Across Diagnostic Boundaries: Genetic Variants for Neuropsychiatric Disorders and their Association with Human Brain Structure

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Statement of published work

This thesis comprises two studies. The first study was published as an original article in *Translational Psychiatry*. The second study was published as an original article in *Translational Psychiatry* and as a conference abstract in *Clinical Neurophysiology*. The original article of the second study was under review at the time of the examination phase. With publication, the reference was subsequently added to the statement of published work and to the captions of the corresponding Figures and Tables. The central sections including the Introduction, Material and Methods, Results, Discussion, and Limitations have been presented in the aforementioned publications.

Federmann, L. M., David, F. S., Jockwitz, C., Mühleisen, T. W., Pelzer, D. I., Nöthen, M. M., Caspers, S., Amunts, K., Goltermann, J., Andlauer, T. F. M., Stein, F., Brosch, K., Kircher, T., Cichon, S., Dannlowski, U., Sindermann, L., & Forstner, A. J. (2024). Associations between antagonistic SNPs for neuropsychiatric disorders and human brain structure. *Translational Psychiatry*, *14*(1), 1–10. https://doi.org/10.1038/s41398-024-03098-1

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List of abbreviations

AAL	Automated anatomical labelling atlas
ADHD	Attention deficit hyperactivity disorder
ANO	Anorexia nervosa
ASD	Autism spectrum disorder
BH	Benjamini-Hochberg
BIP	Bipolar disorder
BP	Basepair position
BRAINEAC	Brain eQTL Almanac
CADD	Combined annotation-dependent depletion
CAT	Computational anatomy toolbox
CEU	Utah residents with Northern and Western European ancestry
CHARGE	Cohorts for Heart and Aging Research in Genomic Epidemiology
CHR	Chromosome
CI	Confidence interval
CNV	Copy number variation
CT	Cortical thickness
DCC	*DCC netrin 1 receptor*
DK	Desikan-Killiany
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EA	Effect allele
ENIGMA	Enhancing NeuroImaging Genetics through Meta Analysis
eQTL	Expression quantitative trait locus
FAM85B	*Family with sequence similarity 85 member B*
FDR	False discovery rate
FWE	Family-wise error
GMV	Gray matter volume
GRCh37	Genome Reference Consortium human build 37
GRS	Genetic risk score
GTEx	Genotype-tissue expression

GWAS	Genome-wide association study
5-HTTLPR	*Serotonin-transporter-linked promoter region*
HWE	Hardy-Weinberg equilibrium
ICD	International Classification of Diseases
ICV	Intracranial volume
IDP	Image-derived phenotype
IGSF9B	*Immunoglobulin superfamily member 9b*
iPSC	Induced pluripotent stem cell
IQ	Intelligence quotient
LD	Linkage disequilibrium
MAF	Minor allele frequency
MDS	Multidimensional scaling
MR	Mendelian randomization
MRI	Magnetic resonance imaging
MSRA	*Methionine sulfoxide reductase A*
n.a.	Not available
NES	Normalized effect size
n.s.	Not significant
OA	Other allele
OCD	Obsessive-compulsive disorder
OR	Odds ratio
PCDHA@	*Protocadherin alpha* gene cluster
PGC	Psychiatric Genomics Consortium
PGC-CDG2	Second cross-disorder GWAS meta-analysis of the PGC
PleioPsych-GRS	GRS of highly pleiotropic SNPs for neuropsychiatric disorders
POU3F2	*POU class 3 homeobox 2*
PRS	Polygenic risk score
RNA	Ribonucleic acid
SA	Surface area
SCZ	Schizophrenia
SCZ-GRS	GRS of predominantly SCZ-associated SNPs
SD	Standard deviation

SLC39A8	*Solute carrier family 39 member 8*
SNP	Single-nucleotide polymorphism
SPM	Statistical parametric mapping
TS	Tourette's syndrome
UKBB	UK Biobank
VBM	Voxel-based morphometry
VEP	Variant effect predictor

1 Introduction

1.1 Motivation

The human brain is the most complex organ, and unraveling its molecular mechanisms is one of our most significant scientific challenges today (Poldrack & Farah, 2015). The human brain is composed of approximately 86 billion neurons (Azevedo et al., 2009), which are intricately interconnected and form the organization of the brain into distinct brain regions (Amunts et al., 2020). While brain regions are often dedicated to specialized functions, at the same time, brain regions act as part of a network to coordinate physiological and cognitive processes such as perception, memory, attention, movement, mood, or social interaction (Bassett & Sporns, 2017). The development of the human brain is orchestrated by molecular events that are genetically regulated (Lindhout et al., 2024). Variations in brain development, shaped by genetic and environmental factors, not only account for interindividual differences in personality, behavior, or cognitive performance but also influence susceptibility to neuropsychiatric disorders (Parikshak et al., 2015).

Neuropsychiatric disorders are characterized by difficulties in emotion regulation, cognitive processing, or social communication (American Psychiatric Association, 2013). These conditions have a profound impact on the quality of life of those affected and are considered to be among the medical conditions with the highest number of years lost to disability (GBD 2019 Mental Disorders Collaborators, 2022). Furthermore, individuals affected by neuropsychiatric disorders are often unable to fully engage in daily activities, including work, social roles, or household. As a result, neuropsychiatric disorders represent a significant societal disease burden in terms of social consequences and time missed from work (Eaton et al., 2008; Knapp & Wong, 2020).

To date, there are few treatment options available to ameliorate the symptoms of neuropsychiatric disorders (Holmes et al., 2018). However, early diagnosis and careful treatment planning, including psychotherapy and medication, can improve patients' quality of life (Lord et al., 2020; Marx et al., 2023). A more profound understanding of the biological etiology of neuropsychiatric disorders will be critical to improving diagnostic specificity and developing effective treatment options (Pardiñas et al., 2021; Rees & Owen, 2020). This may not only improve patients’ quality of life but also mitigate the stigma linked to neuropsychiatric disorders (GBD 2019 Mental Disorders Collaborators, 2022).

Neuropsychiatric disorders such as attention deficit hyperactivity disorder (ADHD), anorexia nervosa (ANO), autism spectrum disorder (ASD), bipolar disorder (BIP), major depression (MD), obsessive-compulsive disorder (OCD), schizophrenia (SCZ), and Tourette's syndrome (TS) are considered to have a multi-factorial etiology with genetic and environmental factors playing a role in disease susceptibility (Sullivan & Geschwind, 2019). Recent advances in genotyping technology and statistical analyses, such as genome-wide association study (GWAS), have identified hundreds of genetic variants for neuropsychiatric disorders (Andreassen et al., 2023). Most genetic variants for neuropsychiatric disorders are located in non-coding regions of the genome (Lappalainen & MacArthur, 2021). Consequently, the precise molecular mechanisms by which these variants contribute to disease risk remain unclear (Lappalainen & MacArthur, 2021). Nevertheless, recent research revealed an enrichment of genetic variants for neuropsychiatric disorders for genes involved in early neurodevelopmental processes (P. H. Lee et al., 2019; Schork et al., 2019).

There is mounting evidence that major neuropsychiatric disorders have overlapping genetic architectures, indicating a potential shared genetic etiology (P. H. Lee et al., 2019). In particular, the second cross-disorder GWAS meta-analysis of the Psychiatric Genomics Consortium (PGC-CDG2), which included 232,964 patients with ADHD, ANO, ASD, BIP, MD, OCD, SCZ, or TS, revealed substantial genetic correlations across neuropsychiatric disorders (P. H. Lee et al., 2019). In addition, single-nucleotide polymorphisms (SNPs) with complex associations across neuropsychiatric disorders were identified, such as antagonistic, highly pleiotropic, and disorder-specific SNPs (P. H. Lee et al., 2019). For the majority of SNPs, the molecular mechanism leading to susceptibility to neuropsychiatric disorders is unknown.

This thesis aims to uncover the neurobiological correlates of selected genetic variants with associations across neuropsychiatric disorders identified by the PGC-CDG2 (P. H. Lee et al., 2019). Section 1.2 provides a comprehensive overview of clinical characteristics, neuroimaging findings, and the genetic architecture of neuropsychiatric disorders. Section 1.3 introduces the field of imaging genetics and discusses the importance of studying brain structural associations for genetic variants for neuropsychiatric disorders. Section 1.4 reviews current findings from cross-disorder GWAS for neuropsychiatric disorders. Finally, Section 1.5 outlines the analyses performed in the present thesis.

1.2 Neuropsychiatric disorders

This section introduces the clinical characteristics of neuropsychiatric disorders (Section 1.2.1), summarizes recent neuroimaging findings in neuropsychiatric disorders (Section 1.2.2), and gives an overview of the genetic architecture of neuropsychiatric disorders (Section 1.2.3). This thesis focuses on the eight neuropsychiatric disorders encompassed by the PGC-CDG2 (P. H. Lee et al., 2019).

1.2.1 Clinical characteristics

Neuropsychiatric disorders vary in clinical characteristics, lifetime prevalence, or SNP-based heritability (Table 1). Diagnostic systems such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) or the International Classification of Diseases (ICD) (World Health Organization, 1992) feature a wide range of descriptive criteria for the diagnosis of specific neuropsychiatric disorders. Nevertheless, recent findings from genetic, transcriptomic, and neuroimaging data suggest that their neurobiological underpinnings transcend these diagnostic boundaries (Smoller et al., 2018).

Table 1 | Overview of the eight neuropsychiatric disorders included in the PGC-CDG2

Disorder	Main clinical characteristics	Lifetime prevalence	h^2_{twin}	GWAS included in the PGC-CDG2	N_{cases}	h^2_{SNP}
ADHD	attention deficits and hyperactivity[1]	0.053	0.76	Demontis et al. (2019)	19,099	0.22
ANO	excessive weight loss owing to reduced food intake[2]	0.009	0.58	Duncan et al. (2017)	3,495	0.20
ASD	difficulties with verbal and non-verbal social communication, repetitive behaviors, or restrictive interests[3]	0.017	0.74	Grove et al.(2019)	18,381	0.11
BIP	(hypo)manic and depressive episodes[4]	0.010	0.85	Stahl et al. (2019)	20,352	0.18
MD	persistent sadness and loss of interest in activities and life[5]	0.162	0.37	Wray et al. (2018)	130,664	0.09
OCD	obsessions and compulsions[6]	0.011	0.47	Arnold et al. (2018)	2,688	0.28
SCZ	hallucinations and delusions[7]	0.004	0.81	Ripke et al. (2014)	33,640	0.22
TS	verbal and non-verbal motoric tics[8]	0.005	0.37	Yu et al. (2019)	4,645	0.20

A more detailed description of the clinical characteristics is provided in Section 1.2.1. Lifetime prevalence and twin-based heritability (h^2_{twin}) were taken from Table 1 in (Sullivan & Geschwind, 2019), whereby MD lifetime prevalence referred to major depressive disorder. Reference for the GWAS originally included in the PGC-CDG2 meta-analysis (P. H. Lee et al., 2019) was given for each disorder. The corresponding number of cases (N_{cases}) and the observed SNP-based heritability (h^2_{SNP}) were provided based on Table 1 in (P. H. Lee et al., 2019). *References.* [1](Faraone et al., 2015), [2](Treasure et al., 2015), [3](Lord et al., 2020), [4](Vieta et al., 2018), [5](Marx et al., 2023), [6](Stein et al., 2019), [7](Kahn et al., 2015), [8](Johnson et al., 2023). *Abbreviations.* ADHD, attention deficit hyperactivity disorder; ANO, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; GWAS, genome-wide association study; MD, major depression; OCD, obsessive-compulsive disorder; PGC-CDG2, second cross-disorder GWAS meta-analysis of the PGC; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; TS, Tourette's syndrome.

Relevant clinical characteristics of (i) early-onset and neurodevelopmental disorders, (ii) disorders with compulsive and perfectionist behaviors, and (iii) mood and psychotic disorders are presented below. The assignment of disorders was adopted from the factor analysis of the PGC-CDG2 (P. H. Lee et al., 2019). While TS and MD loaded on two factors (P. H. Lee et al., 2019), TS was assigned to (i) due to its early age of onset, and MD was assigned to (iii) due to its main clinical feature of depressive mood.

Early-onset and neurodevelopmental disorders such as ADHD (Faraone et al., 2015), ASD (Lord et al., 2020), and TS (Johnson et al., 2023) typically manifest during childhood or adolescence.

ADHD is marked by dysfunctions in attentional processing that manifest as impulsivity, hyperactivity, and difficulties in learning, self-regulation, or social interactions (Faraone et al., 2015).

ASD is characterized by restrictive interests, repetitive behaviors, and difficulties in verbal and non-verbal social communication (Lord et al., 2020). The symptoms of ASD vary in severity, which makes ASD recognized as a spectrum disorder (Lord et al., 2020).

TS is a condition in which the motor system is affected, causing patients to perform vocal or motor tics (Johnson et al., 2023). The tics are involuntary and may exhibited daily or primarily in stressful situations, with a diagnosis of TS being made when the tics occur for at least one year (Johnson et al., 2023).

Disorders with compulsive and perfectionist behaviors such as ANO (Treasure et al., 2015) and OCD (Stein et al., 2019) are characterized by actions that disrupt oneself, with patients often perceiving themselves as unable to control or stop their actions.

ANO is an eating disorder characterized by a distorted perception of one’s body and an excessive concern with weight loss through reduced food intake (Treasure et al., 2015). Abnormal weight loss can lead to various physical consequences like endocrine or cardiovascular system dysfunctions.

OCD is marked by intrusive thoughts and excessive routines that last for more than an hour per day (Stein et al., 2019). This includes obsessions like an urge for symmetry, fear of contamination, or compulsions like excessive hand washing, counting, or cleaning (Stein et al., 2019).

Mood and psychotic disorders such as BIP (Vieta et al., 2018), MD (Marx et al., 2023), and SCZ (Kahn et al., 2015) are typically diagnosed in late adolescence and early adulthood.

BIP is typically characterized by alternating periods of depressed and elevated mood (Vieta et al., 2018). During depressive periods, patients often experience persistent sadness, low energy levels, and a tendency to withdraw socially. During manic or hypomanic periods, patients exhibit elevated levels of energy, enhanced self-esteem, and a lack of need for sleep (Vieta et al., 2018).

MD is a condition in which patients report experiencing persistent depressed mood and loss of interest or pleasure in activities that were previously enjoyed (Marx et al., 2023). Patients often report negative thoughts about themselves and their future, as well as sleep or appetite-related symptoms (Marx et al., 2023).

SCZ is marked by alterations in thought processes, including hallucinations, delusions, and disorganized behavior (Kahn et al., 2015). Patients with SCZ often exhibit anhedonia, social withdrawal, and a range of cognitive dysfunction, including impairments in working memory and concentration (Kahn et al., 2015).

Despite their distinct clinical characteristics, neuropsychiatric disorders share a wide range of symptoms (Borsboom et al., 2011; Forbes et al., 2024) and have high rates of comorbidities (Plana-Ripoll et al., 2019). For example, symptoms of insomnia, inattention, and irritable mood can occur in different neuropsychiatric disorders (Forbes et al., 2024). Furthermore, it was estimated that 66 % of individuals who meet the criteria for one disorder will fulfill the criteria for a second neuropsychiatric disorder in their lifetime (Caspi & Moffitt, 2018). With this in mind, recent research has emphasized the importance of cross-disorder analyses (Caspi & Moffitt, 2018).

1.2.2 Neuroimaging findings in neuropsychiatric disorders

Neuroimaging is a key research tool that sheds light on the biological basis of neuropsychiatric disorders (Etkin, 2019). Various non-invasive imaging techniques are used in research to depict changes in various aspects of the human brain in patients with neuropsychiatric disorders (Linden, 2012). For example, magnetic resonance imaging (MRI) visualizes brain structure, functional MRI and electroencephalography register brain activity,

albeit at different temporal and spatial resolutions, and positron emission tomography depicts neurotransmitter dynamics (Linden, 2012). The following will focus on MRI, as this thesis analyzes brain structure based on brain MRI scans.

The MRI technique relies on the body's magnetic properties, given by its high water content (see Brown & Semelka (2011) for a detailed explanation). Water consists of hydrogen protons that spin randomly about their axes. When the MRI scanner exposes a strong magnetic field, these protons align with its net magnetization vector (Brown & Semelka, 2011). During MRI imaging acquisition, radio frequency pulses are turned on, forcing the protons in the body to absorb energy and change their longitudinal and transverse magnetization. When the radio frequency pulses turn off, the body's protons recover to the magnetization vector's original orientation (Brown & Semelka, 2011). The time required for relaxation depends on the water content of the tissue, a property that allows visualization of contrast between different tissues. The relaxation time can be measured differently (Brown & Semelka, 2011). For example, T1 relaxation captures the longitudinal magnetization to reach 63 % of the initial state. MRI images based on the T1 relaxation time depict contrasts between the white and gray matter of the brain and are most commonly used to analyze brain structure (Brown & Semelka, 2011).

With advances in MRI techniques, research has investigated alterations in brain structure in patients with neuropsychiatric disorders compared to controls (Etkin, 2019). Case-control MRI differences, however, have shown at most small effect sizes, and as a result, expectations to identify putative neuroimaging biomarkers for use in diagnosis, prognosis, or treatment planning have not yet been met (Schmaal et al., 2020). Furthermore, early case-control MRI studies included small sample sizes of less than a hundred, leading to underpowered and false-positive results (Button et al., 2013; Etkin, 2019).

As a field, neuroimaging has emphasized the importance of enhancing replicability, and in the course of this, studies of large-scale neuroimaging data have been initiated (Etkin, 2019; Poldrack et al., 2017). Today, clinical and population-based studies have collected data from thousands of individuals (e.g., Bycroft et al., 2018; Kircher et al., 2019). For example, the FOR2107 study, which aimed to uncover neurobiological correlates of disorders along the mood and psychosis spectrum, comprised, at the time of writing, brain MRI scans from more than 2,000 individuals including patients with BIP, major depressive disorder (MDD), SCZ, or schizoaffective disorder, and healthy controls (Kircher et al.,

2019). Another example is the UK Biobank (UKBB) study, which collected biomedical data, including genetic and health-related data, from more than 500,000 individuals across the middle-aged and older adult population in the UK (Bycroft et al., 2018). In addition, MRI scans were available to researchers for a subset of more than 30,000 individuals at the time of writing.

Coordinated analyses of neuroimaging data across research sites have been conducted to achieve the large sample sizes needed for the robust discovery of neurobiological correlates (Thompson et al., 2020). Fast forwarding within the last decade, the Enhancing NeuroImaging Genetics through Meta Analysis (ENIGMA) consortium fostered data sharing across sites using harmonized data processing pipelines (Thompson et al., 2020). In light of this, the ENIGMA consortium has performed large-scale meta-analyses of case-control MRI studies for several diagnostic groups, including ADHD, ANO, ASD, BIP, MD, OCD, and SCZ (Thompson et al., 2020; Walton et al., 2022). These studies revealed alterations in the volume of subcortical structures and regional and whole-brain measures of cortical thickness (CT) and surface area (SA) in patients with neuropsychiatric disorders compared to controls (Thompson et al., 2020). For example, a case-control MRI study of SCZ by the ENIGMA consortium (N_{cases}=4,474) reported a significant decrease of CT and SA widespread throughout the cortex in patients with SCZ (Van Erp et al., 2018). Here, the most prominent effect sizes were observed in regions of the prefrontal and temporal cortices (Van Erp et al., 2018), which have been suggested to contribute to the severity of negative symptoms observed in patients with SCZ (Kirschner et al., 2021; Walton et al., 2018).

Notably, case-control MRI differences partially overlap across neuropsychiatric disorders (Goodkind et al., 2015; Opel et al., 2020; Wise et al., 2016). For example, case-control MRI differences from the ENIGMA consortium meta-analyses were shown to be correlated across ADHD, ASD, BIP, MD, OCD, and SCZ (Opel et al., 2020). Furthermore, a large-scale voxel-based morphometry (VBM) meta-analysis that included data from patients with anxiety disorders, BIP, MDD, OCD, SCZ, or substance use disorders observed decreased gray matter volume (GMV) in the dorsal anterior cingulate and left and right anterior insula (Goodkind et al., 2015). Both regions are important for executive functions and emotional regulation (Etkin et al., 2015), which are implicated in most neuropsychiatric disorders (American Psychiatric Association, 2013). In addition to shared brain structural

alterations, predominantly disorder-specific case-control MRI differences have been reported for patients with neuropsychiatric disorders compared to controls (McCutcheon et al., 2023).

1.2.3 Genetic architecture

Neuropsychiatric disorders tend to run in families and are partially heritable (Sullivan & Geschwind, 2019). Twin studies have suggested that a large proportion of interindividual variability can be explained by genetics, with estimated twin-based heritability ranging from 37 % for MD and TS to 85 % for BIP (Table 1) (Sullivan & Geschwind, 2019). Over the past few decades, molecular studies have shown that the genetic architecture of neuropsychiatric disorders consists of genetic variants across the allelic spectrum (Sullivan & Geschwind, 2019). These include genetic variants of varying frequencies and types (Uffelmann et al., 2021). Whether a variant is rare or common is specific to the population. However, a common variant is often defined as one that is present in more than 5 % of the population (Agarwala et al., 2013). The variant type determines the deoxyribonucleic acid (DNA) sequence change. For example, SNPs refer to single basepair positions in DNA that are variable in the population with a minor allele frequency (MAF) of ≥1 % (Brookes, 1999). Typically, associations between SNPs and a trait of interest show small effect sizes (Manolio et al., 2009). In contrast, Indels describe the insertion or deletion of nucleotides in the DNA sequence. Short Indels span one to 50 basepairs (Altshuler et al., 2010). Deletions or duplications of DNA sequences that are larger than 1000 basepairs are commonly referred to as copy number variations (CNVs) (Feuk et al., 2006). CNVs are suggested to contribute to the risk for neuropsychiatric disorders with large effect sizes (Rees & Kirov, 2021). Until now, the SNPs, Indels, and CNVs identified so far explain only a fraction of the twin-based heritability of neuropsychiatric disorders, whereby psychiatric genetics demonstrates ongoing efforts to identify novel genetic variants for neuropsychiatric disorders (Sullivan & Geschwind, 2019). The following findings focus on SNPs, as they were examined in the present thesis.

GWAS are a powerful tool to identify SNPs associated with a phenotype of interest (Uffelmann et al., 2021; Visscher et al., 2017). GWAS test the linear association of the allele frequency of SNPs with the phenotype in a large number of individuals (Uffelmann et al., 2021). In doing so, GWAS typically assume an additive biometric model, which

states that the effect on the phenotype increases linearly with the number of copies of the effect allele of the SNP (Uffelmann et al., 2021). As GWAS test associations for millions of SNPs across the genome, the significance threshold is typically set at $p<5x10^{-08}$ (Uffelmann et al., 2021). This corresponds to a Bonferroni threshold for testing approximately one million independent SNPs, the suggested average number of independent SNPs (Uffelmann et al., 2021). Associations with $p<5x10^{-08}$ are hereafter referred to as genome-wide significant. Notably, the power of GWAS is inherently dependent on large sample sizes, and its validity benefits from replication in an independent sample (Uffelmann et al., 2021). Therefore, data sharing and coordinated GWAS meta-analyses such as those conducted by the Psychiatric Genomics Consortium (PGC) are crucial (Sullivan et al., 2018).

Today, GWAS for neuropsychiatric disorders have identified more than four hundred loci (Andreassen et al., 2023). In turn, it has become clear that neuropsychiatric disorders have an extensive polygenic architecture (Andreassen et al., 2023). For example, the most recent GWAS of SCZ comprised 76,755 individuals with SCZ across multiple ancestries and identified 287 loci that are genome-wide significantly associated with SCZ (Trubetskoy et al., 2022). Collectively, SNPs account for 24 % of the risk for SCZ in the sample with European ancestry (Trubetskoy et al., 2022). In addition, the genetic architectures of some neuropsychiatric disorders have been shown to overlap substantially across diagnostic categories, as outlined in more detail in Section 1.4 (P. H. Lee et al., 2021).

The majority of genetic variants identified by GWAS of neuropsychiatric disorders are harbored in non-coding regions (Sullivan & Geschwind, 2019), which inherently complicates the understanding of their molecular mechanisms (Sullivan et al., 2018). To pinpoint relevant biological processes, follow-up analyses are typically performed using functional genomics data (Lappalainen & MacArthur, 2021). To this end, previous research has shown that genetic variants identified by GWAS of neuropsychiatric disorders map to genes implicated in neurobiological pathways, including neurogenesis and synaptic functioning (P. H. Lee et al., 2019; Trubetskoy et al., 2022). For example, the most recent GWAS of SCZ prioritized 120 genes by fine-mapping the 287 loci identified as genome-wide significant (Trubetskoy et al., 2022). These genes were specifically implicated in synaptic structure

and function, whereby they were not confined to pre- or postsynaptic compartments (Trubetskoy et al., 2022).

Functional analyses span many levels of biology (Lappalainen & MacArthur, 2021). In addition to identifying neural pathways, genetic variants have been shown to functionally map to genes globally expressed in the brain (Andreassen et al., 2023). For example, the GWAS of SCZ found that associations were particularly enriched in genes that are expressed in excitatory glutamatergic neurons and inhibitory interneurons of cortical and subcortical regions (Trubetskoy et al., 2022). Beyond that, 48.1 % of the genome-wide significant variants identified by the second GWAS of SCZ from the PGC (Ripke et al., 2014) were associated with gene expression in brain tissue (Jaffe et al., 2018). Such loci that are associated with the expression of a particular gene, as quantified by ribonucleic acid (RNA) sequencing, are referred to as expression quantitative trait loci (eQTLs) (Cookson et al., 2009). Mapping genetic variants, such as SNPs, to genes whose expression they regulate can provide valuable insights into their molecular mechanisms (Watanabe et al., 2017).

As neuropsychiatric disorders have an extensive polygenic architecture, genetic scores, which estimate an individual's genetic predisposition for a particular neuropsychiatric disorder, have become an important research method (Wray et al., 2014, 2021). Genetic scores are calculated by aggregating the count and weight of effect alleles from GWAS carried by an individual (Wray et al., 2014, 2021). Scores based on a limited number of SNPs are referred to as genetic risk scores (GRSs), while scores that aggregate SNPs across the genome are referred to as polygenic risk scores (PRSs) (Igo et al., 2019; Keaton et al., 2024). In research, individual-level genetic scores are used to assess whether the genetic predisposition to a particular trait explains part of the individuals' phenotypic variability (Wray et al., 2014, 2021). For example, research has shown that PRSs for neuropsychiatric disorders were associated with outcomes related to mental health and cognition (Leppert et al., 2020) as well as brain structure (Liu et al., 2023; Rodrigue et al., 2023; Stauffer et al., 2021). PRSs for neuropsychiatric disorders, however, have not shown sufficient predictive power to be used for diagnosis, subtyping, or treatment planning (Wray et al., 2021).

1.3 Imaging genetics

Imaging genetic analyses aim to pinpoint the neurobiological processes underlying genetic variants for neuropsychiatric disorders (Bigos & Weinberger, 2010; Le & Stein, 2019). Taking a mechanistic view, imaging genetic analyses assume that brain structure and function lie in a causal pathway from genetic variation to disease pathology (Le & Stein, 2019). Studying brain structure and function as so-called intermediate phenotypes contributes to understanding how genetic variation alters disease risk (Le & Stein, 2019). To investigate the influences of genetic variants for neuropsychiatric disorders on the structure of the human brain, imaging genetic analyses test the associations of genetic variants with MRI-derived brain measures like subcortical volume, CT, and SA (Le & Stein, 2019). These associations are often studied in healthy controls (Bigos & Weinberger, 2010). This has the advantage that the effects of medication and disease-related influences are eliminated and that analysis in large-scale population-based samples can be conducted (Bigos & Weinberger, 2010).

In the early years of imaging genetics and before the GWAS era, analyses have reported associations between candidate genes for neuropsychiatric disorders and brain structure (Klein et al., 2017). For example, a polymorphism in the *serotonin-transporter-linked promoter region* (*5-HTTLPR*), associated with depression, anxiety, and stress reactivity (Karg et al., 2011), was found to be associated with reduced GMV in the anterior cingulate and medial amygdala regions (Pezawas et al., 2005). As both regions play an important role in emotional processing (Rolls, 2019), it was suggested that their structural changes may lead to increased vulnerability to affective disorders (Pezawas et al., 2005). With the success of larger and more powerful GWAS, it was shown that candidate genes for neuropsychiatric disorders did not yield large effect sizes, raising justified concerns about the candidate gene approach (Farrell et al., 2015; Sullivan, 2017).

Today, research in imaging genetics focuses on common genetic variants, whereby large GWAS of several brain structural phenotypes have been performed (Thompson et al., 2020). For example, the ENIGMA and Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortia coordinated a GWAS of regional and global SA and CT measures, including more than 33,000 samples in the discovery cohort. They identified 369 genome-wide significant loci (Grasby et al., 2020). Subsequent functional analysis

showed that loci associated with SA were rather enriched for genes relevant to the regulation of neural progenitor cells during fetal development. In contrast, CT-associated loci were rather enriched for genes that regulate mid-fetal neurobiological processes such as myelination or synaptic dynamics (Grasby et al., 2020).

Interestingly, significant overlaps between the genetic architectures of brain phenotypes and neuropsychiatric disorders have been reported (Cheng et al., 2021, 2022; Grasby et al., 2020; Satizabal et al., 2019). Furthermore, it was estimated that, depending on the structure, 74 to 96 % of the genetic variants associated with subcortical volumes were also associated with SCZ (Cheng et al., 2022). Although cross-phenotype associations do not signify the same neurobiological processes, these findings support the notion that genetic variants for neuropsychiatric disorders may shape disease susceptibility through their involvement in brain-related processes (Le & Stein, 2019).

Genetic scores are a commonly used research tool to test the associations of an individual's genetic predisposition to a neuropsychiatric disorder with brain structure (Liu et al., 2023; Stauffer et al., 2023). For example, a large-scale study using data from the UKBB found that the PRS for SCZ was positively associated with cortical thinning in the left and right medial orbitofrontal cortex, left pars orbitalis, and left lateral orbitofrontal cortex, as well as increased CT in the right lateral occipital cortex (Liu et al., 2023). However, another large-scale UKBB study reported that brain structural associations of the PRSs for different diagnostic groups were partially overlapping (Rodrigue et al., 2023). For example, the PRS for ADHD and the PRS for MD showed associations with decreased inferior temporal SA, and the PRS for BIP and SCZ were both associated with cortical thinning in the lateral and medial orbitofrontal region (Rodrigue et al., 2023). This overlap may be due to the high degree of pleiotropy of genetic variants identified in GWAS of neuropsychiatric disorders (Rodrigue et al., 2023).

1.4 Genetic overlap across neuropsychiatric disorders

Research has reported a high degree of genetic overlap across neuropsychiatric disorders (Anttila et al., 2018; P. H. Lee et al., 2019). In 2009, a study by Purcell and colleagues was among the first to report that genetic variants identified in GWAS for SCZ were also

associated with BIP (Purcell et al., 2009). At the same time, the Cross-Disorder (Phenotype) Group of the PGC was established to characterize the overlaps and differences in genetic architecture across neuropsychiatric disorders (Craddock et al., 2009).

With advances in statistical methods, the global similarity of genetic variation for two traits could be estimated using SNP-based genetic correlations (Bulik-Sullivan et al., 2015). For most pairs of neuropsychiatric disorders, moderate SNP-based correlations were found (Anttila et al., 2018; P. H. Lee et al., 2019), with SCZ and BIP exhibiting the highest degree of SNP-based genetic correlation with r_g=0.70 (P. H. Lee et al., 2019). Research has shown that genetic correlation across neuropsychiatric disorders was reflected at additional biological levels (Gandal et al., 2022; Patel et al., 2021; Radonjić et al., 2021). For example, the similarity of cortical alterations observed in patients across six neuropsychiatric disorders (ADHD, ASD, BIP, MD, OCD, and SCZ) has been suggested to resemble their genetic correlations (Patel et al., 2021; Radonjić et al., 2021). Furthermore, similarities in gene expression patterns across five neuropsychiatric disorders (ASD, BIP, MD, SCZ, and alcoholism) were found to reflect their genetic correlations (Gandal et al., 2018). However, genetic correlations may be underestimated when genetic variants have a mixture of concordant and discordant effects on two traits (Frei et al., 2019). Univariate and bivariate Gaussian mixture models can be used to quantify the genetic overlap of two traits in the presence of mixed effects (Frei et al., 2019). When applied to neuropsychiatric disorders, it was demonstrated that 95 to 99 % of the genetic variants for anxiety, SCZ, BIP, and ADHD were also influential for MD (Als et al., 2023). These findings suggest that the genetic overlap may contribute to shared neurobiological processes across neuropsychiatric disorders (Mallard et al., 2023).

Over the past decade, several cross-disorder GWAS have been conducted to characterize the genetic overlap across neuropsychiatric disorders (P. H. Lee et al., 2019; Romero et al., 2022; Schork et al., 2019). To date, the largest cross-disorder GWAS by the PGC comprised more than 232,964 cases across eight neuropsychiatric disorders (ADHD, ANO, ASD, BIP, MD, OCD, SCZ, and TS) and identified 146 linkage disequilibrium (LD)-independent SNPs at 136 genome-wide significant loci (P. H. Lee et al., 2019). The PGC-CDG2 used a subset-based meta-analysis framework that allows associations to be captured across a heterogeneous group of disorders (Bhattacharjee et al., 2012). As a result,

a large proportion of the identified genetic variants were shown to have complex associations across neuropsychiatric disorders (Figure 1) (P. H. Lee et al., 2019).

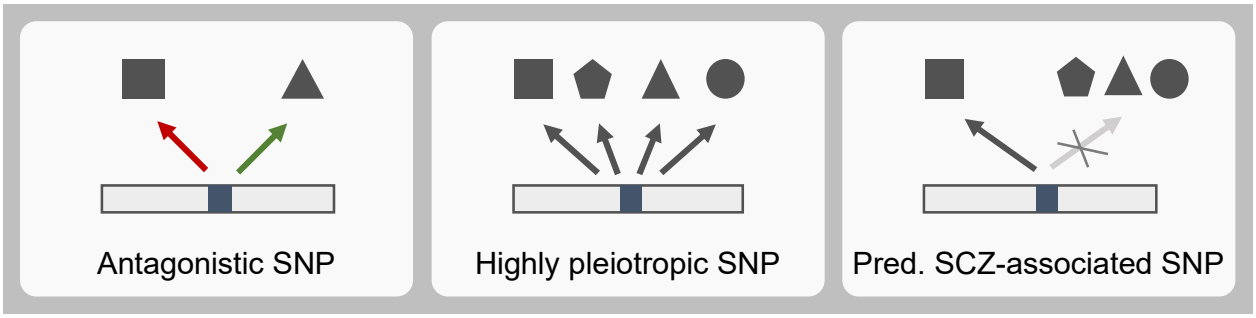


Figure 1 | SNPs with complex associations across neuropsychiatric disorders

The second cross-disorder GWAS by the PGC (P. H. Lee et al., 2019) identified 11 antagonistic SNPs with oppositely directed effects on at least two neuropsychiatric disorders (Section 2.1.1.1; Table 2), 23 highly pleiotropic SNPs that were associated with at least four neuropsychiatric disorders (Section 2.2.2.2; Table S1), and 22 predominantly SCZ-associated SNPs that were associated with SCZ, but showed no evidence for an association with other neuropsychiatric disorders (Section 2.2.2.2; Table S2). The Figure outlines the association between a SNP (blue rectangle) and neuropsychiatric disorders (geometric shapes shown in gray). Regarding the antagonistic SNP, the red arrow indicates an increased risk, and the green arrow indicates a protective effect for a disorder. *Abbreviations.* GWAS, genome-wide association study; PGC, Psychiatric Genomics Consortium; Pred., predominantly; SCZ, schizophrenia; SNP, single-nucleotide polymorphism.

In particular, among the 146 SNPs, 23 highly pleiotropic SNPs were associated with at least four disorders, and 22 SNPs were predominantly associated with SCZ but showed no evidence of association with the other seven neuropsychiatric disorders (P. H. Lee et al., 2019). In addition, among all SNPs with $p \leq 1.0 \times 10^{-06}$, 11 antagonistic SNPs were associated with an increased risk for one neuropsychiatric disorder, while being protective against another disorder (P. H. Lee et al., 2019).

It might be presumed that shared and predominantly disorder-specific genetic variants are involved in different neurobiological processes (P. H. Lee et al., 2019). Using functional genomic data, the PGC-CDG2 showed that pleiotropic (associated with at least two neuropsychiatric disorders) and predominantly disorder-specific genetic variants (associated with a single neuropsychiatric disorder) were enriched for genes of distinct sets of neural cell types and brain tissues (P. H. Lee et al., 2019). Furthermore, genes mapped to pleiotropic genetic variants showed increased expression in the brain with the beginning of the second prenatal trimester compared to genes mapped to non-pleiotropic genetic variants (P. H. Lee et al., 2019).

Several of the shared and predominantly disorder-specific genetic variants are likely to be involved in neurodevelopmental processes. For instance, rs8084351 was particularly interesting because this SNP was associated with all eight disorders (P. H. Lee et al., 2021; Torres-Berrío et al., 2020; Vosberg et al., 2019). rs8084351 is an intronic variant in the *DCC netrin 1 receptor* (*DCC*) gene and may thus influence its transcription (Vosberg et al., 2019). *DCC* has been proposed to mediate axonal growth and axonal guidance for cortical projections (Bendriem & Ross, 2017), suggesting an important effect on the wiring of the human brain (Bendriem & Ross, 2017). Among the predominantly SCZ-associated SNPs, rs75059851 was previously highlighted in the second GWAS of SCZ by the PGC (Ripke et al., 2014). The SNP is located in the first intron of the *immunoglobulin superfamily member 9b* (*IGSF9B*) gene (Barešić et al., 2019), which encodes a cell adhesion molecule important for neurodevelopment (Barešić et al., 2019) and suggested to play a specific role in inhibitory synapses (Clarin et al., 2024).

While (highly) pleiotropic genetic variants are of particular interest for understanding biological processes that are shared across neuropsychiatric disorders, uncovering neurobiological correlates of genetic variants with disorder-specific or even antagonistic effects may shed light on why some neuropsychiatric disorders have distinct symptoms, such as hallucinations, which occur primarily in SCZ (Kahn et al., 2015), or difficulties with social communication, which are characteristic for ASD (Lord et al., 2020). In particular, it may reveal why some neuropsychiatric disorders have contrasting clinical characteristics, such as ASD and SCZ, which, despite their shared cognitive dysfunctions, exhibit opposite extremes in mental state attribution (Ciaramidaro et al., 2015). Here, patients with ASD tend to devoid people's intentions, whereas patients with SCZ tend to attribute intentions where none exist (Ciaramidaro et al., 2015).

1.5 Aim and outline of this thesis

With brain structure recognized as a key intermediate phenotype for neuropsychiatric disorders (Section 1.3) and increasing evidence for a substantial genetic overlap across neuropsychiatric disorders (Section 1.4), this thesis set out to investigate the neurobiological correlates of genetic variants with complex associations across neuropsychiatric disorders (Figure 2). Here, 11 antagonistic, 23 highly pleiotropic, and 22 predominantly SCZ-associated SNPs identified by the PGC-CDG2 (P. H. Lee et al., 2019) (Figure 1) are the subject

of analysis. These genetic variants are of particular interest as they may shed light on shared and distinct neurobiological processes in phenotypically different neuropsychiatric disorders. The findings from this thesis may prioritize SNPs and brain phenotypes for future research across additional neurobiological scales.

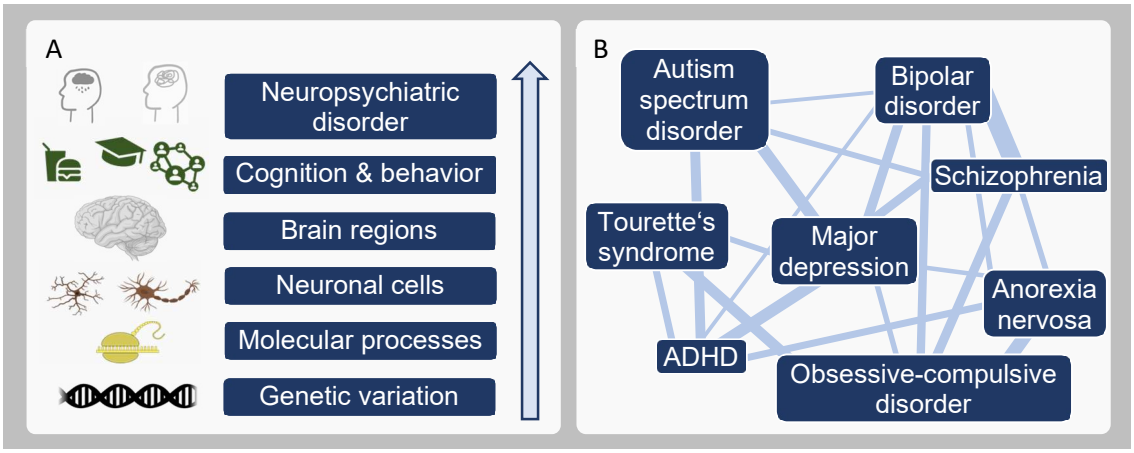


Figure 2 | Neurobiological processes and genetic overlap across neuropsychiatric disorders

This thesis addressed two key challenges in the field of psychiatric genetics (Derks et al., 2022) that include (**A**) understanding the molecular mechanisms of how genetic variants associated with neuropsychiatric disorders influence disease risk, and (**B**) characterizing the genetic cross-disorder landscape of neuropsychiatric disorders. For reasons outlined in Section 1.3, this thesis addressed **A** by investigating the association of selected SNPs with brain structural and brain-related phenotypes. Based on findings introduced in Section 1.4, this thesis advanced **B** by focusing on SNPs with complex associations across multiple neuropsychiatric disorders to improve our understanding of their diagnostic boundaries. Connections in **B** represent genetic correlations, as shown in Figure 1 of (P. H. Lee et al., 2019). The icons were taken from the open NIH BIOART Source (*https://bioart.niaid.nih.gov/*). *Abbreviations*. ADHD, attention deficit hyperactivity disorder; SNP, single-nucleotide polymorphism.

This thesis is structured around two studies. Study 1 shed light on the association of the 11 antagonistic SNPs with brain structure. In a series of subsequent analyses, significantly associated structural phenotypes were examined for their alteration in patients compared to controls, and implicated SNPs were further annotated for their association with gene expression in brain tissue and cognitive-behavioral traits. Moreover, a VBM analysis was performed using data from the FOR2107 study to shed light on brain structural associations beyond atlas-bound regions. Considering brain structure as an intermediate phenotype, as outlined in Section 1.3, it can be presumed that antagonistic SNPs for neuropsychiatric disorders may also be associated with brain structural phenotypes.

Study 2 examined the neurobiological correlates of the 23 highly pleiotropic SNPs and the 22 predominantly SCZ-associated SNPs (P. H. Lee et al., 2019). In light of this, GRSs were calculated in data from the UKBB for each set of SNPs and associated with brain

structural phenotypes. To provide additional insights into their potential influence on participants' psychological well-being, including their emotional stability, ability to cope with stress, or tendency to experience irritable mood, the association of the GRSs with outcomes related to mental health was investigated. Based on the results presented in Section 1.2.2, it was hypothesized that the GRS of highly pleiotropic SNPs would be more likely to be associated with brain regions implicated in multiple neuropsychiatric disorders, including the prefrontal cortex (Goodkind et al., 2015; Opel et al., 2020). In contrast, the GRS of predominantly SCZ-associated SNPs may be associated with brain regions specifically implicated in the pathogenesis of SCZ, such as the superior temporal region (Van Erp et al., 2018). Furthermore, it can be speculated that the GRS of highly pleiotropic SNPs may show pronounced associations with outcomes related to mental health, which are known to be nonspecific factors for neuropsychiatric disorders (Davis et al., 2020).

2 Material and Methods

A schematic overview of the imaging genetic analyses performed in this thesis can be found in Figure 3. The tools and software used throughout this thesis are listed in Table S3. Of note, genetic variants refer to common genetic variants with a MAF of >1 % unless otherwise stated.

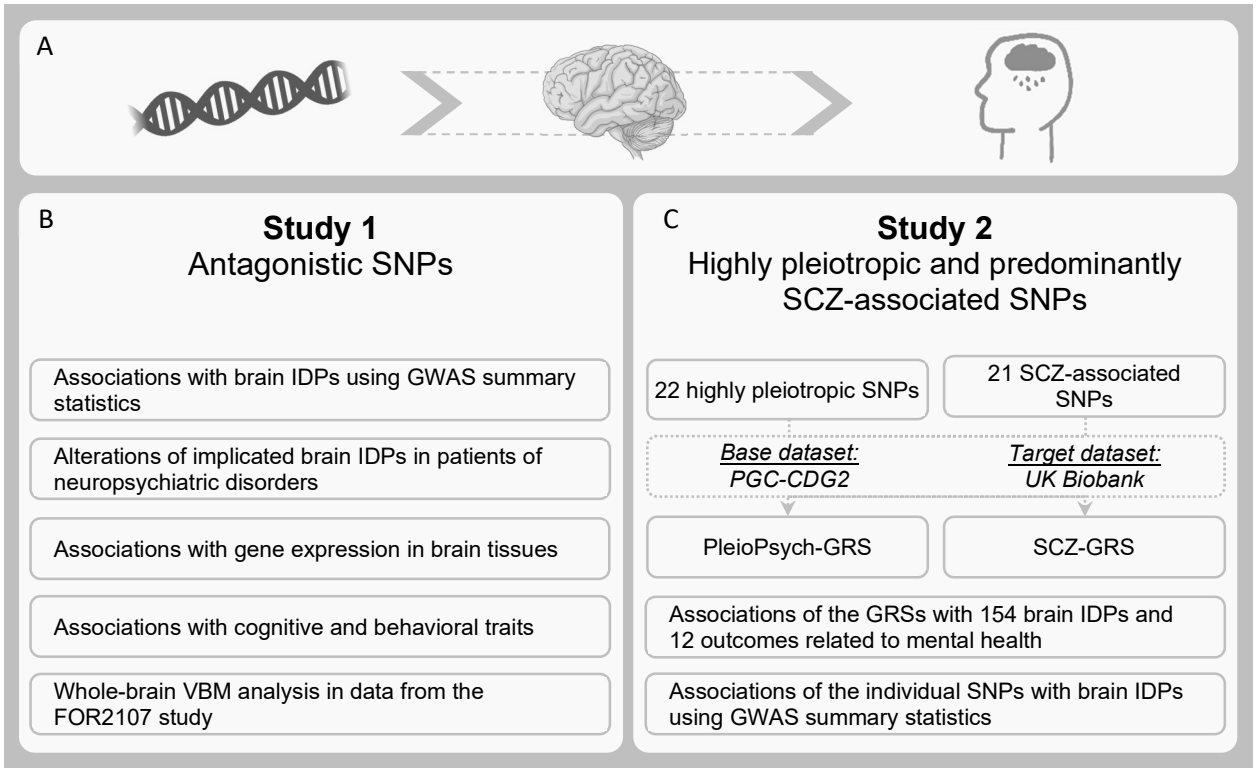


Figure 3 | Schematic overview of the imaging genetic analyses presented in this thesis

This thesis performed two genomic imaging analyses to uncover mechanisms by which genetic variants may contribute to the risk for neuropsychiatric disorders (**A**). Study 1 (**B**) systematically characterized the antagonistic SNPs identified by the PGC-CDG2 (P. H. Lee et al., 2019) for their association with brain-related traits. Study 2 (**C**) examined neurobiological correlates of the highly pleiotropic and predominantly SCZ-associated SNPs identified by the PGC-CDG2 (P. H. Lee et al., 2019). Icons are from the open-source NIH BIOART (*https://bioart.niaid.nih.gov/*). *Abbreviations.* GRS, genetic risk score; GWAS, genome-wide association study; IDP, image-derived phenotype; neuropsy., neuropsychiatric; PGC-CDG2, second cross-disorder GWAS meta-analysis of the PGC; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; SCZ, schizophrenia; SCZ-GRS, GRS of predominantly SCZ-associated SNPs; SNP, single-nucleotide polymorphism; VBM, voxel-based morphometry.

Study 1 investigated the association of the 11 antagonistic SNPs (P. H. Lee et al., 2019) with 78 brain image-derived phenotypes (IDPs), including measures of subcortical volume, CT, and SA, based on GWAS summary statistics from the ENIGMA and CHARGE consortia (Section 2.1.1) (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019).

Subsequently, a bootstrapping test was performed to assess whether the 11 antagonistic SNPs had a significantly higher number of associations with IDPs compared to randomly drawn sets of 11 SNPs (Section 2.1.2). Furthermore, it was determined whether IDPs significantly associated with an antagonistic SNP were altered in patients compared to controls based on the case-control MRI studies by the ENIGMA consortium (Section 2.1.3). In addition, antagonistic SNPs that were significantly associated with an IDP were further annotated for their association with gene expression in the brain using the genotype-tissue expression (GTEx) project and Brain eQTL Almanac (BRAINEAC) eQTL databases (Section 2.1.4) and with cognitive and behavioral traits using the Open Targets Genetics Portal (Section 2.1.5). Finally, a whole-brain VBM analysis was performed in data from the FOR2107 study to provide insights into the association of the 11 antagonistic SNPs with brain structure without being bound to the neuroanatomical boundaries given by the brain atlas (Section 2.1.6).

Study 2 investigated the association of the GRSs of highly pleiotropic SNPs (PleioPsych-GRS) and likewise predominantly SCZ-associated SNPs (SCZ-GRS) with brain structure and outcomes related to mental health in data from the UKBB (*n*=28,952) (Section 2.2). To prioritize SNPs of particular relevance, the associations of individual SNPs with brain structure were assessed based on GWAS summary statistics of the ENIGMA and CHARGE consortia (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019).

2.1 Study 1

Ethical approval for Study 1 was obtained from the local ethics committees of the University of Marburg (AZ: 07/14) and the University of Münster (AZ: 2014-422-b-S), Germany. The methods presented in Study 1 were in line with the relevant guidelines and regulations, and all participants provided informed consent (Federmann et al., 2024).

2.1.1 Association of the antagonistic SNPs with brain image-derived phenotypes

2.1.1.1 Materials

The associations between the 11 antagonistic SNPs (Table 2) and the 78 IDPs (Table S4) were examined using summary statistics of large-scale GWAS from the ENIGMA and CHARGE consortia (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019). GWAS summary statistics provide relevant statistical parameters of the trait associations of

SNPs, such as the effect allele, effect size, and estimated *p*-value (Uffelmann et al., 2021). As GWAS typically rely on large numbers of participants, GWAS summary statistics are a valuable resource with sufficient power to investigate SNP-to-IDP associations.

Table 2 | Antagonistic SNPs

rsID	CHR	BP (GRCh37)	EA	OA	Risk	Protective	CADD	VEP	Nearest gene
rs301805	1	8481016	T	G	MD	SCZ	6.56	Intron variant	*SLC45A1*
rs6748341	2	225377574	C	G	SCZ	ANO	4.84	Intron variant	*CUL3*
rs75595651	4	123133540	T	C	BIP	MD	4.62	Intron variant	*KIAA1109*
rs1363105	5	103917790	T	C	ANO	ADHD/ ASD/MD	3.07	Intron variant	*NUDT12*
rs3806843	5	140212538	T	C	SCZ	MD	0.99	Intron variant	*PCDHA7*
rs2388334	6	98591622	A	G	TS	ASD/BIP	5.76	Intron variant	*POU3F2*
rs1933802	6	105365891	C	G	SCZ	MD	4.16	Intergenic variant	*LIN28B*
rs2867673	7	71752652	T	C	SCZ	ADHD	1.07	Intron variant	*CALN1*
rs9329221	8	10240202	T	G	SCZ	ASD	7.72	Intron variant	*PRSS55*
rs2921036	8	8363897	T	C	ASD	SCZ	3.79	Intergenic variant	*PRAG1*
rs9511168	13	19600475	A	C	ADHD	ANO	8.80	Non-coding transcript exon variant	*TUBA3C*

Information on the genomic position, effect allele, and associated neuropsychiatric disorders of the 11 antagonistic SNPs identified by the PGC-CDG2 were obtained from Table S3.3 in (P. H. Lee et al., 2019) and corresponding GWAS summary statistics excluding 23andMe subjects. PHRED-scaled CADD, Ensembl VEP, and nearest genes were taken from annotations provided in the Open Targets Genetics portal v22.10 (Ghoussaini et al., 2021; Mountjoy et al., 2021). The CADD score estimates the deleteriousness of SNPs (Rentzsch et al., 2019), while the VEP annotates the potential effects of the SNPs (McLaren et al., 2016). *Abbreviations*. ADHD, attention deficit hyperactivity disorder; ANO, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; BP, basepair position; CADD, combined annotation-dependent depletion; CHR, chromosome; EA, effect allele; GRCh37, Genome Reference Consortium human build 37; GWAS, genome-wide association study; MD, major depression; OA, other allele; PGC, Psychiatric Genomics Consortium; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; TS, Tourette's syndrome; VEP, variant effect predictor.

This analysis was based on the following GWAS, which were the most recent GWAS from the ENIGMA and CHARGE consortia for the respective IDPs at the time of analysis: (i) the GWAS of the volumes of the amygdala, brainstem, caudate, nucleus accumbens, pallidum, putamen, and thalamus (n_{IDPs}=7, $n_{samples}$=37,741) (Satizabal et al., 2019), (ii) the GWAS of hippocampal volume (n_{IDPs}=1, $n_{samples}$=26,814) (Hibar et al., 2017), and (iii) the GWAS of CT and SA that encompass each one whole-brain as well as 34 regional measures as delineated by the Desikan-Killiany (DK) atlas (Desikan et al., 2006) (n_{IDPs}=70, $n_{samples}$=33,281) (Grasby et al., 2020). Here, $n_{samples}$ refers to the number of samples given in the GWAS summary statistics of the discovery cohort. The studies were

approved by the respective ethics committees, and all participants provided informed consent as described in the respective publications (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019).

2.1.1.2 Statistical analysis

The GWAS summary statistics were accessed via the ENIGMA-VIS tool (Novak et al., 2012), which allowed the query of statistical parameters like the effect size, effect allele, and *p*-value of the SNP-to-IDP associations. The effect sizes constituted *Z*-scores for subcortical IDPs and *β*-values for cortical IDPs. At the time of analysis, the ENIGMA-Vis tool did not incorporate the GWAS of subcortical volumes (Satizabal et al., 2019). Hence, the corresponding SNP-to-IDP associations were extracted from the original GWAS summary statistics provided upon request by the authors. Furthermore, the antagonistic SNP rs1933802 was replaced by rs314280 (r^2=1; LD in Utah residents with Northern and Western European ancestry (CEU)) as it was not covered in the GWAS summary statistics of cortical IDPs (Grasby et al., 2020). Here, the proxy SNP was queried using the LDproxy tool (Machiela & Chanock, 2015), which uses the haplotypes from the 1000 Genomes Project (Auton et al., 2015) to calculate the LD for a specific population. Finally, correction for multiple testing was performed using the Benjamini-Hochberg (BH) procedure (Benjamini & Hochberg, 1995) that controls the false discovery rate (FDR). SNP-to-IDP associations were deemed significant at p_{FDR}<0.05.

2.1.2 Bootstrapping the number of significant associations

A bootstrapping test was performed to investigate whether the 11 antagonistic SNPs were associated with a higher number of IDPs than expected. This test compared the number of significant SNP-to-IDP associations of the 11 antagonistic SNPs to a sampling distribution. This distribution was constructed by obtaining the number of significant SNP-to-IDP associations for randomly drawn sets of 11 SNPs.

Two separate bootstrapping tests were conducted. In a first test, K_1=10,000 sets of 11 SNPs were randomly drawn from the n=6,559,812 SNPs included in all 78 GWAS summary statistics from the ENIGMA and CHARGE consortia that were provided by the authors upon request (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019). In an independent second test, K_2=1,000 sets of 11 SNPs were randomly drawn from the

n=13,999 SNPs that were included in all 78 GWAS summary statistics and had an association *p*-value of ≤1.0×10^{-06} within the GWAS summary statistics of the PGC-CDG2 (P. H. Lee et al., 2019) without the 23andMe samples.

For each randomly drawn set of 11 SNPs, corresponding *p*-values of association with each of the 78 IDPs were retrieved from GWAS summary statistics. As done in the main analysis, multiple testing correction was applied using the BH procedure, and associations were deemed significant at $p_{FDR}<0.05$. The number of significant SNP-to-IDP associations was obtained across (i) all 78 IDPs as well as across all IDPs specific to one brain measure, namely across (ii) eight IDPs of subcortical volume, (iii) 34 IDPs of CT, and (iv) 34 IDPs of SA. Finally, for each of (i) - (iv), a sampling distribution was constructed over the number of significant SNP-to-IDP associations across K_1 or K_2 sets of 11 SNPs.

The number of significant SNP-to-IDP associations of the 11 antagonistic SNPs *t* was compared to the sampling distribution, which enabled to assess whether this number was significantly higher than expected. To this end, the *p*-value was estimated by $p=\frac{1+\#\{t_k^*\geq t\}}{K+1}$ (Davison & Hinkley, 1997) with $\#\{t_k^*>t\}$ denoting the count of randomly sampled sets of 11 SNPs that showed a higher number of significant SNP-to-IDP associations compared to the 11 antagonistic SNPs. The comparisons were considered significant at $p<6.25\times10^{-03,}$ corresponding to a Bonferroni correction for two bootstrapping tests and four sets of IDPs.

2.1.3 Case-control MRI differences of the implicated brain image-derived phenotypes

For all IDPs that were significantly associated with an antagonistic SNP, it was examined whether these IDPs have previously been found to be altered in patients with neuropsychiatric disorders compared to controls. The present analysis considered disorders associated with the respective antagonistic SNP (P. H. Lee et al., 2019).

Structural alterations were investigated using the case-control MRI meta- and mega-analyses by the ENIGMA consortium for six of the eight neuropsychiatric disorders included in the PGC-CDG2 (see Table 3 for an overview). No case-control MRI study has been performed for TS at the time of writing. In addition, ANO was not included because the ENIGMA case-control MRI study comprised only female participants and, in part, acutely underweight cases whose weight loss may have affected brain structure (Walton et al.,

2022). The six included case-control MRI studies used standardized pipelines for preprocessing and meta-analysis (Thompson et al., 2020). However, the different case-control MRI studies varied in sample size, ranging from 1,658 cases of ASD to 4,474 cases of SCZ, but also in cohort characteristics, including age range, male-to-female ratio, and covariates (Table 3). Each study was approved by the respective ethics committees, and informed consent was obtained from all participants, as described elsewhere (see references in Table 3). These studies incorporated IDPs similar to those used in Section 2.1.1 but examined unilateral compared to bilateral measures (Table S4).

Table 3 | Case-control MRI studies of neuropsychiatric disorders

Disorder	Vol./CT/SA	ENIGMA study	N_{cases} / $N_{controls}$	age	sex	ICV	site	IQ	Multiple testing correction
ADHD	Vol.	Hoogman et al. (2017)	1,713/1,529	x	x	x	x		FDR
	CT, SA	Hoogman et al. (2019)	2,246/1,934	x	x	x[1]			FDR
ASD	Vol., CT, SA	Van Rooij et al. (2018)	1,658/1,606	x	x	x[2]		x	FDR
BIP	Vol.	Hibar et al. (2016)	1,710/2,594	x	x	x			FDR
	CT, SA	Hibar et al. (2018)	1,837/2,582	x	x	x[1]			FDR
MD	Vol.	Schmaal et al. (2016)	1,728/7,199	x	x	x	x		Bonferroni[3]
	CT, SA	Schmaal et al. (2017)	2,148/7,957	x	x		x		FDR
OCD	Vol.	Boedhoe et al. (2018)	1,830/1,759	x	x	x	x		Bonferroni[3]
	CT, SA	Boedhoe et al. (2017)	1,905/1,760	x	x	x[1]	x		FDR
SCZ	Vol.	Van Erp et al. (2016)	2,028/2,540	x	x	x	x		Bonferroni[3]
	CT, SA	Van Erp et al. (2018)	4,474/5,098	x	x				FDR

Overview of the ENIGMA consortium case-control MRI studies of ADHD, ASD, BIP, MD, OCD, and SCZ adapted from Table S2 in (Federmann et al., 2024). Here, the numbers of cases (N_{cases}) and controls ($N_{controls}$) were obtained from the individual studies. The included covariates and the procedure for multiple testing corrections were taken from the study overview of the ENIGMA Toolbox *(https://enigma-toolbox.readthedocs.io/en/latest/pages/04.loadsumstats/index.html*). Site refers to the scanner site. [1]ICV was included as a covariate for SA measures, and [2]ICV for subcortical measures. Significance was considered with [3]$p<5.6\times10^{-03}$. *Abbreviations*. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BIP, bipolar disorder; CT, cortical thickness; ICV, intracranial volume; IQ, intelligence quotient; MD, major depression; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; *p*, *p*-value; SA, surface area; SCZ, schizophrenia; Vol., volume.

Statistical parameters of case-control MRI differences, including uncorrected *p*-values for subcortical IDPs, FDR-corrected *p*-values for cortical IDPs, and effect sizes denoted by Cohen's *d* were accessed for each study using the ENIGMA Toolbox (Larivière et al., 2021). Case-control MRI differences of the main analyses were retrieved and considered significant at $p_{FDR}<0.05$ for cortical IDPs and $p<5.6\times10^{-03}$ after Bonferroni correction for subcortical IDPs.

2.1.4 Antagonistic SNPs and gene expression in brain tissues

Antagonistic SNPs significantly associated with at least one IDP (*n*=8) were investigated for their association with gene expression levels in brain tissues. This analysis is based on eQTLs of 12 brain tissues from the GTEx project database v8 (Lonsdale et al., 2013), including the amygdala, Brodmann area 9, Brodmann area 24, caudate, cerebellum, cerebellar hemisphere, entire cortex, hippocampus, hypothalamus, nucleus accumbens, putamen, and substantia nigra. In addition, the analysis used eQTLs of four brain tissues from the BRAINEAC database (Ramasamy et al., 2014). To avoid overlap with the brain tissues of GTEx, a subset of brain tissues was selected from the BRAINEAC database, namely the frontal cortex, occipital cortex, temporal cortex, and the average across all ten tissues of the BRAINEAC database. The eQTLs from GTEx v8 were based on RNA-Seq data from *n*=205 donors for cortical tissue to *n*=114 donors for substantia nigra tissue (cf., Figure 1 in Aguet et al., 2020). In contrast, eQTLs from BRAINEAC were based on cortical tissues from *n*=134 donors (Ramasamy et al., 2014). For this analysis, rs75595651 was substituted by the proxy SNP rs77087420 (LD in CEU r^2=1) using the LDproxy tool, as it was not covered in both databases.

The antagonistic SNPs were deemed to be part of an eQTL with $p<4.0\times10^{-04}$ using Bonferroni correction for eight SNPs and 16 brain tissues. eQTLs that regulate the expression of pseudogenes as given by the locus type in the database of the HUGO Gene Nomenclature Committee (Tweedie et al., 2021) were not reported.

2.1.5 Antagonistic SNPs and cognitive and behavioral traits

Associations with cognitive and behavioral traits were reported for all antagonistic SNPs significantly associated with at least one IDP (*n*=8). Traits of interest encompassed cognitive performance, educational attainment, lifestyle, personality, food preferences, sleep factors, and mental health outcomes. Trait associations with any of the eight neuropsychiatric disorders of the PGC-CDG2 were excluded.

Trait associations of SNPs were queried from the Open Targets Genetics portal v22.10 (Ghoussaini et al., 2021; Mountjoy et al., 2021), which integrates GWAS summary statistics from the NHGRI-EBI GWAS Catalog (Buniello et al., 2019) as well as GWAS performed in large-scale biobanks such as the UKBB (*https://www.nealelab.is/uk-biobank/*)

and the FinnGen project (Kurki et al., 2023). SNP associations were reported at genome-wide significance ($p<5.0\times10^{-08}$).

2.1.6 Whole-brain voxel-based morphometry analysis in data from the FOR2107 study

Whole-brain VBM analysis was performed using data from the FOR2107 study to shed light on the associations of the antagonistic SNPs with brain structure beyond atlas-bound brain regions. Data collection, preprocessing, and quality control of brain MRI scans and genotype data have been performed by colleagues from the University of Marburg, University of Münster, University of Bonn, and Max Planck Institute of Psychiatry in Munich. These steps are presented in Sections 2.1.6.1 to 2.1.6.5 as described in previous studies (e.g., T. Kircher et al., 2019; Vogelbacher et al., 2018). The whole-brain VBM analysis of the 11 antagonistic SNPs was performed in the context of the present study (Section 2.1.6.6). Thereby, an existing pipeline was used. Here, the pipeline was set up and run to test the association between the antagonistic SNPs and brain structure with the support of Dr. Lisa Sindermann from the University of Bonn.

2.1.6.1 Study design

The FOR2107 study was designed to uncover neurobiological correlates of disorders across the affective disorder-psychosis spectrum (Kircher et al., 2019). In this context, the FOR2107 study collected data from healthy controls as well as individuals with a DSM-IV diagnosis of BIP, MDD, SCZ, or schizoaffective disorder. The collection of multimodal data, including brain MRI scans, genotype data, and detailed cognitive and psychological assessments, took place in Marburg and Münster, Germany (Kircher et al., 2019). The study population comprised more than 2,000 individuals aged 18 to 65 years at the date of analysis. All participants gave written informed consent. Ethical approval was obtained from the local ethics committees of the University of Marburg (AZ: 07/14) and the University of Münster (AZ: 2014-422-b-S), Germany (Kircher et al., 2019).

2.1.6.2 Participants

The VBM analysis was performed in a subsample of *n*=847 healthy controls and *n*=754 patients with MDD. 64.2 % of the subsample were female. The mean age was 35.4 years

(standard deviation (SD)=13.1 years). Patients with BIP, SCZ, and schizoaffective disorder were not included in the present VBM analysis, as structural brain changes are more pronounced in individuals with these disorders (Cheon et al., 2022). Individuals who did not pass the genetic quality control (Section 2.1.6.3) and imaging quality control (Section 2.1.6.5) were excluded previously.

2.1.6.3 Genotyping, genetic quality control, and imputation

The preprocessing of the genetic data of the FOR2107 study was performed in a previous study and is described in the Supplementary Information of Andlauer et al. (2021).
For each sample, DNA was extracted from peripheral blood. Genome-wide genotyping was performed using the Infinium PsychArray-24 BeadChip (Illumina, San Diego, CA, US) (Andlauer et al., 2021). Quality control of genotype data was performed using PLINK v1.90 (Chang et al., 2015) and R v3.5. The following variant and sample filters were used: SNPs with a call rate of <98 % or a MAF of <1 % were removed (Andlauer et al., 2021). Subsequently, samples with genotyping rates of <98 %, sex mismatches, cryptic relatives with *pi-hat*≥12.5, or deviation in autosomal and X-chromosomal heterozygosity (>4 SD from the mean) were removed. Genetic duplicates were dropped. Multidimensional scaling (MDS) ancestry components were computed per sample (Andlauer et al., 2021). Next, all samples with a deviation of >4 SD in the first eight MDS components were removed. The genetic variants were further filtered by removing SNPs with Hardy-Weinberg equilibrium (HWE) *p*-value of $p<1.0\times10^{-06}$, non-autosomal SNPs, or ambiguous SNPs. The genotype data was aligned to the 1000 Genomes phase reference panel using SHAPEIT v2.3.2 (Andlauer et al., 2021). The imputation has been carried out using IMPUTE v2 (B. Howie et al., 2012; B. N. Howie et al., 2009) and post-imputation SNPs with an imputation quality metric (INFO) of <0.8 or a MAF of <1 % were dropped (Andlauer et al., 2021).
As part of this study, genotype dosages of the 11 antagonistic SNPs were extracted for the remaining subsample. Based on this subset, MDS components were calculated per sample using an in-house script for later use as covariates to account for population stratification.

2.1.6.4 MRI acquisition

MRI data, namely T1-weighted brain scans, were acquired on a 3 Tesla Siemens Prisma MRI scanner in Münster and a 3 Tesla Siemens Trio Trim MRI scanner in Marburg

(Vogelbacher et al., 2018). The head matrix Rx coil had 20 channels in Münster and 12 channels in Marburg. An MP-RAGE sequence was performed with a field-of-view of 256 mm, a voxel resolution of 1×1×1 mm^3, and 192 (Münster) and 176 (Marburg) sagittal slices (Vogelbacher et al., 2018).

2.1.6.5 MRI data preprocessing

The T1-weighted brain scans were visually inspected for artifacts and structural abnormalities by a senior clinician (Vogelbacher et al., 2018). Brain MRI scans were preprocessed with the computational anatomy toolbox (CAT)-12 v1184 (Gaser et al., 2024), which extends the statistical parametric mapping (SPM)-12 toolbox (Penny et al., 2011) using default parameters. Brain MRI scans were segmented into cerebrospinal fluid, gray matter, and white matter (Vogelbacher et al., 2018). Next, segmented brain MRI scans were spatially normalized to the MNI152 space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) algorithm (Ashburner, 2007). The reparametrized gray matter segments were smoothed with an 8 mm full width at half maximum Gaussian kernel. Lastly, the total intracranial volume (ICV) has been extracted (Vogelbacher et al., 2018).

2.1.6.6 Statistical analysis

Based on the assumption of an additive biometric model (see Section 1.2.3), this VBM analysis tested the positive and negative associations of genotype dosages for the 11 antagonistic SNPs with voxel-wise GMV using general linear models as implemented in the CAT-12 toolbox v2159 (Gaser et al., 2024) of the SPM12 toolbox v7771 (Penny et al., 2011). It was corrected for age, sex, diagnosis of MDD, ICV, and the first three MDS components. In addition, it was corrected for a scanner Rx coil change in Marburg that took place during data collection.

GMV clusters associated with an antagonistic SNP's allele dosage were presented with a cluster-forming threshold of $p_{uncorrected}<0.001$ and cluster size of $k>10$ voxels. Associations were deemed significant with a peak-level family-wise error (FWE) correction $p_{FWE}<0.05$. Clusters were labeled using the automated anatomical labelling atlas (AAL) v3 (Rolls et al., 2020; Tzourio-Mazoyer et al., 2002). Furthermore, the peak voxel of the GMV cluster was labeled using the Julich Brain Atlas v3.1 (Amunts et al., 2020). Here, a more fine-

grained annotation of the peak voxel was achieved based on cytoarchitectonic maps of the human brain.

2.2 Study 2

2.2.1 Participants

The associations of the PleioPsych-GRS and SCZ-GRS with IDPs and outcomes related to mental health were examined using genotype data, brain MRI scans, and mental health assessments from the UKBB resource (Bycroft et al., 2018). The UKBB is a prospective biobank study that has recruited over 500,000 individuals between the ages of 40 and 69 years to promote research on the determinants of health-related outcomes (Bycroft et al., 2018). Here, genomic, MRI imaging, medical history, and lifestyle questionnaire data were collected at 22 assessment centers across the UK (Bycroft et al., 2018). Ethical approval for the UKBB study was granted by the North West Multi-centre Research Ethics Committee under the reference number 11/NW/0382 (see *https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank/about-us/ethics*). Written informed consent was obtained from all study participants. The present study was conducted under project application 41655.

Individuals with an ICD-10 diagnosis (data-field in the UKBB showcase: 41720; see *https://biobank.ndph.ox.ac.uk/ukb/*) related to the central nervous system were excluded (*n*=1,127; see Supplementary Table S5 for a detailed list of ICD-10 codes). The resulting subsample included *n*=28,952 (46.9 % male) individuals of self-reported White British ancestry with available genotype and brain MRI data that passed genetic quality control. The mean age was 63.8 years (SD=7.4 years).

As the PGC-CDG2 meta-analysis included samples from the UKBB due to a GWAS of MD (Wray et al., 2018), a sensitivity analysis was performed excluding samples with self-reported and diagnosed depression. According to the case ascertainment of the respective GWAS of MD (Wray et al., 2018), samples with an ICD-10 diagnosis of MDD (ICD-10 codes F32 and F33; data-field: 41270) and samples who reported having been depressed or feeling down for at least two weeks (data-field: 4609), or having seen a psychiatrist for anxiety or depression (data-field: 2100) were excluded. For self-reports, data records were taken from the first and second assessments as the GWAS of MD (Wray et al., 2018) was based on the UKBB interim data release. A total of *n*=21,556 samples (48.6 % males)

remained for sensitivity analyses. The subsample had a mean age of 64.0 years (SD=7.4 years).

2.2.2 Materials

2.2.2.1 Genotyping and genetic quality control

The UKBB study team extracted DNA from whole blood samples. The Affymetrix Research Services Laboratory carried out genotyping using the Applied Biosystems UK BiLEVE Axiom® Array and the Applied Biosystems UKBB Axiom® Array (Bycroft et al., 2018). The UKBB provided imputed genotype data positioned according to the GRCh37 (category in the UKBB showcase: 100319).

In light of a previous project (Primus et al., 2024), genetic quality control using PLINK 1.9 and 2.0 (Chang et al., 2015) was performed by collaborators at the Institute of Neurogenomics of the Helmholtz Zentrum München, Germany. Variants with a MAF of <0.01, a call rate of <95 %, a deviation from HWE of $p<1\times10^{-6}$, or an INFO metric of <0.3 were removed. Furthermore, all samples with genotype coverage <95 %, sex mismatch, and heterozygosity rates that extended ±3 SD from the mean were dropped (Primus et al., 2024). In addition, one sample was excluded for each pair of samples with a kinship coefficient >0.088, corresponding to up to and including second-degree relatedness (Manichaikul et al., 2010). Ancestry principal components were calculated using PLINK 2.0 to capture the genetic variance across samples with self-reported White British ancestry (data-field: 21000) (Primus et al., 2024).

2.2.2.2 Single-nucleotide polymorphisms

The highly pleiotropic and predominantly SCZ-associated SNPs were derived from the PGC-CDG2 (P. H. Lee et al., 2019). The meta-analysis framework used by the PGC-CDG2 provided for each SNP the posterior probability of association with each of the eight neuropsychiatric disorders denoted by the *m*-value (Han & Eskin, 2012). Note that associations with $m<0.8$ can be considered ambiguous, and associations with $m\geq0.8$ can be considered evident (see Figure 1 in Han & Eskin, 2012).

The PGC-CDG2 defined a highly pleiotropic SNP if the *m*-values for at least four neuropsychiatric disorders were greater than or equal to 0.9 (P. H. Lee et al., 2019). In total, 23 highly pleiotropic SNPs were identified (see Table 2 in P. H. Lee et al., 2019; and Table

S1). For the following analyses, the palindromic SNP rs11688767 was excluded because its MAF exceeds 40 % and thus, allelic mismatches between the base and target datasets cannot be inferred.

The predominantly SCZ-associated SNPs were derived from Table S3.2 of the PGC-CDG2 (P. H. Lee et al., 2019). Here, any SNP that showed an association of $m \geq 0.9$ for SCZ but $m < 0.8$ for the other neuropsychiatric disorders was considered predominantly SCZ-associated. Applying a threshold of $m < 0.8$ ensures that there is no strong evidence of association between the SNP and other neuropsychiatric disorders. In total, 22 predominantly SCZ-associated SNPs were derived from the PGC-CDG2 (P. H. Lee et al., 2019) (Table S2). One palindromic SNP (rs2801578) with a MAF greater than 40 % was excluded from these SNPs. Furthermore, rs13217619 was replaced by rs34718920 (LD in CEU $r^2=1$) as it was not covered in the GWAS summary statistics of the PGC-CDG2 excluding the 23andMe cohort (P. H. Lee et al., 2019).

2.2.2.3 Genetic risk scores

The calculation of the GRS for individuals in data from the UKBB was performed with the support of Dr. Kaustubh R. Patil from the Institute of Neuroscience and Medicine (INM-7) at the Forschungszentrum Jülich, Germany.

The PleioPsych-GRS and SCZ-GRS, which aggregate the effects of 22 highly pleiotropic SNPs and 21 predominantly SCZ-associated SNPs, respectively, were calculated using PRSice v2.3.5 (Choi & O'Reilly, 2019). SNP effect sizes were taken from the GWAS summary statistics of the PGC-CDG2 without samples from the 23andMe cohort (P. H. Lee et al., 2019). The GRS calculation did not include the steps of LD-clumping or *p*-value thresholding, as the selected SNPs were part of LD-independent and genome-wide significant loci. Lastly, the GRSs were standardized by *Z*-scoring and visually inspected for normality.

It should be noted that the SCZ-GRS was calculated based on effect sizes derived from a cross-disorder GWAS. While it could be argued that other neuropsychiatric disorders influence the effect sizes, it must be pointed out that the PGC-CDG2 applied a subset-based GWAS meta-analysis framework (Bhattacharjee et al., 2012). The effect size of association was maximized across all combinations of disorder subsets (Bhattacharjee et al., 2012), allowing potential disorder-specific effects to be captured. However, to assess

whether the origin of the SNP effect sizes influenced the present results, sensitivity analyses were conducted with the SCZ-GRS calculated based on the effect sizes from the most recent GWAS of SCZ by the PGC (PGC-SCZ3) (Trubetskoy et al., 2022). Here, SNP effect sizes were taken from the core GWAS summary statistics of the PGC-SCZ3, including samples from multiple ancestries (n_{cases}=67,390 and $n_{controls}$=94,015). Of note, the PGC-SCZ3 did not include participants from the UKBB (Trubetskoy et al., 2022). As rs10211550, rs11782089, and rs144158419 were not covered in the GWAS summary statistics, these SNPs were replaced by the following proxy SNPs: rs67657812 (LD in CEU r^2=0.8), rs7839435 (LD in CEU r^2=1), and rs72934586 (LD in CEU r^2=1).

2.2.2.4 Brain structural image acquisition and image-derived phenotypes

T1-weighted MRI scans were acquired at the UKBB recruitment centers in Bristol, Newcastle, Cheadle, and Reading (Bycroft et al., 2018). The brain MRI scans were preprocessed in light of a previous project by colleagues of the Institute of Neuroscience and Medicine (INM-7) at the Forschungszentrum Jülich, Germany, and the Institute of Neurogenomics at the Helmholtz Zentrum München, Germany (Primus et al., 2024). The preprocessing was done with fMRIprep (Esteban et al., 2018). fMRIprep implements the FreeSurfer v6 preprocessing pipeline (Dale et al., 1999) that consists of skull stripping, tissue segmentation, and spatial normalization to reconstruct brain surfaces. Based on these, subcortical segmentation of the amygdala, caudate, hippocampus, nucleus accumbens, pallidum, putamen, and thalamus and cortical parcellation of 34 regions delineated by the DK atlas (Desikan et al., 2006) was performed. Next, regional unilateral measures of subcortical volume, CT, and SA, as well as average CT per hemisphere, total SA per hemisphere, and total ICV were extracted. Finally, the Euler number, a measure of MRI image reconstruction quality, was calculated using FreeSurfer v6. In total, 154 IDPs were incorporated in the association analysis (Table S4). This included unilateral measures of seven subcortical volumes, unilateral CT and SA for 34 cortical regions each, average CT per hemisphere, and total SA per hemisphere. In light of this analysis, IDPs with ±3 SD from the mean were removed, and *Z*-scores were derived.

2.2.2.5 Outcomes related to mental health

The association of the GRS with the following 12 outcomes related to mental health was investigated: Mood swings, miserableness, irritability, sensitivity / hurt feelings, fed-up

feelings, nervous feelings, worrier / anxious feelings, tense feelings / highly strung, worry too long after embarrassment, suffer from nerves, loneliness, and guilty feelings (data-fields: 1920-2030). A self-rated touchscreen questionnaire assessed all outcomes by asking, for instance, 'Does your mood often go up and down?' (data-field: 1920, mood swings). The present analysis included responses with 'yes' or 'no', while responses with 'do not know' or 'prefer not to answer' were dropped. Of note, the assessment was completed for all participants in the UKBB subsample used in this study (*n*=28,952). Data obtained at a visit corresponding to the brain MRI scan were analyzed.

2.2.3 Statistical analysis

2.2.3.1 Main analysis

This study examined the associations between the PleioPsych-GRS and the SCZ-GRS with each of the 154 IDPs. Univariate multiple linear regression models were used with age at MRI scan (data-field: 31-2.0), age^2, and sex (data-field: 21003-2.0) as covariates. Furthermore, similar to the case-control MRI studies by the ENIGMA consortium (Table 3), ICV was included as a covariate for subcortical volume and regional SA measures. Correction for multiple testing was performed using the BH method for each GRS separately. Associations with $p_{FDR}<0.05$ were considered significant.

The associations between the PleioPsych-GRS and the SCZ-GRS with each of the 12 outcomes related to mental health were tested using logistic regression. Again, age, age^2, and sex were included as covariates. Associations were considered significant with $p_{FDR}<0.05$ after correction for multiple testing using the BH method.

2.2.3.2 Sensitivity analysis

The following sensitivity analyses were conducted: First, the association analysis between GRSs and IDPs and between GRSs and outcomes related to mental health was repeated with an expanded set of covariates, including the interaction of sex and age, Euler number as a proxy for surface reconstruction quality, head positions x, y, z in the MRI scanner (data-fields: 25756-2.0, 25757-2.0, 25758-2.0)), the UKBB recruitment center as a dummy variable (data-field: 54), and the first ten ancestry principal components as additional covariates. Second, association analyses were repeated excluding samples with self-reported or diagnosed depression (see Section 2.2.1). Third, the association analyses were

repeated with the SCZ-GRS based on effect sizes from a GWAS of SCZ (Trubetskoy et al., 2022) (see Section 2.2.2.3).

2.2.4 Association of the individual SNPs with brain image-derived phenotypes

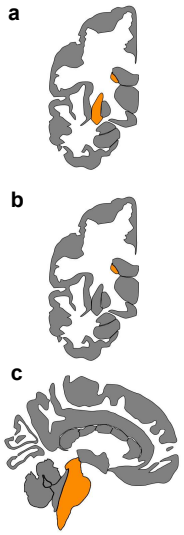
The associations of highly pleiotropic and predominantly SCZ-associated SNPs with 77 bilateral IDPs were investigated using GWAS data from the ENIGMA and CHARGE consortia (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019). The respective GWAS and the procedure for extracting SNP-to-IDP associations from the GWAS summary statistics were previously described for Study 1 in Section 2.1.1. The IDPs included the volumes of seven subcortical structures, as well as CT and SA measures of the whole brain and 34 regions of the DK atlas (see Table S4 for a list of IDPs). Of note, the IDPs aligned with the aforementioned GRS association analysis, but bilateral versus unilateral measures were incorporated. After multiple testing corrections using the BH method separately for the two sets of SNPs, associations were considered significant at $p_{FDR}<0.05$. Proxy SNPs replaced two SNPs because they were not covered in at least one GWAS summary statistics. The predominantly SCZ-associated SNPs rs10211550 was replaced by rs11891750 (LD in CEU $r^2=0.8$) and rs188099135 by rs11780834 (LD in CEU $r^2=1$). For the highly pleiotropic SNP rs117956829 and the predominantly SCZ-associated SNP rs12826178, no proxy SNPs with LD in CEU $r^2>0.6$ were available, and thus they were excluded from the present analysis. In total, 21 highly pleiotropic and 20 predominantly SCZ-associated SNPs remained for analysis.

3 Results

3.1 Study 1

3.1.1 Association of the antagonistic SNPs with brain image-derived phenotypes

Eight of the 11 antagonistic SNPs were significantly associated with at least one IDP (Figure 4 and Figure 5).



rs3806843 – T (effect allele)/C			↗ SCZ, ↘ MD
Brain region	*p*	p_{FDR}	*Z*
putamen	1.6×10^{-05}	3.1×10^{-03}	-4.3
caudate	2.1×10^{-05}	3.1×10^{-03}	-4.3
nucleus accumbens	3.1×10^{-04}	1.6×10^{-02}	-3.6

rs314280 – A/G			↗ SCZ, ↘ MD
caudate	1.4×10^{-03}	4.6×10^{-02}	3.2

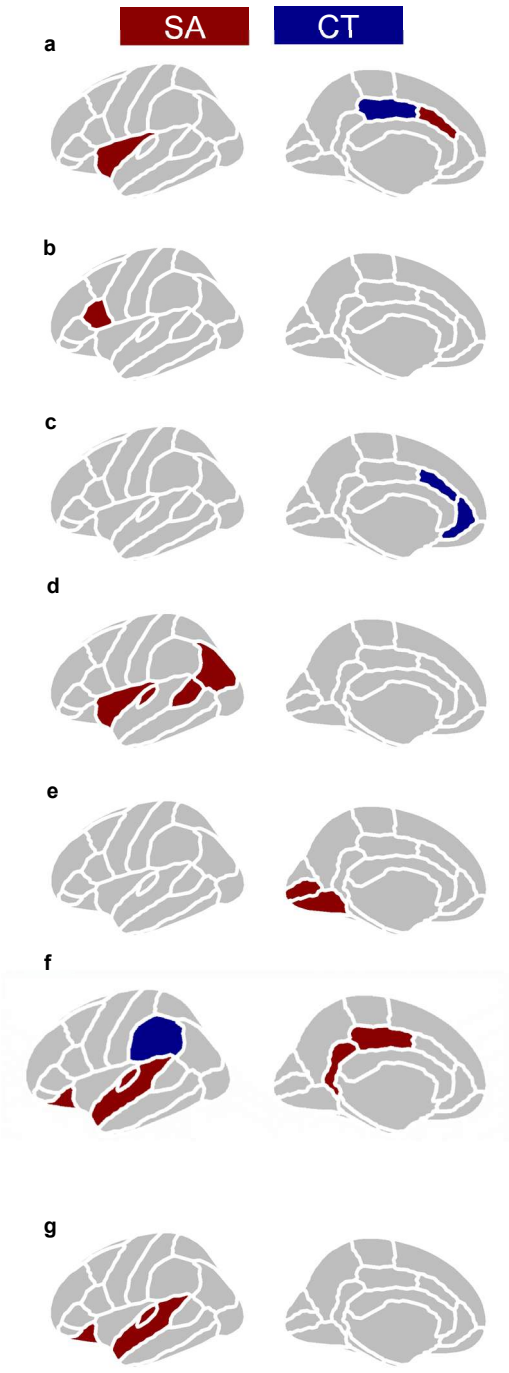
rs2921036 – T/C			↗ ASD, ↘ SCZ
brainstem	2.3×10^{-04}	1.2×10^{-02}	3.7

Figure 4 | Associations of the antagonistic SNPs with subcortical IDPs

Significant associations (p_{FDR}<0.05) with the volume of subcortical structures. ↗ indicates increased risk, whereas ↘ indicates decreased risk for a disorder with respect to the effect allele. The association of rs3806843 with the nucleus accumbens is not shown, as the brain plot does not cover the region. The embedded Tables were adapted from Figure 2 in (Federmann et al., 2024). *Abbreviations*. ASD, autism spectrum disorder; FDR, false discovery rate; IDP, image-derived phenotype; MD, major depression; *p*, *p*-value; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; *Z*, *Z*-score.

These comprised, most frequently, measures of SA. In particular, seven SNPs were associated with SA measures, three SNPs with CT measures, and three SNPs with subcortical volume. The lowest *p*-values were found for the association of the T allele of rs9329221 (increased risk for SCZ; protective against ASD) with decreased SA of the superior temporal region ($p_{FDR}=6.9\times10^{-09}$; β=-12.5) (Figure 5f) and the association of the T allele of rs2921036 (increased risk for ASD; protective against SCZ) with increased SA of the superior temporal region ($p_{FDR}=4.8\times10^{-06}$; β=10.4) (Figure 5g).

Implicated IDPs encompassed brain regions spread across the cortex (Figure 5). Thereby, it can be observed that antagonistic SNPs are likely to be associated with IDPs of neighboring brain regions. For example, the T allele of rs75595651 has been significantly associated with increased CT in the rostral and caudal anterior cingulate (Figure 5c).



rs301805 – T (effect allele)/G			↗ MD, ↘ SCZ	
CT/SA	Brain region	p	p_{FDR}	β
CT	posterior cing.	1.1×10^{-03}	3.7×10^{-02}	3.0×10^{-03}
SA	caudal ant. cing.	7.1×10^{-04}	2.8×10^{-02}	-2.6
	insula	1.0×10^{-03}	3.6×10^{-02}	4.3

rs6748341 – C/G			↗ SCZ, ↘ ANO	
SA	pars opercularis	7.6×10^{-05}	5.7×10^{-03}	5.8

rs75595651 – T/C			↗ BIP, ↘ MD	
CT	rostral ant. cing.	2.9×10^{-05}	3.1×10^{-03}	1.3×10^{-02}
	caudal ant. cing.	2.2×10^{-04}	1.2×10^{-02}	1.3×10^{-02}
SA	frontal pole	7.9×10^{-05}	5.7×10^{-03}	2.0

rs2388334 – A/G			↗ TS, ↘ ASD/BIP	
SA	trans. temporal	2.2×10^{-05}	3.1×10^{-03}	1.6
	banks of sts.	2.9×10^{-05}	3.1×10^{-03}	-3.5
	insula	6.0×10^{-04}	2.5×10^{-02}	4.4
	inferior parietal	1.5×10^{-03}	4.8×10^{-02}	-10.3

rs314280 – A/G			↗ SCZ, ↘ MD	
SA	pericalcarine	5.4×10^{-05}	4.7×10^{-03}	-6.2
	lingual	4.7×10^{-04}	2.0×10^{-02}	-8.1

rs9329221 – T/G			↗ SCZ, ↘ ASD	
CT	supramarginal	3.8×10^{-04}	1.8×10^{-02}	2.0×10^{-03}
SA	sup. temporal	7.9×10^{-12}	6.9×10^{-09}	-12.5
	trans. temporal	1.3×10^{-05}	3.1×10^{-03}	-1.7
	isthmus cing.	2.0×10^{-04}	1.2×10^{-02}	3.3
	lat. orbitofrontal	3.9×10^{-04}	1.8×10^{-02}	5.0
	posterior cing.	8.5×10^{-04}	3.2×10^{-02}	-2.9

rs2921036 – T/C			↗ ASD, ↘ SCZ	
SA	sup. temporal	1.1×10^{-08}	4.8×10^{-06}	10.4
	trans. temporal	3.5×10^{-05}	3.3×10^{-03}	1.6
	lat. orbitofrontal	1.2×10^{-04}	8.0×10^{-03}	-5.4

Figure 5 | Associations of the antagonistic SNPs with cortical IDPs

Significant associations (p_{FDR}<0.05) with CT measures are shown in blue and SA measures in red. ↗ indicates increased risk, whereas ↘ indicates decreased risk for a disorder with respect to the effect allele. The association of rs75595651 with the frontal pole is not shown, as the brain plot does not cover the region. The embedded Tables were adapted from Figure 2 in (Federmann et al., 2024). *Abbreviations*. ANO, anorexia nervosa; ant., anterior; ASD, autism spectrum disorder; β, effect size; BIP, bipolar disorder; cing., cingulate; CT, cortical thickness; FDR, false discovery rate; IDP, image-derived phenotype; lat., lateral; MD, major depression; p, p-value; SA, surface area; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; sts., superior temporal sulcus; sup., superior; TS, Tourette's syndrome; trans., transverse; Vol., volume.

3.1.2 Bootstrapping the number of significant associations

The 11 antagonistic SNPs were significantly associated with an increased number of IDPs compared to the sampling distribution. In the first test, this distribution was constructed by drawing sets of 11 SNPs from all SNPs represented in the 78 GWAS summary statistics of the incorporated IDPs and assessing the number of significant associations with 78 IDPs for each set. Notably, the 11 antagonistic SNPs showed a significantly higher number of associations compared to the sampling distribution across all IDPs (p=1.0×10^{-04}) and all IDPs of a specific measure, namely all IDPs of subcortical volume (p=5.0×10^{-04}), IDPs of CT measures (p=5.0×10^{-03}), and IDPs of SA measures (p=1.0×10^{-04}).

In a second test, the sampling distribution was constructed by drawing sets of 11 SNPs that additionally showed an association at p≤1.0×10^{-06} with neuropsychiatric disorders in the GWAS summary statistics of the PGC-CDG2 excluding samples from the 23andMe cohort (P. H. Lee et al., 2019). Likewise, for each set of 11 SNPs, the number of significant associations with 78 IDPs was obtained. The 11 antagonistic SNPs presented a significantly higher number of associations compared to the sampling distribution across all IDPs (p=3.0×10^{-03}), all IDPs of subcortical volume (p=1.0×10^{-03}), and IDPs of SA measures (p=3.0×10^{-03}). For IDPs of CT measures, the 11 antagonistic SNPs showed only a nominally significant higher number of associations (p=2.0×10^{-02}).

3.1.3 Case-control MRI differences of the implicated brain image-derived phenotypes

IDPs that were significantly associated with an antagonistic SNP showed no oppositely directed case-control MRI differences, meaning that the implicated IDP was not found to be increased in cases compared to controls for one disorder and, at the same time, decreased in cases compared to controls for the other disorder. Here, case-control MRI differences were assessed for disorders associated with the respective antagonistic SNP.

Nonetheless, several implicated IDPs showed significant case-control MRI differences in patients with BIP, MD, or SCZ (Table 4). For example, the T allele of rs9329221 (increased risk for SCZ) was significantly associated with decreased superior temporal SA (p_{FDR}=6.9×10^{-09}, β=-12.5) (Grasby et al., 2020), a region that showed pronounced SA decrease in patients with SCZ compared to controls ($p_{FDR,\ left}$=9.2×10^{-09}, d_{left}=-0.196; $p_{FDR,\ right}$=9.3×10^{-07}, d_{right}=-0.195) (Figure 6) (Van Erp et al., 2018).

Table 4 | Alterations of implicated IDPs in patients with neuropsychiatric disorders

Disorder	Vol./CT/SA	Brain region	*d*		p_{FDR}	
SCZ	Vol.	nucleus accumbens	-0.25		1.5×10^{-05}	
			d_L	$p_{FDR, L}$	d_R	$p_{FDR, R}$
BIP	CT	caudal anterior cingulate	-0.095	4.2×10^{-02}	n.s.	n.s.
		rostral anterior cingulate	-0.153	3.8×10^{-05}	n.s.	n.s.
MD	CT	posterior cingulate	-0.099	1.8×10^{-02}	-0.093	2.2×10^{-02}
		rostral anterior cingulate	-0.130	3.0×10^{-02}	-0.098	3.4×10^{-02}
SCZ	CT	posterior cingulate	-0.298	4.7×10^{-21}	-0.310	1.2×10^{-26}
		supramarginal	-0.395	4.9×10^{-15}	-0.386	1.3×10^{-17}
	SA	caudal anterior cingulate	-0.128	5.1×10^{-04}	-0.156	1.2×10^{-08}
		insula	-0.122	3.5×10^{-03}	-0.113	4.3×10^{-03}
		lateral orbitofrontal	-0.179	4.2×10^{-05}	-0.150	1.1×10^{-04}
		lingual	-0.148	7.8×10^{-05}	-0.168	8.3×10^{-07}
		pars opercularis	-0.151	9.0×10^{-06}	-0.146	2.0×10^{-07}
		pericalcarine	-0.133	1.7×10^{-03}	-0.107	3.8×10^{-03}
		posterior cingulate	-0.117	1.5×10^{-03}	-0.125	1.3×10^{-03}
		superior temporal	-0.196	9.2×10^{-09}	-0.195	9.3×10^{-07}
		transverse temporal	-0.151	7.4×10^{-03}	-0.169	9.0×10^{-09}

Case-control MRI differences of IDPs that were significantly associated with an antagonistic SNP (Figure 4 and Figure 5) are shown at $p_{FDR}<0.05$ for cortical IDPs and $p<5.6\times10^{-03}$ for subcortical IDPs. References are given in Section 2.1.3. Statistics of case-control MRI differences were retrieved from the ENIGMA-Toolbox, corresponding for subcortical IDPs to Table 1 in (Van Erp et al., 2016) for SCZ and for cortical IDPs to Table 1 in (Hibar et al., 2018) for BIP, Table 1 in (Schmaal et al., 2017) for MD, and Table S4a and S5a in (Van Erp et al., 2018) for SCZ. This Table has been adapted from Table S4 in (Federmann et al., 2024). *Abbreviations.* BIP, bipolar disorder; CT, cortical thickness; *d*, Cohens's *d*; FDR, false discovery rate; IDP, image-derived phenotype; L, left; n.s., not significant; MD, major depression; MRI, magnetic resonance imaging; *p*, *p*-value; R, right; SA, surface area; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; Vol., volume.

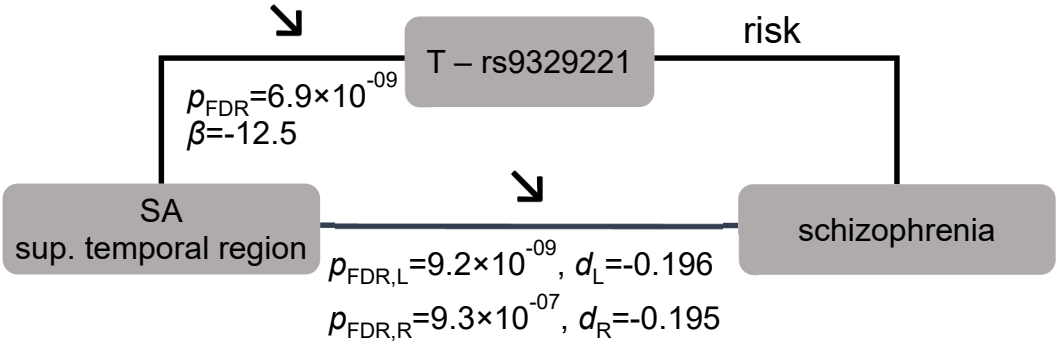


Figure 6 | Case-control MRI differences of IDPs associated with an antagonistic SNP

The T allele of rs9329221 was significantly associated with decreased SA in the superior temporal region. This IDP was significantly decreased in patients with SCZ compared to controls, which may provide a notion of how the T allele of rs9329221 confers an increased risk for SCZ. *d* denotes Cohen's *d*. The relationships shown represent results from association analyses and do not represent results from mediation analyses. Statistics of SNP-to-IDP associations are shown in Figure 5, and statistics of IDP case-control MRI differences are shown in Table 4. The Figure was adapted from Figure 3 in (Federmann et al., 2024). *Abbreviations*. *β*, effect size; FDR, false discovery rate; IDP, image-derived phenotype; L, left; MRI, magnetic resonance imaging; *p*, *p*-value; R, right; SA, surface area; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; sup, superior.

3.1.4 Antagonistic SNPs and gene expression in brain tissues

Based on the BRAINEAC (Ramasamy et al., 2014) and GTEx databases (Lonsdale et al., 2013), six of the eight antagonistic SNPs that were significantly associated with at least one IDP were found to be part of an eQTL in brain tissues (Figure 7).

The lowest *p*-value was found for the C allele of rs2921036 that was associated with reduced expression of the *family with sequence similarity 85 member B* (*FAM85B*) gene in multiple brain tissues including the cortex ($p=3.0\times10^{-16}$, normalized effect size (NES)=-0.67) and the cerebellum ($p=1.4\times10^{-15}$, NES=-0.69), among others. The second lowest *p*-value was observed for the C allele of rs3806843, which was associated with upregulated expression of genes belonging to the *protocadherin alpha* gene cluster (*PCDHA@*) in several brain tissues, including the cerebellum (*PCDHA1*: $p=4.0\times10^{-15}$, NES=0.56), the cerebellar hemisphere (*PCDHA13*: $p=2.9\times10^{-14}$, NES=0.55), and the entire cortex (*PCDHA13*: $p=2.2\times10^{-12}$, NES=0.53).

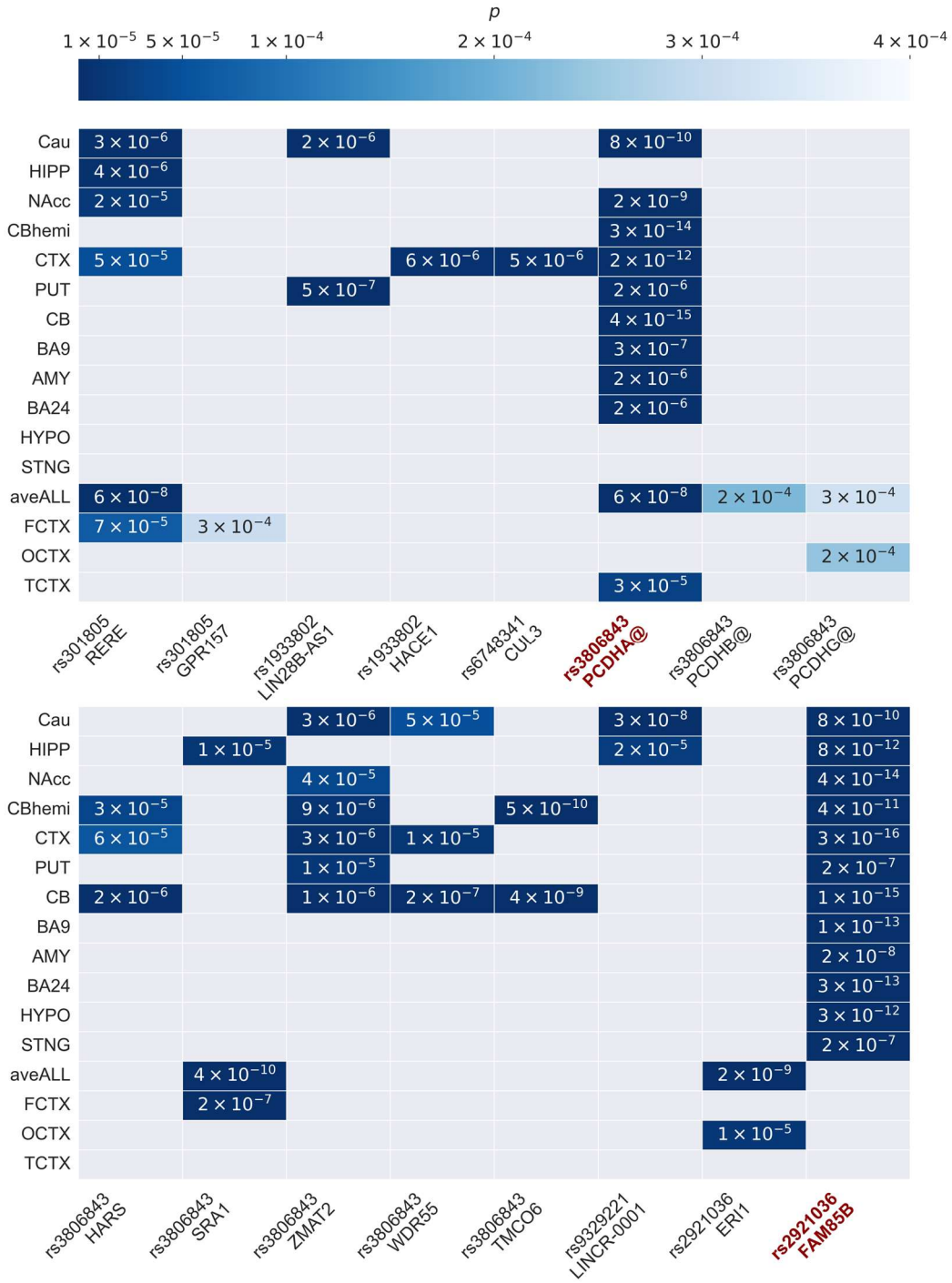


Figure 7 | Antagonistic SNPs as part of eQTLs of brain tissues

Six SNPs were part of an eQTL of human brain tissues with $p<4.0\times10^{-04}$. rs2921036, which is part of an eQTL of the *FAM85B* gene, and rs3806843, which is part of an eQTL of genes of the *PCDHA* cluster, are highlighted in red color as they showed the lowest *p*-values. AveALL refers to the average across all ten brain tissues of the BRAINEAC database. This Figure was adapted from Table S3 in (Federmann et al., 2024). *Abbreviations.* AMY, amygdala; BA9, Brodmann area 9; BA24, Brodmann area 24; BRAINEAC, Brain eQTL Almanac; CAU, caudate; CB, cerebellum; CBhemi, cerebellar hemisphere; CTX, cortex; eQTL, expression quantitative trait locus; FCTX, frontal cortex; HIPP, hippocampus; HYPO, hypothalamus; NAcc, nucleus accumbens; OCTX, occipital cortex; *p*, *p*-value; PUT, putamen; SNP, single-nucleotide polymorphism; STNG, substantia nigra; TCTX, temporal cortex.

3.1.5 Antagonistic SNPs and cognitive and behavioral traits

All eight antagonistic SNPs that were significantly associated with at least one IDP showed significant associations (p<5.0×10^{-08}) with at least one cognitive or behavioral trait (Table 5). Above all, the G allele of rs2388334 (increased risk for ASD/BIP; protective against TS) was positively associated with college or university degree conditioned on qualifications (p=2.8×10^{-37}, *https://www.nealelab.is/uk-biobank/;* lowest p-value*)*, intelligence (p=3.7×10^{-29}, (Savage et al., 2018)), and cognitive performance (p=1.8×10^{-26}, (J. J. Lee et al., 2018)) (Figure 8). The second lowest p-value was found for the C allele of rs2921036, which was negatively associated with neuroticism (p=6.2×10^{-26}; *https://www.nealelab.is/uk-biobank/*).

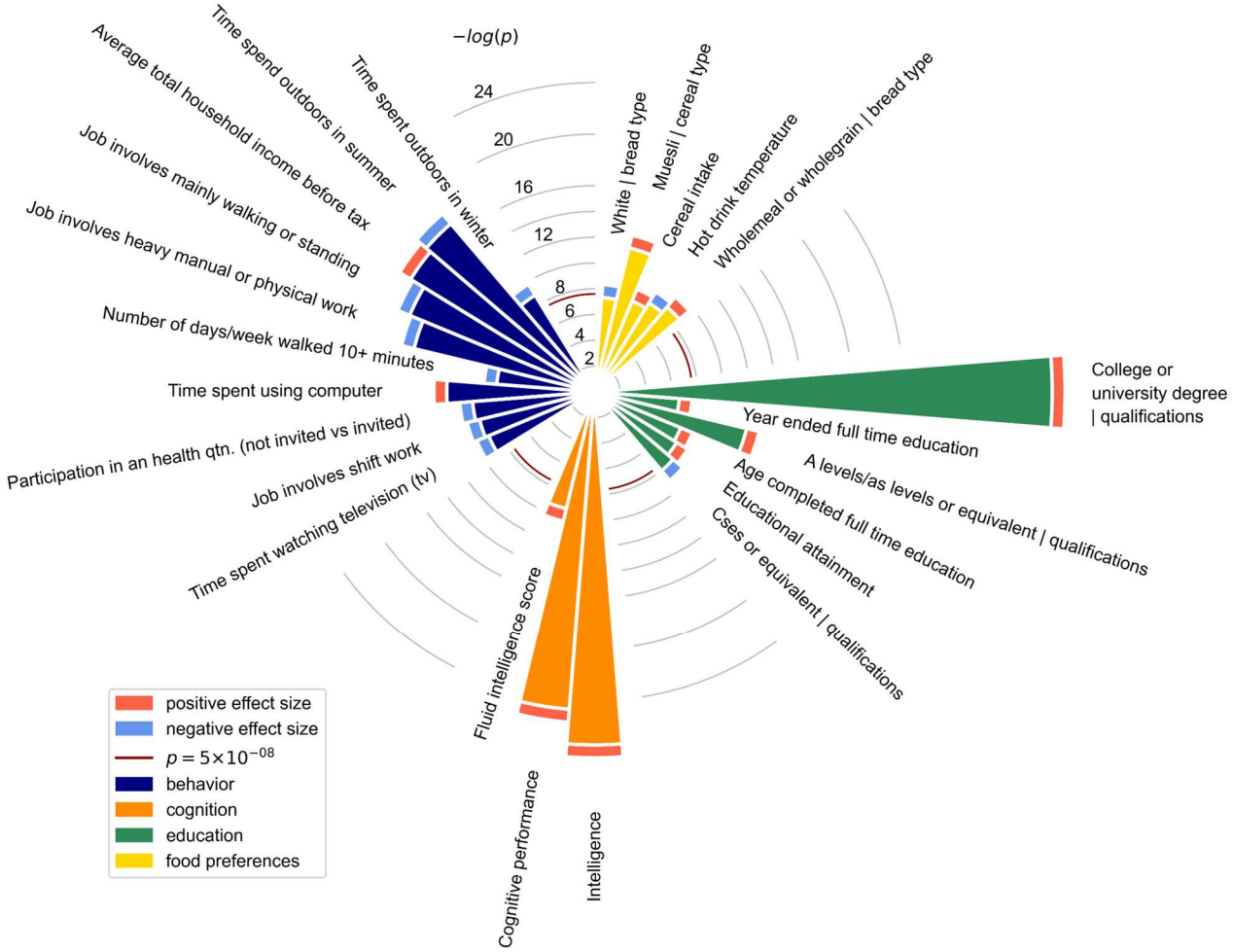


Figure 8 | Cognitive-behavioral fingerprint of rs2388334

rs2388334 showed associations with traits related to behavior, cognition, education, and food preferences. In particular, the G allele of rs2388334 was associated with higher cognitive performance and educational attainment. In addition, the G allele decreased the likelihood of pursuing a job that involves heavy manual or physical work, while increasing average total household income. See Table 5 for statistics. *Abbreviations.* CSE, certificate of secondary education; *p*, *p*-value; qtn., questionnaire.

Table 5 | Associations of antagonistic SNPs with cognitive and behavioral traits

rsID	EA	Category	Trait	*p*	*β*	Reference
rs301805	G	Neuroticism	Feeling tense	7.6×10^{-09}	-0.01	GCST006952
			Feeling miserable	2.7×10^{-08}	-0.01	GCST006943
			Tense / highly strung	3.9×10^{-08}	-0.04	N_1990
			Depressed affect	4.2×10^{-08}	-0.01	GCST006475
		Sleep	Daytime nap	6.9×10^{-09}	0.01	GCST011494
rs6748341	G	Behavior	Age at first sexual intercourse	1.1×10^{-11}	0.01	GCST90000047
			Walk | types of transport used (excluding work)	4.3×10^{-08}	0.03	N_6162_2
rs75595651	T	Neuroticism	Fed-up feelings	6.2×10^{-10}	-0.06	N_1960
				3.0×10^{-08}	-0.03	GCST006947
			Miserableness	1.1×10^{-09}	-0.06	N_1930
				1.5×10^{-08}	-0.03	GCST006943
rs3806843	C	Cognition	Intelligence	1.5×10^{-08}	0.02	GCST006250
rs2388334	G	Behavior	Time spend outdoors in summer	6.9×10^{-19}	-0.02	N_1050
			Average total household income before tax	1.8×10^{-18}	0.02	N_738
			Job involves mainly walking or standing	3.0×10^{-17}	-0.03	N_806
			Job involves heavy manual or physical work	4.0×10^{-16}	-0.02	N_816
			Time spent using computer	3.5×10^{-13}	0.02	N_1080
			Participation in a health questionnaire (not invited vs invited)	3.3×10^{-11}	-0.01	GCST90012794
			Time spent watching television	1.3×10^{-10}	-0.01	N_1070
			Time spent outdoors in winter	1.6×10^{-10}	-0.01	N_1060
			Number of days/weeks walked 10+ minutes	2.5×10^{-09}	-0.03	N_864
		Cognition	Intelligence	3.7×10^{-29}	0.03	GCST006250
			Cognitive performance	1.8×10^{-26}	0.03	GCST006572
			Fluid intelligence score	4.9×10^{-11}	0.06	N_20016_raw
		Education	College or university degree | qualifications	2.8×10^{-37}	0.06	N_6138_1
			A levels/as levels or equivalent | qualifications	7.0×10^{-14}	0.04	N_6138_2
			CSEs or equivalent | qualifications	9.2×10^{-10}	-0.04	N_6138_4
			Educational attainment	3.2×10^{-09}	0.03	GCST003496
			Age completed full time education	5.5×10^{-09}	0.01	N_845
			Year ended full time education	2.4×10^{-08}	0.09	N_22501_raw
		Food pref.	Muesli | cereal type	3.1×10^{-13}	0.05	N_1468_4
			Wholemeal or wholegrain | bread type	2.1×10^{-10}	0.03	N_1448_3
			Hot drink temperature	7.9×10^{-10}	-0.01	N_1518
			Cereal intake	2.3×10^{-09}	0.01	N_1458
			White | bread type	4.4×10^{-09}	-0.03	N_1448_1
rs1933802	G	Neuroticism	Feeling guilty	7.3×10^{-09}	0.01	GCST006945
rs9329221	T	Behavior	Age first had sexual intercourse	1.0×10^{-14}	-0.07	N_2139_raw
				4.2×10^{-13}	-0.02	GCST90000047
		Neuroticism	Neuroticism	8.0×10^{-21}	-0.05	GCST005232;
				1.7×10^{-18}	-0.07	N_20127_raw
				1.6×10^{-15}	-0.02	GCST005327

Table continues on the next page.

Table 5 continued.

rsID	EA	Category	Trait	*p*	*β*	Reference
rs9329221	T	Neuroticism	Neuroticism	6.6×10^{-15}	-0.03	GCST003770
			Worrier / anxious feelings	3.4×10^{-18}	-0.04	N_1980
			Irritability	2.3×10^{-14}	-0.04	N_1940
			Miserableness	2.2×10^{-13}	-0.03	N_1930
			Nervous feelings	1.2×10^{-12}	-0.04	N_1970
		Sleep	Sleep duration	2.3×10^{-08}	0.01	N_1160
		Food pref.	Cheese intake	5.1×10^{-13}	-0.02	N_1408
rs2921036	C	Behavior	Age first had sexual intercourse	6.4×10^{-13}	-0.07	N_2139_raw
				7.1×10^{-12}	-0.01	GCST90000047
		Neuroticism	Neuroticism	6.2×10^{-26}	-0.09	N_20127_raw
				8.0×10^{-26}	-0.06	GCST005232
				8.3×10^{-16}	-0.02	GCST005327
				1.2×10^{-14}	-0.03	GCST003770
			Worrier / anxious feelings	9.5×10^{-23}	-0.05	N_1980
			Irritability	3.0×10^{-15}	-0.04	N_1940
			Nervous feelings	4.2×10^{-15}	-0.04	N_1970
			Miserableness	2.0×10^{-13}	-0.03	N_1930
			Worry too long after embarrassment	1.2×10^{-12}	-0.03	N_2000
			Fed-up feelings	2.2×10^{-12}	-0.03	N_1960
			Tense / highly strung	3.3×10^{-12}	-0.04	N_1990
			Sensitivity / hurt feelings	1.9×10^{-10}	-0.03	N_1950

Behavioral and cognitive trait associations of the eight antagonistic SNPs with $p<5\times10^{-08}$ were retrieved from the Open Targets Genetics portal v22.10 (Ghoussaini et al., 2021; Mountjoy et al., 2021). References beginning with 'GCST' referred to the NHGRI-EBI GWAS Catalog, while those with 'N' referred to GWAS analyses of data from the UKBB (*http://www.nealelab.is/uk-biobank*). The assignment of categories 'Cognition', 'Education', 'Food preferences', and 'Sleep' were based on the categories of the UKBB showcase (*https://biobank.ndph.ox.ac.uk/showcase/*). The category 'Behavior' summarized traits of physical activity, sexual factors, household, and smoking. The category 'Neuroticism' was based on the items of the neuroticism scale of the Eysenck Personality Questionnaire-Revised Short Form (Eysenck et al., 1985). The symbol '|' refers to conditional GWAS. *β* denotes the effect size. The Table was adapted from Table S5 in (Federmann et al., 2024). *Abbreviations.* CSE, certificate of secondary education; EA, effect allele; GWAS, genome-wide association study; *p*, *p*-value; pref., preferences; SNP, single-nucleotide polymorphism; UKBB, UK Biobank.

3.1.6 Whole-brain voxel-based morphometry analysis in data from the FOR2107 study

All 11 antagonistic SNPs were associated ($p_{uncorrected}<0.001$) with increased or decreased GMV within at least one cluster of $k>10$ (Table S6) in data from the FOR2107 study. In particular, significant associations ($p_{FWE}<0.05$) between the allele dosage and GMV were found for rs301805 and rs1933802. The G allele dosage of rs301805 was associated with decreased GMV in the left superior temporal pole ($p_{FWE}=1.2\times10^{-02}$, $k=44$, $T=4.85$) (Figure 9A-B), whereby the peak voxel ($x/y/z$=-28/10/-22) was mapped to the Frontal-to-Temporal-II GapMap using the cytoarchitectural maps of the Julich Brain Atlas v3.1 (Amunts et al., 2020) (Figure 9C).

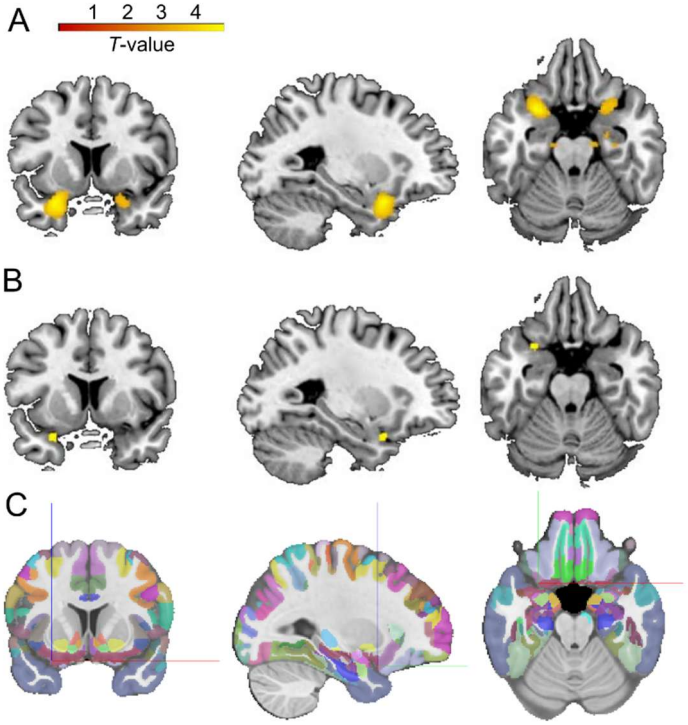


Figure 9 | Associations of the G allele dosage of rs301805 with GMV

GMV clusters associated with $p_{uncorrected}$<0.001 and k>10 (**A**). GMV cluster significantly associated after multiple testing corrections with p_{FWE}<0.05 (**B**). The corresponding peak voxel (*x*/*y*/*z*=-28/10/-22) was mapped to the left Frontal-to-Temporal-II GapMap by the Julich Brain Atlas v3.1 (Amunts et al., 2020) using the EBRAINS viewer (*https://atlases.ebrains.eu/viewer/#/)* (**C**). The Figure was adapted from Figure 4 and Figure S2 in (Federmann et al., 2024). Colors in **A** and **B** represent *T*-values that were provided in Table S6. *Abbreviations.* FWE, family-wise error; GMV, gray matter volume; *p*, *p*-value.

Furthermore, the G allele dosage of rs1933802 was associated with increased GMV in the left superior parietal region (p_{FWE}=2.9×10^{-02}, k=15, T=4.62) (Figure 10A-B). The corresponding peak voxel (*x*/*y*/*z*=-20/-69/62) was mapped to the Area 7A of the superior parietal lobe (Julich Brain Atlas v3.1, Amunts et al., 2020) (Figure 10C).

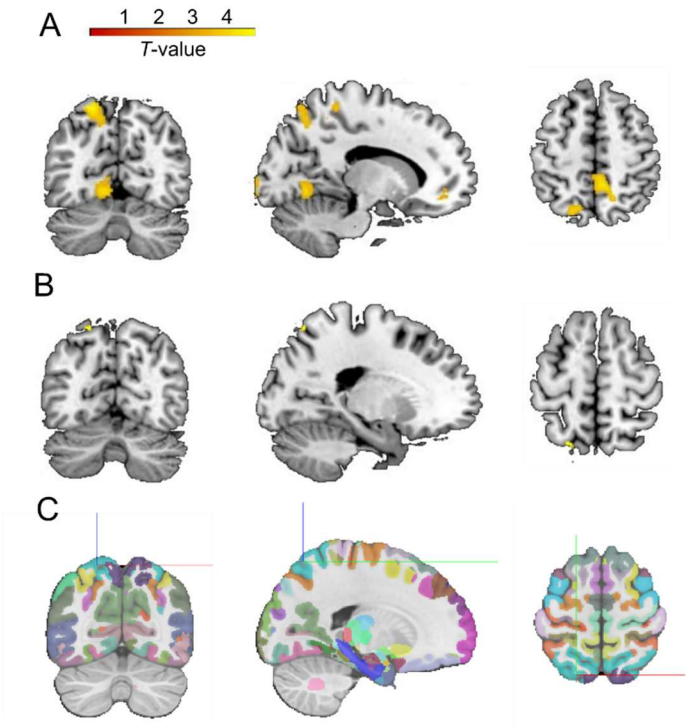


Figure 10 | Associations of the G allele dosage of rs1933802 with GMV

GMV clusters associated with $p_{uncorrected}$<0.001 and k>10 (**A**). GMV cluster significantly associated after multiple testing corrections with p_{FWE}<0.05 (**B**). The corresponding peak voxel (x/y/z=-20/-69/62) was mapped to the left Area 7A of the superior parietal lobe by the Julich Brain Atlas v3.1 (Amunts et al., 2020) using the EBRAINS viewer (*https://atlases.ebrains.eu/viewer/#/)* (**C**). Colors in **A** and **B** represent *T*-values that were provided in Table S6. The Figure was adapted from Figure 4 and Figure S2 in (Federmann et al., 2024). *Abbreviations.* FWE, family-wise error; GMV, gray matter volume; *p*, *p*-value.

3.2 Study 2

3.2.1 Association of the GRSs with brain image-derived phenotypes

No significant association was observed between the PleioPsych-GRS and IDPs after correction for multiple testing. Albeit, nominally significant associations ($p_{uncorrected}$<0.05) were found between the PleioPsych-GRS and decreased volume in the left thalamus, left and right caudate, right nucleus accumbens, left and right amygdala, increased CT in the left precentral region, and decreased SA in the right caudal and rostral anterior cingulate, left pars opercularis, left rostral middle frontal, and left lateral orbitofrontal regions (Figure 11A and Table 6).

Table 6 | Associations of the PleioPsych-GRS and brain structure

Vol./CT/SA	L/R	Brain region	*p*	p_{FDR}	*BETA*	CI_{lower}	CI_{upper}
Vol.	L	thalamus	0.003	0.460	-0.012	-0.021	-0.004
	R	caudate	0.019	0.563	-0.012	-0.021	-0.002
	L	caudate	0.022	0.563	-0.012	-0.021	-0.002
	R	accumbens	0.027	0.583	-0.011	-0.021	-0.001
	R	amygdala	0.037	0.600	-0.010	-0.019	-0.001
	L	amygdala	0.039	0.600	-0.010	-0.019	-0.001
CT	L	precentral	0.044	0.612	0.011	3.2×10^{-04}	0.022
SA	R	caudal anterior cingulate	0.008	0.460	-0.014	-0.025	-0.004
	R	rostral anterior cingulate	0.009	0.460	-0.013	-0.023	-0.003
	L	pars opercularis	0.012	0.460	-0.013	-0.024	-0.003
	L	rostral middle frontal	0.030	0.583	-0.009	-0.017	-0.001
	L	lateral orbitofrontal	0.048	0.622	-0.008	-0.017	5.7×10^{-05}

Nominally significant associations ($p<0.05$) between the PleioPsych-GRS and IDPs. CIs refer to 95 %. This Table has been adapted from Table 1 in (Federmann et al., 2025). *Abbreviations. BETA*, effect size; CI, confidence interval; CT, cortical thickness; FDR, false discovery rate; IDP, image-derived phenotype; L, left; *p*, *p*-value; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; R, right; SA, surface area; Vol., volume.

Significant associations ($p_{FDR}<0.05$) were identified between the SCZ-GRS and eight IDPs (Figure 11B and Table 7). The lowest *p*-values were observed for increased SA in the left lateral orbitofrontal region and increased volume in the left putamen. In addition, the SCZ-GRS was significantly associated with increased volume in the right putamen, decreased CT in the left pars orbitalis, left insula, and left lateral orbitofrontal region and increased SA in the right paracentral region, and right lateral orbitofrontal region. When controlling for the extended set of covariates, the associations remained significant except for the association of the SCZ-GRS with left orbitofrontal CT (Table S7).

Table 7 | Associations of the SCZ-GRS and brain structure

Vol./CT/SA	L/R	Brain region	*p*	p_{FDR}	*BETA*	CI_{lower}	CI_{upper}
Vol.	L	putamen	<0.001	0.008	0.019	0.010	0.028
	R	putamen	0.001	0.030	0.016	0.006	0.025
CT	L	pars orbitalis	0.001	0.025	-0.019	-0.031	-0.008
	L	insula	0.002	0.033	-0.019	-0.030	-0.007
	L	lateral orbitofrontal	0.002	0.045	-0.018	-0.029	-0.006
SA	L	lateral orbitofrontal	<0.001	0.008	0.017	0.008	0.025
	R	paracentral	<0.001	0.013	0.018	0.008	0.027
	R	lateral orbitofrontal	<0.001	0.019	0.016	0.007	0.025

Significant associations after multiple testing corrections ($p_{FDR}<0.05$) between the SCZ-GRS and IDPs. CIs refer to 95 %. This Table has been adapted from Table 1 in (Federmann et al., 2025). *Abbreviations. BETA*, effect size; CI, confidence interval; CT, cortical thickness; FDR, false discovery rate; IDP, image-derived phenotype; L, left; *p*, *p*-value; R, right; SA, surface area; SCZ-GRS, GRS of predominantly SCZ-associated SNPs; Vol., volume.

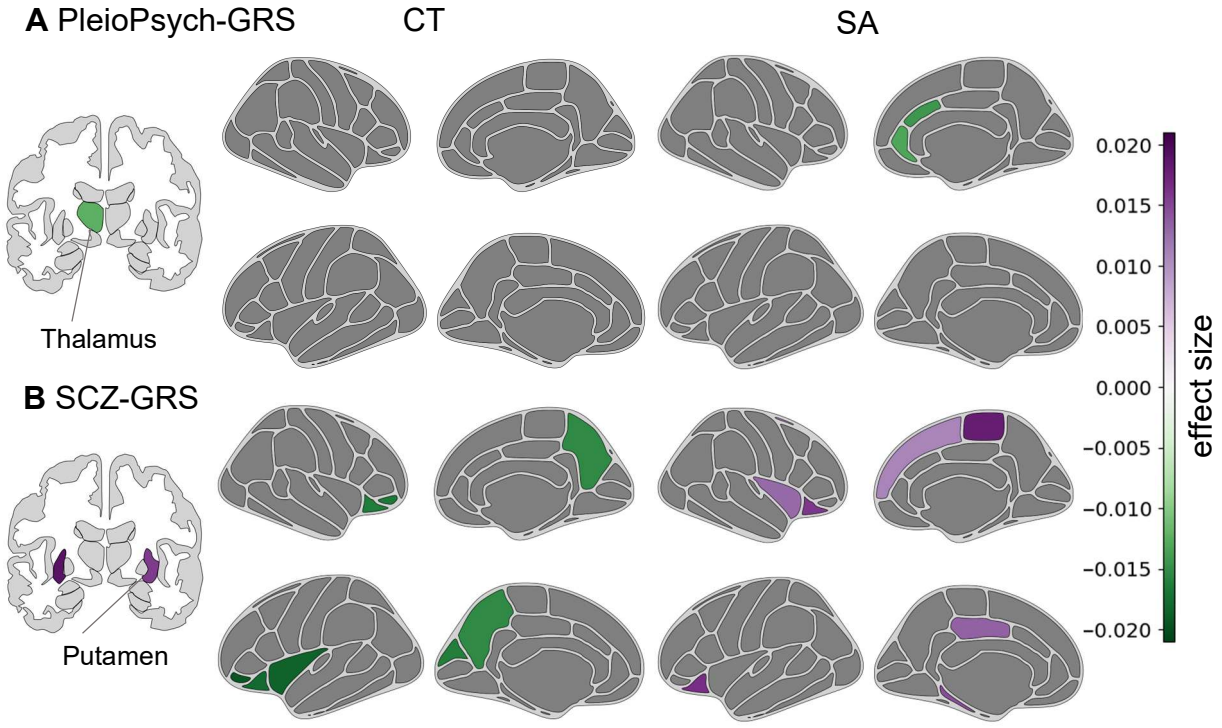


Figure 11 | Associations of the GRSs with brain structure

Associations of the PleioPsych-GRS (**A**) and the SCZ-GRS (**B**) with IDPs of subcortical volume (left column), CT (middle column), and SA (right column) are shown with $p_{uncorrected}<0.01$. The color-bar shows positive standardized effect sizes in purple and negative ones in green. This Figure has been adapted from Figure 3 in (Federmann et al., 2025). *Abbreviations.* CT, cortical thickness; GRS, genetic risk score; IDP, image-derived phenotype; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; SA, surface area; SCZ, schizophrenia; SCZ-GRS, GRS of predominantly SCZ-associated SNPs.

In the sensitivity analysis excluding samples with self-reported or diagnosed depression, the effect sizes of the association between the GRSs and IDPs were concordant with the main analysis (ρ=0.94 with ρ referring to the concordance correlation coefficient (Lin, 1989)). Notably, the association between the SCZ-GRS and six IDPs remained significant (Table S8). In addition, the SCZ-GRS showed significant positive associations with left amygdala volume and left parahippocampal SA (Table S8).

In the sensitivity analysis of the effect sizes used to calculate the SCZ-GRS, high correlations were observed between the effect sizes of the predominantly SCZ-associated SNPs from the PGC-CDG2 and the corresponding effect sizes from the PGC-SCZ3 (Figure 12). In this context, it should be noted that the PGC-CDG2 and PGC-SCZ3 datasets have largely overlapping samples of patients with SCZ and controls (P. H. Lee et al., 2019; Trubetskoy et al., 2022). Furthermore, the SCZ-GRS based on the effect sizes of the PGC-

SCZ3 was significantly associated with 29 IDPs (Table S9). In the main analysis, the association between the SCZ-GRS and eight IDPs was significant after correction for multiple testing, while it was nominally significant for the other 21 IDPs (data not shown).

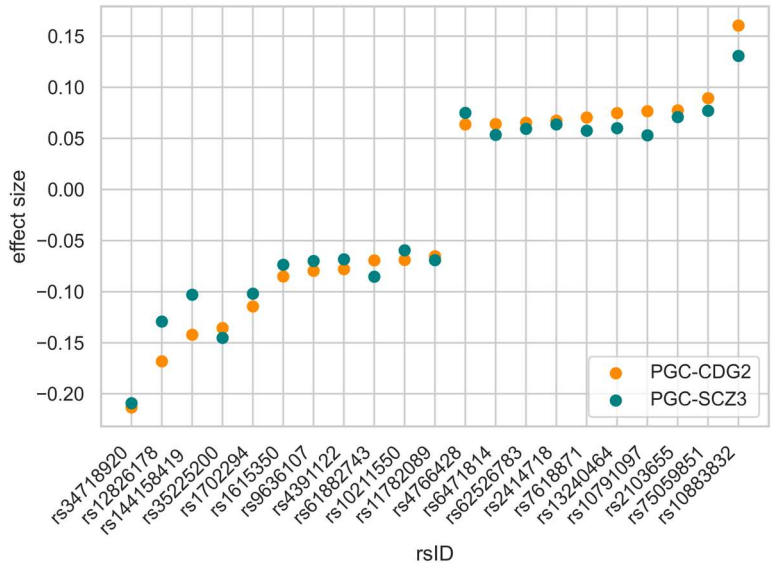


Figure 12 | Effect sizes of the predominantly SCZ-associated SNPs from the PGC-CDG2 and a GWAS of SCZ

A sensitivity analysis was conducted to investigate the influence of the origin of the effect size. This Figure displays the effect sizes of the predominantly SCZ-associated SNPs for the PGC-CDG2 in orange and for the PGC-SCZ3 (Trubetskoy et al., 2022) in blue. Here, the proxy SNPs rs7839435, rs67657812, and rs72934586 were used to replace rs11782089, rs10211550, and rs144158419, as stated in Section 2.2.3.2. This Figure has been adapted from Supplementary Figure S1 in (Federmann et al., 2025). *Abbreviations.* GWAS, genome-wide association study; PGC-CDG2, second cross-disorder GWAS meta-analysis of the Psychiatric Genomics Consortium; PGC-SCZ3, third GWAS of SCZ of the PGC; SCZ, schizophrenia; SNP, single-nucleotide polymorphism.

3.2.2 Association of the GRSs with outcomes related to mental health

The PleioPsych-GRS and the SCZ-GRS were both significantly associated (p_{FDR}<0.05) with the following outcomes related to mental health: worrier / anxious feelings, sensitivity / hurt feelings, and tense feelings / highly strung (Figure 13 and Table S10). In addition, the PleioPsych-GRS showed significant associations with irritability, miserableness, fed-up feelings, mood swings, and nervous feelings. The SCZ-GRS showed an additional significant association with guilty feelings.

When the analysis was repeated using an extended set of covariates, all the associations reported above between the GRSs and the outcomes related to mental health remained significant (Table S11).

Furthermore, in the sensitivity analysis excluding samples with self-reported or diagnosed depression, correlated odds ratios (ORs) (ρ=0.72) were observed compared to the main analysis. Nine of the 12 previously found associations between the GRSs and outcomes related to mental health reported in the main analysis remained significant (Table S12). In particular, the PleioPsych-GRS was associated with fewer outcomes. In contrast, all four associations between the SCZ-GRS and outcomes related to mental health were also significant when the GRS was calculated based on effect sizes from a GWAS of SCZ (Table S13), whereby no additional associations were found.

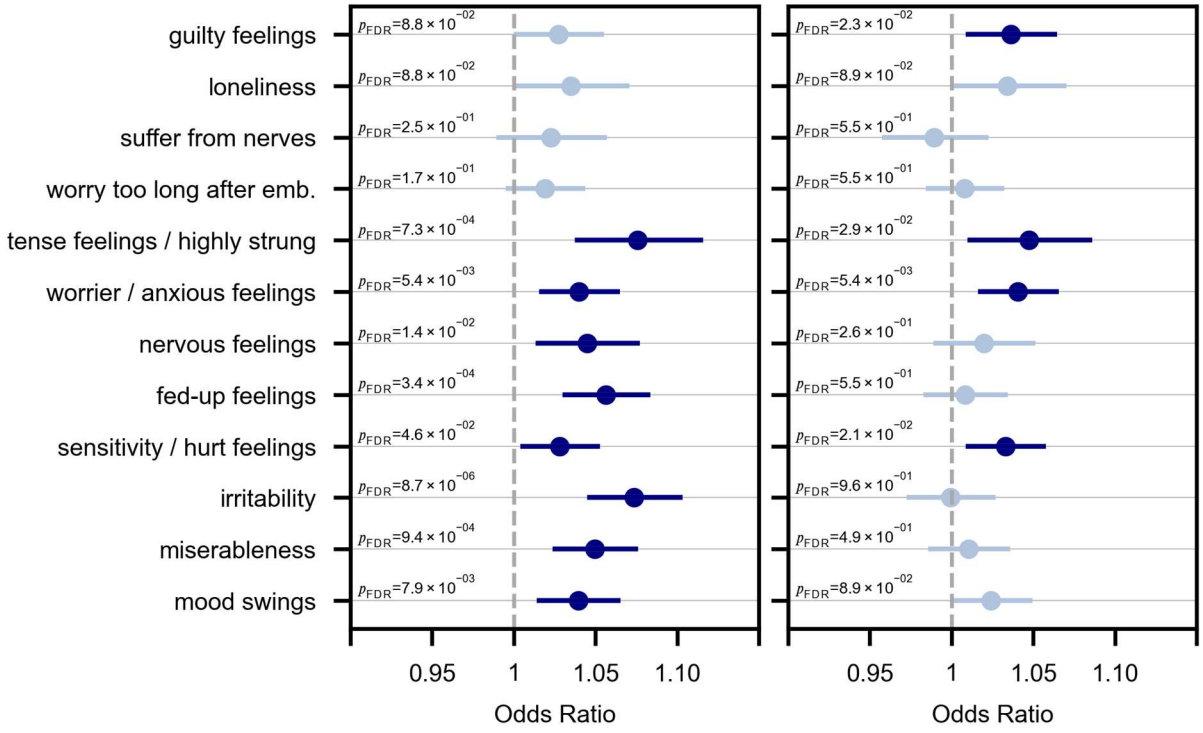


Figure 13 | Associations of the GRSs with outcomes related to mental health

Significant associations (p_{FDR}<0.05) between the PleioPsych-GRS (left) and the SCZ-GRS (right) with outcomes related to mental health are depicted in dark blue. Bars represent 95 % CIs. Corresponding statistical parameters are presented in Table S10. This Figure has been adapted from Table 2 in (Federmann et al., 2025). *Abbreviations.* CI, confidence interval; emb., embarrassment; FDR, false discovery rate; GRS, genetic risk score; *p*, *p*-value; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; SCZ-GRS, GRS of predominantly SCZ-associated SNPs.

3.2.3 Association of the individual SNPs with brain image-derived phenotypes

Two of the 21 highly pleiotropic SNPs were significantly associated (p_{FDR}<0.05) with at least one IDP (Table 8). The A allele of rs8084351 was significantly associated with in-

creased putamen volume (p_{FDR}=2.0×10^{-07}, Z=6.4). The A allele of rs10149470 was significantly associated with decreased pallidum volume (p_{FDR}= 2.7×10^{-02}, Z=-4.1) and decreased postcentral gyrus CT (p_{FDR}= 1.8×10^{-02}, β=-2.9×10^{-03}).

Furthermore, ten of the 20 predominantly SCZ-associated SNPs were significantly associated (p_{FDR}<0.05) with at least one IDP (Table 8). The lowest p-value was found for the association of the A allele of rs4391122 with decreased SA in the pericalcarine region (p_{FDR}=4.1×10^{-07}; β=-9.7). Of note, the A allele of rs35225200 was significantly associated with three subcortical IDPs, nine regional CT measures, nine regional SA measures, average CT, and total SA. The lowest p-value was found for increased cuneus CT (p_{FDR}=1.0×10^{-05}; β=0.009) and decreased nucleus accumbens volume (p_{FDR}=2.2×10^{-05}, Z=-5.5). Interestingly, rs35225200 was associated with increased and decreased CT and SA measures (Figure 14).

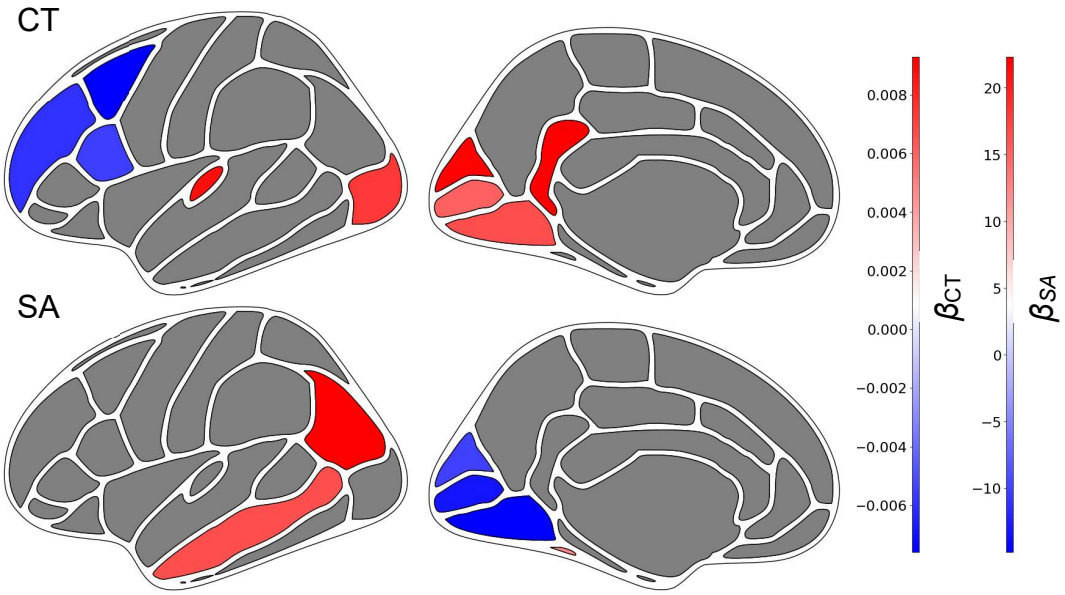


Figure 14 | Associations of rs35225200 with IDPs

rs35225200 was significantly associated (p_{FDR}<0.05) with nine regional IDPs of CT and nine regional IDPs of SA. Positive associations are depicted in red, and negative associations in blue. Effect size is denoted by β, and corresponding statistical parameters are presented in Table 8. The association with the frontal pole was not shown, as the region is not part of the brain plot. *Abbreviations.* CT, cortical thickness; FDR, false discovery rate; IDP, image-derived phenotype; p, p-value; SA, surface area.

Table 8 | Associations of the highly pleiotropic and predominantly SCZ-associated SNPs with IDPs

rsID	CHR	EA	OA	Vol./CT/SA	Brain region	p	p_{FDR}	Effect
rs10149470	14	A	G	CT	postcentral	2.2×10^{-05}	1.8×10^{-02}	-2.9×10^{-03}
				Vol.	pallidum	5.0×10^{-05}	2.7×10^{-02}	-4.06
rs8084351	18	A	G	Vol.	putamen	1.2×10^{-10}	2.0×10^{-07}	6.44
rs1702294	1	T	C	CT	postcentral	3.5×10^{-05}	3.6×10^{-03}	3.6×10^{-03}
rs11891750	2	A	G	SA	superior frontal	5.9×10^{-05}	5.6×10^{-03}	-12.56
				SA	fusiform	1.9×10^{-04}	1.1×10^{-02}	7.27
rs7618871	3	T	G	SA	temporal pole	1.5×10^{-04}	1.1×10^{-02}	-1.39
rs35225200	4	A	C	CT	cuneus	1.3×10^{-08}	1.0×10^{-05}	0.01
				Vol.	nuc. accumbens	4.7×10^{-08}	2.2×10^{-05}	-5.46
				CT	lateral occipital	5.7×10^{-08}	2.2×10^{-05}	0.01
				CT	caudal middle frontal	1.2×10^{-07}	3.3×10^{-05}	-0.01
				SA	temporal pole	1.9×10^{-07}	4.8×10^{-05}	3.68
				CT	rostral middle frontal	1.5×10^{-06}	3.0×10^{-04}	-0.01
				CT	average CT	2.2×10^{-06}	3.5×10^{-04}	0.01
				CT	lingual	2.3×10^{-06}	3.5×10^{-04}	0.01
				SA	middle temporal	5.3×10^{-06}	7.5×10^{-04}	16.44
				SA	cuneus	7.4×10^{-06}	8.9×10^{-04}	-10.07
				SA	pericalcarine	8.1×10^{-06}	8.9×10^{-04}	-13.25
				Vol.	caudate	8.1×10^{-06}	8.9×10^{-04}	-4.46
				CT	pars opercularis	6.7×10^{-05}	6.0×10^{-03}	-0.01
				SA	total SA	8.0×10^{-05}	6.8×10^{-03}	-838.40
				CT	pericalcarine	1.6×10^{-04}	1.1×10^{-02}	0.01
				SA	frontal pole	1.9×10^{-04}	1.1×10^{-02}	1.64
				SA	inferior temporal	2.3×10^{-04}	1.3×10^{-02}	15.47
				CT	isthmus cingulate	2.8×10^{-04}	1.5×10^{-02}	0.01
				SA	inferior parietal	4.0×10^{-04}	2.0×10^{-02}	22.33
				SA	fusiform	6.6×10^{-04}	3.2×10^{-02}	12.60
				Vol.	amygdala	8.1×10^{-04}	3.6×10^{-02}	-3.35
				CT	transverse temporal	8.2×10^{-04}	3.6×10^{-02}	0.01
				SA	lingual	9.9×10^{-04}	4.1×10^{-02}	-14.77
rs4391122	5	A	G	SA	pericalcarine	2.7×10^{-10}	4.1×10^{-07}	-9.71
				CT	inferior parietal	1.0×10^{-04}	8.3×10^{-03}	0.002
				SA	inferior parietal	1.2×10^{-04}	9.2×10^{-03}	12.54
rs62526783	8	A	G	SA	isthmus cingulate	7.9×10^{-04}	3.6×10^{-02}	-3.60
rs6471814	8	T	G	CT	parahippocampal	5.8×10^{-04}	2.9×10^{-02}	0.01
rs10883832	10	T	G	CT	transverse temporal	8.7×10^{-07}	1.9×10^{-04}	-0.01
				SA	transverse temporal	1.5×10^{-04}	1.1×10^{-02}	2.63
				SA	supramarginal	9.0×10^{-04}	3.3×10^{-02}	14.88
rs61882743	11	C	G	SA	total SA	2.2×10^{-04}	1.3×10^{-02}	-532.26
rs1615350	12	T	C	SA	cuneus	1.6×10^{-04}	1.1×10^{-02}	4.92

SNP-to-IDP associations with $p_{FDR}<0.05$ for two highly pleiotropic SNPs (rs10149470, and rs8084351) and ten predominantly SCZ-associated SNPs. Note that effect sizes refer to β for cortical IDPs and Z-scores for subcortical IDPs. *Abbreviations*. CT, cortical thickness; EA, effect allele; FDR, false discovery rate; IDP, image-derived phenotype; nuc., nucleus; OA, other allele; p, p-value; SA, surface area; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; Vol., volume.

4 Discussion

This thesis sheds light on the neurobiological correlates of antagonistic and highly pleiotropic SNPs for neuropsychiatric disorders as well as SCZ-associated SNPs identified by the PGC-CDG2 (P. H. Lee et al., 2019).

Study 1 investigated the associations of brain structure with 11 antagonistic SNPs whose alleles increased the risk for one neuropsychiatric disorder and were protective against another disorder. Here, eight antagonistic SNPs were significantly associated with at least one IDP based on GWAS summary statistics of subcortical volume, CT, and SA by the ENIGMA and CHARGE consortia (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019). Several implicated IDPs were altered in patients with SCZ, BIP, or MD compared to controls. In addition, six of the eight SNPs were part of an eQTL in brain tissues, and all eight SNPs were significantly associated with cognitive-behavioral traits. Furthermore, rs301805 and rs1933802 were significantly associated with voxel-wise GMV in data from the FOR2107 study.

Study 2 examined neurobiological correlates of the GRS of highly pleiotropic SNPs and the GRS of predominantly SCZ-associated SNPs in data from the UKBB. The GRS for highly pleiotropic SNPs was significantly associated with several outcomes related to mental health but not with brain structure. The GRS for SCZ-associated SNPs was significantly associated with eight IDPs, including left lateral orbitofrontal SA and left putamen volume. Furthermore, two highly pleiotropic and ten predominantly SCZ-associated SNPs were significantly associated with at least one IDP based on GWAS from the ENIGMA and CHARGE consortia (Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019).

Sections 4.1 and 4.2 discuss the results of Study 1 and Study 2 in light of the current literature. Section 4.3 presents the limitations of both studies, while Section 4.4 places the results of this thesis in a broader context and addresses future directions.

4.1 Study 1

4.1.1 Association of the antagonistic SNPs with brain image-derived phenotypes

Eight of the 11 antagonistic SNPs were associated with at least one IDP. The number of significant SNP-to-IDP associations was higher for the 11 antagonistic SNPs compared to randomly sampled sets of 11 SNPs, as shown by a bootstrapping test. The SNP-to-IDP

associations with the most statistically robust evidence are discussed below for each brain measure.

Three antagonistic SNPs were significantly associated with the volume of subcortical structures. These include the T allele of rs3806843, which was associated with decreased volume in the putamen, caudate, and nucleus accumbens. The striatal divisions are primarily involved in motor control and reward processing, including the response to positive stimuli, decision-making, and motivation (Cox & Witten, 2019). Brain structural changes in striatal regions have previously been reported in patients with MD or SCZ compared to controls (Arnone et al., 2012; Van Erp et al., 2016). However, the findings have been inconsistent, with other large-scale studies reporting no brain structural alterations in these regions in patients with MD (Schmaal et al., 2016). Moreover, research has suggested that medical treatment may partially account for increased volume in striatal regions in patients with SCZ (Kirschner et al., 2021). Nevertheless, the association of rs3806843 with the volume of the putamen, caudate, and nucleus accumbens prioritizes the striatum for follow-up investigations. Future studies could examine the association of rs3806843 with neural activity in the striatum during behavioral paradigms related to reward processing, which is known to be dysfunctional in patients with MD and SCZ (Whitton et al., 2015). In addition, future studies could investigate the role of *PCDHA@* genes in striatal circuit development, as rs3806843 is associated with gene expression of *PCDHA@* genes in striatal tissues, among others (see Section 4.1.3).

Three antagonistic SNPs were significantly associated with at least one CT measure. These include the T allele of rs75595651, which was associated with increased CT in the caudal and rostral anterior cingulate. Interestingly, rs75595651 was previously associated with white matter tracts of the cingulum (Smith et al., 2021), as provided in the Interactive PheWeb server of the brain imaging GWAS using data from the UKBB resource (see *https://open.win.ox.ac.uk/ukbiobank/big40/pheweb33k/variant/4:123133540-C-T*). Of note, GMV volume in the anterior cingulate was reported to be reduced in patients with MD and patients with BIP compared to controls (Wise et al., 2016). As the anterior cingulate is strongly implicated in the processing of affective states (Etkin et al., 2015), structural changes in this region could be a contributing factor to the dysfunctional affective processing observed in MD and BIP (Marx et al., 2023; Vieta et al., 2018). Future work could shed light on neurobiological processes underlying the association of rs75595651 with the

anterior cingulate region. Based on previous findings (Smith et al., 2021), follow-up studies of rs75595651 may incorporate IDPs of white matter microstructure. In addition, future studies might explore the association of rs75595651 with neural activation of the anterior cingulate during affective tasks, given the region's implications in emotional processing (Etkin et al., 2015).

Most antagonistic SNPs (*n*=7) were associated with at least one SA measure. For example, rs2921036 and rs9329221, which are in partial LD (r^2=0.46 in CEU) and showed oppositely directed effects for SCZ and ASD, were significantly associated with SA in the superior temporal region. This region mainly involves auditory and language processing (Yi et al., 2019). Beyond that, the superior temporal region plays a role in social information processing, such as understanding others' thoughts and intentions (Deen et al., 2015). This is of interest because previous studies have demonstrated that patients with ASD and SCZ exhibit opposite difficulties in terms of mentalizing (Ciaramidaro et al., 2015). These deficits may be, in part, explained by structural changes in the superior temporal region (Mitelman et al., 2017). However, future studies are warranted to uncover whether and how the association of rs2921036 and rs9329221 with superior temporal SA leads to their oppositely directed SNP associations with ASD and SCZ. In this context, structural changes of the superior temporal region in patients with SCZ and ASD are discussed in more detail in Section 4.1.2. Beyond that, future analyses could be motivated by further findings from the systematic annotation of rs2921036 and rs9329221. For instance, rs2921036 was found to regulate the expression of the *FAM85B* gene (see Section 4.1.3), while rs9329221 was nominally significant associated with the expression of the *methionine sulfoxide reductase A* (*MSRA*) gene in brain tissue of the temporal cortex (Ramasamy et al., 2014) (see *http://www.braineac.org/*). Notably, gene ontology terms from the Open Targets platform (Ochoa et al., 2021) suggest that the *MSRA* gene is involved in protein repair, cellular responses to oxidative stress, and methionine metabolism. In light of this, future studies could examine, for example, how rs2921036 and rs9329221 regulate brain-region specific gene expression in the superior temporal region.

4.1.2 Case-control MRI differences of the implicated brain image-derived phenotypes

An increase and, at the same time, a decrease of one IDP for the neuropsychiatric disorders linked to the respective antagonistic SNP was not observed based on the case-control MRI studies by the ENIGMA consortium. One reason may be that the case-control MRI differences showed striking similarities across neuropsychiatric disorders (Cheon et al., 2022). Furthermore, it must be recognized that hundreds of SNPs regulate brain structure with small effect sizes (Grasby et al., 2020). Therefore, a potential SNP effect on brain structure may not contribute to observable case-control MRI differences and the link of case-control MRI differences with the SNP-to-IDP associations must be interpreted cautiously.

Nevertheless, several implicated IDPs were found to be altered in patients compared to controls. For example, the T allele of rs9329221 (increased the risk for SCZ; protective against ASD) was associated with decreased SA in the superior temporal region. Notably, it was observed that superior temporal SA was disproportionally decreased in patients with SCZ (Van Erp et al., 2018). While this IDP was not observed to be altered in patients with ASD in the case-control MRI studies by the ENIGMA consortium (Van Rooij et al., 2018), another study found increased GMV volume in the right superior temporal region in majorly healthy children with autistic cognitive style (Kobayashi et al., 2020). In addition, another case-control MRI study reported decreased GMV in the superior temporal region in patients with SCZ and increased GMV in this region in patients with ASD (Mitelman et al., 2017). While this may provide a notion of how rs9329221 could exert opposing effects on SCZ and ASD, future studies at the cellular and molecular level are needed to establish a functional interpretation of the link of genetic variation for neuropsychiatric disorders with structural brain alterations in patients with neuropsychiatric disorders. For example, the spatial distribution of structural alterations can be compared with maps of microstructural determinants to gain insight into possible relationships with molecular features like neurotransmitter density or myelination (Hansen et al., 2022).

4.1.3 Antagonistic SNPs and gene expression in brain tissues

In this analysis, six of eight antagonistic SNPs were significantly associated with gene expression in brain tissues. Among these, the lowest *p*-value was observed for the C allele

of rs2921036 with reduced expression of the *FAM85B* gene in brain tissues of the caudate, hippocampus, nucleus accumbens, cerebellum, cerebellar hemisphere, putamen, frontal cortex, hypothalamus, anterior cingulate, amygdala, substantia nigra, and the whole cortex. Previously, a potential link between the proxy SNP rs2980439 (LD in CEU r^2=0.54) with SCZ and the expression of *FAM85B* was suggested by a colocalization analysis (Sieberts et al., 2020) and likewise for rs2980436 (r^2=0.56) by a Mendelian randomization (MR) analysis (Baird et al., 2021). Future studies are needed to examine underlying molecular processes of how rs2921036 impacts the gene expression of *FAM85B.* As *FAM85B* is considered a long non-coding RNA gene, molecular processes may include RNA interference or post-transcriptional events (Ward et al., 2019). Above all, such future analysis may focus on the gene expression of *FAM85B* in brain regions like the superior temporal or lateral orbitofrontal region, whose SA was associated with rs2921036 in the SNP-to-IDP analysis (see Section 4.1.1).

The second lowest *p*-value was found for the C allele of rs3806843 with increased expression of genes that are members of the *PCDHA* cluster. According to the Gene Cards database (Stelzer et al., 2016), genes of the *PCDHA* cluster promote cadherin-like cell adhesion in neural populations, which is crucial for neural cell-cell recognition. As such, these genes are relevant for the formation of neural circuits (Peek et al., 2017; Wu & Maniatis, 1999). In light of this, studies using animal models found that the dysfunction of *Pcdha* genes could result in incorrect or incomplete synaptic formation and arborization (Shao et al., 2019). Furthermore, studies using cellular models reported that cortical interneurons derived from induced pluripotent stem cells (iPSCs) of SCZ patients (*n*=14) exhibited dysregulated expression of genes of the *PCDHA* cluster (Shao et al., 2019). Future studies are needed to elucidate the functional implications of genes of the *PCDHA* cluster in the development of neural circuitry, which might influence the risk for distinct neuropsychiatric disorders (Flaherty & Maniatis, 2020). This may shed light on the antagonistic effect of rs3806843 on SCZ and MD, which was previously suggested by Byrne et al. to be affected by changes in the expression of genes of the *PCDHA* cluster (Byrne et al., 2021). Also, at this point, further studies could focus on gene expression in striatal regions, which have already been discussed in the context of the SNP-to-IDP analysis for rs3806843 (see Section 4.1.1).

4.1.4 Antagonistic SNPs and cognitive and behavioral traits

All antagonistic SNPs significantly associated with at least one IDP were genome-wide significantly associated with cognitive-behavioral traits. Foremost, the G allele of rs2388334 was associated with higher educational degrees, intelligence, and cognitive performance. Previously, a study highlighted the association of a close proxy SNP, rs1906252 (LD in CEU r^2=1), with the general cognitive ability factor *g* (Trampush et al., 2015). One might speculate that the association of rs2388334 with cognitive ability accounts, in part, for its trait associations with educational attainment, intelligence (Savage et al., 2018), or response behavior to survey questionnaires (Mignogna et al., 2023). Future studies could uncover the cross-phenotype associations of rs2388334 with cognitive traits and specific neuropsychiatric disorders. Furthermore, future studies may elaborate on whether the association of rs2388334 with brain structure, such as the SA of the transverse temporal region (see Section 3.1.1), mediates the observed association with cognitive traits.

In addition, the G allele of rs2388334 was significantly associated with food preferences. Factors influencing food preferences are multi-faced and include food-related, physical, psychological, social, and society-related features (P. J. Chen & Antonelli, 2020). Interestingly, the gene closest to rs2388334, *POU class 3 homeobox 2* (*POU3F2*) – an important neuronal transcription factor (C. Chen et al., 2018) – was also suggested by previous studies to be essential for the development of the hypothalamus that is highly relevant to food intake and appetite regulation (Andersen & Rosenfeld, 2001; Kasher et al., 2016). Future studies are needed to shed light on the association of rs2388334 with hypothalamic structure, which was not incorporated in this study.

The C allele of rs2921036, which showed the second lowest *p*-values, was significantly associated with lower measures of neuroticism and several items of the Eysenck Personality Questionnaire-Revised Short Form (Eysenck et al., 1985), including worrier, irritability, and miserableness. Of note, a previous study showed that rs2945232, a SNP in partial LD (LD in CEU r^2=0.54), presented colocalized associations with SCZ and neuroticism (Smeland et al., 2017). Patients with SCZ have been observed to have higher levels of neuroticism (Van Os & Jones, 2001). However, symptom severity of ASD has also been reported to correlate with higher levels of neuroticism (Schwartzman et al., 2016). Moreover, higher levels of neuroticism were genetically negatively correlated with total SA

(Grasby et al., 2020); specifically, the item worrier was genetically negatively correlated with total brain volume (Zhao et al., 2019). Future studies may elaborate on a cross-phenotype association of rs2921036 with brain structure and neuroticism and how this contributes to its antagonistic effect with ASD and SCZ.

4.1.5 Whole-brain voxel-based morphometry analysis in data from the FOR2017 study

The allele dosages of rs301805 and rs1933802 were significantly associated with voxel-wise GMV in data from the FOR2107 study. First, the G allele dosage of rs301805 was linked to lower GMV in a larger cluster. While the cluster mapped by the AAL atlas to the left superior temporal pole, it extended to the left insula and left posterior orbital gyrus. Notably, the G allele of rs301805 was significantly associated with SA in the insula in the SNP-to-IDP analysis (Section 3.1.1). The insula and the temporal pole are highly interconnected (Herlin et al., 2021). Both regions have been implicated in socio-emotional functioning and semantic processing, among others (Gasquoine, 2014; Herlin et al., 2021). Furthermore, the temporal pole and insula showed a progressive GMV decline that was previously related to symptom severity in patients with first-episode SCZ (S. H. Lee et al., 2016). Overall, the results of the VBM analysis, together with the SNP-to-IDP analysis, prioritized the left superior temporal pole, the insula, and the orbital part of the inferior frontal region for future research on the influence of the genomic region of rs301805 on brain structure.

Second, the G allele dosage of rs1933802 was linked to increased GMV in the left superior parietal region. In particular, the superior parietal region has been implicated in higher cognitive processes such as visual motion perception, spatial processing, attentional shifts, and processing of self-related information (Husain & Nachev, 2007; Kircher et al., 2000; Sulpizio et al., 2023). However, rs1933802 was not associated with this region in the SNP-to-IDP analysis (Section 3.1.1). Thus, future VBM analyses in larger cohorts are needed to assess the reproducibility of the finding.

4.2 Study 2

4.2.1 Association of the GRSs with brain image-derived phenotypes

This analysis found no significant associations between the PleioPsych-GRS and IDPs after correction for multiple testing. This is noteworthy as the PGC-CDG2 highlighted a

distinct involvement in neurodevelopmental processes for the pleiotropic genetic variants associated with at least two neuropsychiatric disorders (P. H. Lee et al., 2019). Furthermore, previous studies focusing on individual highly pleiotropic SNPs have also highlighted their role in neurodevelopmental processes (P. H. Lee et al., 2021; O'Leary et al., 2022; Vosberg et al., 2019). However, one reason for the lack of significant brain structural associations might be that highly pleiotropic SNPs are implicated in multifaceted neurobiological processes (P. H. Lee et al., 2019). Here, their aggregated effect may dilute their impact on brain structure. Moreover, it might be plausible that the highly pleiotropic SNPs collectively affect neural processes reflected by other brain measures, such as structural and functional connectivity (Moreau et al., 2022; Whalley et al., 2014). Future studies need to examine the associations of the PleioPsych-GRS with additional brain measures.

Nevertheless, the PleioPsych-GRS was nominally associated with 12 IDPs. These included, with the lowest *p*-values ($p<0.01$), volumetric decrease in the left thalamus and decreased SA in the right caudal and rostral anterior cingulate. While the thalamus is traditionally known to relay sensory input (Acsády, 2017), the current view of the thalamus suggests a more general role in modulating information processing throughout the cortex (Shine et al., 2023). As such, the thalamus regulates key cognitive functions such as working memory, emotion regulation, and attention (Shine et al., 2023). Recent research suggested that thalamic structure and connectivity are subtly altered in patients with neuropsychiatric disorders (Hettwer et al., 2022; Hwang et al., 2022). Notably, these changes were partially shared across neuropsychiatric disorders (Hettwer et al., 2022; Hwang et al., 2022). Future studies are needed to explore whether the highly pleiotropic SNPs influence structural changes in the thalamus observed across neuropsychiatric disorders. In this context, it would be interesting to include the volume of thalamic subnuclei (Elvsåshagen et al., 2021) or thalamic connectivity (Hwang et al., 2022), which could provide insights into anatomical and information processing facets.

In addition, the PleioPsych-GRS was nominally associated with SA of the right caudal and rostral anterior cingulate. A key role of the anterior cingulate is the regulation of emotions and affective states (Etkin et al., 2011). While previous reports have highlighted that the anterior cingulate shows similar structural changes in patients across multiple neuropsychiatric disorders (Romer & Pizzagalli, 2022; Wise et al., 2016), other studies have not supported cross-disorder morphological changes in the anterior cingulate (Hansen et al.,

2022; Opel et al., 2020). Therefore, the extent to which brain structural alterations in the anterior cingulate observed in patients with neuropsychiatric disorders are shaped by genetic factors, especially highly pleiotropic SNPs, must be investigated by future studies.
Significant associations between the SCZ-GRS and IDPs were found for eight IDPs. The lowest *p*-values were observed for increased SA in the left lateral orbitofrontal region. Furthermore, an association was found between the SCZ-GRS and decreased CT in the left and increased SA in the left and right lateral orbitofrontal region. A case-control MRI study of 4,474 individuals with SCZ showed that the lateral orbitofrontal region was thinner in patients with SCZ compared to controls (Van Erp et al., 2018). While SCZ was associated with cortical thinning globally, the effect was suggested to be pronounced in prefrontal and temporal regions (Van Erp et al., 2018). In addition, morphological changes in the prefrontal cortex, including the lateral orbitofrontal region, have also been reported in other neuroimaging case-control MRI studies of SCZ (e.g., Howes et al., 2022; Madre et al., 2020; Nenadic et al., 2015). Notably, the lateral orbitofrontal region plays an important role in reward, motivation, and emotional regulation (Kringelbach, 2005). In light of this, it has been demonstrated that decreased CT in the orbitofrontal region is linked to the negative symptoms observed in patients with first-episode SCZ (Kirschner et al., 2021). Future studies should focus on this region to uncover which molecular and cellular mechanisms underlie the association between the SCZ-GRS and the lateral orbitofrontal region. While the lateral orbitofrontal region may play an important role in the pathophysiology of SCZ, it remains unclear whether the observed neurobiological correlates are specific to SCZ compared to other neuropsychiatric disorders. While previous studies revealed significant associations of the PRS for SCZ and decreased CT in the lateral orbitofrontal region (Alnæs et al., 2019), further studies reported significant associations of the PRS for BIP with decreased CT and increased SA in the lateral orbitofrontal region (Rodrigue et al., 2023) as well as significant associations of the PRS for MD and cortical complexity in this region (Schmitt et al., 2022). Therefore, it remains to be investigated whether the aggregated effect of the predominantly SCZ-associated SNPs may differently affect the structure of the lateral orbitofrontal region. For example, the association could be based on microstructural changes in different subregions or underlying molecular processes like synaptic density or myelination.

The SCZ-GRS was also significantly associated with increased volume in the left putamen. The putamen, along with the caudate, forms the striatum, which is critical for controlling movement but is also important for higher cognitive functions such as goal-directed behavior, reinforcement learning, or decision-making (Cox & Witten, 2019). Putamen volume was found to be increased in SCZ and BIP, whereas it has been reported to be decreased in other neuropsychiatric disorders such as ADHD and MD (X. Luo et al., 2019). These distinct case-control MRI differences may indicate that distinct molecular processes are implicated in psychotic but not other neuropsychiatric disorders. While an increased number of dopaminergic neurons may contribute to the increased putamen volume observed in SCZ (X. Luo et al., 2019), certain antipsychotic medications could impact the reported volumetric increase (Ho et al., 2011). To further understand the relationship between the SCZ-GRS and putamen volume, future studies could investigate the association in patients with SCZ. In addition, future studies could explore whether predominantly SCZ-associated SNPs are linked to gene expression in the putamen (Q. Luo et al., 2019), which may shed further light on the underlying molecular mechanisms.

4.2.2 Association of the GRSs with outcomes related to mental health

The PleioPsych-GRS was significantly associated with self-reports of irritability, fed-up feelings, tense feelings, miserableness, worrier, mood swings, nervous feelings, and sensitivity. These results suggest that the collective effect of the highly pleiotropic SNPs does indeed explain some of the phenotypic variance, although the GRS was not significantly associated with brain structure. Of note, the implicated outcomes related to mental health constitute items of the Eysenck Personality Questionnaire-Revised Short Form (Eysenck et al., 1985), which is frequently used to assess neuroticism. This rather broad personality trait is considered an unspecific risk factor for neuropsychiatric disorders (Ormel et al., 2013). While it could be suggested that higher levels of neuroticism increase the susceptibility to neuropsychiatric disorders, the link may also be due to a common underlying etiology (Ormel et al., 2013).

Interestingly, the sensitivity analysis excluding samples with self-reported and diagnosed depression found that the PleioPsych-GRS was not significantly associated with worrier,

nervous feelings, and sensitivity. The exclusion of these samples likely affected the distribution of outcomes with mental health, with fewer samples tending towards lower emotional stability and higher stress reactivity.

The SCZ-GRS was significantly associated with worrier, guilty feelings, sensitivity, and tense feelings. These outcomes relate to the negative symptoms in SCZ (Kahn et al., 2015). However, an implication of these findings for SCZ pathology cannot be established as the analysis is based on majorly healthy controls. Therefore, future studies in clinical cohorts are warranted to elucidate whether the SCZ-GRS accounts for part of the clinical features observed in patients with SCZ.

4.2.3 Association of the individual SNPs with brain image-derived phenotypes

Two highly pleiotropic and ten predominantly SCZ-associated SNPs were significantly associated with at least one IDP. This reflects the observation that the PleioPsych-GRS showed limited associations with brain structure, and the SCZ-GRS was significantly associated with several IDPs (Section 3.2.1). Interestingly, the predominantly SCZ-associated SNPs were, in particular, associated with CT and SA in the temporal and occipital regions. This is noteworthy as gene enrichment analysis by the PGC-CDG2 (cf., Figure 5C in P. H. Lee et al., 2019) found that loci predominantly associated with a specific disorder compared to pleiotropic loci were enriched for genes with heightened expression in the occipital cortex. Future studies should investigate the implicated SNPs and their influence on gene expression in the occipital cortex.

In addition, rs35225200, a predominantly SCZ-associated SNP, was significantly associated with 23 IDPs. Moreover, rs35225200 and several LD-dependent SNPs were previously reported to be associated with brain structure, including subcortical GMVs and white matter tracts in the midbrain (Elliott et al., 2018). Notably, rs35225200 was located near the *solute carrier family 39 member 8* (*SLC39A8*) gene, which is involved in important cellular functions like the transport of several metals, including zinc, manganese, and cadmium (Mealer et al., 2022). Previous studies (e.g., Costas, 2018; Mealer et al., 2020; Smart et al., 2024) have primarily focused on a functional missense variant of *SLC39A8*, namely rs13107325 (LD in CEU r^2=0.85) (p.Ala391Thr). This variant has been associated with reduced cellular transport of zinc (Tseng et al., 2021) and altered manganese-related phenotypes relevant to brain development (Mealer et al., 2022). The relationship between

genetic variation in *SCL39A8* and the pathophysiology of SCZ is largely unknown (Costas, 2018). Further characterization of the genetic variants rs13107325 and rs35225200 may focus on cellular functions related to metal uptake or transport, such as glycosylation (Mealer et al., 2022), neuroinflammation (Tseng et al., 2021) or altered neurotransmission (Costas, 2018).

4.3 Limitations

The limitations of Study 1 and Study 2 are discussed in detail in the respective articles. The present thesis focuses on the limitations of fundamental aspects, including the choice of the datasets (Section 4.3.1), the selected genetic variants (Section 4.3.2), and the brain IDPs (Section 4.3.3). By reflecting on these, valuable insights for future research are given.

4.3.1 Choice of the datasets

The datasets used in Study 1 and Study 2 are discussed below regarding their sample sizes, cohort characteristics, availability of phenotypic assessments, and potential sample overlap.

Imaging genetic analyses require large sample sizes to obtain robust statistical results (Carter et al., 2017). The SNP-to-IDP analysis of Study 1 was based on large-scale GWAS summary statistics from the ENIGMA and CHARGE consortia, each of which included more than 26,000 samples in the discovery cohort, while Study 2 analyzed genetic and neuroimaging data from 28,952 UKBB participants. Although these datasets are among the largest data resources available today, future studies with even larger datasets will be able to assess the reproducibility of the findings presented in these studies.

The large sample sizes incorporated in Study 1 and Study 2 were only achieved by comprising datasets of majorly healthy individuals (Bycroft et al., 2018; Grasby et al., 2020; Hibar et al., 2017; Satizabal et al., 2019). Therefore, it remains unexplored whether the associations between SNPs and GRSs with IDPs identified in Study 1 and Study 2 were potentially pronounced in patients with neuropsychiatric disorders. As previous research has uncovered associations between genetic variants for neuropsychiatric disorders in brain structural phenotypes reported to be altered in patients compared to controls (Radonjić et al., 2021; Stauffer et al., 2021), future studies are encouraged to follow up the findings of Study 1 and Study 2 using data from clinical cohorts.

Cohort characteristics such as ancestry, age, and sex ratio influence the generalizability of results (Schmaal et al., 2020). Study 1 and Study 2 primarily included data from participants with European ancestry. Thus, it remains unclear whether the results are generalizable to other ancestry groups (Mufford et al., 2017). Strikingly, including imaging and genetic data from samples of diverse ancestries is one of the key goals of the ENIGMA consortium (Thompson et al., 2017) and the PGC (Peterson et al., 2019). This effort might open up future studies to incorporate samples from various ancestries, which is necessary to realize benefits in clinical care across ancestries.

Furthermore, Study 2 primarily included data from middle-aged to older adults. As previous studies have found that genetic variants for neuropsychiatric disorders may influence brain development (Alex et al., 2023) and brain aging (Kaufmann et al., 2019), future studies may elaborate on whether the association between genetic variants and brain structure observed in Study 1 and Study 2 changes across the lifespan. Understanding how an effect evolves with age may provide insights into the points in time at which the genetic variation exerts its effect on brain-related processes (Le & Stein, 2019).

In addition, Study 1 and Study 2 did not investigate sex differences. Prospective studies could address this, as previous research has demonstrated sex differences in the genetic architecture of neuropsychiatric disorders (Blokland et al., 2022) and in the case-control MRI differences for neuropsychiatric disorders (Hibar et al., 2018).

The availability and depth of phenotypic assessment limited the exploration of how the selected genetic variants for neuropsychiatric disorders influence cognition and behavior. For example, Study 2 explored the association of the GRSs with outcomes related to mental health, which were assessed by a dichotomous questionnaire. However, these outcomes may not precisely reflect the participants' mental health as the records are self-reported and assessed through brief dichotomous questions (Davis et al., 2020). Therefore, future studies might explore whether the GRSs are associated with more comprehensive mental health assessments that can provide greater specificity in specific domains like anxiety, mood, and stress reactivity.

Finally, it is important to note that the datasets used in these studies partially overlap, which could subtly affect the results. In Study 1, the GWAS of CT and SA measures used in the SNP-to-IDP analysis (Grasby et al., 2020) comprised a subset of participants from the FOR2107 study on which the VBM analysis was based. In Study 2, data from the

UKBB were partially comprised in a GWAS of MD (Wray et al., 2018), which was included in the meta-analyses of the PGC-CDG2 (P. H. Lee et al., 2019). Sensitivity analyses were performed excluding samples with self-reported or diagnosed depression (Wray et al., 2018). The effect sizes of the association of GRSs with both brain structure and outcomes related to mental health observed in the sensitivity analyses correlated with the corresponding effect sizes of the main analysis. While this suggests that sample overlap did not substantially influence the results, it should be noted that controls for the GWAS of MD could not be excluded.

4.3.2 Choice of the selected genetic variants

The selected SNPs that were the subject of Study 1 and Study 2 were based on the most recent cross-disorder GWAS by the PGC today (P. H. Lee et al., 2019). It should be noted that the PGC-CDG2 included more than 230,000 patients with neuropsychiatric disorders, which allowed for the identification of robust genetic associations (P. H. Lee et al., 2019). However, sample sizes for ANO, OCD, and TS were smaller than for the other neuropsychiatric disorders (Table 1). This might explain why antagonistic and highly pleiotropic SNPs were mainly associated with ASD, BIP, MD, and SCZ but showed much fewer associations with ANO, OCD, or TS (Table S1). Hence, the results of Study 1 and Study 2 are more likely to reflect the underlying neurobiology of the more strongly represented disorders. Future cross-disorder studies, including larger numbers of cases with ANO, OCD, or TS, may provide better insights into these disorders.

Furthermore, Study 1 and Study 2 investigated a limited number of SNPs (P. H. Lee et al., 2019). Future cross-disorder GWAS with larger sample sizes and alternative GWAS methods like case-case GWAS (Peyrot & Price, 2021) may expand the set of SNPs with complex associations across neuropsychiatric disorders. Concerning Study 1, an increased number of antagonistic SNPs may open up the possibility of investigating GRSs that aggregate SNPs with opposing effects for two specific disorders (e.g., a GRS of ASD vs. SCZ), which was not done in Study 1 due to the different combinations of disorder associations for each antagonistic SNP. In addition, it is conceivable that antagonistic SNPs are associated with more than two disorders. Thus, they represent antagonistic associations for two subgroups of neuropsychiatric disorders or antagonistic associations that distinguish one from other neuropsychiatric disorders. For example, the G allele of

rs2388334 increased the risk for ASD and BIP while being protective against TS (P. H. Lee et al., 2019). Nevertheless, it may be hypothesized that rs2388334 poses an effect that distinguishes TS from other neuropsychiatric disorders as further cross-disorder GWAS showed that the identified LD-dependent SNP rs1906252 (LD in CEU r^2=1) showed an oppositely direct effect on TS vs. ANO (Grotzinger et al., 2022; Peyrot & Price, 2021), and rs9401593 (r^2=1) on TS vs. SCZ (Peyrot & Price, 2021). Together, this may hint that the genomic region of rs2388334 affects biological processes whose dysfunctions particularly distinguish TS from other neuropsychiatric disorders. Concerning Study 2, the possible identification of further SNPs predominantly associated with one specific neuropsychiatric disorder other than SCZ may allow the investigation of the neurobiological correlates of genetic variants predominantly specific for ASD, BIP, or MD, among others.
Finally, the two studies included SNPs previously associated with the eight neuropsychiatric disorders in the PGC-CDG2 (P. H. Lee et al., 2019). Future imaging studies may incorporate SNPs identified by cross-disorder GWAS that include additional neuropsychiatric disorders such as anxiety, insomnia, and substance use disorders (Romero et al., 2022).

4.3.3 Choice of the brain image-derived phenotypes

Genetic variants for neuropsychiatric disorders may influence different aspects of the human brain (Warrier et al., 2023). Study 1 and Study 2 investigated the association of selected SNPs with subcortical volume, CT, and SA measures. These reflect macroscopic measures such as the number and density of neurons in the brain (Warrier et al., 2023). Future studies could further explore the associations of the SNPs with IDPs of additional MRI measures. These could include IDPs of white matter structure, which reflect microscopic measures such as fiber dispersion (Warrier et al., 2023), and IDPs of structural and functional connectivity, which provide insight into brain networks (van den Heuvel & Hulshoff Pol, 2010). Testing the association of the selected SNPs with these IDPs may provide supplementary insights into their influences on neural processes.
Study 1 and Study 2 assessed the association of selected SNPs with cortical IDPs delineated by the DK atlas (Desikan et al., 2006). This made it possible to use GWAS summary statistics of IDPs and to investigate whether the implicated IDPs were altered in patients with neuropsychiatric disorders using large-scale studies coordinated by the ENIGMA

consortium. The DK atlas represents a coarse parcellation (Desikan et al., 2006), limiting the detection of genetic influences on fine-grained brain regions (Warrier et al., 2023). Future imaging genetic studies are encouraged to use other parcellations like the Julich-brain atlas (Amunts et al., 2020). This may support the discovery of genetic influences on subregions (Mufford et al., 2024; Van der Meer et al., 2018). Nevertheless, it is plausible that while some genetic variants influence small, localized regions, others have a widespread influence on brain structure (Alexander-Bloch et al., 2019; Grasby et al., 2020).

4.4 Implications for future research

4.4.1 Building a mechanistic understanding of genetic variants for neuropsychiatric disorders

Studying how genetic variants exert their risk on the pathophysiology of neuropsychiatric disorders requires converging insights alongside molecular, cellular, and neuroimaging studies (Le & Stein, 2019). As a field, imaging genetics approaches this by studying brain structure and function as intermediate phenotypes (Meyer-Lindenberg & Weinberger, 2006). However, imaging genetic analyses, including the present studies, are limited in (i) unraveling the causal mechanisms underlying cross-phenotype associations, (ii) integrating insights across biological scales, and (iii) uncovering biological processes underlying GRS-phenotype associations.

4.4.1.1 Cross-phenotype associations

Imaging genetic analyses – including Study 1 of this thesis – aim to investigate whether genetic variants associated with neuropsychiatric disorders are also associated with brain structure. Such cross-phenotype associations, however, can be inherently caused by different scenarios, from true biological pleiotropy in that a single causal variant influences two phenotypes, over colocalization in that two causal variants in the same gene influence two phenotypes, to spurious pleiotropy in that two causal variants in different genes exists, whereby their strong LD results in a cross-phenotype association (cf., P. H. Lee et al., 2021; Solovieff et al., 2013). In sum, associations between genetic variants and brain phenotypes do not infer causation but allow research to identify genetic variants with potential prominent neurobiological implications (Le & Stein, 2019).

To infer the causal relationship between brain structure and neuropsychiatric disorders, a two-sample MR may be performed (Sanderson et al., 2022). MR uses genetic variants as

instrumental variables to test the relationship between exposure and outcome based on GWAS summary statistics (Sanderson et al., 2022). However, due to technical considerations, such an analysis is only partly feasible concerning Study 1 and Study 2. First, choosing a limited number of SNPs as an instrumental variable may result in weak instrument bias (Sanderson et al., 2022). Second, SNPs associated with neuropsychiatric disorders are likely associated with cognitive and behavioral traits (Hindley et al., 2022). These SNPs were typically excluded (e.g., Guo et al., 2022) as one assumption of MR analyses states that the outcome must not influence the exposure through another variable (Sanderson et al., 2022). As neither technical requirement was met, a two-sample MR analysis to estimate the causal genetic relationships between brain structure (exposure) and neuropsychiatric disorder (outcome) was not conducted in the courses of Study 1 and Study 2.

4.4.1.2 Integrate insights across biological scales

Imaging genetic analyses aim to explore the association of disease-associated variants with multiple phenotypes across different biological scales (Le & Stein, 2019). For example, Study 1 systematically characterized 11 antagonistic SNPs for their association with brain structure, gene expression in brain tissues, and cognitive-behavioral traits. However, integrating findings across different biological scales is not sufficient to unravel a mechanistic understanding (Parikshak et al., 2015). In light of this, selected genetic variants need to be followed up for their association with brain structure at finer resolutions that capture cellular or synaptic microstructure (Le & Stein, 2019). Furthermore, prioritized genetic variants can be followed up by functional characterization (Gallagher & Chen-Plotkin, 2018), including animal models (Gottesman & Gould, 2003) or cellular models (Y. Zhang et al., 2013). For instance, iPSC-derived models can be used to explore how genetic variants affect neural differentiation, gene expression, or epigenetic regulation (De Los Angeles et al., 2021). Here, the use of CRISPR/Cas9 enables the editing of genetic variants in iPSCs to create isogenic lines that can be compared in terms of molecular and cellular processes (De Los Angeles et al., 2021).

4.4.1.3 Biological processes underlying GRS-phenotype associations

Study 2 of this thesis reported a significant association between the SCZ-GRS and several IDPs. Due to the aggregated effect of genetic variants potentially involved in different molecular processes, insight into the underlying biological processes was limited. One approach to elucidate implicated pathways can be the calculation of pathway-specific GRSs (Barbu et al., 2019). Therein, GRSs were calculated for gene sets contributing to SCZ pathophysiology, including GRSs that aggregate genetic variants involved in the NETRIN1 signaling pathway (Barbu et al., 2019) or that implicate postsynaptic density (Barbu et al., 2023). Notably, the construction of pathway-specific GRSs is often limited because many genetic variants identified by GWAS are located in non-coding regions of the genome (Sullivan & Geschwind, 2019). For this reason, and because of the limited number of SNPs in Study 2, pathway-specific GRSs were not examined in the present thesis. However, with additional genetic variants to be identified, building GRSs of pathways relevant to general psychopathology or predominantly SCZ-related will become realizable (Warren et al., 2024).

4.4.2 Translational challenges and clinical opportunities in imaging genetics

The translation of findings from biological psychiatry for clinical utility has not been achieved (Derks et al., 2022). This subsection outlines how imaging genetic analysis presented herein could lay the foundation for developing biomarkers and addressing transdiagnostic perspectives. In addition, it will be illustrated that further research on interindividual variability is warranted.

4.4.2.1 Biomarker development

Biomarkers provide essential information about an individual's health status to aid in diagnosis, treatment planning, and monitoring of disease progression (García-Gutiérrez et al., 2020). To date, biomarkers in psychiatry have limited predictive validity for patient outcomes (Abi-Dargham et al., 2023), making the development of biomarkers to support clinical research and clinical care vitally important.

Imaging genetic analyses may guide the discovery of clinical biomarkers by prioritizing SNPs and IDPs for future research (J. Chen et al., 2019; Mufford et al., 2017). For example, in Study 2, the predominantly SCZ-associated SNP rs35225200 was prominently associated with brain structure. In the next step, it may further be investigated whether the

finding is potentially enhanced in patients with SCZ and other neuropsychiatric disorders compared to controls. In such an analysis, the nearby missense variant rs13107325 (LD in CEU r^2=0.85) should also be incorporated (see Section 4.2.3). Findings of differences in the association between the genetic variant and brain structure within patient cohorts may encourage further studies of clinical biomarkers.

Furthermore, imaging genetics analyses support the integration of biomarkers from multiple modalities, including genomics, neuroimaging, and cognitive-behavioral assessments that capture different aspects of disease etiology (Schmaal et al., 2020). For example, Study 1 found that the T allele of rs2921036 was significantly associated with superior temporal SA but also with higher levels of neuroticism. This suggests intercorrelations across distinct biological levels, encouraging future research on the meaningful integration of phenotypes across multiple modalities to develop biomarkers (Sui et al., 2023). In light of this, machine learning has emerged as a promising tool for multi-modal integration, particularly for handling the high-dimensional nature of the data (Quinn et al., 2024).

4.4.2.2 Transdiagnostic perspectives

Neuropsychiatric disorders exhibit high rates of comorbidity, highlighting the need for transdiagnostic perspectives in research and clinical care (Allsopp et al., 2019). In particular, psychiatric genetics and neuroimaging studies have emphasized that current diagnostic criteria do not represent biologically distinct conditions (Smoller et al., 2018). To address this challenge, this thesis focused on antagonistic, highly pleiotropic, and predominantly SCZ-associated SNPs. In particular, Study 2 investigated neurobiological correlates of a GRS that aggregates the effect of 22 predominantly SCZ-associated SNPs. Future research on disorder-specific genetic scores is encouraged as it is important to improve the specificity of PRSs across neuropsychiatric disorders (Rodrigue et al., 2023). Such disorder-specific PRSs may be more clinically relevant descriptors to investigate correlates of genetic risk with phenotypic traits, to predict treatment response, or to stratify patients across neuropsychiatric disorders (Fusar-Poli et al., 2022; Smeland & Andreassen, 2021).

4.4.2.3 Inter-individual variability

Neuropsychiatric disorders feature a considerable degree of phenotypic heterogeneity (Allsopp et al., 2019). On this basis, personalized treatment in psychiatry has become a

promising research topic (McMahon & Insel, 2012; Schmaal et al., 2020). Nevertheless, much research, including Study 1 and Study 2, investigated group averages. Investigations of the interindividual variability of patients with neuropsychiatric disorders will be critical to tailor the needs of the individual in clinical care (Jockwitz et al., 2021; Schmaal et al., 2020). One step in this direction can be the identification of patient subtypes. Especially in BIP, two major subtypes, BIP type 1 and type 2, are distinguished (Vieta et al., 2018). It has been shown that the two subtypes present clinical and genetic differences (Guzman-Parra et al., 2021) and benefit from different treatment approaches (Nierenberg et al., 2023). Subtyping based on neuroimaging and genetics has also shown potential for refining treatment in other neuropsychiatric disorders, including MD (Nguyen et al., 2022) or ADHD (W. Zhang et al., 2023).

4.5 Conclusion

This thesis uncovered associations between antagonistic, highly pleiotropic, and predominantly SCZ-associated SNPs with brain structure and brain-related traits, supporting that genetic variants may alter the risk for specific neuropsychiatric disorders through brain structure. Overall, the results from this work prioritize individual SNPs and phenotypic traits for future investigation.

Study 1 found that eight of the 11 antagonistic SNPs, which increase the risk for one neuropsychiatric disorder and are protective against another, were significantly associated with brain structure. Systematic characterization of the implicated SNPs highlighted their association with gene expression in brain tissue and cognitive-behavioral traits. Notably, Study 1 prioritized rs9329221 and rs2921036, which are in partial LD and showed oppositely directed effects for SCZ and ASD. Both SNPs were significantly associated with the lowest *p*-values to the superior temporal SA, a region that was found to be altered in patients with SCZ compared to controls. In addition, rs9329221 and rs2921036 were significantly associated with higher neuroticism scores, and rs2921036 was significantly associated with gene expression of *FAM85B* in several brain tissues. Given their association with brain-related traits at multiple neurobiological levels, future studies are encouraged to elucidate their underlying molecular mechanisms.

Study 2 revealed, based on data from the UKBB, that the GRS of predominantly SCZ-associated SNPs was significantly associated with the left lateral orbitofrontal SA and left

putamen volume, among others. Future studies could follow up on this association by examining the association of the GRS with additional brain measures, such as the structural and functional connectivity of these regions as part of the fronto-striatal network. Among the predominantly SCZ-associated SNPs, rs35225200 is noteworthy as it was found to be associated with 23 brain structural phenotypes. While the GRS of highly pleiotropic SNPs showed limited evidence of association with brain structure, it was broadly associated with outcomes related to mental health that are implicated across neuropsychiatric disorders. Future studies are needed to elaborate on this association in clinical cohorts to evaluate its significance for further clinical research.

This thesis contributes important insights into how antagonistic, highly pleiotropic, and predominantly SCZ-associated SNPs may confer risk for specific neuropsychiatric disorders by studying their associations with brain-related traits. Future studies, including additional brain measures, cellular models, and clinical cohorts, are warranted to further advance our understanding of their underlying neurobiology.

5 Abstract

With the advances in genome-wide association studies (GWAS), hundreds of genetic variants have been identified for neuropsychiatric disorders. Strikingly, many of these genetic variants showed complex associations across diagnostic groups. For example, the second cross-disorder GWAS meta-analysis by the Psychiatric Genomics Consortium (P. H. Lee et al., 2019) comprised 232,964 patients with eight neuropsychiatric disorders and identified 11 antagonistic single-nucleotide polymorphisms (SNPs) that were associated with an increased risk for one neuropsychiatric disorder, while being protective against another neuropsychiatric disorder. Furthermore, the cross-disorder GWAS meta-analysis uncovered 23 highly pleiotropic SNPs that were associated with at least four neuropsychiatric disorders and 22 SNPs that were predominantly associated with schizophrenia (SCZ) but not with the other disorders (P. H. Lee et al., 2019). The underlying molecular mechanisms by which these genetic variants alter the risk of distinct neuropsychiatric disorders are largely unclear. The present thesis conducted two imaging genetic studies to uncover the associations between antagonistic, highly pleiotropic, and predominantly SCZ-associated SNPs with brain structure and brain-related traits.

Study 1 performed a systematic characterization of the 11 antagonistic SNPs (Federmann et al., 2024). Here, the association of the SNPs with T1-weighted magnetic resonance brain structural phenotypes using GWAS summary statistics from the ENIGMA and CHARGE consortia was investigated. The implicated SNPs were further annotated for their association with gene expression in human brain tissue and cognitive-behavioral traits. To examine the brain structural association at the voxel-wise level, a whole-brain voxel-based morphometry (VBM) analysis in data from the FOR2107 study was performed. Study 2 used data from the UK Biobank (*n*=28,952) to examine the association of a genetic risk score of highly pleiotropic SNPs for neuropsychiatric disorders (PleioPsych-GRS) and a genetic risk score of predominantly SCZ-associated SNPs (SCZ-GRS) with brain structure and outcomes related to mental health. To prioritize individual SNPs, the association of each SNP with brain structure was investigated.

The results of Study 1 showed that eight of the 11 antagonistic SNPs were significantly associated with at least one brain structural phenotype. Several of the implicated phenotypes were found to be altered in patients with bipolar disorder, major depression, or SCZ

compared to controls. Six of the eight antagonistic SNPs were significantly associated with gene expression in brain tissue, and all eight antagonistic SNPs were significantly associated with cognitive-behavioral traits. The VBM analysis in data from the FOR2107 study found that rs301805 and rs1933802 were significantly associated with clusters of gray matter volume.

Study 2 found that the PleioPsych-GRS was not significantly associated with brain structural phenotypes after multiple testing corrections, whereas the SCZ-GRS was significantly associated with left and right putamen volume and left and right lateral orbitofrontal surface area, among others. While the PleioPsych-GRS was significantly associated with eight outcomes related to mental health, including irritability, fed-up feelings, and tense feelings, the SCZ-GRS was significantly associated with four outcomes related to mental health, including worrier, sensitivity, and guilty feelings. Furthermore, two highly pleiotropic and ten predominantly SCZ-associated SNPs were significantly associated with at least one brain structural phenotype.

In conclusion, this thesis showed that antagonistic, predominantly SCZ-associated and, to a lesser extent, highly pleiotropic SNPs for neuropsychiatric disorders were associated with brain structure. In addition, the SNPs were associated with traits related to mental health, cognition, and behavior. These findings provided a notion of how these SNPs might influence disease development and led to the prioritization of selected SNPs and brain regions relevant for further investigations. Future work should extend these findings by exploring the association of these SNPs with additional brain modalities, including white matter microstructure and structural and functional connectivity of the human brain.

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9 APPENDIX

Table S1 | Highly pleiotropic SNPs

rsID	CHR	BP (GRCh37)	EA	OA	*BETA*	ADHD	ANO	ASD	BIP	MD	OCD	SCZ	TS	CADD	VEP	Nearest gene
rs7531118	1	72837239	T	C	-0.035		×	×		×		×	×	11.35	Reg. region var.	*NEGR1*
rs12129573	1	73768366	A	C	0.053	×			×	×		×		5.32	Up. g. var.	*LRRIQ3*
rs1518367	2	198807015	A	T	-0.050			×	×	×		×		0.08	Intron var.	*PLCL1*
rs34215985	4	42047778	C	G	-0.052	×	×	×		×		×	×	6.84	Intron var.	*SLC30A9*
rs1484144	4	80217597	T	C	0.036	×		×	×	×		×		3.35	Intron var.	*NAA11*
rs12658451	5	103904037	T	C	0.037	×		×	×	×		×	×	5.86	Intron var.	*NUDT12*
rs9360557	6	73132745	C	G	0.034	×	×	×	×	×		×		0.95	Reg. region var.	*KCNQ5*
rs79879286	7	24826589	C	G	0.046			×	×	×		×		2.13	Reg. region var.	*GSDME*
rs6969410	7	110069015	T	G	0.051			×	×	×	×	×		2.13	Downstream. gene var.	*LRRN3*
rs10265001	7	140665521	C	G	-0.053			×	×		×	×		8.94	Interg. var.	*BRAF*
rs9787523	10	106460460	T	C	0.035	×		×		×	×		×	9.77	Intron var.	*SORCS3*
rs61867293	10	106563924	T	C	-0.050	×	×	×	×	×		×		8.24	Intron var.	*SORCS3*
rs11570190	11	57560452	A	C	-0.034	×		×		×	×	×		6.11	Intron var.	*CTNND1*
rs117956829	11	89339666	A	G	0.109		×	×	×	×		×		0.97	Reg. region var.	*TRIM77*
rs78337797	12	23987925	T	G	0.042			×	×	×		×		2.21	Intron var.	*SOX5*
rs2332700	14	72417326	C	G	0.047			×	×	×		×		4.26	Intron var.	*RGS6*
rs10149470	14	104017953	A	G	-0.039			×	×	×		×	×	0.47	Up. g. var.	*KLC1*
rs7193263	16	6315880	A	G	-0.039	×		×	×	×	×	×	×	0.14	Intron var.	*RBFOX1*
rs7405404	16	13749859	T	C	0.070			×	×	×		×		1.33	Interg. var.	*ERCC4*
rs8084351	18	50726559	A	G	0.044	×	×	×	×	×	×	×	×	4.03	Intron var.	*DCC*
rs6125656	20	48090779	A	G	0.063			×	×	×		×		0.93	Intron var.	*KCNB1*
rs5758265	22	41617897	A	G	0.073					×	×	×	×	7.61	Intron var.	*L3MBTL2*

Information on the genomic position, effect allele, effect size (*BETA*), and associated neuropsychiatric disorders of the 22 highly pleiotropic SNPs identified by the PGC-CDG2 were taken from Table 2 and Table S3.2 in (P. H. Lee et al., 2019). Note that rs11688767 was removed due to non-inferable allele ambiguity (see Section 2.2.2.2). Resources of PHRED-scaled CADD, VEP, and nearest gene are given in Table 2. *Abbreviations.* ADHD, attention deficit hyperactivity disorder; ANO, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; BP, basepair position; CADD, combined annotation-dependent depletion; CHR, chromosome; down., downstream; EA, effect allele; g., gene; GRCh37, Genome Reference Consortium human build 37; Interg., intergenic; MD, major depression; OA, other allele; OCD, obsessive-compulsive disorder; PGC-CDG2, second cross-disorder GWAS meta-analysis of the PGC; reg., regulatory; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; TS, Tourette's syndrome; up., upstream; var., variant; VEP, variant effect predictor.

Table S2 | Predominantly SCZ-associated SNPs

rsID	CHR	BP (GRCh37)	EA	OA	*BETA*	CADD	VEP	Nearest gene
rs1702294	1	98501984	T	C	-0.115	0.13	Intron var.	*DPYD*
rs10211550	2	198383299	T	G	-0.069	0.05	Intron var.	*HSPD1*
rs7618871	3	136400420	T	G	0.070	0.19	Intron var.	*STAG1*
rs35225200	4	103146888	A	C	-0.135	2.40	Intergenic var.	*SLC39A8*
rs4391122	5	60598543	A	G	-0.078	4.56	Intergenic var.	*ZSWIM6*
rs34718920	6	27783941	T	C	-0.213	3.62	Up. gene var.	*H2BC14*
rs13240464	7	110898915	T	C	0.075	0.72	Intron var.	*LRRN3*
rs188099135	8	27411792	A	G	-0.065	2.12	Intergenic var.	*CLU*
rs6471814	8	60697874	T	G	0.064	1.26	Intergenic var.	*CA8*
rs62526783	8	111471166	A	G	0.065	2.51	Intergenic var.	*KCNV1*
rs10883832	10	104871279	T	G	0.161	12.48	Intron var.	*RPEL1*
rs61882743	11	46548754	C	G	-0.069	0.22	Intron var.	*AMBRA1*
rs10791097	11	130718630	T	G	0.077	9.19	Intron var.	*SNX19*
rs75059851	11	133822569	A	G	0.089	6.03	Intron var.	*IGSF9B*
rs12826178	12	57622371	T	G	-0.168	2.50	Up. gene var.	*SHMT2*
rs4766428	12	110723245	T	C	0.064	2.01	Intron var.	*ATP2A2*
rs1615350	12	123650335	T	C	-0.085	7.91	Intron var.	*PITPNM2*
rs2414718	15	61863133	A	G	0.068	0.23	Intron var.	*RORA*
rs9636107	18	53200117	A	G	-0.080	5.05	Intron var.	*TCF4*
rs144158419	18	53554733	T	C	-0.142	0.65	Intron var.	*TCF4*
rs2103655	20	37425958	A	G	0.077	2.48	Intergenic var.	*PPP1R16B*

Information on the genomic position, effect allele, and effect size (*BETA*) of the 21 predominantly SCZ-associated SNPs derived from the PGC-CDG2 were obtained from Table S3.2 in (P. H. Lee et al., 2019). rs2801578 was excluded due to non-inferable allele ambiguity, and rs13217619 was replaced by rs34718920. Note that the rsID rs188099135, as given by the PGC-CDG2 (P. H. Lee et al., 2019), was merged to rs11782089. The latter rsID was used for the database query. Resources of PHRED-scaled CADD, VEP, and nearest gene are given in Table 2. *Abbreviations*. BP, basepair position; CADD, combined annotation-dependent depletion; CHR, chromosome; EA, effect allele; GRCh37, Genome Reference Consortium human build 37; OA, other allele; PGC-CDG2, second cross-disorder GWAS meta-analysis of the PGC; SCZ, schizophrenia; SNP, single-nucleotide polymorphism; up., upstream; var., variant; VEP, variant effect predictor.

Table S3 | Overview of toolsets and databases

Toolset / databases	Version	Description in relation to this thesis
BRAINEAC[1]	n.a.	The BRAINEAC database is a resource of eQTL data from ten brain tissues.
CAT-12[2]	v2159	The CAT-12 toolbox extends the SPM12 software package for various morphometry-based analyses to study brain structure.
EBRAINS Atlas Viewer[3]	v3.1	The 3D atlas viewer from EBRAINS allows the exploration of regional features of the human brain. In the present thesis, it is used for the anatomical labeling of the peak voxels based on the Julich Brain Atlas v3.1.
ENIGMA Toolbox[4]	n.a.	The ENIGMA toolbox can be used to query the results of the case-control MRI studies conducted by the ENIGMA working groups.
ENIGMA-Vis[5]	n.a.	The ENIGMA-Vis tool allows the retrieval of associations between SNPs and brain IDPs from GWAS of the ENIGMA and CHARGE consortia.
fMRIPrep[6]	n.a.	The fMRIprep pipeline simplifies running software such as FreeSurfer.
FreeSurfer[7]	v6	The FreeSurfer software is tailored to the preprocessing of brain MRI scans and the surface-based brain structure analysis.
LDproxy[8]	n.a.	The LDproxy tool assists in finding a proxy SNP in LD, given a selected ancestral population.
GTEx[9]	v8	The GTEx database is a resource of eQTL data from 54 tissues.
Open Targets Genetics[10]	v22.10	The Open Targets Genetics portal is a resource for SNP trait associations. In addition, functional genomic information of SNPs is provided.
PLINK[11]	1.9 / 2.0	The PLINK toolset enables the analysis of whole genome data, including genetic quality control of microarray data.
PRSice-2[12]	v2.3.5	The PRSice-2 software supports the calculation of genetic risk scores at the individual level.
SPM12[13]	V7771	The SPM software package allows brain imaging data, such as brain MRI scans, to be analyzed regarding statistical hypotheses.

Description of toolsets and databases incorporated in Study 1 and Study 2. Version information is provided if applicable. *References.* [1](Ramasamy et al., 2014), [2](Gaser et al., 2024), [3](Amunts et al., 2020), [4](Larivière et al., 2021), [5](Novak et al., 2012), [6](Esteban et al., 2018), [7](Dale et al., 1999), [8](Machiela & Chanock, 2015), [9](Lonsdale et al., 2013), [10](Ghoussaini et al., 2021; Mountjoy et al., 2021), [11](Chang et al., 2015; Purcell et al., 2007), [12](Choi & O'Reilly, 2019), [13](Penny et al., 2011). *Abbreviations.* BRAINEAC, Brain eQTL Almanac; CAT, computational anatomy toolbox; CHARGE, Cohorts for Heart and Aging Research in Genomic Epidemiology; ENIGMA, Enhancing NeuroImaging Genetics through Meta Analysis; eQTL, expression quantitative trait locus; GTEx, genotype-tissue expression; IDP, image-derived phenotype; LD, linkage disequilibrium; MRI, magnetic resonance imaging; n.a., not available; SNP, single-nucleotide polymorphism; SPM, statistical parametric mapping.

Table S4 | Image-derived phenotypes

Brain region	Vol./ CT/SA	Study 1 SNP-IDP	Study 2 GRS-IDP	Study 2 SNP-IDP	GWAS	$N_{discovery}$
hippocampus	Vol.	×	×	×	Hibar et al. (2017)	26,814
amygdala	Vol.	×	×	×	Satizabal et al. (2019)	37,741
brainstem	Vol.	×				
caudate	Vol.	×	×	×		
nucleus accumbens	Vol.	×	×	×		
pallidum	Vol.	×	×	×		
putamen	Vol.	×	×	×		
thalamus	Vol.	×	×	×		
banks of the sts.	CT, SA	×	×	×	Grasby et al. (2020)	33,281
caudal anterior cingulate	CT, SA	×	×	×		
caudal middle frontal	CT, SA	×	×	×		
cuneus	CT, SA	×	×	×		
entorhinal	CT, SA	×	×	×		
frontal pole	CT, SA	×	×	×		
fusiform	CT, SA	×	×	×		
inferior parietal	CT, SA	×	×	×		
inferior temporal	CT, SA	×	×	×		
insula	CT, SA	×	×	×		
isthmus cingulate	CT, SA	×	×	×		
lateral occipital	CT, SA	×	×	×		
lateral orbitofrontal	CT, SA	×	×	×		
lingual	CT, SA	×	×	×		
medial orbitofrontal	CT, SA	×	×	×		
middle temporal	CT, SA	×	×	×		
paracentral	CT, SA	×	×	×		
parahippocampal	CT, SA	×	×	×		
pars opercularis	CT, SA	×	×	×		
pars orbitalis	CT, SA	×	×	×		
pars triangularis	CT, SA	×	×	×		
pericalcarine	CT, SA	×	×	×		
postcentral	CT, SA	×	×	×		
posterior cingulate	CT, SA	×	×	×		
precentral	CT, SA	×	×	×		
precuneus	CT, SA	×	×	×		
rostral anterior cingulate	CT, SA	×	×	×		
rostral middle frontal	CT, SA	×	×	×		
superior frontal	CT, SA	×	×	×		
superior parietal	CT, SA	×	×	×		
superior temporal	CT, SA	×	×	×		
supramarginal	CT, SA	×	×	×		
temporal pole	CT, SA	×	×	×		
transverse temporal	CT, SA	×	×	×		
average CT	CT, SA	×	×	×		
total SA	CT, SA	×	×	×		
bi-/unilateral		bilateral	unilateral	bilateral		
total number of IDPs		78	154	77		

Overview of IDPs included in Study 1 and Study 2. Subcortical IDPs comprised volumes of structures segmented by using FreeSurfer or FSL-FIRST depending on the study site (Fischl et al., 2002; Patenaude et al., 2011; Satizabal et al., 2019). Cortical IDPs comprised CT and SA measures of brain regions as delineated by the Desikan-Killiany atlas (Desikan et al., 2006). For each analysis, it was outlined whether bilateral or unilateral brain measures were used. The corresponding sample sizes of the GWAS discovery cohort ($N_{discovery}$) were given. With regard to Study 1, the information presented in this Table was adapted from Table S1 in (Federmann et al., 2024) and

and Table S3 in (Federmann et al., 2025). *Abbreviations*. CT, cortical thickness; GRS, genetic risk score; GWAS, genome-wide association study; IDP, image-derived phenotype; SA, surface area; SNP, single-nucleotide polymorphism; sts, superior temporal sulcus; Vol., volume.

Table S5 | ICD-10 diagnoses that represented an exclusion criterion

ICD-10 code	Description
A80-89	Viral infections of the central nervous system
C70-72	Malignant neoplasm
F00-09	Organic, including symptomatic mental disorders
G00-09	Inflammatory diseases of the Central nervous system
G10-G14	Systemic atrophies
G20-26	Extrapyramidal and movement disorders
G30-32	Other degenerative disorders
G35-G37	Demyelinating diseases
I60-69	Cerebrovascular diseases
S06-09	Injuries to the head
T90	Sequelae of injuries of the head
Q00-Q07	Congenital malformations of the nervous system
Q90-Q99	Chromosomal abnormalities

More information on the ICD-10 codes can be found in the UKBB showcase portal (*https://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=41270*). *Abbreviations.* ICD-10, International Classification of Diseases version 10; UKBB, UK Biobank.

Table S6 | VBM analyses in data from the FOR2107 study

rsID	EA/ OA	Dir.	L/ R	Labelling cluster using AAL atlas	Labelling peak voxel using Julich brain atlas	*k*	*x*/*y*/*z*	*T*	p_{FWE}	η^2
rs2388334	G/A	+	L	Angular	Area PGa (IPL)	148	-57/-58/32	3.95	0.331	0.010
			L	Temporal_Sup	Temporal-to-Parietal (GM)	49	-52/-44/14	3.55	0.763	0.008
			R	Outside	Temporal-to-Parietal (GM)	15	34/-3/-26	3.47	0.844	0.008
			L	Occipital_Mid	Area hOc4la (LOC)	17	-44/-88/2	3.33	0.938	0.007
			R	Temporal_Sup	Area Te 3 (STG)	42	66/-30/2	3.31	0.945	0.007
			L	Temporal_Mid	Temporal-to-Parietal (GM)	14	-62/-60/18	3.29	0.955	0.007
		-	R	Cerebellum_3	n.a.	39	10/-36/-18	3.34	0.946	0.007
			L	Frontal_Mid_2	Area 8d2 (SFG)	18	-28/28/44	3.31	0.974	0.007
			L	Cerebellum_3	n.a.	26	-9/-36/-15	3.23	0.964	0.007
rs301805	G/T	+	R	Precuneus	Frontal-to-Occipital (GM)	18	10/-62/44	3.45	0.873	0.007
		-	**L**	**Tem-poral_Pole_Sup**	**Frontal-to-Temporal-II (GM)**	**998**	**-28/10/-22**	**4.85**	**0.012**	**0.015**
			R	OFCpost	Frontal-to-Temporal-II (GM)	274	26/12/-22	3.78	0.526	0.009
			L	Lingual	Subc (Hippocampus, Subicular complex)	81	-14/-40/-2	3.60	0.734	0.008
			R	Outside	Frontal-to-Temporal-II (GM)	34	14/-16/-21	3.58	0.752	0.008
			R	Temporal_Inf	Temporal-to-Parietal (GM)	208	52/-4/-34	3.57	0.767	0.008
			R	Hippocampus	VTM (Amygdala)	55	26/-9/-20	3.22	0.981	0.006
			R	ParaHippocampal	Temporal-to-Parietal (GM)	25	32/-1/-22	3.19	0.985	0.006
			R	Lingual	Temporal-to-Parietal (GM)	15	15/-42/-6	3.19	0.985	0.006
			L	ParaHippocampal	n.a.	10	-15/-16/-22	3.18	0.986	0.006
rs75595651	T/C	+	L	Calcarine	n.a.	490	-2/-100/-6	3.81	0.470	0.009
			L	Fusiform	Area FG4 (FusG)	35	-39/-60/-16	3.54	0.776	0.008
			R	Frontal_Sup_2	Area SFG2 (SFG)	26	21/52/39	3.32	0.973	0.007
		-	n.a.	Outside	n.a.	16	15/-15/-32	3.36	0.920	0.007
rs1933802	G/C	+	**L**	**Parietal_Sup**	**Area 7A (SPL)**	**448**	**-20/-69/62**	**4.62**	**0.029**	**0.013**
			R	Precuneus	Area 5M (SPL)	957	8/-46/54	4.28	0.108	0.011
			L	Lingual	Area hOc2 (V2, 18)	387	-9/-68/-4	4.16	0.166	0.011
			L	Precuneus	Area 5M (SPL)	79	-16/-42/58	3.81	0.461	0.009
			L	Frontal_Mid_2	Frontal-I.1 (GM)	20	-34/45/-6	3.76	0.514	0.009
			L	Frontal_Med_Orb	n.a.	199	-2/69/-2	3.74	0.537	0.009
			L	Calcarine	Area hOc1 (V1, 17, CalcS)	559	-3/-102/-2	3.69	0.597	0.009
			R	Frontal_Sup_2	Area Fp1 (FPole)	143	20/63/-4	3.40	0.885	0.007
			R	Parietal_Sup	Area 7A (SPL)	23	30/-58/62	3.38	0.902	0.007
			L	Outside	Area p32 (pACC)	66	-15/46/-10	3.37	0.906	0.007
			R	Rolandic_Oper	Area Op5 (Frontal Oper.)	23	52/2/8	3.24	0.967	0.007
			L	Outside	Area hOc3v (LingG)	14	-28/-98/-15	3.23	0.968	0.007
		-	R	Cerebellum_7b	n.a.	37	46/-52/-54	3.50	0.803	0.008
			L	Parietal_Inf	Area PGa (IPL)	18	-44/-56/56	3.29	0.948	0.007
			n.a.	Outside	n.a.	19	0/-10/2	3.22	0.971	0.006
rs6748341	G/C	+	L	Fusiform	Temporal-to-Parietal (GM)	183	-28/-28/-22	3.83	0.421	0.009
			R	Temporal_Sup	Area TPJ (STG, SMG)	56	64/-21/15	3.65	0.626	0.008
			R	Hippocampus	CA1 (Hippocampus)	42	39/-33/-9	3.53	0.756	0.008
			R	Temporal_Sup	Area Te 2.2 (STG)	10	54/-20/9	3.21	0.989	0.006
		-	R	ACC_pre	Area p32 (pACC)	19	14/46/21	3.50	0.790	0.008
rs3806843	C/T	+	R	Outside	Area Id4 (Insula)	29	32/-9/14	3.42	0.871	0.008
		-	n.a.	Outside	n.a.	302	6/-74/-46	3.57	0.733	0.008
			n.a.	Outside	n.a.	44	18/-93/-21	3.51	0.793	0.008
			R	Temporal_Inf	Temporal-to-Parietal (GM)	55	46/-16/-40	3.45	0.847	0.008
			R	Cerebellum_6	n.a.	28	12/-69/-27	3.32	0.931	0.007

Table continues on the next page.

Table S6 continued.

rsID	EA/ OA	Dir.	L/ R	Labelling cluster using AAL atlas	Labelling peak voxel using Julich brain atlas	*k*	*x*/*y*/*z*	*T*	p_{FWE}	η^2
rs9329221	T/G	+	R	Temporal_Mid	Area hIP4 (IPS)	95	39/-64/18	3.77	0.510	0.009
			L	Temporal_Mid	Temporal-to-Parietal (GM)	39	-69/-26/-18	3.52	0.788	0.008
			L	Temporal_Mid	Temporal-to-Parietal (GM)	113	-58/-66/-2	3.47	0.838	0.008
			R	Cingulate_Mid	Frontal-to-Occipital (GM)	37	8/-9/39	3.36	0.916	0.007
			L	Hippocampus	DG (Hippocampus)	74	-28/-27/-10	3.34	0.925	0.007
			R	Hippocampus	CA3 (Hippocampus)	59	32/-28/-8	3.26	0.961	0.007
		-	n.a.	Outside	n.a.	57	18/-21/-33	4.23	0.129	0.011
			R	Occipital_Mid	Area hIP7 (IPS)	508	30/-84/21	4.08	0.218	0.011
			L	Lingual	Area hOc3v (LingG)	19	-20/-68/-2	3.58	0.723	0.008
			L	Cerebellum_4_5	n.a.	262	-6/-57/-20	3.38	0.906	0.007
rs2921036	C/T	+	L	Postcentral	Area hIP3 (IPS)	564	-33/-45/52	4.27	0.114	0.012
			R	Cingulate_Mid	Frontal-to-Occipital (GM)	619	8/-9/38	4.09	0.207	0.011
			R	Outside	Frontal-to-Occipital (GM)	219	9/-39/28	3.92	0.347	0.010
			L	Precuneus	n.a.	47	-4/-46/75	3.63	0.662	0.008
			L	Hippocampus	CGL (Metathalamus)	79	-28/-28/-8	3.58	0.716	0.008
		-	L	Cerebellum_6	n.a.	1204	-3/-66/-16	4.41	0.066	0.012
			R	Occipital_Sup	Area hIP7 (IPS)	321	28/-86/24	3.68	0.603	0.009
			L	Cerebellum_6	n.a.	56	-22/-64/-14	3.34	0.924	0.007
rs2867673	C/T	+	R	Parietal_Sup	Area 7P (SPL)	19	21/-74/54	3.46	0.859	0.007
		-	L	Rolandic_Oper	Area Op6 (Frontal Oper.)	417	-48/2/10	4.11	0.206	0.010
			R	Outside	Temporal-to-Parietal (GM)	224	20/12/-42	3.85	0.441	0.009
			R	Lingual	Temporal-to-Parietal (GM)	13	9/-40/-4	3.26	0.966	0.007
			L	OFCpost	Frontal-to-Temporal-II (GM)	10	-21/12/-18	3.18	0.986	0.006
rs9511168	A/C	+	R	Precuneus	n.a.	97	18/-54/26	3.66	0.641	0.008
			L	Frontal_Sup_2	Area SFG2 (SFG)	37	-16/60/30	3.56	0.752	0.008
			R	Cuneus	Area hOc4d (Cuneus)	44	10/-76/28	3.54	0.772	0.008
			L	Fusiform	Temporal-to-Parietal (GM)	176	-34/0/-34	3.48	0.833	0.008
			R	Olfactory	n.a.	60	10/26/-12	3.39	0.897	0.007
			L	Paracentralobule	n.a.	18	-2/-20/76	3.33	0.933	0.007
		-	R	OFCmed	Area Fo3 (OFC)	67	21/48/-21	3.50	0.806	0.008
			L	Precuneus	Frontal-to-Occipital (GM)	16	-9/-45/54	3.37	0.911	0.007
rs1363105	T/C	+	R	Frontal_Inf_Tri	Area 45 (IFG)	565	51/24/18	4.13	0.190	0.011
			n.a.	Outside	n.a.	96	16/-21/-30	3.89	0.391	0.009
			L	Calcarine	Area hOc1 (V1, 17, CalcS)	172	-8/-99/-6	3.74	0.555	0.009
			R	Lingual	Temporal-to-Parietal (GM)	71	10/-56/2	3.51	0.815	0.008
			R	Calcarine	Area hOc1 (V1, 17, CalcS)	42	15/-69/4	3.43	0.884	0.007
			R	Temporal_Inf	Temporal-to-Parietal (GM)	24	50/-60/-4	3.33	0.941	0.007
			R	Frontal_Sup_2	Area 6d3 (SFS)	21	22/12/58	3.25	0.970	0.007
		-	R	Frontal_Mid_2	Area 6v2 (PreCG)	13	34/9/38	3.30	0.954	0.007
			L	Frontal_Mid_2	Frontal-II (GM)	28	-36/14/38	3.29	0.956	0.007

Results of the association between genotype dosages of the 11 antagonistic SNPs and voxel-wise GMV in data from the FOR2107 study are reported with cluster size $k>10$ and $p_{uncorrected}<0.001$. Note that positive (+) and negative (-) associations are presented for each SNP. rs301805 and rs1933802 were significantly associated with GMV $p_{FWE}<0.05$ and highlighted in bold font. Clusters were labeled using the AAL atlas v3 (Rolls et al., 2020; Tzourio-Mazoyer et al., 2002) . Using an in-house script, the peak voxels (*x*/*y*/*z* in MNI152 space) were labeled using the Julich brain atlas v3.1. For an overview of the anatomical regions' full names, see Rolls et al. (2020) for the AAL atlas and *https://atlases.ebrains.eu/viewer/#/* for the Julich brain atlas. Equation 4 in Mordkoff (2019) was applied to compute partial effect sizes denoted by η^2. *Abbreviations*. AAL, automated anatomical labelling atlas; Dir., direction of association; EA, effect allele; FWE, family-wise error; GM, GapMap; GMV, gray matter volume; L, left; OA, other allele; Oper., operculum; *p*, *p*-value; R, right; SNP, single-nucleotide polymorphism; *T*, *T*-value; VBM, voxel-based morphometry.

Table S7 | Associations of the GRSs with brain structure using an extended set of covariates

GRS	Vol./CT/SA	L/R	Brain region	*p*	p_{FDR}	*BETA*	CI_{lower}	CI_{upper}
Pleio-Psych-GRS	Vol.	L	thalamus	0.002	0.357	-0.013	-0.021	-0.005
		R	caudate	0.023	0.490	-0.011	-0.021	-0.002
		L	caudate	0.028	0.490	-0.011	-0.021	-0.001
		R	nucleus accumbens	0.029	0.490	-0.011	-0.021	-0.001
		L	amygdala	0.029	0.490	-0.010	-0.020	-0.001
		R	amygdala	0.032	0.490	-0.010	-0.019	-0.001
		R	thalamus	0.043	0.605	-0.008	-0.016	2.4×10^{-04}
	SA	R	caudal ACC	0.010	0.490	-0.014	-0.025	-0.003
		R	rostral ACC	0.012	0.490	-0.013	-0.023	-0.003
		L	pars opercularis	0.015	0.490	-0.013	-0.023	-0.002
		L	rostral middle frontal	0.032	0.490	-0.009	-0.017	-0.001
SCZ-GRS	Vol.	L	putamen	<0.001	**0.006**	0.020	0.010	0.029
		R	putamen	0.001	**0.022**	0.016	0.007	0.026
	CT	L	pars orbitalis	0.001	**0.027**	-0.019	-0.030	-0.008
		L	insula	0.002	**0.037**	-0.018	-0.030	-0.007
	SA	L	lateral orbitofrontal	<0.001	**0.007**	0.017	0.008	0.025
		R	lateral orbitofrontal	<0.001	**0.016**	0.016	0.007	0.025
		R	paracentral	<0.001	**0.016**	0.017	0.008	0.027

Nominally significant associations ($p<0.05$) between the PleioPsych-GRS and IDPs. Significant associations after multiple testing corrections ($p_{FDR}<0.05$) between the SCZ-GRS and IDPs in bold font. CIs refer to 95 %. This Table has been adapted from Table S4 in (Federmann et al., 2025). *Abbreviations. BETA*, effect size; CI, confidence interval; CT, cortical thickness; FDR, false discovery rate; GRS, genetic risk score; IDP, image-derived phenotype; L, left; *p*, *p*-value; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; R, right; SA, surface area; SCZ-GRS, GRS of predominantly SCZ-associated SNPs; Vol., volume.

Table S8 | Associations of the GRSs with brain structure excluding samples with self-reported and diagnosed depression

GRS	Vol./CT/SA	L/R	Brain region	*p*	p_{FDR}	*BETA*	CI_{lower}	CI_{upper}
Pleio-Psych-GRS	Vol.	L	thalamus	0.004	0.568	-0.014	-0.024	-0.005
		R	caudate	0.041	0.736	-0.012	-0.023	0.0005
		R	thalamus	0.041	0.736	-0.009	-0.019	0.0004
	CT	L	precentral	0.029	0.736	0.014	0.001	0.027
		R	isthmus cingulate	0.034	0.736	0.014	0.001	0.027
	SA	R	pars triangularis	0.007	0.575	-0.016	-0.028	-0.004
		L	pars opercularis	0.012	0.633	-0.015	-0.027	-0.003
		L	rostral middle frontal	0.044	0.736	-0.010	-0.020	0.0003
SCZ-GRS	Vol.	L	putamen	<0.001	**0.003**	0.024	0.013	0.035
		R	putamen	0.001	**0.020**	0.019	0.008	0.030
		L	amygdala	0.002	**0.047**	0.017	0.006	0.028
	CT	L	pars orbitalis	<0.001	**0.020**	-0.024	-0.037	-0.011
		L	insula	0.002	**0.047**	-0.021	-0.034	-0.007
	SA	L	lateral orbitofrontal	<0.001	**0.010**	0.019	0.009	0.029
		R	lateral orbitofrontal	0.002	**0.047**	0.017	0.006	0.027
		L	parahippocampal	0.002	**0.047**	0.018	0.007	0.030

Sensitivity analyses excluding samples with self-reported and diagnosed depression. Nominally significant associations (p<0.05) between the PleioPsych-GRS and IDPs. Significant associations after multiple testing corrections (p_{FDR}<0.05) between the SCZ-GRS and IDPs in bold font. CIs refer to 95 %. This Table has been adapted from Table S5 in (Federmann et al., 2025). *Abbreviations. BETA*, effect size; CI, confidence interval; CT, cortical thickness; FDR, false discovery rate; GRS, genetic risk score; IDP, image-derived phenotype; L, left; *p*, *p*-value; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; R, right; SA, surface area; SCZ-GRS, GRS of predominantly SCZ-associated SNPs; Vol., volume.

Table S9 | Associations of the SCZ-GRS based on a GWAS of SCZ and brain structure

Vol./CT/SA	L/R	Brain region	*p*	p_{FDR}	*BETA*	CI_{lower}	CI_{upper}
Vol.	L	putamen	<0.001	0.001	0.021	0.012	0.030
	R	putamen	<0.001	0.007	0.018	0.008	0.027
CT	L	insula	0.001	0.014	-0.020	-0.031	-0.009
	L	pars orbitalis	0.001	0.014	-0.020	-0.031	-0.008
	L	lateral orbitofrontal	0.001	0.014	-0.020	-0.031	-0.008
	R	lateral orbitofrontal	0.002	0.027	-0.019	-0.030	-0.007
	L	paracentral	0.002	0.027	-0.018	-0.029	-0.006
	L	cuneus	0.002	0.027	-0.018	-0.029	-0.007
	R	pars orbitalis	0.003	0.027	-0.017	-0.029	-0.006
	R	precuneus	0.004	0.029	-0.016	-0.027	-0.005
	R	lingual	0.004	0.029	-0.017	-0.028	-0.005
	L	precuneus	0.004	0.030	-0.016	-0.027	-0.005
	R	cuneus	0.005	0.032	-0.016	-0.028	-0.005
	R	insula	0.007	0.042	-0.016	-0.027	-0.004
	R	pars opercularis	0.008	0.045	-0.015	-0.026	-0.004
SA	L	lateral orbitofrontal	<0.001	0.001	0.018	0.010	0.027
	R	paracentral	<0.001	0.004	0.019	0.010	0.029
	R	lateral orbitofrontal	<0.001	0.005	0.017	0.008	0.026
	R	superior frontal	0.002	0.027	0.013	0.005	0.021
	R	insula	0.002	0.027	0.014	0.005	0.023
	L	posterior cingulate	0.003	0.027	0.015	0.005	0.024
	R	total	0.003	0.027	0.014	0.005	0.024
	L	total	0.003	0.027	0.014	0.005	0.024
	R	precuneus	0.003	0.028	0.013	0.004	0.022
	L	parahippocampal	0.004	0.029	0.015	0.005	0.025
	R	posterior cingulate	0.005	0.032	0.014	0.004	0.023
	L	paracentral	0.005	0.032	0.014	0.004	0.023
	L	superior frontal	0.005	0.032	0.011	0.003	0.019
	L	middle temporal	0.009	0.048	0.011	0.003	0.020

Significant associations after multiple testing corrections (p_{FDR}<0.05) between the SCZ-GRS based on a GWAS of SCZ (Trubetskoy et al., 2022). CIs refer to 95 %. This Table has been adapted from Table S6 in (Federmann et al., 2025). *Abbreviations. BETA*, effect size; CI, confidence interval; CT, cortical thickness; FDR, false discovery rate; GRS, genetic risk score; GWAS, genome-wide association study; IDP, image-derived phenotype; L, left; *p*, *p*-value; R, right; SA, surface area; SCZ, schizophrenia; SCZ-GRS, GRS of predominantly SCZ-associated SNPs; Vol., volume.

Table S10 | Associations of the GRSs with outcomes related to mental health

Outcomes related to mental health	PleioPsych-GRS			SCZ-GRS		
	p_{FDR}	OR	CI	p_{FDR}	OR	CI
mood swings	**0.008**	1.039	[1.014, 1.065]	0.089	1.024	[0.999, 1.049]
miserableness	**9.4×10^{-04}**	1.049	[1.024, 1.076]	0.491	1.010	[0.986, 1.036]
irritability	**8.7×10^{-06}**	1.074	[1.045, 1.103]	0.963	0.999	[0.973, 1.027]
sensitivity/hurt feelings	**0.046**	1.028	[1.004, 1.053]	**0.021**	1.033	[1.008, 1.058]
fed-up feelings	**3.4×10^{-04}**	1.056	[1.030, 1.083]	0.549	1.008	[0.983, 1.034]
nervous feelings	**0.014**	1.045	[1.013, 1.077]	0.263	1.020	[0.989, 1.051]
worrier/anxious feelings	**0.005**	1.040	[1.016, 1.065]	**0.005**	1.041	[1.016, 1.066]
tense feelings/ highly strung	**7.3×10^{-04}**	1.076	[1.037, 1.116]	**0.029**	1.047	[1.010, 1.086]
worry too long after embarrassment	0.175	1.019	[0.995, 1.044]	0.549	1.008	[0.984, 1.032]
suffer from nerves	0.253	1.023	[0.989, 1.057]	0.549	0.989	[0.957, 1.023]
loneliness	0.088	1.035	[1.000, 1.071]	0.089	1.034	[0.999, 1.070]
guilty feelings	0.088	1.027	[1.000, 1.071]	**0.023**	1.036	[1.009, 1.064]

Significant associations (p_{FDR}<0.05) are highlighted in bold font. CI represents a 95 % confidence interval. This Table has been adapted from Table 2 in (Federmann et al., 2025). *Abbreviations.* CI, confidence interval; FDR, false discovery rate; GRS, genetic risk score; *p*, *p*-value; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; OR, odds ratio; SCZ-GRS, GRS of predominantly SCZ-associated SNPs.

Table S11 | Associations of the GRSs with outcomes related to mental health using an extended set of covariates

Outcomes related to mental health	PleioPsych-GRS			SCZ-GRS		
	p_{FDR}	OR	CI	p_{FDR}	OR	CI
mood swings	**0.009**	1.039	[1.014, 1.065]	0.083	1.025	[1.000, 1.051]
miserableness	**0.001**	1.049	[1.023, 1.076]	0.422	1.012	[0.987, 1.037]
irritability	**8.7×10^{-06}**	1.074	[1.045, 1.103]	0.875	0.998	[0.971, 1.025]
sensitivity/hurt feelings	**0.043**	1.028	[1.004, 1.053]	**0.016**	1.035	[1.010, 1.060]
fed-up feelings	**4.2×10^{-04}**	1.056	[1.029, 1.083]	0.473	1.010	[0.985, 1.036]
nervous feelings	**0.016**	1.045	[1.013, 1.077]	0.235	1.021	[0.991, 1.053]
worrier/anxious feelings	**0.007**	1.039	[1.015, 1.064]	**3.2×10^{-03}**	1.043	[1.018, 1.068]
tense feelings/ highly strung	**6.9×10^{-04}**	1.076	[1.038, 1.116]	**0.033**	1.047	[1.009, 1.086]
worry too long after embarrassment	0.167	1.019	[0.995, 1.044]	0.432	1.011	[0.987, 1.035]
suffer from nerves	0.235	1.022	[0.989, 1.057]	0.712	0.993	[0.961, 1.027]
loneliness	0.086	1.034	[0.999, 1.070]	0.083	1.035	[1.000, 1.071]
guilty feelings	0.083	1.027	[1.000, 1.055]	**0.021**	1.037	[1.009, 1.065]

Significant associations after multiple testing corrections (p_{FDR}<0.05) are indicated in bold font. CIs refer to 95 %. This Table has been adapted from Table S7 in (Federmann et al., 2025). *Abbreviations.* CI, confidence interval; FDR, false discovery rate; GRS, genetic risk score; *p*, *p*-value; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; OR, odds ratio; SCZ-GRS, GRS of predominantly SCZ-associated SNPs.

Table S12 | Associations of the GRSs with outcomes related to mental health excluding samples with self-reported and diagnosed depression

Outcomes related to mental health	PleioPsych-GRS			SCZ-GRS		
	p_{FDR}	OR	CI	p_{FDR}	OR	CI
mood swings	**0.029**	1.038	[1.008, 1.069]	**0.029**	1.040	[1.009, 1.071]
miserableness	**0.023**	1.043	[1.012, 1.075]	**0.029**	1.038	[1.008, 1.070]
irritability	**0.001**	1.069	[1.035, 1.105]	0.916	0.998	[0.966, 1.031]
sensitivity/hurt feelings	0.344	1.015	[0.987, 1.044]	**0.023**	1.039	[1.011, 1.069]
fed-up feelings	**0.029**	1.039	[1.008, 1.072]	0.114	1.029	[0.998, 1.061]
nervous feelings	0.240	1.026	[0.988, 1.066]	0.104	1.038	[0.999, 1.078]
worrier/anxious feelings	0.161	1.023	[0.995, 1.052]	**0.001**	1.056	[1.028, 1.086]
tense feelings/ highly strung	**0.023**	1.068	[1.019, 1.119]	**0.029**	1.061	[1.012, 1.112]
worry too long after embarrassment	0.344	1.015	[0.987, 1.044]	0.344	1.015	[0.987, 1.044]
suffer from nerves	0.916	0.997	[0.956, 1.040]	0.766	1.008	[0.967, 1.052]
loneliness	0.240	1.031	[0.987, 1.076]	**0.023**	1.062	[1.017, 1.108]
guilty feelings	0.240	1.023	[0.990, 1.057]	**0.021**	1.052	[1.018, 1.086]

Significant associations after multiple testing corrections (p_{FDR}<0.05) are indicated in bold font. CIs refer to 95 %. This Table has been adapted from Table S8 in (Federmann et al., 2025). *Abbreviations.* CI, confidence interval; FDR, false discovery rate; GRS, genetic risk score; *p*, *p*-value; PleioPsych-GRS, GRS of highly pleiotropic SNPs for neuropsychiatric disorders; OR, odds ratio; SCZ-GRS, GRS of predominantly SCZ-associated SNPs.

Table S13 | Associations of the SCZ-GRS based on a GWAS of SCZ with outcomes related to mental health

Outcomes related to mental health	SCZ-GRS		
	p_{FDR}	OR	CI
mood swings	0.065	1.027	[1.001,1.052]
miserableness	0.456	1.010	[0.985,1.036]
irritability	0.831	0.997	[0.970,1.025]
sensitivity/hurt feelings	**0.017**	1.034	[1.010,1.059]
fed-up feelings	0.456	1.011	[0.985,1.037]
nervous feelings	0.256	1.020	[0.989,1.052]
worrier/anxious feelings	**0.004**	1.042	[1.017,1.067]
tense feelings/ highly strung	**0.034**	1.046	[1.009,1.085]
worry too long after embarrassment	0.450	1.011	[0.987,1.036]
suffer from nerves	0.624	0.991	[0.959,1.025]
loneliness	0.062	1.038	[1.003,1.075]
guilty feelings	**0.022**	1.037	[1.009,1.065]

Significant associations after multiple testing corrections (p_{FDR}<0.05) are indicated in bold font. CIs refer to 95 %. This Table has been adapted from Table S9 in (Federmann et al., 2025). *Abbreviations.* CI, confidence interval; FDR, false discovery rate; GRS, genetic risk score; GWAS, genome-wide association study; *p*, *p*-value; OR, odds ratio; SCZ, schizophrenia; SCZ-GRS, GRS of predominantly SCZ-associated SNPs.

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