Investigation of the Shared Genetic Influences on Bipolar Disorder, Borderline Personality Disorder and Regional Brain Structures

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List of Abbreviations

Abbreviation	Term
A1	Reference allele
A2	Alternate allele
ACC	Anterior Cingulate Cortex
ADHD	Attention Deficit Hyperactivity Disorder
BD	Bipolar Disorder
BD NOS	BD Not Otherwise Specified
BDI	Bipolar Disorder Type I
BDII	Bipolar Disorder Type II
BP	Base-pairs
BPD	Borderline Personality Disorder
CACNA1C	Calcium Voltage-Gated Channel Subunit Alpha1 C
cFDR	Conditional False Discovery Rate
CHARGE	Cohorts for Heart and Ageing Research in Genomic Epidemiology
CHR	Chromosome
DPYD	Dihydropyrimidine Dehydrogenase
DSM-V	The Diagnostic and Statistical Manual of Mental Disorders 5th edition
ENIGMA	Enhancing Neuroimaging through Genetic Meta-Analysis
FDR	False Discovery Rate
FUMA	Functional Mapping and Annotation
GSEA	Gene Set Enrichment Analysis
GWAS	Genome-Wide Association Study
$\mathbf{h^2_{SNP}}$	SNP-based heritability estimate
ICV	Intracranial Volume
IVW	Inverse-Variance-Weighted
LD	Linkage disequilibrium
LDSC	Linkage Disequilibrium Score Regression
MAF	Minor Allele Frequency
MAGMA	Multi-marker Analysis of GenoMic Annotation
MDD	Major depressive disorder
MR	Mendelian Randomization
MRI	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
OR	Odds Ratio
$\mathbf{P_{adj}}$	Benjamini-Hochberg (FDR) adjusted p-value
PGC	Psychiatric Genomics Consortium
PKP4	Plakophilin-4
PTSD	Post-Traumatic Stress Disorder
QQ-plot	Quantile-Quantile plot
$\mathbf{r^2}$	The linkage disequilibrium metric, refers to the squared correlation based on genotypic allele counts

r_g	Genetic correlation
SCZ	Schizophrenia
SD	Standard Deviation
SE	Standard Error
SECA	SNP-effect Concordance Analysis
SERINC5	Serine incorporator 5
SNP	Single Nucleotide Polymorphism
TDR	True Discovery Rate
TS	Tourette Syndrome
$\bar{X}$	Mean

Abstract

Background: The heritabilities of bipolar disorder (BD) and borderline personality disorder (BPD) are 80% and 65%, respectively, indicating substantial genetic contributions to both disorders. BD and BPD are often comorbid, and both disorders have a polygenic architecture. These variants are thought to subtly affect multiple pathways, associated with structural brain abnormalities commonly observed in patients with BD and BPD. Brain regions have been shown to be highly heritable and under distinct genetic influences. However, the overlap in genetic risk between BD and BPD and altered brain regions, respectively, has not yet been determined.

Aims and Objectives: The aim of this project was to determine whether genetic risk for BD and BPD overlaps with genetic risk for altered brain regions.

Methods: Genome-wide association study (GWAS) summary statistics for BD (N_{cases}=20,352; $N_{controls}$= 31,358), BPD (N_{case}=998; $N_{control}$=1,545), eight subcortical brain volumes (nucleus accumbens, amygdala, caudate nucleus, hippocampus, pallidum, putamen and thalamus) and intracranial volume (ICV) (N=27,087), and cortical surface area and thickness (N=37,479) were obtained. Pleiotropy and concordance were assessed using SNP-Effect Concordance Analysis. Conditional false discovery rate (cFDR) was used to condition BD and BPD GWAS results on genetic variants that influence brain regions. Linkage Disequilibrium Score Regression was used to examine genome-wide correlations between BD, BPD and brain regions. Mendelian randomization was used to test for causal associations between BD, BPD and each brain region, respectively.

Results: There was evidence of significant pleiotropy and positive concordance between BD and BPD ($p_{pleiotropy}=5x10^{-4}$; $p_{concordance}=1x10^{-6}$, OR=1.29). Significant pleiotropy was observed between BD and the thickness of several cortical regions and two gyri, namely the lateral occipital ($p=2.25x10^{-5}$), pars triangularis ($p=1.1x10^{-4}$), rostral anterior cingulate regions ($p=2.18x10^{-4}$) and post central ($p=7.9x10^{-6}$) and supramarginal gyri ($p=1.45x10^{-7}$). Significant positive concordance was noted between BPD and thickness of the lateral occipital region ($p=3x10^{-4;}$ OR=1.02). After conditioning BD onto BPD and each regional brain GWAS, 171 additional variants were significantly associated with BD (FDR<0.05). Three additional SNPs were significantly associated with BPD when conditioned on thickness of the lateral orbitofrontal, lingual, precentral and supramarginal regions.

Discussion: The findings here of genetic overlap between BD, BPD and altered brain structure, while novel, are consistent with previous work. The cFDR analyses, highlight synapse and neurotransmitter regulation as a key underlying mechanism between BD and altered brain regions. Further fine-grained delineation of the role of the environment in these relationships and the inclusion of non-European populations are critical next steps, as they may provide insight into risk factors, new areas of treatment and aid in early detection of at risk individuals.

1 Introduction

This chapter includes a background to this study, providing context to the aims. Firstly, an overview of the epidemiology, diagnosis and risk factors of BD and BPD are presented. This chapter also summarises the structural brain changes that have previously been associated with these disorders and describes the genetic architecture of the brain regions under investigation. The aims and objectives of this study are listed at the end of this chapter.

1.1. Bipolar Disorder

1.1.1. Epidemiology and Diagnosis of Bipolar Disorder

Bipolar disorder (BD) affects approximately 1% of the global population (Merikangas et al., 2007). The relatively early onset of this disorder, combined with the severity of its symptoms, make BD a major public health concern and contributor to the global burden of disease (Ferrari et al., 2016). BD often co-occurs with other psychiatric disorders, such as borderline personality disorder (BPD), anxiety disorders, eating disorders and substance abuse disorders, as well as disorders of lifestyle (e.g. obesity, cardiovascular disease and cancer), contributing to the decreased life expectancy associated with the disorder and increased burden on health care systems (Lund et al., 2013).

BD is characterized by mood lability, resulting in fluctuations between a positive, manic or hypomanic state and a negative or depressive state (Ikeda et al., 2018). Manic episodes are defined by prolonged periods of increased energy with erratic and impulsive behavior while the depressive state is described as a prolonged period accompanied by feelings of hopelessness, apathy, social withdrawal and often, suicidal ideation (Merikangas et al., 2008). The Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V), indicates that BD is spectral with several subtypes (American Psychiatric Association, 2013) which are dependent on the pattern and duration of the manic and depressive states (Mühleisen et al., 2014). The clinical subtypes include bipolar disorder type I (BDI), bipolar disorder type II (BDII), Cyclothymia and BD not otherwise specified (BD NOS) (Charney et al., 2017). Manic episodes tend to alternate with a depressive state in BDI, while BDII is characterized by the occurrence of at least one depressive and one hypomanic episode during an individual's lifetime (Ferrari et al., 2016). BD affects all ethnicities and genders equally (Merikangas et al.,

2007); however, the manifestation of BD tends to differ between males and females, whereby women are more likely to suffer from depressive episodes and tend to experience manic episodes later in the disease process (Merikangas et al., 2007).

1.1.2. Risk Factors for Bipolar Disorder

1.1.2.1. Environmental Factors

A number of factors have been reported to influence the aetiology and risk of BD onset. Certain environmental influences, thought to occur in combination with genetic risk, have been associated with an increased risk for developing BD (Tsuchiya et al., 2003). Psychosocial factors such as socioeconomic status, educational attainment, substance abuse (including cannabis and alcohol abuse), smoking, sexual abuse, childhood trauma and stressful life events have repeatedly shown an association with BD (Brent, 1995, Agid et al., 1999, Tsuchiya et al., 2003, Swann et al., 2004, Alloy et al., 2005). It must be noted that studies focusing on psychosocial factors impacting the onset, course and expression of BD have limitations; often retrospective, this type of research is unable to determine if the environmental factors are causes or consequences of the disorder (Alloy et al., 2005). Many of these studies use self-report measures, rendering the study open to biases (Alloy et al., 2005).

1.1.2.2. Genetic Factors

The heritability of BD, as determined by twin studies, is thought to be as high as 80% (McGuffin et al., 2003, Edvardsen et al., 2008). This implies that while environmental factors may contribute to the disorder, there is a substantial genetic component that influences its onset and development. The spectral quality of BD may be attributable to its polygenic nature, which describes the cumulative effect of many genetic variants, each with a small individual effect size (Ikeda et al., 2018). While the genetic etiology of this disorder is largely unknown, genome-wide association studies (GWAS) have discovered significant associations between common genetic variants, mainly single nucleotide polymorphisms (SNPs), and disease status (Schulze et al., 2009, Smith et al., 2009, Sklar et al., 2011, Mühleisen et al., 2014). GWASs utilize high-throughput genotyping methods on very large cohorts to determine whether genetic variants spread across the genome, have an association with disease status, compared to controls. The 'common disease-common variant' model proposes that multiple common alleles (minor allele frequency; MAF > 5%) in a population, contribute a small-to-moderate additive effect to the phenotype (Cook Jr and Scherer, 2008). To date, common genetic variants have

been shown to account for 25 to 30% of BD heritability (Stahl et al., 2017), with the remaining heritability still unknown. Genes that have consistently been associated with BD, such as *CACNA1C*, have shown associations with other psychiatric disorders such as schizophrenia (SCZ), major depressive disorder (MDD) and more recently BPD indicating that there may be a common genetic influence underlying the etiology of psychiatric disorders (Green et al., 2010, Witt et al., 2017, Gandal et al., 2018, Lee et al., 2019).

1.2. Borderline Personality Disorder

1.2.1. Epidemiology and Diagnosis of Borderline Personality Disorder

BPD is a severe neuropsychiatric disorder with a lifetime prevalence of approximately 3% in the general population and is estimated to affect 20% of all psychiatric inpatients (Tomko et al., 2014, Witt et al., 2017). Furthermore, approximately 20% of BPD patients have previously been diagnosed with either BDI or BDII, suggesting a highly comorbid relationship between the two psychiatric disorders (Fornaro et al., 2016). The high prevalence of BPD, and the severity of its symptoms (outlined below), make patients frequent users of mental-health resources, and presents an increased burden on health care facilities (Tomko et al., 2014).

BPD is characterized by instability across several domains- mood regulation, impulse control, interpersonal relationships and self-image (Lieb et al., 2004). The core clinical symptoms of BPD include impulsivity, dysfunction in emotional processing, repeated self-injury and chronic suicidal tendencies (Tsanas et al., 2016). Emotional dysregulation refers to the inappropriate emotional responses to emotive stimuli, often seen in BPD patients (Austin et al., 2007), while impulsivity refers to inappropriate behaviours that are risky and unduly thought out, with little consideration of the consequences (Chamberlain et al., 2018). The disorder is associated with self-destructive behaviours- suicide rates range from 6 to 8% in BPD patients, with 30% of patients reporting to have attempted suicide multiple times throughout their life. A total of 90% of BPD patients engage in non-suicidal self-injurious behaviour (Zanarini et al., 2008).

1.2.2. Risk Factors for Borderline Personality Disorder

1.2.2.1 Environmental Factors

The pathogenesis of BPD is complex and involves the interaction of several factors including genetics and the environment (Figure 1.1).Various types of adverse events during

childhood, such as experiences of neglect and abuse are reported by many patients (Lieb et al., 2004). Adverse childhood experiences may contribute to emotional dysregulation and impulsivity, leading to dysfunctional behaviours and psychosocial conflicts and deficits, which might reinforce the emotional dysregulation and impulsive characteristic of BPD (Lieb et al., 2004). A study by Fatimah et al. (2019) found parental conduct such as antisocial behaviour , substance dependence (for example nicotine, alcohol and narcotics) and sexual abuse to be predictive of children developing BPD. However, BPD is unlikely to be the direct consequence of early trauma; for example, up to 80% of individuals with a history of sexual abuse do not develop personality disorders, indicating that while environmental factors influence the onset and development of BPD, there may also be a genetic component to the disorder (Amad et al., 2014).

1.2.2.2 Genetic Factors

Twin studies of BPD show a concordance of 35% and 7% in monozygotic and dizygotic twins, respectively-indicating a genetic contribution to this disorder (Torgersen et al., 2000). Genetic research into the underlying aetiology of BPD remains limited; however, common variants have been estimated to account for 23% of the heritability of this disorder (Lubke et al., 2014). Gene-set analyses, from the only BPD GWAS to date, found exocytosis (the active transport of molecules out of the cell) to be significantly associated with the disorder (Witt et al., 2017). In neuronal synapses, exocytosis is triggered by an influx of calcium and underlies synaptic signalling (Witt et al., 2017). The importance of synaptic function is further supported by the association of serine incorporator 5 (*SERINC5*) with BPD (Lubke et al., 2014, Witt et al., 2017). *SERINC5* is critical in myelination, suggesting that reduced myelination may play a role in the pathology of BPD (Lubke et al., 2014, Witt et al., 2017). Altered myelination is thought to impair information processing between cortical regions and has been established to play a critical role in psychiatric disorders (Lee and Fields, 2009); highlighting the need to consider the role of the brain in the development of the disorder.

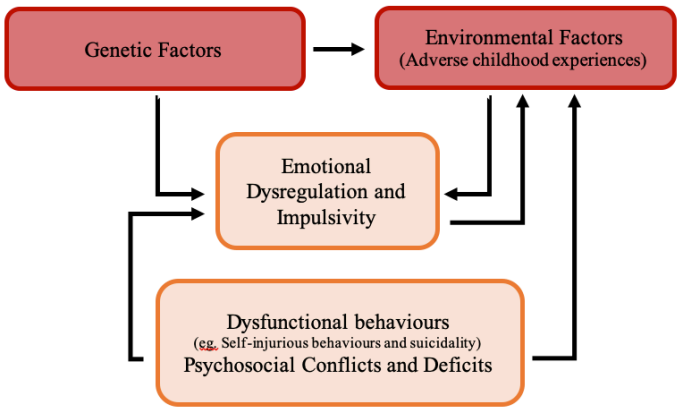


Figure 1.1 A neurobehavioral model of BPD, adapted from *Lieb et al., (2004)*

1.3. Structural Brain Changes in Bipolar Disorder and Borderline Personality Disorder

1.3.1. Structural Brain Changes Associated with Bipolar Disorder

As mentioned above, it is hypothesized that the BD phenotype is the result of polygenic variation, with each variant having a small effect size (Ikeda et al., 2018). These variants are thought to subtly affect multiple biological pathways, possibly leading to structural brain abnormalities which have been observed in patients with established BD (Demjaha et al., 2011, Allardyce et al., 2017). At first onset of the illness, total grey matter appears to be unaffected (Chang et al., 2005); however, as the illness progresses, reduced cortical thickness in frontal, medial parietal and occipital regions are observed (Rimol et al., 2010, Demjaha et al., 2011, Hallahan et al., 2011, Hibar et al., 2018).

Since the defining symptom of BD is mood dysregulation, it is likely that disruptions in the neural pathways thought to modulate emotional function, i.e. the limbic (amygdala)-thalamic-prefrontal-cortical circuit and limbic-striatal-pallidal-thalamic circuit (Strakowski et al., 1999), may contribute to the pathological mood states and neurovegetative symptoms of BD (Demjaha et al., 2011). However, studies looking at these brain structures have shown inconsistent results. The amygdala has been shown to be enlarged (Bitter et al., 2011), smaller than (Chang et al., 2005) and equal in size in individuals with BD compared to healthy controls (Pfeifer et al., 2008, Hibar et al., 2016), with similar mixed results seen for the hippocampus (Altshuler et al., 2000, Rimol et al., 2010, Hibar et al., 2016), thalamus (Rimol et al., 2010, Hibar et al., 2016)

and prefrontal cortex (Chang et al., 2005, Dickstein et al., 2005, Blumberg et al., 2006, Lim et al., 2013).

The underlying etiology of the brain abnormalities seen in BD patients remains under debate. There is equal evidence to suggest two alternative hypotheses: brain abnormalities precede the onset of the disorder or brain abnormalities occur as the disorder progresses. It has been proposed that stress-related increases in cortisol, cannabis and alcohol abuse, smoking and antipsychotics (a common treatment for BD), may account for some of these changes in brain structure (Demjaha et al., 2011); indicating that there may be an accumulation of changes in the brain with the progression of the disorder (Hallahan et al., 2011). However, there is also evidence to suggest that there may not be an association between regional brain volumes and the duration of the disorder, suggesting that many of the structural abnormalities occur before the onset of the disorder (Bitter et al., 2011). The inconsistent findings across imaging studies illustrate the possible heterogeneity of the disorder, highlighting the need to look at BD through a combined approach, such as imaging-genetics.

1.3.2. Structural Brain Changes Associated with Borderline Personality Disorder

Structural and functional neuroimaging has revealed a dysfunctional fronto-limbic network that seem to mediate important aspects of BPD symptomatology (Lischke et al., 2015). This dysfunctional network consists of the anterior cingulate cortex, the orbitofrontal and dorsolateral prefrontal cortex, the hippocampus, and the amygdala (Soloff et al., 2012). One of the characteristic features of BPD, emotional dysregulation, may be related to irregular functioning of the anterior cingulate cortex (Lieb et al., 2004). The anterior cingulate cortex is thought to mediate affective control and has consistently been found to be reduced in BPD patients when compared to healthy controls (O'Neill and Frodl, 2012). Lesions to the orbitofrontal cortex mimic some of the symptoms noted in BPD, such as socially inappropriate behaviour and emotional dysfunction (Berlin et al., 2005). This indicates that dysfunction in this region, may contribute to some of the characteristics of BPD (Berlin et al., 2005). Reduced dorsolateral prefrontal cortex, hippocampal and amygdala volumes have also consistently been noted in BPD patients, indicating that the limbic system may play a role in the pathology of this disorder (Sala et al., 2011, O'Neill and Frodl, 2012). Animal models have established the important contribution of the amygdala to emotional regulation, thus reduced volume and poor

white matter integrity in tracts connecting the amygdala to prefrontal regions may account for the mood lability of the disorder (Lischke et al., 2015). Reduced hippocampal volumes are the most consistently associated neuroimaging alteration observed in BPD (O'Neill and Frodl, 2012) but this may be due to factors other than the pathology of the disorder itself (Fatimah et al., 2019). For example, reduced hippocampal volumes have also been associated with early childhood trauma, indicating that the reduced volumes seen in many BPD patients may be due to the high levels of adverse childhood experiences associated with the disorder (Fatimah et al., 2019). This highlights that the underlying cause of the brain abnormalities noted in the disorder remains unknown. The neurobiological dysfunctions may be due to genetic, pre- or post-natal factors, adverse childhood experiences or a consequence of the disorder itself (Lieb et al., 2004).

1.4. The Genetic Architecture of Brain Regions

1.4.1. Cortical Brain Structure

The cerebral cortex is the outer, grey matter layer of the brain and is characterized by gyral and sulcal regions, dividing the brain into four lobes: frontal, parietal, occipital and temporal (Figure 1.2A). The cortical brain can be separated based on different factors however, for the purpose of this study, we will focus on Desikan-Killiany's atlas which divides the cortical brain into 34 regions (Figure 1.2B) (Desikan et al., 2006). Twin and family studies have shown the thickness and surface area of some of these regions to be heritable, ranging from not heritable to 0.65 for global surface area (Figure 1.3) (Winkler et al., 2010, Strike et al., 2019). The thickness and surface area of these 34 regions have been shown to have distinct trajectories over the lifespan, moreover there is evidence to suggest a substantial degree of shared genetic architecture contributing to both traits (Figure 1.4) (Hogstrom et al., 2013, van der Meer et al., 2019). The radial unit hypothesis indicates that cortical surface area is driven by the proliferation of neuronal progenitor cells, whereas thickness is determined by the number of neurogenic divisions (Rakic, 1988); adding further evidence to studies that found cortical thickness and surface area to be influenced by distinct sets of genes (Kremen et al., 2010, Blokland et al., 2012).

Earlier studies have focused on the effect of rare, highly-penetrant variants on cortical volumes. However, a GWAS investigating the contribution of common variants to both surface area and thickness found 150 significant loci associated with altered cortical structures (140 surface

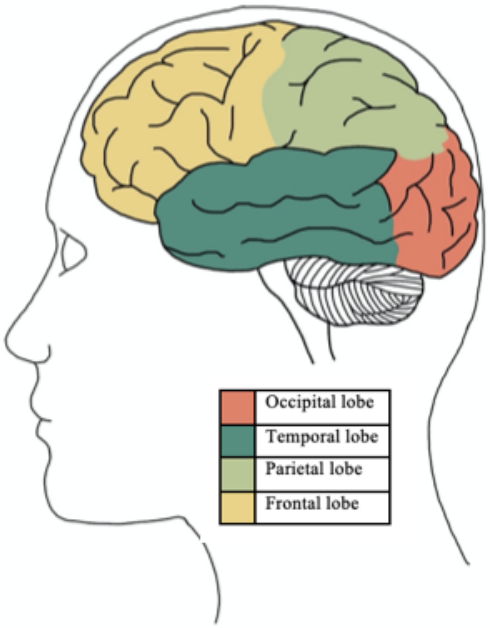
area; 10 thickness) (Grasby et al., 2020). Variants associated with total surface area were found to be within regulatory elements, active during prenatal cortical development- supporting the radial unit hypothesis (Grasby et al., 2020). Furthermore, variants associated with regional surface area implicated *Wnt* signalling pathways which are known to influence progenitor expansion and identity (Grasby et al., 2020). Variants influencing cortical surface area and thickness were correlated with cognitive function, Parkinson's disease, insomnia, depression and attention deficit hyperactivity disorder (ADHD), implying that there may be a shared underlying genetic aetiology between altered surface area and thickness of cortical regions and psychiatric disorders (Grasby et al., 2020).

1.4.2 Subcortical Brain Volumes

The subcortical brain regions are neural structures deep within the brain, consisting of the nucleus accumbens, amygdala, caudate nucleus, hippocampus, putamen, globus pallidus, thalamus and brainstem (including the mesencephalon, pons and medulla oblongata) (Roshchupkin et al., 2016). Neural circuits extending between subcortical and cortical brain regions are crucial for the coordination of movement, memory, learning and motivation (Salzman and Fusi, 2010, Hikosaka et al., 2014, McDonald and Mott, 2017). Alterations in these circuits have been associated with abnormal behaviour and psychiatric disorders (Pereira et al., 2017).

Variation in subcortical brain structures is affected by environmental factors, such as education, diet and stress but there is evidence to suggest that brain structures have an underlying genetic contribution (Peper et al., 2007, Blokland et al., 2012). Earlier twin and family studies have suggested that overall brain volume and certain brain regions are under genetic influence (Figure 1.5) (Tramo et al., 1998, Pfefferbaum et al., 2000, Satizabal et al., 2019). Consortia such as the Enhancing Neuroimaging through Genetic Meta-Analysis (ENIGMA) and the Cohorts for Heart and Ageing Research in Genomic Epidemiology (CHARGE) conduct large-scale GWAS in order to identify the genetic contributions to regional brain volumes. GWASs investigating the genetic architecture of subcortical brain regions have identified common genetic variants influencing regional brain volume (Hibar et al., 2015, Satizabal et al., 2019). These variants are clustered near developmental genes that regulated apoptosis, axon guidance and vesicle transport (Hibar et al., 2015, Satizabal et al., 2019).

A)



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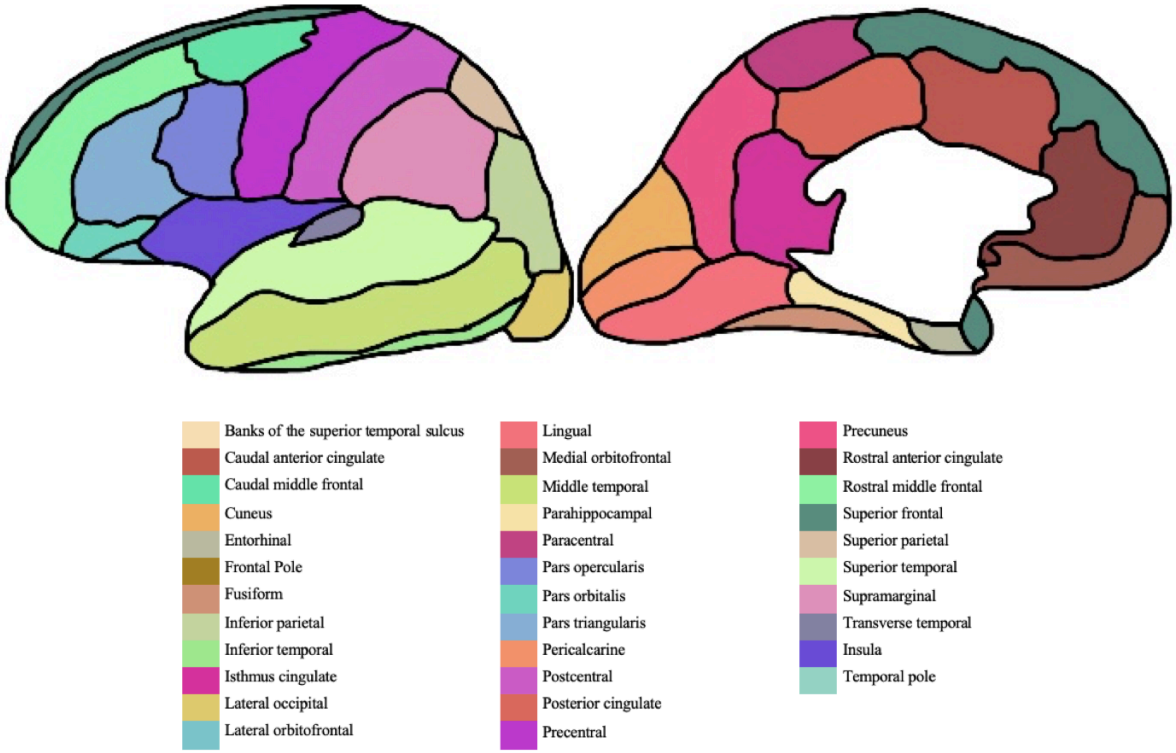


Figure 1.2 Divisions of the cortical brain

A) The four major divisions of the cortical brain B) The 34 functional regions of the cortical brain, defined by the Desikan-Killiany atlas (Desikan et al., 2006)

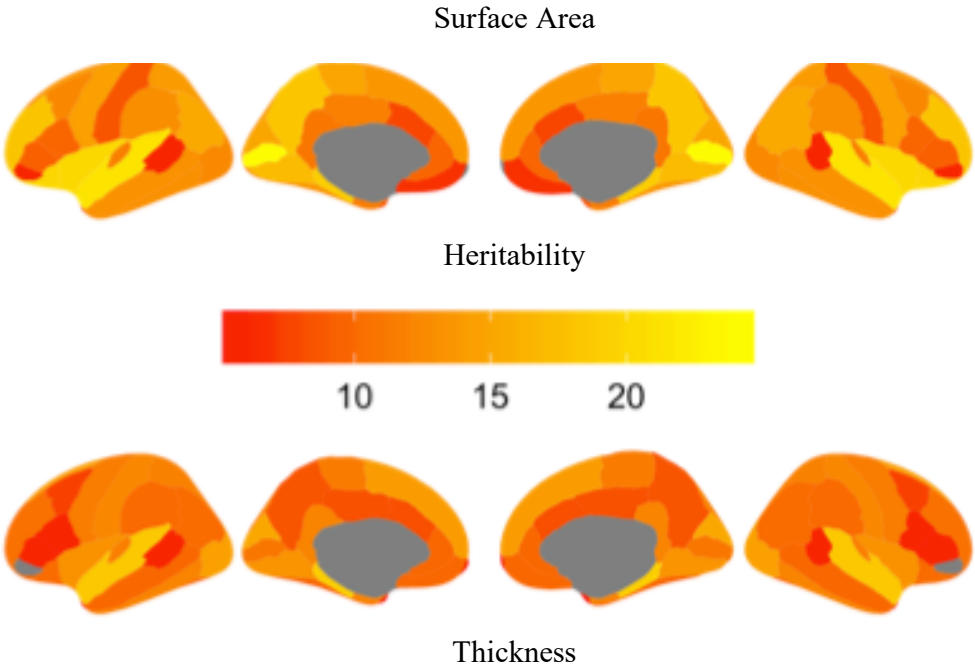


Figure 1.3 The estimated heritability of regional surface area and mean thickness ***(image adapted from van der Meer et al, 2020)***

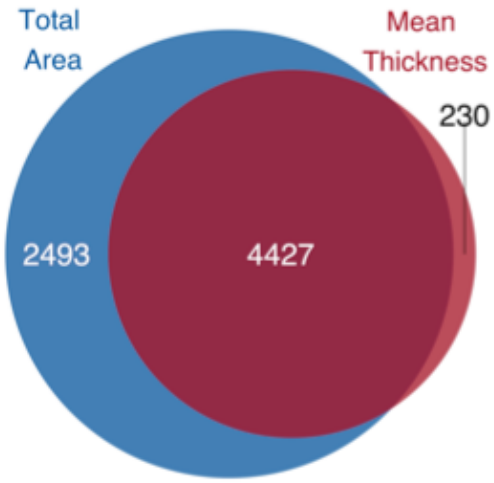


Figure 1.4 A Venn diagram depicting the estimated number of variants shared between total surface area and thickness ***(image adapted from van der Meer et al., 2020)***

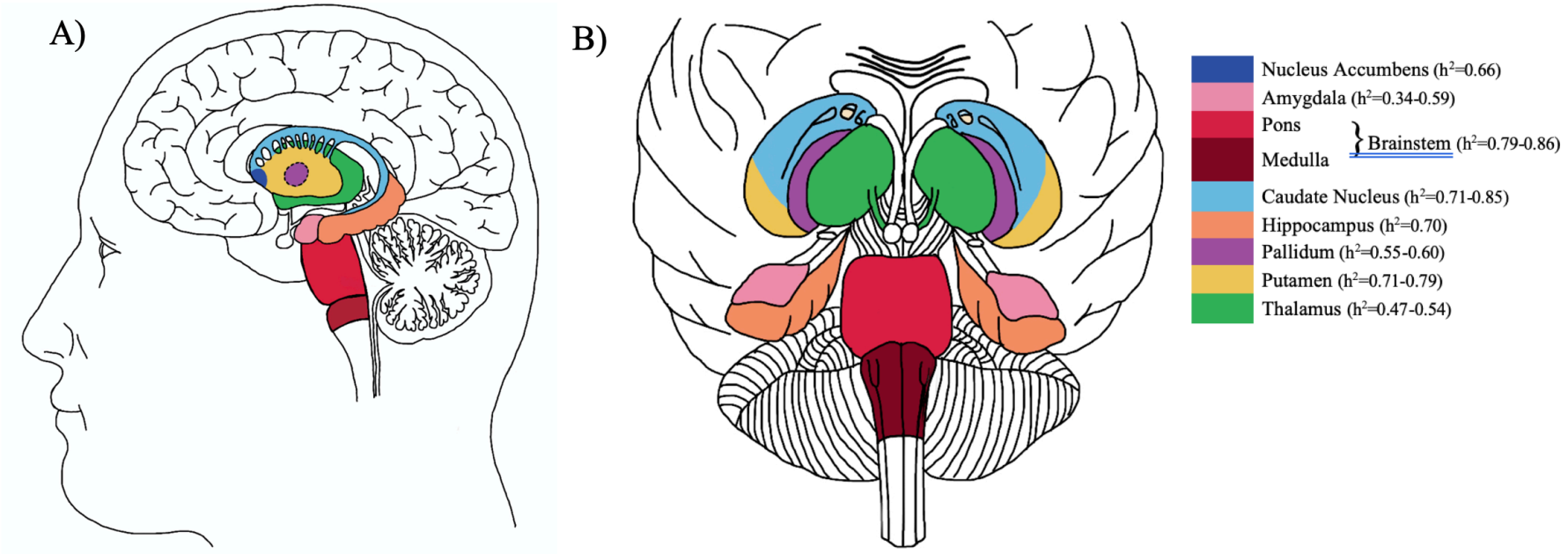


Figure 1.5 The subcortical structures of the brain, included in this study

A) A sagittal view of the brain showing all nine structures included in this study. B) A coronal section of the brain, showing eight of the nine structures included in this study. Heritability estimates reported here for the nucleus accumbens, amygdala, brainstem, caudate nucleus, pallidum, putamen and thalamus refer to family-based heritability (h^2) estimates, performed with SOLAR in the FHS (n = 895) and ASPS-Fam (n = 370) in Satizabal et al. (2019). The heritability estimate reported for the hippocampus refers to that reported by Rentería et al. (2014) which conducted a twin-based study design.

1.5 Aims and Objectives

In magnetic resonance imaging (MRI) scans of patients with BD and BPD, reductions in brain volume are often apparent (Tesli et al., 2013). However, it is unknown whether these brain abnormalities are influenced by genetic determinants that overlap with those underlying BD and BPD aetiology. We hypothesise that the genetic architecture underlying both psychiatric disorders and brain structure can be elucidated through a well-powered study, utilizing several robust analytical techniques. The foremost aims of this project are to determine whether there is genetic overlap between BD and BPD and BD, BPD and the volume, surface area and thickness of brain regions, respectively.

In order to address the aim of this study, the following objectives were met (Figure 1.6):

a) Genetic overlap (pleiotropy) and direction of effect (concordance) were measured between subcortical brain volumes, BD and BPD using SNP-Effect Concordance Analysis (SECA).

b) Genetic correlation was estimated using linkage disequilibrium score regression (LDSC).

c) A conditional false discovery rate (cFDR) analysis was performed to identify common variants associated with BD and BPD.

d) Mendelian randomization (MR) was used to test for causal associations between traits, using variants significantly associated with BD, BPD and each brain region

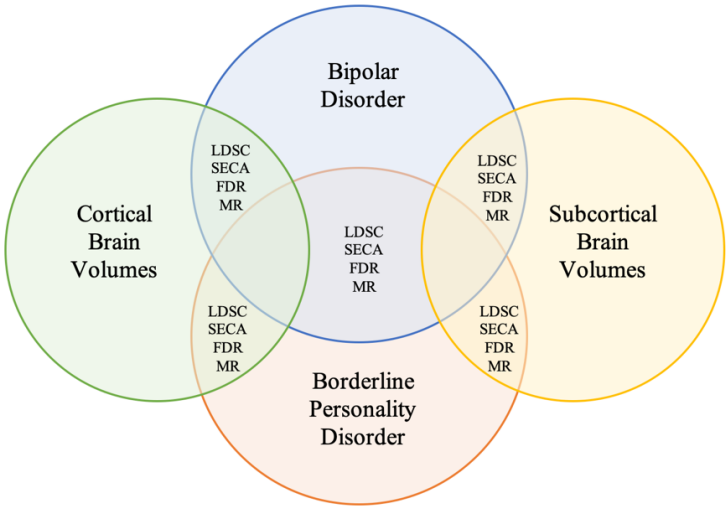


Figure 1.6 A Venn diagram depicting the aim and objectives of this project

2 Methods and Materials

This study was approved by the Human Research Ethics Committee at the University of Cape Town (HREC: 029/2020, Appendix A). As previously mentioned, this study assessed overlap in genetic risk using four approaches. Although similar, each approach provides slightly different information, providing a comprehensive overview of genetic risk between two traits. Pleiotropy occurs when a gene (or SNP in this context) exerts effects on more than one trait. Concordance is a measure of the direction of the genetic effect (i.e. are the odds ratios risk increasing for both traits, protective in one trait and risk increasing in the other or protective in both traits). Genetic correlation is the proportion of variance that two traits share due to genetic causes and is interpreted as a regression coefficient. Finally, Mendelian randomisation is a statistical technique that assess the causal effect of a SNP on a trait. Each method is discussed in more detail below.

2.1 Description of GWAS Summary Statistics

In order to assess the genetic overlap between disorders and brain phenotypes of interest, GWAS summary statistics were obtained from the following groups and are described in greater detail below:

i. Psychiatric Genomics Consortium (PGC) BD (Stahl et al., 2019)
ii. BPD GWAS (Witt et al., 2017)
iii. CHARGE-ENIGMA GWAS of subcortical brain volumes (Hibar et al., 2015, Adams et al., 2016, Satizabal et al., 2019)
iv. ENIGMA Cortical GWAS (Grasby et al., 2020)

2.1.1 Bipolar Disorder GWAS

Summary statistics from the largest GWAS for BD from the PGC are publicly available and were analysed for the purpose of this study (downloaded at https://www.med.unc.edu/pgc/download-results/; accessed 8 February 2019). The data consisted of 51,710 individuals (N_{case}= 20,352; $N_{control}$= 31,358) and comprised 4,338,013 SNPs (Stahl et al., 2019), imputed from the 1000 Genomes world reference panel (Siva, 2008). In order to reduce the bias from population stratification, all participants were of European descent. Cases were required to meet criteria for a lifetime diagnosis of BD, according to the DSM-IV, and controls were screened for the absence of lifetime psychiatric disorders and randomly selected from the respective population (Stahl et al., 2019).

2.1.2 Borderline Personality Disorder GWAS

GWAS summary statistics from the only published GWAS of BPD to date were obtained from the corresponding author (Witt et al., 2017). The BPD GWAS consisted of a total of 2,543 individuals of European ancestry (N_{case}=998 and $N_{control}$=1545) and comprised 10,736,317 SNPs, imputed from the 1000 Genomes world reference panel (Siva, 2008). Inclusion criteria for patients were: 16 to 65 years of age, European ancestry and a lifetime diagnosis of BPD. The diagnosis of BPD was assigned according to DSM-IV criteria and on the basis of structured clinical interviews. Individuals with a comorbid diagnosis of BD or SCZ were excluded from the study (Witt et al., 2017).

2.1.3 Subcortical Brain Volume GWAS

The CHARGE consortium conducted a GWAS of eight subcortical brain volumes (nucleus accumbens, amygdala, brainstem, caudate nucleus, hippocampus, globus pallidus, putamen, thalamus) and total intracranial volume (ICV) in 38,851 individuals (Adams et al., 2016, Hibar et al., 2017, Satizabal et al., 2019). These data consisted of individuals of European ancestry from 48 cohorts across CHARGE, ENIGMA (http://enigma.ini.usc.edu/research/; accessed 17 March 2020) and the UK Biobank (Biobank, 2014). Individuals were excluded on the basis of prevalent dementia, stroke or the presence of large brain infarcts or other neurological pathologies that could influence the measurement of brain volumes (Satizabal et al., 2019).

Summary statistics were requested for 8 brain regions which included the nucleus accumbens, amygdala, brainstem, caudate nucleus, hippocampus, globus pallidus, putamen, thalamus and ICV (Figure 1.5). Each regional brain volume was defined as the mean volume (in cm^3) of the left and right hemispheres, aside from the brainstem for which the total volume in cm^3 was used. MRI scans were obtained from diverse scanners, using various field strengths and acquisition protocols- these confounding factors were controlled for in the original analysis (Satizabal et al., 2019). More detail regarding the MRI analyses are outlined in the original study (Satizabal et al., 2019). Each subcortical brain region had genotype data for a different number of imputed SNPs, ranging from 6,778,919 to 7,609,352.

2.1.4 ENIGMA GWAS of Cortical Brain Regions

The ENIGMA Consortium conducted a GWAS which aimed to identify genetic variants impacting cortical structure from MRI data of 35,660 individuals (Grasby et al., 2020). The dataset consisted of individuals of European ancestry, from 34 ENIGMA cohorts and the UK Biobank (Grasby et al., 2020). The surface area (SA) and average thickness (TH) of the whole cortex and 34 regions with functional specialisations were examined (Figure 1.2) (Grasby et al., 2020). Surface area and thickness were derived from *in-vivo* whole brain T1-weighted MRI scans using FreeSurfer MRI processing software, further detailed in the original GWAS paper (Grasby et al., 2020). Summary statistics for this study were requested via the ENIGMA website (http://enigma.ini.usc.edu/research/; accessed 3 June 2020).

2.2 SNP-based Heritability and Genetic Correlation

Heritability describes the proportion of phenotypic variance explained by genetic variance (Speed and Balding, 2018). Since downstream analyses required traits to be heritable, the SNP-based heritability of all traits in this study (BD, BPD, brain- volumes, surface area and thickness) were examined. Genetic correlation describes the shared genetic architecture of complex traits and diseases (Bulik-Sullivan et al., 2015a). Since the calculation of genetic correlation generally only requires summary statistic level data, and is not biased by sample overlap, it has become a robust and widely used technique . LDSC is based on the assumption that the effect size for a given SNP incorporates the effects of all SNPs in that linkage disequilibrium (LD) block (Yang et al., 2011, Bulik-Sullivan et al., 2015b). The method considers all SNPs, including those that do not reach genome-wide significance and assesses their contribution to each trait under investigation (Bulik-Sullivan et al., 2015a). The sign of the estimated genetic correlation is used to determine the direction of the relationship between the traits (Bulik-Sullivan et al., 2015a). Genetic correlation was estimated using a fitted linear model of Z-scores, obtained from the product of the statistics for each SNP in a given set of GWAS results, compared to the level of LD at a given SNP (Yang et al., 2011). SNPs in high LD are expected to have high Z-scores in polygenic traits with common genetic overlap (Bulik-Sullivan et al., 2015a). SNP-based heritability and genetic correlation were both computed using the command line tool ldsc (available for download https://github.com/bulik/ldsc.git; accessed 16 February 2019).

2.3 SNP Effect Concordance Analysis

2.3.1 Linkage Disequilibrium Clumping

Plink v1.9 (Chang et al., 2015) was used to identify SNPs in linkage equilibrium, based on the 1000 Genome European Phase 1 (version 3) reference dataset (Siva, 2008). This involved clumping the SNPs from each brain region GWAS respectively, using a 500kb window (i.e. SNPs within 500kb distance of one another) and an r^2 of > 0.2 to identify variants in LD with the index SNP. The LD metric (r^2) refers to the squared correlation between SNPs based on genotypic allele counts (VanLiere and Rosenberg, 2008). The index SNP is representative of that LD block and all other SNPs in the LD block are dropped from the analysis. Clumping was performed using a p-value informed approach, whereby the lowest p-value within each LD block was selected as the index SNP. A second round of LD clumping was performed to ensure that none of the index SNPs were in long-range (<10Mb) LD (r^2>0.1). This approach identifies SNPs that are independent and have the most significant p-values in the brain region dataset. After LD-clumping, independent sets of SNPs remained, representing the total variation explained across the genome for each brain region GWAS. Overlapping SNPs present in the respective brain region GWASs and the BD and BPD datasets, respectively, were used for downstream analyses.

2.3.2 Tests of Pleiotropy

Pleiotropy, loci showing an association with more than one distinct phenotype, was examined using SNP effect concordance analysis (SECA) (https://sites.google.com/site/qutsgel/software/seca-local-version; accessed 7 March 2019) (Nyholt, 2014). In order to determine if there was an excess of SNPs associated with the respective traits, SECA performs exact binomial statistical tests across the two datasets under consideration (BD or BPD and each brain region, respectively) for subsets of SNPs at 12 p-value thresholds, $P \leq (0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0)$. For a given subcortical region and BD or BPD paired set, SNPs were ranked based on their p-value association with each trait. Empirical p-values, adjusted for all 144 subsets (12 p-value thresholds for two datasets), were calculated by performing 10,000 permutations. During the process of permutation, betas and the corresponding p-values are randomly shuffled between SNPs in the brain GWAS, to create uncorrelated datasets, and the analysis of the 144 subsets was repeated. The total number of SNPs overlapping between the two traits at each p-value

threshold was determined and compared to the expected random overlap under the null hypothesis of no pleiotropy.

2.3.3 Tests of Concordance

SECA performs Fisher's exact statistical tests to determine whether there is an excess of SNPs where the direction of effect (beta) is concordant across datasets for each of the subsets. SECA performs Fisher's exact statistical tests across the two datasets under consideration (for example, BD vs BPD) for subsets of SNPs at 12 p-value thresholds, $P \leq (0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0)$. The global level of concordance was estimated by generating 10,000 permutations to determine if the number of significant overlapping thresholds was greater than expected by chance. We determined whether there was a significant positive or negative trend in the effect of the overlapping SNPs at each threshold. In the BD and BPD GWAS, a positive beta for a particular SNP was associated with an increased risk of developing the psychiatric disorder and a positive beta for a SNP in the brain volume GWAS indicates an association with an increase in brain volume. Thus, positive concordance would be interpreted as an increased risk for the development of a psychiatric disorder with an increased brain volume and negative concordance would be an increased risk for the psychiatric disorder with reduced regional brain volume.

2.3.4 Conditional False Discovery Rate

GWASs have been unable to explain a large proportion of the heritability seen in complex disorders (Crow, 2011). Pleiotropy-informed conditional false discovery (cFDR) is based on the assumption that some genes affect multiple phenotypes and aims to capture more of the polygenic effects seen in complex disorders (Nyholt, 2014). Thus, multiple independent GWASs from associated traits or comorbid disorders can be used to investigate the missing heritability not accounted for in traditional GWASs (Nyholt, 2014, Smeland et al., 2019). Combining GWASs from two traits allows for increased power which may aid in the identification of common biological pathways, improve our ability to detect novel variants and prioritise variants for follow-up analyses (Andreassen, et al., 2013).

Quantile-quantile (QQ) and true discovery rate (TDR) plots for brain GWAS p-values conditional on the association of BD and BPD SNPs, at subsets of $p \leq (0.1, 0.2, 0.3, 0.4, 0.5, 0.75, 1.0)$, were generated. These were used to visualize if there was an excess of pleiotropic

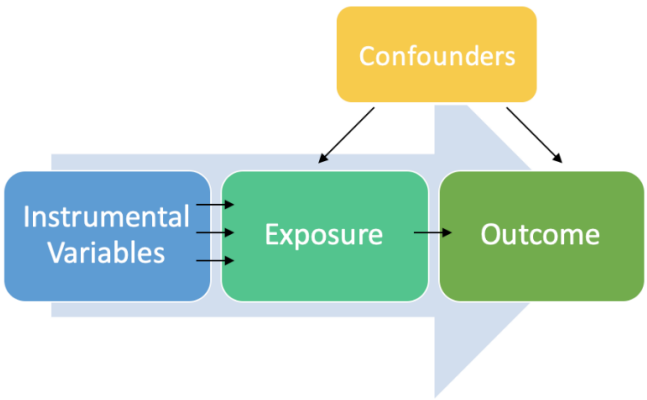
SNPs; a leftward shift in either plot corresponds to an excess of SNPs with smaller p-values. In the presence of pleiotropy, successive leftward shifts in the curve would be expected for the brain volume datasets conditional on smaller p-values in BD and BPD, respectively. The cFDR method was applied to each brain region for a subset of SNPs at 14 false discovery rate (FDR) threshold q-values $\leq (1x10^{-5}, 1x10^{-4}, 1x10^{-3}, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1)$ (Nyholt, 2014). Individual SNPs were considered significant if the p-value was lower than the significance threshold allowing for a FDR of 5% (Andreassen et al., 2013). These SNPs were annotated using SNPnexus (http://snp-nexus.org/; accessed 28 October 2019).

2.3.5 Gene Set Enrichment Analysis

Gene set enrichment analysis (GSEA) was performed using Multi-marker Analysis of GenoMic Annotation (MAGMA) (de Leeuw et al., 2015), accessed through the online tool Functional Mapping and Annotation of GWAS (FUMA; https://fuma.ctglab.nl; Accessed 27 May 2020). GSEA determines if a pre-determined set of genes (i.e. the gene list from the significant cFDR variants) is statistically overrepresented in sets of biologically related or disease associated gene sets (de Leeuw et al., 2015). Genes implicated by the significant cFDR variants were used as input for the GSEA. The Benjamani-Hochberg FDR method was used to correct for multiple testing and a gene-set was considered significant if $p_{adj}<0.05$.

2.4 Mendelian Randomization

In complex disorders, it is often unclear whether risk factors are a cause or consequence of the disorder. MR is a multi-SNP technique that uses GWAS summary statistics to test for causal associations (Zhu et al., 2018) (Figure 2.1). MR can be used to identify risk variants as potential targets for clinical or behavioural intervention (Burgess et al., 2015). This approach has shown to be successful in prioritising lipoprotein(a) and interleukin-6 receptor in the



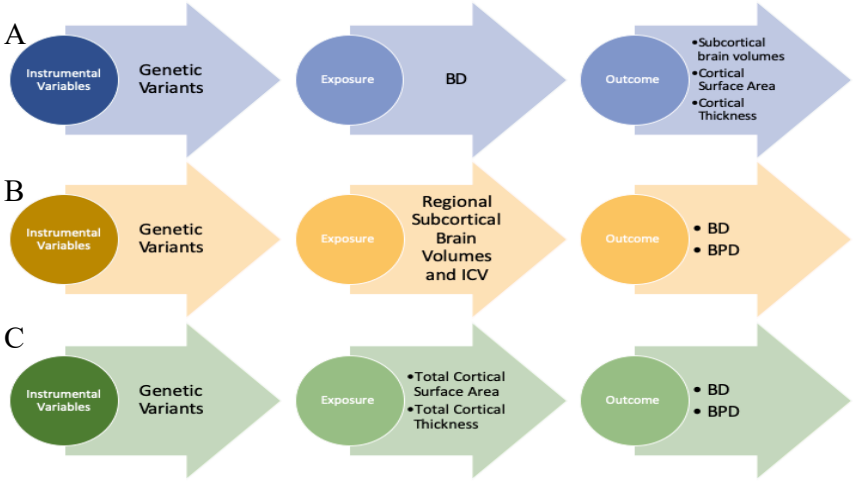
pathology of cardiovascular disease as well as reducing the priority of other factors once thought to be causative- fibrinogen, C-reactive protein (CRP) and uric acid (Keavney et al., 2006, Kamstrup et al., 2009, Collaboration, 2011, Brainstorm Consortium, 2012, Palmer et al., 2013) Thus, the use of MR may provide novel insight into biomarkers for psychiatric disorders.

Figure 2.1 A diagrammatic overview of the MR procedure

2.4.1 Two Sample Mendelian Randomization

In order for a genetic variant to be considered an instrumental variable (Figure 2.1), it must satisfy three requirements: First, the variant is robustly associated with the outcome (in this case, BD and each brain region, respectively). Second, the variant is not associated with any confounding variables and third, the variant is not associated with the outcome via any pathway other than that through the risk factor of interest (Burgess et al., 2015). For BD and each brain GWAS, SNPs that reached genome-wide significance for each GWAS (BD, each subcortical brain volume GWAS, ICV, total cortical surface area and total cortical thickness) were used as instrumental variables for MR ($p< 5x10^{-8}$). In the case of BPD, where no SNPs were significant after multiple testing in the original GWAS, this dataset was only considered as an outcome in the analysis and was not assessed as an exposure. Figure 2.2 A-C, illustrates an overview of each MR analysis. LD-clumping was performed using the parameters recommended for the MR ($r^2=1x10^{-3}$; 10,000 kb window) (Hemani et al., 2018). LD was calculated between the significant SNPs; SNPs that had an r^2 exceeding the threshold of $1x10^{-3}$ and the lowest p-value were retained and used as instrumental variables in the MR analysis.

Once instruments for the exposure trait have been identified, those variants are extracted from the outcome trait dataset. The SNPs are then aligned to ensure that the effect of the SNP



on the exposure and the effect of the SNP on the outcome, correspond to the same allele. The R-package *TwoSampleMR* was used to conduct the MR analyses (Hemani et al., 2018). The MR-Egger regression intercept was considered to verify the presence of pleiotropic effects of the instrumental variables on the outcome (horizontal pleiotropy), a potential violation of MR (Bowden et al., 2015). Inverse-variance-weighted (IVW) approach was used to assess the overall estimate of the causal effect (Burgess et al., 2013). Effects due to population stratification were minimized as the GWAS data consisted primarily of European individuals.

Figure 2.2 An overview of each MR analysis

3 Results

3.1 Description of GWAS summary data

3.1.1 Bipolar Disorder GWAS

Summary statistics from the largest BD GWAS from the PGC were analysed for the purpose of this study. The data consisted of 51,710 individuals (N_{case}= 20,352; $N_{control}$= 31,358) of European ancestry, from 32 cohorts, across 14 countries in Europe, North America and Australia (Figure 3.1) (Stahl et al., 2019). In the original meta-analysis, 30 loci reached genome-wide significance, 20 of these were novel. These loci implicated genes encoding ion channels, neurotransmitter transporters, synaptic components, immune and energy metabolism components and potential therapeutic targets for mood stabilizer drugs (Stahl et al., 2019).

3.1.1.1 Removal of Sample Overlap

The CHARGE subcortical brain volume, the ENIGMA cortical surface area and thickness and the PGC-BD GWAS included data from the ENIGMA consortium. In order to reduce bias due to sample overlap in the downstream analyses, the ENIGMA cohort was removed from the BD sample. The total number of overlapping participants was 1,419 (N_{case}=726; $N_{control}$=693). These samples were removed from the original PGC dataset and the BD GWAS was conducted on the remaining 51,291 individuals (N_{case}= 19,626; $N_{control}$=31,665).

3.1.2 Borderline Personality Disorder GWAS

GWAS summary statistics from GWAS of BPD were obtained from the corresponding author (Witt et al., 2017). The cohort consisted of 2,543 individuals (N_{case}=998; $N_{control}$=1,545), 71% of which were female. All individuals included in the study were of central European ancestry. A full breakdown of the BPD cohort is shown in

Figure 3.1.

3.1.3 Subcortical Brain Regions

GWAS summary statistics for seven subcortical brain volumes (nucleus accumbens, amygdala, brainstem, caudate nucleus, globus pallidus, putamen and thalamus) were accessed via the ENIGMA website (Satizabal et al., 2019). Two additional GWAS for ICV (Adams et al., 2016) and hippocampus volume (Hibar et al., 2017) were also accessed through the ENIGMA website. Each subcortical brain region had genotype data for a different number of

SNPs, ranging from 6,778,919 to 7,609,352. Each subcortical brain region had genotype data for a different number of SNPs, ranging from 6,778,919 to 7,609,352. The mean age of the cohorts was 51 years old (SD=8) and had an age range from 9 to 98 years. Of the total 41,667 participants in the subcortical GWAS (Satizabal et al., 2019), 53% were female (Figure 3.1). The original subcortical GWAS identified 20 novel loci, from a total of 25 significant loci, that showed an association with altered subcortical brain volumes. These loci implicated genes involved in neurodevelopment, synaptic signalling, axonal transport, apoptosis and susceptibility to neurological disorders (Satizabal et al., 2019).

3.1.4 Cortical Brain Regions

The ENIGMA Consortium conducted a GWAS which aimed to identify genetic variants impacting cortical structure from MRI data of 35,660 individuals (Grasby et al., 2020). The dataset consisted of individuals of European ancestry, from 34 ENIGMA cohorts and the UK Biobank (Grasby et al., 2020). The cohort consisted of predominantly healthy individuals, however some individuals with psychiatric diagnoses were included (Figure 3.1).

3.2 SNP-based Heritability

Estimates for h^2_{SNP} were calculated for BD, BPD and each brain region. Only brain region GWASs that were sufficiently powered for LDSC were used in downstream analyses to test for pleiotropy. This was defined as phenotypes with a non-extreme Z-score ($-4 \leq$ Z-score ≤ 4) (Bulik-Sullivan et al., 2015b). Z-scores were calculated as $h^2_{SNP}/(h^2_{SNP}$ SE) .

3.2.1 Bipolar Disorder and Borderline Personality Disorder

The heritability of each phenotype was estimated using the SNP-based heritability component (h^2_{SNP}) of LDSR. The heritability estimate for BD was 0.20 (SE=0.01; p= 1.22×10^{-22}) and BPD was 0.35 (SE=0.12; p=8.32×10^{-8}).

3.2.2 Subcortical Brain Volumes

The h^2_{SNP} estimates for all subcortical brain volumes and ICV are listed in Table 3.1. Amygdala volume was shown to have the lowest heritability estimate (h^2_{SNP}=0.09) while the volume of the brainstem showed the highest heritability estimate (h^2_{SNP}=0.33). The median heritability estimate for volumes of the subcortical structures was 0.18 (SD=0.075).

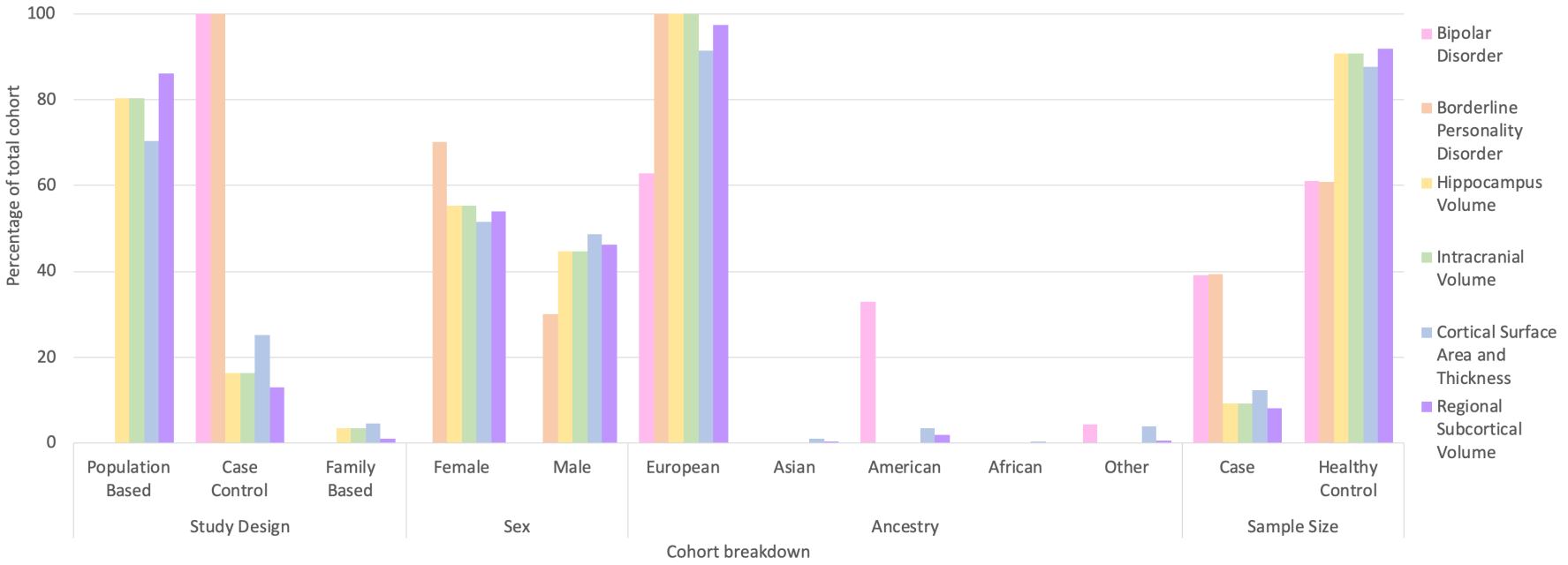


Figure 3.1 Cohort description of the each GWAS

Each bar displays the sample breakdown as a percentage of the total sample size: $N_{Bipolar\ Disorder}$= 50,291; $N_{Borderline\ Personality\ Disorder}$= 2,543; $N_{Subcortical\ Brain\ Volume}$=41667; $N_{intracranial\ volume}$=27,087; $N_{hippocampus\ volume}$=27,087; $N_{cortical}$=37,479. Ancestry 'other' includes cohorts with ancestry listed as 'Brazilian', 'European and African American', 'Mixed', 'Singaporean' and 'Non-European' in the original study. Ancestry 'Asian' includes individuals listed as 'Chinese' and 'Japanese' in the original GWAS. A full breakdown of each cohort can be found in Appendix B, Table 1.

Table 3.1 SNP-based heritability estimates of eight subcortical regions and ICV

Subcortical Brain Region	Heritability Estimate (h^2_{SNP})	Z-score
Accumbens	0.18	5.36
Amygdala	0.09	9.22
Brainstem	0.33	9.63
Caudate Nucleus	0.25	10.48
Hippocampus	0.14	4.82
Pallidum	0.17	9.86
Putamen	0.27	5.36
Thalamus	0.17	9.22
ICV	0.25	7.22

Only phenotypes that had non-extreme Z-scores (-4≤Z-score≤4) were used in downstream analyses. No subcortical regions were retained for downstream analyses

3.2.3 Cortical Brain Regions

The h^2_{SNP} for regional cortical surface area and thickness are listed in Table 3.2. Overall regional surface area showed a higher heritability estimate than regional thickness ($\bar{X}_{\text{regional surface area}}$ h^2_{SNP}= 17.1%; $\bar{X}_{\text{regional thickness}}$ h^2_{SNP}= 6.31%). This trend is also noted in global surface area and thickness: global surface area showed a higher heritability estimate (h^2_{SNP}=0.31) when compared to global cortical thickness (h^2_{SNP}=0.24). Heritability estimates for regional cortical surface area ranged from 0.08% in the frontal pole region to 0.29 in the precentral region; cortical thickness ranged 0.01 (paracentral region) to 0.12 (superior parietal region).

3.3 SNP Effect Concordance Analysis

3.3.1 Bipolar Disorder and Borderline Personality Disorder

There was evidence of pleiotropy, same SNP regardless of direction, for BD and BPD risk variants ($p=5x10^{-4}$). In addition, positive concordance was noted between the two disorders ($p=1x10^{-4}$), this finding remained significant after correction for multiple testing (Bonferroni, $p<0.05/(2 \text{ phenotypes}*4 \text{ tests}*17 \text{ brain regions}=3.67x10^{-4})$.

3.3.2 Bipolar Disorder and Brain Regions

Significant pleiotropy was noted between BD and the thickness of several cortical regions, namely the lateral occipital ($p=2.25x10^{-5}$), pars triangularis ($p=1.1x10^{-4}$), post central ($p=7.9x10^{-6}$), rostral anterior cingulate ($p=2.18x10^{-4}$) and the supramarginal ($p=1.45x10^{-7}$). These findings remained significant after correction for multiple testing. There was no evidence of significant concordance between BD and any brain region (Table 3.3).

3.3.3 Borderline Personality Disorder and Brain Regions

Several regions showed suggestive ($p<0.05$) concordance with BPD (Table 3.3). After correction for multiple testing (Bonferroni, $p<0.05/4$ tests*2 traits*17 brain regions=$5.56x10^{-4}$), significant positive concordance was noted between BPD and thickness of the lateral occipital region ($p=3x10^{-4}$), indicating the presence of allelic effects that may increase risk for both traits.

Table 3.2 SNP-based heritability estimates of cortical brain regions, by surface area and thickness

Cortical Brain Region	Surface Area		Thickness	
	h^2_{SNP}	Z-score	h^2_{SNP}	Z-score
Banks of the Superior Temporal Sulcus	0.15	7.10	0.15	2.95
Caudal Anterior Cingulate	0.15	7.87	0.05	4.83
Caudal Middle Frontal	0.18	8.42	0.08	3.04
Cuneus	0.16	7.58	0.05	3.01
Entorhinal	0.15	8.18	0.05	0.60
Frontal pole	0.08	4.85	0.01	2.58
Fusiform	0.17	8.85	0.05	5.71
Isthmus Cingulate	0.18	9.06	0.09	5.10
Inferior Parietal	0.17	8.85	0.07	4.25
Inferior Temporal	0.22	9.55	0.08	5.37
Insula	0.13	6.71	0.08	4.53
Lingual	0.20	9.22	0.08	2.94
Lateral Orbitofrontal	0.24	9.92	0.04	3.84
Lateral Occipital	0.21	8.90	0.07	3.06
Middle Temporal	0.13	6.17	0.05	4.09
Medial Orbitofrontal	0.19	8.03	0.07	4.89
Parahippocampal	0.14	7.94	0.08	5.87
Pars Opercularis	0.14	6.78	0.09	3.01
Pars Triangularis	0.14	7.43	0.05	0.67
Paracentral	0.15	7.01	0.01	3.48
Posterior Cingulate	0.19	9.16	0.06	3.01
Precentral	0.29	9.08	0.04	5.26
Pericalcarine	0.16	7.51	0.09	4.00
Postcentral	0.15	8.36	0.06	4.86
Pars Orbitalis	0.17	7.74	0.08	3.25
Precuneus	0.19	9.50	0.06	2.74
Rostral Anterior Cingulate	0.14	7.36	0.04	3.66
Rostral Middle Frontal	0.20	9.63	0.06	4.05
Superior Frontal	0.15	7.83	0.08	4.33
Supramarginal	0.17	7.61	0.06	1.25
Superior Parietal	0.25	6.15	0.12	6.16
Superior Temporal	0.15	6.73	0.09	6.54
Temporal Pole	0.11	6.16	0.02	5.16
Transverse Temporal	0.21	9.38	0.09	10.30
Global	0.31	10.68	0.24	10.68

Only phenotypes that had non-extreme Z-scores (-4≤Z-score≤4) were used in downstream pleiotropy analyses, underlined in this table

Table 3.3 Pleiotropy and concordance results for BD, BPD and cortical brain regions

	BD			BPD		
Cortical Region	**Pleiotropy p-value[1]**	**Concordance p-value[1]**	**Direction of Concordance (OR)**	**Pleiotropy p-value[1]**	**Concordance p-value[1]**	**Direction of Concordance (OR)**
Banks of the superior temporal sulcus	$2.8x10^{-3}$	0.54	Negative (1.04)	0.3	0.26	Positive (0.99)
Caudal middle frontal	$3.13x10^{-3}$	0.79	Negative (1.02)	1	0.13	Positive (0.84)
Cuneus	$3.10x10^{-3}$	0.36	Negative (1.08)	1	0.02	Negative (1.05)
Entorhinal	$9.05x10^{-2}$	0.42	Positive (0.94)	0.06	1	Positive (0.92)
Frontal pole	$1.52x10^{-3}$	0.14	Positive (0.89)	0.04	0.32	Negative (1.04)
Lingual	$5.11x10^{-4}$	0.85	Negative (1.01)	1	0.01	Positive (0.92)
Lateral orbitofrontal	$1.95x10^{-2}$	0.05	Negative (1.16)	1	1	Positive (0.93)
Lateral occipital	$2.25x10^{-5}$**	0.52	Positive (0.95)	1	$3x10^{-4}$**	Negative (1.02)
Parahippocampal	$9.44x10^{-4}$	0.03	Negative (1.18)	1	1	Negative (1.07)
Pars opercularis	$1.01x10^{-2}$	0.39	Negative (1.07)	0.09	0.23	Positive (0.94)
Pars triangularis	$1.15x10^{-4}$**	0.07	Positive (0.87)	0.3	0.19	Negative (1.13)
Precentral	$2.53x10^{-3}$	0.73	Positive (0.97)	1	1	Negative (1.06)
Post central	$7.90x10^{-6}$**	0.41	Negative (1.06)	0.16	0.24	Negative (1.02)
Pars orbitalis	$1.36x10^{-2}$	0.49	Positive (0.94)	0.01	0.04	Negative (1.08)
Precuneus	$8.23x10^{-3}$	0.64	Positive (0.96)	0.31	1	Positive (0.96)
Rostral anterior cingulate	$2.18x10^{-4}$**	0.62	Positive (0.96)	0.16	0.42	Negative (1.01)
Supramarginal	$1.45x10^{-7}$**	0.05	Negative (1.17)	1	0.27	Negative (1.02)

*Bonferroni corrected p-value at 0.05/(4 tests*2 traits*17 brain regions)=$3.67x10^{-4}$;** Significant; [1] p-values are empirical; OR, odds ratio. Only brain regions that had non-extreme Z-scores (-4 ≤ Z-score ≤ 4) in the prior, h^2_{SNP} analysis were used in downstream pleiotropic analyses.*

3.4 Conditional false discovery rate

3.4.1 Bipolar Disorder and Borderline Personality Disorder

A pleiotropy-informed cFDR analysis was performed to identify variants associated with BD, conditional on the variants associated with BPD. After LD-pruning, 409,789 SNPs remained for downstream analysis. Testing for conditional effects, 15 independent SNPs gained in association with BD after conditioning on their strength of association with BPD (Table 3.4) (FDR<0.05). This can also be seen by the leftward deflections in the conditional QQ-plot in Figure 3.2A. Successive leftward shifts for decreasing BPD p-values indicates that the non-null effects in BD varies considerably across different levels of association with BPD. Thirteen of these SNPs have not previously been associated with any phenotype; however, rs60960031 and rs12555870, have been associated with BD Type I (Stahl et al., 2019) and remission after Selective Serotonin Reuptake Inhibitor (SSRI) treatment in MDD and neuroticism (Amare et al., 2018), respectively. Testing for conditional effects of BPD associated SNPs, no variants became significant, conditional on their association with BD (Figure 3.2B).

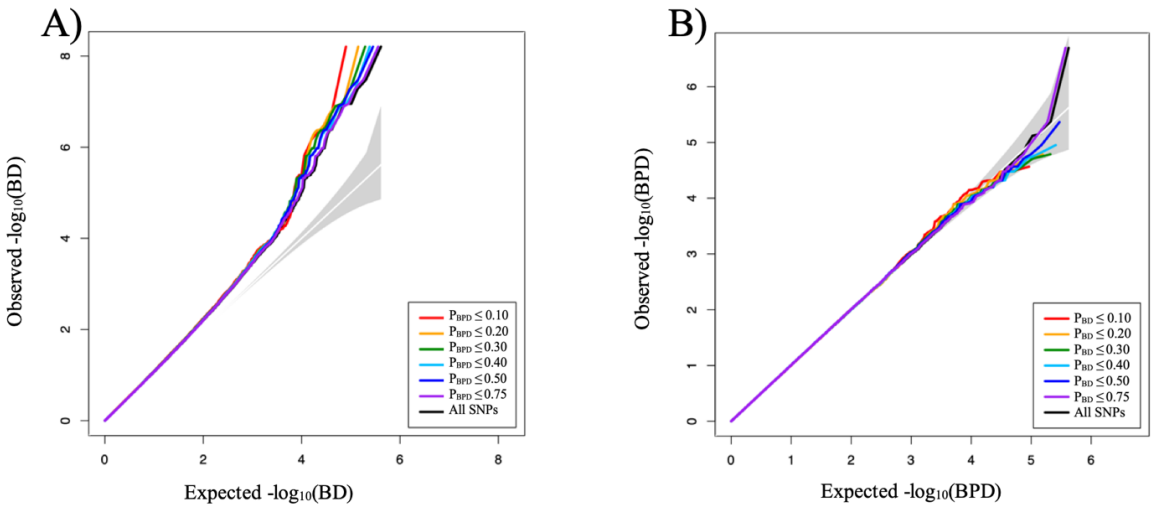


Figure 3.2 Stratified QQ-plots of observed versus expected -log$_{10}$(p-values)

Stratified QQ plots of observed versus expected -log10 p-values in A) Bipolar disorder (BD) conditioned on borderline personality disorder (BPD) for p≤1, p≤0.75, p≤0.50, p≤0.40, p≤0.30,p≤0.20 and p≤0.10, respectively. B) BPD conditioned on BD for p≤1, p≤0.75, p≤0.50, p≤0.40, p≤0.30,p≤0.20 and p≤0.10, respectively. The shaded grey region indicates the null hypothesis of no pleiotropic enrichment.

Table 3.4 Significant variants after testing for conditional effects of BD onto BPD GWAS

SNP	CHR	BP	A1	A2	MAF	BETA IN BD GWAS (SE)	p-value in BD GWAS	Gene	Annotation	$P_{FDR\text{-}NoCond}$	$P_{FDR\text{-}Cond}$
rs12138423	1	60986573	A	G	0.11	0.07(0.01)	$4.09X10^{-6}$	*LINC01748*	non-coding, intronic	0.06	0.04
rs11062161	12	2220804	T	C	0.24	-0.06 (0.01)	$3.33X10^{-6}$	*CACNA1C*	intronic	0.06	0.04
rs7296288	12	49086185	A	C	0.5	-0.06 (0.01)	$4.71X10^{-6}$	N/A	intergenic	0.06	0.03
rs17680262	12	109916731	T	C	0.03	0.11 (0.025)	$4.23X10^{-6}$	*TCHP*	intronic, 3' UTR, non-coding	0.06	0.04
rs6497540	16	9841209	T	G	0.3	-0.06 (0.01)	$7.74X10^{-6}$	*GRIN2A*	non-coding, intronic	0.09	0.04
rs34867153	17	40060883	T	C	0.11	0.11 (0.02)	$4.22X10^{-6}$	*MED24*	intronic	0.06	0.04
rs60960031	2	21530659	A	G	0.41	-0.061 (0.01)	$5.01X10^{-6}$	*AC018742.1*	non-coding, intronic	0.06	0.04
rs17537498	2	60672327	T	C	0.05	-0.10 (0.02)	$4.73X10^{-6}$	N/A	intergenic	0.06	0.04
rs1641470	2	65559472	A	G	0.02	0.19 (0.04)	$3.67X10^{-6}$	*AC007389.1*	non-coding, intronic	0.06	0.04
rs4848363	2	115066099	T	C	0.5	-0.07 (0.01)	$4.11X10^{-6}$	N/A	intergenic	0.06	0.04
rs10190023	5	94118789	A	C	0.41	0.07 (0.014)	$3.62X10^{-6}$	N/A	intergenic	0.06	0.04
rs185310	5	94783084	A	G	0.47	0.07 (0.014)	$2.78X10^{-6}$	*MCTP1*	non-coding, intronic	0.05	0.03
rs55698168	5	95644533	T	G	0.01	0.19 (0.04)	$3.30X10^{-6}$	N/A	intergenic	0.06	0.04
rs35668708	6	50639183	A	C	0.01	-0.21 (0.05)	$4.77X10^{-6}$	N/A	intergenic	0.06	0.04
rs12555870	9	23347726	A	G	0.37	-0.06 (0.01)	$4.21X10^{-6}$	*AL391117.1*	non-coding, intronic	0.06	0.04

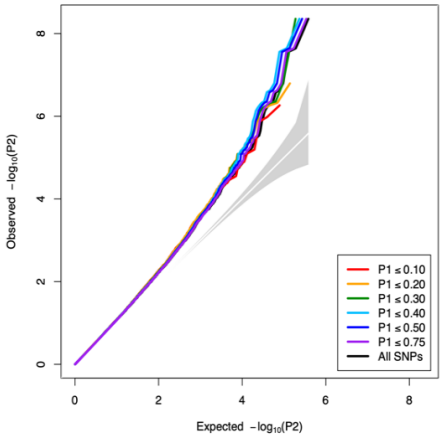
CHR, chromosome; BP, base-pair position; A1, reference allele; A2, alternate allele; MAF, Minor Allele Frequency; SE, standard error; BD, Bipolar Disorder; FDR, false-discovery rate; UTR, untranslated region.

3.4.2 Bipolar Disorder and Brain Regions

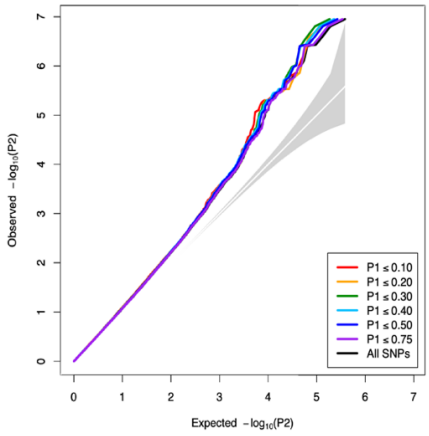
The BD risk variants were assessed conditional on their association with each cortical brain region GWAS. A total of 156 additional variants were significant (FDR<0.05) after conditioning (Appendix C, Table 1). QQ-plots illustrating the pleiotropic enrichment for BD conditioned onto each cortical thickness GWAS are shown in Figure 3.3 (A-O). No variants gained in significance for BD conditioned on thickness of the pars opercularis and banks of the superior temporal sulcus. The significant biological processes implicated by these significant variants from the cFDR analyses are shown in Table 3.5. The top biological processes were vesicle mediated transport in synapses ($p=3.22x10^{-4}$), the synaptic vesicle cycle ($p=2.72x10^{-3}$) and regulation of neurotransmitter levels ($p=3.07x10^{-3}$). GSEA were corrected for multiple correction using the Benjamini-Hochberg FDR method.

3.4.3 Borderline Personality Disorder and Brain Regions

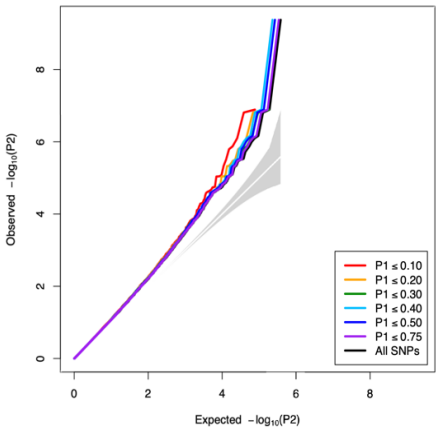
The BPD risk variants were assessed conditional on their association with each cortical brain region GWAS, seperately. Individual SNPs were considered significant if the p-value was lower than the significance threshold, allowing for an FDR of 5%. Three SNPs gained in significance when BPD was conditioned on thickness of the lateral orbitofrontal, lingual, precentral and supramarginal regions (Table 3.6). One variant, rs113507694, located within *DPPA3,* gained in significance when conditioned on three of the above-mentioned brain regions. Leftward deflections, albeit small, in the QQ-plots are indicative of pleiotropic enrichment between BPD and each brain region, respectively (Figure 3.4 A-D). No biological processes were over-represented by these three variants.



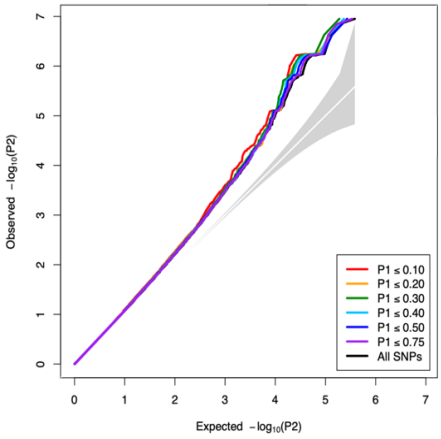
A) BD conditioned on caudal middle frontal



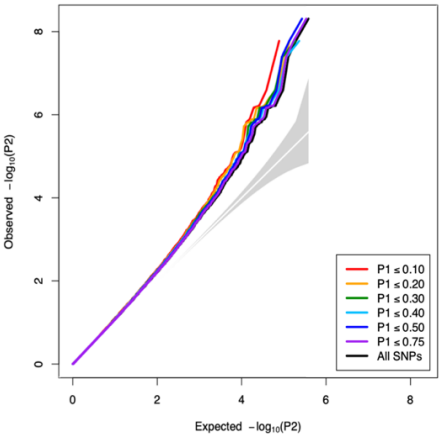
B) BD conditioned on cuneus



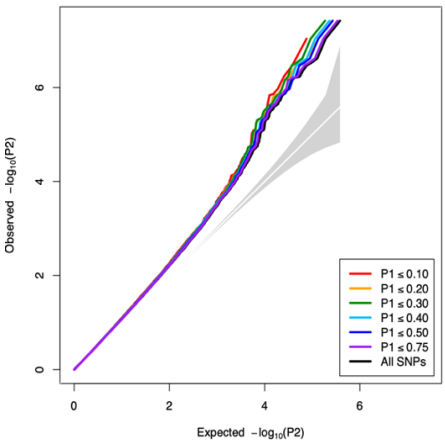
C) BD conditioned on entorhinal



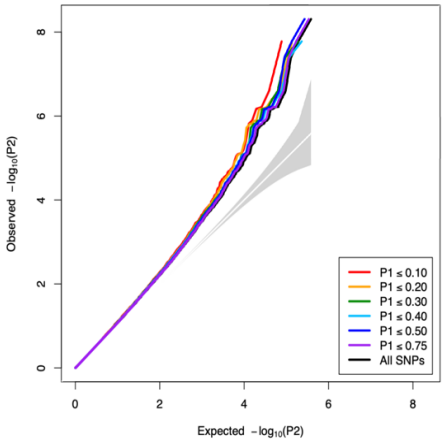
D) BD conditioned on frontal pole



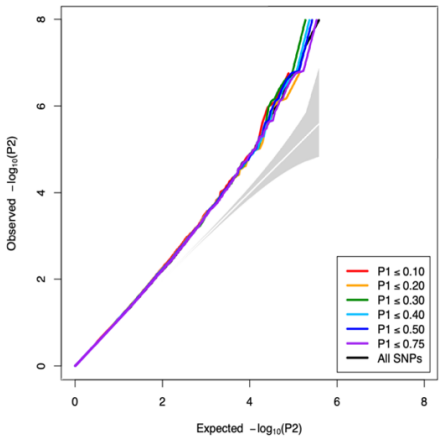
E) BD conditioned on lateral orbitofrontal



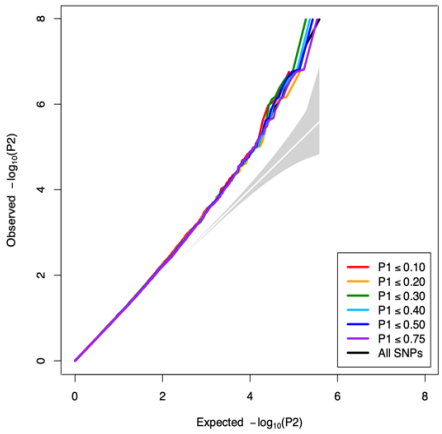
F) BD conditioned on lateral occipital



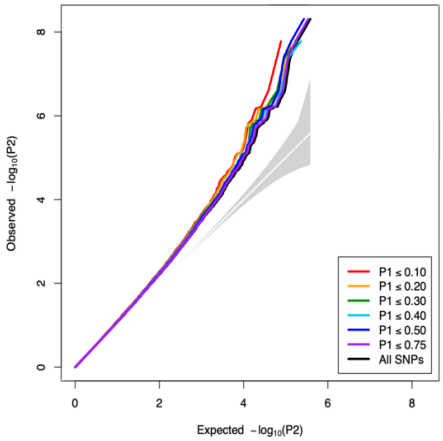
G) BD conditioned on lingual



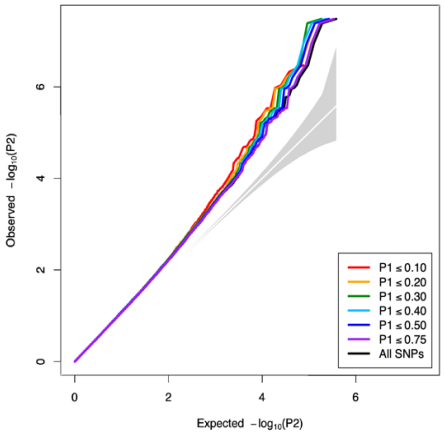
H) BD conditioned on parahippocampal



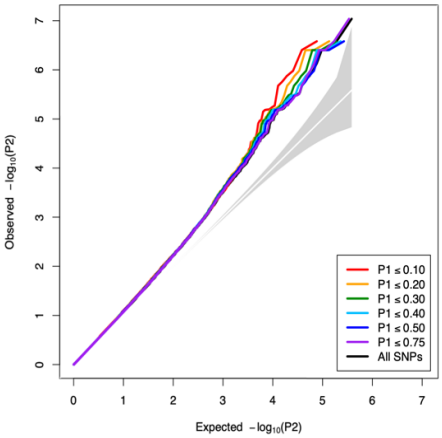
I) BD conditioned on pars orbitalis



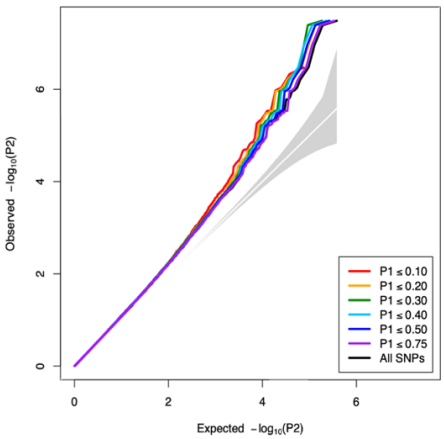
J) BD conditioned on pars triangularis



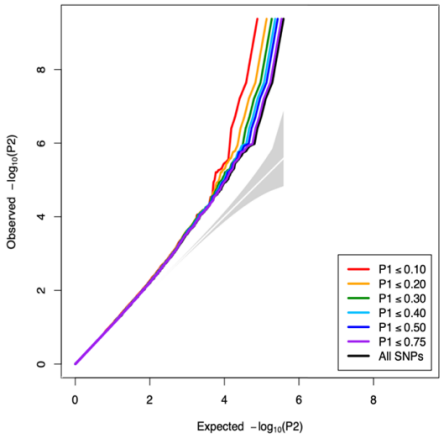
K) BD conditioned on post central



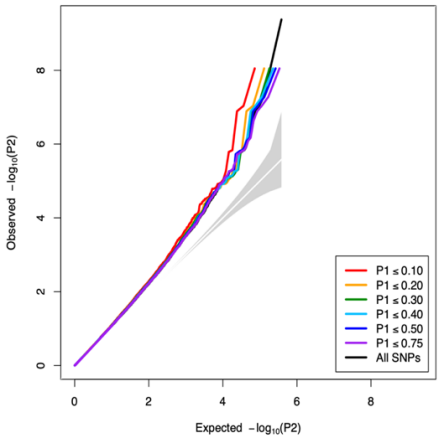
L) BD conditioned on precentral



M) BD conditioned precuneus



N) BD conditioned on rostral anterior cingulate



O) BD conditioned on supramarginal

Figure 3.3 A-O Stratified QQ-plots of BD conditioned onto regional cortical thickness GWAS
Stratified QQ plots of observed versus expected -log10 p- values of BD conditioned on regional cortical thickness of A) caudal middle frontal B) cuneus C) entorhinal D) frontal pole E) lateral orbitofrontal F) lateral occipital G) lingual H) Parahippocampal I) pars orbitalis J) pars triangularis K) post central L) precentral M) precuneus N) rostral anterior cingulate and O) supramarginal for p≤1, p≤0.75, p≤0.50, p≤0.40, p≤0.30,p≤0.20 and p≤0.10, respectively. The shaded grey region indicates the null hypothesis of no pleiotropic enrichment.

Table 3.5 Biological processes implicated by the significant cFDR variants

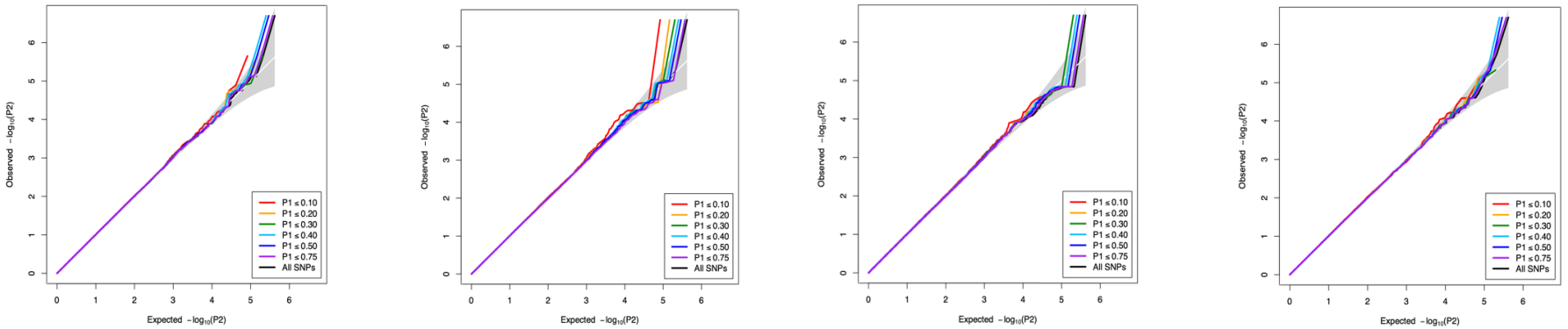
Biological Process	Number of Genes in Process	Number of Overlapping Genes	P_{adj}
Vesicle mediated transport in synapse	202	7	$3.22X10^{-4}$
Synaptic vesicle cycle	190	6	$2.72X10^{-3}$
Regulation of neurotransmitter levels	332	7	$3.07X10^{-3}$
Neurotransmitter transport	267	6	$7.81X10^{-3}$
Membrane depolarization during cardiac muscle cell action potential	23	3	$7.81X10^{-3}$
Synaptic vesicle localization	163	5	$7.81X10^{-3}$
Signal release from synapse	170	5	$7.81X10^{-3}$
Protein localization to synapse	80	4	$7.81X10^{-3}$
Secretion	1628	12	$7.81X10^{-3}$
Ion transport	1663	12	$7.81X10^{-3}$
Exocytosis	897	9	$7.81X10^{-3}$
Positive regulation of catalytic activity	1397	11	$7.81X10^{-3}$
Establishment of organelle localization	491	7	$7.81X10^{-3}$
Organelle localization	685	8	$7.81X10^{-3}$
Cation transport	1145	10	$7.81X10^{-3}$
Regulation of cation transmembrane transport	328	6	$7.81X10^{-3}$
Positive regulation of molecular function	1740	12	$9.66X10^{-3}$
Membrane depolarization during action potential	37	3	$1.30X10^{-2}$
Synaptic vesicle exocytosis	120	4	$1.84X10^{-2}$
Inorganic ion transmembrane transport	821	8	$2.15X10^{-2}$
Cation transmembrane transport	834	8	$2.29X10^{-2}$
Regulation of membrane potential	430	6	$2.56X10^{-2}$
Regulation of transporter activity	270	5	$2.70X10^{-2}$
Ion transmembrane transport	1125	9	$2.70X10^{-2}$
Metal ion transport	880	8	$2.70X10^{-2}$
Positive regulation of adenylate cyclase activity	9	2	$2.70X10^{-2}$
Localization within membrane	146	4	$2.77X10^{-2}$
Signal release	460	6	$2.91X10^{-2}$
Macropinocytosis	10	2	$2.95X10^{-2}$
Regulation of ion transmembrane transport	467	6	$2.95X10^{-2}$
Calcium ion regulated exocytosis	154	4	$2.97X10^{-2}$
Vesicle localization	303	5	$3.34X10^{-2}$
Regulation of potassium ion transmembrane transporter activity	62	3	$3.35X10^{-2}$
Protein localization to cell periphery	311	5	$3.45X10^{-2}$
Synaptic signaling	712	7	$3.45X10^{-2}$
Calcium ion transmembrane transport	313	5	$3.45X10^{-2}$
Immune system development	968	8	$3.54X10^{-2}$
Positive regulation of synaptic transmission	170	4	$3.54X10^{-2}$
Regulation of vesicle mediated transport	517	6	$3.93X10^{-2}$
Cardiac muscle cell action potential	71	3	$4.14X10^{-2}$
Transmembrane transport	1574	10	$4.14X10^{-2}$
Regulation of synaptic plasticity	182	4	$4.15X10^{-2}$
Calcium ion import	77	3	$4.89X10^{-2}$
Regulation of transmembrane transport	553	6	5.00X10-2

Padj, Benjamini-Hochberg (FDR); Number of overlapping genes refers to the number of genes present in the biological process and in the gene list from the cFDR analysis

Table 3.6 Significant variants after conditioning BPD on each regional cortical thickness GWAS

Cortical Region	SNP	A1	A2	BETA IN BPD GWAS (SE)	p-value in BPDGWAS	Gene	Annotation	$P_{FDR\text{-}NoCond}$	$P_{FDR\text{-}Cond}$
Lateral orbitofrontal	rs61975652	A	G	-0.42 (0.11)	5.84E-05	*SLC24A4*	intronic	$9.20X10^{-1}$	0.01
	rs184059380	A	G	-1.79 (0.07)	5.75E-04	*ADAM18*	intronic	$9.20X10^{-1}$	0.04
Lingual	rs113507694	A	G	-1.04 (0.20)	2.01E-07	*DPPA3*	intronic	$8.44X10^{-2}$	0.02
Precentral	rs113507694	A	G	-1.04 (0.20)	2.01E-07	*DPPA3*	intronic	$8.44X10^{-2}$	0.04
Supramarginal	rs113507694	A	G	-1.04 (0.20)	2.01E-07	*DPPA3*	intronic	$8.40X10^{-2}$	0.05

CHR, chromosome; BP, base-pair position; A1, reference allele; A2, alternate allele; SE, standard error; BPD, Borderline Personality Disorder; FDR, false-discovery rate



A) BPD conditioned on lateral orbitofrontal **B) BPD conditioned on lingual** **C) BPD conditioned on precentral** **D) BPD conditioned on supramarginal**

Figure 3.4 Stratified QQ-plots of BPD conditioned on each GWAS of regional cortical thickness

Stratified QQ plots of observed versus expected -log10 p- values of BPD conditioned on regional cortical thickness of A) lateral orbitofrontal B) lingual C) precentral D) supramarginal for p≤1, p≤0.75, p≤0.50, p≤0.40, p≤0.30,p≤0.20 and p≤0.10, respectively. The shaded grey region indicates the null hypothesis of no pleiotropic enrichment.

3.5 Genetic Correlation

Genetic correlation was used to determine if BD and BPD have a shared genetic aetiology with thickness of any of the cortical regions of interest. There were no significant findings after correction for multiple testing (Bonferroni; p<0.05/4 test*2 traits*17 brain regions < 3.67x10-4) (Table 3.7). Significant genetic correlation between BPD and BD was reported in the original BPD GWAS paper (r_g= 0.28, p= 2.99 x 10^{-3}) (Witt et al., 2017).

Table 3.7 Genetic correlation results for BD, BPD and each cortical GWAS

Regional Cortical Thickness GWAS	Bipolar Disorder		Borderline Personality Disorder	
	r_g (SE)	p-value	r_g (SE)	p-value
Banks of the superior temporal sulcus	0.15 (0.11)	0.19	-0.15 (0.28)	0.6
Caudal middle frontal	0.15 (0.06)	0.01	0.22 (0.15)	0.13
Cuneus	0.15 (0.08)	0.06	0.24 (0.21)	0.26
Entorhinal	-0.08 (0.08)	0.3	-0.16 (0.22)	0.46
Frontal pole	0.04 (0.17)	0.82	0.29 (0.46)	0.54
Lateral occipital	-0.01 (0.07)	0.88	-0.07 (0.16)	0.68
Lateral orbitofrontal	$-4.4x10^{-5}$ (0.09)	0.99	0.35 (0.23)	0.14
Lingual	0.09 (0.07)	0.2	0.12 (0.18)	0.5
Parahippocampal	0.04 (0.06)	0.52	$4x10^{-3}$ (0.15)	0.98
Pars opercularis	0.16 (0.09)	0.07	0.03 (0.19)	0.86
Pars orbitalis	0.17 (0.28)	0.55	0.60 (0.74)	0.42
Pars triangularis	0.05 (0.08)	0.52	0.22 (0.19)	0.25
Post central	0.04 (0.06)	0.56	-0.07 (0.16)	0.67
Precentral	0.02 (0.07)	0.73	0.01 (0.16)	0.93
Precuneus	$4x10^{-3}$ (0.07)	0.95	-0.09 (0.18)	0.61
Rostral anterior cingulate	-0.018 (0.09)	0.84	0.15 (0.23)	0.51
Supramarginal	-0.02 (0.06)	0.79	-0.03 (0.15)	0.86

rg, regression coefficient; SE, standard error

3.6 Mendelian Randomization

MR was used to examine the causal relationship between BD, BPD and altered brain regions. Since this method is not designed to examine pleiotropy, all brain regions (cortical and subcortical) from each GWAS were used in this analysis. A total of 101 tests for MR were performed: 79 tests with BD as the exposure and each brain region as the outcome, 11 with BD as the outcome and each subcortical brain region and total thickness and surface area as the exposure and 11 tests with BPD as the outcome and each subcortical brain region and total thickness and surface area as the exposures. For each test IVW and MR-egger were calculated thus, Bonferroni correction for multiple testing was done as follows: $p< 0.05/101$ causal relationships* 2 MR tests$< 2.47x10^{-4}$).

3.6.1 Bipolar disorder and altered brain regions

Genetic variants that were significantly associated with BD (Appendix D, Table 1) were used as instruments to examine the causal relationship between BD and altered regional cortical surface area and thickness, regional subcortical brain volume and total ICV. After correction for multiple testing ($p<2.47x10^{-4}$), no findings remained significant (Table 3.8). To assess if altered brain regions affect BD, genetic variants that achieved statistical significance in global cortical surface area and thickness and each subcortical brain region GWAS (Appendix D, Table 1) were used as instrumental variables in the respective analyses. Although there was suggestive evidence to support this relationship, no findings remained significant after correction for multiple testing.

3.6.2 Borderline Personality Disorder and Altered Brain Regions

Since no variants were significantly associated with BPD in the original GWAS, the causal effects of altered brain regions on BPD was examined. Variants that were significantly associated with global surface area and thickness, regional subcortical volume and total ICV were used as instrumental variables, in each respective analysis. No findings remained significant after correction for multiple testing (Table 3.8).

Table 3.8 Suggestive findings from the MR analyses

Exposure	Outcome	Number of SNPs	Inverse Weighted Variance			Mr Egger		
			Estimate	SE	p-value	Estimate	SE	p-value
BD	Amygdala	14	0.07	0.04	$4.7x10^{-2}$	0.02	0.25	0.94
BD	Entorhinal Surface Area	14	3.49	1.62	0.03	11.51	10.33	0.29
BD	Posterior Cingulate Surface Area	14	-6.82	2.93	0.02	-22.34	18.73	0.26
BD	Rostral Anterior Cingulate Surface Area	14	5.52	2.47	0.03	2.74	15.82	0.87
BD	Inferior Parietal Thickness	14	0.01	2.32x10-2	0.01	0.01	0.01	0.60
Amygdala	BD	3	-0.33	0.13	0.01	0.58	0.70	0.56
Putamen	BD	10	0.16	0.06	0.01	0.26	0.32	0.44
Global Thickness	BD	5	26.43	6.80	0.03	26.43	6.80	0.03

'Number of SNPs' refers to the number of genome-wide significant SNPs in the original GWAS that are used as instrumental variables in the MR analyses; Suggestive finding $p<0.05$. The MR-Egger regression intercept was considered to verify the presence of pleiotropic effects of the instrumental variables on the outcome (horizontal pleiotropy), a potential violation of MR. Inverse-variance-weighted (IVW) approach was used to assess the overall estimate of the causal effect. A full table of all MR results is available in Appendix D, Table 2.

4 Discussion

The aim of this study was to determine if there is genetic overlap between BD, BPD and altered brain regions. Results from this study suggest a shared genetic aetiology between BD and BPD shown by significant pleiotropy ($p=5x10^{-4}$) and concordance ($p=1x10^{-4}$) between the two disorders. There was also evidence to suggest genetic overlap between BD and the thickness of several cortical regions, based on significant findings of pleiotropy (lateral occipital, $p=2.25x10^{-5}$; pars triangularis, $p=1.1x10^{-4}$; post central, $p=7.9x10^{-6}$; rostral anterior cingulate, $p=2.18x10^{-4}$; supramarginal gyris, $p=1.45x10^{-7}$). Significant concordance was observed for BPD and thickness of the lateral occipital region ($p=3x10^{-4}$), suggesting that some genetic overlap exists between these traits. Lastly, this study identified new loci which may contribute to each BD and BPD and may provide novel insight into the genetic architecture of these disorders and brain regions. We did not identify any causal associations between BD, BPD and any of the examined brain regions.

4.1 Bipolar Disorder and Borderline Personality Disorder

This study provides several lines of evidence for a shared genetic aetiology between BD and BPD: i) significant pleiotropy ($p=5x10^{-4}$), ii) significant positive concordance ($p=1x10^{-4}$; OR=1.29) and iii) significant positive genetic correlation between the two disorders ($r_g= 0.28$; $p= 2.99x10^{-3}$). These findings are in line with previous work suggesting a shared genetic basis between BD and BPD (Witt et al., 2014, Witt et al., 2017). Although patients with prior BD diagnoses were excluded in the BPD study, the possibility that the observed genetic overlap could be due to misdiagnosis cannot be excluded (Fornaro et al., 2016).

Individuals with BPD show high comorbidity and considerable overlap in symptomology with BD such as, impulsivity, affective instability, suicidal tendencies and unstable interpersonal relationships (Witt et al., 2014). These shared symptoms may contribute to some of the comorbidity seen between the two disorders (Zimmerman and Morgan, 2013). It is more likely, however, that these results are indicative of genetic overlap between the two disorders which has been extensively documented and may be partially responsible for some of the shared symptoms (Witt et al., 2014, Fornaro et al., 2016). Shared loci that exhibit effects on both disorders may elucidate targets for the development of broad spectrum treatments with a wider range of efficacy (Lee et al., 2019).

4.2 Bipolar Disorder and Altered Brain Regions

There was evidence to suggest pleiotropy between BD and the thickness of several cortical brain regions and two gyri, namely the lateral occipital region, pars triangularis region, rostral anterior cingulate and the post central and supramarginal gyri. This indicates that variants that influence BD may also influence thickness in several cortical regions. This is in line with previous work that found individuals with BD to have significant cortical thinning in these regions (Lyoo et al., 2006, Hatton et al., 2013, Maller et al., 2014, Lan et al., 2014). Decreased density of cingulate neurons has been reported in post-mortem studies of BD as well as reduced gray-matter volume in the anterior cingulate in drug naïve BD subjects (Lyoo et al., 2006). Cortical thinning in the cingulate and frontal brain regions may underlie the abnormal autonomic response to emotional stimuli seen in individuals diagnosed with BD (Hibar et al., 2018). These brain cortices are implicated in emotional processing and emotional experience, thus may be related to the mood lability characteristic of BD (Hanford et al., 2016). Significant pleiotropy between BD and these cortical regions indicates shared genetic variants that contribute to both traits. However, the lack of significant findings that would provide insight into the directional effects of these variants (concordance findings noted in Table 3.3 and genetic correlation, in Table 3.7) could indicate that there are local genetic correlations between BD and altered cortical thickness that, when combined, result in poor global genetic correlations (Shi et al., 2017).

Examinations of structural brain abnormalities associated with BD may increase our understanding of the neurobiological progression of the illness. BD patients show alterations in cortical thickness, surface area and global gray matter volume. Cortical thickness has been shown to be highly heritable and influenced by distinct sets of genes (Kremen et al., 2010, Blokland et al., 2012, Hibar et al., 2018). Thus, identifying the genomic regions associated with both cortical thickness and BD may provide insight into the functional impairments in cognition, behaviour and symptom domains noted in the disorder (Hibar et al., 2018). When conditioning BD onto each cortical GWAS, 156 genetic variants gained significance (compared to the original BD GWAS). These variants implicated biological processes involved in synapse and neurotransmitter regulation, providing further evidence of the role these pathways may play in the pathogenesis of BD.

The exact cause of the brain abnormalities seen in BD patients remains under debate. There is evidence to suggest two alternative hypotheses: brain abnormalities precede the onset of the disorder or brain abnormalities occur as the disorder progresses (Demjaha et al., 2011). MR was used to examine the causal relationship between BD and altered brain regions, in both directions. We did not detect any significant findings. This could be due to insufficient power to detect causality. Alternatively, this may add evidence to the hypothesis that brain changes occur as the disorder progresses and may be a result of the environment that is created by the manifestation of the disorder i.e. stress-related increases in cortisol, cannabis and alcohol abuse, smoking and antipsychotics, a common treatment for BD. These environmental factors may account for some of these changes in brain structure (Demjaha et al., 2011); indicating that there may be an accumulation of changes in the brain with the progression of the disorder (Hallahan et al., 2011)

4.3 Borderline Personality Disorder and Altered Brain Regions

Structural alterations in several brain regions have consistently been observed in individuals diagnosed with BPD (Austin et al., 2007, Soloff et al., 2008, O'Neill and Frodl, 2012, Soloff et al., 2012, Lischke et al., 2015, Quattrini et al., 2019). This study did not find any evidence to support significant pleiotropy or genetic correlation between cortical thickness and BPD. However, positive concordance was noted between the lateral occipital region and BPD, indicating that genetic variants that contribute to increased risk for BPD may also increase thickness of this region. However, the lateral occipital cortex has been shown to have both reduced activity and volume in patients with established BPD (Visintin et al., 2016). The lateral occipital region is functionally associated with visual perception and individuals with BPD have been shown to take significantly longer to identify visual stimuli when compared to individuals without psychiatric diagnoses (Stevens et al., 2004). Thus, evidence provided here may support the role of shared genetic aetiology influencing BPD onset and thickness of the lateral occipital region.

There was no evidence to suggest a causal relationship between BPD and altered brain regions from the MR analyses conducted in this study. Altered brain regions in BPD may also be due to factors other than the pathology of the disorder itself (Fatimah et al., 2019). For example, high levels of childhood trauma are consistently noted in individuals diagnosed with BPD (Fatimah et al., 2019). Therefore, structural brain changes associated with BPD may be

influenced by the same environmental factors that influence BPD onset but are not causative or a consequence of the disorder itself (Fatimah et al., 2019).

4.4 Limitations and Future Directions

This study represents a step forwards in delineating the genetic relationship between BD, BPD and altered brain regions. However, there are several limitations that deserve emphasis: i) power of the original GWASs used in this study, ii) the inclusion of individuals with psychiatric diagnoses in the brain GWAS iii) the effect of the environment on psychiatric disorder onset and altered brain regions and iv) the inclusion of mainly European individuals. Each of these limitations are discussed further below.

Underpowered studies remain a problem in the genetic research of complex disorders (Yang et al., 2010). The BPD GWAS used here is the largest to date, however, it remains under powered to confidently identify regions significantly associated with BPD (Witt et al., 2017). Thus, it is possible that negative findings for BPD in the current study may be due to insufficient power. Given the well documented differences in BPD manifestation between sexes, stratification by sex could provide novel insight into the aetiology of this disorder (Lieb et al., 2004). Due to insufficient sample size, we were unable to consider this in the current study but this could be done in future, better-powered studies.

Second, the inclusion of individuals with a psychiatric diagnosis in the cortical and subcortical GWAS could, in theory, bias findings. However, diagnostic status was controlled for in the original GWASs (Adams et al., 2016, Hibar et al., 2017, Satizabal et al., 2019, Grasby et al., 2020). The original GWAS analyses were run with and without the individuals with psychiatric diagnoses and a very high correlation was demonstrated (Pearson's $r > 0.99$) (Satizabal et al., 2019). This indicates that the results seen in the brain GWAS is unlikely to be driven by disease status.

Third, the relationship between genetic variants influencing brain volume and psychiatric disorder risk may be influenced by a wide range of confounders. Environmental factors such as stress, medication and body mass index have been shown to have an effect on brain structure and disease risk, independent of genetic aetiology (Navari and Dazzan, 2009). Discovering the pathways by which genetic variants may influence brain structure and convey risk for BD and

BPD may be hindered by these environmental factors, which could obscure genetic relationships. However, identifying genetic overlap between brain structure and psychiatric disorder risk, as we have done here, shows some insight suggesting that our understanding may be further improved if environmental influences are incorporated into future analyses.

Finally, as illustrated in the Figure 3.1, the majority of participants in each GWAS consisted of individuals of European ancestry. This is indicative of a larger study bias where non-European populations remain underrepresented in current GWAS research (Dalvie et al., 2015, Martin et al., 2019). Approximately 79% of published GWAS participants are of European ancestry, despite making up only 16% of the global population (Martin et al., 2019). This bias is statistically unfounded since individuals of non-European ancestry contribute to an increased number of associations relative to studies of similar size done in European populations (Morales et al., 2018). The high genetic diversity seen in genomes of African populations may provide insight into disease causing alleles (Dalvie et al., 2015). Increased representation of non-European ancestral groups will lead to improved global health outcomes and reduce current disparities seen in treatment outcomes. It should thus be a focus and priority for future genetic research.

4.5 Conclusions

In conclusion, the findings here of genetic overlap between BD, BPD and altered brain structure, while novel, are consistent with previous work. The findings from the cFDR analyses, highlighting synapse and neurotransmitter regulation as a key underlying mechanism between BD and altered brain regions is consistent with current understandings of the genetic aetiology underlying this disorder. Further fine-grained delineation of the role of the environment in these relationships and the inclusion of non-European populations are critical next steps, as they may provide insight into risk factors, new areas of treatment and aid in early detection of at risk individuals.

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7 Appendices

Appendix A: Ethical Approval

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

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Observatory 7925
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20 January 2020

HREC REF:029/2020

Dr S Dalvie
Psychiatry & Mental Health
Room 35, H-Floor OPD
GSH

Dear Dr Dalvie

PROJECT TITLE: INVESTIGATION OF THE GENETIC INFLUENCES ON BIPOLAR DISORDER AND SUBCORTICAL BRAIN VOLUMES. (MSC DEGREE - MS MEGAN CAMPBELL)

Thank you for submitting your study to the Faculty Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, subject to all permissions being granted to access the data.

Approval is granted for one year until the 30 January 2021.

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: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Ms Megan Campbell will also be involved in this study.

Please quote the HREC REF in all your correspondence.

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

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.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.

HREC 029/2020sa

Appendix B: Full breakdown of each cohort

GWAS	Study Design			Case Diagnoses			Sex		Ancestry					Sample Breakdown		Total N
	Population Based	Case-Control	Family Based	BD Type I	BD Type II	SAB	Female	Male	African	American	Asian	European	Other	Case	Control	
BD (Stahl et al., 2019)	0	50291	0	14269	3399	977	0	0	0	16499	0	31653	2139	19626	30665	50291
BPD (Witt et al., 2017)	0	2543	0	-	-	-	1782	761	0	0	0	2543	0	998	1545	2543
Subcortical (Satizabal et al., 2019)	35891	5387	389	-	-	-	22057	19610	769	0	341	40557	0	2765	38902	41667
Hippocampal (Hibar et al., 2017)	21755	4418	914	-	-	-	15001	12086	0	0	0	27087	0	2488	24599	27087
ICV (Adams et al., 2016)	21755	4418	914	-	-	-	15001	12086	0	0	0	27087	0	2488	24599	27087
Cortical (Grasby et al., 2020)	13809	9391	1675	-	-	-	19281	18198	0	0	553	34253	2673	4650	32829	37479

BD, Bipolar Disorder; BPD, Borderline Personality Disorder; ICV, Intracranial Volume; SAB, Substance Abuse Disorder; N, Sample Size; 'Case' refers to individuals with a psychiatric diagnosis included in the brain GWAS and those individuals diagnosed with BD or BPD in the respective GWAS. 'Other' in column 'Ancestry' refers to cohorts with ancestry classified as 'Brazilian', 'European and African', 'Mixed', 'Non-European' and 'Singaporean'.

Appendix C: Significant variants after conditioning BD on to cortical GWAS

GWAS	Brain Region	SNP	Chr	BP	A1	A2	Freq	BETA in BD GWAS (SE)	p-value in BD GWAS	Gene	Annotation	$P_{FDR-NoCond}$	$P_{FDR-Cond}$
Cortical Thickness	**Caudal Middle Frontal**	rs79891548	2	165481308	T	C	0.11	0.13 (0.02)	$2.25x10^{-6}$	*AC018742.1*	non'-coding	0.06	0.04
		rs12468729	2	161476919	A	G	0.42	-0.08 (0.02)	$2.93x10^{-6}$	*SLC27A5*	3downstream,non'-coding	0.07	0.05
		rs55698168	5	95644533	T	G	0.04	0.19 (0.04)	$3.30x10^{-6}$	None	Intergenic	0.07	0.05
		rs72694961	1	150175253	T	C	0.05	-0.09 (0.02)	$3.47x10^{-6}$	*AC244033.2*	3downstream,non'-coding	0.07	0.06
		rs4687339	3	192513856	T	C	0.09	-0.13 (0.03)	$7.22x10^{-6}$	*WDR82*	intronic,non'-coding	0.10	0.03
		rs261009	5	169913151	A	G	0.43	-0.06 (0.01)	$2.80x10^{-5}$	*KIAA1109*	non'-coding	0.16	0.04
	Cuneus	rs6073631	20	45080265	T	G	0.16	-0.07 (0.02)	$1.37x10^{-6}$	*SCHLAP1*	non'-coding	0.05	0.04
		rs78476389	4	184055508	T	G	0.05	0.14 (0.03)	$1.52x10^{-6}$	*CADPS*	intronic,5upstream	0.05	0.05
		rs10505139	8	110139444	A	G	0.24	-0.09 (0.02)	$1.73x10^{-6}$	*AL132671.2*	intronic	0.05	0.04
		rs77927505	19	19236558	A	G	0.05	0.13 (0.13)	$1.84x10^{-6}$	None	Intergenic	0.05	0.04
		rs7297582	12	2246640	T	C	0.19	0.07 (0.01)	$1.97x10^{-6}$	None	Intergenic	0.05	0.04
		rs11698868	20	34962143	T	C	0.19	0.08 (0.02)	$2.15x10^{-6}$	*CNTNAP5*	non'-coding	0.05	0.06
		rs79891548	2	165481308	T	C	0.11	0.12 (0.02)	$2.25x10^{-6}$	*AC018742.1*	non'-coding	0.05	0.05
		rs7916271	10	84194464	T	C	0.49	-0.07 (0.02)	$2.30x10^{-6}$	*ANK3*	intronic,non'-coding	0.05	0.05
		rs12468729	2	161476919	A	G	0.42	-0.08 (0.02)	$2.93x10^{-6}$	*SLC27A5*	3downstream,non'-coding	0.05	0.05
		rs7554367	1	150047605	A	G	0.23	0.09 (0.02)	$2.94x10^{-6}$	None	Intergenic	0.05	0.04
		rs6682989	1	50360504	T	C	0.15	0.08 (0.03)	$2.97x10^{-6}$	None	Intergenic	0.05	0.04
		rs10182434	2	193486957	A	G	0.49	0.08 (0.01)	$3.33x10^{-6}$	*AC007100.1*	non'-coding	0.05	0.04
		rs1054442	12	48995537	A	C	0.48	-0.07 (0.01)	$3.45x10^{-6}$	None	Intergenic	0.05	0.05
		rs13014440	2	114289509	A	G	0.43	-0.07 (0.02)	$3.49x10^{-6}$	*NCAN*	non'-coding	0.05	0.04
		rs1985694	1	60607612	A	C	0.41	0.06 (0.01)	$3.56x10^{-6}$	*LINC01748*	non'-coding	0.05	0.04

	rs7644022	3	10468934	A	C	0.39	0.06 (0.01)	$3.85x10^{-6}$	*BFSP1*	non'-coding	0.06	0.04
	rs11794152	9	23345349	A	G	0.33	-0.06 (0.01)	$4.59x10^{-6}$	*NHSL1*	non'-coding	0.06	0.04
	rs6017496	20	45140661	A	G	0.34	0.06 (0.01)	$4.73x10^{-6}$	None	Intergenic	0.06	0.04
	rs77723439	6	138573415	T	C	0.11	0.11 (0.03)	$4.92x10^{-6}$	*FAM172A*	intronic	0.06	0.04
	rs112782591	3	36912846	A	G	0.01	-0.18 (0.04)	$4.97x10^{-6}$	*AL049767.1*	3downstream,non'-coding	0.06	0.04
	rs4652745	1	182746703	A	G	0.17	-0.09 (0.02)	$5.01x10^{-6}$	None	Intergenic	0.06	0.04
	rs155023	5	169915513	A	G	0.41	-0.07 (0.02)	$5.39x10^{-6}$	*KIAA1109*	intronic	0.06	0.04
	rs1483245	2	185182339	A	G	0.46	0.06 (0.01)	$5.84x10^{-6}$	None	Intergenic	0.06	0.05
	rs55882033	3	36804905	A	C	0.12	0.07 (0.02)	$6.12x10^{-6}$	None	Intergenic	0.07	0.03
	rs68118663	6	50847654	T	C	0.16	0.10 (0.02)	$6.31x10^{-6}$	*FSTL5*	non'-coding	0.07	0.05
	rs9906807	17	44225937	T	C	0.43	0.07 (0.02)	$7.96x10^{-6}$	*AC020763.3*	non'-coding	0.08	0.03
	rs72673100	14	21205210	A	C	0.34	-0.07 (0.02)	$8.21x10^{-6}$	*ANKS1B*	non'-coding	0.08	0.03
	rs11981847	7	44942099	T	G	0.46	0.07 (0.03)	$8.68x10^{-6}$	*DOCK2*	non'-coding	0.08	0.04
Entorhinal	rs976498	16	64687040	T	C	0.17	0.10 (0.02)	$6.83x10^{-7}$	None	Intergenic	0.06	0.04
	rs12805133	11	66715794	A	G	0.44	-0.07 (0.01)	$7.93x10^{-7}$	*MARK2*	intronic	0.06	0.01
	rs6979567	7	141000438	A	G	0.24	0.08 (0.02)	$9.86x10^{-7}$	*DOCK2*	intronic,non'-coding	0.06	0.04
	rs11652139	17	39992780	A	G	0.39	0.07 (0.01)	$1.34x10^{-6}$	*VPS4A*	non'-coding	0.07	0.03
	rs35662827	2	193608889	A	G	0.46	-0.07 (0.01)	$1.60x10^{-6}$	None	Intergenic	0.08	0.02
	rs1819204	13	113229001	A	G	0.44	0.08 (0.025)	$3.10x10^{-6}$	*ANKS1B*	non'-coding	0.09	0.04
	rs7975384	12	99074034	T	C	0.31	0.06 (0.01)	$4.65x10^{-6}$	*CACNA1C*	intronic	0.11	0.05
Frontal Pole	rs12474837	2	180877628	A	C	0.10	-0.14 (0.03)	$2.72x10^{-6}$	*AC018742.1*	non'-coding	0.06	0.05
	rs12468729	2	161476919	A	G	0.42	-0.08 (0.02)	$2.93x10^{-6}$	*SLC27A5*	3downstream,non'-coding	0.06	0.06
	rs1641470	2	65559472	A	G	0.04	0.19 (0.04)	$3.67x10^{-6}$	*DNM2*	intronic	0.06	0.06
	rs17680262	12	109916731	T	C	0.04	0.11 (0.03)	$4.23x10^{-6}$	*DDN*	3utr	0.07	0.05
	rs34568676	4	37245637	A	G	0.25	0.08 (0.02)	$8.24x10^{-6}$	*PBRM1*	intronic	0.09	0.04

	rs11075779	16	70689411	T	C	0.38	0.06 (0.01)	$2.37x10^{-5}$	*GRIN2A*	non'-coding	0.15	0.03
Lingual	rs12468729	2	161476919	A	G	0.42	-0.08 (0.02)	$2.93x10^{-6}$	*SLC27A5*	3downstream,non'-coding	0.06	0.05
	rs55698168	5	95644533	T	G	0.04	0.19 (0.04)	$3.30x10^{-6}$	None	Intergenic	0.06	0.05
	rs7644022	3	10468934	A	C	0.39	0.06 (0.01)	$3.85x10^{-6}$	*BFSP1*	non'-coding	0.07	0.02
	rs7515509	1	77483438	A	G	0.25	-0.08 (0.01)	$4.82x10^{-6}$	*ROR1'-AS1*	non'-coding	0.07	0.05
	rs11134596	5	169880071	T	C	0.31	0.06 (0.01)	$6.40x10^{-6}$	*MAPK10*	non'-coding	0.09	0.02
	rs4665698	2	21311231	T	C	0.45	-0.06 (0.01)	$7.68x10^{-6}$	*HLF*	non'-coding	0.10	0.04
	rs36134929	6	50917895	T	C	0.47	-0.07 (0.02)	$7.89x10^{-6}$	*ADCY2*	intronic,non'-coding	0.10	0.04
	rs261008	5	169912032	T	C	0.36	0.07 (0.02)	$8.13x10^{-6}$	*KIAA1109*	non'-coding	0.10	0.04
	rs13159500	5	81501617	T	C	0.42	0.07 (0.03)	$9.10x10^{-6}$	None	Intergenic	0.11	0.04
	rs7043042	9	114542391	T	C	0.10	-0.09 (0.02)	$1.15x10^{-5}$	*THSD7A*	intronic	0.12	0.05
Lateral Orbitofrontal	rs2721921	8	132499596	A	G	0.30	-0.07 (0.02)	$2.96x10^{-6}$	None	Intergenic	0.05	0.05
	rs3755799	3	52775177	A	G	0.35	-0.07 (0.02)	$3.08x10^{-6}$	None	Intergenic	0.05	0.05
	rs55698168	5	95644533	T	G	0.04	0.19 (0.04)	$3.30x10^{-6}$	None	Intergenic	0.05	0.05
	rs6791926	3	192501099	T	C	0.10	0.12 (0.03)	$3.39x10^{-6}$	*AC097637.1*	intronic	0.05	0.05
	rs77087420	4	122201701	A	G	0.03	-0.14 (0.03)	$4.25x10^{-6}$	*TMEM110'-MUSTN1*	intronic	0.07	0.04
Lateral Occipital	rs78808294	7	129709674	T	C	0.01	0.18 (0.04)	$4.14x10^{-6}$	*DOCK2*	intronic,non'-coding	0.05	0.03
	rs7496809	15	38695179	A	G	0.31	0.07 (0.01)	$4.42x10^{-6}$	*SLC8A3*	intronic	0.05	0.04
	rs11097328	4	91770488	T	C	0.43	-0.07 (0.02)	$4.67x10^{-6}$	*AC006254.1*	intronic	0.05	0.04
	rs326341	3	108092295	A	G	0.42	-0.06 (0.01)	$4.72x10^{-6}$	*TRANK1*	intronic	0.05	0.03
	rs17537498	2	60672327	T	C	0.05	-0.10 (0.02)	$4.73x10^{-6}$	*SLC44A2*	intronic,non'-coding	0.05	0.03
	rs648514	3	52433247	A	G	0.43	0.06 (0.01)	$4.97x10^{-6}$	None	Intergenic	0.05	0.03
	rs6119569	20	35084568	A	G	None	0.08 (0.03)	$5.28x10^{-6}$	*SLC4A10*	non'-coding	0.05	0.04
	rs138230813	18	44474667	T	C	0.00	-0.35 (0.08)	$5.70x10^{-6}$	*ALOX12P1*	non'-coding	0.06	0.04

	rs9906807	17	44225937	T	C	0.43	0.07 (0.02)	$7.96x10^{-6}$	*AC020763.3*	non'-coding	0.07	0.05
	rs3774605	3	53796740	A	G	0.26	-0.06 (0.02)	$8.13x10^{-6}$	*TPTEP2'-CSNK1E*	intronic	0.07	0.04
	rs12677998	8	38391683	A	G	0.08	-0.11 (0.03)	$9.54x10^{-6}$	*RIMS1*	intronic,non'-coding	0.08	0.04
	rs75378506	18	68357299	A	C	0.13	0.17 (0.04)	$7.27x10^{-5}$	*ORMDL3*	5upstream,3downstream,intronic	0.22	0.05
Parahippocampal	rs10106152	8	98086703	T	C	0.25	-0.09 (0.02)	$1.46x10^{-6}$	*AL365214.2*	non'-coding	0.06	0.04
	rs7191614	16	69348292	A	G	0.28	-0.07 (0.02)	$1.68x10^{-6}$	*AC048382.5*	non'-coding	0.06	0.02
	rs10994415	10	60562276	T	C	0.15	-0.12 (0.02)	$1.86x10^{-6}$	*ANK3*	intronic	0.06	0.02
	rs4981166	14	32905336	A	G	0.22	-0.13 (0.03)	$2.12x10^{-6}$	None	Intergenic	0.06	0.02
	rs7916271	10	84194464	T	C	0.49	-0.07 (0.02)	$2.30x10^{-6}$	*ANK3*	intronic,non'-coding	0.06	0.04
	rs8079998	17	55308138	A	G	0.38	-0.08 (0.01)	$2.35x10^{-6}$	*ABHD15'-AS1*	non'-coding	0.06	0.02
	rs12468729	2	161476919	A	G	0.42	-0.08 (0.02)	$2.93x10^{-6}$	*SLC27A5*	3downstream,non'-coding	0.06	0.05
	rs6682989	1	50360504	T	C	0.15	0.08 (0.03)	$2.97x10^{-6}$	None	Intergenic	0.06	0.05
	rs61156785	8	144008019	T	C	0.24	0.07 (0.02)	$3.11x10^{-6}$	*NHSL1*	non'-coding	0.06	0.03
	rs55698168	5	95644533	T	G	0.04	0.19 (0.04)	$3.30x10^{-6}$	None	Intergenic	0.06	0.04
	rs151116230	5	15104551	A	G	0.02	-0.32 (0.07)	$3.38x10^{-6}$	*AC117462.1*	non'-coding	0.06	0.04
	rs2857482	6	50822929	T	C	0.11	0.10 (0.03)	$3.60x10^{-6}$	*FSTL5*	intronic	0.07	0.02
	rs11097326	4	91767526	A	G	0.43	0.07 (0.02)	$4.14x10^{-6}$	*ITIH4*	5upstream,non'-coding	0.07	0.05
	rs12423277	12	2205153	A	C	0.42	-0.07 (0.01)	$4.56x10^{-6}$	*TENM4*	non'-coding	0.07	0.03
	rs484201	11	64023459	T	C	0.39	0.08 (0.02)	$5.12x10^{-6}$	*TMEM258*	non'-coding	0.07	0.03
	rs11764361	7	105402782	A	G	0.39	0.07 (0.02)	$5.23x10^{-6}$	*DOCK2*	non'-coding	0.07	0.03
	rs840788	2	65548959	A	G	0.04	0.18 (0.04)	$5.34x10^{-6}$	None	Intergenic	0.07	0.04
	rs553046	7	141076601	T	C	0.34	-0.08 (0.02)	$5.79x10^{-6}$	*ADAMTS2*	non'-coding	0.07	0.03

	rs1717671	11	66171618	T	C	0.33	0.09 (0.03)	$7.76x10^{-6}$	*TMEM258*	non'-coding	0.10	0.04
	rs6721691	2	28302592	T	C	0.27	-0.09 (0.02)	$5.57x10^{-5}$	None	Intergenic	0.21	0.04
	rs596861	18	76469671	A	G	0.22	0.08 (0.02)	$7.07x10^{-5}$	*GSDMA*	coding	0.23	0.04
	rs3796186	3	36834663	T	C	0.21	-0.06 (0.03)	$1.79x10^{-4}$	*STK4*	intronic	0.30	0.03
Pars Orbitalis Pars Triangularis	rs113779084	7	11832161	A	G	0.20	0.07 (0.02)	$2.45x10^{-6}$	*LINC01202*	non'-coding	0.06	0.03
	rs34476536	5	7543925	A	G	0.11	-0.09 (0.02)	$1.35x10^{-6}$	*CADPS*	intronic	0.05	0.06
	rs78476389	4	184055508	T	G	0.05	0.14 (0.03)	$1.52x10^{-6}$	*CADPS*	intronic,5upstream	0.05	0.06
	rs117697841	17	44130179	A	G	0.04	0.12 (0.03)	$1.59x10^{-6}$	*TERF2*	non'-coding	0.05	0.05
	rs6788153	3	192499942	T	C	0.10	0.13 (0.03)	$2.13x10^{-6}$	*TLR9*	intronic	0.06	0.03
	rs352139	3	52224356	T	C	0.49	0.08 (0.01)	$2.26x10^{-6}$	None	Intergenic	0.06	0.04
	rs45510500	4	122258745	T	C	0.03	0.14 (0.03)	$4.82x10^{-6}$	*TMEM110'-MUSTN1*	intronic	0.08	0.04
	rs4652745	1	182746703	A	G	0.17	-0.09 (0.02)	$5.01x10^{-6}$	None	Intergenic	0.08	0.04
	rs73091785	2	237663923	T	C	0.29	0.08 (0.02)	$1.19x10^{-5}$	*TMEM131*	non'-coding	0.12	0.04
	rs116495417	3	107848869	T	C	0.02	0.15 (0.04)	$1.58x10^{-5}$	None	Intergenic	0.13	0.04
	rs1424000	16	64787448	T	C	0.26	-0.07 (0.02)	$1.63x10^{-5}$	*AC243562.2*	non'-coding	0.13	0
	rs74652956	2	197889523	T	C	0.19	-0.08 (0.02)	$2.17x10^{-5}$	*AC007389.1*	non'-coding	0.13	0.04
	rs75876041	2	165418820	T	C	0.01	0.16 (0.04)	$2.70x10^{-5}$	*AC018742.1*	non'-coding	0.14	0.04
	rs111473203	7	131169861	T	C	0.04	0.11 (0.03)	$5.71x10^{-5}$	*INSYN2B*	intronic,non'-coding	0.21	0.04
Precentral	rs12754946	1	77524238	T	C	0.21	0.07 (0.01)	$7.39x10^{-7}$	*AK5*	non'-coding	0.06	0.05
	rs114534140	4	161495241	A	G	0.00	-0.43 (0.09)	$1.05x10^{-6}$	*CACNA1D*	3downstream,non'-coding,3utr	0.07	0.03
	rs11652139	17	39992780	A	G	0.39	0.07 (0.01)	$1.34x10^{-6}$	*VPS4A*	non'-coding	0.07	0.01
	rs734784	20	45094986	T	C	0.41	0.08 (0.01)	$1.76x10^{-6}$	*SCHLAP1*	non'-coding	0.08	0.03
	rs185308	5	94787403	T	C	0.45	0.07 (0.01)	$2.11x10^{-6}$	*AC109779.1*	non'-coding	0.08	0
	rs12411130	1	78036836	A	C	0.16	-0.08 (0.01)	$5.34x10^{-6}$	*GIPC2*	non'-coding	0.09	0.05
	rs2797617	1	94964544	T	C	0.42	-0.07 (0.02)	$5.81x10^{-6}$	None	Intergenic	0.09	0.01

	rs11134596	5	169880071	T	C	0.31	0.06 (0.01)	$6.40x10^{-6}$	*MAPK10*	non'-coding	0.09	0.01
	rs55943631	16	9842924	T	C	0.26	0.07 (0.03)	$6.46x10^{-6}$	*SNAP23*	intronic	0.09	0.01
	rs150970	15	84526150	A	G	0.15	-0.09 (0.03)	$6.56x10^{-6}$	None	Intergenic	0.09	0.01
	rs9607340	22	21868030	T	G	0.44	0.07 (0.01)	$7.13x10^{-6}$	*SPATS2L*	intronic,non'-coding	0.09	0.03
	rs11646834	16	70685073	T	C	0.35	-0.06 (0.01)	$1.09x10^{-5}$	*GRIN2A*	non'-coding	0.10	0
	rs71474496	15	42625943	A	G	0.11	-0.09 (0.02)	$1.23x10^{-5}$	*BCL11B*	intronic	0.11	0.01
	rs17073012	6	111858435	T	G	0.21	-0.08 (0.02)	$1.91x10^{-5}$	*SSBP2*	non'-coding	0.14	0.02
	rs77817202	2	97918271	T	C	0.02	-0.11 (0.03)	$4.94x10^{-5}$	*NFIX*	intronic	0.20	0.05
	rs11630879	15	78391709	A	G	0.45	0.05 (0.01)	$1.48x10^{-3}$	*BCL11B*	intronic	0.48	0.02
Post Central	rs12468729	2	161476919	A	G	0.42	-0.08 (0.02)	$2.93x10^{-6}$	*SLC27A5*	3downstream,non'-coding	0.07	0.04
Precuneus	rs12468729	2	161476919	A	G	0.42	-0.08 (0.02)	$2.93x10^{-6}$	*SLC27A5*	3downstream,non'-coding	0.05	0.04
	rs61156785	8	144008019	T	C	0.24	0.07 (0.02)	$3.11x10^{-6}$	*NHSL1*	non'-coding	0.05	0.04
	rs13011184	2	124331691	A	G	0.00	-0.26 (0.06)	$3.11x10^{-6}$	*SEC1P*	non'-coding	0.05	0.04
	rs55698168	5	95644533	T	G	0.04	0.19 (0.04)	$3.30x10^{-6}$	None	Intergenic	0.05	0.05
	rs7768747	6	50964049	A	G	0.14	0.10 (0.03)	$3.31x10^{-6}$	*ADCY2*	non'-coding	0.05	0.05
	rs4656250	1	159983469	A	G	0.15	-0.10 (0.01)	$3.80x10^{-6}$	*KIRREL1*	3utr,3downstream	0.06	0.05
	rs72673100	14	21205210	A	C	0.34	-0.07 (0.02)	$8.21x10^{-6}$	*ANKS1B*	non'-coding	0.08	0.01
Rostral Anterior Cingulate	rs114534140	4	161495241	A	G	0.00	-0.43 (0.09)	$1.05x10^{-6}$	*CACNA1D*	3downstream,non'-coding,3utr	0.06	0.03
	rs78286375	11	79364161	A	G	0.10	0.09 (0.03)	$1.12x10^{-6}$	*PACS1*	non'-coding	0.06	0.03
	rs59225836	1	51020240	A	C	0.06	0.12 (0.036)	$1.20x10^{-6}$	None	Intergenic	0.06	0.03
	rs10058613	5	138358306	T	C	0.24	-0.09 (0.03)	$1.38x10^{-6}$	*AC093607.1*	non'-coding	0.06	0.05
	rs11930030	4	122595930	A	G	0.18	0.07 (0.02)	$1.63x10^{-6}$	*SFMBT1*	non'-coding	0.06	0.03
	rs10505139	8	110139444	A	G	0.24	-0.09 (0.02)	$1.73x10^{-6}$	*AL132671.2*	intronic	0.06	0.04
	rs734784	20	45094986	T	C	0.41	0.08 (0.01)	$1.76x10^{-6}$	*SCHLAP1*	non'-coding	0.06	0.03

	rs59250950	10	110185644	A	C	0.09	0.11 (0.01)	$2.52x10^{-6}$	None	Intergenic	0.06	0.04
	rs7126075	11	66173092	T	G	0.20	0.10 (0.02)	$2.79x10^{-6}$	*FADS2*	intronic	0.07	0
	rs55698168	5	95644533	T	G	0.04	0.19 (0.04)	$3.30x10^{-6}$	None	Intergenic	0.07	0.03
	rs155022	5	169914272	A	G	0.43	-0.07 (0.02)	$3.66x10^{-6}$	*KIAA1109*	coding	0.07	0.04
	rs76194173	14	57648367	T	C	0.22	0.08 (0.02)	$4.80x10^{-6}$	*CUL4A*	intronic,3downstream,non'-coding	0.09	0.03
	rs11764361	7	105402782	A	G	0.39	0.07 (0.02)	$5.23x10^{-6}$	*DOCK2*	non'-coding	0.09	0.03
	rs2344714	6	166597404	T	C	0.17	-0.07 (0.01)	$5.39x10^{-6}$	*MCTP1*	intronic	0.09	0.02
	rs62202890	20	14576635	A	C	0.12	0.07 (0.03)	$6.18x10^{-6}$	None	Intergenic	0.09	0
	rs6475736	9	23349114	T	C	0.36	-0.07 (0.01)	$6.20x10^{-6}$	*SYNE1*	non'-coding	0.09	0.04
	rs79170240	2	97812346	T	C	0.03	0.10 (0.03)	$6.50x10^{-5}$	*NFIX*	intronic	0.20	0.01
	rs77616118	9	78083262	T	C	0.01	-0.15 (0.04)	$1.45x10^{-4}$	*MAD1L1*	intronic	0.25	0.05
	rs4719531	7	840861	T	C	0.22	0.06 (0.02)	$2.55x10^{-4}$	None	Intergenic	0.28	0.02
Supramarginal	rs865010	3	62593921	T	C	0.48	-0.06 (0.02)	$2.11x10^{-4}$	*NUP50'-DT*	non'-coding	0.29	0.03

Appendix D

Appendix D Table 1: Significant variants from each GWAS, used as instrumental variables in the MR analyses

GWAS	SNP	A1	A2	BETA (SE)	p-value
BD Stahl et al., (2018)	rs2302417	A	T	-0.08 (0.01)	$1.7x10^{-9}$
	rs884303	A	G	-0.08 (0.01)	$1.6x10^{-8}$
	rs17150022	T	C	-0.12 (0.02)	$3.5x10^{-8}$
	rs6746896	A	G	0.08 (0.01)	$1.0x10^{-8}$
	rs6079463	A	G	-0.09 (0.02)	$3.1x10^{-8}$
	rs13231398	C	G	-0.12 (0.02)	$2.7x10^{-8}$
	rs11724116	T	C	-0.11 (0.02)	$2.7x10^{-8}$
	rs3804640	A	G	0.08 (0.01)	$2.9x10^{-8}$
	rs10744560	T	C	0.08 (0.01)	$3.7x10^{-9}$
	rs138321	A	G	0.08 (0.01)	$1.1x10^{-8}$
	rs960145	A	C	0.08 (0.01)	$3.1x10^{-8}$
	rs9834970	T	C	-0.1 (0.01)	$1.3x10^{-12}$
	rs11237821	T	C	0.12 (0.02)	$2.1x10^{-8}$
	rs550049	A	G	-0.08 (0.01)	$4.1x10^{-8}$
	rs329319	A	G	0.08 (0.01)	$2.2x10^{-8}$
	rs111444407	T	C	0.12 (0.02)	$4.5x10^{-10}$
Accumbens Satizabal et al., (2019)	rs429358	T	C	0.09 (0.02)	$4.2x10^{-8}$
	rs13107325	T	C	0.14 (0.02)	$7.7x10^{-10}$
	rs868202	T	C	0.07 (0.01)	$3.5x10^{-9}$
	rs9818981	A	G	-0.12 (0.02)	$4.7x10^{-10}$
	rs11747514	T	G	-0.08 (0.01)	$2.1x10^{-9}$
Amygdala Satizabal et al., (2019)	rs17178006	T	G	0.1 (0.02)	$8.9x10^{-9}$
	rs10774183	T	C	0.06 (0.01)	$3.4x10^{-8}$
	rs11111293	T	C	0.08 (0.01)	$4.1x10^{-10}$
Brainstem Satizabal et al., (2019)	rs9398173	T	C	-0.1 (0.01)	$1.8x10^{-15}$
	rs555925	T	G	0.08 (0.01)	$1.8x10^{-10}$
	rs4784256	A	G	0.08 (0.01)	$1.4x10^{-11}$
	rs9322194	T	C	0.09 (0.01)	$4.9x10^{-12}$
	rs112178027	T	C	-0.09 (0.02)	$3.6x10^{-9}$
	rs9505301	A	G	-0.12 (0.02)	$1.4x10^{-9}$
	rs869640	A	C	-0.11 (0.01)	$4.3x10^{-17}$
	rs11111090	A	C	0.13 (0.01)	$3.7x10^{-27}$
	rs11113061	A	T	0.11 (0.02)	$6.3x10^{-12}$
	rs4396983	A	G	-0.08 (0.01)	$2.2x10^{-12}$
	rs10217651	A	G	0.12 (0.01)	$1.4x10^{-22}$
	rs13388394	A	G	-0.17 (0.03)	$1.5x10^{-8}$
	rs2206656	C	G	0.08 (0.01)	$8.2x10^{-12}$
	rs12479469	A	G	-0.09 (0.01)	$1.0x10^{-11}$
	rs11684404	T	C	-0.07 (0.01)	$2.7x10^{-9}$
	rs7121816	T	G	-0.09 (0.01)	$2.5x10^{-14}$
Caudate	rs55989340	A	G	-0.07 (0.01)	$4.6x10^{-9}$

Satizabal et al., (2019)	rs12952581	A	G	-0.06 (0.01)	$1.5x10^{-8}$
	rs77634202	C	G	0.13 (0.02)	$1.6x10^{-8}$
	rs12445022	A	G	0.06 (0.01)	$4.4x10^{-9}$
	rs7040561	A	T	-0.09 (0.02)	$3.8x10^{-10}$
	rs77819784	A	T	-0.14 (0.02)	$1.4x10^{-8}$
	rs2817145	A	T	0.08 (0.01)	$5.7x10^{-10}$
	rs35305377	A	G	-0.06 (0.01)	$5.3x10^{-9}$
	rs3133370	T	C	0.08 (0.01)	$5.5x10^{-14}$
	rs148470213	T	C	0.07 (0.01)	$6.4x10^{-10}$
	rs4888010	A	G	0.06 (0.01)	$4.6x10^{-9}$
	rs2680700	T	G	-0.06 (0.01)	$2.6x10^{-8}$
	rs6060983	T	C	0.08 (0.01)	$1.9x10^{-12}$
	rs1987471	T	G	0.06 (0.01)	$4.4x10^{-9}$
Pallidum Satizabal et al., (2019)	rs196807	A	G	0.09 (0.01)	$1.1x10^{-10}$
	rs74904971	A	C	-0.1 (0.02)	$9.1x10^{-9}$
	rs79800814	A	T	-0.2 (0.04)	$3.7x10^{-8}$
	rs2923447	T	G	0.09 (0.01)	$4.8x10^{-16}$
	rs10129414	A	G	-0.08 (0.01)	$5.1x10^{-14}$
	rs6658127	A	G	0.07 (0.01)	$9.3x10^{-9}$
	rs10439607	A	G	-0.07 (0.01)	$3.3x10^{-10}$
	rs4952211	T	C	-0.06 (0.01)	$4.7x10^{-9}$
	rs10838731	T	C	0.07 (0.01)	$1.4x10^{-8}$
Putamen Satizabal et al., (2019)	rs35200015	A	G	-0.11 (0.01)	$2.5x10^{-16}$
	rs2410767	C	G	0.07 (0.01)	$3.9x10^{-9}$
	rs62098013	A	G	0.09 (0.01)	$4.5x10^{-19}$
	rs6060857	A	G	0.1 (0.01)	$4.2x10^{-18}$
	rs7902527	A	G	0.08 (0.01)	$3.1x10^{-10}$
	rs2244479	T	C	-0.07 (0.01)	$3.1x10^{-9}$
	rs398652	A	G	0.08 (0.02)	$1.6x10^{-8}$
	rs1432054	A	G	-0.09 (0.01)	$2.1x10^{-15}$
	rs945270	C	G	0.16 (0.01)	$5.0x10^{-51}$
	rs10045172	T	C	-0.06 (0.01)	$3.2x10^{-8}$
	rs3807729	T	C	-0.07 (0.01)	$3.0x10^{-8}$
	rs10143642	T	C	0.13 (0.02)	$4.0x10^{-8}$
Thalamus Satizabal et al., (2019)	rs35200015	A	G	-0.11 (0.01)	$2.5x10^{-16}$
	rs2410767	C	G	0.07 (0.01)	$3.9x10^{-9}$
	rs62098013	A	G	0.09 (0.01)	$4.5x10^{-19}$
	rs6060857	A	G	0.1 (0.01)	$4.2x10^{-18}$
	rs7902527	A	G	0.08 (0.01)	$3.1x10^{-10}$
	rs2244479	T	C	-0.07 (0.01)	$3.1x10^{-9}$
	rs398652	A	G	0.08 (0.02)	$1.6x10^{-8}$
	rs1432054	A	G	-0.09 (0.01)	$2.1x10^{-15}$
	rs945270	C	G	0.16 (0.01)	$5.0x10^{-51}$
	rs10045172	T	C	-0.06 (0.01)	$3.2x10^{-8}$
	rs3807729	T	C	-0.07 (0.01)	$3.0x10^{-8}$
	rs10143642	T	C	0.13 (0.02)	$4.0x10^{-8}$
Hippocampus	rs2268894	T	C	-0.08 (0.01)	$5.8x10^{-11}$

Hibar et al., (2017)	rs11979341	C	G	-0.09 (0.01)	$1.4x10^{-11}$
	rs61921502	T	G	0.15 (0.02)	$1.9x10^{-19}$
	rs77956314	T	C	-0.23 (0.02)	$2.0x10^{-25}$
	rs2289881	T	G	-0.07 (0.01)	$2.7x10^{-8}$
	rs7020341	C	G	0.08 (0.01)	$3.0x10^{-11}$
ICV Adams et al., (2016)	rs9811910	C	G	0.14 (0.02)	$1.9x10^{-9}$
	rs2195243	C	G	-0.08 (0.01)	$1.4x10^{-8}$
	rs11191683	T	G	0.08 (0.01)	$1.0x10^{-10}$
	rs11759026	A	G	-0.13 (0.01)	$2.2x10^{-20}$
	rs1042725	T	C	-0.07 (0.01)	$6.4x10^{-9}$
	rs199525	T	G	0.14 (0.02)	$3.7x10^{-21}$
	rs2022464	A	C	-0.09 (0.01)	$3.7x10^{-11}$
	rs1936792	A	G	0.09 (0.01)	$8.6x10^{-10}$
Global Thickness Grasby et al., (2018)	rs6738528	A	T	0.01 ($8.0 x10^{-3}$)	$7.3x10^{-9}$
	rs11692435	A	G	-0.01 ($1.5 x10^{-2}$)	$3.1x10^{-10}$
	rs533577	T	C	-0.01 ($8.0 x10^{-3}$)	$8.4x10^{-11}$
	rs35021943	A	C	-0.01 ($9.0 x10^{-3}$)	$2.9x10^{-9}$
	rs7824177	A	G	0.01 ($1.0 x10^{-2}$)	$8.9x10^{-9}$
	rs62054804	T	C	0.01 ($1.0 x10^{-2}$)	$2.3x10^{-9}$
Global Surface Area Grasby et al., (2018)	rs12630663	T	C	-632.81 (111.21)	$1.2x10^{-8}$
	rs34464850	C	G	1233.19 (152.72)	$6.7x10^{-16}$
	rs2301718	A	G	737.22 (132.36)	$2.5x10^{-8}$
	rs386424	T	G	-656.54 (120.04)	$4.5x10^{-8}$
	rs7715167	T	C	-662.75 (119.14)	$2.6x10^{-8}$
	rs2802295	A	G	-714.59 (112.99)	$2.5x10^{-10}$
	rs11759026	A	G	-1301.52 (134.62)	$4.1x10^{-22}$
	rs12357321	A	G	-698.75 (119.65)	$5.2x10^{-9}$
	rs1628768	T	C	-972.98 (132)	$1.7x10^{-13}$
	rs10876864	A	G	-628.59 (112.69)	$2.4x10^{-8}$
	rs10878349	A	G	1039.99 (110.49)	$4.8x10^{-21}$
	rs79600142	T	C	1696.83 (143.27)	$2.3x10^{-32}$

SE, Standard Error; BETA, SE and p-value are reprted from the original GWAS

Appendix D Table 2: Full results from all MR analyses with BD as the exposure

Brain GWAS	Outcome	Number of SNPs	Inverse Weighted Variance			Mr Egger		
			Estimate	SE	p-value	Estimate	SE	p-value
Cortical Thickness (Grasby et al., 2018)	Banks of the Superior Temporal Sulcus	14	4.8×10^{-3}	3.3×10^{-3}	0.15	2.0×10^{-2}	2.1×10^{-2}	0.36
	Caudal Anterior Cingulate	14	$-3.\times10^{-3}$	5.3×10^{-3}	0.54	3.6×10^{-2}	3.3×10^{-2}	0.30
	Caudal Middle Frontal	14	6.0×10^{-4}	2.6×10^{-3}	0.82	$-4.\times10^{-3}$	1.6×10^{-2}	0.81
	Cuneus	14	$-2.\times10^{-4}$	2.9×10^{-3}	0.92	$-1.\times10^{-2}$	1.9×10^{-2}	0.33
	Entorhinal	14	1.1×10^{-3}	8.2×10^{-3}	0.89	$-4.\times10^{-2}$	0.05	0.46
	Frontal pole	14	2.7×10^{-3}	5.7×10^{-3}	0.64	$-2.\times10^{-2}$	3.6×10^{-2}	0.59
	Fusiform	14	4.6×10^{-4}	2.6×10^{-3}	0.86	1.6×10^{-2}	1.7×10^{-2}	0.38
	Inferior Parietal	14	5.8×10^{-3}	2.3×10^{-3}	0.01	8.0×10^{-3}	1.5×10^{-2}	0.60
	Inferior Temporal	14	2.2×10^{-3}	3.8×10^{-3}	0.55	2.8×10^{-2}	2.4×10^{-2}	0.27
	Insula	14	1.2×10^{-3}	3.3×10^{-3}	0.70	9.4×10^{-3}	2.1×10^{-2}	0.66
	Isthmus Cingulate	14	$-1.\times10^{-3}$	4.8×10^{-3}	0.71	3.6×10^{-2}	3.0×10^{-2}	0.25
	Lateral Occipital	14	3.2×10^{-3}	2.5×10^{-3}	0.20	3.6×10^{-3}	1.6×10^{-2}	0.82
	Lateral Orbitofrontal	14	$-5.\times10^{-4}$	3.2×10^{-3}	0.87	1.7×10^{-2}	2.0×10^{-2}	0.40
	Lingual	14	$-4.\times10^{-4}$	2.6×10^{-3}	0.86	$-1.\times10^{-3}$	1.8×10^{-2}	0.96
	Medial Orbitofrontal	14	$-4.\times10^{-3}$	4.3×10^{-3}	0.34	1.7×10^{-2}	2.8×10^{-2}	0.56
	Middle Temporal	14	1.6×10^{-3}	3.7×10^{-3}	0.67	6.0×10^{-3}	2.5×10^{-2}	0.81
	Paracentral	14	5.4×10^{-3}	2.9×10^{-3}	0.07	$-7.\times10^{-3}$	1.9×10^{-2}	0.69
	Parahippocampal	14	4.5×10^{-3}	6.9×10^{-3}	0.51	$-2.\times10^{-2}$	4.4×10^{-2}	0.64
	Pars Opercularis	14	$-6.\times10^{-4}$	2.6×10^{-3}	0.80	$-3.\times10^{-3}$	1.7×10^{-2}	0.85
	Pars Orbatalis	14	$-3.\times10^{-3}$	6.0×10^{-3}	0.61	$-2.\times10^{-2}$	3.9×10^{-2}	0.52
	Pars Triangularis	14	1.8×10^{-4}	3.4×10^{-3}	0.96	$-3.\times10^{-2}$	2.0×10^{-2}	0.15
	Pericalcarine	14	1.2×10^{-3}	2.9×10^{-3}	0.66	$-1.\times10^{-2}$	1.8×10^{-2}	0.56
	Post Central	14	$-1.\times10^{-4}$	2.4×10^{-3}	0.96	$-1.\times10^{-2}$	1.5×10^{-2}	0.51
	Posterior Cingulate	14	$-9.\times10^{-4}$	4.0×10^{-3}	0.80	5.4×10^{-2}	2.1×10^{-2}	2.5×10^{-2}
	Precentral	14	$-1.\times10^{-3}$	2.7×10^{-3}	0.51	$-1.\times10^{-2}$	1.6×10^{-2}	0.31
	Precuneus	14	2.6×10^{-3}	2.3×10^{-3}	0.25	1.1×10^{-2}	1.5×10^{-2}	0.47
	Rostral Anterior Cingulate	14	$-3.\times10^{-3}$	6.5×10^{-3}	0.64	5.2×10^{-4}	4.3×10^{-2}	0.99
	Rostral Middle Frontal	14	$-3.\times10^{-3}$	2.6×10^{-3}	0.26	$-3.\times10^{-3}$	1.8×10^{-2}	0.85
	Superior Temporal	14	$-4.\times10^{-3}$	3.1×10^{-3}	0.16	6.8×10^{-3}	2.0×10^{-2}	0.75

	Superior Parietal	14	$2.0x10^{-3}$	$2.8x10^{-3}$	0.47	$1.6x10^{-3}$	$1.9x10^{-2}$	0.93
	Superior Temporal	14	$8.9x10^{-4}$	$3.0x10^{-3}$	0.77	$-2.x10^{-2}$	$1.9x10^{-2}$	0.25
	Supramarginal	14	$-2.x10^{-4}$	$2.6x10^{-3}$	0.92	$1.4x10^{-2}$	$1.6x10^{-2}$	0.40
	Temporal Pole	14	$2.7x10^{-3}$	$7.2x10^{-3}$	0.70	$-1.x10^{-2}$	$4.6x10^{-2}$	0.77
	Global Thickness	14	$-1.x10^{-3}$	$3.9x10^{-3}$	0.66	$9.4x10^{-4}$	$2.6x10^{-2}$	0.97
Cortical Surface Area (Grasby et al., 2018)ea	Banks of the Superior Temporal Sulcus	14	3.18	3.18	0.82	12.49	20.88	0.56
	Caudal Anterior Cingulate	14	2.84	2.84	0.90	5.37	18.83	0.78
	Caudal Middle Frontal	14	6.73	6.73	0.36	-16.19	43.00	0.71
	Cuneus	14	3.87	3.87	0.58	-29.13	24.73	0.26
	Entorhinal	14	1.62	1.62	0.03	11.51	10.33	0.29
	Frontal pole	14	0.78	0.78	0.97	-2.71	5.16	0.61
	Fusiform	14	6.40	6.40	0.16	43.36	40.90	0.31
	Inferior Parietal	14	12.20	12.20	0.90	-32.21	80.62	0.70
	Inferior Temporal	14	8.69	8.69	0.91	63.44	54.83	0.27
	Insula	14	4.36	4.36	0.87	-31.48	27.86	0.28
	Isthmus Cingulate	14	2.99	2.99	0.78	12.23	19.59	0.54
	Lateral Occipital	14	9.97	9.97	0.71	-63.41	63.92	0.34
	Lateral Orbitofrontal	14	4.70	4.70	0.17	26.20	30.03	0.40
	Lingual	14	7.76	7.76	0.83	-77.99	49.60	0.14
	Medial Orbitofrontal	14	3.49	3.49	0.55	4.35	22.30	0.85
	Middle Temporal	14	6.27	6.27	0.42	15.44	40.04	0.71
	Paracentral	14	5.62	5.62	0.71	19.04	37.05	0.62
	Parahippocampal	14	2.20	2.20	0.96	3.25	14.64	0.83
	Pars Opercularis	14	6.01	6.01	0.71	-10.92	39.76	0.79
	Pars Orbatalis	14	1.58	1.58	0.05	20.29	10.11	0.07
	Pars Triangularis	14	4.25	4.25	0.69	40.18	26.69	0.16
	Pericalcarine	14	6.50	6.50	0.74	-91.24	34.55	0.02
	Post Central	14	10.61	10.61	0.79	79.28	66.41	0.26
	Posterior Cingulate	14	2.93	2.93	0.02	-22.34	18.73	0.26
	Precentral	14	10.08	10.08	0.48	10.99	66.80	0.87
	Precuneus	14	8.96	8.96	0.67	102.06	52.19	0.07
	Rostral Anterior Cingulate	14	2.47	2.47	0.03	2.74	15.82	0.87
	Rostral Middle Frontal	14	10.27	10.27	0.89	17.58	65.60	0.79

	Superior Temporal	14	12.23	12.23	0.69	-82.50	77.23	0.31
	Superior Parietal	14	11.53	11.53	0.15	-17.34	76.72	0.82
	Superior Temporal	14	6.06	6.06	0.51	38.11	38.70	0.34
	Supramarginal	14	8.37	8.37	0.73	21.43	53.50	0.70
	Temporal Pole	14	1.22	1.22	0.32	6.34	7.81	0.43
	Global Surface Area	14	375.18	375.18	0.00	1826.16	2485.04	0.48
	Transverse Temporal	14	1.48	1.48	0.73	9.07	9.53	0.36
Subcortical Volume (Satizabal et al., 2019)	Accumbens	14	0.05	0.05	0.70	-0.15	0.32	0.64
	Amygdala	14	0.04	0.04	0.05	0.02	0.25	0.94
	Brainstem	14	0.04	0.04	0.23	-0.23	0.25	0.37
	Caudate	14	0.03	0.03	0.06	0.41	0.22	0.09
	Hippocampus	14	0.04	0.04	0.76	-0.17	0.26	0.53
	ICV	14	0.05	0.05	0.35	0.48	0.28	0.11
	Pallidum	14	0.04	0.04	0.36	-0.14	0.24	0.58
	Putamen	14	0.04	0.04	0.33	-0.01	0.26	0.96
	Thalamus	14	0.04	0.04	0.56	0.10	0.29	0.73

‘Number of SNPs’ refers to the number of genome-wide significant SNPs in the original GWAS that are used as instrumental variables in the MR analyses

Appendix D Table 3: Full results from all MR analyses with brain GWAS as the exposure and BD and BPD as the outcome

Brain GWAS	Exposure	Outcome	Number of SNPs	Inverse Weighted Variance			Mr Egger		
				Estimate	SE	P-value	Estimate	SE	P-value
Cortical (Grasby et al., 2018)	Global Surface Area	Bipolar Disorder	11.00	$1.12x10^{-5}$	$7.98 x10^{-6}$	0.16	$1.75 x10^{-6}$	$2.47 x10^{-5}$	0.95
	Global Surface Area	Borderline	11	$-2.29 x10^{-4}$	$3.12 x10^{-4}$	0.46	0.01	$7.42 x10^{-4}$	0.05
	Global Thickness	Bipolar Disorder	5.00	0.93	2.67	0.73	26.43	6.80	0.03
	Global Thickness	Borderline	5	-11.16	85.88	0.90	-147.83	442.76	0.76
Subcortical Volume (Satizabal et al., 2019)	Amygdala	Bipolar Disorder	3.00	-0.33	0.13	0.01	0.58	0.70	0.56
	Amygdala	Borderline	5	2.02	5.30	0.70	-9.39	21.79	0.70
	Accumbens	Bipolar Disorder	5.00	0.16	0.10	0.13	0.43	0.41	0.37
	Accumbens	Borderline	3		1.27	0.46	3.64	3.26	0.46
	Brainstem	Bipolar Disorder	14.00	-0.03	0.07	0.67	0.71	0.31	0.04
	Brainstem	Borderline	16	0.17	2.61	0.95	4.32	14.47	0.77
	Caudate	Bipolar Disorder	10.00	-0.04	0.09	0.69	0.30	0.81	0.72
	Caudate	Borderline	14	3.03	3.76	0.42	7.02	17.99	0.70
	Pallidum	Bipolar Disorder	8.00	0.03	0.11	0.78	0.94	0.70	0.23
	Pallidum	Borderline	9	-0.16	4.37	0.97	-5.50	20.47	0.80
	Putamen	Bipolar Disorder	10	0.16	0.06	0.01	0.26	0.32	0.44
	Putamen	Borderline	11	0.72	3.99	0.86	24.64	18.51	0.22
	Thalamus	Bipolar Disorder	4	0.11	0.12	0.34	-0.47	0.53	0.47
	Thalamus	Borderline	5	4.15	6.77	0.54	-13.96	39.44	0.75
Hippocampus Volume (Hibar et al., 2017)	Hippocampus	Bipolar Disorder	4.00	0.12	0.09	0.18	0.05	0.23	0.85
	Hippocampus	Borderline	6	-2.50	3.93	0.52	2.22	10.81	0.85
ICV Adams et al., (2016)	ICV	Bipolar Disorder	6.00	0.02	0.11	0.89	0.21	0.45	0.66
	ICV	Borderline	8	-0.42	3.71	0.91	9.38	15.04	0.56

Appendix E Table 1: Summary of Results

Cortical Region	SNP Based Heritability		SECA			Genetic Correlation		SECA			Genetic Correlation	
	h^2_{SNP}	Z-score	Pleiotropy p-value[1]	Concordance p-value[1]	Direction of Concordance (OR)	r_g (SE)	p-value	Pleiotropy p-value1	Concordance p-value1	Direction of Concordance (OR)	r_g (SE)	p-value
Banks of the superior temporal sulcus	0.15	2.95	$2.8x10^{-3}$	0.54	Negative (1.04)	0.15 (0.11)	0.19	0.3	0.26	Positive (0.99)	-0.15 (0.28)	0.6
Caudal middle frontal	0.08	3.04	$3.13x10^{-3}$	0.79	Negative (1.02)	0.15 (0.06)	0.01	1	0.13	Positive (0.84)	0.22 (0.15)	0.13
Cuneus	0.05	3.01	$3.10x10^{-3}$	0.36	Negative (1.08)	0.15 (0.08)	0.06	1	0.02	Negative (1.05)	0.24 (0.21)	0.26
Entorhinal	0.05	0.6	$9.05x10^{-2}$	0.42	Positive (0.94)	-0.08 (0.08)	0.3	0.06	1	Positive (0.92)	-0.16 (0.22)	0.46
Frontal pole	0.01	2.58	$1.52x10^{-3}$	0.14	Positive (0.89)	0.04 (0.17)	0.82	0.04	0.32	Negative (1.04)	0.29 (0.46)	0.54
Lingual	0.08	2.94	$5.11x10^{-4}$	0.85	Negative (1.01)	-0.01 (0.07)	0.88	1	0.01	Positive (0.92)	-0.07 (0.16)	0.68
Lateral orbitofrontal	0.04	3.84	$1.95x10^{-2}$	0.05	Negative (1.16)	$-4.4x10^{-5}$ (0.09)	0.99	1	1	Positive (0.93)	0.35 (0.23)	0.14
Lateral occipital	0.07	3.06	$2.25x10^{-5}$**	0.52	Positive (0.95)	0.09 (0.07)	0.2	1	$3x10^{-4}$**	Negative (1.02)	0.12 (0.18)	0.5
Pars opercularis	0.09	3.01	$1.01x10^{-2}$	0.39	Negative (1.07)	0.16 (0.09)	0.07	0.09	0.23	Positive (0.94)	0.03 (0.19)	0.86
Pars triangularis	0.05	0.67	$1.15x10^{-4}$**	0.07	Positive (0.87)	0.17 (0.28)	0.55	0.3	0.19	Negative (1.13)	0.60 (0.74)	0.42
Precentral	0.01	3.48	$2.53x10^{-3}$	0.73	Positive (0.97)	0.05 (0.08)	0.52	1	1	Negative (1.06)	0.22 (0.19)	0.25
Post central	0.06	3.01	$7.90x10^{-6}$**	0.41	Negative (1.06)	0.04 (0.06)	0.56	0.16	0.24	Negative (1.02)	-0.07 (0.16)	0.67
Pars orbitalis	0.08	3.25	$1.36x10^{-2}$	0.49	Positive (0.94)	0.02 (0.07)	0.73	0.01	0.04	Negative (1.08)	0.01 (0.16)	0.93
Precuneus	0.06	2.74	$8.23x10^{-3}$	0.64	Positive (0.96)	$4x10^{-3}$ (0.07)	0.95	0.31	1	Positive (0.96)	-0.09 (0.18)	0.61

Rostral anterior cingulate	0.04	3.66	2.18x10^{-4}**	0.62	Positive (0.96)	-0.018 (0.09)	0.84	0.16	0.42	Negative (1.01)	0.15 (0.23)	0.51
Supramarginal	0.06	1.25	1.45x10^{-7}**	0.05	Negative (1.17)	-0.02 (0.06)	0.79	1	0.27	Negative (1.02)	-0.03 (0.15)	0.86

*Bonferroni corrected p-value at 0.05/(4 tests*2 traits*17 brain regions)=3.67x10^{-4} ;** Significant; [1] p-values are empirical; OR, odds ratio. Only brain regions that had non-extreme Z-scores (-4 ≤ Z-score ≤ 4) in the prior, h^2_{SNP} analysis were used in downstream pleiotropic analyses.*