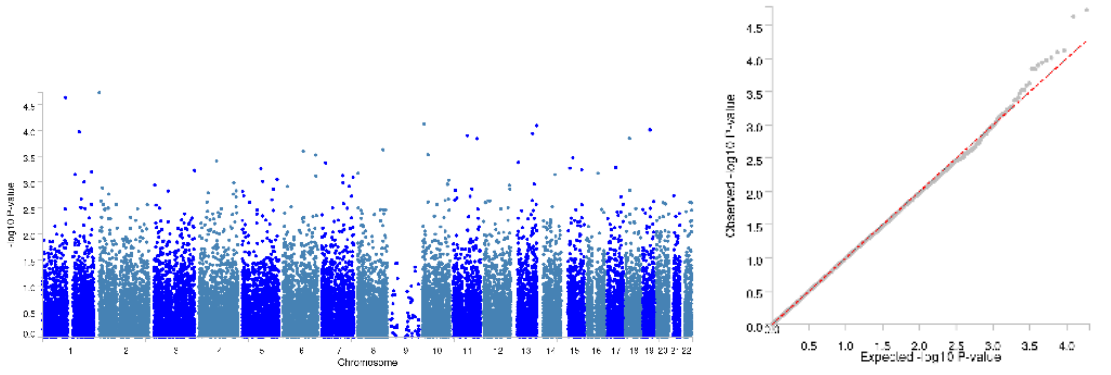
	Pallidum	183.696	77.773	2.362	0.407	4.12^{-9}
	Left Pallidum	100.458	46.648	2.154	0.345	2.04^{-7}
	Right Pallidum	83.238	38.027	2.189	0.399	6.93^{-9}
	Hippocampus	-23.562	117.926	-0.200	0.468	6.85^{-11}
	Left Hippocampus	-11.014	55.851	-0.197	0.521	1.37^{-12}
	Right Hippocampus	-12.549	68.775	-0.182	0.363	7.54^{-8}
	Amygdala	87.581	60.797	1.441	0.418	2.23^{-9}
	Left Amygdala	43.486	30.342	1.433	0.412	3.13^{-9}
	Right Amygdala	44.095	36.476	1.209	0.334	4.07^{-7}
	Accumbens	-11.736	34.185	-0.343	0.279	1.17^{-5}
	Left Accumbens	-4.499	19.669	-0.229	0.256	3.98^{-5}
	Right Accumbens	-7.238	18.068	-0.401	0.219	2.59^{-4}

Appendix 9 shows all the models run across all subcortical brain regions. SE: standard error; FDR: false-discovery rate.

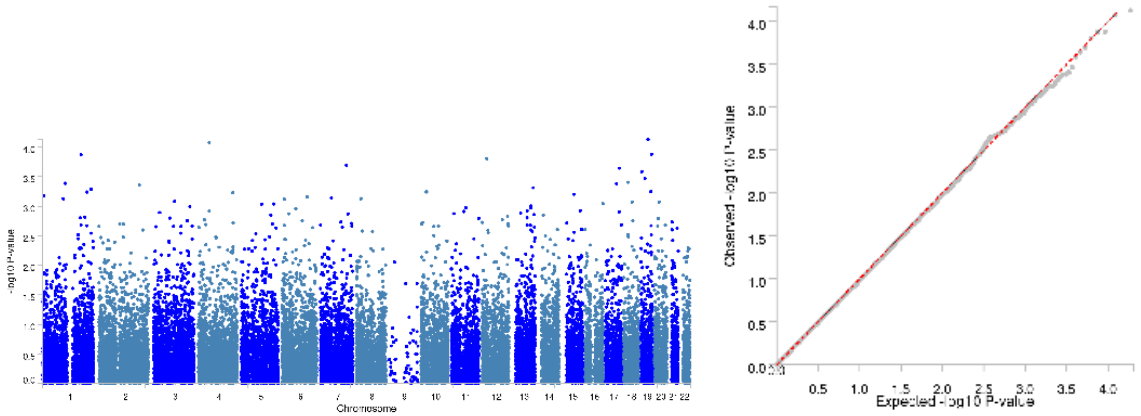
Appendix 10: GWAS Manhattan and QQ-plots for 19 subcortical brain regions



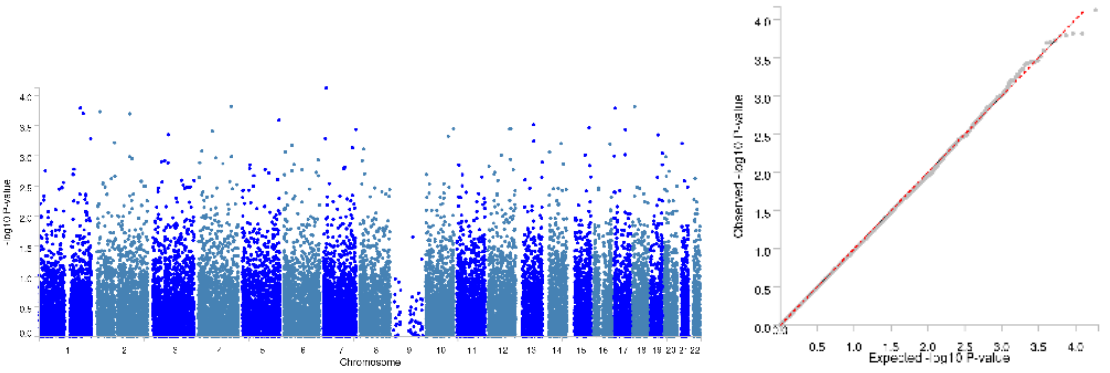
Left accumbens



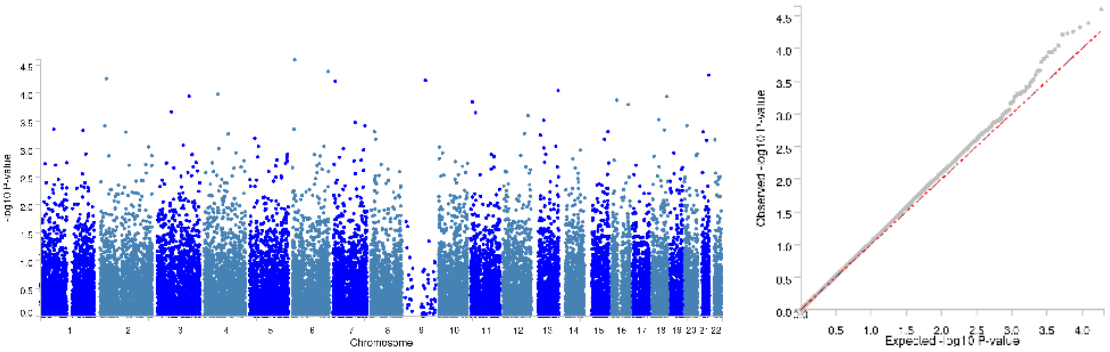
Right accumbens



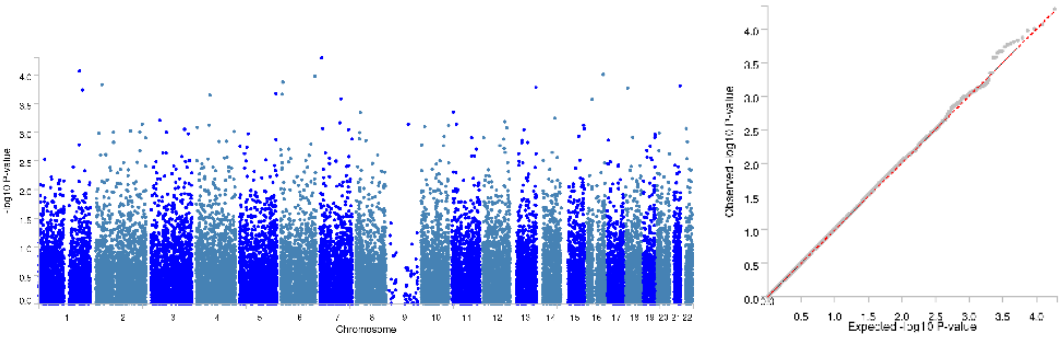
Bilateral accumbens



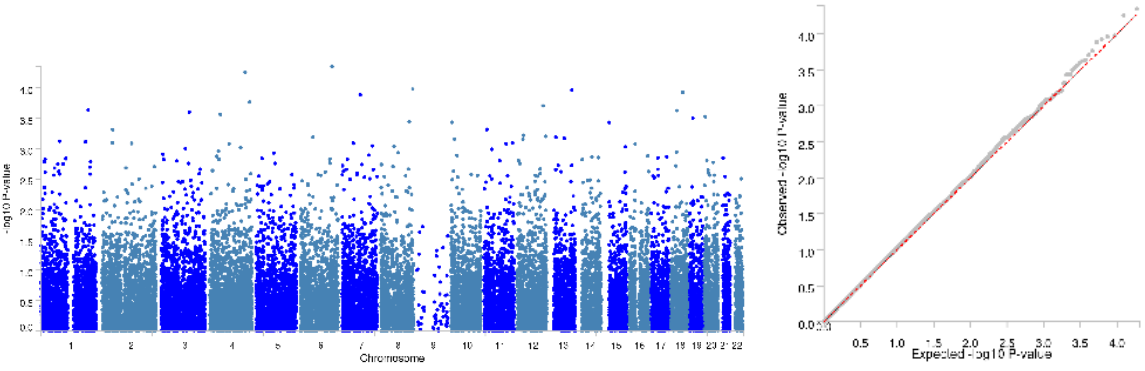
Left amygdala



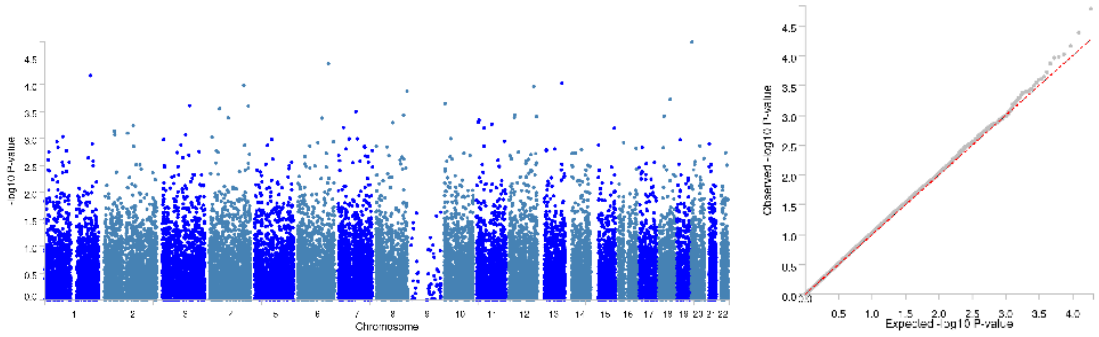
Right amygdala



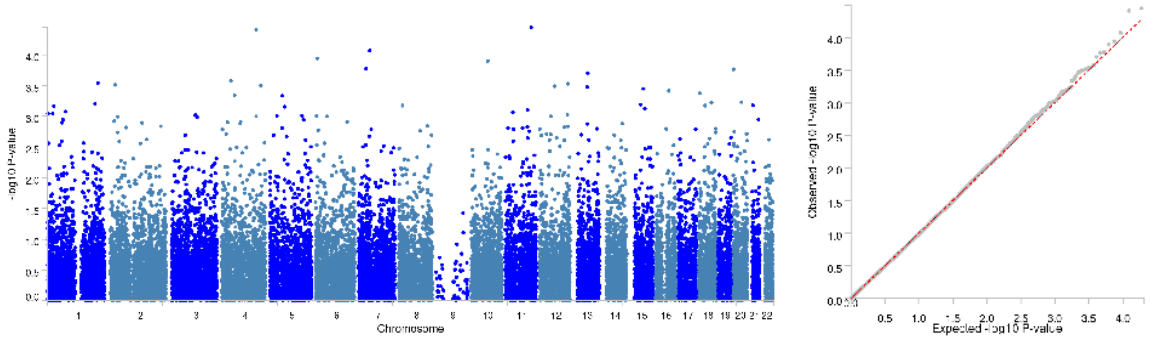
Bilateral amygdala



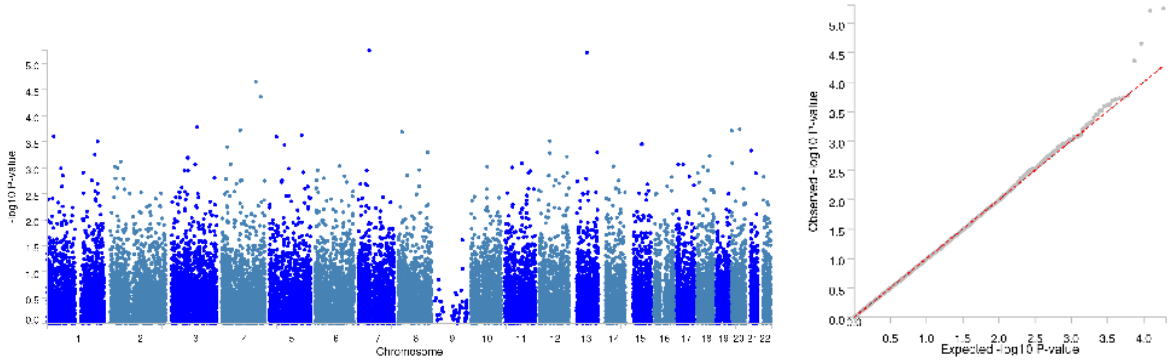
Right caudate



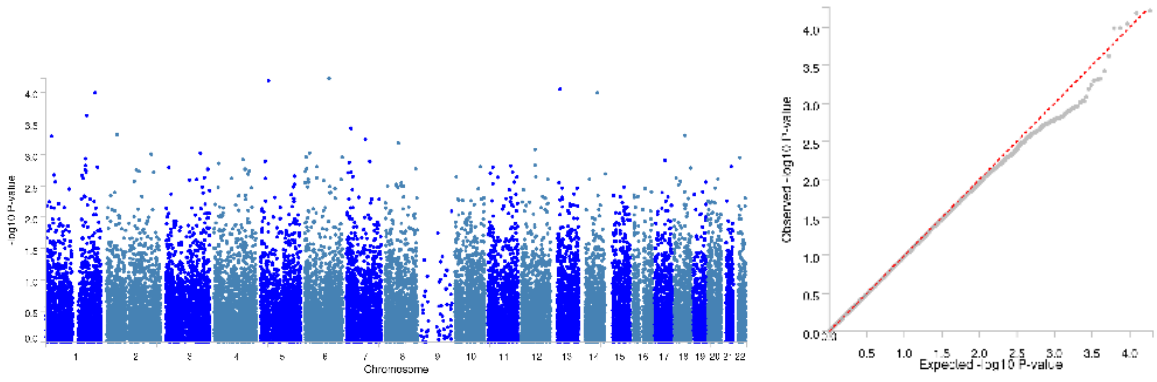
Bilateral caudate



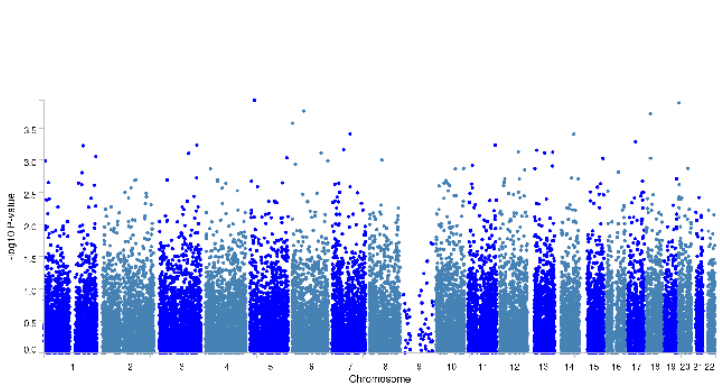
Left hippocampus

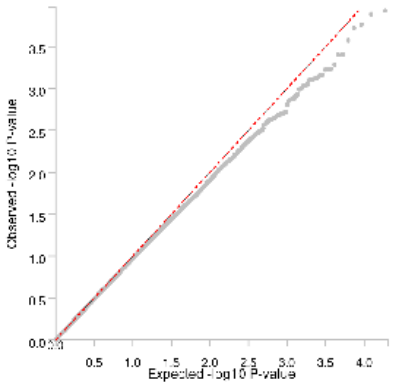


Bilateral hippocampus

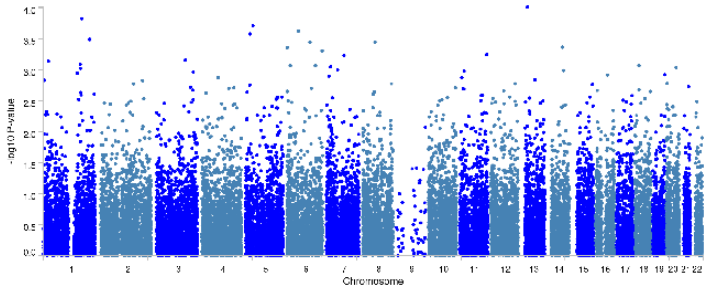


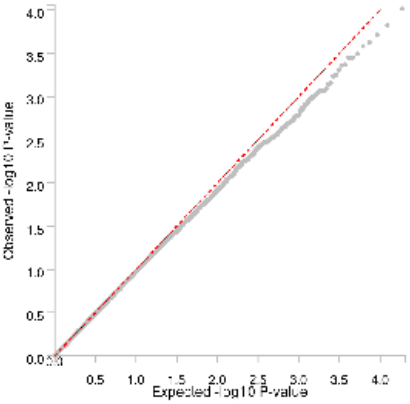
Left pallidum



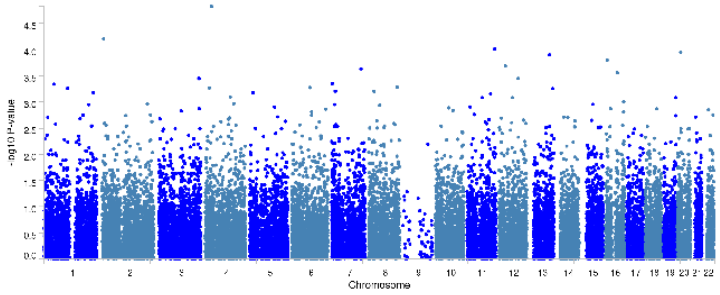


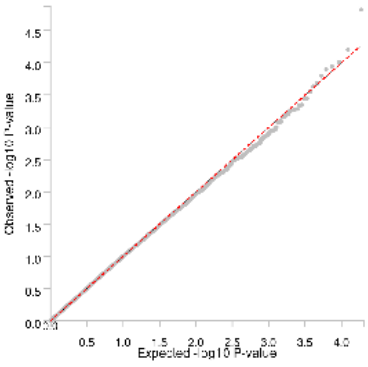
Right pallidum



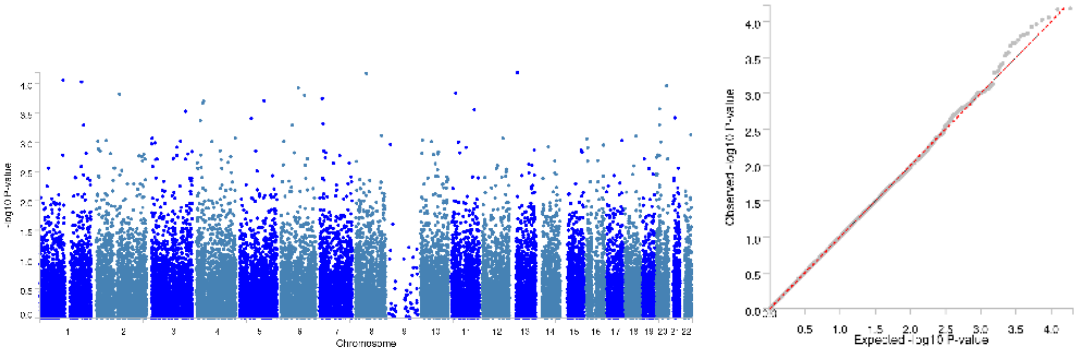


Bilateral pallidum

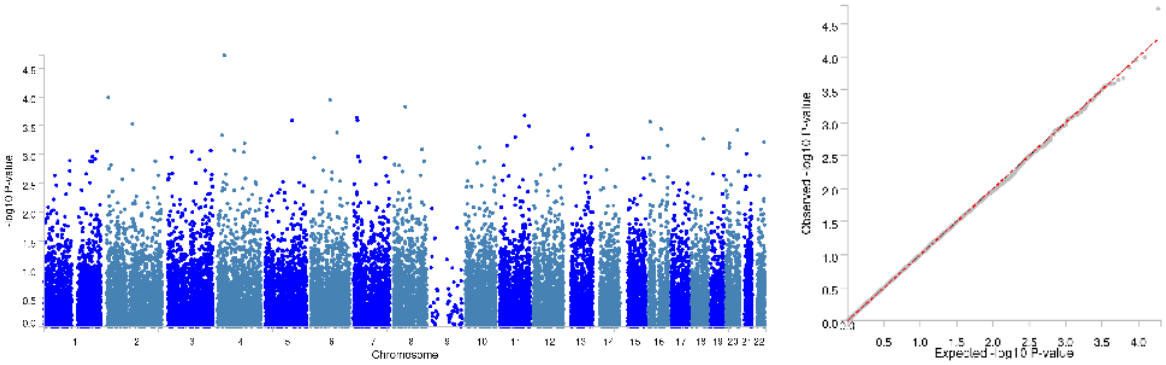




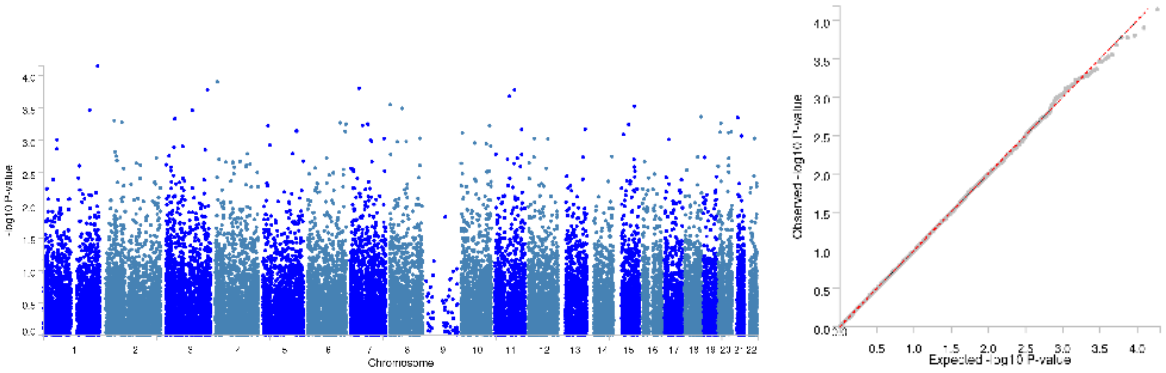
Left putamen



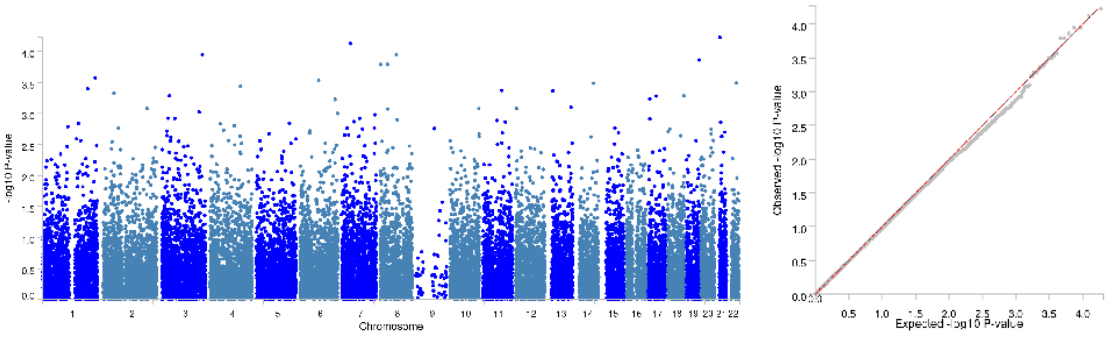
Right putamen



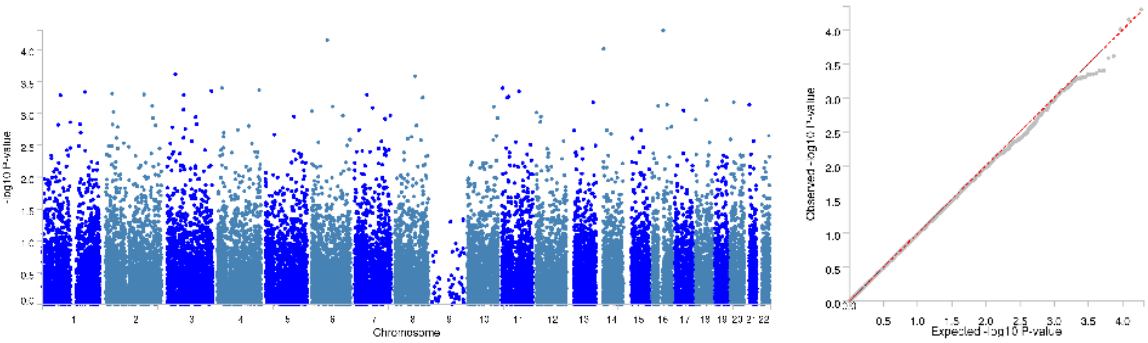
Bilateral putamen



Left thalamus



Right thalamus



Bilateral thalamus

Appendix 10 shows the GWAS results for 19 subcortical brain regions, excluding the right hippocampus and left caudate (shown in main text).

A. Manhattan plot: shows the associated SNPs on 22 human chromosomes, indicated on the x-axis, with the -log10 p-value on the y-axis. No significant SNPs were found. B. QQ-plot: shows the normal distribution that fits the theoretical distribution when comparing the expected -log10 p-value, on the x-axis, and the observed -log10 p-value, on the y-axis. These figures were generated using SNP2GENE on the FUMA website [https://fuma.ctglab.nl/snp2gene]. GWAS: Genome-Wide Association Study.

8. Websites referenced

- ENSEMBL. https://www.ensembl.org/index.html. Accessed 14 October 2024.
- FUMA. https://fuma.ctglab.nl. Accessed 9 July 2024.
- FUMA tutorials. https://fuma.ctglab.nl/tutorial. Accessed 7 July 2024.
- Infinium PsychArray-24 Kit. Psychiatric predisposition microarray. https://www.illumina.com/products/by-type/microarray-kits/infinium-psycharray.html. Accessed 22 August 2024.
- Infinium Global Screening Array-24 Kit. Population-scale genetics. https://www.illumina.com/products/by-type/microarray-kits/infinium-global-screening.html. Accessed 22 August 2024.
- Map of the Western Cape with Drakenstein highlighted in 2011 https://en.wikipedia.org/wiki/File:Map_of_the_Western_Cape_with_Drakenstein_highlighted_(2011).svg. Accessed 27 July 2024.
- PLINK guideline website. https://zzz.bwh.harvard.edu/plink. Accessed 13 July 2023.
- Popcorn GitHub page. https://github.com/brielin/Popcorn. Accessed 27 July 2024.
- PRS-CSx GitHub page. https://github.com/getian107/PRScsx. Accessed 17 July 2023.

9. References

Abdellaoui, A., Dolan, C. V., Verweij, K. J. H., & Nivard, M. G. (2022). Gene–environment correlations across geographic regions affect genome-wide association studies. *Nature Genetics*, *54*(9), 1345–1354. https://doi.org/10.1038/s41588-022-01158-0

Abdellaoui, A., Yengo, L., Verweij, K. J. H., & Visscher, P. M. (2023). 15 years of GWAS discovery: Realizing the promise. *The American Journal of Human Genetics*, *110*(2), 179–194. https://doi.org/10.1016/j.ajhg.2022.12.011

Abegaz, F., Chaichoompu, K., Génin, E., Fardo, D. W., König, I. R., Mahachie John, J. M., & Van Steen, K. (2019). Principals about principal components in statistical genetics. *Briefings in Bioinformatics*, *20*(6), 2200–2216. https://doi.org/10.1093/bib/bby081

Acosta, H., Kantojärvi, K., Hashempour, N., Pelto, J., Scheinin, N. M., Lehtola, S. J., Lewis, J. D., Fonov, V. S., Collins, D. L., Evans, A., Parkkola, R., Lähdesmäki, T., Saunavaara, J., Karlsson, L., Merisaari, H., Paunio, T., Karlsson, H., & Tuulari, J. J. (2020). Partial support for an interaction between a polygenic risk score for major depressive disorder and prenatal maternal depressive symptoms on infant right amygdalar volumes. *Cerebral Cortex*, *30*(12), 6121–6134. https://doi.org/10.1093/cercor/bhaa158

Acosta, H., Kantojärvi, K., Tuulari, J. J., Lewis, J. D., Hashempour, N., Scheinin, N. M., Lehtola, S. J., Fonov, V. S., Collins, D. L., Evans, A., Parkkola, R., Lähdesmäki, T., Saunavaara, J., Merisaari, H., Karlsson, L., Paunio, T., & Karlsson, H. (2020). Sex-specific association between infant caudate volumes and a polygenic risk score for major depressive disorder. *Journal of Neuroscience Research*, *98*(12), 2529–2540. https://doi.org/10.1002/jnr.24722

Acosta, H., Tuulari, J. J., Kantojärvi, K., Lewis, J. D., Hashempour, N., Scheinin, N. M., Lehtola, S. J., Fonov, V. S., Collins, D. L., Evans, A., Parkkola, R., Lähdesmäki, T., Saunavaara, J., Merisaari, H., Karlsson, L., Paunio, T., & Karlsson, H. (2021). A variation in the infant oxytocin receptor gene modulates infant hippocampal volumes in association with sex and prenatal maternal anxiety. *Psychiatry Research: Neuroimaging*, *307*, 111207. https://doi.org/10.1016/j.pscychresns.2020.111207

Acosta H, Tuulari JJ, Scheinin NM, Hashempour N, Rajasilta O, Lavonius TI, Pelto J, Saunavaara V, Parkkola R, Lähdesmäki T, Karlsson L, & Karlsson H. (2020). Prenatal maternal depressive symptoms are associated with smaller amygdalar volumes of four-year-old children. *Psychiatry Research: Neuroimaging*, *304*, 111153. https://doi.org/10.1016/j.pscychresns.2020.111153

Adam, Y., Sadeeq, S., Kumuthini, J., Ajayi, O., Wells, G., Solomon, R., Ogunlana, O., Adetiba, E., Iweala, E., Brors, B., & Adebiyi, E. (2022). Polygenic Risk Score in African populations: progress and challenges. *F1000Research*, *11*, 175. https://doi.org/10.12688/f1000research.76218.1

Alex, A. M., Buss, C., Davis, E. P., Campos, G. de los, Donald, K. A., Fair, D. A., Gaab, N., Gao, W., Gilmore, J. H., Girault, J. B., Grewen, K., Groenewold, N. A., Hankin, B. L., Ipser, J., Kapoor, S., Kim, P., Lin, W., Luo, S., Norton, E. S., … Knickmeyer, R. (2023). Genetic Influences on the Developing Young Brain and Risk for Neuropsychiatric Disorders. *Biological Psychiatry*, *93*(10), 905–920. https://doi.org/10.1016/j.biopsych.2023.01.013

American Psychiatric Association. (2022a). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). American Psychiatric Association Publishing. https://doi.org/10.1176/appi.books.9780890425787

American Psychiatric Association. (2022b). Trauma- and Stressor-Related Disorders. *Diagnostic and Statistical Manual of Mental Disorders*, *5*.

Anderson, C. A., Pettersson, F. H., Clarke, G. M., Cardon, L. R., Morris, A. P., & Zondervan, K. T. (2010). Data quality control in genetic case-control association studies. *Nature Protocols*, *5*(9), 1564–1573. https://doi.org/10.1038/nprot.2010.116

Armstrong-Carter, E., Trejo, S., Hill, L. J. B., Crossley, K. L., Mason, D., & Domingue, B. W. (2020). The Earliest Origins of Genetic Nurture: The Prenatal Environment Mediates the Association Between Maternal Genetics and Child Development. *Psychological Science*, *31*(7), 781–791. https://doi.org/10.1177/0956797620917209

Asnaani, A., & Hall-Clark, B. (2017). Recent developments in understanding ethnocultural and race differences in trauma exposure and PTSD. *Current Opinion in Psychology*, *14*, 96–101. https://doi.org/10.1016/j.copsyc.2016.12.005

Auton, A., Abecasis, G. R., Altshuler, D. M., Durbin, R. M., Abecasis, G. R., Bentley, D. R., Chakravarti, A., Clark, A. G., Donnelly, P., Eichler, E. E., Flicek, P., Gabriel, S. B., Gibbs, R. A., Green, E. D., Hurles, M. E., Knoppers, B. M., Korbel, J. O., Lander, E. S., Lee, C., … Abecasis, G. R. (2015a). A global reference for human genetic variation. *Nature*, *526*(7571), 68–74. https://doi.org/10.1038/nature15393

Auton, A., Abecasis, G. R., Altshuler, D. M., Durbin, R. M., Abecasis, G. R., Bentley, D. R., Chakravarti, A., Clark, A. G., Donnelly, P., Eichler, E. E., Flicek, P., Gabriel, S. B., Gibbs, R. A., Green, E. D., Hurles, M. E., Knoppers, B. M., Korbel, J. O., Lander, E. S., Lee, C., … Abecasis, G. R. (2015b). A global reference for human genetic variation. *Nature*, *526*(7571), 68–74. https://doi.org/10.1038/nature15393

Aw, A.J., McRae, J., Rahmani, E., Song, Y.S., (2024). *Highly parameterized polygenic scores tend to overfit to population stratification via random effects. bioRxiv : the preprint server for biology*, *1*. https://doi.org/10.1101/2024.01.27.577589

Beck, A. T., Steer, R. A., & Garbin, M. G. (1988). Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*, *8*(1), 77–100.

Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry*, *4*, 561–571.

Belsky, D. W., & Domingue, B. W. (2023). Progress and Challenges in GxE Research on Depression. *American Journal of Psychiatry*, *180*(2), 111–113. https://doi.org/10.1176/appi.ajp.20221039

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*, 289–300.

Beusenberg, M. O., John, H., & World Health Organization. (1994). A User's guide to the self reporting questionnaire. *Division of Mental Health*.

Beyer, J. L., Kuchibhatla, M., Payne, M., Moo-Young, M., Cassidy, F., MacFall, J., & R. Krishnan, K. R. (2004). Caudate volume measurement in older adults with bipolar disorder. *International Journal of Geriatric Psychiatry*, *19*(2), 109–114. https://doi.org/10.1002/gps.1030

Bhatia, D. (2023). Neuroscience Engagement and Outreach on Neurodevelopmental Disorders: A Report from India. *Annals of Neurosciences*, *30*(2), 119–123. https://doi.org/10.1177/09727531231176122

Biau, D. J., Kernéis, S., & Porcher, R. (2008). Statistics in Brief: The Importance of Sample Size in the Planning and Interpretation of Medical Research. *Clinical Orthopaedics and Related Research*, *466*(9), 2282–2288. https://doi.org/10.1007/s11999-008-0346-9

Bigdeli, T. B., Voloudakis, G., Barr, P. B., Gorman, B. R., Genovese, G., Peterson, R. E., Burstein, D. E., Velicu, V. I., Li, Y., Gupta, R., Mattheisen, M., Tomasi, S., Rajeevan, N., Sayward, F., Radhakrishnan, K., Natarajan, S., Malhotra, A. K., Shi, Y., Zhao, H., … Whittle, J. (2022). Penetrance and Pleiotropy of Polygenic Risk Scores for

Schizophrenia, Bipolar Disorder, and Depression Among Adults in the US Veterans Affairs Health Care System. *JAMA Psychiatry*, *79*(11), 1092. https://doi.org/10.1001/jamapsychiatry.2022.2742

Bitarello, B. D., & Mathieson, I. (2020). Polygenic Scores for Height in Admixed Populations. *G3 (Bethesda, Md.)*, *10*(11), 4027–4036. https://doi.org/10.1534/g3.120.401658

Blake, D. D., Weathers, F. W., Nagy, L. M., Kaloupek, D. G., Gusman, F. D., Charney, D. S., & Keane, T. M. (1995). The development of a clinician-administered PTSD scale. *Journal of Traumatic Stress*, *8*, 75–90.

Boukezzi, S., Baunez, C., Rousseau, P.-F., Warrot, D., Silva, C., Guyon, V., Zendjidjian, X., Nicolas, F., Guedj, E., Nazarian, B., Trousselard, M., Chaminade, T., & Khalfa, S. (2020). Posttraumatic Stress Disorder is associated with altered reward mechanisms during the anticipation and the outcome of monetary incentive cues. *NeuroImage. Clinical*, *25*, 102073. https://doi.org/10.1016/j.nicl.2019.102073

Bremner, J. D. (2006). Traumatic stress: effects on the brain. *Dialogues in Clinical Neuroscience*, *8*(4), 445–461. https://doi.org/10.31887/DCNS.2006.8.4/jbremner

Bromet, E., Andrade, L. H., Hwang, I., Sampson, N. A., Alonso, J., de Girolamo, G., de Graaf, R., Demyttenaere, K., Hu, C., Iwata, N., Karam, A. N., Kaur, J., Kostyuchenko, S., Lépine, J.-P., Levinson, D., Matschinger, H., Mora, M. E. M., Browne, M. O., Posada-Villa, J., … Kessler, R. C. (2011). Cross-national epidemiology of DSM-IV major depressive episode. *BMC Medicine*, *9*(1), 90. https://doi.org/10.1186/1741-7015-9-90

Brown, B. C., Ye, C. J., Price, A. L., & Zaitlen, N. (2016). Transethnic Genetic-Correlation Estimates from Summary Statistics. *The American Journal of Human Genetics*, *99*(1), 76–88. https://doi.org/10.1016/j.ajhg.2016.05.001

Browning, S. R., & Browning, B. L. (2011). Haplotype phasing: existing methods and new developments. *Nature Reviews Genetics*, *12*(10), 703–714. https://doi.org/10.1038/nrg3054

Bumgarner, R. (2013). Overview of DNA Microarrays: Types, Applications, and Their Future. *Current Protocols in Molecular Biology*, *101*(1). https://doi.org/10.1002/0471142727.mb2201s101

Burra, N., Hervais-Adelman, A., Celeghin, A., de Gelder, B., & Pegna, A. J. (2019). Affective blindsight relies on low spatial frequencies. *Neuropsychologia*, *128*, 44–49. https://doi.org/10.1016/j.neuropsychologia.2017.10.009

Burton, P. R., Clayton, D. G., Cardon, L. R., Craddock, N., Deloukas, P., Duncanson, A., Kwiatkowski, D. P., McCarthy, M. I., Ouwehand, W. H., Samani, N. J., Todd, J. A., Donnelly, P., Barrett, J. C., Burton, P. R., Davison, D., Donnelly, P., Easton, D., Evans, D., Leung, H.-T., … Worthington, J. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature*, *447*(7145), 661–678. https://doi.org/10.1038/nature05911

Bush, W. S., & Moore, J. H. (2012). Chapter 11: Genome-Wide Association Studies. *PLoS Computational Biology*, *8*(12), e1002822. https://doi.org/10.1371/journal.pcbi.1002822

Button, K., Ioannidis, J., Mokrysz, C., Nosek, B., Flint, J., Robinson, E., & Munafo, M. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience Volume*, *14*, 365–376.

Campbell, M. C., & Tishkoff, S. A. (2008). African Genetic Diversity: Implications for Human Demographic History, Modern Human Origins, and Complex Disease Mapping. *Annual Review of Genomics and Human Genetics*, *9*(1), 403–433. https://doi.org/10.1146/annurev.genom.9.081307.164258

Cantor, R. M., Lange, K., & Sinsheimer, J. S. (2010). Prioritizing GWAS Results: A Review of Statistical Methods and Recommendations for Their Application. *The American Journal of Human Genetics*, *86*(1), 6–22. https://doi.org/10.1016/j.ajhg.2009.11.017

Chang, C. C. (2020). Data Management and Summary Statistics with PLINK. In J. Y. Dutheil (Ed.), *Statistical Population Genomics* (Vol. 2090, pp. 49–65). Humana, New York, NY. https://doi.org/10.1007/978-1-0716-0199-0_3

Chang, C. C., Chow, C. C., Tellier, L. C., Vattikuti, S., Purcell, S. M., & Lee, J. J. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. *GigaScience*, *4*(1), 7. https://doi.org/10.1186/s13742-015-0047-8

Charlson, F. J., Flaxman, A., Ferrari, A. J., Vos, T., Steel, Z., & Whiteford, H. A. (2016). Post-traumatic stress disorder and major depression in conflict-affected populations: an epidemiological model and predictor analysis. *Global Mental Health*, *3*, e4. https://doi.org/10.1017/gmh.2015.26

Chen, C., Han, J., Hunter, D. J., Kraft, P., & Price, A. L. (2015). Explicit Modeling of Ancestry Improves Polygenic Risk Scores and BLUP Prediction. *Genetic Epidemiology*, *39*(6), 427–438. https://doi.org/10.1002/gepi.21906

Cherry, K. (2020, December 1). *What Is the Edinburgh Postnatal Depression Scale (EPDS)?* Very Well Mind.

Choi, S. W., Mak, T. S.-H., & O'Reilly, P. F. (2020). Tutorial: a guide to performing polygenic risk score analyses. *Nature Protocols*, *15*(9), 2759–2772. https://doi.org/10.1038/s41596-020-0353-1

Choudhury, A., Hazelhurst, S., Meintjes, A., Achinike-Oduaran, O., Aron, S., Gamieldien, J., Jalali Sefid Dashti, M., Mulder, N., Tiffin, N., & Ramsay, M. (2014). Population-specific common SNPs reflect demographic histories and highlight regions of genomic plasticity with functional relevance. *BMC Genomics*, *15*(1), 437. https://doi.org/10.1186/1471-2164-15-437

Choudhury, A., Ramsay, M., Hazelhurst, S., Aron, S., Bardien, S., Botha, G., Chimusa, E. R., Christoffels, A., Gamieldien, J., Sefid-Dashti, M. J., Joubert, F., Meintjes, A., Mulder, N., Ramesar, R., Rees, J., Scholtz, K., Sengupta, D., Soodyall, H., Venter, P., … Pepper, M. S. (2017). Whole-genome sequencing for an enhanced understanding of genetic variation among South Africans. *Nature Communications*, *8*(1), 2062. https://doi.org/10.1038/s41467-017-00663-9

Collister, J. A., Liu, X., & Clifton, L. (2022). Calculating Polygenic Risk Scores (PRS) in UK Biobank: A Practical Guide for Epidemiologists. *Frontiers in Genetics*, *13*. https://doi.org/10.Col3389/fgene.2022.818574

Colquhoun, D. (2014) An investigation of the false discovery rate and the misinterpretation of p-values. *Royal Society Open Science*, *1*. https://doi.org/10.1098/rsos.140216

Conrad, D. F., Jakobsson, M., Coop, G., Wen, X., Wall, J. D., Rosenberg, N. A., & Pritchard, J. K. (2006). A worldwide survey of haplotype variation and linkage disequilibrium in the human genome. *Nature Genetics*, *38*(11), 1251–1260. https://doi.org/10.1038/ng1911

Coram, M. A., Candille, S. I., Duan, Q., Chan, K. H. K., Li, Y., Kooperberg, C., Reiner, A. P., & Tang, H. (2015). Leveraging Multi-ethnic Evidence for Mapping Complex Traits in Minority Populations: An Empirical Bayes Approach. *The American Journal of Human Genetics*, *96*(5), 740–752. https://doi.org/10.1016/j.ajhg.2015.03.008

Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Detection of Postnatal Depression. *British Journal of Psychiatry*, *150*(6), 782–786. https://doi.org/10.1192/bjp.150.6.782

Cross, B., Turner, R., & Pirmohamed, M. (2022). Polygenic risk scores: An overview from bench to bedside for personalised medicine. *Frontiers in Genetics*, *13*, 1000667. https://doi.org/10.3389/fgene.2022.1000667

Cullen, H., Dimitrakopoulou, K., Patel, H., Curtis, C., Batalle, D., Gale-Grant, O., Cordero-Grande, L., Price, A., Hajnal, J., & David Edwards, A. (2022). Common Genetic Variation Important in Early Subcortical Brain Development. *MedRxiv*. https://doi.org/10.1101/2022.08.11.22278677

Daya, M., Rafaels, N., Brunetti, T. M., Chavan, S., Levin, A. M., Shetty, A., Gignoux, C. R., Boorgula, M. P., Wojcik, G., Campbell, M., Vergara, C., Torgerson, D. G., Ortega, V. E., Doumatey, A., Johnston, H. R., Acevedo, N., Araujo, M. I., Avila, P. C., Belbin, G., … Yazdanbakhsh, M. (2019). Association study in African-admixed populations across the Americas recapitulates asthma risk loci in non-African populations. *Nature Communications*, *10*(1), 880. https://doi.org/10.1038/s41467-019-08469-7

Didion, J. P., Yang, H., Sheppard, K., Fu, C.-P., McMillan, L., de Villena, F. P.-M., & Churchill, G. A. (2012). Discovery of novel variants in genotyping arrays improves genotype retention and reduces ascertainment bias. *BMC Genomics*, *13*(1), 34. https://doi.org/10.1186/1471-2164-13-34

Dieckmann, L., & Czamara, D. (2024). Epigenetics of prenatal stress in humans: the current research landscape. *Clinical Epigenetics*, *16*(1), 20. https://doi.org/10.1186/s13148-024-01635-9

Donald, K. A., Hoogenhout, M., du Plooy, C. P., Wedderburn, C. J., Nhapi, R. T., Barnett, W., Hoffman, N., Malcolm-Smith, S., Zar, H. J., & Stein, D. J. (2018). Drakenstein Child Health Study (DCHS): investigating determinants of early child development and cognition. *BMJ Paediatrics Open*, *2*(1), e000282. https://doi.org/10.1136/bmjpo-2018-000282

D.R. Cox, & E. J. Snell. (1989). *Analysis of Binary Data, Second Edition Volume 32 of Chapman & Hall/CRC Monographs on Statistics & Applied Probability* (2nd ed., Vol. 32). CRC Press.

Drevets, W. C., Price, J. L., & Furey, M. L. (2008a). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure and Function*, *213*(1–2), 93–118. https://doi.org/10.1007/s00429-008-0189-x

Drevets, W. C., Price, J. L., & Furey, M. L. (2008b). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure & Function*, *213*(1–2), 93–118. https://doi.org/10.1007/s00429-008-0189-x

Du, J., Zhu, M., Bao, H., Li, B., Dong, Y., Xiao, C., Zhang, G. Y., Henter, I., Rudorfer, M., & Vitiello, B. (2016). The Role of Nutrients in Protecting Mitochondrial Function and Neurotransmitter Signaling: Implications for the Treatment of Depression, PTSD, and Suicidal Behaviors. *Critical Reviews in Food Science and Nutrition*, *56*(15), 2560–2578. https://doi.org/10.1080/10408398.2013.876960

Dufford, A. J., Spann, M., & Scheinost, D. (2021). How prenatal exposures shape the infant brain: Insights from infant neuroimaging studies. In *Neuroscience and Biobehavioral Reviews* (Vol. 131, pp. 47–58). Elsevier Ltd. https://doi.org/10.1016/j.neubiorev.2021.09.017

Duncan, L. E., Ratanatharathorn, A., Aiello, A. E., Almli, L. M., Amstadter, A. B., Ashley-Koch, A. E., Baker, D. G., Beckham, J. C., Bierut, L. J., Bisson, J., Bradley, B., Chen, C.-Y., Dalvie, S., Farrer, L. A., Galea, S., Garrett, M. E., Gelernter, J. E., Guffanti, G., Hauser, M. A., … Koenen, K. C. (2018). Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. *Molecular Psychiatry*, *23*(3), 666–673. https://doi.org/10.1038/mp.2017.77

Eggins, P. S., Hatton, S. N., Hermens, D. F., Hickie, I. B., & Lagopoulos, J. (2018). Subcortical volumetric differences between clinical stages of young people with

affective and psychotic disorders. *Psychiatry Research: Neuroimaging*, *271*, 8–16. https://doi.org/10.1016/j.pscychresns.2017.11.015
Elhaik, E. (2022). Principal Component Analyses (PCA)-based findings in population genetic studies are highly biased and must be reevaluated. *Scientific Reports*, *12*(1), 14683. https://doi.org/10.1038/s41598-022-14395-4
Elliott, L. T., Sharp, K., Alfaro-Almagro, F., Shi, S., Miller, K. L., Douaud, G., Marchini, J., & Smith, S. M. (2018). Genome-wide association studies of brain imaging phenotypes in UK Biobank. *Nature*, *562*(7726), 210–216. https://doi.org/10.1038/s41586-018-0571-7
Erickson, K. I., Miller, D. L., & Roecklein, K. A. (2012). The aging hippocampus: Interactions between exercise, depression, and BDNF. *Neuroscientist*, *18*(1), 82–97. https://doi.org/10.1177/1073858410397054
Espinoza Oyarce, D. A., Shaw, M. E., Alateeq, K., & Cherbuin, N. (2020). Volumetric brain differences in clinical depression in association with anxiety: a systematic review with meta-analysis. *Journal of Psychiatry and Neuroscience*, *45*(6), 406–429. https://doi.org/10.1503/jpn.190156
Falah-Hassani, K., Shiri, R., & Dennis, C.-L. (2017). The prevalence of antenatal and postnatal co-morbid anxiety and depression: a meta-analysis. *Psychological Medicine*, *47*(12), 2041–2053. https://doi.org/10.1017/S0033291717000617
Falsetti, S. A., Resnick, H. S., Resick, P. A., & Kilpatrick, D. G. (1993). The Modified PTSD Symptom Scale: A brief self-report measure of posttraumatic stress disorder. *The Behavior Therapist*, *16*, 161–162.
Fatumo, S., Chikowore, T., Choudhury, A., Ayub, M., Martin, A. R., & Kuchenbaecker, K. (2022). A roadmap to increase diversity in genomic studies. *Nature Medicine*, *28*(2), 243–250. https://doi.org/10.1038/s41591-021-01672-4
Flint, J. (2023). The genetic basis of major depressive disorder. *Molecular Psychiatry*, *28*(6), 2254–2265. https://doi.org/10.1038/s41380-023-01957-9
Flory, J. D., & Yehuda, R. (2015). Comorbidity between post-traumatic stress disorder and major depressive disorder: alternative explanations and treatment considerations. *Dialogues in Clinical Neuroscience*, *17*(2), 141–150. https://doi.org/10.31887/DCNS.2015.17.2/jflory
Friedman, M. J., Resick, P. A., Bryant, R. A., & Brewin, C. R. (2011). Considering PTSD for DSM-5. *Depression and Anxiety*, *28*(9), 750–769. https://doi.org/10.1002/da.20767
García-Batista, Z. E., Guerra-Peña, K., Cano-Vindel, A., Herrera-Martínez, S. X., & Medrano, L. A. (2018). Validity and reliability of the Beck Depression Inventory (BDI-II) in general and hospital population of Dominican Republic. *PLOS ONE*, *13*(6), e0199750. https://doi.org/10.1371/journal.pone.0199750
Garza, K., & Jovanovic, T. (2017). Impact of Gender on Child and Adolescent PTSD. *Current Psychiatry Reports*, *19*(11), 87. https://doi.org/10.1007/s11920-017-0830-6
Gavin, N. I., Gaynes, B. N., Lohr, K. N., Meltzer-Brody, S., Gartlehner, G., & Swinson, T. (2005). Perinatal Depression. *Obstetrics & Gynecology*, *106*(5, Part 1), 1071–1083. https://doi.org/10.1097/01.AOG.0000183597.31630.db
Gbadamosi, I. T., Henneh, I. T., Aluko, O. M., Yawson, E. O., Fokoua, A. R., Koomson, A., Torbi, J., Olorunnado, S. E., Lewu, F. S., Yusha'u, Y., Keji-Taofik, S. T., Biney, R. P., & Tagoe, T. A. (2022). Depression in Sub-Saharan Africa. *IBRO Neuroscience Reports*, *12*, 309–322. https://doi.org/10.1016/j.ibneur.2022.03.005
Ge, T., Irvin, M. R., Patki, A., Srinivasasainagendra, V., Lin, Y.-F., Tiwari, H. K., Armstrong, N. D., Benoit, B., Chen, C.-Y., Choi, K. W., Cimino, J. J., Davis, B. H., Dikilitas, O., Etheridge, B., Feng, Y.-C. A., Gainer, V., Huang, H., Jarvik, G. P., Kachulis, C., … Karlson, E. W. (2022). Development and validation of a trans-ancestry

polygenic risk score for type 2 diabetes in diverse populations. *Genome Medicine*, *14*(1), 70. https://doi.org/10.1186/s13073-022-01074-2

Gentile, S. (2017). Untreated depression during pregnancy: Short- and long-term effects in offspring. A systematic review. *Neuroscience*, *342*, 154–166. https://doi.org/10.1016/j.neuroscience.2015.09.001

Giannakopoulou, O., Lin, K., Meng, X., Su, M. H., Kuo, P. H., Peterson, R. E., Awasthi, S., Moscati, A., Coleman, J. R. I., Bass, N., Millwood, I. Y., Chen, Y., Chen, Z., Chen, H. C., Lu, M. L., Huang, M. C., Chen, C. H., Stahl, E. A., Loos, R. J. F., … Kuchenbaecker, K. (2021). The Genetic Architecture of Depression in Individuals of East Asian Ancestry: A Genome-Wide Association Study. *JAMA Psychiatry*, *78*(11), 1258–1269. https://doi.org/10.1001/jamapsychiatry.2021.2099

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

Glover, V. (2020). Prenatal mental health and the effects of stress on the foetus and the child. Should psychiatrists look beyond mental disorders? *World Psychiatry*, *19*(3), 331–332. https://doi.org/10.1002/wps.20777

Gong, L., He, C., Yin, Y., Wang, H., Ye, Q., Bai, F., Yuan, Y., Zhang, H., Lv, L., Zhang, H., Zhang, Z., & Xie, C. (2017). Mediating Role of the Reward Network in the Relationship between the Dopamine Multilocus Genetic Profile and Depression. *Frontiers in Molecular Neuroscience*, *10*. https://doi.org/10.3389/fnmol.2017.00292

Grahn, J. A., Parkinson, J. A., & Owen, A. M. (2008). The cognitive functions of the caudate nucleus. *Progress in Neurobiology*, *86*(3), 141–155. https://doi.org/10.1016/j.pneurobio.2008.09.004

Green, E. D., Gunter, C., Biesecker, L. G., Di Francesco, V., Easter, C. L., Feingold, E. A., Felsenfeld, A. L., Kaufman, D. J., Ostrander, E. A., Pavan, W. J., Phillippy, A. M., Wise, A. L., Dayal, J. G., Kish, B. J., Mandich, A., Wellington, C. R., Wetterstrand, K. A., Bates, S. A., Leja, D., … Manolio, T. A. (2020). Strategic vision for improving human health at The Forefront of Genomics. *Nature*, *586*(7831), 683–692. https://doi.org/10.1038/s41586-020-2817-4

Groenewold, N. A., Wedderburn, C. J., Pellowski, J. A., Fouché, J.-P., Michalak, L., Roos, A., Woods, R. P., Narr, K. L., Zar, H. J., Donald, K. A., & Stein, D. J. (2022). Subcortical brain volumes in young infants exposed to antenatal maternal depression: Findings from a South African birth cohort. *NeuroImage: Clinical*, *36*, 103206. https://doi.org/10.1016/j.nicl.2022.103206

Ham, S., & Lee, S.-J. V. (2020). Advances in transcriptome analysis of human brain aging. *Experimental & Molecular Medicine*, *52*(11), 1787–1797. https://doi.org/10.1038/s12276-020-00522-6

Hancock, D. B., Levy, J. L., Gaddis, N. C., Bierut, L. J., Saccone, N. L., Page, G. P., & Johnson, E. O. (2012). Assessment of Genotype Imputation Performance Using 1000 Genomes in African American Studies. *PLoS ONE*, *7*(11), e50610. https://doi.org/10.1371/journal.pone.0050610

Harris, S. E., Riggio, V., Evenden, L., Gilchrist, T., Mccafferty, S., Murphy, L., Wrobel, N., Taylor, A. M., Corley, J., Pattie, A., Cox, S. R., Martin-Ruiz, C., Prendergast, J., Starr, J. M., Marioni, R. E., & Deary, I. J. (2017). *Age-related gene expression changes, and transcriptome wide association study of physical and cognitive aging traits, in the Lothian Birth Cohort 1936 Equal contribution* (Vol. 9, Issue 12). www.aging-us.com

Hartley, M., Tomlinson, M., Greco, E., Comulada, W. S., Stewart, J., le Roux, I., Mbewu, N., & Rotheram-Borus, M. J. (2011). Depressed mood in pregnancy: Prevalence and

correlates in two Cape Town peri-urban settlements. *Reproductive Health*, *8*(1), 9. https://doi.org/10.1186/1742-4755-8-9

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., Scheimann, J., & Myers, B. (2016). Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. *Comprehensive Physiology*, *6*(2), 603–621. https://doi.org/10.1002/cphy.c150015

Herringa, R., Phillips, M., Almeida, J., Insana, S., & Germain, A. (2012). Post-traumatic stress symptoms correlate with smaller subgenual cingulate, caudate, and insula volumes in unmedicated combat veterans. *Psychiatry Research: Neuroimaging*, *203*(2–3), 139–145. https://doi.org/10.1016/j.pscychresns.2012.02.005

Hibar, D. P., Stein, J. L., Renteria, M. E., Arias-Vasquez, A., Desrivières, S., Jahanshad, N., Toro, R., Wittfeld, K., Abramovic, L., Andersson, M., Aribisala, B. S., Armstrong, N. J., Bernard, M., Bohlken, M. M., Boks, M. P., Bralten, J., Brown, A. A., Mallar Chakravarty, M., Chen, Q., … Medland, S. E. (2015). Common genetic variants influence human subcortical brain structures. *Nature*, *520*(7546), 224–229. https://doi.org/10.1038/nature14101

Ho, T. C., Teresi, G. I., Ojha, A., Walker, J. C., Kirshenbaum, J. S., Singh, M. K., & Gotlib, I. H. (2021). Smaller caudate gray matter volume is associated with greater implicit suicidal ideation in depressed adolescents. *Journal of Affective Disorders*, *278*, 650–657. https://doi.org/10.1016/j.jad.2020.09.046

Hoggart, C. J., Choi, S. W., García-González, J., Souaiaia, T., Preuss, M., & O'Reilly, P. F. (2024). BridgePRS leverages shared genetic effects across ancestries to increase polygenic risk score portability. *Nature Genetics*, *56*(1), 180–186. https://doi.org/10.1038/s41588-023-01583-9

Hosmer, D. W., Lemeshow, S., & Sturdivant, R. X. (2013). *Applied Logistic Regression*. Wiley. https://doi.org/10.1002/9781118548387

Hou, J., Hess, J. L., Armstrong, N., Bis, J. C., Grenier-Boley, B., Karlsson, I. K., Leonenko, G., Numbers, K., O'Brien, E. K., Shadrin, A., Thalamuthu, A., Yang, Q., Andreassen, O. A., Brodaty, H., Gatz, M., Kochan, N. A., Lambert, J.-C., Laws, S. M., Masters, C. L., … Glatt, S. J. (2022). Polygenic resilience scores capture protective genetic effects for Alzheimer's disease. *Translational Psychiatry*, *12*(1), 296. https://doi.org/10.1038/s41398-022-02055-0

Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shirali, M., Coleman, J. R. I., Hagenaars, S. P., Ward, J., Wigmore, E. M., Alloza, C., Shen, X., Barbu, M. C., Xu, E. Y., Whalley, H. C., Marioni, R. E., Porteous, D. J., Davies, G., Deary, I. J., … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, *22*(3), 343–352. https://doi.org/10.1038/s41593-018-0326-7

Huang, K.-W., Qiao, M., Liu, X., Liu, S., & Dai, M. (2019). *Computer Vision and Metrics Learning for Hypothesis Testing: An Application of Q-Q Plot for Normality Test*.

Hubley, A. M. (2022). Beck Depression Inventory. In *Encyclopedia of Quality of Life and Well-Being Research* (pp. 1–11). Springer International Publishing. https://doi.org/10.1007/978-3-319-69909-7_156-2

Institute of Medicine (US) Committee on Assessing Interactions Among Social, B. and G. F. in H. (2006). Genetics and Health. In Hernandez LM & Blazer DG (Eds.), *Genes, Behavior, and the Social Environment: Moving Beyond the Nature/Nurture Debate*. National Academies Press (US).

Jackson-Koku, G. (2016). Beck Depression Inventory. *Occupational Medicine*, *66*(2), 174–175. https://doi.org/10.1093/occmed/kqv087

Jagtap, A., Jagtap, B., Jagtap, R., Lamture, Y., & Gomase, K. (2023). Effects of Prenatal Stress on Behavior, Cognition, and Psychopathology: A Comprehensive Review. *Cureus*, *15*(10), e47044. https://doi.org/10.7759/cureus.47044

Janssens, A. C. J. W. (2019). Validity of polygenic risk scores: are we measuring what we think we are? *Human Molecular Genetics*, *28*(R2), R143–R150. https://doi.org/10.1093/hmg/ddz205

Ji, J. L., Spronk, M., Kulkarni, K., Repovš, G., Anticevic, A., & Cole, M. W. (2019). Mapping the human brain's cortical-subcortical functional network organization. *NeuroImage*, *185*, 35–57. https://doi.org/10.1016/j.neuroimage.2018.10.006

Jiang, J., Ferraro, S., Zhao, Y., Wu, B., Lin, J., Chen, T., Gao, J., & Li, L. (2024). Common and divergent neuroimaging features in major depression, posttraumatic stress disorder, and their comorbidity. *Psychoradiology*, *4*. https://doi.org/10.1093/psyrad/kkae022

Jones, B. (2015). The African Genome Variation Project. *Nature Reviews Genetics*, *16*(2), 68–69. https://doi.org/10.1038/nrg3886

Kachuri, L., Chatterjee, N., Hirbo, J., Schaid, D. J., Martin, I., Kullo, I. J., Kenny, E. E., Pasaniuc, B., Auer, P. L., Conomos, M. P., Conti, D. V., Ding, Y., Wang, Y., Zhang, H., Zhang, Y., Witte, J. S., & Ge, T. (2024). Principles and methods for transferring polygenic risk scores across global populations. *Nature Reviews Genetics*, *25*(1), 8–25. https://doi.org/10.1038/s41576-023-00637-2

Kanai, R., & Rees, G. (2011). The structural basis of inter-individual differences in human behaviour and cognition. *Nature Reviews Neuroscience*, *12*(4), 231–242. https://doi.org/10.1038/nrn3000

Kanjira, S. C., Adams, M. J., Jiang, Y., Tian, C., Lewis, C. M., Kuchenbaecker, K., & McIntosh, A. M. (2024). Polygenic prediction of major depressive disorder and related traits in African ancestries UK Biobank participants. *Molecular Psychiatry*. https://doi.org/10.1038/s41380-024-02662-x

Karcher, N. R., & Barch, D. M. (2021). The ABCD study: understanding the development of risk for mental and physical health outcomes. *Neuropsychopharmacology*, *46*(1), 131–142. https://doi.org/10.1038/s41386-020-0736-6

Kardia, S. L. R., Modell, S. M., & Peyser, P. A. (2003). Family-centered approaches to understanding and preventing coronary heart disease. *American Journal of Preventive Medicine*, *24*(2), 143–151. https://doi.org/10.1016/S0749-3797(02)00587-1

Karmiloff-Smith, A., Casey, B. J., Massand, E., Tomalski, P., & Thomas, M. S. C. (2014). Environmental and Genetic Influences on Neurocognitive Development. *Clinical Psychological Science*, *2*(5), 628–637. https://doi.org/10.1177/2167702614521188

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Benjet, C., Bromet, E. J., Cardoso, G., Degenhardt, L., de Girolamo, G., Dinolova, R. V., Ferry, F., Florescu, S., Gureje, O., Haro, J. M., Huang, Y., Karam, E. G., Kawakami, N., Lee, S., Lepine, J.-P., Levinson, D., … Koenen, K. C. (2017). Trauma and PTSD in the WHO World Mental Health Surveys. *European Journal of Psychotraumatology*, *8*(sup5). https://doi.org/10.1080/20008198.2017.1353383

Kim, M. J., Hamilton, J. P., & Gotlib, I. H. (2008). Reduced caudate gray matter volume in women with major depressive disorder. *Psychiatry Research: Neuroimaging*, *164*(2), 114–122. https://doi.org/10.1016/j.pscychresns.2007.12.020

Kim, M. K., Lee, S. M., Bae, S.-H., Kim, H. J., Lim, N. G., Yoon, S.-J., Lee, J. Y., & Jo, M.-W. (2018). Socioeconomic status can affect pregnancy outcomes and complications, even with a universal healthcare system. *International Journal for Equity in Health*, *17*(1), 2. https://doi.org/10.1186/s12939-017-0715-7

Kingston, D., Tough, S., & Whitfield, H. (2012). Prenatal and Postpartum Maternal Psychological Distress and Infant Development: A Systematic Review. *Child Psychiatry & Human Development*, *43*(5), 683–714. https://doi.org/10.1007/s10578-012-0291-4

Kinsella Michael T., & Monk, C. (2009). Impact of Maternal Stress, Depression and Anxiety on Fetal Neurobehavioral Development. *Clinical Obstetrics & Gynecology*, *52*(3), 425–440. https://doi.org/10.1097/GRF.0b013e3181b52df1

Knierim, J. J. (2015). The hippocampus. *Current Biology*, *25*(23), R1116–R1121. https://doi.org/10.1016/j.cub.2015.10.049

Knifton, L., & Inglis, G. (2020). Poverty and mental health: policy, practice and research implications. *BJPsych Bulletin*, *44*(5), 193–196. https://doi.org/10.1192/bjb.2020.78

Koen, N., Brittain, K., Donald, K. A., Barnett, W., Koopowitz, S., Maré, K., Zar, H. J., & Stein, D. J. (2017). Maternal posttraumatic stress disorder and infant developmental outcomes in a South African birth cohort study. *Psychological Trauma: Theory, Research, Practice, and Policy*, *9*(3), 292–300. https://doi.org/10.1037/tra0000234

Koenen, K. C., Ratanatharathorn, A., Ng, L., McLaughlin, K. A., Bromet, E. J., Stein, D. J., Karam, E. G., Meron Ruscio, A., Benjet, C., Scott, K., Atwoli, L., Petukhova, M., Lim, C. C. W., Aguilar-Gaxiola, S., Al-Hamzawi, A., Alonso, J., Bunting, B., Ciutan, M., de Girolamo, G., … Kessler, R. C. (2017). Posttraumatic stress disorder in the World Mental Health Surveys. *Psychological Medicine*, *47*(13), 2260–2274. https://doi.org/10.1017/S0033291717000708

Kovač, V., & Čurin Šerbec, V. (2022). Prion Protein: The Molecule of Many Forms and Faces. *International Journal of Molecular Sciences*, *23*(3), 1232. https://doi.org/10.3390/ijms23031232

Kroes, M. C. W., Rugg, M. D., Whalley, M. G., & Brewin, C. R. (2011). Structural brain abnormalities common to posttraumatic stress disorder and depression. *Journal of Psychiatry and Neuroscience*, *36*(4), 256–265. https://doi.org/10.1503/jpn.100077

Kuehner, C. (2017). Why is depression more common among women than among men? *The Lancet Psychiatry*, *4*(2), 146–158. https://doi.org/10.1016/S2215-0366(16)30263-2

Ladd-Acosta, C., & Fallin, M. D. (2016). The Role of Epigenetics in Genetic and Environmental Epidemiology. *Epigenomics*, *8*(2), 271–283. https://doi.org/10.2217/epi.15.102

Lambert, S. A., Abraham, G., & Inouye, M. (2019). Towards clinical utility of polygenic risk scores. *Human Molecular Genetics*, *28*(R2), R133–R142. https://doi.org/10.1093/hmg/ddz187

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harbor Perspectives in Medicine*, *2*(12), a009621. https://doi.org/10.1101/cshperspect.a009621

Landré, L., Destrieux, C., Baudry, M., Barantin, L., Cottier, J.-P., Martineau, J., Hommet, C., Isingrini, M., Belzung, C., Gaillard, P., Camus, V., & El Hage, W. (2010). Preserved subcortical volumes and cortical thickness in women with sexual abuse-related PTSD. *Psychiatry Research: Neuroimaging*, *183*(3), 181–186. https://doi.org/10.1016/j.pscychresns.2010.01.015

Lane, S. P., & Kelleher, B. L. (2023). Statistical power for longitudinal developmental trajectories: The (non-)impact of age matching within measurement occasions. *Developmental Psychology*, *59*(2), 207–215. https://doi.org/10.1037/dev0001459

Laurie, C. C., Doheny, K. F., Mirel, D. B., Pugh, E. W., Bierut, L. J., Bhangale, T., Boehm, F., Caporaso, N. E., Cornelis, M. C., Edenberg, H. J., Gabriel, S. B., Harris, E. L., Hu, F. B., Jacobs, K. B., Kraft, P., Landi, M. T., Lumley, T., Manolio, T. A., McHugh, C., … Weir, B. S. (2010). Quality control and quality assurance in genotypic data for genome-

wide association studies. *Genetic Epidemiology*, *34*(6), 591–602. https://doi.org/10.1002/gepi.20516

Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, I., Sheehan, K. H., Janavs, J., & Dunbar, G. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European Psychiatry*, *12*(5), 224–231. https://doi.org/10.1016/S0924-9338(97)83296-8

Levey, D. F., Gelernter, J., Polimanti, R., Zhou, H., Cheng, Z., Aslan, M., Quaden, R., Concato, J., Radhakrishnan, K., Bryois, J., Sullivan, P. F., & Stein, M. B. (2020). Reproducible Genetic Risk Loci for Anxiety: Results From ∼200,000 Participants in the Million Veteran Program. *American Journal of Psychiatry*, *177*(3), 223–232. https://doi.org/10.1176/appi.ajp.2019.19030256

Levey, D. F., Stein, M. B., Wendt, F. R., Pathak, G. A., Zhou, H., Aslan, M., Quaden, R., Harrington, K. M., Nuñez, Y. Z., Overstreet, C., Radhakrishnan, K., Sanacora, G., McIntosh, A. M., Shi, J., Shringarpure, S. S., Concato, J., Polimanti, R., & Gelernter, J. (2021). Bi-ancestral depression GWAS in the Million Veteran Program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. *Nature Neuroscience*, *24*(7), 954–963. https://doi.org/10.1038/s41593-021-00860-2

Levis, B., Negeri, Z., Sun, Y., Benedetti, A., & Thombs, B. D. (2020). Accuracy of the Edinburgh Postnatal Depression Scale (EPDS) for screening to detect major depression among pregnant and postpartum women: systematic review and meta-analysis of individual participant data. *BMJ*, m4022. https://doi.org/10.1136/bmj.m4022

Levitt, J. J., McCarley, R. W., Dickey, C. C., Voglmaier, M. M., Niznikiewicz, M. A., Seidman, L. J., Hirayasu, Y., Ciszewski, A. A., Kikinis, R., Jolesz, F. A., & Shenton, M. E. (2002). MRI study of caudate nucleus volume and its cognitive correlates in neuroleptic-naive patients with schizotypal personality disorder. *The American Journal of Psychiatry*, *159*(7), 1190–1197. https://doi.org/10.1176/appi.ajp.159.7.1190

Lewis, C. M., & Vassos, E. (2020). Polygenic risk scores: from research tools to clinical instruments. *Genome Medicine*, *12*(1), 44. https://doi.org/10.1186/s13073-020-00742-5

Liang, S., Wu, Y., Hanxiaoran, L., Greenshaw, A. J., & Li, T. (2022). Anhedonia in Depression and Schizophrenia: Brain Reward and Aversion Circuits. *Neuropsychiatric Disease and Treatment*, *18*, 1385–1396. https://doi.org/10.2147/NDT.S367839

Liu, E. Y., Buyske, S., Aragaki, A. K., Peters, U., Boerwinkle, E., Carlson, C., Carty, C., Crawford, D. C., Haessler, J., Hindorff, L. A., Marchand, L. Le, Manolio, T. A., Matise, T., Wang, W., Kooperberg, C., North, K. E., & Li, Y. (2012). Genotype Imputation of Metabochip SNPs Using a Study-Specific Reference Panel of ∼4,000 Haplotypes in African Americans From the Women's Health Initiative. *Genetic Epidemiology*, *36*(2), 107–117. https://doi.org/10.1002/gepi.21603

Liu, M., Wang, L., Zhang, Y., Dong, H., Wang, C., Chen, Y., Qian, Q., Zhang, N., Wang, S., Zhao, G., Zhang, Z., Lei, M., Wang, S., Zhao, Q., & Liu, F. (2024). Investigating the shared genetic architecture between depression and subcortical volumes. *Nature Communications*, *15*(1), 7647. https://doi.org/10.1038/s41467-024-52121-y

Logue, M. W., van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., Densmore, M., Haswell, C. C., Ipser, J., Koch, S. B. J., Korgaonkar, M., Lebois, L. A. M., Peverill, M., Baker, J. T., Boedhoe, P. S. W., Frijling, J. L., Gruber, S. A., Harpaz-Rotem, I., Jahanshad, N., … Morey, R. A. (2018a). Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. *Biological Psychiatry*, *83*(3), 244–253. https://doi.org/10.1016/j.biopsych.2017.09.006

Logue, M. W., van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., Densmore, M., Haswell, C. C., Ipser, J., Koch, S. B. J., Korgaonkar, M., Lebois, L. A.

M., Peverill, M., Baker, J. T., Boedhoe, P. S. W., Frijling, J. L., Gruber, S. A., Harpaz-Rotem, I., Jahanshad, N., … Morey, R. A. (2018b). Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. *Biological Psychiatry*, *83*(3), 244–253. https://doi.org/10.1016/j.biopsych.2017.09.006

Logue, M. W., van Rooij, S. J. H., Dennis, E. L., Davis, S. L., Hayes, J. P., Stevens, J. S., Densmore, M., Haswell, C. C., Ipser, J., Koch, S. B. J., Korgaonkar, M., Lebois, L. A. M., Peverill, M., Baker, J. T., Boedhoe, P. S. W., Frijling, J. L., Gruber, S. A., Harpaz-Rotem, I., Jahanshad, N., … Morey, R. A. (2018c). Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia. *Biological Psychiatry*, *83*(3), 244–253. https://doi.org/10.1016/j.biopsych.2017.09.006

Mabizela, S., & Van Wyk, B. (2022). Viral suppression among adolescents on HIV treatment in the Sedibeng District, Gauteng province. *Curationis*, *45*(1). https://doi.org/10.4102/curationis.v45i1.2312

Maćkiewicz, A., & Ratajczak, W. (1993). Principal components analysis (PCA). *Computers & Geosciences*, *19*(3), 303–342. https://doi.org/10.1016/0098-3004(93)90090-R

Maihofer, A. X., Choi, K. W., Coleman, J. R. I., Daskalakis, N. P., Denckla, C. A., Ketema, E., Morey, R. A., Polimanti, R., Ratanatharathorn, A., Torres, K., Wingo, A. P., Zai, C. C., Aiello, A. E., Almli, L. M., Amstadter, A. B., Andersen, S. B., Andreassen, O. A., Arbisi, P. A., Ashley-Koch, A. E., … Nievergelt, C. M. (2022). Enhancing Discovery of Genetic Variants for Posttraumatic Stress Disorder Through Integration of Quantitative Phenotypes and Trauma Exposure Information. *Biological Psychiatry*, *91*(7), 626–636. https://doi.org/10.1016/j.biopsych.2021.09.020

Majara, L., Kalungi, A., Koen, N., Tsuo, K., Wang, Y., Gupta, R., Nkambule, L. L., Zar, H., Stein, D. J., Kinyanda, E., Atkinson, E. G., & Martin, A. R. (2023). Low and differential polygenic score generalizability among African populations due largely to genetic diversity. *Human Genetics and Genomics Advances*, *4*(2), 100184. https://doi.org/10.1016/j.xhgg.2023.100184

Malhotra, D., & Sebat, J. (2012). CNVs: harbingers of a rare variant revolution in psychiatric genetics. *Cell*, *148*(6), 1223–1241. https://doi.org/10.1016/j.cell.2012.02.039

Mandl, S., Alexopoulos, J., Doering, S., Wildner, B., Seidl, R., & Bartha-Doering, L. (2024). The effect of prenatal maternal distress on offspring brain development: A systematic review. In *Early Human Development* (Vol. 192). Elsevier Ireland Ltd. https://doi.org/10.1016/j.earlhumdev.2024.106009

Manning, K. Y., Jaffer, A., & Lebel, C. (2024). Windows of Opportunity: How Age and Sex Shape the Influence of Prenatal Depression on the Child Brain. *Biological Psychiatry*, *97*(3), 227–247. https://doi.org/10.1016/j.biopsych.2024.07.022

Marchese, S., & Huckins, L. M. (2022). Trauma Matters: Integrating Genetic and Environmental Components of PTSD. *Advanced Genetics*, 2200017. https://doi.org/10.1002/ggn2.202200017

Marshall, C. R., Howrigan, D. P., Merico, D., Thiruvahindrapuram, B., Wu, W., Greer, D. S., Antaki, D., Shetty, A., Holmans, P. A., Pinto, D., Gujral, M., Brandler, W. M., Malhotra, D., Wang, Z., Fajarado, K. V. F., Maile, M. S., Ripke, S., Agartz, I., Albus, M., … Sebat, J. (2017). Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nature Genetics*, *49*(1), 27–35. https://doi.org/10.1038/ng.3725

Martin, A. R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B. M., & Daly, M. J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. *Nature Genetics*, *51*(4), 584–591. https://doi.org/10.1038/s41588-019-0379-x

Martin, A. R., Teferra, S., Möller, M., Hoal, E. G., & Daly, M. J. (2018). The critical needs and challenges for genetic architecture studies in Africa. *Current Opinion in Genetics & Development*, *53*, 113–120. https://doi.org/10.1016/j.gde.2018.08.005

Martin, R. E., & Ochsner, K. N. (2016). The neuroscience of emotion regulation development: implications for education. *Current Opinion in Behavioral Sciences*, *10*, 142–148. https://doi.org/10.1016/j.cobeha.2016.06.006

McClellan, J. M., Lehner, T., & King, M.-C. (2017). Gene Discovery for Complex Traits: Lessons from Africa. *Cell*, *171*(2), 261–264. https://doi.org/10.1016/j.cell.2017.09.037

McLaughlin, K. A., & Sheridan, M. A. (2016). Beyond Cumulative Risk. *Current Directions in Psychological Science*, *25*(4), 239–245. https://doi.org/10.1177/0963721416655883

McMaughan, D. J., Oloruntoba, O., & Smith, M. L. (2020). Socioeconomic Status and Access to Healthcare: Interrelated Drivers for Healthy Aging. *Frontiers in Public Health*, *8*, 231. https://doi.org/10.3389/fpubh.2020.00231

Meng, X., Navoly, G., Giannakopoulou, O., Levey, D. F., Koller, D., Pathak, G. A., Koen, N., Lin, K., Adams, M. J., Rentería, M. E., Feng, Y., Gaziano, J. M., Stein, D. J., Zar, H. J., Campbell, M. L., van Heel, D. A., Trivedi, B., Finer, S., McQuillin, A., … Kuchenbaecker, K. (2024). Multi-ancestry genome-wide association study of major depression aids locus discovery, fine mapping, gene prioritization and causal inference. *Nature Genetics*, *56*(2), 222–233. https://doi.org/10.1038/s41588-023-01596-4

Mercer, T. R., Dinger, M. E., Sunkin, S. M., Mehler, M. F., & Mattick, J. S. (2008). Specific expression of long noncoding RNAs in the mouse brain. *Proceedings of the National Academy of Sciences*, *105*(2), 716–721. https://doi.org/10.1073/pnas.0706729105

Meyer, C., Rumpf, H.-J., Hapke, U., & John, U. (2004). Impact of psychiatric disorders in the general population: satisfaction with life and the influence of comorbidity and disorder duration. *Social Psychiatry and Psychiatric Epidemiology*, *39*(6). https://doi.org/10.1007/s00127-004-0755-3

Miguel, P. M., Pereira, L. O., Silveira, P. P., & Meaney, M. J. (2019). Early environmental influences on the development of children's brain structure and function. *Developmental Medicine and Child Neurology*, *61*(10), 1127–1133. https://doi.org/10.1111/dmcn.14182

Misganaw, B., Guffanti, G., Lori, A., Abu-Amara, D., Flory, J. D., Hammamieh, R., Gautam, A., Yang, R., Daigle, B. J., Hood, L., Wang, K., Lee, I., Mellon, S. H., Wolkowitz, O. M., Mueller, S., Yehuda, R., Jett, M., Marmar, C. R., Ressler, K. J., & Doyle, F. J. (2019). Polygenic risk associated with post-traumatic stress disorder onset and severity. *Translational Psychiatry*, *9*(1), 165. https://doi.org/10.1038/s41398-019-0497-3

Morina, N., Malek, M., Nickerson, A., & Bryant, R. A. (2017). Psychological interventions for post-traumatic stress disorder and depression in young survivors of mass violence in low- and middle-income countries: Meta-analysis. *British Journal of Psychiatry*, *210*(4), 247–254. https://doi.org/10.1192/bjp.bp.115.180265

Mufford, M. S., van der Meer, D., Andreassen, O. A., Ramesar, R., Stein, D. J., & Dalvie, S. (2021). A review of systems biology research of anxiety disorders. *Brazilian Journal of Psychiatry*, *43*(4), 414–423. https://doi.org/10.1590/1516-4446-2020-1090

Muglia, L. J., Benhalima, K., Tong, S., & Ozanne, S. (2022). Maternal factors during pregnancy influencing maternal, fetal, and childhood outcomes. *BMC Medicine*, *20*(1), 418. https://doi.org/10.1186/s12916-022-02632-6

Mulder, N., Lombard, Z., Owolabi, M. O., & Ofori-Acquah, S. F. (2020). Editorial: The Genetic and Environmental Basis for Diseases in Understudied Populations. *Frontiers in Genetics*, *11*. https://doi.org/10.3389/fgene.2020.559956

Munafò, M. R., Zammit, S., & Flint, J. (2014). Practitioner Review: A critical perspective on gene–environment interaction models – what impact should they have on clinical

perceptions and practice? *Journal of Child Psychology and Psychiatry*, *55*(10), 1092–1101. https://doi.org/10.1111/jcpp.12261

Mundy, J., Hübel, C., Gelernter, J., Levey, D., Murray, R. M., Skelton, M., Stein, M. B., Vassos, E., Breen, G., & Coleman, J. R. I. (2022). Psychological trauma and the genetic overlap between posttraumatic stress disorder and major depressive disorder. *Psychological Medicine*, *52*(16), 3975–3984. https://doi.org/10.1017/S0033291721000830

Muniz Carvalho, C., Wendt, F. R., Maihofer, A. X., Stein, D. J., Stein, M. B., Sumner, J. A., Hemmings, S. M. J., Nievergelt, C. M., Koenen, K. C., Gelernter, J., Belangero, S. I., & Polimanti, R. (2021). Dissecting the genetic association of C-reactive protein with PTSD, traumatic events, and social support. *Neuropsychopharmacology*, *46*(6), 1071–1077. https://doi.org/10.1038/s41386-020-0655-6

Murray, D., & Cox, J. L. (1990). Screening for depression during pregnancy with the edinburgh depression scale (EDDS). *Journal of Reproductive and Infant Psychology*, *8*(2), 99–107. https://doi.org/10.1080/02646839008403615

Musci, R. J., Augustinavicius, J. L., & Volk, H. (2019). Gene-Environment Interactions in Psychiatry: Recent Evidence and Clinical Implications. *Current Psychiatry Reports*, *21*(9), 81. https://doi.org/10.1007/s11920-019-1065-5

Myer, L., Stein, D. J., Grimsrud, A., Seedat, S., & Williams, D. R. (2008). Social determinants of psychological distress in a nationally-representative sample of South African adults. *Social Science & Medicine*, *66*(8), 1828–1840. https://doi.org/10.1016/j.socscimed.2008.01.025

Nagelkerke, N. J. D. (1991). A note on a general definition of the coefficient of determination. *Biometrika*, *78*(3), 691–692. https://doi.org/10.1093/biomet/78.3.691

Naumova, O. Y., Lee, M., Rychkov, S. Y., Vlasova, N. V., & Grigorenko, E. L. (2013). Gene Expression in the Human Brain: The Current State of the Study of Specificity and Spatiotemporal Dynamics. *Child Development*, *84*(1), 76–88. https://doi.org/10.1111/cdev.12014

Ndungu, J., Ramsoomar, L., Willan, S., Washington, L., Ngcobo-Sithole, M., & Gibbs, A. (2020). Depression, posttraumatic stress disorder (PTSD) and their comorbidity: Implications of adversity amongst young women living in informal settlements in Durban, South Africa. *Journal of Affective Disorders Reports*, *1*, 100022. https://doi.org/10.1016/j.jadr.2020.100022

Negriff, S., Gordis, E. B., & Susman, E. J. (2023). Associations between HPA axis reactivity and PTSD and depressive symptoms: Importance of maltreatment type and puberty. *Development and Psychopathology*, *35*(1), 130–141. https://doi.org/10.1017/S095457942100050X

Neter, J., Kutner, M. H., Nachtsheim, C. J., & Wasserman, W. (1996). *Applied Linear Statistical Models* (4th ed.).

Ng, L. C., Stevenson, A., Kalapurakkel, S. S., Hanlon, C., Seedat, S., Harerimana, B., Chiliza, B., & Koenen, K. C. (2020). National and regional prevalence of posttraumatic stress disorder in sub-Saharan Africa: A systematic review and meta-analysis. *PLoS Medicine*, *17*(5). https://doi.org/10.1371/journal.pmed.1003090

Ni, G., Zeng, J., Revez, J. A., Wang, Y., Zheng, Z., Ge, T., Restuadi, R., Kiewa, J., Nyholt, D. R., Coleman, J. R. I., Smoller, J. W., Yang, J., Visscher, P. M., Wray, N. R., Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K.-H., … Pedersen, N. L. (2021). A Comparison of Ten Polygenic Score Methods for Psychiatric Disorders Applied Across Multiple Cohorts. *Biological Psychiatry*, *90*(9), 611–620. https://doi.org/10.1016/j.biopsych.2021.04.018

Nievergelt, C. M., Ashley-Koch, A. E., Dalvie, S., Hauser, M. A., Morey, R. A., Smith, A. K., & Uddin, M. (2018). Genomic Approaches to Posttraumatic Stress Disorder: The Psychiatric Genomic Consortium Initiative. *Biological Psychiatry*, *83*(10), 831–839. https://doi.org/10.1016/j.biopsych.2018.01.020

Nievergelt, C. M., Maihofer, A. X., Klengel, T., Atkinson, E. G., Chen, C.-Y., Choi, K. W., Coleman, J. R. I., Dalvie, S., Duncan, L. E., Gelernter, J., Levey, D. F., Logue, M. W., Polimanti, R., Provost, A. C., Ratanatharathorn, A., Stein, M. B., Torres, K., Aiello, A. E., Almli, L. M., … Koenen, K. C. (2019). International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nature Communications*, *10*(1), 4558. https://doi.org/10.1038/s41467-019-12576-w

Nolvi, S., Merz, E. C., Kataja, E.-L., & Parsons, C. E. (2023). Prenatal Stress and the Developing Brain: Postnatal Environments Promoting Resilience. *Biological Psychiatry*, *93*(10), 942–952. https://doi.org/10.1016/j.biopsych.2022.11.023

Northoff, G. (2013). Gene, brains, and environment-genetic neuroimaging of depression. *Current Opinion in Neurobiology*, *23*(1), 133–142. https://doi.org/10.1016/j.conb.2012.08.004

O'Doherty, D. C. M., Tickell, A., Ryder, W., Chan, C., Hermens, D. F., Bennett, M. R., & Lagopoulos, J. (2017). Frontal and subcortical grey matter reductions in PTSD. *Psychiatry Research: Neuroimaging*, *266*, 1–9. https://doi.org/10.1016/j.pscychresns.2017.05.008

Ohi, K., Shimada, T., Kataoka, Y., Yasuyama, T., Kawasaki, Y., Shioiri, T., & Thompson, P. M. (2020a). Genetic correlations between subcortical brain volumes and psychiatric disorders. *British Journal of Psychiatry*, *216*(5), 280–283. https://doi.org/10.1192/bjp.2019.277

Ohi, K., Shimada, T., Kataoka, Y., Yasuyama, T., Kawasaki, Y., Shioiri, T., & Thompson, P. M. (2020b). Genetic correlations between subcortical brain volumes and psychiatric disorders. *The British Journal of Psychiatry*, *216*(5), 280–283. https://doi.org/10.1192/bjp.2019.277

Olff, M. (2017). Sex and gender differences in post-traumatic stress disorder: an update. *European Journal of Psychotraumatology*, *8*(sup4). https://doi.org/10.1080/20008198.2017.1351204

Opel, N., Redlich, R., Zwanzger, P., Grotegerd, D., Arolt, V., Heindel, W., Konrad, C., Kugel, H., & Dannlowski, U. (2014). Hippocampal Atrophy in Major Depression: a Function of Childhood Maltreatment Rather than Diagnosis? *Neuropsychopharmacology*, *39*(12), 2723–2731. https://doi.org/10.1038/npp.2014.145

Osafo, C., Raji, Y. R., Burke, D., Tayo, B. O., Tiffin, N., Moxey-Mims, M. M., Rasooly, R. S., Kimmel, P. L., Ojo, A., Adu, D., & Parekh, R. S. (2015). Human Heredity and Health (H3) in Africa Kidney Disease Research Network. *Clinical Journal of the American Society of Nephrology*, *10*(12), 2279–2287. https://doi.org/10.2215/CJN.11951214

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., Botteron, K. N., Harms, M. P., & Barch, D. M. (2015). HPA axis genetic variation, pubertal status, and sex interact to predict amygdala and hippocampus responses to negative emotional faces in school-age children. *NeuroImage*, *109*, 1–11. https://doi.org/10.1016/j.neuroimage.2015.01.017

Park, C., Rosenblat, J. D., Brietzke, E., Pan, Z., Lee, Y., Cao, B., Zuckerman, H., Kalantarova, A., & McIntyre, R. S. (2019). Stress, epigenetics and depression: A systematic review. *Neuroscience & Biobehavioral Reviews*, *102*, 139–152. https://doi.org/10.1016/j.neubiorev.2019.04.010

Pellowski, J. A., Wedderburn, C. J., Groenewold, N. A., Roos, A., Subramoney, S., Hoffman, N., Fouche, J.-P., Joshi, S. H., Woods, R. P., Narr, K. L., Zar, H. J., Donald, K. A., & Stein, D. J. (2023). Maternal perinatal depression and child brain structure at 2-3 years in a South African birth cohort study. *Translational Psychiatry*, *13*(1), 96. https://doi.org/10.1038/s41398-023-02395-5

Peterson, R. E., Kuchenbaecker, K., Walters, R. K., Chen, C. Y., Popejoy, A. B., Periyasamy, S., Lam, M., Iyegbe, C., Strawbridge, R. J., Brick, L., Carey, C. E., Martin, A. R., Meyers, J. L., Su, J., Chen, J., Edwards, A. C., Kalungi, A., Koen, N., Majara, L., … Duncan, L. E. (2019). Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations. In *Cell* (Vol. 179, Issue 3, pp. 589–603). Cell Press. https://doi.org/10.1016/j.cell.2019.08.051

Pettersson, E., Lichtenstein, P., Larsson, H., Song, J., Agrawal, A., Børglum, A. D., Bulik, C. M., Daly, M. J., Davis, L. K., Demontis, D., Edenberg, H. J., Grove, J., Gelernter, J., Neale, B. M., Pardiñas, A. F., Stahl, E., Walters, J. T. R., Walters, R., Sullivan, P. F., … Polderman, T. J. C. (2019). Genetic influences on eight psychiatric disorders based on family data of 4 408 646 full and half-siblings, and genetic data of 333 748 cases and controls. *Psychological Medicine*, *49*(07), 1166–1173. https://doi.org/10.1017/S0033291718002039

Ploski, J. E., & Vaidya, V. A. (2021). The Neurocircuitry of Posttraumatic Stress Disorder and Major Depression: Insights Into Overlapping and Distinct Circuit Dysfunction—A Tribute to Ron Duman. *Biological Psychiatry*, *90*(2), 109–117. https://doi.org/10.1016/j.biopsych.2021.04.009

Popejoy, A. B., & Fullerton, S. M. (2016). Genomics is failing on diversity. *Nature*, *538*(7624), 161–164. https://doi.org/10.1038/538161a

Pradhan, S., MacMaster, F., Jaworska, N., & Ramasubbu, R. (2014). Volume of caudate nucleus in major depressive disorder. *European Psychiatry*, *29*, 1. https://doi.org/10.1016/S0924-9338(14)77574-1

Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics*, *38*(8), 904–909. https://doi.org/10.1038/ng1847

Puljak, L., & Vari, S. G. (2014). Significance of research networking for enhancing collaboration and research productivity. *Croatian Medical Journal*, *55*(3), 181–183. https://doi.org/10.3325/cmj.2014.55.181

Qiu, A., Shen, M., Buss, C., Chong, Y. S., Kwek, K., Saw, S. M., Gluckman, P. D., Wadhwa, P. D., Entringer, S., Styner, M., Karnani, N., Heim, C. M., O'donnell, K. J., Holbrook, J. D., Fortier, M. V., & Meaney, M. J. (2017). Effects of Antenatal Maternal Depressive Symptoms and Socio-Economic Status on Neonatal Brain Development are Modulated by Genetic Risk. *Cerebral Cortex*, *27*(5), 3080–3092. https://doi.org/10.1093/cercor/bhx065

R Core Team. (2023). *R: A Language and Environment for Statistical Computing* (2023.06.2+561). R Foundation for Statistical Computing.

Rentería, M. E., Hansell, N. K., Strike, L. T., McMahon, K. L., de Zubicaray, G. I., Hickie, I. B., Thompson, P. M., Martin, N. G., Medland, S. E., & Wright, M. J. (2014). Genetic architecture of subcortical brain regions: common and region-specific genetic contributions. *Genes, Brain and Behavior*, *13*(8), 821–830. https://doi.org/10.1111/gbb.12177

Reus, L. M., Shen, X., Gibson, J., Wigmore, E., Ligthart, L., Adams, M. J., Davies, G., Cox, S. R., Hagenaars, S. P., Bastin, M. E., Deary, I. J., Whalley, H. C., & McIntosh, A. M. (2017). Association of polygenic risk for major psychiatric illness with subcortical

volumes and white matter integrity in UK Biobank. *Scientific Reports*, *7*(1), 42140. https://doi.org/10.1038/srep42140
Riefski, K., & Terry, S. (2023). The Applicability of Polygenic Risk Scores in Under-Represented Populations. *Genetic Testing and Molecular Biomarkers*, *27*(6).
Riley, R. D., Ensor, J., Snell, K. I. E., Harrell, F. E., Martin, G. P., Reitsma, J. B., Moons, K. G. M., Collins, G., & van Smeden, M. (2020). Calculating the sample size required for developing a clinical prediction model. *BMJ*, m441. https://doi.org/10.1136/bmj.m441
Roberts, T. C., Morris, K. V., & Wood, M. J. A. (2014). The role of long non-coding RNAs in neurodevelopment, brain function and neurological disease. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1652), 20130507. https://doi.org/10.1098/rstb.2013.0507
Roddy Mitchell, A., Gordon, H., Lindquist, A., Walker, S. P., Homer, C. S. E., Middleton, A., Cluver, C. A., Tong, S., & Hastie, R. (2023). Prevalence of Perinatal Depression in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *80*(5), 425–431. https://doi.org/10.1001/jamapsychiatry.2023.0069
Roubinov, D., Browne, D., LeWinn, K. Z., Lisha, N., Mason, W. A., & Bush, N. R. (2022). Intergenerational transmission of maternal childhood adversity and depression on children's internalizing problems. *Journal of Affective Disorders*, *308*, 205–212. https://doi.org/10.1016/j.jad.2022.04.030
Ruan, Y., Lin, Y.-F., Feng, Y.-C. A., Chen, C.-Y., Lam, M., Guo, Z., Ahn, Y. M., Akiyama, K., Arai, M., Baek, J. H., Chen, W. J., Chung, Y.-C., Feng, G., Fujii, K., Glatt, S. J., Ha, K., Hattori, K., Higuchi, T., Hishimoto, A., … Ge, T. (2022). Improving polygenic prediction in ancestrally diverse populations. *Nature Genetics*, *54*(5), 573–580. https://doi.org/10.1038/s41588-022-01054-7
Rubin, M., & Donkin, C. (2022). Exploratory hypothesis tests can be more compelling than confirmatory hypothesis tests. *Philosophical Psychology*, *37*(8), 2019–2047. https://doi.org/10.1080/09515089.2022.2113771
Rumble, S., Swartz, L., Parry, C., & Zwarenstein, M. (1996). Prevalence of psychiatric morbidity in the adult population of a rural South African village. *Psychological Medicine*, *26*(5), 997–1007. https://doi.org/10.1017/S0033291700035327
Rusconi, F., Battaglioli, E., & Venturin, M. (2020). Psychiatric Disorders and lncRNAs: A Synaptic Match. *International Journal of Molecular Sciences*, *21*(9), 3030. https://doi.org/10.3390/ijms21093030
Ryckman, K., & Williams, S. M. (2008). Calculation and Use of the Hardy-Weinberg Model in Association Studies. *Current Protocols in Human Genetics*, *57*(1). https://doi.org/10.1002/0471142905.hg0118s57
Rytwinski, N. K., Scur, M. D., Feeny, N. C., & Youngstrom, E. A. (2013). The Co-Occurrence of Major Depressive Disorder Among Individuals With Posttraumatic Stress Disorder: A Meta-Analysis. *Journal of Traumatic Stress*, *26*(3), 299–309. https://doi.org/10.1002/jts.21814
Salk, R. H., Hyde, J. S., & Abramson, L. Y. (2017). Gender differences in depression in representative national samples: Meta-analyses of diagnoses and symptoms. *Psychological Bulletin*, *143*(8), 783–822. https://doi.org/10.1037/bul0000102
Santiago Papini, L. M. R. (2014). Psychometric Properties of the Modified Posttraumatic Stress Disorder Symptom Scale among Women with Posttraumatic Stress Disorder and Substance Use Disorders Receiving Outpatient Group Treatments. *Journal of Traumatic Stress Disorders & Treatment*, *04*(01). https://doi.org/10.4172/2324-8947.1000139
Sartor, C. E., McCutcheon, V. V., Pommer, N. E., Nelson, E. C., Grant, J. D., Duncan, A. E., Waldron, M., Bucholz, K. K., Madden, P. A. F., & Heath, A. C. (2011). Common genetic and environmental contributions to post-traumatic stress disorder and alcohol

dependence in young women. *Psychological Medicine*, *41*(7), 1497–1505. https://doi.org/10.1017/S0033291710002072

Satizabal, C. L., Adams, H. H. H., Hibar, D. P., White, C. C., Knol, M. J., Stein, J. L., Scholz, M., Sargurupremraj, M., Jahanshad, N., Roshchupkin, G. V., Smith, A. V., Bis, J. C., Jian, X., Luciano, M., Hofer, E., Teumer, A., van der Lee, S. J., Yang, J., Yanek, L. R., … Ikram, M. A. (2019). Genetic architecture of subcortical brain structures in 38,851 individuals. *Nature Genetics*, *51*(11), 1624–1636. https://doi.org/10.1038/s41588-019-0511-y

Satyanarayana, V., Lukose, A., & Srinivasan, K. (2011a). Maternal mental health in pregnancy and child behavior. *Indian Journal of Psychiatry*, *53*(4), 351. https://doi.org/10.4103/0019-5545.91911

Satyanarayana, V., Lukose, A., & Srinivasan, K. (2011b). Maternal mental health in pregnancy and child behavior. *Indian Journal of Psychiatry*, *53*(4), 351. https://doi.org/10.4103/0019-5545.91911

Schmaal, L., Pozzi, E., C. Ho, T., van Velzen, L. S., Veer, I. M., Opel, N., Van Someren, E. J. W., Han, L. K. M., Aftanas, L., Aleman, A., Baune, B. T., Berger, K., Blanken, T. F., Capitão, L., Couvy-Duchesne, B., R. Cullen, K., Dannlowski, U., Davey, C., Erwin-Grabner, T., … Veltman, D. J. (2020). ENIGMA MDD: seven years of global neuroimaging studies of major depression through worldwide data sharing. *Translational Psychiatry*, *10*(1), 172. https://doi.org/10.1038/s41398-020-0842-6

Schmidt, C. W. (2007). Environmental Connections: A Deeper Look into Mental Illness. *Environmental Health Perspectives*, *115*(8). https://doi.org/10.1289/ehp.115-a404

Schmitt, A., Malchow, B., Hasan, A., & Falkai, P. (2014). The impact of environmental factors in severe psychiatric disorders. *Frontiers in Neuroscience*, *8*. https://doi.org/10.3389/fnins.2014.00019

Shea, L., Pesa, J., Geonnotti, G., Powell, V., Kahn, C., & Peters, W. (2022). Improving diversity in study participation: Patient perspectives on barriers, racial differences and the role of communities. *Health Expectations*, *25*(4), 1979–1987. https://doi.org/10.1111/hex.13554

Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., Schinka, J., Knapp, E., Sheehan, M., & Dunbar, G. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, *12*(5), 232–241. https://doi.org/10.1016/S0924-9338(97)83297-X

Sheehan, D. V, Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*, *59 Suppl 20*, 22-33;quiz 34-57.

Sirugo, G., Williams, S. M., & Tishkoff, S. A. (2019). The Missing Diversity in Human Genetic Studies. *Cell*, *177*(1), 26–31. https://doi.org/10.1016/j.cell.2019.02.048

Skol, A. D., Scott, L. J., Abecasis, G. R., & Boehnke, M. (2006). Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. *Nature Genetics*, *38*(2), 209–213. https://doi.org/10.1038/ng1706

Skórzewska, A., Lehner, M., Wisłowska-Stanek, A., Turzyńska, D., Sobolewska, A., Krząścik, P., Szyndler, J., Maciejak, P., Chmielewska, N., Kołosowska, K., & Płaźnik, A. (2020). Individual susceptibility or resistance to posttraumatic stress disorder-like behaviours. *Behavioural Brain Research*, *386*, 112591. https://doi.org/10.1016/j.bbr.2020.112591

Slatkin, M. (2008). Linkage disequilibrium — understanding the evolutionary past and mapping the medical future. *Nature Reviews Genetics*, *9*(6), 477–485. https://doi.org/10.1038/nrg2361

Slunecka, J. L., van der Zee, M. D., Beck, J. J., Johnson, B. N., Finnicum, C. T., Pool, R., Hottenga, J.-J., de Geus, E. J. C., & Ehli, E. A. (2021). Implementation and implications for polygenic risk scores in healthcare. *Human Genomics*, *15*(1), 46. https://doi.org/10.1186/s40246-021-00339-y

Smith, C. J., Steinbrekera, B., & Dagle, J. M. (2019). Genetic Basis of Patent Ductus Arteriosus. In *Hematology, Immunology and Genetics* (pp. 137–148). Elsevier. https://doi.org/10.1016/B978-0-323-54400-9.00012-6

Smoller, J. W. (2016a). The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. *Neuropsychopharmacology*, *41*(1), 297–319. https://doi.org/10.1038/npp.2015.266

Smoller, J. W. (2016b). The Genetics of Stress-Related Disorders: PTSD, Depression, and Anxiety Disorders. *Neuropsychopharmacology*, *41*(1), 297–319. https://doi.org/10.1038/npp.2015.266

Smoller, J. W., Block, S. R., & Young, M. M. (2009). Genetics of anxiety disorders: the complex road from DSM to DNA. *Depression and Anxiety*, *26*(11), 965–975. https://doi.org/10.1002/da.20623

Sommer, M. A. (2003). The role of the thalamus in motor control. *Current Opinion in Neurobiology*, *13*(6), 663–670. https://doi.org/10.1016/j.conb.2003.10.014

Song, P. X. (2007). *Correlated Data Analysis: Modeling, Analytics, and Applications*. Springer New York. https://doi.org/10.1007/978-0-387-71393-9

Stein, D. J., Koen, N., Donald, K. A., Adnams, C. M., Koopowitz, S., Lund, C., Marais, A., Myers, B., Roos, A., Sorsdahl, K., Stern, M., Tomlinson, M., van der Westhuizen, C., Vythilingum, B., Myer, L., Barnett, W., Brittain, K., & Zar, H. J. (2015). Investigating the psychosocial determinants of child health in Africa: The Drakenstein Child Health Study. *Journal of Neuroscience Methods*, *252*, 27–35. https://doi.org/10.1016/j.jneumeth.2015.03.016

Sthle, L., & Wold, S. (1989). Analysis of variance (ANOVA). *Chemometrics and Intelligent Laboratory Systems*, *6*(4), 259–272. https://doi.org/10.1016/0169-7439(89)80095-4

Suarez-Pajes, E., Díaz-de Usera, A., Marcelino-Rodríguez, I., Guillen-Guio, B., & Flores, C. (2021). Genetic Ancestry Inference and Its Application for the Genetic Mapping of Human Diseases. *International Journal of Molecular Sciences*, *22*(13), 6962. https://doi.org/10.3390/ijms22136962

Sugrue, L. P., & Desikan, R. S. (2019). What Are Polygenic Scores and Why Are They Important? *JAMA*, *321*(18), 1820. https://doi.org/10.1001/jama.2019.3893

Sutter-Dallay, A.-L., Murray, L., Dequae-Merchadou, L., Glatigny-Dallay, E., Bourgeois, M.-L., & Verdoux, H. (2011). A prospective longitudinal study of the impact of early postnatal vs. chronic maternal depressive symptoms on child development. *European Psychiatry*, *26*(8), 484–489. https://doi.org/10.1016/j.eurpsy.2010.05.004

Swain, K. D., Pillay, B. J., & Kliewer, W. (2017). Traumatic stress and psychological functioning in a South African adolescent community sample. *South African Journal of Psychiatry*, *23*. https://doi.org/10.4102/sajpsychiatry.v23i0.1008

Swart, P. C., van den Heuvel, L. L., Lewis, C. M., Seedat, S., & Hemmings, S. M. J. (2021). A Genome-Wide Association Study and Polygenic Risk Score Analysis of Posttraumatic Stress Disorder and Metabolic Syndrome in a South African Population. *Frontiers in Neuroscience*, *15*. https://doi.org/10.3389/fnins.2021.677800

Talati, A., van Dijk, M. T., Pan, L., Hao, X., Wang, Z., Gameroff, M., Dong, Z., Kayser, J., Shankman, S., Wickramaratne, P. J., Posner, J., & Weissman, M. M. (2022). Putamen

Structure and Function in Familial Risk for Depression: A Multimodal Imaging Study. *Biological Psychiatry*, *92*(12), 932–941. https://doi.org/10.1016/j.biopsych.2022.06.035
Tan, T., & Atkinson, E. G. (2023a). Strategies for the Genomic Analysis of Admixed Populations. *Annual Review of Biomedical Data Science*, *6*(1), 105–127. https://doi.org/10.1146/annurev-biodatasci-020722-014310
Tan, T., & Atkinson, E. G. (2023b). Strategies for the Genomic Analysis of Admixed Populations. *Annual Review of Biomedical Data Science*, *6*(1), 105–127. https://doi.org/10.1146/annurev-biodatasci-020722-014310
The Lancet. (2013). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *The Lancet*, *381*(9875), 1371–1379. https://doi.org/10.1016/S0140-6736(12)62129-1
Thorp, J. G., Gerring, Z. F., Colodro-Conde, L., Byrne, E. M., Medland, S. E., Middeldorp, C. M., & Derks, E. M. (2023). The association between trauma exposure, polygenic risk and individual depression symptoms. *Psychiatry Research*, *321*, 115101. https://doi.org/10.1016/j.psychres.2023.115101
Turner, S., Armstrong, L. L., Bradford, Y., Carlsony, C. S., Crawford, D. C., Crenshaw, A. T., de Andrade, M., Doheny, K. F., Haines, J. L., Hayes, G., Jarvik, G., Jiang, L., Kullo, I. J., Li, R., Ling, H., Manolio, T. A., Matsumoto, M. M., McCarty, C. A., McDavid, A. N., … Ritchie, M. D. (2011). Quality control procedures for genome-wide association studies. *Current Protocols in Human Genetics*, *SUPPL.68*. https://doi.org/10.1002/0471142905.hg0119s68
Uffelmann, E., Huang, Q. Q., Munung, N. S., de Vries, J., Okada, Y., Martin, A. R., Martin, H. C., Lappalainen, T., & Posthuma, D. (2021). Genome-wide association studies. *Nature Reviews Methods Primers*, *1*(1), 59. https://doi.org/10.1038/s43586-021-00056-9
van der Merwe, C., Jahanshad, N., Cheung, J. W., Mufford, M., Groenewold, N. A., Koen, N., Ramesar, R., Dalvie, S., Knowles, J. A., Hibar, D. P., Nievergelt, C. M., Koenen, K. C., Liberzon, I., Ressler, K. J., Medland, S. E., Morey, R. A., Thompson, P. M., & Stein, D. J. (2019). Concordance of genetic variation that increases risk for anxiety disorders and posttraumatic stress disorders and that influences their underlying neurocircuitry. *Journal of Affective Disorders*, *245*, 885–896. https://doi.org/10.1016/j.jad.2018.11.082
van der Wal, J. M., Arjadi, R., Nauta, M. H., Burger, H., & Bockting, C. L. H. (2020). Guided internet interventions for depression: impact of sociodemographic factors on treatment outcome in Indonesia. *Behaviour Research and Therapy*, *130*, 103589. https://doi.org/10.1016/j.brat.2020.103589
van Dijk, M. T., Tartt, A. N., Murphy, E., Gameroff, M. J., Semanek, D., Cha, J., Weissman, M. M., Posner, J., & Talati, A. (2024). Subcortical volumes in offspring with a multigenerational family history of depression – A study across two cohorts. *Journal of Affective Disorders*, *363*, 192–197. https://doi.org/10.1016/j.jad.2024.07.107
Visscher, P. M., Brown, M. A., McCarthy, M. I., & Yang, J. (2012). Five Years of GWAS Discovery. *The American Journal of Human Genetics*, *90*(1), 7–24. https://doi.org/10.1016/j.ajhg.2011.11.029
Volkow, N. D., Gordon, J. A., Bianchi, D. W., Chiang, M. F., Clayton, J. A., Klein, W. M., Koob, G. F., Koroshetz, W. J., Pérez-Stable, E. J., Simoni, J. M., Tromberg, B. J., Woychik, R. P., Hommer, R., Spotts, E. L., Xu, B., Zehr, J. L., Cole, K. M., Dowling, G. J., Freund, M. P., … Weiss, S. R. B. (2024). The HEALthy Brain and Child Development Study (HBCD): NIH collaboration to understand the impacts of prenatal and early life experiences on brain development. *Developmental Cognitive Neuroscience*, *69*, 101423. https://doi.org/10.1016/j.dcn.2024.101423
Waldron, E. M., Burnett-Zeigler, I., Wee, V., Ng, Y. W., Koenig, L. J., Pederson, A. B., Tomaszewski, E., & Miller, E. S. (2021). Mental Health in Women Living With HIV:

The Unique and Unmet Needs. *Journal of the International Association of Providers of AIDS Care (JIAPAC)*, *20*. https://doi.org/10.1177/2325958220985665

Wand, H., Lambert, S. A., Tamburro, C., Iacocca, M. A., O'Sullivan, J. W., Sillari, C., Kullo, I. J., Rowley, R., Dron, J. S., Brockman, D., Venner, E., McCarthy, M. I., Antoniou, A. C., Easton, D. F., Hegele, R. A., Khera, A. V., Chatterjee, N., Kooperberg, C., Edwards, K., … Wojcik, G. L. (2021). Improving reporting standards for polygenic scores in risk prediction studies. *Nature*, *591*(7849), 211–219. https://doi.org/10.1038/s41586-021-03243-6

Wang, S.-K., Feng, M., Fang, Y., Lv, L., Sun, G.-L., Yang, S.-L., Guo, P., Cheng, S.-F., Qian, M.-C., & Chen, H.-X. (2023). Psychological trauma, posttraumatic stress disorder and trauma-related depression: A mini-review. *World Journal of Psychiatry*, *13*(6), 331–339. https://doi.org/10.5498/wjp.v13.i6.331

Wang, Y., Kanai, M., Tan, T., Kamariza, M., Tsuo, K., Yuan, K., Zhou, W., Okada, Y., Huang, H., Turley, P., Atkinson, E. G., & Martin, A. R. (2023). Polygenic prediction across populations is influenced by ancestry, genetic architecture, and methodology. *Cell Genomics*, *3*(10), 100408. https://doi.org/10.1016/j.xgen.2023.100408

Watanabe, K., Taskesen, E., van Bochoven, A., & Posthuma, D. (2017). Functional mapping and annotation of genetic associations with FUMA. *Nature Communications*, *8*(1), 1826. https://doi.org/10.1038/s41467-017-01261-5

Weale, M. E. (2010). *Quality Control for Genome-Wide Association Studies* (pp. 341–372). https://doi.org/10.1007/978-1-60327-367-1_19

Weathers, F. W., Keane, T. M., & Davidson, J. R. T. (2001). Clinician-administered PTSD scale: A review of the first ten years of research. In *Depression and Anxiety* (Vol. 13, Issue 3, pp. 132–156). https://doi.org/10.1002/da.1029

Wedderburn, C. J., Subramoney, S., Yeung, S., Fouche, J.-P., Joshi, S. H., Narr, K. L., Rehman, A. M., Roos, A., Ipser, J., Robertson, F. C., Groenewold, N. A., Gibb, D. M., Zar, H. J., Stein, D. J., & Donald, K. A. (2020). Neuroimaging young children and associations with neurocognitive development in a South African birth cohort study. *NeuroImage*, *219*, 116846. https://doi.org/10.1016/j.neuroimage.2020.116846

Weinberger, D. R., Dzirasa, K., & Crumpton-Young, L. L. (2020). Missing in Action: African Ancestry Brain Research. *Neuron*, *107*(3), 407–411. https://doi.org/10.1016/j.neuron.2020.07.008

Weller, J. I., Song, J. Z., Heyen, D. W., Lewin, H. A., & Ron, M. (1998). A New Approach to the Problem of Multiple Comparisons in the Genetic Dissection of Complex Traits. *Genetics*, *150*(4), 1699–1706. https://doi.org/10.1093/genetics/150.4.1699

WHO ASSIST Working Group. (2002). The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST): development, reliability and feasibility. *Addiction*, *97*(9), 1183–1194. https://doi.org/10.1046/j.1360-0443.2002.00185.x

Wium-Andersen, M. K., Villumsen, M. D., Wium-Andersen, I. K., Jørgensen, M. B., Hjelmborg, J. B., Christensen, K., & Osler, M. (2020). Familial risk and heritability of depression by age at first diagnosis in Danish twins. *Acta Psychiatrica Scandinavica*, *142*(6), 446–455. https://doi.org/10.1111/acps.13238

Wonkam, A., Munung, N. S., Dandara, C., Esoh, K. K., Hanchard, N. A., & Landoure, G. (2022). Five Priorities of African Genomics Research: The Next Frontier. *Annual Review of Genomics and Human Genetics*, *23*(1), 499–521. https://doi.org/10.1146/annurev-genom-111521-102452

World Health Organization. (2017). Depression and Common Mental Disorders: Global Health Estimates. *World Health Organization*.

Wray, N. R., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., Murray, G. K., & Visscher, P. M. (2021). From Basic Science to Clinical Application of Polygenic Risk Scores. *JAMA Psychiatry*, *78*(1), 101. https://doi.org/10.1001/jamapsychiatry.2020.3049

Wu, G., Du, X., Li, Z., Du, Y., Lv, J., Li, X., Xu, Y., & Liu, S. (2022). The emerging role of long non-coding RNAs in schizophrenia. *Frontiers in Psychiatry*, *13*. https://doi.org/10.3389/fpsyt.2022.995956

Wu, Y., Zhang, H., Wang, C., Broekman, B. F. P., Chong, Y.-S., Shek, L. P., Gluckman, P. D., Meaney, M. J., Fortier, M. V., & Qiu, A. (2021). Inflammatory modulation of the associations between prenatal maternal depression and neonatal brain. *Neuropsychopharmacology*, *46*(2), 470–477. https://doi.org/10.1038/s41386-020-0774-0

Wu, Y.-K., Su, Y.-A., Zhu, L.-L., Yan, C., Li, J.-T., Lin, J.-Y., Chen, J., Chen, L., Li, K., Stein, D. J., & Si, T.-M. (2024). A distinctive subcortical functional connectivity pattern linking negative affect and treatment outcome in major depressive disorder. *Translational Psychiatry*, *14*(1), 136. https://doi.org/10.1038/s41398-024-02838-7

Xu, Z. M., Rüeger, S., Zwyer, M., Brites, D., Hiza, H., Reinhard, M., Rutaihwa, L., Borrell, S., Isihaka, F., Temba, H., Maroa, T., Naftari, R., Hella, J., Sasamalo, M., Reither, K., Portevin, D., Gagneux, S., & Fellay, J. (2022). Using population-specific add-on polymorphisms to improve genotype imputation in underrepresented populations. *PLOS Computational Biology*, *18*(1), e1009628. https://doi.org/10.1371/journal.pcbi.1009628

Yang, Z., Cieza, B., Reyes-Dumeyer, D., Montesinos, R., Soto-Añari, M., Custodio, N., & Tosto, G. (2023). A benchmark study on current GWAS models in admixed populations. *Briefings in Bioinformatics*, *25*(1). https://doi.org/10.1093/bib/bbad437

Yatham, S., Sivathasan, S., Yoon, R., da Silva, T. L., & Ravindran, A. V. (2018). Depression, anxiety, and post-traumatic stress disorder among youth in low and middle income countries: A review of prevalence and treatment interventions. *Asian Journal of Psychiatry*, *38*, 78–91. https://doi.org/10.1016/j.ajp.2017.10.029

Yehuda, R., Hoge, C. W., McFarlane, A. C., Vermetten, E., Lanius, R. A., Nievergelt, C. M., Hobfoll, S. E., Koenen, K. C., Neylan, T. C., & Hyman, S. E. (2015). Post-traumatic stress disorder. *Nature Reviews Disease Primers*, *1*(1), 15057. https://doi.org/10.1038/nrdp.2015.57

Yoshii, T. (2021a). The Role of the Thalamus in Post-Traumatic Stress Disorder. *International Journal of Molecular Sciences*, *22*(4). https://doi.org/10.3390/ijms22041730

Yoshii, T. (2021b). The Role of the Thalamus in Post-Traumatic Stress Disorder. *International Journal of Molecular Sciences*, *22*(4). https://doi.org/10.3390/ijms22041730

Yoshii, T., Oishi, N., Ikoma, K., Nishimura, I., Sakai, Y., Matsuda, K., Yamada, S., Tanaka, M., Kawata, M., Narumoto, J., & Fukui, K. (2017). Brain atrophy in the visual cortex and thalamus induced by severe stress in animal model. *Scientific Reports*, *7*(1), 12731. https://doi.org/10.1038/s41598-017-12917-z

Zar, H. J., Barnett, W., Myer, L., Stein, D. J., & Nicol, M. P. (2015). Investigating the early-life determinants of illness in Africa: the Drakenstein Child Health Study. *Thorax*, *70*(6), 592–594. https://doi.org/10.1136/thoraxjnl-2014-206242

Zar, H. J., Pellowski, J. A., Cohen, S., Barnett, W., Vanker, A., Koen, N., & Stein, D. J. (2019). Maternal health and birth outcomes in a South African birth cohort study. *PLOS ONE*, *14*(11), e0222399. https://doi.org/10.1371/journal.pone.0222399

Zhang, F., Rao, S., Cao, H., Zhang, X., Wang, Q., Xu, Y., Sun, J., Wang, C., Chen, J., Xu, X., Zhang, N., Tian, L., Yuan, J., Wang, G., Cai, L., Xu, M., & Baranova, A. (2022). Genetic evidence suggests posttraumatic stress disorder as a subtype of major depressive

disorder. *The Journal of Clinical Investigation*, *132*(3). https://doi.org/10.1172/JCI145942

Zhang, F., Wang, Y., & Deng, H.-W. (2008). Comparison of Population-Based Association Study Methods Correcting for Population Stratification. *PLoS ONE*, *3*(10), e3392. https://doi.org/10.1371/journal.pone.0003392

Zhang, F.-F., Peng, W., Sweeney, J. A., Jia, Z.-Y., & Gong, Q.-Y. (2018). Brain structure alterations in depression: Psychoradiological evidence. *CNS Neuroscience & Therapeutics*, *24*(11), 994–1003. https://doi.org/10.1111/cns.12835

Zhou, W., Zhao, Z., Nielsen, J. B., Fritsche, L. G., LeFaive, J., Gagliano Taliun, S. A., Bi, W., Gabrielsen, M. E., Daly, M. J., Neale, B. M., Hveem, K., Abecasis, G. R., Willer, C. J., & Lee, S. (2020). Scalable generalized linear mixed model for region-based association tests in large biobanks and cohorts. *Nature Genetics*, *52*(6), 634–639. https://doi.org/10.1038/s41588-020-0621-6

Zhou, X., Liao, W.-J., Liao, J.-M., Liao, P., & Lu, H. (2015). Ribosomal proteins: functions beyond the ribosome. *Journal of Molecular Cell Biology*, *7*(2), 92–104. https://doi.org/10.1093/jmcb/mjv014

Zuo, L., Tan, Y., Wang, Z., Wang, K.-S., Zhang, X., Chen, X., Li, C.-S. R., Wang, T., & Luo, X. (2016). Long noncoding RNAs in psychiatric disorders. *Psychiatric Genetics*, *26*(3), 109–116. https://doi.org/10.1097/YPG.0000000000000129