It's all *relative*

A cross-disorder approach into brain structure, cognition, and familial risk in schizophrenia and bipolar disorder

Sonja M.C. de Zwarte

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Cover: Bas Willemsen Photography · www.baswillemsen.net
Printing: Gildeprint · www.gildeprint.nl

ISBN: 978-94-6402-104-2

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Alles is relatief

Trans-diagnostisch onderzoek naar hersenstructuur, cognitie en familiair risico in schizofrenie en bipolaire stoornis

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de
Universiteit Utrecht
op gezag van de
rector magnificus, prof.dr. H.R.B.M. Kummeling,
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

vrijdag 20 maart 2020 des middags te 2.30 uur

door

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geboren op 28 november 1986
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General introduction

Almost everyone, either directly or indirectly, will be confronted with mental illness at some point in their lives. According to the World Health Organization, around 23 million people worldwide have a diagnosis of schizophrenia, bipolar disorder affects around 60 million people, and an estimated 300 million people are diagnosed with severe depression (World Health Organization, 2018). This means that roughly 1 in every 20 individuals is affected by a severe mental illness and the impact on the lives of these individuals, but also on their family, friends, and society as a whole, can be tremendous. Yet we still know little about the etiology (i.e. what causes disease or leads to becoming ill) of these disorders, how to effectively treat patients, and, even more importantly, how to prevent people from becoming ill.

SCHIZOPHRENIA vs. BIPOLAR DISORDER

Psychiatric diseases are characterized by affective, behavioral, and cognitive abnormalities. The Diagnostic and Statistical Manual of Mental Disorders (DSM), published by the American Psychiatric Association (5th edition, 2013), lists 18 distinct disorders, including neurodevelopmental disorders, schizophrenia spectrum and psychotic disorders, bipolar and related disorders, depressive disorders and anxiety disorders.

Schizophrenia and bipolar disorder are two severe psychiatric disorders listed in the DSM. Schizophrenia is characterized by delusions, hallucinations, disorganized speech and behavior, while bipolar disorder is primarily known for the (alternating) manic and depressive episodes. This distinction between these two illnesses dates back to the early 20th century, when Kraepelin divided them into two categories: *dementia praecox* and *manic depressive insanity* (Kraepelin, 1910). Although the clinical presentation is often different, schizophrenia and bipolar disorder also share symptoms, which can make it difficult to distinguish between the two illnesses. For instance, approximately two-thirds of patients diagnosed with bipolar disorder have a life-time history of at least one psychotic episode (Goodwin & Jamison, 2007). Similarly, it is estimated that comorbid depression occurs in 50% of the patients diagnosed with schizophrenia (Buckley et al., 2009). The overlapping elements lead researchers to believe that schizophrenia and bipolar disorder may be two ends of a continuum, rather than discrete diagnostic entities, with overlap and blurred boundaries (Guloksuz & Van Os, 2018).

Schizophrenia and bipolar disorder have been both characterized as neurodevelopmental disorders (Murray & Lewis, 1987; Nasrallah, 1991; Weinberger, 1987), although it has been proposed that abnormal neurodevelopment may play a larger role in the onset of schizophrenia than bipolar disorder (Murray et al., 2004; Parellada et al., 2017; Walker et al., 2002). The neurodevelopmental hypothesis suggests that a disruption of early brain development, which can occur as early as the prenatal period, underlies the emergence of symptoms during late adolescence or adulthood. The onset and persistence of both disorders are influenced by complex interactions of both unique and overlapping biological and environmental factors. It is therefore important to not only study the disorders in isolation but to take a *cross-disorder*

approach with the aim to identify similarities and differences in the underlying neurobiology between schizophrenia and bipolar disorder.

In this thesis, I investigate three important neurodevelopmental components related to schizophrenia and bipolar disorder: i) brain abnormalities, ii) cognitive deficits and iii) risk genes. To increase insight into the biological underpinnings underlying the development of each disorder, I aim to examine which of those components, and to what degree, are related to risk of developing schizophrenia or bipolar disorder, and whether these are shared components or unique to either illness. Understanding these components could help us to identify who is at increased risk of becoming ill, which is crucial for developing future detection and prevention strategies.

BRAIN IMAGING

Since the 19th century, schizophrenia and bipolar disorder have been considered disorders of the brain, but researching the brain in-vivo remained challenging until the arrival of non-invasive imaging methods in the 1970s. The first studies investigating the brain in psychiatric disorders used Computer Tomography (CT), but not long after Magnetic Resonance Imaging (MRI) was introduced. This invention kickstarted a long tradition of MRI studies investigating the presence of brain abnormalities in patients by comparing them to healthy volunteers. From then onwards, structural brain abnormalities have been consistently reported in schizophrenia and bipolar disorder. The most consistent and robust structural findings in patients are smaller total brain, thinner cortex and hippocampal volumes, and larger ventricular volumes compared to a control group, albeit with smaller effect sizes in patients with bipolar disorder than in schizophrenia (Arnone et al., 2009; Ellison-Wright & Bullmore, 2010; Haijma et al., 2013; Hibar et al., 2016, 2017; McDonald et al., 2004; Okada et al., 2016; Van Erp et al., 2015, 2018). However, whether these brain abnormalities are caused by the genetic predisposition for the illness, are driven by disease-related factors, or by interactions between genes and environment, is still not completely established.

COGNITION

Cognitive deficits are a key feature in schizophrenia (Kahn & Keefe, 2013), and, to a lesser extent, cognitive deficits are also present in patients with bipolar disorder (Trotta et al., 2015; Vreeker et al., 2016). Understanding cognitive dysfunction in neuropsychiatric patients is important for several reasons. It is associated with worse social and occupational functioning and a more severe course of illness (Martínez-Arán et al., 2004; Zubieta et al., 2001). In addition, decline in intelligence may be the first indicator of deviations in the brain and have therefore the potential to contribute to early detection of symptoms (Pantelis et al., 2003; Thompson et al., 2001). Indeed, differential neurodevelopmental trajectories in

schizophrenia and bipolar disorder have been linked to intelligence quotient (IQ; a measure of general cognitive functioning) development and school performance (Parellada et al., 2017). Schizophrenia has been associated with poorer cognitive performance or even decreases over time years before onset (Agnew-Blais & Seidman, 2013; Dickson et al., 2012; Hochberger et al., 2018; Kendler et al., 2015; Khandaker et al., 2011; Reichenberg et al., 2005; Woodberry et al., 2008), while premorbid IQ or educational attainment are often not affected or are even higher in individuals who later develop bipolar disorder (MacCabe et al., 2010; Smith et al., 2015; Tiihonen et al., 2005; Zammit et al., 2004).

Brain abnormalities in schizophrenia and bipolar disorder are not independent from level of cognitive functioning (Bohlken et al., 2016; Toulopoulou et al., 2015; Vreeker et al., 2017). This may not be surprising given the correlation between intelligence and brain size (r = 0.33, McDaniel, 2005). This relationship is explained by genetic factors that influence both IQ and total brain volume (Posthuma et al., 2002). Taken together, these findings suggest that brain structure, IQ, schizophrenia, and bipolar disorder are intertwined to some extent.

(IMAGING) GENETICS

Schizophrenia and bipolar disorder are both highly heritable disorders, with heritability estimates of up to 80% based on twin study findings (Cardno & Gottesman, 2000; McGuffin et al., 2003; Sullivan et al., 2003). These high heritability estimates show that schizophrenia and bipolar disorder have a pronounced genetic origin. The genetic architectures of these disorders are highly polygenic, i.e. not one or few genes lead to the illness but thousands of common single nucleotide polymorphisms (SNPs) of very small individual effects are involved. Large-scale genome-wide association studies (GWASs) have identified more than 100 SNPs that are significantly associated with an increased risk of developing schizophrenia (Ripke et al., 2014) and 30 SNPs associated with bipolar disorder (Stahl et al., 2019). To determine to what degree schizophrenia and bipolar disorder are genetically related, a genetic correlation can be calculated. A genetic correlation (r_g) is the property of variance that two traits share due to genetic causes. Using the schizophrenia and bipolar disorder GWAS data sets, the genetic correlation between schizophrenia and bipolar disorder is considered high with r_g = +0.68 (Anttila et al., 2018; Lee et al., 2013). However, it is important to note that genetic studies have also shown disease-specific genetic variation based on these same GWASs (Ruderfer et al., 2018).

The most common approach of GWASs is the case-control setup, which compares the genome of two large groups of individuals: one healthy control group and one group of patients. These findings cannot be directly transferred to the individual. One approach to make that transition is via *polygenic scores*, a method that calculates the combined effect of a large number of SNPs, each with a very subtle individual effect (Purcell et al., 2009). For each individual a 'risk' score for the illness can be calculated based on the GWAS findings.

This means that if an individual has many genetic variants that are associated with the illness there will be a higher polygenic score, and if someone only has few genetic variants that are associated with the disease there will be a lower score. Several studies have shown that such polygenic scores differ between patients and controls, thus providing a useful tool to measure genetic liability to the illness in independent samples (Bramon et al., 2014; Derks et al., 2012; Purcell et al., 2009; Vassos et al., 2017). Polygenic scores potentially provide us with a tool to predict who is at high risk of developing the illness. It also offers a tool to investigate how genetic risk of disease is related to other measures that are related to illness, such as brain structure. Discovering the impact of genetic factors on brain systems may help determine whether these genetic factors underlie manifestation of disorders within the brain, and to identify diagnostic and prognostic neuroimaging biomarkers.

WHY STUDYING FIRST-DEGREE RELATIVES?

A major challenge of studying individuals with psychiatric disorders are confounders known to have an effect on the brain, such as medication use and illness duration. Therefore, it often remains uncertain whether you are investigating the illness itself or the effects of these confounders. As previously mentioned, schizophrenia and bipolar disorder are both highly heritable disorders. In addition, large population studies and adoption studies have shown that when you have a family member with the disorder you are at increased risk of developing the disorder yourself (Gottesman, 1991; Lichtenstein et al., 2009). Unaffected first-degree relatives (i.e. offspring, siblings, parents or co-twins) share, on average, half of the genes with their ill relative (except for monozygotic co-twins who share all their genes) but they themselves do not have the diagnosis. First-degree relatives thus represent an interesting alternative population for investigating the etiology of psychiatric disorders.

One approach to bridge the gap between risk genes and illness onset is investigating *endophenotypes*. Endophenotypes are biological markers that are heritable, quantitative traits (rather than a clinical observation) associated with the illness, and are to a lesser degree present in unaffected relatives of patients (Braff & Tamminga, 2017; Gottesman & Gould, 2003; Meyer-Lindenberg & Weinberger, 2006). As endophenotypes are considered to be related to the genetic factors underlying disorders, it is likely that a subset of the genes leading to the illness also influence the endophenotypes (Lencz et al., 2014; Toulopoulou et al., 2015). Two of measures that have been proposed as endophenotypes are brain structure and cognition, as both are highly heritable traits (Baaré et al., 2001; Devlin et al., 1997; Pfefferbaum et al., 2000; Toga & Thompson, 2005) and, as mentioned previously, deficits are present in both schizophrenia and bipolar disorder. Therefore, through studying the brains and cognition in unaffected family members I aim to unravel the underlying (genetic) mechanisms leading to the illness.

It is important to note that there is a difference between *familial* risk and *genetic* risk. Besides genes, first-degree relatives share to some extent environmental factors that may increase risk for developing psychiatric disorders with the patient (for example, childhood trauma, socioeconomic status, urbanicity (Rowland & Marwaha, 2018; Stilo & Murray, 2019)). As I investigate different categories of family members of patients, and not only twins, I will consistently refer to familial risk in this thesis, because the family study design does not allow to differentiate genetic risk from shared environmental risk factors.

ENIGMA — RELATIVES

The ENIGMA (Enhancing NeuroImaging Genetics through Meta Analysis) Consortium is a collaboration of more than 1,400 scientists from 43 countries studying the human brain (Thompson et al., 2019). ENIGMA started ten years ago with the initial aim of performing a large-scale neuroimaging genetic study, and has since diversified into 50 working groups, which pool worldwide data, resources and expertise to answer fundamental questions in neuroscience, psychiatry, neurology, and genetics.

The ENIGMA—Relatives Working Group was initiated in 2014, and has primary focused on measures of brain structure in first-degree relatives of patients with psychiatric disorders. Imaging studies of relatives of patients with schizophrenia and bipolar disorder have often been small, with varying results and only few studies looked cross-disorder. Currently, 38 schizophrenia and/or bipolar disorder family cohorts with MRI data of over 6,000 relatives, patients, and control volunteers that have been collected all over the world have joined this collaboration. The ENIGMA—Relatives initiative is driven by the conviction that with joined forces, we can shed new light on the (genetics and) pathophysiology of schizophrenia and bipolar disorder. By doing so, our ultimate goal is to contribute to the development of early detection, personalized treatment and prevention strategies.

AIM AND OUTLINE OF THE THESIS

The main aim of this thesis is to examine the relationship between brain structure, cognition, and familial risk for schizophrenia and bipolar disorder. To investigate these relationships, I make use of the many schizophrenia and bipolar family cohorts that have been collected in the last two decades at the UMC Utrecht, comprising of extensive imaging, genetics, and behavioral data, as well as two large international datasets: ENIGMA—Relatives and United Kingdom (UK) Biobank.

First-degree relatives of patients with schizophrenia all share on average 50% of their genes with their ill family member (except monozygotic co-twins who share 100%). However, population studies have shown that the risk to development schizophrenia differs per type of first-degree relative: monozygotic co-twins 48%–50%, dizygotic co-twins 4%–17%, offspring 7%–13%, siblings 9%, and parents 4%–6% (Cardno & Gottesman, 2000; Chou et

al., 2016; Gottesman, 1991; Gottesman et al., 2010; Kahn et al., 2015; Lichtenstein et al., 2009). This suggests that not only genetic factors but also environmental factors determine the risk of developing schizophrenia. For instance, growing up with an ill parent could likely expose someone to a more stressful environment in early life (when the brain is still developing) than when experiencing the stress of an ill child, which occurs at an older age. Previous studies have shown that structural brain abnormalities are present in first-degree relatives of patients with schizophrenia (Boos et al., 2007; Moran et al., 2013; Thermenos et al., 2013); however, it remains unclear whether these abnormalities vary among the different types of first-degree relatives. In **Chapter 2**, I investigate in five of our previously collected schizophrenia family cohorts at UMC Utrecht whether different types of first-degree relatives show different kinds of brain abnormalities, and if the brain abnormalities present in the relatives are related to IQ. In addition, it is well recognized that nonpsychotic psychopathology is more frequent in family members of patients with schizophrenia than in the general population (Glatt et al., 2006; Keshavan et al., 2008). Therefore, I also investigate whether findings of brain abnormalities in relatives are influenced by the fact that not all of these participants are completely healthy.

Replication is key in scientific discovery. To investigate whether the findings of **Chapter 2** replicate in a larger sample and whether relatives of patients with bipolar disorder show similar or diverting patterns of brain abnormalities, I have joined forces with over thirty other schizophrenia and bipolar disorder family cohorts through the ENIGMA—Relatives initiative. Where the literature shows consistent evidence that relatives of schizophrenia have smaller brain volumes – similar to patients diagnosed with schizophrenia but with much smaller effects – the literature is more ambivalent regarding brain abnormalities in relatives of patients with bipolar disorder. In **Chapter 3**, I investigate brain structure (both global brain measures and subcortical volumes) in a harmonized prospective meta-analysis, comparing all types of first-degree relatives of patients with bipolar disorder and schizophrenia to control individuals. I investigate whether relatives of patients with bipolar disorder differ from relatives of patient with schizophrenia and whether they show similar patterns of brain abnormalities as their ill family member. In addition, I also investigate here on a larger scale if the presence of psychopathology in the relatives and controls influences the brain abnormality findings.

Intracranial volume (ICV) is an approximation of overall head size, and comprises the gray and white matter of the brain and the cerebrospinal fluid inside the dura. ICV is considered a proxy for the maximal brain growth during development and maturation, whose changes may represent a possible indicator of neurodevelopmental anomaly. Therefore, I aim to further investigate one of the main findings in **Chapter 3**, in which I have demonstrated that first-degree relatives of patients with bipolar disorder have a larger ICV compared to control individuals, while there was no difference in ICV in the relatives of patients with schizophrenia. This finding suggests that different neurodevelopment trajectories in family members of patients with bipolar disorder and schizophrenia may play a role in developing the disease. Building on these findings, I continue with two follow-up studies in **Chapters 4** and **5**.

In **Chapter 4**, I extend the ENIGMA—Relatives collaboration by exploring the presence of regional cortical thickness and surface area differences in the relatives of patients with bipolar disorder or schizophrenia. Cognitive deficits have previously been reported in first-degree relatives of patients with schizophrenia compared to controls (Hughes et al., 2005; Kremen et al., 1998; McIntosh et al., 2005; Niendam et al., 2003; Sitskoorn et al., 2004; Van Haren et al., 2019; Vreeker et al., 2016) and, to a lesser degree, in relatives of patients with bipolar disorder (Vonk et al., 2012; Vreeker et al., 2016). Similar to work presented in **Chapter 2**, I investigate through meta-analysis in 36 schizophrenia and bipolar disorder family cohorts whether relatives have lower IQ and/or lower educational attainment (i.e. years of education completed), and whether brain abnormalities in family members are related to these differences in IQ or educational attainment. In particular, I am interested in whether differences in IQ and/or educational attainment may explain the larger ICV reported in relatives of patients with bipolar disorder.

In **Chapter 5**, I investigate the relationship between genetic risk for schizophrenia and bipolar disorder with regard to ICV. Using the UK Biobank dataset, I investigate if and to what degree the relationships between ICV, schizophrenia risk genes and bipolar disorder risk genes are present in the general population. Furthermore, I examine whether these relationships can be measured on an individual level through polygenic scoring.

The UK Biobank Study is a large prospective cohort study, established primarily to investigate the genetic and lifestyle determinants of a wide range of diseases of middle and later life (Sudlow et al., 2015). This valuable resource involves over 500,000 men and women recruited between 2006 and 2010 throughout England, Wales, and Scotland at the age of 40 – 69 years. Extensive questionnaire data, physical measurements, and biological samples were collected at recruitment, and there is ongoing enhanced data collection in large subsets of the cohort, including a repeat baseline assessment, genotyping, biochemical assays, web-based questionnaires, physical activity monitoring, and multimodal imaging. All participants are followed up for health conditions through linkage to national electronic health-related data sets. Currently, over 20,000 participants have a processed T1 MRI scan as well as genotype data, which makes this one of the largest datasets to date for imaging genetics purposes. The UK Biobank enables me to investigate to what degree risk genes for schizophrenia or bipolar disorder are related to genes that lead to larger ICV in healthy individuals, and to analyze whether the genetic 'risk' for a larger brain is related to the actual brain size. Studying risk factors such as the effect of psychiatric risk genes in relation to ICV in healthy individuals (**Chapter 5**) alongside investigating risk factors for neuropsychiatric disorders in a clinical sample (**Chapters 2**, **3** and **4**) facilitates insight into the etiology of neuropsychiatric disorders.

Finally, **Chapter 6** provides a discussion of the main findings of this thesis in relation to the relevant literature. The final chapter also discusses methodological considerations and proposes directions for future research.

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Running in the family? Structural brain abnormalities and IQ in offspring, siblings, parents, and co-twins of patients with schizophrenia

Schizophrenia Bulletin, 2019; 45(6):1209–1217

ABSTRACT

Structural brain abnormalities and cognitive deficits have been reported in patients with schizophrenia and to a lesser extent in their first-degree relatives (FDRs). Here we investigated whether brain abnormalities in nonpsychotic relatives differ per type of FDR and how these abnormalities are related to intelligent quotient (IQ). Nine hundred eighty individuals from 5 schizophrenia family cohorts (330 FDRs, 432 controls, 218 patients) were included. Effect sizes were calculated to compare brain measures of FDRs and patients with controls, and between each type of FDR. Analyses were repeated with a correction for IQ, having a nonpsychotic diagnosis, and intracranial volume (ICV). FDRs had significantly smaller ICV, surface area, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, thalamus, putamen, amygdala, and accumbens volumes as compared with controls (ds < -0.19, $q < 0.05$ corrected). Offspring showed the largest effect sizes relative to the other FDRs; however, none of the effects in the different relative types survived correction for multiple comparisons. After IQ correction, all effects disappeared in the FDRs after correction for multiple comparisons. The findings in FDRs were not explained by having a nonpsychotic disorder and were only partly explained by ICV. FDRs show brain abnormalities that are strongly covarying with IQ. On the basis of consistent evidence of genetic overlap between schizophrenia, IQ, and brain measures, we suggest that the brain abnormalities in FDRs are at least partly explained by genes predisposing to both schizophrenia risk and IQ.

INTRODUCTION

Widespread structural brain abnormalities have consistently been reported in patients with schizophrenia, with total brain, gray matter and hippocampal volume reduction, ventricle enlargement, and cortical thinning being among the most replicated findings (Haijma et al., 2013; Van Erp et al., 2015). However, the etiology of brain structure abnormalities in schizophrenia is largely unknown. To address a possible (familial and genetic) cause of these brain abnormalities, studies of family members of patients with schizophrenia are of particular interest, as relatives share part of the genetic makeup and environment with the patient.

Multiple studies have investigated individuals at high familial risk to develop schizophrenia, varying from multiplex families and mixed first-degree relative (FDR) samples to studies focusing only on offspring, siblings, or discordant twins (as reviewed in Boos et al. (2007), Thermenos et al. (2013) and Moran et al. (2013)). In young relatives (age ≤ 30 years), smaller hippocampal volume, global brain size, and prefrontal cortical volume, thickness, or surface area have been found, but also negative findings have been reported (see review by Thermenos et al. (2013)). Moran et al. (2013) suggested that the cortical gray matter abnormalities are likely to be an age-dependent endophenotype, which normalizes after the typical age of onset of schizophrenia. Alternatively, the environmental influence of having an ill relative may vary substantially with the type of kinship. Indeed, population-based studies have shown that different kind of FDRs vary in the relative risk for developing schizophrenia: monozygotic (MZ) co-twins 48%–50%, dizygotic (DZ) co-twins 4%–17%, offspring 7%–13%, siblings 9%, and parents 4%–6% (Cardno & Gottesman, 2000; Chou et al., 2016; Gottesman, 1991; Gottesman et al., 2010; Kahn et al., 2015; Lichtenstein et al., 2009). All FDRs share on average 50% of their genetic makeup (expect for MZ twin pairs who share 100%) with their affected family member. Therefore, the variation in relative risk among the different relative types must represent differences in environmental factors that determine the risk of developing schizophrenia.

In addition to familial factors, cognitive impairment has been suggested to play a role in the brain abnormalities in schizophrenia (Kahn & Keefe, 2013). Toulopoulou et al. (2010) reported that patients and their unaffected relatives had impaired cognitive performance compared with controls, and they found that 89% of the phenotypic covariance between liability to schizophrenia and intelligent quotient (IQ) was due to shared genetic factors. This suggests that genetic risk for schizophrenia shows an association with cognitive impairment, which was recently confirmed by the finding from genome-wide association studies (GWAS) that intelligence and schizophrenia have a shared genetic origin (Smeland et al., 2017a; Sniekers et al., 2017).

In healthy populations, IQ is positively correlated with total brain volume (McDaniel, 2005), but also in patients with schizophrenia and their relatives, correlations between IQ and intracranial, total, and gray matter volumes have been reported (Antonova et al., 2005; Rais et

al., 2012; Toulopoulou et al., 2004). IQ shares a substantial genetic origin with global brain deficits seen in schizophrenia (Bohlken et al., 2016; Toulopoulou et al., 2015).

Here we conducted a reanalysis of previous collected data from 5 schizophrenia family cohorts, and for the first time, the association of IQ and the presence of a psychiatric diagnosis other than psychosis in relatives with brain measures is investigated. The aim of our study was 3-fold. First, we investigated the familial effect on global and subcortical brain structures in FDRs per relative type and as one group through meta-analysis. Next, to investigate the influence of the association between IQ and familial risk on structural brain abnormalities, analyses were repeated with a correction for IQ. Finally, it is well recognized that nonpsychotic psychopathology is more frequent in FDRs of patients with schizophrenia than in the general population (Glatt et al., 2006; Keshavan et al., 2008), but as far as we know, whether this has an influence on brain measures has never been systematically investigated. Therefore, all analyses were repeated with a correction for having a nonpsychotic psychiatric diagnosis.

METHODS

Participants and Data Acquisition

This study included 980 participants from 5 family cohorts, which have been included over the course of the last 20 years at the Department of Psychiatry at the University Medical Center Utrecht (UMCU), the Netherlands (Table 1; for detailed cohort description, including inclusion criteria, IQ test battery, and magnetic resonance imaging parameters used, see Supplementary Methods). All studies were approved by the medical ethics committee for research in humans of the UMCU and informed consent was obtained from the participants (and/or their parents in the case of minors).

Image Processing

Cortical and subcortical reconstruction and volumetric segmentation were performed with the FreeSurfer version 5.1 (cohort IV) or 5.3 (cohort I, II, III, V) image analysis suite for Linux for morphometric analysis (Fischl, 2012) (http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/). See Supplementary Methods for details.

Statistical Analyses

All statistical analyses were conducted using R version 3.1.2 (http://www.r-project.org. Accessed December 11, 2018). Linear mixed model analyses were performed comparing FDRs (as a group or per relative type) and, if present, patients to controls, while taking family relatedness into account (http://CRAN.R-project.org/package=nlme) (Pinheiro & Bates, 2000). Centered age, age squared, and sex were included as covariates. Analyses of the twin studies included a binary dummy variable because subjects were included from 2 twin cohorts. Cohen's *d* effect sizes and 95% confidence intervals (CIs) were calculated and

pooled using an inverse variance-weighted random-effects meta-analysis. All random-effects models were fitted using the restricted maximum likelihood method. We base significance on the CIs, as these are more informative that just reporting *P*-values. In addition, to correct for multiple testing, a false discovery rate correction ($q < 0.05$) was performed within each analyzed group, i.e., FDRs, patients, and different types of relatives across all phenotypes. Effect sizes were compared between the different types of FDRs (Supplementary Methods). To investigate the role of IQ, the analyses were performed with and without covarying for IQ. In cohort I, II, and IV, some subjects were excluded due to missing IQ measures (Table 1). In addition, to confirm the relationship between brain and IQ, additional mixed model analyses were performed across all subjects in each cohort individually and combined to calculate the correlations between brain measures and IQ. We investigated the role of having a DSM diagnosis other than a psychotic disorder in the relatives and controls by (1) with and without adding a dummy variable to the analyses in which relatives and control subjects with a diagnosis were coded as 1, and (2) by comparing only the *healthy* relatives with the *healthy* controls. Further analyses were performed to investigate the role of intracranial volume (ICV) in the brain measures, by adding ICV as a covariate.

RESULTS

Demographics

Table 1 and Supplementary Table S1a–e provide an overview of the demographics of each individual family cohort. Means and standard deviations for all brain measures in all cohorts can be found in Supplementary Table S2a and b.

Table 1. Demographics

			Age	Gender	IQ	IQ	Diagnoses other than
		N	Mean (SD)	(M/F)	*N*	Score (SD)	Psychotic Disorder (Y/N)
Cohort I	MZ co-twins	13	33.6 (11.0)	8/5	12	95.8 (13.0)	7/6
(3T)	DZ co-twins	18	38.5 (12.3)	13/5	17	110.4 (15.0)	4/14
	Patients	35	35.4 (10.7)	24/11	32	92.1 (13.4)	*NA*
	Controls	169	32.0 (13.4)	75/94	156	104.9 (12.9)	16/153
Cohort II	MZ co-twins	7	40.5 (11.2)	4/3	4	111.5 (15.9)	3/4
(1.5T)	DZ co-twins	7	36.0 (13.3)	4/3	5	120.4 (14.5)	1/6
	Patients	21	35.9 (10.8)	9/12	13	108.0 (12.9)	*NA*
	Controls	15	29.2 (6.3)	9/6	12	119.7 (11.3)	1/14
Cohort III	Offspring	40	13.7 (3.0)	12/28	40	100.6 (19.2)	24/16
	Controls	40	12.7 (2.1)	21/19	40	117.0 (13.0)	7/33
Cohort IV	Sibllings	201	27.7 (7.1)	95/106	199	101.4 (14.3)	52/149
	Patients	162	27.0 (5.8)	130/32	153	93.5 (15.5)	*NA*
	Controls	167	27.7 (8.2)	83/84	164	111.9 (14.8)	13/154
Cohort V	Parents	44	52.9 (4.3)	13/31	44	116.9 (14.7)	11/33
	Controls	41	52.8 (4.6)	14/27	41	119.0 (13.1)	0/41

Note: DZ, dizygotic; IQ, intelligent quotient; MZ, monozygotic; NA, not applicable.

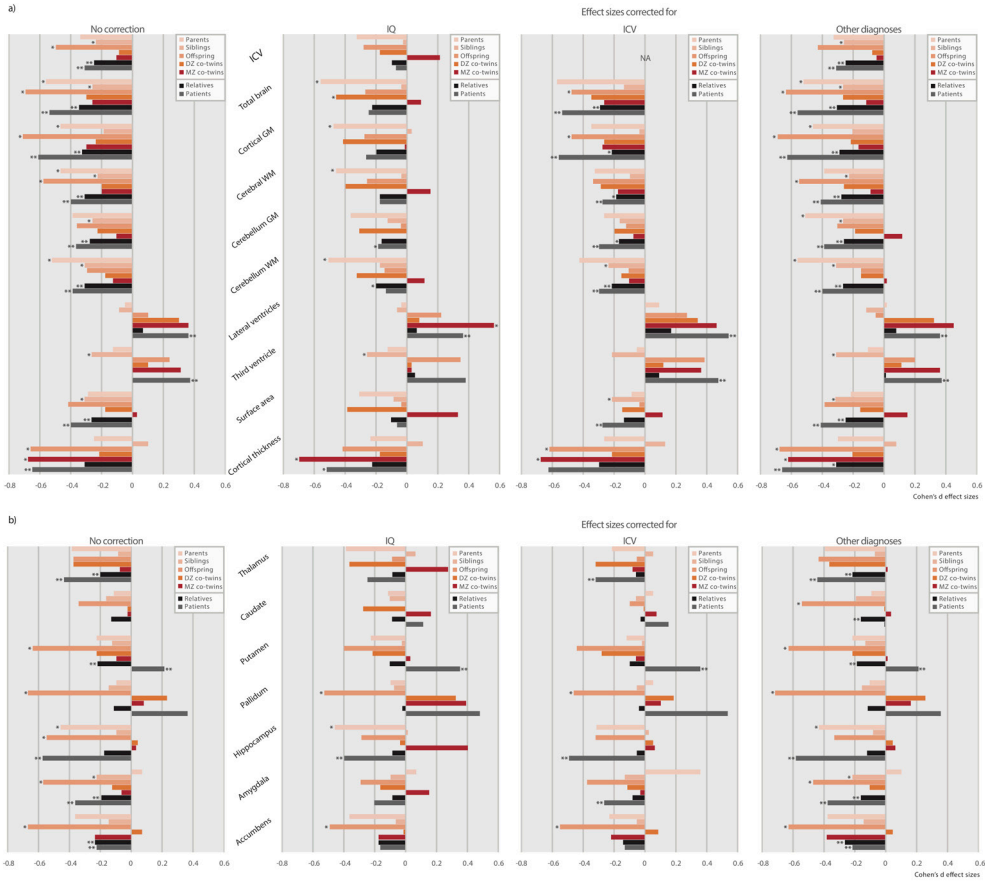

Figure 1. Cohen's *d* effect sizes comparing each type of first-degree relative (i.e., parents, siblings, offspring, dizygotic [DZ] co-twins, and monozygotic [MZ] co-twins), the relatives combined, and patients with controls for (a) global brain measures and (b) subcortical brain volumes. The effect sizes in the second panel are corrected for intelligent quotient (IQ), in the third panel corrected for intracranial volume (ICV) and in the right panel corrected for other diagnoses than a psychotic disorder in the relatives and controls. The asterisks (*) denote the significant effect sizes $P < 0.05$, uncorrected; ** $q < 0.05$, corrected. GM = gray matter; WM = white matter.

Global Measures

FDRs had smaller volumes in the intracranium, total brain, cortical gray and cerebral white matter, and cerebellar gray and white matter, and smaller total surface areas compared with controls (all *d*s < –0.24; $q < 0.05$, corrected; Supplementary Table S3a, Figure 1a). The largest effect sizes were found in the offspring, but none of the effect sizes in the subgroups separately survived correction for multiple testing. See Supplementary Table S4 for effect sizes, nominal significance, and direct comparisons between groups. Patients differed significantly in all global measures compared with controls in the expected direction (i.e., smaller volumes, smaller surface area, thinner cortex, enlarged ventricles; $q < 0.05$, corrected; Supplementary Table S3a).

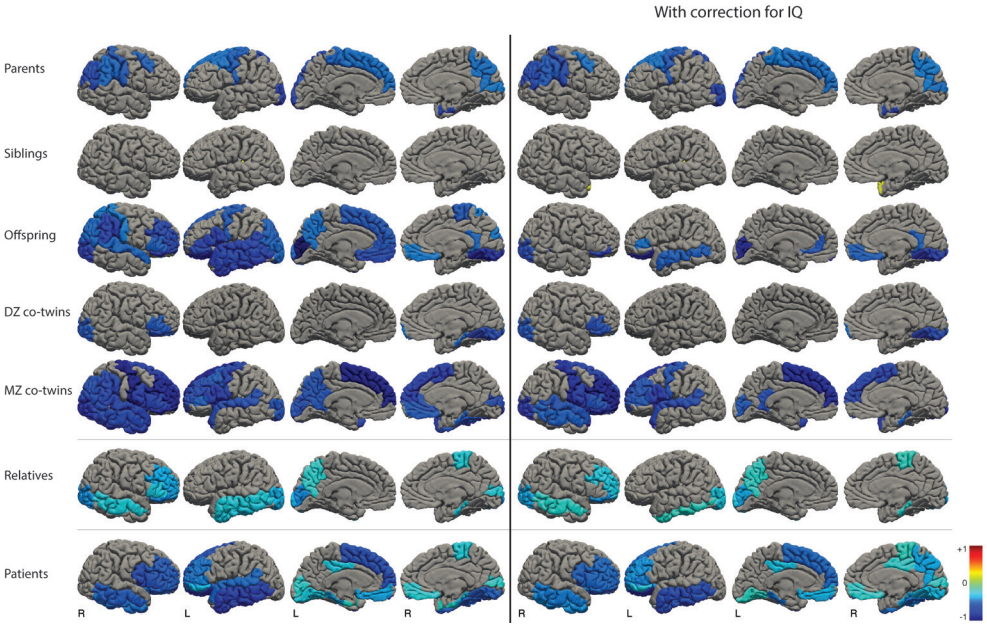

Figure 2. Cohen's *d* effect sizes for regions that showed significant differences in cortical thickness between each type of first-degree relative (i.e., parents, siblings, offspring, dizygotic [DZ] co-twins, and monozygotic [MZ] co-twins), the relatives combined, patients, and controls. The effect sizes in the right panel are corrected for intelligent quotient (IQ). Negative effect sizes (shown in blue) indicate thinner cortices as compared with controls. None of the effects in the relatives combined survived correction for multiple testing, whereas in the patients they did. In the MZ co-twins, left and right insula and right rostral middle frontal thickness, and in the offspring left cuneus thickness survived false discovery rate correction. After correction for IQ, only the effects in patients survived correction for multiple testing. R = right side; L = left side.

Regional Cortical Measures

Figures 2 and 3 display significant effect sizes of the comparison between FDRs and controls of regional cortical thickness and surface area, respectively. FDRs and patients showed a similar pattern of a thinner cortex when compared with controls, albeit with smaller effect sizes in the FDRs. None of the cortical thickness effects in the FDRs combined survived correction for multiple testing, where in the patients they did (Figure 2). The effect in the FDRs was mostly driven by the MZ co-twins and offspring. FDRs showed a similar pattern of smaller regional surface area as seen in patients, relative to controls, but with smaller effect sizes. In the FDRs as a group, only right middle temporal and postcentral surface area survived correction for multiple testing, whereas in patients, most cortical surface area regions survived false discovery rate correction (Figure 3).

Subcortical Volumes

Thalamus, putamen, amygdala, and accumbens volumes were smaller in FDRs as compared with controls (all *d*s < –0.19, $q < 0.05$, corrected; Supplementary Table S3a, Figure 1b). The largest effect sizes were found in the offspring, but none of the effect sizes in the subgroups separately survived correction for multiple testing. See Supplementary Table S4

for effect sizes, nominal significance, and direct comparisons between groups. Patients had significantly smaller thalamus, pallidum, hippocampal, amygdala, accumbens, and higher putamen volume than controls ($q < 0.05$, corrected; Supplementary Table S3a).

Intracranial Volume

After adding ICV as a covariate, total brain and cerebellar white matter remained significant when comparing FDRs with controls ($q < 0.05$, corrected; Figure 1a and b, Supplementary Table S3b). All subcortical effects disappeared when taking ICV into account (Figure 1b, Supplementary Table S3b), implicating that subcortical findings in the FDRs are a representation of the smaller brain size. In the different relative types, none of the effect sizes survived correction for multiple testing (Supplementary Table S6). In patients, ICV correction did not change the pattern of significant findings.

Intelligent Quotient

Offspring, siblings, and MZ co-twins had a significantly lower IQ than controls (respectively, $d = -0.97$, $d = -0.78$, $d = -0.46$), whereas the DZ co-twins had a significantly higher IQ ($d = +0.69$). At inclusion, the parents were matched on IQ. FDRs (without parents) had a lower IQ as compared with controls ($d = -0.39$), which did not reach significance. The patients had significantly lower IQ than controls ($d = -1.03$). IQ and almost all brain measures, except for caudate, putamen, pallidum, lateral, and third ventricle volume, were significantly positively correlated, most surviving correction for multiple comparisons ($r = 0.10$ to 0.27, Supplementary Table S11a). ICV and IQ have a positive relationship of $r = 0.17$. After ICV correction, cortical thickness, total brain, cerebral white matter, cerebellar gray and white matter, thalamus, and amygdala volume were positively correlated with IQ ($r = 0.08$ to 0.19, Supplementary Table S11b). Pallidum, third, and lateral ventricle volume were negatively correlated with IQ ($r = -0.06$ to -0.10, Supplementary Table S11b). Most regions survived correction for multiple comparisons (Supplementary Table S11a and b).

When correcting the global brain measures for IQ, only cerebellar white matter volume remained significantly smaller in FDRs as compared with controls but this finding did not survive correction for multiple comparisons (Supplementary Table S3a). Adding IQ as a covariate changed the effect sizes of brain abnormalities differently for the different relative types (Supplementary Table S5) but no effects survived correction for multiple comparisons. See Supplementary Table S5 for effect sizes, nominal significance, and direct comparisons between groups. In patients, a thinner cortex, smaller cerebellar gray matter volume, and a larger lateral ventricle volume remained significant after correction for IQ of which only the latter survived correction for multiple comparisons (Supplementary Table S3a). The right panels of Figures 2 and 3 visualize the effect of covarying for IQ on local cortical thickness and surface area. The pattern of cortical thickness differences compared with controls remained similar for patients and FDRs. Comparing between relative types showed that the results in FDRs were mainly driven by the MZ co-twins (Figure 2). Furthermore, most signif-

icant differences in local surface area in both patients and relatives compared with controls disappeared after covarying for IQ (Figure 3). After IQ correction, subcortical volumes were no longer significantly smaller in FDRs as compared with controls (Supplementary Table S3a and S5). In patients, only a larger putamen and a smaller hippocampal volume than in controls survived correction for IQ ($q < 0.05$, corrected; Supplementary Table S3a). IQ and ICV corrected analyses can be found in Supplementary Tables S3b and S7.

Diagnosis Other Than Psychotic Disorder in the Relatives

Psychiatric diagnoses other than a psychotic disorder were present in 44.7% of the FDRs, and 9.4% of the controls (Table 1). After a correction for having a diagnosis other than a psychotic disorder, most findings remained similar ($q < 0.05$, corrected; Figure 1a and b, Supplementary Table S8). When comparing between different relative types, correction for the presence of another diagnosis than a psychotic disorder did not change the pattern of significant findings (Supplementary Table S9). The analyses in the healthy-only group showed similar effect sizes, although not all measures reached significance, presumably because of the smaller sample size (Supplementary Table S8). When comparing between different relative types, in particular, the offspring showed higher effect sizes than when both healthy and affected offspring were analyzed combined (Supplementary Table S10).

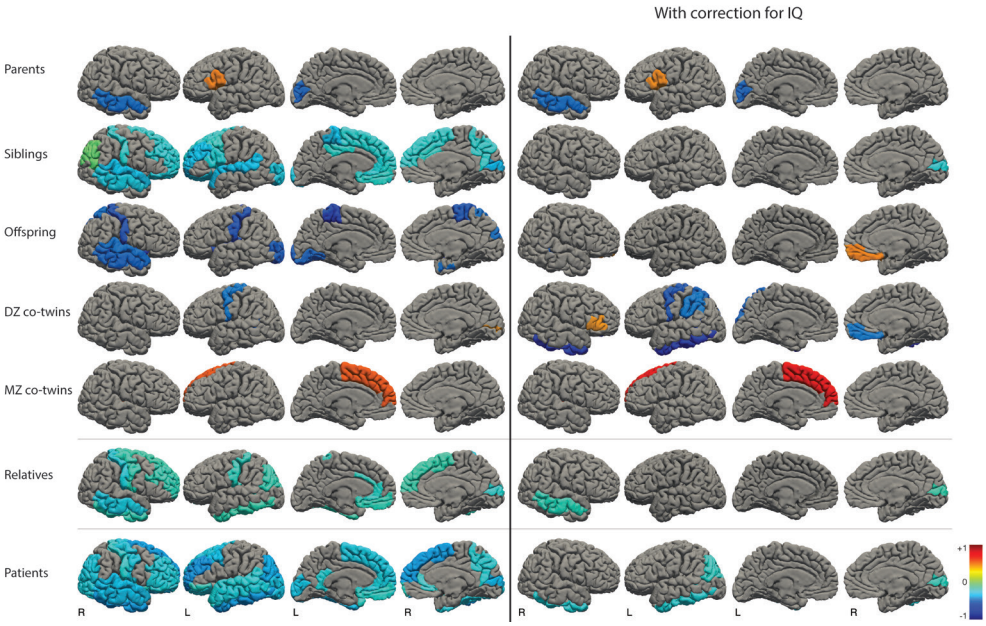

Figure 3. Cohen's *d* effect sizes for regions that showed significant differences in surface area between each type of first-degree relative (i.e., parents, siblings, offspring, dizygotic [DZ] co-twins, and monozygotic [MZ] co-twins), the relatives combined, patients, and controls. The effect sizes in the right panel are corrected for intelligent quotient (IQ). Negative effect sizes indicate smaller surface area as compared with controls. In the relatives as a group, only right middle temporal and postcentral surface area survived correction for multiple testing. In the patients, most cortical surface area regions survived false discovery rate correction. After correction for IQ, no regions survived correction for multiple testing. R = right side; L = left side.

DISCUSSION

In this study in 980 subjects, we examined whether FDRs of patients with schizophrenia (n = 330) share brain abnormalities with their ill family member (n = 218), and whether the extent of the abnormality varies among the different types of FDRs. All included relatives shared on average 50% of their genes with the proband, with the exception of the MZ co-twins. None of the FDRs had a diagnosis in the psychosis spectrum (although other psychiatric diagnoses were present). We examined the role of the presence of nonpsychotic diagnoses in the relatives and that of IQ. The main findings were 3-fold: (1) FDRs had smaller brain volumes as compared with controls, and these were most pronounced in offspring; (2) IQ and ICV (albeit to a slightly lesser extent) were associated with most of the brain abnormalities found in FDRs; and (3) having a nonpsychotic disorder in the relatives did not explain the brain abnormalities.

That FDRs had smaller brain volumes than controls is in line with previous published meta-analyses (Boos et al., 2007; Chan et al., 2011; Cooper et al., 2014; Fusar-Poli et al., 2011; Fusar-Poli et al., 2014). Importantly, having a diagnosis other than a psychotic disorder did not explain the findings in any of our FDRs cohorts, implicating that the brain abnormalities found in FDRs do not reflect the presence of other psychiatric diagnoses.

We found the largest effect sizes in the offspring. A possible explanation may be that offspring are young and still younger than the usual age of illness onset (which is approximately between 20 and 25 years (Kessler et al., 2007; Rajji et al., 2009). Consequently, some offspring will in fact develop schizophrenia, which may explain the relatively large effect sizes. Alternatively, those children who will ultimately not develop a disorder may show a developmental pattern where brain abnormalities are present in early adolescence but disappear when they reach adulthood (Moran et al., 2013). This is consistent with the pattern reported in (young) siblings of patients with childhood-onset schizophrenia (Gogtay et al., 2007). In addition, one could argue that offspring, growing up with an ill parent, are exposed to a more stressful environment early in life than the other FDRs. The brain undergoes major developmental changes until early adulthood (Giedd, 2004); consequently, these environmental risk factors may influence (early) brain development as well as IQ.

Offspring, siblings, and MZ co-twins had significantly lower IQ than their respective controls. In addition, IQ and most brain measures were significantly correlated in all groups, in line with previous findings (McDaniel, 2005). Specifically, IQ and ICV were positively correlated (r = +.17); however, when comparing the IQ-corrected effect sizes with the ICV-corrected effect sizes, one could argue that IQ covaries more strongly with brain abnormalities than ICV. After correcting the group differences in brain structure for IQ, most brain abnormalities disappeared in all types of FDRs. This implies that there is a familial factor (being either shared environmental or genetic) that predisposes to lower IQ, increased risk for schizophrenia, and smaller brain volumes, irrespective of type of kinship. On the basis of

earlier twin and GWAS findings, we suggest that at least part of the familial risk is genetic. That is, twin and familial population studies have shown that both IQ and brain structure share genetic variance with schizophrenia liability (Bohlken et al., 2016; Kendler et al, 2015; Toulopoulou et al., 2015). Consistent with the findings in these studies, GWAS studies show that schizophrenia, IQ, and brain volume share a genetic origin (Lencz et al., 2014; Smeland et al., 2017a, 2017b; Sniekers et al., 2017), but it is not clear at this point how these phenotypes interact. It is possible that the genetic vulnerability of FDRs cause brain deficits that in turn influence IQ but alternatively, a genetic predisposition for lower IQ may influence brain development and hence brain morphology. In addition, we cannot rule out the influence of environment on the brain abnormalities we find in FDRs. The different relative types, who all share on average 50% of their genome with the proband except for the MZ co-twins, show different brain abnormalities. This suggests that environmental factors or gene-by-environment interactions also play a role.

Although not significant after correction for multiple comparisons, the effect sizes in MZ co-twins for a thinner cortex and larger lateral ventricles were remarkably high. Cortical thinning and ventricle enlargement are among the strongest findings in schizophrenia (Haijma et al., 2013; Van Erp et al., 2015). That MZ co-twins share these abnormalities with the probands suggests that another factor related to schizophrenia risk, independent of IQ, is causing a thinner cortex and lateral ventricle enlargement in schizophrenia. This factor is likely genetic, because the MZ co-twins arguably have a higher genetic risk than the other relative types. Indeed, previous studies from other twin cohorts show a genetic factor implicated in schizophrenia liability and whole-brain volume (Borgwardt et al., 2010; Van Haren et al., 2004). There are mixed findings for the existence of genetic overlap between schizophrenia liability and lateral ventricle volume: direct genetic overlap was absent in one study (Van Haren et al., 2004) but genetic overlap was found between schizophrenia liability and altered callosum morphology (Narr et al., 2002). The latter was significantly associated with lateral ventricle enlargement, providing indirect evidence for shared genetic influences between schizophrenia liability and lateral ventricle enlargements (Narr et al., 2002).

Some limitations must be taken into account when interpreting the results. In the current study design, it is not possible to separate the influence of both IQ and ICV on brain measures in FDRs, especially considering the fact they are genetically correlated (r = +0.29) (Sniekers et al., 2017). However, both phenotypes fit in the neurodevelopmental theory of schizophrenia (Murray & Lewis, 1987; Weinberger, 1987) and perhaps a cross-sectional family design is not suited to separate between the familial influences of IQ and ICV on brain measures. Longitudinal follow-up of individuals from early in life into adulthood is needed. Second, we used a simplistic approach to correct for other diagnosis than psychotic disorders in the relatives and controls by looking at the presence of none vs "any" diagnosis. However, considering both the analyses with correction for other diagnoses than a psychotic disorder as covariate and looking at only the healthy relatives as compared with the healthy controls showed similar results, we believe that our findings are not explained by the presences of

another diagnosis than a psychotic disorder in the relatives and controls. Third, although we included almost 1,000 subjects, sample sizes per FDR subtype were sometimes modest at most. In particular the MZ co-twin group, which showed some of the most prominent differences, was small. By far the largest group was siblings, and therefore, they drove the findings in the overall FDRs analyses in terms of significance (not necessarily in term of effect size). Fourth, mean age differed between relative types. Although we applied a non-linear correction for age within each cohort, we were not able to perform a meta-regression using age as covariate due to the limited number of cohorts. Fifth, there may be a selection bias, as all cohorts were recruited in a clinical setting. Sixth, even though we chose a meta-analysis approach to account for differences across the different cohorts (among others acquisition protocols, field strength, inclusion/exclusion criteria), it might not fully control for this variance. Finally, the parents of the patients were matched on IQ with those of the controls. Therefore, they potentially represent a "healthy" subpopulation of parents of patients with schizophrenia.

In conclusion, we find that FDRs of patients with schizophrenia show structural brain abnormalities, suggesting that the familial risk to develop schizophrenia explains at least partly the brain abnormalities seen in patients. Thus, brain abnormalities are not only caused by disease-related factors, such as cannabis use, antipsychotics, and duration of psychotic symptoms (Cahn et al., 2009; Haijma et al., 2013; Rais et al., 2008), but we identified 3 components of familial risk that may play a role. First, based on the finding that the offspring showed the largest effect sizes, there is an environmental component that contributes to brain abnormalities in subjects at risk for schizophrenia. Second, IQ strongly covaried with the brain abnormalities in the relatives, which suggests an overlap between familial risk factors leading to low IQ and to risk for schizophrenia. Given the genetic correlation between brain volume, IQ, and risk for schizophrenia, based on twin and GWAS studies, this familial risk component is likely to be of genetic origin. Finally, our data suggest another genetic risk factor that is unrelated to IQ, influencing cortical thickness and lateral ventricle size in patients and their FDRs.

SUPPLEMENTARY METHODS

Cohort description

Cohort I – Twin study. Between 2008 and 2013, 25 MZ twins discordant for schizophrenia (11 pairs, 13 MZ co-twins, 11 patients), 4 MZ twins concordant for schizophrenia (2 pairs), 38 DZ twins discordant for schizophrenia (17 pairs, 18 DZ co-twins, 20 patients) and 169 control twins (80 pairs) were included (for detailed description see (Bohlken et al., 2016)). All subjects underwent psychiatric assessment using the Comprehensive Assessment of Symptoms and History (CASH) interview (Andreasen et al., 1992). The probands were diagnosed with a psychotic disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (American Psychiatric Association, 2000); including schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder NOS. The unaffected co-twins did not have a psychotic disorder; however, non-psychotic disorders were present is some (Table S1a). Control twins were excluded if they ever met criteria for a psychotic or manic disorder or substance dependence, or had a first-degree relative with schizophrenia, or were diagnosed as having a neurologic disorder. An evaluation of intellectual ability was obtained by a shortened version of the Wechsler Adult Intelligence Scale (WAIS) III general intelligence test, consisting of five subtests: Digit Symbol-Coding, Block Design, Arithmetic, Digit Span, and Information (Wechsler, 1997). The five subtests were used to calculate a proxy measure for the full-scale IQ. Magnetic resonance imaging (MRI) scans were acquired on a Philips Achieva scanner operating at 3T (Best, The Netherlands). The T1-weighted 3-dimensional fast-field echo scans were acquired with the following parameters: 220 0.8 mm contiguous slices, echo time = 4.6 ms, repetition time = 10 ms, flip angle = 8°, in-plane voxel size 0.75 x 0.75 mm^2.

Cohort II – Twin study. A subset of a schizophrenia twin cohort consisting of 16 MZ twins discordant for schizophrenia (6 pairs, 7 MZ co-twins, 9 patients), 6 MZ twins concordant for schizophrenia (3 pairs), 13 DZ twins discordant for schizophrenia (5 pairs, 7 DZ co-twins, 6 patients) and 15 control twins (4 pairs) were included between 1995 and 2002. This sample is a subset of the original twin cohort described previously (Baaré et al., 2001; Brans et al., 2008) because some twin pairs in cohort I overlap with cohort II. In these cases, data from cohort I was included because of the higher field strength of the MRI scanner. This cohort was also part of two large twin studies (Hulshoff Pol et al., 2012; Toulopoulou et al., 2015). Patients were diagnosed with schizophrenia according to criteria of DSM-IV based on the CASH interview (Andreasen et al., 1992). None of the discordant co-twins received a diagnosis of schizophrenia but other diagnoses were reported (Table S1b). Control twins were excluded if they had a first-degree relative with a history of psychiatric illness, and/or a second-degree relative with a psychotic disorder. Four subtests of the Dutch version of the WAIS (Stinissen et al., 1970) were used as a proxy for IQ, i.e. vocabulary, block design, picture arrangement and comprehension. The four subtests were used to calculate a proxy measure for the full-scale IQ. MRI scans were acquired on a Philips NT scanner operating at 1.5T for all participants (Best, The Netherlands). The acquired scans were T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256 x 256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1 x 1 x 1.2 mm^3 voxels, field of view = 256mm/70%).

Cohort III – Offspring study. A total of 80 children and adolescents, aged between 8 and 18 years participated in this study included between 2011 and 2015 Forty-one subjects had at least one parent affected with schizophrenia. Forty-three control offspring without any lifetime DSM-IV axis I disorder and without an affected first-degree relative were included (for detailed description see (Collin et al., 2017)). None of the participants had contraindications for MRI, suffered from alcohol or drug dependence, had a history of a neurological diagnosis, or psychotic disorder, but other diagnoses were reported (Table S1c). The total IQ score for each study group was estimated based on the performance of four subtests, Picture Arrangement, Block

Design, Vocabulary and Information, of the Dutch version of the WAIS III in participants older than 16 years old (Wechsler, 1997), or the Dutch version of the Wechsler Intelligence Scale for Children-Revised Wechsler Intelligence Scale for Children (WISC) III in the case of younger offspring (Wechsler, 1991). The same 3T scanner and protocol were used as in cohort I.

Cohort IV – Sibling study. A sample of 162 patients with schizophrenia, 201 non-psychotic siblings, and 167 healthy control subjects, collected at the UMCU as part of an ongoing longitudinal collaborative in the Netherlands, was included between 2004 and 2008 (Genetic Risk and Outcome of Psychosis (Korver et al., 2012); for detailed description sample see (Boos et al., 2012; Kubota et al., 2015)). All participants were aged between 16 and 50 years old. Patients met DSM-IV criteria for a non-affective psychotic disorder (including schizophrenia, schizophreniform disorder, and schizoaffective disorder) based on the CASH interview. The unaffected siblings were defined as not having a psychotic disorder (Table S1d). Healthy controls did not have a lifetime psychotic disorder and/or use of lithium medication (in the past), and no first- or second-degree family member with a lifetime psychotic disorder. Subjects with substance dependence/abuse and a major medical or neurological illness were excluded. The IQ scores were based on four subtests of the Dutch version of the WAIS III, digit-symbol coding, information, arithmetic, and block design (Wechsler, 1997). The four subtests were used to calculate a proxy measure for the full-scale IQ. Structural MRI scans of the whole brain were obtained on a 1.5T Achieva scanner (Philips, Best, the Netherlands) with the same scan protocol as cohort II.

Cohort V – Parents study. A total of 44 parents of patients with schizophrenia and 41 healthy controls were included in 1999 and 2000, and groups were matched on age, handedness, IQ, and level of education (for detailed description see (Appels et al. 2004; Boos, 2011)). The parents of the patients had at least one child meeting DSM-IV criteria for schizophrenia and they were excluded if they had a history of a schizophrenia spectrum disorder themselves (Table S1e). All participants were physically healthy and had no history of neurological illness and no history of drug or alcohol abuse. Control parents were excluded if they or their first-degree relatives had a history of drug or alcohol abuse, a personality disorder, or a history of a psychiatric illness. Furthermore, healthy controls were excluded if their second-degree relatives had a history of psychotic illness. Current IQ was estimated using a short form of the Groningen Intelligence Test (Luteyn & Van der Ploeg, 1983). MRI was performed the same 1.5T scanner and protocol as cohort II.

Image Processing

The basic image processing steps used by FreeSurfer entail motion correction, the removal of non-brain tissue, an automated Talairach transformation, the segmentation of the subcortical white matter and deep gray matter volumetric structures as well as intensity normalization and the tessellation of the pial and white surface boundaries. Each scan was thoroughly checked for errors of template registration, skull strip, segmentation and parcellation, and manually edited if needed (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/PialEdits_freeview). Subsequently, the resulting segmentation was quality checked according to the ENIGMA quality control protocol (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Subcortical and global measures outliers (i.e. values outside of the distribution) were visualized with histograms. All subcortical and cortical segmentations were visually checked based on an overlay of the segmentation on the original scan and the cortical segmentations were in addition checked by the use of inflated cortical surfaces. Wrongly segmented areas were excluded and statistical outliers (mean ± 2.689 SD) were only excluded when also visually verified as a bad segmentation. The global brain volumes, cortical thickness, surface area and subcortical volumes were extracted from individual images as well as regional thickness and surface area according to the Desikan-Killiany Atlas (Desikan et al., 2006).

Comparing effect sizes

To compare the effect sizes between the different types of FDRs, the following approach was applied. If d is the observed Cohen's d value, then the sampling variance of d is approximately equal to:

$$v = \frac{1}{n_1} + \frac{1}{n_2} + \frac{d^2}{2(n_1 + n_2)}$$

where n_1 and n_2 are the sample sizes of relatives and controls, respectively.

To test H_0: $\delta_1 = \delta_2$ (where δ_1 and δ_2 denote the true d values of the two types of relatives), compute:

$z = \frac{d_1 - d_2}{\sqrt{v_1 + v_2}}$, which follows approximately a standard normal distribution under H_0.

If $|z| \geq 1.96$, H_0 can be rejected at $\alpha = 0.05$ (two-sided).

SUPPLEMENTARY TABLES

Table S1a. Primary diagnoses subjects cohort I (3T twins)

Diagnosis according to DSM IV	MZ co-twins (n = 13)	DZ co-twins (n = 18)	Patients (n = 35)	Controls (n = 169)
Schizophrenia (295.x / 295.1 / 295.3 / 295.6)	-	-	26	-
Schizoaffective disorder (295.7)	-	-	8	-
Psychotic disorder NOS (298.9)	-	-	1	-
Borderline personality disorder (301.8)	1	-	-	-
Major depression (296.22 / 296.23 / 296.25 / 296.26 / 296.35 / 296.36)	3	2	-	13
Depressive disorder NOS (311)	1	1	-	2
Schizotypal personality disorder (301.22)	-	1	-	-
Rett's disorder (299.80)	-	-	-	1
Cannabis Abuse (304.3)	1	-	-	-
Cannabis dependence (305.2)	1	-	-	-
No diagnosis (v71.09)	6	14	-	153

Table S1b. Primary diagnoses subjects cohort II (1.5T twins)

Diagnosis according to DSM IV	MZ co-twins (n = 7)	DZ co-twins (n = 7)	Patients (n = 21)	Controls (n = 15)
Schizophrenia (295.1 / 295.2 / 295.3/ 295.6 / 295.9)	-	-	21	-
Major depression (296.26)	1	-	-	-
Paranoid personality disorder (301.0)	-	1	-	-
Schizotypal personality disorder (301.22)	2	-	-	-
Adjustment disorder (309.0)	-	-	-	1
No diagnosis (v71.09)	4	6	-	14

Table S1c. Primary diagnoses subjects cohort III (Offspring study)

Diagnosis according to DSM IV	Offspring (n = 40)	Controls (n = 40)
Major depression (296.20 / 296.25 / 296.2x)	4	-
Mood Disorder NOS (296.90)	1	1
Depressive disorder NOS (311)	1	-
Dysthymic disorder (300.4)	1	1
Obsessive-compulsive disorder (300.3)	1	-
Anxiety disorders (300.00 / 300.02 / 300.29)	3	1
Rett's disorder (299.80)	4	-
Adjustment disorder (309.0 / 309.4)	1	2
Attention-deficit and disruptive behavior disorders (314.00 / 314.01)	4	1
Learning disorder NOS (315.9)	1	-
Childhood Disintegrative Disorder (299.10)	1	-
Elimination disorder (307.6)	1	1
Parent-child relational problem (v61.20)	1	-
No diagnosis (v71.09)	16	33

Table S1d. Primary diagnoses subjects cohort IV (Sibling study)

Diagnosis according to DSM IV	Siblings (n = 201)	Patients (n = 162)	Controls (n = 167)
Schizophrenia (295.1 / 295.2 / 295.3/ 295.6 / 295.9)	-	119	-
Schizophreniform disorder (295.4)	-	8	-
Schizoaffective disorder (295.7)	-	18	-
Psychotic disorder NOS (298.9)	-	11	-
Delirium (293.0)	-	1	-
Delusional disorder (297.1)	-	2	-
Brief psychotic disorder (298.8)	-	3	-
Bipolar disorder I (296.00 / 296.50 / 296.51 / 296.54 / 296.56 / 296.7)	8	-	-
Major depression (296.20 / 296.21 / 296.25 / 296.26 / 296.31 / 296.32 / 296.33 / 296.35 / 296.36 / 296.3X)	36	-	10
Autistic Disorder (299.00)	1	-	-
Schizotypal personality disorder (301.22)	1	-	-
Adjustment disorder (309.0)	1	-	1
Alcohol dependence (303.90)	1	-	-
Cannabis dependence (304.30)	1	-	-
Anorexia nervosa (307.1)	1	-	-
Diagnosis deferred on Axis I/II (799.9)	2	-	1
Bereavement (v62.82)	-	-	1
No diagnosis (v71.09)	149	-	154

Table S1e. Primary diagnoses subjects cohort V (Parent study)

Diagnosis according to DSM IV	Parents (n = 44)	Controls (n = 41)
Bipolar disorder I (296.53)	1	-
Major depression (296.21 / 296.30 / 296.33)	8	-
Dysthymic disorder (300.4)	1	-
Impulse-Control Disorder (312.31)	1	-
No diagnosis (v71.09)	33	41

Table S2a. Uncorrected mean (SD) for each family cohort for global brain measures (volumes ml, surface area in cm^2; cortical thickness in mm)

		ICV	Total brain	Cortical GM	Cerebral WM	Cerebellum GM	Cerebellum WM	Lateral ventricles	Third ventricle	Surface area	Cortical thickness
Cohort I	MZ co-twins	1457 (245)	1103 (110)	461 (43)	456 (56)	96 (11)	31 (4)	22 (12)	0.95 (0.27)	1732 (162)	2.38 (0.07)
	DZ co-twins	1485 (209)	1111 (110)	461 (53)	466 (48)	95 (17)	31 (6)	20 (11)	0.91 (0.37)	1727 (177)	2.40 (0.10)
	Patients	1417 (220)	1088 (116)	453 (53)	451 (59)	94 (11)	31 (4)	21 (9)	0.97 (0.35)	1708 (174)	2.38 (0.11)
	Controls	1445 (164)	1106 (88)	471 (43)	451 (47)	95 (10)	31 (4)	18 (8)	0.82 (0.30)	1712 (140)	2.45 (0.10)
Cohort II	MZ co-twins	1507 (207)	1120 (128)	431 (34)	492 (87)	113 (12)	27 (4)	12 (5)	0.94 (0.26)	1685 (196)	2.37 (0.09)
	DZ co-twins	1591 (177)	1132 (121)	439 (62)	498 (65)	109 (13)	27 (2)	18 (1)	1.06 (0.30)	1658 (186)	2.42 (0.16)
	Patients	1459 (123)	1043 (109)	391 (52)	464 (51)	107 (15)	25 (4)	18 (7)	1.04 (0.37)	1595 (172)	2.28 (0.16)
	Controls	1562 (90)	1163 (81)	448 (33)	508 (47)	119 (10)	29 (2)	13 (6)	0.94 (0.33)	1713 (115)	2.42 (0.10)
Cohort III	Offspring	1446 (200)	1127 (128)	526 (69)	411 (53)	100 (13)	30 (4)	12 (6)	0.76 (0.23)	1751 (197)	2.62 (0.12)
	Controls	1566 (161)	1225 (108)	578 (48)	444 (54)	107 (11)	31 (4)	11 (4)	0.70 (0.21)	1860 (167)	2.70 (0.10)
Cohort IV	Siblings	1601 (157)	1184 (112)	470 (49)	500 (58)	125 (13)	29 (3)	14 (7)	0.94 (0.21)	1726 (161)	2.54 (0.11)
	Patients	1651 (163)	1203 (115)	473 (50)	511 (60)	128 (13)	29 (3)	17 (9)	1.08 (0.25)	1767 (173)	2.49 (0.11)
	Controls	1622 (164)	1205 (129)	477 (55)	510 (66)	128 (14)	29 (4)	14 (7)	0.99 (0.27)	1764 (187)	2.53 (0.11)
Cohort V	Parents	1515 (136)	1083 (94)	403 (36)	489 (57)	109 (9)	27 (3)	18 (8)	1.19 (0.28)	1620 (134)	2.31 (0.10)
	Controls	1562 (143)	1133 (100)	420 (31)	515 (66)	112 (10)	29 (3)	18 (8)	1.23 (0.42)	1666 (164)	2.33 (0.11)

Table S2b. Uncorrected mean (SD) for each family cohort for subcortical volumes (ml)

		Thalamus	Caudate	Putamen	Pallidum	Hippocampus	Amygdala	Accumbens
Cohort I	MZ co-twins	7.41 (0.77)	3.88 (0.41)	6.24 (0.75)	1.64 (0.20)	4.35 (0.46)	1.89 (0.25)	0.66 (0.10)
	DZ co-twins	7.16 (0.72)	3.77 (0.64)	6.17 (0.78)	1.71 (0.27)	4.23 (0.45)	1.88 (0.20)	0.70 (0.10)
	Patients	7.03 (0.68)	3.91 (0.45)	6.47 (0.80)	1.75 (0.25)	4.02 (0.48)	1.87 (0.24)	0.67 (0.11)
	Controls	7.14 (0.61)	3.91 (0.46)	6.23 (0.61)	1.65 (0.19)	4.21 (0.33)	1.87 (0.19)	0.69 (0.10)
Cohort II	MZ co-twins	7.99 (1.11)	3.45 (0.34)	4.71 (0.60)	1.47 (0.20)	4.24 (0.36)	1.48 (0.21)	0.46 (0.05)
	DZ co-twins	7.89 (1.04)	3.49 (0.56)	4.86 (0.89)	1.48 (0.23)	4.48 (0.53)	1.52 (0.28)	0.45 (0.10)
	Patients	7.44 (0.85)	3.63 (0.67)	5.01 (0.72)	1.53 (0.20)	4.04 (0.49)	1.33 (0.18)	0.44 (0.09)
	Controls	8.35 (0.54)	3.39 (0.32)	5.07 (0.46)	1.47 (0.14)	4.39 (0.36)	1.52 (0.15)	0.49 (0.08)
Cohort III	Offspring	7.33 (0.77)	4.17 (0.53)	6.54 (0.60)	1.79 (0.18)	4.17 (0.35)	1.84 (0.19)	0.80 (0.10)
	Controls	7.73 (0.74)	4.36 (0.50)	7.00 (0.53)	1.94 (0.17)	4.41 (0.44)	1.97 (0.23)	0.88 (0.11)
Cohort IV	Siblings	8.14 (0.78)	3.69 (0.50)	5.20 (0.64)	1.68 (0.21)	4.56 (0.43)	1.55 (0.17)	0.49 (0.08)
	Patients	8.18 (0.82)	3.82 (0.53)	5.53 (0.63)	1.79 (0.21)	4.53 (0.48)	1.58 (0.19)	0.51 (0.08)
	Controls	8.20 (0.88)	3.74 (0.53)	5.25 (0.64)	1.70 (0.23)	4.59 (0.45)	1.58 (0.19)	0.50 (0.09)
Cohort V	Parents	7.57 (0.79)	3.30 (0.36)	4.47 (0.57)	1.38 (0.19)	4.33 (0.42)	1.44 (0.17)	0.42 (0.08)
	Controls	7.85 (0.62)	3.34 (0.34)	4.59 (0.46)	1.40 (0.16)	4.51 (0.37)	1.44 (0.15)	0.45 (0.07)

Table S3a. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, combined relatives and patients as compared with controls. *p < 0.05, uncorrected, **q < 0.05, corrected

			With correction for IQ	
	Relatives ES ± 95% CI	Patients ES ± 95% CI	Relatives ES ± 95% CI	Patients ES ± 95% CI
Global measures				
ICV	-0.24 [-0.39 , -0.09]**	-0.30 [-0.47 , -0.12]**	-0.08 [-0.24 , 0.07]	-0.05 [-0.41 , 0.31]
Total brain	-0.34 [-0.50 , -0.18]**	-0.53 [-0.73 , -0.33]**	-0.22 [-0.45 , 0.02]	-0.24 [-0.59 , 0.12]
Cortical GM	-0.31 [-0.50 , -0.13]**	-0.60 [-0.88 , -0.32]**	-0.19 [-0.41 , 0.04]	-0.26 [-0.64 , 0.12]
Cerebral WM	-0.29 [-0.44 , -0.14]**	-0.39 [-0.56 , -0.21]**	-0.17 [-0.37 , 0.04]	-0.17 [-0.48 , 0.15]
Cerebellum GM	-0.26 [-0.41 , -0.11]**	-0.36 [-0.54 , -0.19]**	-0.15 [-0.31 , 0.00]	-0.18 [-0.37 , -0.00]*
Cerebellum WM	-0.29 [-0.44 , -0.14]**	-0.38 [-0.56 , -0.20]**	-0.20 [-0.35 , -0.05]*	-0.13 [-0.31 , 0.06]
Lateral ventricles	0.08 [-0.11 , 0.26]	0.36 [0.18 , 0.54]**	0.09 [-0.11 , 0.28]	0.36 [0.18 , 0.55]**
Third ventricle	0.00 [-0.23 , 0.24]	0.37 [0.05 , 0.70]**	0.05 [-0.23 , 0.32]	0.38 [0.01 , 0.76]
Surface area	-0.26 [-0.41 , -0.11]**	-0.39 [-0.56 , -0.21]**	-0.10 [-0.25 , 0.06]	-0.06 [-0.25 , 0.12]
Cortical thickness	-0.30 [-0.61 , 0.01]	-0.64 [-1.23 , -0.05]**	-0.23 [-0.50 , 0.05]	-0.51 [-0.94 , -0.08]*
Subcortical volumes				
Thalamus	-0.20 [-0.37 , -0.03]**	-0.43 [-0.61 , -0.25]**	-0.08 [-0.30 , 0.13]	-0.24 [-0.50 , 0.01]
Caudate	-0.14 [-0.29 , 0.01]	0.00 [-0.22 , 0.22]	-0.09 [-0.24 , 0.07]	0.11 [-0.10 , 0.31]
Putamen	-0.21 [-0.37 , -0.04]**	0.21 [0.03 , 0.40]**	-0.11 [-0.27 , 0.05]	0.35 [0.16 , 0.54]**
Pallidum	-0.12 [-0.38 , 0.14]	0.36 [-0.11 , 0.84]	-0.02 [-0.31 , 0.26]	0.48 [-0.01 , 0.96]
Hippocampus	-0.18 [-0.39 , 0.02]	-0.57 [-0.82 , -0.33]**	-0.08 [-0.32 , 0.16]	-0.39 [-0.65 , -0.14]**
Amygdala	-0.19 [-0.34 , -0.04]**	-0.36 [-0.54 , -0.19]**	-0.08 [-0.23 , 0.07]	-0.20 [-0.41 , 0.01]
Accumbens	-0.23 [-0.44 , -0.02]**	-0.22 [-0.40 , -0.05]**	-0.17 [-0.34 , 0.01]	-0.16 [-0.47 , 0.15]

Table S3b. Cohen's d effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, combined relatives and patients compared with controls corrected for intracranial volume (ICV). *p < 0.05, uncorrected, **q < 0.05, corrected

	With correction for ICV		*With correction for ICV and IQ*	
	Relatives ES ± 95% CI	Patients ES ± 95% CI	Relatives ES ± 95% CI	Patients ES ± 95% CI
Global measures				
ICV	-	-	-	-
Total brain	-0.29 [-0.48 , -0.11]**	-0.53 [-0.70 , -0.35]**	-0.22 [-0.45 , -0.00]*	-0.36 [-0.54 , -0.17]**
Cortical GM	-0.21 [-0.40 , -0.02]*	-0.55 [-0.80 , -0.31]**	-0.15 [-0.35 , 0.06]	-0.34 [-0.52 , -0.15]**
Cerebral WM	-0.18 [-0.33 , -0.03]*	-0.27 [-0.44 , -0.09]**	-0.12 [-0.27 , 0.03]	-0.21 [-0.39 , -0.02]**
Cerebellum GM	-0.16 [-0.31 , -0.01]*	-0.29 [-0.46 , -0.11]**	-0.12 [-0.28 , 0.03]	-0.22 [-0.41 , -0.04]**
Cerebellum WM	-0.21 [-0.36 , -0.06]**	-0.29 [-0.47 , -0.12]**	-0.19 [-0.34 , -0.03]*	-0.12 [-0.42 , 0.19]
Lateral ventricles	0.17 [-0.02 , 0.37]	0.54 [0.24 , 0.85]**	0.13 [-0.07 , 0.34]	0.46 [0.10 , 0.82]**
Third ventricle	0.08 [-0.17 , 0.33]	0.47 [0.08 , 0.85]**	0.08 [-0.21 , 0.37]	0.42 [-0.06 , 0.91]
Surface area	-0.13 [-0.28 , 0.02]	-0.27 [-0.50 , -0.04]**	-0.06 [-0.21 , 0.09]	-0.11 [-0.32 , 0.09]
Cortical thickness	-0.29 [-0.60 , 0.02]	-0.62 [-1.24 , 0.00]	-0.23 [-0.51 , 0.05]	-0.51 [-0.93 , -0.09]**
Subcortical volumes				
Thalamus	-0.06 [-0.23 , 0.10]	-0.32 [-0.50 , -0.14]**	0.00 [-0.15 , 0.16]	-0.27 [-0.46 , -0.08]**
Caudate	-0.03 [-0.18 , 0.12]	0.15 [-0.13 , 0.44]	-0.05 [-0.20 , 0.10]	0.15 [-0.23 , 0.52]
Putamen	-0.12 [-0.28 , 0.04]	0.35 [0.17 , 0.54]**	-0.09 [-0.24 , 0.07]	0.36 [0.17 , 0.55]**
Pallidum	-0.04 [-0.20 , 0.11]	0.53 [-0.03 , 1.08]	-0.02 [-0.26 , 0.21]	0.55 [-0.11 , 1.21]
Hippocampus	-0.05 [-0.21 , 0.10]	-0.49 [-0.70 , -0.27]**	-0.03 [-0.19 , 0.12]	-0.45 [-0.63 , -0.26]**
Amygdala	-0.08 [-0.27 , 0.11]	-0.26 [-0.44 , -0.09]**	-0.04 [-0.21 , 0.12]	-0.24 [-0.42 , -0.05]**
Accumbens	-0.15 [-0.34 , 0.03]	-0.13 [-0.31 , 0.04]	-0.14 [-0.29 , 0.01]	-0.15 [-0.37 , 0.06]

Table S4. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with controls. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

Global measures	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI	Significant difference between groups
ICV	-0.10 [-0.56 , 0.36]	-0.08 [-0.50 , 0.34]	-0.49 [-0.93 , -0.04]*	-0.23 [-0.44 , -0.02]*	-0.33 [-0.76 , 0.10]	
Total brain	-0.25 [-0.71 , 0.21]	-0.29 [-0.71 , 0.13]	-0.66 [-1.11 , -0.21]*	-0.25 [-0.45 , -0.04]*	-0.55 [-0.99 , -0.12]*	
Cortical GM	-0.29 [-0.75 , 0.18]	-0.23 [-0.65 , 0.19]	-0.67 [-1.12 , -0.22]*	-0.18 [-0.38 , 0.03]	-0.46 [-0.90 , -0.03]*	OFF<SIB
Cerebral WM	-0.19 [-0.65 , 0.285]	-0.27 [-0.69 , 0.15]	-0.58 [-1.03 , -0.13]*	-0.22 [-0.43 , -0.02]*	-0.46 [-0.89 , -0.03]*	
Cerebellum GM	-0.10 [-0.56 , 0.37]	-0.22 [-0.64 , 0.20]	-0.36 [-0.80 , 0.09]	-0.25 [-0.46 , -0.05]*	-0.38 [-0.81 , 0.05]	
Cerebellum WM	-0.12 [-0.59 , 0.35]	-0.17 [-0.59 , 0.25]	-0.29 [-0.73 , 0.15]	-0.30 [-0.51 , -0.10]*	-0.51 [-0.94 , -0.08]*	
Lateral ventricles	0.36 [-0.10 , 0.83]	0.30 [-0.12 , 0.72]	0.10 [-0.34 , 0.54]	-0.08 [-0.29 , 0.13]	-0.04 [-0.46 , 0.39]	
Third ventricle	0.31 [-0.15 , 0.77]	0.10 [-0.32 , 0.51]	0.22 [-0.22 , 0.65]	-0.26 [-0.47 , -0.05]*	-0.12 [-0.55 , 0.31]	MZ>SIB
Surface area	0.03 [-0.43 , 0.49]	-0.17 [-0.59 , 0.25]	-0.41 [-0.85 , 0.04]	-0.30 [-0.51 , -0.09]*	-0.29 [-0.71 , 0.14]	
Cortical thickness	-0.67 [-1.14 , -0.21]*	-0.21 [-0.63 , 0.21]	-0.65 [-1.10 , -0.20]*	0.10 [-0.11 , 0.30]	-0.24 [-0.67 , 0.18]	MZ<SIB; OFF<SIB
Subcortical volumes						
Thalamus	-0.07 [-0.55 , 0.42]	-0.37 [-0.80 , 0.05]	-0.37 [-0.81 , 0.07]	-0.08 [-0.28 , 0.13]	-0.38 [-0.81 , 0.05]	
Caudate	-0.02 [-0.50 , 0.44]	-0.02 [-0.45 , 0.40]	-0.33 [-0.77 , 0.11]	-0.16 [-0.37 , 0.04]	-0.11 [-0.54 , 0.32]	
Putamen	-0.09 [-0.58 , 0.40]	-0.24 [-0.68 , 0.24]	-0.62 [-1.07 , -0.16]*	-0.12 [-0.32 , 0.09]	-0.22 [-0.65 , 0.20]	OFF<SIB
Pallidum	0.08 [-0.41 , 0.57]	0.23 [-0.23 , 0.69]	-0.66 [-1.11 , -0.21]*	-0.14 [-0.34 , 0.07]	-0.09 [-0.52 , 0.33]	OFF<MZ; OFF<DZ; OFF<SIB
Hippocampus	0.03 [-0.44 , 0.50]	0.04 [-0.40 , 0.47]	-0.54 [-0.98 , -0.09]*	-0.09 [-0.30 , 0.12]	-0.45 [-0.89 , -0.02]*	
Amygdala	-0.07 [-0.53 , 0.40]	-0.12 [-0.54 , 0.30]	-0.57 [-1.02 , -0.13]*	-0.22 [-0.42 , -0.01]*	0.07 [-0.36 , 0.50]	OFF<PAR
Accumbens	-0.23 [-0.70 , 0.23]	0.07 [-0.35 , 0.49]	-0.66 [-1.11 , -0.21]*	-0.14 [-0.34 , 0.07]	-0.36 [-0.79 , 0.07]	OFF<DZ; OFF<SIB

Table S5. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with controls, corrected for IQ. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

Global measures	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI	Significant difference between groups
ICV	0.21 [-0.31 , 0.72]	-0.17 [-0.61 , 0.28]	-0.26 [-0.70 , 0.18]	-0.02 [-0.23 , 0.19]	-0.32 [-0.75 , 0.11]	
Total brain	0.10 [-0.42 , 0.61]	-0.46 [-0.90 , -0.01]*	-0.25 [-0.69 , 0.19]	-0.03 [-0.24 , 0.18]	-0.55 [-0.98 , -0.11]*	PAR<SIB
Cortical GM	-0.01 [-0.53 , 0.50]	-0.41 [-0.85 , 0.04]	-0.26 [-0.70 , 0.18]	0.03 [-0.18 , 0.24]	-0.47 [-0.90 , -0.03]*	PAR<SIB
Cerebral WM	0.16 [-0.36 , 0.67]	-0.39 [-0.83 , 0.06]	-0.25 [-0.69 , 0.19]	-0.03 [-0.24 , 0.18]	-0.45 [-0.88 , -0.02]*	
Cerebellum GM	-0.00 [-0.52 , 0.51]	-0.30 [-0.75 , 0.14]	-0.03 [-0.46 , 0.41]	-0.12 [-0.33 , 0.08]	-0.36 [-0.79 , 0.07]	
Cerebellum WM	0.11 [-0.40 , 0.62]	-0.32 [-0.77 , 0.12]	-0.15 [-0.59 , 0.29]	-0.17 [-0.38 , 0.04]	-0.50 [-0.93 , -0.07]*	
Lateral ventricles	0.56 [0.05 , 1.08]*	0.09 [-0.36 , 0.53]	0.22 [-0.22 , 0.65]	-0.06 [-0.27 , 0.14]	-0.03 [-0.45 , 0.40]	MZ>SIB
Third ventricle	0.45 [-0.07 , 0.97]	0.03 [-0.42 , 0.47]	0.36 [-0.09 , 0.80]	-0.26 [-0.46 , -0.05]*	-0.12 [-0.54 , 0.31]	MZ>SIB; OFF>SIB
Surface area	0.33 [-0.18 , 0.85]	-0.38 [-0.83 , 0.07]	-0.03 [-0.47 , 0.41]	-0.08 [-0.28 , 0.13]	-0.30 [-0.72 , 0.13]	MZ>DZ
Cortical thickness	-0.69 [-1.21 , -0.17]*	-0.17 [-0.62 , 0.27]	-0.41 [-0.85 , 0.03]	0.10 [-0.10 , 0.31]	-0.23 [-0.66 , 0.20]	MZ<SIB; OFF<SIB
Subcortical volumes						
Thalamus	0.27 [-0.27 , 0.80]	-0.36 [-0.81 , 0.09]	-0.07 [-0.51 , 0.37]	0.06 [-0.15 , 0.27]	-0.38 [-0.81 , 0.05]	
Caudate	0.16 [-0.36 , 0.67]	-0.27 [-0.73 , 0.19]	0.00 [-0.44 , 0.44]	-0.10 [-0.30 , 0.11]	-0.13 [-0.56 , 0.30]	
Putamen	0.03 [-0.50 , 0.57]	-0.21 [-0.71 , 0.28]	-0.40 [-0.85 , 0.04]	-0.02 [-0.23 , 0.18]	-0.22 [-0.65 , 0.21]	
Pallidum	0.39 [-0.15 , 0.92]	0.32 [-0.18 , 0.81]	-0.52 [-0.97 , -0.08]*	-0.07 [-0.28 , 0.14]	-0.10 [-0.53 , 0.33]	OFF<MZ; OFF<DZ
Hippocampus	0.40 [-0.13 , 0.93]	-0.03 [-0.49 , 0.44]	-0.28 [-0.72 , 0.16]	0.01 [-0.20 , 0.22]	-0.46 [-0.89 , -0.03]*	PAR<MZ
Amygdala	0.15 [-0.37 , 0.66]	-0.16 [-0.61 , 0.29]	-0.29 [-0.73 , 0.15]	-0.09 [-0.30 , 0.12]	0.07 [-0.36 , 0.50]	
Accumbens	-0.17 [-0.68 , 0.35]	-0.01 [-0.46 , 0.43]	-0.48 [-0.92 , -0.03]*	-0.06 [-0.27 , 0.14]	-0.36 [-0.79 , 0.07]	

Table S6. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with controls, corrected for intracranial volume (ICV). *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

Global measures	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
ICV	-	-	-	-	-
Total brain	-0.26 [-0.72 , 0.21]	-0.34 [-0.76 , 0.08]	-0.45 [-0.90 , -0.01]*	-0.13 [-0.34 , 0.08]	-0.56 [-1.00 , -0.13]*
Cortical GM	-0.28 [-0.74 , 0.19]	-0.26 [-0.68 , 0.16]	-0.45 [-0.89 , -0.00]*	-0.03 [-0.24 , 0.18]	-0.34 [-0.76 , 0.09]
Cerebral WM	-0.17 [-0.63 , 0.29]	-0.28 [-0.70 , 0.14]	-0.33 [-0.77 , 0.11]	-0.09 [-0.30 , 0.11]	-0.32 [-0.75 , 0.11]
Cerebellum GM	-0.07 [-0.53 , 0.39]	-0.19 [-0.61 , 0.23]	-0.12 [-0.56 , 0.32]	-0.16 [-0.36 , 0.05]	-0.26 [-0.68 , 0.17]
Cerebellum WM	-0.10 [-0.56 , 0.36]	-0.15 [-0.57 , 0.27]	-0.09 [-0.53 , 0.35]	-0.23 [-0.43 , -0.02]*	-0.42 [-0.85 , 0.01]
Lateral ventricles	0.46 [-0.00 , 0.93]	0.34 [-0.08 , 0.76]	0.27 [-0.17 , 0.71]	-0.01 [-0.21 , 0.20]	0.09 [-0.33 , 0.52]
Third ventricle	0.36 [-0.11 , 0.82]	0.12 [-0.30 , 0.54]	0.39 [-0.05 , 0.83]	-0.21 [-0.41 , -0.00]*	-0.05 [-0.48 , 0.38]
Surface area	0.11 [-0.35 , 0.57]	-0.14 [-0.56 , 0.28]	-0.03 [-0.46 , 0.41]	-0.21 [-0.41 , -0.00]*	-0.08 [-0.50 , 0.35]
Cortical thickness	-0.67 [-1.14 , -0.21]*	-0.21 [-0.63 , 0.21]	-0.61 [-1.06 , -0.17]*	0.13 [-0.08 , 0.33]	-0.26 [-0.68 , 0.17]
Subcortical volumes					
Thalamus	-0.09 [-0.57 , 0.40]	-0.32 [-0.74 , 0.10]	-0.05 [-0.49 , 0.39]	0.05 [-0.15 , 0.26]	-0.21 [-0.64 , 0.22]
Caudate	0.07 [-0.39 , 0.53]	-0.01 [-0.44 , 0.42]	-0.09 [-0.53 , 0.35]	-0.06 [-0.27 , 0.14]	0.05 [-0.38 , 0.47]
Putamen	-0.06 [-0.55 , 0.43]	-0.28 [-0.75 , 0.18]	-0.43 [-0.88 , 0.02]	-0.02 [-0.22 , 0.19]	-0.12 [-0.55 , 0.30]
Pallidum	0.10 [-0.39 , 0.59]	0.18 [-0.28 , 0.64]	-0.46 [-0.91 , -0.02]*	-0.05 [-0.25 , 0.16]	0.05 [-0.38 , 0.47]
Hippocampus	0.06 [-0.41 , 0.54]	0.05 [-0.38 , 0.48]	-0.33 [-0.77 , 0.11]	0.02 [-0.18 , 0.23]	-0.31 [-0.74 , 0.12]
Amygdala	-0.03 [-0.49 , 0.43]	-0.11 [-0.53 , 0.38]	-0.39 [-0.83 , 0.05]	-0.13 [-0.33 , 0.08]	0.35 [-0.08 , 0.78]
Accumbens	-0.22 [-0.68 , 0.25]	0.08 [-0.34 , 0.50]	-0.55 [-1.00 , -0.11]*	-0.05 [-0.26 , 0.15]	-0.24 [-0.66 , 0.19]

Table S7. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with controls, corrected for intracranial volume (ICV) and IQ. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

Global measures	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
ICV	-	-	-	-	-
Total brain	-0.07 [-0.58 , 0.44]	-0.47 [-0.92 , -0.02]*	-0.09 [-0.53 , 0.34]	-0.05 [-0.26 , 0.15]	-0.58 [-1.01 , -0.14]*
Cortical GM	-0.17 [-0.68 , 0.35]	-0.40 [-0.85 , 0.05]	-0.11 [-0.55 , 0.33]	0.04 [-0.17 , 0.24]	-0.36 [-0.79 , 0.07]
Cerebral WM	0.01 [-0.50 , 0.52]	-0.35 [-0.80 , 0.09]	-0.10 [-0.54 , 0.34]	-0.05 [-0.26 , 0.16]	-0.33 [-0.76 , 0.10]
Cerebellum GM	-0.09 [-0.60 , 0.42]	-0.25 [-0.70 , 0.19]	0.08 [-0.36 , 0.52]	-0.12 [-0.33 , 0.09]	-0.24 [-0.67 , 0.19]
Cerebellum WM	0.04 [-0.48 , 0.55]	-0.28 [-0.72 , 0.17]	-0.04 [-0.48 , 0.40]	-0.18 [-0.39 , 0.03]	-0.41 [-0.84 , 0.02]
Lateral ventricles	0.53 [0.01 , 1.04]*	0.16 [-0.29 , 0.60]	0.27 [-0.17 , 0.71]	-0.06 [-0.26 , 0.15]	0.10 [-0.33 , 0.52]
Third ventricle	0.40 [-0.11 , 0.92]	0.08 [-0.37 , 0.52]	0.46 [0.01 , 0.90]*	-0.25 [-0.46 , -0.05]*	-0.05 [-0.48 , 0.37]
Surface area	0.24 [-0.28 , 0.75]	-0.34 [-0.78 , 0.11]	0.26 [-0.18 , 0.70]	-0.11 [-0.31 , 0.10]	-0.11 [-0.53 , 0.32]
Cortical thickness	-0.69 [-1.21 , -0.17]*	-0.17 [-0.62 , 0.27]	-0.41 [-0.85 , 0.04]	0.10 [-0.10 , 0.31]	-0.25 [-0.67 , 0.18]
Subcortical volumes					
Thalamus	0.16 [-0.37 , 0.69]	-0.29 [-0.74 , 0.16]	0.13 [-0.31 , 0.57]	0.06 [-0.14 , 0.27]	-0.23 [-0.65 , 0.20]
Caudate	0.13 [-0.38 , 0.65]	-0.25 [-0.70 , 0.21]	0.14 [-0.29 , 0.58]	-0.10 [-0.30 , 0.11]	0.02 [-0.40 , 0.45]
Putamen	-0.02 [-0.56 , 0.52]	-0.24 [-0.73 , 0.26]	-0.32 [-0.76 , 0.12]	-0.01 [-0.22 , 0.19]	-0.12 [-0.55 , 0.30]
Pallidum	0.26 [-0.27 , 0.80]	0.29 [-0.21 , 0.78]	-0.49 [-0.94 , -0.05]*	-0.07 [-0.27 , 0.14]	0.04 [-0.39 , 0.46]
Hippocampus	0.33 [-0.20 , 0.86]	0.00 [-0.46 , 0.47]	-0.19 [-0.63 , 0.25]	0.01 [-0.20 , 0.22]	-0.32 [-0.75 , 0.11]
Amygdala	0.10 [-0.42 , 0.61]	-0.13 [-0.58 , 0.31]	-0.21 [-0.65 , 0.23]	-0.11 [-0.32 , 0.09]	0.34 [-0.09 , 0.77]
Accumbens	-0.21 [-0.72 , 0.31]	0.02 [-0.43 , 0.46]	-0.45 [-0.89 , -0.01]*	-0.07 [-0.28 , 0.14]	-0.24 [-0.67 , 0.18]

Table S8. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, combined relatives compared with controls corrected for having a diagnosis other than a psychotic disorder in the relatives (left) and *healthy* relatives only compared with *healthy* controls (right), both with and without correction for ICV. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

	With correction for diagnoses	*Healthy relatives only*	*With correction for diagnoses & ICV*	*Healthy relatives only with correction for ICV*
	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI
Global measures				
ICV	-0.23 [-0.38 , -0.08]**	-0.29 [-0.64 , 0.06]	-	-
Total brain	-0.31 [-0.46 , -0.16]**	-0.41 [-0.70 , -0.11]**	-0.25 [-0.43 , -0.07]*	-0.27 [-0.47 , -0.07]*
Cortical GM	-0.29 [-0.46 , -0.13]**	-0.39 [-0.68 , -0.09]**	-0.21 [-0.39 , -0.02]*	-0.23 [-0.46 , 0.01]
Cerebral WM	-0.26 [-0.41 , -0.11]**	-0.31 [-0.48 , -0.14]**	-0.14 [-0.29 , 0.01]	-0.17 [-0.34 , 0.00]
Cerebellum GM	-0.24 [-0.39 , -0.09]**	-0.26 [-0.51 , 0.00]	-0.15 [-0.29 , 0.00]	-0.15 [-0.32 , 0.02]
Cerebellum WM	-0.26 [-0.41 , -0.11]**	-0.22 [-0.47 , 0.03]	-0.18 [-0.33 , -0.03]*	-0.14 [-0.33 , 0.06]
Lateral ventricles	0.08 [-0.14 , 0.30]	0.09 [-0.31 , 0.50]	0.17 [-0.04 , 0.38]	0.20 [-0.08 , 0.49]
Third ventricle	0.01 [-0.25 , 0.28]	0.05 [-0.29 , 0.39]	0.08 [-0.19 , 0.35]	0.11 [-0.19 , 0.41]
Surface area	-0.24 [-0.39 , -0.09]**	-0.31 [-0.48 , -0.13]**	-0.10 [-0.25 , 0.04]	-0.16 [-0.33 , 0.01]
Cortical thickness	-0.31 [-0.62 , -0.01]*	-0.26 [-0.61 , 0.09]	-0.30 [-0.61 , 0.01]	-0.23 [-0.58 , 0.11]
Subcortical volumes				
Thalamus	-0.21 [-0.39 , -0.03]**	-0.24 [-0.48 , -0.00]*	-0.09 [-0.27 , 0.09]	-0.05 [-0.28 , 0.17]
Caudate	-0.17 [-0.32 , -0.02]**	-0.23 [-0.40 , -0.05]**	-0.07 [-0.22 , 0.08]	-0.11 [-0.28 , 0.06]
Putamen	-0.19 [-0.34 , -0.04]**	-0.24 [-0.42 , -0.06]**	-0.12 [-0.28 , 0.04]	-0.14 [-0.32 , 0.03]
Pallidum	-0.12 [-0.42 , 0.18]	-0.23 [-0.62 , 0.15]	-0.06 [-0.28 , 0.16]	-0.13 [-0.31 , 0.04]
Hippocampus	-0.13 [-0.28 , 0.03]	-0.25 [-0.45 , -0.04]**	-0.01 [-0.17 , 0.14]	-0.10 [-0.28 , 0.07]
Amygdala	-0.17 [-0.32 , -0.02]**	-0.21 [-0.39 , -0.04]**	-0.05 [-0.23 , 0.14]	-0.08 [-0.31 , 0.15]
Accumbens	-0.25 [-0.45 , -0.05]**	-0.32 [-0.54 , -0.10]**	-0.19 [-0.40 , 0.01]	-0.21 [-0.40 , -0.03]*

Table S9a. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with controls, corrected for having a diagnosis other than a psychotic disorder in the relatives. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

Global measures	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
ICV	-0.03 [-0.49 , 0.43]	-0.07 [-0.48 , 0.35]	-0.42 [-0.86 , 0.02]	-0.25 [-0.46 , -0.04]*	-0.33 [-0.75 , 0.10]
Total brain	-0.12 [-0.58 , 0.35]	-0.26 [-0.68 , 0.16]	-0.63 [-1.08 , -0.18]*	-0.26 [-0.46 , -0.05]*	-0.51 [-0.94 , -0.08]*
Cortical GM	-0.19 [-0.65 , 0.28]	-0.21 [-0.63 , 0.21]	-0.68 [-1.13 , -0.23]*	-0.20 [-0.40 , 0.01]	-0.45 [-0.88 , -0.02]*
Cerebral WM	-0.08 [-0.54 , 0.38]	-0.25 [-0.66 , 0.17]	-0.54 [-0.99 , -0.10]*	-0.22 [-0.42 , -0.01]*	-0.38 [-0.81 , 0.05]
Cerebellum GM	0.11 [-0.36 , 0.57]	-0.17 [-0.59 , 0.25]	-0.30 [-0.74 , 0.14]	-0.26 [-0.46 , -0.05]*	-0.50 [-0.93 , -0.07]*
Cerebellum WM	0.01 [-0.45 , 0.47]	-0.14 [-0.56 , 0.28]	-0.15 [-0.59 , 0.29]	-0.30 [-0.50 , -0.09]*	-0.55 [-0.98 , -0.11]*
Lateral ventricles	0.45 [-0.02 , 0.91]	0.32 [-0.10 , 0.74]	-0.05 [-0.49 , 0.39]	-0.11 [-0.32 , 0.09]	0.02 [-0.41 , 0.44]
Third ventricle	0.38 [-0.08 , 0.84]	0.11 [-0.31 , 0.53]	0.20 [-0.24 , 0.64]	-0.30 [-0.51 , -0.09]*	-0.10 [-0.53 , 0.32]
Surface area	0.15 [-0.31 , 0.61]	-0.14 [-0.56 , 0.27]	-0.39 [-0.83 , 0.05]	-0.31 [-0.52 , -0.10]*	-0.21 [-0.64 , 0.22]
Cortical thickness	-0.64 [-1.11 , -0.18]*	-0.21 [-0.62 , 0.21]	-0.70 [-1.15 , -0.24]*	0.08 [-0.12 , 0.29]	-0.29 [-0.72 , 0.14]
Subcortical volumes					
Thalamus	0.00 [-0.49 , 0.48]	-0.36 [-0.78 , 0.07]	-0.43 [-0.88 , 0.01]	-0.07 [-0.28 , 0.13]	-0.39 [-0.82 , 0.04]
Caudate	0.03 [-0.44 , 0.49]	-0.01 [-0.44 , 0.41]	-0.55 [-0.99 , -0.10]*	-0.19 [-0.39 , 0.02]	-0.09 [-0.52 , 0.33]
Putamen	0.00 [-0.49 , 0.50]	-0.20 [-0.66 , 0.26]	-0.62 [-1.07 , -0.16]*	-0.13 [-0.34 , 0.07]	-0.21 [-0.63 , 0.22]
Pallidum	0.16 [-0.33 , 0.65]	0.25 [-0.21 , 0.71]	-0.72 [-1.17 , -0.27]*	-0.15 [-0.36 , 0.05]	-0.10 [-0.53 , 0.32]
Hippocampus	0.06 [-0.41 , 0.53]	0.04 [-0.39 , 0.48]	-0.34 [-0.78 , 0.10]	-0.08 [-0.29 , 0.13]	-0.43 [-0.86 , -0.00]*
Amygdala	-0.01 [-0.47 , 0.45]	-0.10 [-0.52 , 0.31]	-0.47 [-0.92 , -0.03]*	-0.21 [-0.42 , -0.01]*	0.10 [-0.33 , 0.53]
Accumbens	-0.37 [-0.84 , 0.09]	0.04 [-0.38 , 0.45]	-0.62 [-1.07 , -0.17]*	-0.14 [-0.35 , 0.06]	-0.37 [-0.80 , 0.06]

Table S9b. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with controls, corrected intracranial volume (ICV) and for having a diagnosis other than a psychotic disorder in the relatives. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

Global measures	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
ICV	-	-	-	-	-
Total brain	-0.13 [-0.59 , 0.33]	-0.31 [-0.73 , 0.11]	-0.49 [-0.94 , -0.05]*	-0.11 [-0.32 , 0.09]	-0.49 [-0.92 , -0.06]*
Cortical GM	-0.19 [-0.65 , 0.27]	-0.24 [-0.66 , 0.18]	-0.52 [-0.97 , -0.08]*	-0.05 [-0.25 , 0.16]	-0.33 [-0.75 , 0.10]
Cerebral WM	-0.09 [-0.55 , 0.38]	-0.26 [-0.68 , 0.16]	-0.37 [-0.81 , 0.07]	-0.06 [-0.26 , 0.15]	-0.19 [-0.62 , 0.23]
Cerebellum GM	0.12 [-0.34 , 0.58]	-0.15 [-0.57 , 0.27]	-0.09 [-0.53 , 0.35]	-0.15 [-0.36 , 0.05]	-0.39 [-0.82 , 0.04]
Cerebellum WM	0.02 [-0.44 , 0.48]	-0.12 [-0.54 , 0.29]	0.02 [-0.42 , 0.46]	-0.21 [-0.42 , -0.01]*	-0.45 [-0.88 , -0.02]*
Lateral ventricles	0.53 [0.06 , 0.99]*	0.35 [-0.07 , 0.77]	0.10 [-0.34 , 0.54]	-0.03 [-0.24 , 0.17]	0.15 [-0.27 , 0.58]
Third ventricle	0.41 [-0.05 , 0.88]	0.13 [-0.29 , 0.55]	0.35 [-0.09 , 0.80]	-0.24 [-0.45 , -0.04]*	-0.04 [-0.46 , 0.39]
Surface area	0.20 [-0.26 , 0.66]	-0.12 [-0.54 , 0.30]	-0.09 [-0.53 , 0.35]	-0.20 [-0.40 , 0.01]	0.04 [-0.39 , 0.46]
Cortical thickness	-0.64 [-1.11 , -0.17]*	-0.21 [-0.62 , 0.21]	-0.66 [-1.11 , -0.21]*	0.11 [-0.09 , 0.32]	-0.30 [-0.73 , 0.13]
Subcortical volumes					
Thalamus	-0.03 [-0.52 , 0.45]	-0.31 [-0.73 , 0.11]	-0.2 [-0.64 , 0.24]	0.07 [-0.14 , 0.27]	-0.24 [-0.67 , 0.19]
Caudate	0.09 [-0.37 , 0.56]	0.00 [-0.43 , 0.42]	-0.39 [-0.83 , 0.06]	-0.08 [-0.28 , 0.13]	0.06 [-0.37 , 0.48]
Putamen	0.01 [-0.48 , 0.50]	-0.27 [-0.73 , 0.19]	-0.47 [-0.91 , -0.02]*	-0.03 [-0.23 , 0.18]	-0.11 [-0.53 , 0.32]
Pallidum	0.14 [-0.35 , 0.63]	0.19 [-0.26 , 0.65]	-0.57 [-1.01 , -0.12]*	-0.06 [-0.26 , 0.15]	0.03 [-0.40 , 0.45]
Hippocampus	0.06 [-0.41 , 0.54]	0.05 [-0.38 , 0.48]	-0.12 [-0.56 , 0.32]	0.05 [-0.16 , 0.25]	-0.29 [-0.72 , 0.13]
Amygdala	0.01 [-0.45 , 0.47]	-0.10 [-0.52 , 0.32]	-0.31 [-0.75 , 0.13]	-0.11 [-0.31 , 0.10]	0.39 [-0.04 , 0.82]
Accumbens	-0.37 [-0.83 , 0.10]	0.05 [-0.37 , 0.46]	-0.56 [-1.01 , -0.12]*	-0.05 [-0.25 , 0.16]	-0.26 [-0.68 , 0.17]

Table S10a. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, only *healthy* monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with *healthy* controls. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

	MZ co-twins	DZ co-twins	Offspring	Siblings	Parents
Global measures	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI
ICV	0.13 [-0.51 , 0.77]	0.03 [-0.44 , 0.49]	-1.12 [-1.76 , -0.48]**	-0.28 [-0.50 , -0.05]*	-0.32 [-0.78 , 0.14]
Total brain	-0.18 [-0.82 , 0.46]	-0.13 [-0.59 , 0.33]	-1.19 [-1.83 , -0.54]**	-0.29 [-0.51 , -0.06]*	-0.50 [-0.96 , -0.03]*
Cortical GM	-0.32 [-0.96 , 0.32]	-0.16 [-0.62 , 0.31]	-1.16 [-1.80 , -0.52]**	-0.19 [-0.42 , 0.03]	-0.44 [-0.91 , 0.02]
Cerebral WM	-0.08 [-0.72 , 0.56]	-0.15 [-0.61 , 0.32]	-1.07 [-1.71 , -0.44]**	-0.27 [-0.49 , -0.04]*	-0.37 [-0.83 , 0.09]
Cerebellum GM	0.04 [-0.60 , 0.68]	0.15 [-0.32 , 0.61]	-0.72 [-1.33 , -0.11]*	-0.27 [-0.50 , -0.05]*	-0.50 [-0.97 , -0.04]*
Cerebellum WM	0.11 [-0.53 , 0.75]	0.18 [-0.28 , 0.65]	-0.38 [-0.98 , 0.22]	-0.31 [-0.54 , -0.08]*	-0.53 [-0.99 , -0.06]*
Lateral ventricles	0.80 [0.16 , 1.44]*	0.40 [-0.06 , 0.87]	-0.62 [-1.23 , -0.01]*	-0.07 [-0.29 , 0.16]	0.02 [-0.44 , 0.48]
Third ventricle	0.88 [0.24 , 1.53]*	0.14 [-0.32 , 0.61]	-0.21 [-0.81 , 0.39]	-0.21 [-0.43 , 0.02]	-0.10 [-0.56 , 0.36]
Surface area	0.07 [-0.57 , 0.71]	-0.10 [-0.57 , 0.36]	-0.85 [-1.47 , -0.23]**	-0.36 [-0.58 , -0.13]*	-0.20 [-0.66 , 0.26]
Cortical thickness	-0.80 [-1.44 , -0.15]*	-0.09 [-0.55 , 0.38]	-0.64 [-1.25 , -0.03]*	0.15 [-0.07 , 0.38]	-0.28 [-0.74 , 0.18]
Subcortical volumes					
Thalamus	0.13 [-0.51 , 0.77]	-0.40 [-0.87 , 0.07]	-0.68 [-1.29 , -0.07]*	-0.07 [-0.29 , 0.16]	-0.40 [-0.87 , 0.06]
Caudate	-0.13 [-0.77 , 0.51]	-0.05 [-0.53 , 0.42]	-0.95 [-1.58 , -0.33]**	-0.22 [-0.44 , 0.01]	-0.09 [-0.55 , 0.37]
Putamen	-0.03 [-0.71 , 0.65]	-0.22 [-0.72 , 0.29]	-1.00 [-1.63 , -0.36]**	-0.18 [-0.40 , 0.05]	-0.20 [-0.66 , 0.26]
Pallidum	0.02 [-0.66 , 0.69]	0.17 [-0.34 , 0.68]	-1.13 [-1.77 , -0.49]**	-0.23 [-0.46 , -0.01]*	-0.10 [-0.56 , 0.36]
Hippocampus	-0.10 [-0.77 , 0.57]	-0.13 [-0.61 , 0.34]	-0.79 [-1.41 , -0.17]**	-0.14 [-0.37 , 0.09]	-0.43 [-0.89 , 0.03]
Amygdala	-0.12 [-0.75 , 0.52]	-0.16 [-0.63 , 0.30]	-0.85 [-1.47 , -0.23]**	-0.23 [-0.46 , -0.00]*	0.10 [-0.36 , 0.56]
Accumbens	-0.36 [-1.00 , 0.28]	-0.05 [-0.52 , 0.41]	-1.00 [-1.63 , -0.37]**	-0.22 [-0.45 , 0.00]	-0.37 [-0.84 , 0.09]

Table S10b. Cohen's *d* effect sizes ± 95% confidence interval (CI) in global brain measures and subcortical volumes, only *healthy* monozygotic (MZ) co-twins, dizygotic (DZ) co-twins, offspring, siblings and parents compared with *healthy* controls corrected for intracranial volume (ICV). *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

	MZ co-twins	DZ co-twins	Offspring	Siblings	Parents
Global measures	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI
ICV	-	-	-	-	-
Total brain	-0.38 [-1.02 , 0.26]	-0.23 [-0.69 , 0.24]	-0.61 [-1.22 , -0.01]*	-0.12 [-0.35 , 0.10]	-0.46 [-0.93 , 0.00]
Cortical GM	-0.47 [-1.11 , 0.17]	-0.25 [-0.71 , 0.21]	-0.57 [-1.17 , 0.04]	-0.01 [-0.23 , 0.22]	-0.32 [-0.78 , 0.14]
Cerebral WM	-0.26 [-0.90 , 0.38]	-0.22 [-0.69 , 0.24]	-0.44 [-1.05 , 0.16]	-0.10 [-0.33 , 0.12]	-0.19 [-0.65 , 0.27]
Cerebellum GM	-0.03 [-0.67 , 0.61]	0.15 [-0.31 , 0.61]	-0.26 [-0.86 , 0.34]	-0.16 [-0.38 , 0.07]	-0.40 [-0.86 , 0.07]
Cerebellum WM	0.06 [-0.58 , 0.70]	0.19 [-0.27 , 0.66]	0.02 [-0.58 , 0.61]	-0.21 [-0.43 , 0.02]	-0.44 [-0.90 , 0.02]
Lateral ventricles	0.87 [0.23 , 1.51]*	0.41 [-0.06 , 0.87]	-0.21 [-0.81 , 0.39]	0.03 [-0.20 , 0.25]	0.15 [-0.31 , 0.61]
Third ventricle	0.89 [0.24 , 1.53]*	0.14 [-0.32 , 0.60]	0.08 [-0.52 , 0.67]	-0.14 [-0.37 , 0.08]	-0.04 [-0.50 , 0.42]
Surface area	-0.06 [-0.70 , 0.58]	-0.14 [-0.61 , 0.32]	-0.05 [-0.65 , 0.55]	-0.24 [-0.47 , -0.02]*	0.03 [-0.42 , 0.49]
Cortical thickness	-0.80 [-1.44 , -0.15]*	-0.09 [-0.55 , 0.37]	-0.54 [-1.15 , 0.06]	0.19 [-0.04 , 0.41]	-0.29 [-0.75 , 0.17]
Subcortical volumes					
Thalamus	0.05 [-0.59 , 0.69]	-0.40 [-0.87 , 0.07]	0.10 [-0.50 , 0.69]	0.10 [-0.13 , 0.33]	-0.24 [-0.70 , 0.22]
Caudate	-0.11 [-0.75 , 0.53]	-0.10 [-0.58 , 0.37]	-0.47 [-1.08 , 0.13]	-0.10 [-0.33 , 0.13]	0.05 [-0.40 , 0.51]
Putamen	-0.04 [-0.72 , 0.64]	-0.33 [-0.84 , 0.18]	-0.55 [-1.16 , 0.06]	-0.07 [-0.30 , 0.16]	-0.11 [-0.56 , 0.35]
Pallidum	-0.04 [-0.71 , 0.64]	0.07 [-0.44 , 0.57]	-0.76 [-1.38 , -0.15]*	-0.14 [-0.36 , 0.09]	0.03 [-0.43 , 0.49]
Hippocampus	-0.20 [-0.87 , 0.47]	-0.17 [-0.64 , 0.31]	-0.34 [-0.94 , 0.27]	0.00 [-0.23 , 0.23]	-0.29 [-0.75 , 0.17]
Amygdala	-0.15 [-0.78 , 0.49]	-0.19 [-0.65 , 0.27]	-0.45 [-1.06 , 0.15]	-0.12 [-0.34 , 0.11]	0.40 [-0.06 , 0.86]
Accumbens	-0.38 [-1.02 , 0.26]	-0.06 [-0.53 , 0.40]	-0.82 [-1.44 , -0.20]*	-0.12 [-0.35 , 0.10]	-0.25 [-0.71 , 0.21]

Table S11a. Correlations between IQ and brain. *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

	Total	Cohort I & II	Cohort III	Cohort IV	Cohort V
Global measures	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI
ICV	0.17 [0.06 , 0.29]**	0.06 [-0.07 , 0.18]	0.29 [0.07 , 0.52]**	0.25 [0.16 , 0.34]**	0.10 [-0.12 , 0.31]
Total brain	0.26 [0.11 , 0.41]**	0.20 [0.07 , 0.32]*	0.50 [0.28 , 0.72]**	0.29 [0.20 , 0.38]**	0.06 [-0.16 , 0.27]
Cortical GM	0.27 [0.10 , 0.44]**	0.25 [0.12 , 0.37]*	0.51 [0.28 , 0.73]**	0.29 [0.21 , 0.38]**	0.01 [-0.20 , 0.23]
Cerebral WM	0.20 [0.08 , 0.32]**	0.12 [-0.00 , 0.24]	0.41 [0.18 , 0.63]**	0.24 [0.15 , 0.33]**	0.05 [-0.16 , 0.27]
Cerebellum GM	0.18 [0.07 , 0.29]**	0.06 [-0.06 , 0.19]	0.38 [0.16 , 0.60]**	0.19 [0.11 , 0.28]**	0.16 [-0.05 , 0.38]
Cerebellum WM	0.19 [0.12 , 0.25]**	0.21 [0.08 , 0.33]*	0.19 [-0.04 , 0.41]	0.19 [0.10 , 0.27]**	0.14 [-0.08 , 0.35]
Lateral ventricles	-0.03 [-0.09 , 0.04]	-0.05 [-0.18 , 0.07]	0.08 [-0.14 , 0.31]	-0.05 [-0.13 , 0.04]	0.05 [-0.17 , 0.26]
Third ventricle	-0.06 [-0.12 , 0.01]	-0.13 [-0.25 , -0.01]*	0.09 [-0.13 , 0.32]	-0.05 [-0.14 , 0.03]	0.01 [-0.21 , 0.23]
Surface area	0.20 [0.01 , 0.39]*	0.15 [0.03 , 0.28]*	0.41 [0.18 , 0.63]**	0.30 [0.21 , 0.39]**	-0.08 [-0.30 , 0.14]
Cortical thickness	0.15 [0.05 , 0.26]**	0.19 [0.07 , 0.32]*	0.34 [0.12 , 0.56]**	0.07 [-0.01 , 0.16]	0.09 [-0.13 , 0.30]
Subcortical volumes					
Thalamus	0.16 [0.06 , 0.27]**	0.12 [-0.02 , 0.25]	0.34 [0.12 , 0.57]**	0.20 [0.11 , 0.28]**	-0.02 [-0.24 , 0.20]
Caudate	0.10 [-0.06 , 0.26]	0.08 [-0.05 , 0.21]	0.36 [0.14 , 0.59]**	0.08 [-0.01 , 0.17]	-0.11 [-0.33 , 0.11]
Putamen	0.07 [-0.05 , 0.18]	-0.03 [-0.17 , 0.12]	0.31 [0.09 , 0.54]**	0.04 [-0.05 , 0.12]	0.04 [-0.18 , 0.25]
Pallidum	0.03 [-0.04 , 0.10]	0.00 [-0.15 , 0.14]	0.24 [0.02 , 0.46]*	0.02 [-0.06 , 0.11]	-0.04 [-0.25 , 0.18]
Hippocampus	0.20 [0.13 , 0.28]**	0.26 [0.13 , 0.38]**	0.33 [0.11 , 0.56]**	0.18 [0.10 , 0.27]**	0.01 [-0.20 , 0.23]
Amygdala	0.18 [0.12 , 0.25]**	0.15 [0.03 , 0.28]**	0.37 [0.14 , 0.59]**	0.20 [0.11 , 0.28]**	-0.01 [-0.23 , 0.21]
Accumbens	0.10 [0.04 , 0.17]**	0.10 [-0.02 , 0.22]	0.28 [0.05 , 0.50]**	0.09 [0.00 , 0.18]*	0.01 [-0.21 , 0.23]

Table S11b. Correlations between IQ and brain corrected for intracranial volume (ICV). *$p < 0.05$, uncorrected, **$q < 0.05$, corrected

	Total	Cohort I & II	Cohort III	Cohort IV	Cohort V
Global measures	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI	ES ± 95%CI
ICV	-	-	-	-	-
Total brain	0.19 [0.01 , 0.37]*	0.22 [0.09 , 0.34]**	0.45 [0.23 , 0.68]**	0.16 [0.08 , 0.25]**	-0.07 [-0.28 , 0.15]
Cortical GM	0.19 [-0.01 , 0.39]	0.26 [0.13 , 0.38]**	0.45 [0.22 , 0.67]**	0.16 [0.07 , 0.25]**	-0.11 [-0.32 , 0.11]
Cerebral WM	0.09 [0.03 , 0.16]**	0.11 [-0.01 , 0.24]	0.30 [0.07 , 0.52]*	0.07 [-0.01 , 0.16]	-0.05 [-0.27 , 0.17]
Cerebellum GM	0.10 [0.03 , 0.16]**	0.05 [-0.08 , 0.17]	0.26 [0.03 , 0.48]*	0.09 [0.01 , 0.18]*	0.13 [-0.09 , 0.34]
Cerebellum WM	0.12 [0.05 , 0.19]**	0.20 [0.08 , 0.33]**	0.07 [-0.15 , 0.29]	0.09 [-0.00 , 0.17]	0.11 [-0.11 , 0.33]
Lateral ventricles	-0.10 [-0.16 , -0.03]**	-0.09 [-0.21 , 0.04]	-0.04 [-0.26 , 0.18]	-0.13 [-0.21 , -0.04]**	0.02 [-0.20 , 0.23]
Third ventricle	-0.10 [-0.17 , -0.04]**	-0.15 [-0.27 , -0.02]*	0.01 [-0.21 , 0.23]	-0.11 [-0.20 , -0.03]**	-0.01 [-0.23 , 0.20]
Surface area	0.11 [-0.08 , 0.30]	0.16 [0.04 , 0.29]**	0.28 [0.06 , 0.50]*	0.17 [0.09 , 0.26]**	-0.21 [-0.42 , 0.01]
Cortical thickness	0.14 [0.03 , 0.26]**	0.19 [0.07 , 0.32]**	0.32 [0.09 , 0.54]*	0.04 [-0.04 , 0.13]	0.09 [-0.13 , 0.31]
Subcortical volumes					
Thalamus	0.08 [0.01 , 0.14]**	0.13 [0.00 , 0.27]*	0.20 [-0.02 , 0.43]	0.06 [-0.03 , 0.15]	-0.10 [-0.32 , 0.11]
Caudate	0.02 [-0.13 , 0.16]	0.06 [-0.07 , 0.19]	0.25 [0.03 , 0.48]*	-0.04 [-0.13 , 0.05]	-0.17 [-0.39 , 0.04]
Putamen	-0.03 [-0.11 , 0.06]	-0.05 [-0.20 , 0.09]	0.18 [-0.04 , 0.41]	-0.07 [-0.16 , 0.02]	0.00 [-0.22 , 0.22]
Pallidum	-0.06 [-0.13 , 0.00]	-0.05 [-0.19 , 0.09]	0.04 [-0.18 , 0.26]	-0.08 [-0.17 , 0.01]	-0.09 [-0.30 , 0.13]
Hippocampus	0.12 [-0.01 , 0.24]	0.25 [0.12 , 0.37]**	0.19 [-0.03 , 0.42]	0.06 [-0.02 , 0.15]	-0.06 [-0.28 , 0.15]
Amygdala	0.09 [0.01 , 0.17]**	0.14 [0.02 , 0.27]*	0.25 [0.03 , 0.48]*	0.07 [-0.02 , 0.16]	-0.08 [-0.30 , 0.14]
Accumbens	0.04 [-0.05 , 0.12]	0.09 [-0.04 , 0.21]	0.19 [-0.04 , 0.41]	-0.02 [-0.10 , 0.07]	-0.05 [-0.26 , 0.17]

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The association between familial risk and brain abnormalities is disease specific: an ENIGMA—Relatives study of schizophrenia and bipolar disorder

Biological Psychiatry, 2019; 86(7): 545–556

ABSTRACT

Schizophrenia and bipolar disorder share genetic liability, and some structural brain abnormalities are common to both conditions. First-degree relatives of patients with schizophrenia (FDRs-SZ) show similar brain abnormalities to patients, albeit with smaller effect sizes. Imaging findings in first-degree relatives of patients with bipolar disorder (FDRs-BD) have been inconsistent in the past, but recent studies report regionally greater volumes compared with control subjects. We performed a meta-analysis of global and subcortical brain measures of 6,008 individuals (1,228 FDRs-SZ, 852 FDRs-BD, 2246 control subjects, 1,016 patients with schizophrenia, 666 patients with bipolar disorder) from 34 schizophrenia and/or bipolar disorder family cohorts with standardized methods. Analyses were repeated with a correction for intracranial volume (ICV) and for the presence of any psychopathology in the relatives and control subjects. FDRs-BD had significantly larger ICV ($d = +0.16$, $q < .05$ corrected), whereas FDRs-SZ showed smaller thalamic volumes than control subjects ($d = –0.12$, $q < .05$ corrected). ICV explained the enlargements in the brain measures in FDRs-BD. In FDRs-SZ, after correction for ICV, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, and thalamus volumes were significantly smaller; the cortex was thinner ($d < –0.09$, $q < .05$ corrected); and third ventricle was larger ($d = +0.15$, $q < .05$ corrected). The findings were not explained by psychopathology in the relatives or control subjects. Despite shared genetic liability, FDRs-SZ and FDRs-BD show a differential pattern of structural brain abnormalities, specifically a divergent effect in ICV. This may imply that the neurodevelopmental trajectories leading to brain anomalies in schizophrenia or bipolar disorder are distinct.

INTRODUCTION

Schizophrenia and bipolar disorder are highly heritable disorders with partially overlapping symptoms and a genetic correlation (r_g) of 0.60–0.68 (Anttila et al., 2018; Lee et al., 2013; Lichtenstein et al., 2009). Both disorders are characterized by structural brain abnormalities, with smaller total brain and hippocampal volumes, on average, and larger ventricular volumes. These are among the most consistent and robust structural findings, albeit with smaller effect sizes in patients with bipolar disorder (Arnone et al., 2009; Ellison-Wright & Bullmore, 2010; Haijma et al., 2013; Hibar et al., 2016, 2017; McDonald et al., 2004; Okada et al., 2016; Van Erp et al., 2015, 2018). On one hand, the shared genetic liability between schizophrenia and bipolar disorder (Anttila et al., 2018; Lee et al., 2013; Lichtenstein et al., 2009) is partly reflected in the brain by overlapping findings of smaller white matter volumes and common areas of thinner cortex, suggesting that the disorders share genetic (possibly neurodevelopmental) roots (Hulshoff Pol et al., 2012). On the other hand, disease-specific brain abnormalities were also reported in the same twin study; genetic liability for schizophrenia was associated with thicker right parietal cortex, whereas genetic liability for bipolar disorder was associated with larger intracranial volume (ICV) (Hulshoff Pol et al., 2012).

Family members of patients can represent individuals at familial risk for the disorder who do not themselves have confounds, such as medication or illness duration, and can therefore provide unique insight into the effect of familial risk for the disorder on the brain. Multiple imaging studies have investigated individuals at high familial risk for schizophrenia and/or bipolar disorder, but results of these often small studies have been variable. First-degree relatives of patients with schizophrenia (FDRs-SZ) tend to show smaller brain volumes and larger ventricle volumes compared with control subjects (Boos et al., 2007; De Zwarte et al., 2019a). In contrast, first-degree relatives of patients with bipolar disorder (FDRs-BD) show regionally larger volumes (Bauer et al., 2014; Drobinin et al., 2018; Frangou, 2011; Hajek et al., 2013; Kempton et al., 2009; Ladouceur et al., 2008; Lin et al., 2015; Macoveanu et al., 2018; Nery et al., 2013; Roberts et al., 2016; Sarıçiçek et al., 2015). Many of these schizophrenia and bipolar disorder family studies grouped all FDRs together regardless of kinship. It remains unclear whether structural brain abnormalities in high-risk individuals are consistent across FDRs, or whether they vary depending on the generational relationship with the proband. In addition, a few studies compared brain structure between FDRs-BD and FDRs-SZ directly, usually in cohorts of modest sample sizes (Collin et al., 2017; Hulshoff Pol et al., 2012; McDonald et al., 2004, 2006; McIntosh et al., 2004; Sugranyes et al., 2015). These studies showed brain abnormalities both specific and overlapping for FDRs-SZ and FDRs-BD; if anything, findings were more pronounced in FDRs-SZ than FDRs-BD.

Large-scale multicenter studies offer increased power and generalizability to evaluate the pattern and extent of brain variation in FDRs-BD and FDRs-SZ. Through the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA)—Relatives Working Group, we have performed meta-analyses of magnetic resonance imaging data sets consisting of FDRs-

SZ and/or FDRs-BD, probands, and matched control participants on harmonized global and subcortical brain measures. For each disorder, relatives were analyzed as a group as well as per relative type, i.e., monozygotic co-twins, dizygotic co-twins, offspring, siblings, and parents. To investigate potential confounders, analyses were performed both with and without correction for ICV and with and without a correction for having a psychiatric diagnosis in the relatives and control subjects. The latter correction was performed by 1) adding a single dummy variable coding for the presence of any psychiatric diagnosis and 2) by comparing only the healthy relatives with the healthy control subjects. We hypothesized that FDRs-SZ (as a group) would exhibit a pattern of brain volume abnormalities similar to patterns observed in patients, but with smaller effect sizes. Based on dissimilarities in the literature between FDRs-SZ and FDRs-BD, we expected divergent effect sizes. Furthermore, we explored the pattern and extent of brain volume abnormalities per relative type.

METHODS AND MATERIALS

Study Samples

This study included 6,008 participants from 34 family cohorts. In total, 1,228 FDRs-SZ (49 monozygotic co-twins, 62 dizygotic co-twins, 171 offspring, 842 siblings, 104 parents), 852 FDRs-BD (41 monozygotic co-twins, 48 dizygotic co-twins, 443 offspring, 302 siblings, 18 parents), 2,246 control subjects, 1,016 patients with schizophrenia, and 666 patients with bipolar disorder were included (Tables 1 and 2). All cohorts included their own control participants. Control subjects did not have a family history of schizophrenia or bipolar disorder. FDRs-SZ or FDRs-BD are defined by having a first-degree family member with schizophrenia or bipolar disorder, respectively, and not having experienced (hypo)mania and/or psychosis themselves. Several cohorts allowed FDRs-SZ, FDRs-BD, or control subjects to have psychiatric diagnoses other than schizophrenia or bipolar disorder (Tables 1 and 2). Demographic characteristics for each cohort and their inclusion criteria are summarized in Tables 1 and 2 and Supplementary Table S1. All study centers obtained approval from their respective medical ethics committee for research following the Declaration of Helsinki. Informed consent was obtained from all participants (and/or parent guardians in the case of minors).

Image Acquisition and Processing

Structural T1-weighted brain magnetic resonance imaging scans were acquired at each research center (see Supplementary Table S2 for acquisition parameters of each cohort). Cortical and subcortical reconstruction and volumetric segmentations were performed with the FreeSurfer pipeline (see Supplementary Table S2 for FreeSurfer version and operating system used in each cohort) (http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/) (Fischl, 2012). The resulting segmentations were quality checked according to the ENIGMA quality control protocol for subcortical volumes (http://enigma.ini.usc.edu/protocols/imaging-protocols/). Global brain measures (i.e., ICV [estimated Total Intracranial Volume from

FreeSurfer], total brain [including cerebellum, excluding brainstem], cortical gray matter, cerebral white matter, cerebellar gray and white matter, third and lateral ventricle volume, surface area, and mean cortical thickness) and subcortical volumes (i.e., thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and accumbens) were extracted from individual images (Fischl & Dale, 2000; Fischl et al., 1999).

Statistical Meta-analyses

All statistical analyses were performed using R (http://www.rproject.org). Linear mixed model analyses were performed within each cohort for bipolar disorder and schizophrenia separately, comparing relatives (per relative type) with control subjects and, if present, patients with control subjects, while taking family relatedness into account (http://CRAN.R-project.org/package=nlme) (Pinheiro & Bates, 2000). Given known age and sex effects on brain measures, we included centered age, age squared, and sex as covariates. Brain measures were corrected for lithium use at time of scan (yes/no) in patients with bipolar disorder only. Analysis of multiscanner studies included binary dummy covariates for n − 1 scanners. Cohen's d effect sizes and 95% confidence intervals were calculated within each cohort separately and pooled per disorder for each relative type, for all relatives, and for patients as a group, using an inverse variance-weighted random-effects meta-analysis. All random-effects models were fitted using the restricted maximum likelihood method. False discovery rate ($q < .05$) thresholding across all phenotypes was used to control for multiple comparisons for each pairwise analysis between relatives, patients, and control subjects or between the different relative types (Hochberg, 1995). Analyses were performed locally by the research center that contributed the cohort, using codes created within the ENIGMA-Relatives Working Group (scripts available on request). The focus of this study is on first-degree relatives, but patient effects were also computed to show that the effects in patients are in line with earlier work (Arnone et al., 2009; Ellison-Wright & Bullmore, 2010; Haijma et al., 2013; Hibar et al., 2016, 2017; McDonald et al., 2004; Okada et al., 2016; Van Erp et al., 2015, 2018). Effect sizes were statistically compared between FDRs-BD and FDRs-SZ, FDRs-BD and patients with bipolar disorder, and FDRs-SZ and patients with schizophrenia, and between the different relative types within one disorder (Supplementary Methods). The latter analysis was performed only when more than one cohort was included per relative type.

The regional specificity of the findings was examined by repeating the analyses of the global brain measures and subcortical volumes with ICV added as a covariate. In addition, we repeated the analyses to investigate the effect of psychopathology in the relatives and control subjects using two different approaches. First, we added a single dummy variable for relatives and control subjects with a DSM "No diagnosis" or ICD-9 code V71.09 (other diagnosis = 1, V71.09 = 0). Second, we compared healthy relatives with healthy control subjects. Finally, effects of age were examined using meta-regressions.

Table 1. Sample Demographics Bipolar Disorder Family Cohorts

	Controls				Cases			Relatives																			
								Total	MZ Co-twins				DZ Co-twins				Offspring				Siblings				Parents			
Sample	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Total *N*	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)
BPO_FLB	7	3/4	12.9	0/7	9	5/4	13.3	22	—				—				22	10/12	10.0	0/22	—				—			
Cardiff	79	28/51	39.8	0/79	120	42/78	41.9	33	—				—				—				33	13/20	45.9	2/31	—			
CliNG-BD[a]	19	6/13	30.9	0/19	—			19	—				—				11	4/7	23.4	0/11	8	2/6	43.8	0/8	—			
DEU	29	11/18	33.1	0/29	27	10/17	36.3	23	—				—				6	2/4	21.7	0/6	17	9/8	34.8	0/17	—			
EGEU	33	13/20	33.6	0/33	27	16/11	36.7	27	—				—				—				27	10/17	34.5	0/27	—			
ENBD_UT	36	13/23	34.8	0/36	72	23/49	36.9	52	—				—				—				52	10/42	44.3	17/35	—			
HHR	42	17/25	21.9	0/42	8	2/6	23.3	52	—				—				52	18/34	19.5	14/38	—				—			
IDIBAPS[a]	53	21/32	12.3	12/41	—			61	—				—				61	31/30	12.3	27/34	—				—			
IoP-BD	39	9/30	35.4	9/30	34	15/19	40.6	17	11	2/9	43.5	6/5	6	2/4	42.4	0/6	—				—				—			
MFS-BD[a]	54	25/29	40.2	0/54	38	15/23	41.0	41	—				—				—				23	11/12	42.9	0/23	18	6/12	57.6	0/18
MooDS-BD[a]	63	25/38	30.3	0/63	—			63	—				—				53	18/35	29.2	0/53	10	7/3	36.6	0/10	—			
MSSM	52	25/27	35.2	0/52	41	21/20	44.3	50	—				—				27	14/13	24.9	15/12	23	12/11	44.2	8/15	—			
Olin	68	25/43	32.2	7/61	108	34/74	34.5	78	—				—				—				78	30/48	32.0	21/57	—			
PHHR	18	7/11	23.0	0/18	8	3/5	24.0	26	—				—				26	10/16	19.9	6/20	—				—			
STAR-BD[a]	114	55/59	48.8	42/72	53	19/34	49.2	38	16	6/10	49.2	3/13	22	10/12	50.8	6/16	—				—				—			
SydneyBipolarGroup	117	54/63	22.2	30/87	59	17/42	25.1	150	—				—				119	53/66	19.2	58/61	31	12/19	22.6	21/10	—			
UMCU-BD Twins[a]	129	55/74	39.2	4/125	62	19/43	40.3	34	14	4/10	38.2	6/8	20	8/12	44.3	4/16	—				—				—			
UMCU-DBSOS[a]	40	21/19	12.7	7/33	—			66	—				—				66	37/29	14.7	31/35	—				—			

DZ, dizygotic; F, female; M, male; MZ, monozygotic; N, no; Y, yes.

BPO_FLB, Bipolar Offspring - Fronto-Limbic; Cardiff, Cardiff University; CliNG-BD, Clinical Neuroscience Goettingen- Bipolar Disorder; DEU, Dokuz Eylul University; EGEU, Ege University; ENBD_UT, Endophenotypes of Bipolar Disorder - University of Texas; HHR, Halifax High Risk Study; IDIBAPS, August Pi i Sunyer Biomedical Research Institute; IoP-BD, Institute of Psychiatry - Bipolar Disorder Twin Study; MFS-BD, Maudsley Family Study - Bipolar Disorder; MooDS-BD, Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia - Bipolar Disorder; MSSM, Mount Sinai School of Medicine; Olin, Olin Neuropsychiatry Research Center; PHHR, Prague High Risk Study; STAR-BD, Schizophrenia and Bipolar Twin Study in Sweden - Bipolar Disorder; SydneyBipolarGroup, The Sydney Bipolar Kids and Sibs Study; UMCU-BD Twins, University Medical Center Utrecht - Bipolar Disorder Twin Study; UMCU-DBSOS, University Medical Center Utrecht - Dutch Bipolar and Schizophrenia Offspring Study.

[a]Overlapping control subjects with schizophrenia sample from the same site, i.e., with CliNG-SZ ($n = 10$), IDIBAPS ($n = 53$), MFS-SZ ($n = 54$), MooDS-SZ ($n = 36$), STAR-SZ ($n = 100$), UMCU-UTWINS ($n = 27$), UMCU-DBSOS ($n = 40$).

Table 2. Sample Demographics Schizophrenia Family Cohorts

	Controls				Cases			Relatives																
								Total	MZ Co-twins				DZ Co-twins				Offspring				Siblings				Parents			
Sample	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Total *N*	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)	*n*	M/F	Age	Other Diagnoses (Y/N)
C_SFS	23	11/12	40.2	7/16	25	13/12	40.8	23	–				–				–				13	7/6	32.5	4/9	10	1/9	54.6	3/7
CliNG-SZ[a]	20	11/9	35.7	0/20	–			20	–				–				6	3/3	26.7	0/6	7	5/2	28.4	0/7	7	3/4	51.9	0/7
EHRS	89	44/45	21.0	0/89	31	19/12	21.8	90	–				–				57	26/31	20.9	0/57	33	18/15	21.8	0/33	–			
HUBIN	102	69/33	41.9	29/73	103	77/26	41.2	33	–				–				–				33	23/10	39.4	8/25	–			
IDIBAPS[a]	53	21/32	12.3	12/41	–			37	–				–				37	22/15	11.0	18/19	–				–			
IoP-SZ	67	35/32	40.9	7/60	54	39/15	34.7	18	14	7/7	31.0	6/8	4	1/3	40.0	1/3	–				–				–			
LIBD	364	163/201	32.4	3/361	215	164/51	35.3	242	–				–				–				242	100/142	36.2	83/159	–			
Maastricht-GROUP	87	33/54	30.8	14/73	87	59/28	28.2	95	–				–				–				95	49/46	29.5	19/76	–			
MFS-SZ[a]	54	25/29	40.2	0/54	42	31/11	36.4	56	–				–				–				20	10/10	36.4	0/20	36	11/25	56.6	0/36
MooDS-SZ[a]	65	26/39	30.6	0/65	–			63	–				–				31	10/21	26.5	0/31	25	12/13	30.2	0/25	7	2/5	49.7	0/7
NU	92	51/41	31.9	7/85	108	74/34	34.2	83	–				–				–				83	29/54	21.1	45/38	–			
STAR-SZ[a]	104	49/55	48.9	22/82	49	28/21	49.5	48	15	9/6	41.9	0/15	33	17/16	52.3	0/33	–				–				–			
UMCG-GROUP	37	16/21	34.0	0/37	–			45	–				–				–				45	22/23	30.9	0/45	–			
UMCU-DBSOS[a]	40	21/19	12.7	7/33	–			40	–				–				40	12/28	13.7	24/16	–				–			
UMCU-GROUP	167	83/84	27.7	13/154	162	130/32	27.0	201	–				–				–				201	95/106	27.7	52/149	–			
UMCU-Parents	41	14/27	52.8	0/41	–			44	–				–				–				–				44	13/31	52.9	11/33
UMCU-UTWINS[a]	184	84/100	31.8	17/167	56	33/23	35.6	45	20	12/8	36.0	11/9	25	17/8	37.8	5/20	–				–				–			
UNIBA	78	52/26	31.4	0/78	84	58/26	33.3	45	–				–				–				45	23/22	33.4	4/41	–			

DZ, dizygotic; F, female; M, male; MZ, monozygotic; N, no; Y, yes.

C_SFS, Calgary Schizophrenia Family Study; CliNG-SZ, Clinical Neuroscience Goettingen - Schizophrenia; EHRS, Edinburgh High Risk Study; HUBIN, Human Brain Informatics; IDIBAPS, August Pi i Sunyer Biomedical Research Institute; IoP-SZ, Institute of Psychiatry - Schizophrenia Twin Study; LIBD, Lieber Institute for Brain Development; Maastricht-GROUP, Maastricht - Genetic Risk and Outcome of Psychosis; MFS-SZ, Maudsley Family Study - Schizophrenia; MooDS-SZ, Systematic Investigation of the Molecular Causes of Major Mood Disorders and Schizophrenia - Schizophrenia; NU, Northwestern University; STAR-SZ, Schizophrenia and Bipolar Twin Study in Sweden - Schizophrenia; UMCG-GROUP, University Medical Center Groningen - Genetic Risk and Outcome of Psychosis; UMCU-DBSOS, University Medical Center Utrecht - Dutch Bipolar and Schizophrenia Offspring Study; UMCU-GROUP, University Medical Center Utrecht - Genetic Risk and Outcome of Psychosis; UMCU-Parents, University Medical Center Utrecht - Parents Study; UMCU-UTWINS, University Medical Center Utrecht - Utrecht Twin Schizophrenia Studies; UNIBA, University of Bari "Aldo Moro."

[a]Overlapping control subjects with bipolar sample from the same site, i.e., with CliNG-BD (n = 10), IDIBAPS (n = 53), MFS-BD (n = 54), MooDS-BD (n = 36), STAR-BD (n = 100), UMCU-BD twins (n = 27), UMCU-DBSOS (n = 40).

RESULTS

Patients

Effects in patients with schizophrenia and bipolar disorder were not the main focus of this study. In short, a thinner cortex and smaller thalamus volume were found in patients with bipolar disorder ($d < –0.33$, $q < .05$ corrected); in patients with schizophrenia, smaller volumes of total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, thalamus, hippocampus, amygdala, and accumbens, thinner cortex ($d < –0.18$, $q < .05$ corrected), and larger volumes of the lateral ventricles, third ventricle, caudate, pallidum, and putamen ($d > +0.16$, $q < .05$ corrected) were found. The findings are summarized in Figures 1 and 2, Supplementary Figure S1i–xvii, and Supplementary Tables S3 and S4.

FDRs-BD and FDRs-SZ vs. Control Subjects

FDRs-BD had significantly larger ICVs than control subjects ($d = +0.16$, $q < .05$ corrected) (Figures 1A and 2A, Supplementary Figure S1i–xvii, and Supplementary Table S3). FDRs-SZ had significantly smaller thalamic volume than control subjects ($d = –0.12$, $q < .05$ corrected) (Figures 1A and 2A, Supplementary Figure S1i–xvii, and Supplementary Table S3). When comparing the effect sizes of FDRs-BD and FDRs-SZ directly, FDRs-BD had significantly larger ICV, surface area, total brain, cortical gray matter, cerebral white matter, cerebellar gray matter, thalamus, and accumbens volumes and smaller third ventricle volumes than FDRs-SZ ($q < .05$ corrected) (Supplementary Table S3). For all nominally significant effect sizes ($p < .05$ uncorrected, 2-tailed) and comparisons, see Supplementary Table S3.

Regional Specificity of Findings: Correction for ICV

When controlling for ICV, there were no significant differences in brain measures between FDRs-BD and control subjects (Figures 1B and 2B and Supplementary Table S4). In contrast, in FDRs-SZ, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, and thalamus volumes were significantly smaller, cortex was thinner ($d < –0.09$, $q < .05$ corrected), and third ventricle was larger ($d = +0.15$, $q < .05$ corrected) than in control subjects (Figures 1B and 2B and Supplementary Table S4). FDRs-BD had significantly larger total brain, cortical, and cerebellar gray matter volumes and smaller third ventricle volumes than FDRs-SZ ($q < .05$ corrected) (Supplementary Table S4).

First-Degree Relatives Subtype Analyses

None of the effect sizes comparing FDRs-BD and FDRs-SZ subtypes with control subjects survived correction for multiple comparisons. Direct comparison between the different relative subtypes showed some significant differences between groups; see Supplementary Tables S7 and S8, Supplementary Figure S1i–xvii and Supplementary Results.

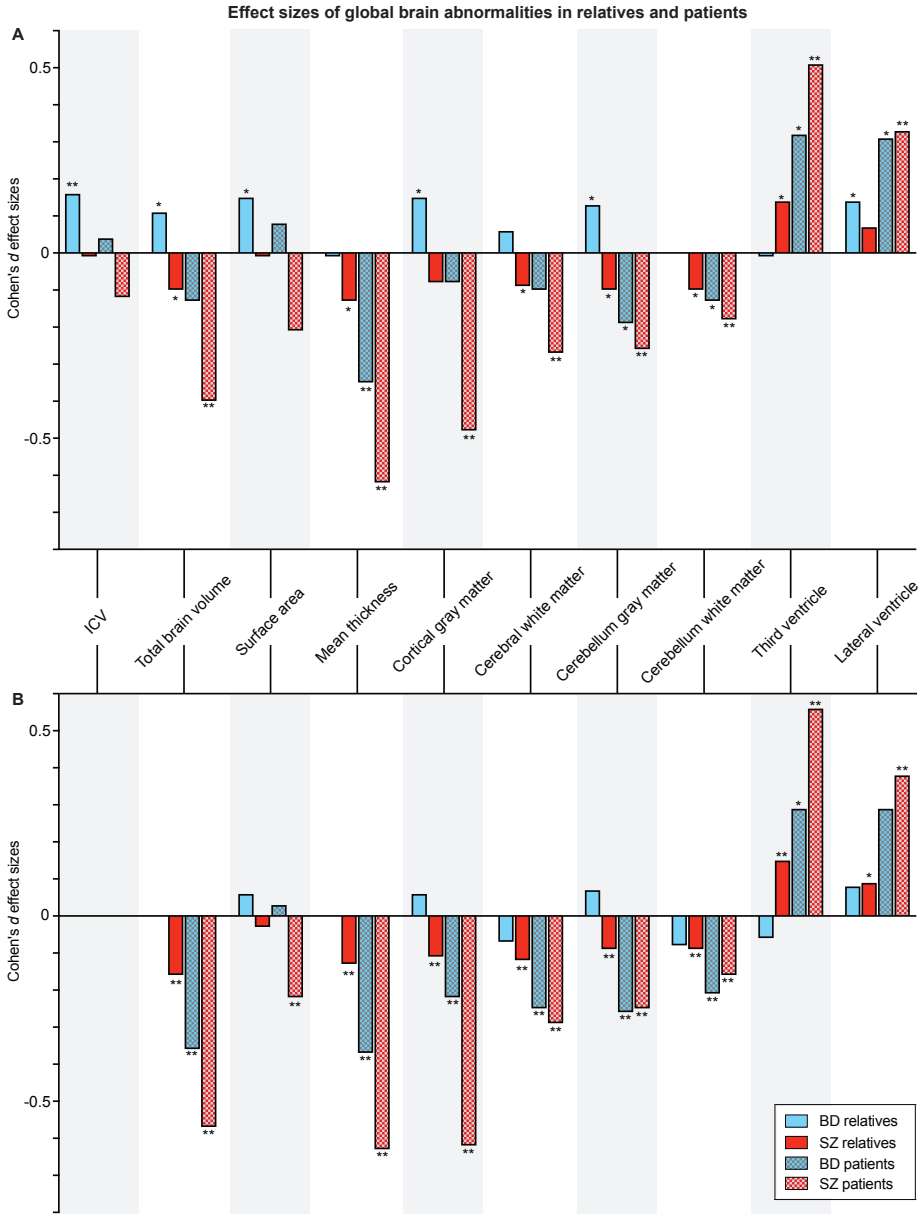


Figure 1. (A) Cohen's *d* effect sizes comparing relatives and patients with bipolar disorder (BD) (blue) and relatives and patients with schizophrenia (SZ) (red) with control subjects for global brain measures, (B) controlled for intracranial volume (ICV). *Nominally significant effect sizes ($p < .05$, uncorrected); **$q < .05$, corrected.

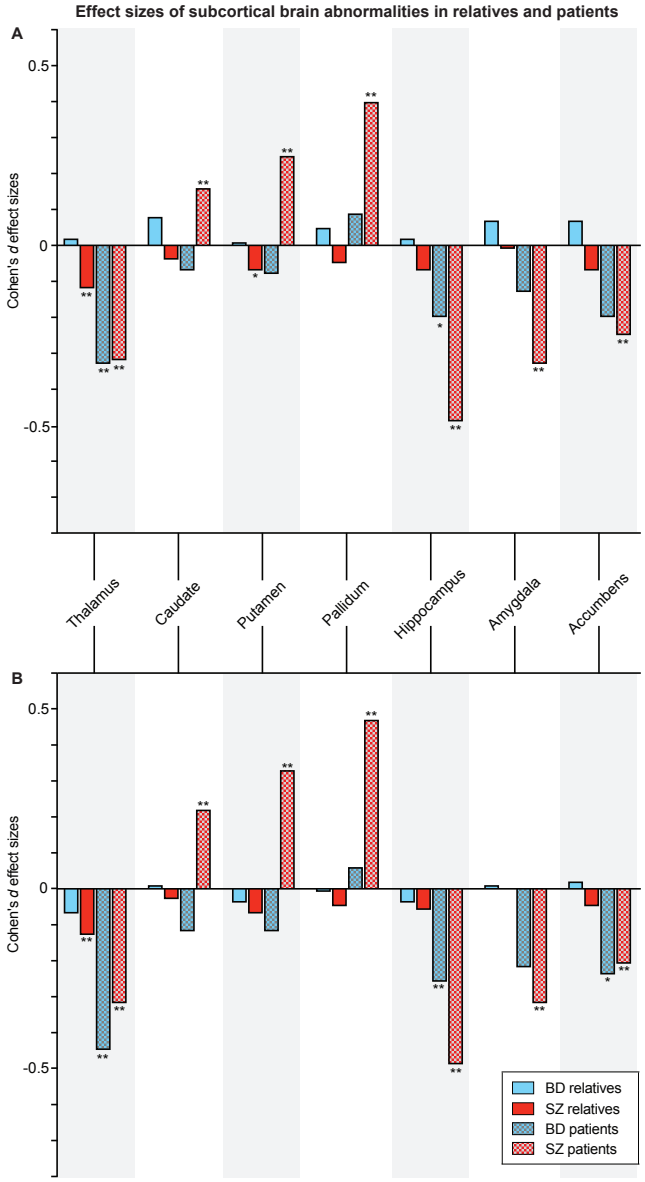


Figure 2. (A) Cohen's *d* effect sizes comparing relatives and patients with bipolar disorder (BD) (blue) and relatives and patients with schizophrenia (SZ) (red) with controls for subcortical volumes, (B) con-trolled for intracranial volume. *Nominally significant effect sizes ($p < .05$, un-corrected); **$q < .05$, corrected.

Psychopathology in Relatives

Psychiatric diagnoses other than bipolar disorder or a psychotic disorder were present in 40.4% of FDRs-BD, 31.5% of FDRs-SZ, 12.6% of control subjects in the bipolar sample, and 9.0% of control subjects in the schizophrenia sample (Tables 1 and 2). Controlling for any diagnosis by adding affected status (1 = yes/0 = no) as a covariate in the analysis did not change the pattern of findings in either FDRs-BD or FDRs-SZ (Supplementary Tables S9 and S10). Also, when comparing only healthy relatives with healthy control subjects, the pattern was similar (Supplementary Tables S11 and S12).

Effect of Age

Meta-regression analyses showed no relationship between age and FDRs-BD effect sizes (Supplementary Table S13 and Figure S2i–xvii). A positive relationship between age and FDRs-SZ effect sizes reached nominal significance only in the amygdala ($p = .008$, which did not survive false discovery rate correction for multiple comparisons) (Supplementary Table S13 and Figure S2i–xvii).

DISCUSSION

This ENIGMA-Relatives initiative allowed for the largest examination to date of FDRs-BD and FDRs-SZ. Through meta-analysis, we investigated whether harmonized subcortical and global brain measures differed between FDRs-BD and FDRs-SZ and control subjects and whether these brain measures differed between the different relative types. The main findings were that 1) FDRs-BD had larger ICVs, whereas FDRs-SZ showed smaller thalamic volumes compared with control subjects; 2) in FDRs-BD, ICV explained enlargements in other brain measures, whereas in FDRs-SZ, brain volumes and thickness became significantly smaller than in control subjects after correction for ICV; 3) abnormalities differed between the relative types, but no clear pattern was detected; and 4) the findings were not confounded by other psychiatric diagnoses in the relatives and control subjects.

Effects in patients with schizophrenia and bipolar disorder were in line with prior studies (Arnone et al., 2009; Ellison-Wright & Bullmore, 2010; Haijma et al., 2013; Hibar et al., 2016, 2017; McDonald et al., 2004; Okada et al., 2016; Van Erp et al., 2015, 2018). In contrast to smaller brain volumes in patients with bipolar disorder (Hibar et al., 2016, 2017), we found larger brain volumes in their relatives. This is in keeping with other studies, which have reported larger regional gray matter volumes in participants at genetic risk (Bauer et al., 2014; Drobinin et al., 2018; Frangou, 2011; Hajek et al., 2013; Kempton et al., 2009; Ladouceur et al., 2008; Lin et al., 2015; Macoveanu et al., 2018; Nery et al., 2013; Roberts et al., 2016; Sarıçiçek et al., 2015). As expected, FDRs-SZ had smaller brain volumes, similar to findings in patients with schizophrenia (Haijma et al., 2013; Okada et al., 2016; Van Erp et al., 2015, 2018), but with smaller effect sizes, in line with a previous retrospective meta- analysis and a review (Boos et al., 2007; Moran et al., 2013). Effect sizes in both FDRs-SZ and FDRs-BD are small ($|d| \leq 0.16$), suggesting that the brain abnormalities in individuals at familial risk are subtle and can be detected only with large sample sizes. These small effect sizes and potential subtle differences could still be meaningful, as they may give information on the familial background of brain deficits in disease. That said, it remains unclear whether brain deficits with these small effect sizes have functional or clinical relevance for FDRs-BD and FDRs-SZ.

Bipolar disorder and schizophrenia have a partially overlapping genetic etiology, with a genetic correlation of $r_g = 0.60–0.68$ based on population and genome-wide association studies

(Anttila et al., 2018; Lee et al., 2013; Lichtenstein et al., 2009), suggesting that they share to some extent the same risk genes. However, combined large genome-wide association studies of schizophrenia and bipolar disorder have also identified unique risk factors associated with each of these disorders (Ruderfer et al., 2018). That FDRs-BD and FDRs-SZ show different global brain volume effects compared with control subjects implies that these brain abnormalities are associated with genetic variants unique to each disorder.

Twin studies have shown that schizophrenia (Baaré et al., 2001; Cannon et al., 2002; Rijsdijk et al., 2005; Van Haren et al., 2012) and bipolar disorder (Kieseppä et al., 2002; Van der Schot et al., 2009) have a shared genetic origin for brain volume, and overlapping brain abnormalities have been reported between the two patient groups (Arnone et al., 2009; Ellison-Wright & Bullmore, 2010; Hulshoff Pol et al., 2012; McDonald et al., 2004). However, the available evidence for an association between common variants in both schizophrenia and bipolar disorder and brain volume is inconsistent (Franke et al., 2016; Grasby et al., 2018; Ruderfer et al., 2018; Smeland et al., 2017b). For example, Smeland et al. (2017b) used novel conditional false discovery rate methodology and identified 6 shared loci between intracranial, hippocampus, and putamen volumes and schizophrenia, whereas no significant genetic correlation was reported in another study that applied standard statistical tools (Franke et al., 2016). Genetic risk for bipolar disorder was unrelated to the genetic variants associated with brain measures (Grasby et al., 2018; Ruderfer et al., 2018). This could suggest either that rare genetic variants, such as copy number variants that are shared between relatives and probands, lead to brain abnormalities or that nongenetic overlap, i.e., shared environmental factors, leads to brain abnormalities in the family members.

The enlargement in several brain measures in FDRs-BD was driven by a larger ICV, whereas the decrements in brain measures in FDRs-SZ were more pronounced when controlling for ICV. This suggests that in contrast to the global ICV finding in FDRs-BD, brain abnormalities in FDRs-SZ not only are a global effect but also represent more regional differences in individuals at familial risk for schizophrenia. ICV reaches its maximum size between the ages of 10 and 15 (Blakemore, 2012; Sgouros et al., 1999); therefore, ICV may be interpreted as a direct marker for neurodevelopment. Indeed, both schizophrenia and bipolar disorder have been characterized as neurodevelopmental disorders (Murray & Lewis, 1987; Nasrallah, 1991; Weinberger, 1987); abnormal neurodevelopment may play a larger role in the onset of schizophrenia than bipolar disorder (Murray et al., 2004; Parellada et al, 2017; Walker et al., 2002). This is in line with differential trajectories of IQ development and school performance found in relation to risk for schizophrenia and bipolar disorder, showing respectively poorer cognitive performance or even decreases over time years before schizophrenia onset and a U-shaped relationship between IQ and later development of bipolar disorder (Parellada et al., 2017). This is also in keeping with a previous study, which found advanced brain age relative to chronological age in participants in early stages of schizophrenia, but not in participants in early stages of bipolar disorder (Hajek et al., 2017). Given the discrepancy in ICV findings between FDRs-BD and FDRs-SZ, individuals at familial risk for either bipolar disorder or

schizophrenia may deviate during early neurodevelopment in a disease-specific manner.

Interestingly, in contrast to FDRs-BD, patients with bipolar disorder did not show an ICV enlargement, confirming previous findings in a large meta-analysis (Hibar et al., 2016). In the early stages of the disease, however, regional increases have been reported (Adleman et al., 2012; Adler et al., 2005; Drobinin et al., 2018; Hajek et al., 2013; Macoveanu et al., 2018; Sarıçiçek et al., 2015). Given the positive relationship between genetic risk for bipolar disorder and ICV reported in twins (Hulshoff Pol et al., 2012), one could argue that the genetic liability for bipolar disorder leads to a larger ICV as represented in our findings of larger ICV in FDRs-BD. That combination of a genetic predisposition for increased ICV and an ICV that is similar between patients with bipolar disorder and control subjects may imply that patient ICV is decreased owing to illness-related factors. Therefore, the discrepancy in ICV findings between patients with bipolar disorder and their relatives might suggest that smaller ICV in patients compared with their relatives can be regarded as a (possibly prodromal) disease effect, similar to what has been reported in schizophrenia. Alternatively, larger ICV in FDRs-BD could represent a relative resilience to developing bipolar disorder, as was suggested in a prior report on hippocampal shape abnormalities in co-twins without bipolar disorder (Van Erp et al., 2012).

The pattern and extent of brain abnormalities varied with respect to the type of relationship to the proband. This again suggests a role for environmental influences, as all FDRs share approximately 50% of their common genetic variants with the affected proband (except for monozygotic co-twins). Given that many environmental risk factors, e.g., age, childhood trauma, physical inactivity, and famine, are associated with brain structure (Dannlowski et al., 2012; Hulshoff Pol et al., 2000; Voelcker-Rehage & Niemann, 2013), environmental risk and/or gene-by-environment interplay are likely also associated with differences in brain abnormalities in individuals at familial risk for schizophrenia or bipolar disorder. However, despite the large sample size, we did not find a consistent pattern of abnormalities among different relative types. Power may still not be sufficient to detect these subtle differences. Alternatively, there are many environmental factors that are unique for an individual—and thus not specific to the relative type—and these could have influenced brain structure.

Psychopathology is more prevalent in individuals at familial risk for either bipolar disorder or schizophrenia than in the general population; for example, offspring studies have shown that 55% to 72% of individuals with a parent with bipolar disorder or schizophrenia developed a lifetime mental disorder (Mesman et al., 2013; Rasic et al., 2014). We showed that the presence of a psychiatric diagnosis in relatives and control subjects did not influence our findings. This suggests that brain abnormalities seen in the relatives represent the familial liability for the disorder and not the presence of psychopathology.

Some limitations should be considered in interpreting the results. This study is a meta-analysis of multiple cohorts from research centers around the world, with heterogeneity

across samples (among others, acquisition protocols, field strength, FreeSurfer version, inclusion and exclusion criteria). Meta-analysis will find consistent effects despite this variance but cannot remove all sources of heterogeneity. However, clinical heterogeneity within and across sites is representative of the broad, clinically varied, and ecologically valid nature of bipolar disorder and schizophrenia and allows generalizable alterations to be detected. One source of heterogeneity in the offspring in particular might also be the substantial age differences between the different offspring cohorts. Both adult and children/adolescent offspring cohorts were included in the analyses, and the fact that the brains of the child and adolescent offspring have not reached adult size might have influenced the findings of the overall offspring effects. In addition, inclusion criteria varied with respect to psychopathology in FDRs or control subjects at the different research centers. For example, some cohorts included only healthy relatives, yet others included relatives with other psychiatric diagnosis (except for having the disorder itself). We accounted for this with additional analyses covarying for any diagnosis or assessing only the healthy relatives. These approaches might not be sufficient. In addition, the composition of the FDRs-SZ and FDRs-BD groups differed. FDRs-SZ had a greater sample size and consisted in particular of more siblings, whereas there were more offspring in the FDRs-BD group. Finally, the discrepancy in ICV between FDRs-BD and FDRs-SZ may be associated with current IQ or parental socioeconomic status (SES). Both IQ and parental SES have been associated with brain structure (Lawson et al., 2013; McDaniel, 2005; Noble et al., 2015; Staff et al., 2012). This might suggest that the larger ICV found in FDRs-BD is related to higher IQ or parental SES. Lower IQ has been reported in FDRs-SZ (Van Haren et al., 2019). However, the literature regarding current IQ in individuals at familial risk for bipolar disorder is less clear. Cognitive deficits have been associated with genetic risk for bipolar disorder (Arts et al., 2008; Glahn et al., 2010). One study showed that siblings of patients with bipolar disorder had lower IQ but that they did not differ on educational level compared with control subjects (Vreeker et al., 2016). In contrast, a bipolar twin study showed that both the proband and the co-twin without bipolar disorder completed significantly fewer years of education than control twins (Vonk et al., 2012). Furthermore, population studies show that premorbid IQ or educational attainment are often not affected or are even higher in individuals who later develop bipolar disorder (MacCabe et al., 2010; Smith et al., 2015; Tiihonen et al., 2005; Zammit et al., 2004), whereas IQ during childhood and adolescence is lower in individuals who develop schizophrenia later in life (Agnew-Blais & Seidman, 2013; Dickson et al., 2012; Hochberger et al., 2018; Kendler et al., 2015; Khandaker et al., 2011; Woodberry et al., 2008). The question remains how these measures interact with brain development in individuals at familial risk. As recently reported in a study that included only FDRs-SZ from one site (Utrecht, The Netherlands), current IQ was intertwined with most of the brain abnormalities (De Zwarte et al., 2019a). However, in FDRs-BD, it still remains unclear how IQ and risk for bipolar disorder act on the brain. In the current study, few cohorts had information available on parental SES or subjects' IQ, thereby excluding the possibility to address these variables as potential confounders. Investigating the influence of current IQ on the difference in brain measures between relatives and control subjects was outside the scope of this study, and we

are collecting and harmonizing these data from the cohorts for future analysis.

In conclusion, FDRs of patients with schizophrenia or bipolar disorder represent a group of individuals who can provide insight into the effect of familial risk on the brain. Although liability for schizophrenia and bipolar disorder overlap in the general populations, individuals at familial risk assessed here showed a differential pattern of structural brain abnormalities. This study found differences in brain abnormalities between FDRs-SZ and FDRs-BD, in particular, a divergent effect in ICV. This converse effect on ICV suggests that there may be different neurodevelopmental trajectories for each disorder early in life. Taken together, our findings may imply that brain abnormalities in schizophrenia and bipolar disorder are due to genetic variants or gene-by-environment interplay specific to each disorder.

SUPPLEMENTARY METHODS

To compare the effect sizes between bipolar disorder and schizophrenia and between the different types of first-degree relatives, the following approach was applied;

If d is the observed Cohen's *d* value, then the sampling variance of d is approximately equal to:

$$v = \frac{1}{n_1} + \frac{1}{n_2} + \frac{d^2}{2(n_1 + n_2)}$$

With d the effect size as analyzed, and n1 and n2 the two corresponding sample sizes.

To test the null hypothesis H0: $\delta_1 = \delta_2$ (where δ_1 and δ_2 denote the true d values of the two effect sizes), we can compute a Z-score:

$$z = \frac{d_1 - d_2}{\sqrt{v_1 + v_2}}$$

Which follows approximately a standard normal distribution under H_0.
If $|z| \geq 1.96$, H_0 can be rejected at $\alpha = 0.05$ (two-sided).

SUPPLEMENTARY RESULTS

FDRs Subtype Analyses

Bipolar disorder

FDRs-BD parents were not included in these analyses as only one cohort included parents. None of the effect sizes was significant after correction for multiple comparisons (please see Table S7a and Figure S1i-xvii for all nominally significant effect sizes).

Correction for intracranial volume: After correction for ICV, hippocampal volume was significantly smaller in offspring than in siblings and thalamus volume was smaller in monozygotic co-twins compared to dizygotic co-twins ($q < 0.05$ corrected; Table S8a).

Schizophrenia

The largest effects, when comparing the FDRs-SZ subtypes to controls, were reported in the offspring, but none of the effect sizes was significant after correction for multiple comparisons (see Table S7b and Figure S1i-xvii for all nominally significant effect sizes). Direct comparison between relatives showed differences between offspring and siblings, i.e., offspring had significantly smaller ICV, surface area, total brain, cortical gray matter, cerebral white matter, thalamus, caudate, putamen, pallidum, hippocampus, and amygdala volumes than siblings ($q < 0.05$ corrected; Table S7b). In addition, parents had larger amygdala volumes than monozygotic co-twins and offspring; dizygotic co-twins had a thinner cortex than siblings and parents; and offspring had smaller pallidum and cortical gray matter volume than parents ($q < 0.05$ corrected; Table S7b).

Correction for intracranial volume: When controlling for ICV, again, none of the effect sizes comparing FDRs-SZ subtypes with controls was significant after correction for multiple comparisons (please see Table S8b for all nominally significant effect sizes). Direct comparison of relative types showed thinner cortex and smaller cortical gray matter in dizygotic co-twins compared to siblings and parents; larger amygdala volume in parents than reported in monozygotic co-twins, offspring and siblings; and smaller cerebellar white matter in parents than monozygotic co-twins ($q < 0.05$ corrected, Table S8b).

SUPPLEMENTARY TABLES

Table S1. Sample inclusion criteria

Sample	Inclusion criteria
BPO_FLB	BD patients were diagnosed with either type I or type II BD (BD I and BD II), or BD not otherwise specified (BD NOS) according to DSM-IV. Patients exclusion criteria included substance use within the past six months and general medical problems. Inclusion criteria for offspring of BD patients included diagnosis of BD in biological father and or mother according to SCID. Inclusion criteria for healthy controls included those without a history of any psychiatric/neurological disorders or mood disorders in first-degree relatives. Exclusion criteria for patient, healthy control and offspring groups included head injury with loss of consciousness, presence of metallic objects in the body, family history of hereditary neurological disorders, and pregnancy.
C_SFS	Schizophrenia and schizoaffective patients participated. Inclusion criteria for all participants included: 1) age 18-65; 2) minimum intelligence quotient (IQ) of 70 as measured by Wechsler Abbreviated Scale of Intelligence; 3) no current diagnosis of drug or alcohol dependence or abuse; 4) no history of head injury or being unconscious for more than 20 minutes; 5) no history of electroconvulsive therapy; and 6) no history of a neurological condition. Further criteria for inclusion of relatives and controls were no lifetime diagnosis of a psychotic or bipolar disorder, Axis II Cluster A disorder, or history of anti-psychotic medication use. Further criterion for inclusion of community controls was no family history of a psychotic or bipolar disorder.
Cardiff	All participants were age 35 years or older and included: 1) individuals with confirmed diagnosis of bipolar disorder type I or type II, euthymic at time of recruitment and reporting mood stability and no-change in medication for one month prior scanning; 2) unaffected relatives of bipolar participants with no personal history of mood disorders or psychosis; 3) healthy controls with no personal or first-degree family history of mental disorders. All DSM-IV diagnoses were confirmed through the Mini-international neuropsychiatric interview (1). Patients were recruited through the Bipolar Disorder Research Network (BDRN) and the National Centre for Mental Health (NCMH) both at Cardiff University, non-affected siblings were recruited via BD participants, and healthy controls from the community via advertisement.
CLiNG – BD	Inclusion criteria for participants were a) age between 18 and 60 years, b) parents, siblings or offspring of index patients with bipolar disorder, c) no own diagnosis of a mental disorder and d) right-handedness. Diagnosis of bipolar disorder in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, unless a medical report confirming diagnosis of bipolar disorder was provided. Exclusion criteria included history of neurological and severe medical disorders, current or past psychopathology as well as substance dependence and substance abuse.
CLiNG – SZ	Inclusion criteria for participants were a) age between 18 and 60 years, b) parents, siblings or offspring of index patients with schizophrenia, c) no own diagnosis of a mental disorder and d) right-handedness. Diagnosis of schizophrenia in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, unless a medical report confirming diagnosis of schizophrenia was provided. Exclusion criteria included history of neurological and severe medical disorders, current or past psychopathology as well as substance dependence and substance abuse.
DEU	The inclusion criteria for patient group were having a diagnosis of bipolar disorder type I according to DSM-IV, aging between 18 and 65 years, being in euthymic state (according to DSM-IV and scoring ≤ 7 on both Young Mania Rating Scale and Hamilton Rating Scale for Depression) for at least six months and having no axis I comorbidity. The inclusion criteria for first degree relatives of bipolar disorder patients were having no lifetime axis I diagnosis, and for healthy controls, having no lifetime axis I diagnosis and family history for psychiatric disorders at the time of recruitment. The following exclusion criteria were applied to all groups: presence of auditory or visual impairment, history of neurosurgical intervention, being pregnant or breastfeeding, diagnosis of neurocognitive illness or substance use during the preceding six weeks before participating in the study. All participants were evaluated using the Structured Clinical Interview for Diagnostic Statistical Manual-IV (DSM-IV) (SCID-I).
EGEU	All participants were aged between 20 and 55 years old and included: 1) patients with bipolar disorder type 1, euthymic at the time of recruitment (defined as scoring less than five on the Young Mania Rating Scale (YMRS), and less than 11 on the Hamilton Depression Rating Scale-17 item (HAM-D-17) for at least three months prior to and during the MRI scanning); 2) healthy siblings of bipolar participants, never diagnosed with mental illness; 3) unrelated healthy controls, no personal or family history of mental illness. All patients were recruited from the Ege University School of Medicine's Department of Psychiatry, where the patients had been receiving follow-up care with monthly assessments for at least three years, healthy siblings were recruited via BD patients, and unrelated healthy controls from community via local advertisement.
EHRS	All participants were aged between 16 and 25 years old and recruited across Scotland. High-risk individuals were included if they had no history of serious psychiatric problems and had at least two first- or second-degree relatives affected with schizophrenia. Participants for the control group were recruited from the social network of the high-risk individuals themselves; they had no personal or family history of other psychotic illness, but could have a family history of other psychiatric illness and otherwise were similar to the high-risk participants as possible. First-episode individuals were recruited from local hospitals, were balanced group-wise for age with the high-risk individuals and had no family history of schizophrenia.

Sample	Inclusion criteria
ENBD_UT	Specific inclusion criteria for the BD sibling pairs are: a) BD proband with diagnosis of BD I or II, based on DSM-IV criteria, b) having a same-gender sibling not affected by BD; c) ages 18-65 years old; d) BD proband and unaffected sibling no more than 10 years apart in age; e) BD proband at any current mood state at the time of the study; f) BD proband preferably off pharmacological treatment at the time of study, but if not feasible, being on antidepressants and mood stabilizers (including anticonvulsants, typical and atypical antipsychotics, and lithium will be allowed; g) BD proband and unaffected sibling brought up together in the same family. Exclusion criteria for the BD sibling pairs: a) diagnosis of Bipolar Disorder, Schizoaffective Disorder or Schizophrenia is not allowed. Alcohol and substance abuse/ dependence (if in remission in the past 6 months) and anxiety disorders are allowed; b) being on a regular dose of benzodiazepines within two weeks of study participation; c) pregnancy d) ineligibility or inability of one of the members of the sibling pair to participate in the study. Exclusion criteria for controls: a) a lifetime psychiatric diagnosis, b) family history of psychiatric illness in a first-degree relative.
HHR	Participants were recruited from an ongoing Offspring Risk for BD Imaging Study–ORBIS. We recruited offspring from families of well-characterized adult BD probands who had participated in previous genetic and HR studies in Halifax, Nova Scotia. The inclusion criterion was 15–30 years of age. We included participants with BD type I or type II, but not with BD NOS as probands for this study. The offspring from BD probands were divided into two subgroups. 1) The unaffected HR group, which included offspring without a personal history of Axis I psychiatric disorders. These individuals were considered HR because they came from multiplex families (more than one member affected with BD) and had one parent affected with a primary mood disorder. 2) The affected familial group, which included offspring meeting criteria for a lifetime Axis I diagnosis of mood disorders (i.e. a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria) and had one parent affected with a primary mood disorder. Depressive episodes were included because unipolar depression is characteristically the first manifestation of illness in patients who later develop BD. Lastly, we recruited control participants free of personal or family history of DSM-IV Axis I psychiatric disorders. Common exclusion criteria for all groups were a personal history of 1) any serious medical or neurologic disorders, 2) substance abuse/dependence during the previous 6 months, or 3) magnetic resonance imaging (MRI) exclusion criteria.
HUBIN	Patients diagnosed with long term psychotic disorder were recruited from outpatient clinics in the North-Western part of Stockholm County. The patients were diagnosed according to DSM-III-R and DSM-IV based on information from interviews and medical records. Non-psychotic siblings of patients with psychosis were asked to participate when their relative with a psychotic disorder had agreed to their participation. Control subjects were recruited among students, hospital staff members or from a population register. All controls with the exception of those recruited from a population register had earlier attended in biological research at the Karolinska Institute. The controls consisted of non-psychotic individuals unrelated to the patients. Neither the siblings, nor the controls received any psychotic diagnosis according to DSM-III-R and DSM-IV.
IDIBAPS	The study was conducted in the Child and Adolescent Psychiatry Department of the Hospital Clinic of Barcelona, Spain. The protocol was approved by the local ethics review board. Patients with a diagnosis of schizophrenia or bipolar disorder from adult psychiatry units with offspring 6 to 17 years old were identified and invited to participate in the study. The exclusion criteria for proband parents were intellectual disability and drug or medically induced psychosis or mania. Exclusion criteria for offspring included intellectual disability, head injury with loss of consciousness, or severe neurological conditions. Community control parents were recruited through advertisements posted in primary health care centers and other community locations within the same geographic area as the patients. The exclusion criteria were intellectual disability, severe neurological conditions and personal or first-degree family history of schizophrenia or bipolar spectrum disorders. All 6- to 17-year old offspring of community control parents were invited to participate in the study; exclusion criteria were the same as those for high-risk offspring. To decrease selection bias, parents who stated they were specifically motivated to participate because of concerns about school performance or emotional or behavioral problems in their offspring were excluded.
IoP – BD	Twins were recruited using a variety of methods, these were: 1. Direct contact with health professionals, including psychiatrists, clinical psychologists, occupational therapists and so on; 2. Advertising: Adverts were placed national and local newspapers as well as in specific user group publications such as Pendulum, the Manic Depression Fellowship's quarterly newsletter. Flyers for the study were also distributed in hospitals, clinics and chemists. Links were also placed on various internet sites such as Wikipedia.org and self-help groups; and 3. Talks were given by team members at service user and professional conferences. Control subjects were recruited primarily via advertising in the national media, with further recruitment from a pool of research participants obtained for previous studies conducted at the Institute of Psychiatry (IoP, now IoPPN), with a smaller group being referred by members of staff at the Bethlem and Maudsley Hospital Trust and word of mouth. Exclusion criteria for all participants were a history of neurologic illness or of systemic illness with known neurologic complication, history of head injury with loss of consciousness, and current substance misuse or dependence. Controls had no personal or family history of psychotic illness. Controls and unaffected relatives with a nonpsychotic psychiatric diagnosis were included. All participants were between 16 and 65 years-old at the time of participation. All the studies were approved by institutional review boards, and all the participants gave written informed consent before participating.

Sample	Inclusion criteria
IoP – SZ	Twins were referred from across the United Kingdom by their treating psychiatrists. Control twins were recruited from the Institute of Psychiatry Volunteer Twin Register and by national media advertisements. Families were referred from clinics and voluntary organizations across the United Kingdom. Control subjects were ascertained from a pool of research participants obtained for previous studies conducted at the Institute of Psychiatry, from members of staff at the Bethlem and Maudsley Hospital Trust, and through advertisements in the press. Exclusion criteria for all participants were a history of neurologic illness or of systemic illness with known neurologic complication, history of head injury with loss of consciousness, and current substance misuse or dependence. Controls had no personal or family history of psychotic illness. Controls and unaffected relatives with a nonpsychotic psychiatric diagnosis were included. All the studies were approved by institutional review boards, and all the participants gave written informed consent before participating.
LIBD	Participants were recruited nationwide as part of a study at the National Institute of Mental Health, Bethesda, MD. Samples used in this study were under a standard procedure including a structured diagnostic interview (Structured Clinical Interview for DSM-IV) and a formal neurological examination. All patients met DSM-IV criteria for schizophrenia or related diagnoses including schizoaffective disorder, psychosis (not otherwise specified), and schizoid, paranoid, and schizotypal personality disorders. The majority of patients were taking antipsychotic medication at the time of scan, and a minority had a lifetime history of comorbid mental illness or substance abuse/dependence (including alcohol). Exclusion criteria for normal controls included a current or past history of neurological or psychiatric disorders, hypertension or drug abuse. A minority of siblings had a past lifetime history of a non-psychotic mental illness and/or substance abuse and/or dependence (39.7%), but none met criteria at the time of evaluation. No subjects in any group had a current history of alcohol or substance abuse within 6 months of being scanned. All subjects provided written informed consent, and participated according to the guidelines of the National Institute of Mental Health Institutional Review Board.
Maastricht – GROUP	Participants were recruited in selected representative geographical areas in the Netherlands and Belgium, patients were identified through representative clinicians providing health care for patients with psychotic disorder. Siblings were contacted through participating patients. Mailings and advertisements were effectuated in local newspapers of the same geographical area in order to recruit control participants. Inclusion criteria were; age range 16-50 years, fluent in Dutch language and for patients: a diagnosis of non-affective psychotic disorder with illness duration of <10 years. Siblings and controls were excluded if they had a lifetime diagnosis of any non-affective psychotic disorder. In addition, controls were excluded if they had a first-degree relative with a lifetime diagnosis of any psychotic disorder. This was assessed using the Family Interview for Genetic Studies (FIGS). Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria, measured with the Comprehensive Assessment of Symptoms and History (CASH) interview. All participants were screened before MRI scanning and excluded based on the following: brain injury with unconsciousness of > than 1 hour, meningitis or other neurological diseases with possible impact on brain structure or function, cardiac arrhythmia requiring medical treatment and severe claustrophobia. Participants with metal corpora aliena were excluded from the study, as were women with intrauterine device status and (suspected) pregnancy.
MFS	All individuals were aged 16-70. Participant groups included (i) patients with DSM-IV confirmed diagnoses of schizophrenia or bipolar 1 disorder; (ii) unaffected first-degree relatives of these patients including parents, siblings and offspring; (iii) healthy volunteers with no personal or family history of psychotic illness. Families were recruited through voluntary organizations or by direct psychiatric referral and on the basis of either being multiply affected, where the index patient had one or more first- or second- degree relatives with a psychotic disorder, or singly-affected where there was no known family history of psychotic disorder. All of the bipolar disorder patients and relatives were from multiply affected families. Exclusion criteria for all participants included organic brain disease, head trauma resulting in loss of consciousness for more than 5 minutes, or DSM-IV substance or alcohol dependence in the 12 months before the assessment.
MooDS – BD	Participants were aged between 18 and 53 years. First-degree relatives were offspring or siblings of index patients with BPD. Diagnosis of BPD in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, or the patients provided a medical report confirming diagnosis of BPD. All participants had no history of any neurologic disorder or current psychiatric Axis I disorder including drug or alcohol dependence as verified by the nonpatient version of the Structured Clinical Interview for DSM-IV and had no MRI contraindications.
MooDS – SZ	Participants were aged between 18 and 55 years. First-degree relatives were parents, offspring or siblings of index patients with SCZ. Diagnosis of SCZ in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, or the patients provided a medical report confirming diagnosis of SCZ. All participants had no history of any neurologic disorder or current psychiatric Axis I disorder including drug or alcohol dependence as verified by the nonpatient version of the Structured Clinical Interview for DSM-IV and had no MRI contraindications.
MSSM	All participants were aged 18 to 67 years. The eligibility criteria for all participants were (a) IQ>70; (b) no history of head trauma or loss of consciousness; (c) no current or lifetime history of medical or neurological disorders; (d) no lifetime history of substance use disorder; (e) no MRI contraindications (e.g. metal implants, claustrophobia). Patients were required to fulfil diagnostic DSM-IV criteria for BD type-I or type II, while healthy volunteers were included if they had no lifetime personal history of mental disorders and no family history (up to second-degree relatives) of BD. Unaffected relatives of bipolar participants were included if they had no personal history of bipolar disorder or psychosis.

Sample	Inclusion criteria
NU	Participants were recruited through the Conte Center for the Neuroscience of Mental Disorders at Washington University in St. Louis. SCZ participants were recruited from local inpatient and outpatient treatment facilities and had to meet the criteria for DSM-IV schizophrenia. CON participants were recruited using local advertisements from the same community. Exclusion criteria for CON participants included a lifetime history of any Axis I psychiatric disorder and having a first-degree relative with a psychotic disorder. Both SCZ-SIB and CON-SIB were excluded for a lifetime history of Axis I psychotic disorders (including bipolar disorder) and current major depression, but not other Axis I disorders. Participants from any of the 4 groups were excluded if they 1) met DSM-IV criteria for substance abuse or dependence within the past 6 months; 2) had a clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous; 3) had head injury (past or present) with documented neurological sequelae or resulting in loss of consciousness; and 4) met DSM-IV criteria for mental retardation.
Olin	BD I patients, their unaffected siblings, and unrelated healthy volunteers were recruited from psychiatric facilities and community advertisements in Hartford, CT. Patients were included if they met DSM-IV criteria for BD I based on the Structured Clinical Interview for DSM-IV disorders; had no history of major medical or neurological conditions (e.g. epilepsy, migraine, head trauma with loss of consciousness); had an IQ > 80 (based on WASI); and had a sibling willing to participate in the study. Eligibility criteria for siblings and unrelated healthy volunteers were identical to those for patients, with the exception of a personal lifetime diagnosis of bipolar or psychosis spectrum disorders (having a DSM-IV diagnosis other than bipolar or psychosis spectrum disorders was not an exclusion criterium). In addition, unrelated healthy volunteers could not have a family history of mood or psychotic disorders. All participants provided informed consent as approved by the institutional review board at Hartford Hospital and Yale University.
PHHR	Families were identified through adult probands with BD, who had participated in the Czech Bipolar Disorder Case Registry. Only offspring from these families, not probands, were a part of the MRI study. The inclusion criterion was 15–30 years of age. We included participants with BD type I or type II, but not with BD NOS as probands for this study. The offspring from BD parents were divided into two subgroups: 1) the Unaffected HR group, which consisted of offspring with no lifetime history of psychiatric disorders. These individuals were at an increased risk for BD because they had one parent affected with a primary mood disorder. 2) The Affected Familial group, which consisted of offspring who met criteria for a lifetime Axis I diagnosis of mood disorders (i.e., a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria). Also, we recruited control participants free of personal or family history of DSM-IV Axis I psychiatric disorders. Common exclusion criteria for all groups were a personal history of 1) any serious medical or neurologic disorders, 2) substance abuse/dependence during the previous 6 months, or 3) MRI exclusion criteria.
STAR (Swedish) BD twin cohort	Subjects were identified on a nation-wide basis through the Sweden Twin Registry. Twin pairs were eligible for inclusion if they were same sex, between the ages of 25 and 65, and born in Sweden between 1940 and 1985 (inclusive). To ascertain twin pairs comprising at least one twin with a diagnosis of schizophrenia or bipolar disorder, this set of twins was screened using hospital admission and discharge diagnosis information from the Swedish National Patient Registry. Monozygotic and dizygotic pairs were recruited from all counties in Sweden and invited to Karolinska Institute for structured diagnostic interviews and additional evaluations, including neuroimaging. Final diagnoses were determined by a consensus procedure. Zygosity was determined for nearly all twin pairs using DNA testing or a well-validated screening measure for those without DNA available on both co-twins. Exclusion criteria were presence of a neurological disorder, history of significant head injury with loss of consciousness, mental retardation, history of substance dependence within 6 months of the screening interview, or inability to read or comprehend spoken and written Swedish. Healthy control pairs were recruited to match proband pairs on age, sex, and zygosity. Healthy controls were excluded if they had a family history of schizophrenia or bipolar disorder according to medical records or self-report.
STAR (Swedish) SZ twin cohort	Subjects were identified on a nation-wide basis through the Sweden Twin Registry. Twin pairs were eligible for inclusion if they were same sex, between the ages of 25 and 65, and born in Sweden between 1940 and 1985 (inclusive). To ascertain twin pairs comprising at least one twin with a diagnosis of schizophrenia or bipolar disorder, this set of twins was screened using hospital admission and discharge diagnosis information from the Swedish National Patient Registry. Monozygotic and dizygotic pairs were recruited from all counties in Sweden and invited to Karolinska Institute for structured diagnostic interviews and additional evaluations, including neuroimaging. Final diagnoses were determined by a consensus procedure. Zygosity was determined for nearly all twin pairs using DNA testing or a well-validated screening measure for those without DNA available on both co-twins. Exclusion criteria were presence of a neurological disorder, history of significant head injury with loss of consciousness, mental retardation, history of substance dependence within 6 months of the screening interview, or inability to read or comprehend spoken and written Swedish. Healthy control pairs were recruited to match proband pairs on age, sex, and zygosity. Healthy controls were excluded if they had a family history of schizophrenia or bipolar disorder according to medical records or self-report.
SydneyBipolar-Group	All participants were aged 12 and 30 years and included: 1) individuals with a confirmed diagnosis of BD I, II, or schizoaffective disorder; 2) offspring or siblings of a proband with a DSM-IV diagnosis of BD I, II, or schizoaffective disorder; 3) controls with no family history of BD I or II, schizoaffective disorder, schizophrenia, recurrent major depression, recurrent substance abuse, or psychiatric hospitalization, and no personal history of BD I, II, or schizoaffective disorder. Current or lifetime diagnoses of psychiatric disorders other than bipolar disorder were not considered an exclusion factor for controls or bipolar relatives. All DSM-IV diagnoses were confirmed by two independent raters using Best Estimate Methodology and the K-SADS-BP or DIGS Version 4, the FIGS, and available medical records. Participants were recruited from bipolar research clinics, mental health organizations, families participating in alternate bipolar research projects, electronic and printed media, and public notice boards.

Sample	Inclusion criteria
UMCG – GROUP	Fifty siblings of patients with schizophrenia and fifty matched healthy controls without any first- or second-degree family members with a psychotic disorder were included in this study. All 80 siblings and 56 controls were included from a multi-center (Groningen and Amsterdam) add-on study from the GROUP project [Genetic Risk & Outcome of Psychosis]. This sample partially overlaps with a previous study from our group [nsiblings=20, ncontrols=8]. The other 24 controls were recruited outside of the GROUP study through advertisements. None of the participants reported a presence or history of any psychiatric or neurological disorder.
UMCU – BD twins	All twins were raised together, except for one control pair where twins were separated at 12 years of age when both parents died. Subjects were between 18 and 60 years of age at the time of enrolment in the study. Clinical diagnosis of Axis I psychiatric disorders and Axis II personality disorders was confirmed using the SCID and SIDP, respectively, and through available medical records. Patients were also interviewed on their medication history. The twin pairs had no history of drug or alcohol dependency for the last 6 months prior to inclusion in the study, for this was an exclusion criterion. Moreover, none had severe medical illness, verified with a medical history inventory. The current mood state of BD patients was assessed using the YMRS and the IDS. Upon inclusion, all patients were euthymic with a YMRS score of 4 or less and an IDS score of 12 or less, except for nine BD patients who were mildly to severely depressed or hypomanic. Healthy control pairs were matched to the bipolar pairs for zygosity, gender, age and parental education. Control pairs had no history of severe medical illness and had no first-degree relative with a history of a major Axis I psychiatric disorder (DSM-IV). Family histories of all twins were obtained via the Family Interview Genetic Studies, performed with both twins of each pair. Zygosity was determined with DNA fingerprinting using high polymorphic microsatellite markers 9 to 11. The medical ethics review board of the University Medical Center Utrecht approved the study and all participants gave written informed consent after full explanation of the study aims and procedures.
UMCU – DBSOS	This study includes participants between 8 and 18 years of age, including offspring of a patient with schizophrenia, offspring of a patient with bipolar disorder, and community control subjects. None met DSM-V criteria for schizophrenia or a related psychotic disorder at the time of baseline assessment (present and lifetime). For each family, all offspring in the appropriate age range entered our study to prevent a biased selection of participants within the family, as offspring with (subthreshold) symptoms may otherwise be more likely to be signed up for study participation than offspring with no (subthreshold) symptoms. Clinical diagnoses of parents were confirmed using the SCID. Control parents were screened for psychopathology using the mini-SCAN. The medical ethics committee of the UMC Utrecht approved the study, and all participating children and their parents provided written informed consent. The K-SADS-PL was used to evaluate symptoms and DSM-V diagnoses of all participants. The majority of the offspring were naïve to psychotropic medication.
UMCU – GROUP	Patients had to fulfil the following criteria: 1) age between 16 and 50 years, 2) meeting DSM-IV criteria for a nonaffective psychotic disorder (including schizophrenia, schizophreniform disorder, and schizoaffective disorder), 3) fluent in Dutch, and 4) able and willing to give written informed consent. Eligible siblings had to fulfil the criteria of 1) age between 16 and 50 years, 2) fluent in Dutch, and 3) able and willing to give written informed consent. Eligible healthy control subjects had to fulfil the criteria of 1) age between 16 and 50 years, 2) no lifetime psychotic disorder and/or use of lithium medication (in the past), 3) no first- or second-degree family member with a lifetime psychotic disorder, 4) fluent in Dutch, and 5) able and willing to give written informed consent. Presence or absence of psychopathology was established by using the CASH. Diagnosis was based on the DSM-IV criteria. Of all subjects, urine was screened for cocaine, amphetamines, and for cannabis. Subjects with substance dependence/abuse (based on the criteria of the CIDI [sections B, J, and L]) and a major medical or neurological illness were excluded.
UMCU – Parents	Both parents of patients with schizophrenia were recruited at the University Medical Center Utrecht, as well as healthy control couples. The CASH, SADS-L, SIDP-IV, and the FIGS were obtained from all participants. Psychiatric diagnosis was established according to DSM-IV criteria. At least one of the children of the parents met DSM-IV criteria for schizophrenia on the basis of the CASH. Parents of patients were excluded if they had a history of psychotic illness. For control couples, exclusion followed in case of any axis-I DSM-IV diagnosis, or diagnosis of depression, manic depression, or psychotic disorder in first-degree family, or psychotic disorder in second-degree family. In both groups all participants were physically healthy and had no history of neurological illness, or drug or alcohol abuse.
UMCU – UTWINS	1.5T: Twin pairs discordant for schizophrenia, and healthy control twins were pairwise matched on zygosity, sex, age, and birth order took part in the study. Subjects were recruited in collaboration with psychiatric services and by advertisements in national newspapers. All subjects gave written informed consent to participate in the study. Zygosity was determined by DNA fingerprinting. Except for 1 control twin pair, all twins were reared together. The 1 control twin pair was separated at age 12 years when both their parents died. All subjects underwent extensive psychiatric assessment procedures using the CASH interview, the SADS-L, the Structured Interviews for DSM-III-R and DSM-IV, the FIGS, and a medical history inventory. Psychiatric diagnosis was established according to criteria of DSM- IV. The following subtypes were diagnosed in the twins with schizophrenia: paranoid, disorganized, undifferentiated, residual, and catatonic. Diagnoses in non-schizophrenic co-twins included paranoid personality disorder, schizotypal personality disorder, schizoid personality disorder, major depressive disorder, avoidant personality disorder, generalized anxiety disorder with a dependent personality disorder, and no psychiatric diagnoses. Moreover, some patients and co-twins had histories of substance or alcohol abuse. Healthy control twins had no schizophrenic spectrum disorders, no first-degree relatives with a history of psychiatric illness, and no second-degree relatives with a psychotic disorder. Two patients had never been on antipsychotic medication.

Sample	Inclusion criteria
UMCU – UTWINS	3T: U-TWIN consists of twins with discordance for schizophrenia and control twins. The control twins were selected to match the discordant twins on age, handedness, and parental educational level. There were more males in the discordant twin group compared with the control twins, which was corrected for statistically. Control twins were excluded if they ever met criteria for a psychotic or manic disorder or substance dependence, had a first-degree relative with schizophrenia, or were diagnosed as having a neurologic disorder. Zygosity of all twins was determined through testing polygenic genetic markers. The zygosity of incomplete pairs was known from participation in earlier studies. All subjects underwent psychiatric assessment by means of the CASH interview, symptom severity in the patients was assessed using the PANSS. Diagnoses were established using DSM-IV criteria. All but one patient received antipsychotic medication. The twins were recruited through the UMC Utrecht twin database, the participant database of the GROUP cohort, 3 national newspaper advertisement and local psychiatry clinics. All subjects from the previous cohort agreed to participate again in this new 3T MRI study; no data from previous measurements was used. The Medical Ethical Committee of the University Medical Center Utrecht approved this study, and the experiments were in accordance with the Declaration of Helsinki. All participants gave their written informed consent. The subject overlap with our previous twin cohort is 30.5% (and in case of overlap, only the 3T measurement was included).
UNIBA	Participants included patients with schizophrenia, unaffected siblings and healthy subjects. All individuals were white Caucasian, from the province of Bari, and they were aged 18 to 65 years. The eligibility criteria for all participants were (a) IQ>70; (b) no history of head trauma or loss of consciousness; (c) no current or lifetime history of medical or neurological disorders; (d) no lifetime history of substance use disorder; (e) no MRI contraindications (e.g. metal implants). Patients were required to fulfil diagnostic DSM-IV criteria for Schizophrenia, while unaffected relatives of schizophrenic patients and healthy volunteers were included if they had no lifetime history of psychiatric disorders.

Table S2. Sample image acquisition and image processing details

Sample	# of Scanners	Scanner Vendor & Type	Imaging Protocols	Slice Orientation	FreeSurfer Version	Operating System/Linux Kernel Version
BPO_FLB	1	3.0T Siemens Allegra	T1-weighted scans were acquired using a three-dimensional magnetization prepared rapid gradient echo (3DMPRAGE) protocol with the following parameters. Repetition time (TR) = 1750 ms, echo time (TE) = 4.38 ms, flip angle = 8°, Slice thickness = 1mm, matrix size = 256 x 208 and voxel size = 1 mm.		v5.3.0	
C_SFS	1	3T General Electric Discovery MR750	Each scan consisted of a whole-brain T1-weighted 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: echo time (TE)=3.1ms, inversion time (TI)=650ms, repetition time (TR)=7.4ms, flip angle=11°, field of view (FOV)=25.6, matrix=256 x 256, slice thickness=1mm, 236 coronal slices.		v6.0.0	
Cardiff	1	GE HDx 3T scanner	T1 - axial 3D fast spoiled gradient recalled (FSPGR) sequence (TR/TE/TI = 8/3/ 450 ms; Flip Angle = 200; acquisition matrix= 256(AP) x192(LR)x172(SI), 1mm isotropic voxels)		v5.3.0	3.0.80-0.7-default
CLiNG	1	3T Magnetom TIM Trio	MRI scanning was performed on a 3.0-Tesla Magnetom TIM Trio (Siemens, Erlangen, Germany). A T1-weighted, 3D magnetization prepared rapid gradient echo sequence (MPRAGE) (TR/TE/TI/FA=2250 ms/3.26 ms/900 ms/9°; image matrix = 256 x 256; duration 8 min and 26 sec) was acquired generating 192 sagittal slices with a voxel size of 1 mm^3.	Sagittal	v5.3.0	Ubuntu 12.04: 2.6.32-431.17.1.el6.x86_64
DEU	1	1.5 T Philips Tesla Achieva MRI	3D T1-fast field echo (FFE) axial images were acquired with the following parameters: repetition time (TR) =8.7 ms, echo time (TE) =4 ms, flip angle=8 o, field of view (FOV) =230 mm x 220 mm, slice thickness=1 mm, number of signal averages (NSA) =1, matrix=192		v5.3.0	2.6.32-573.12.1.el6.x86_64
EGEU	1	Siemens 3T Magnetom Verio	T1-weighted anatomical 3D (MP-RAGE) 1 mm3 isotropic (FoV=256, TR=1600 msec, TE=221 msec, TI= 900 msec, FA=9°), matrix 256X256		v5.3.0	2.6.32-431.17.1.el6.x86_64
EHRS	1	1T Siemens	Scanned with a 1T 42 SPE Siemens MRI scanner (Siemens, Erlangen, Germany). 128 contiguous coronal T1-weighted slices (thickness 1.88 mm, field-of-view 250 x 250 mm) were obtained using a Magnetisation Prepared Rapid Acquisition of Gradient Echo (MPRAGE) sequence (TR=10ms, TE=4ms, TI=200ms, relaxation time 500ms).	Coronal	v5.3.0	Linux: 2.6.32-754.2.1.e16.x86_64
ENBD_UT	1	Philips 3 T	T1-weighted, 25.6cmx25.6cm square field-of-view (1.0mm slice, Tr=1750msec, Te=4.4msec, Ti=900msec, flip=80, data acquisition matrix-=256(phase)x256(frequency)x(160 slice).	Axial	v5.3.0	
HHR	1	1.5-T GE Signa	We acquired T1-weighted SPGR (Spoiled Gradient Recalled) scans: flip angle=40°, TE=5 ms, TR=25 ms, FOV=24 cm x18 cm, matrix-=256x160 pixels, NEX=1, no inter-slice gap, 124 coronal, 1.5 mm thick slices.		v5.3.0	macOS: Darwin kernel 15.6.0
HUBIN	1	1.5T GE Signa	3D spoiled gradient recalled pulse sequence for T1-weighted images: 1.5 mm coronal slices, no gap, 35° flip angle, repetition time 24 ms, echo time 6.0 ms, number of excitations 2, field of view 24 cm, acquisition matrix 256 x 192.		v5.3.0	3.13.0-79-generic
IDIBAPS	1	Siemens Trio 3T	240 sagittal slices, 2,300-ms repetition time, 3.01-ms echo time, 1-mm slice thickness, 900-ms inversion time, 394x240 field of view, 256x256 matrix size, and 9 degrees flip angle.		v5.3.0	2.6.32.12-0.7; 3.0.76-0.11; 3.2.0-23

Sample	# of Scanners	Scanner Vendor & Type	Imaging Protocols	Slice Orientation	FreeSurfer Version	Operating System/Linux Kernel Version
IoP – BD	1	1.5 Tesla GE N/Vi Signa System	Coronal FSPGR. Matrix: 256 X 256, 124 slices with 1.5mm slice thickness. FOV: 220x160. Flip angle: 20°. Number of excitations: 1. No gap. RT=13.1ms echo time = 5.8ms TI=450ms. Matched to MFS.		v5.3.0	2.6.32-358.6.2.el6.x86_64
IoP – SZ	1	1.5 Tesla GE N/Vi Signa System	3D T1-weighted, spoiled gradient (SPGR) (TE=5ms, TR=35ms, flip angle=30°, NEX=1, FOV=200x200mm, voxel dimensions=1x1x1.5mm), yielding 124 contiguous slices 1.5mm thick.	Coronal	v5.3.0	2.6.32-358.6.2.el6.x86_64
LIBD	1	1.5T GE	T1-weighted spoiled gradient recalled sequence (spgr). Repetition time, 24ms; echo time, 5ms; number of excitations, 1; flip angle, 45 degrees; matrix size 256 x 256; field of view, 24 x 24cm; 124 sagittal slices (0.94 x 0.94 x 1.5mm).	Sagittal	v5.0.0	Linux: 2.6.32-696.23.1.e16.x86_64
Maastricht–GROUP	1	3T Siemens Magnetom Allegra	Modified Driven Equilibrium Fourier Transform sequence (MDEFT); TR=7.92msec, TE=2.4msec, IR=910msec, flip angle=15°, FOV=256x240. Acquisition Matrix=256x240x176 (1 x 1 x 1mm). Magnetisation Prepared Rapid Acquisition of Gradient Echo (MPRAGE); TR=2250msec, TE=2.6msec, IR=900msec, flip angle=9°, FOV=256x256. Acquisition Matrix=256x256x192 (1 x 1 x 1mm).		v5.3.0	macOS: 10.8.0
MFS	1	1.5T GE N/Vi Signa System	3D T1-weighted spoiled gradient recall echo sequence (SPGR). TR=13.1 ms, TI=450 ms, TE=5.8 ms, number of excitations=1, flip angle=20°, acquisition matrix=256X256X128, 1.5mm thick contiguous coronal slices.	Coronal	v5.3.0	3.0.0-21-generic
MooDS	1	Siemens Trio 3T	T1-weighted 3D (MP-RAGE) 1 mm3 isotropic (FoV=192, TR=1.57 s, TE=2.74 ms, FA=15°)		v5.3.0	4.4.0-142-generic
MSSM	1	1.5T GE Signa	3D T1-weighted spoiled gradient recalled acquisition in steady state; Voxel Size: 0.9375x0.9375x1.5mm3, TR/TE/TI=5.1/18/450 ms, Flip Angle: 20°.	Axial	v5.3.0	2.6.32-358.6.2.el6.x86_64
NU	1	Siemens Vision 1.5T	MPRAGE; 1.25mm x 1mm x 1mm; TR: 9.70 msec, TE: 4.00 msec, TI: 20.00 msec, flip angle: 10.00 degrees, FOV: 256		v5.3.0	
Olin	1	Siemens Magnetom Allegra 3T	3D magnetization-prepared rapid gradient-echo (MPRage) sequence: TI=766; TR=2200; TE=4.13; flip angle 13 deg; FOV 256 mm; 0.8mm iso; axial slices parallel to the AC-PC line. To increase signal-to-noise ratio, four volumes were acquired per subject.		v5.3.0	Linux: 2.6.32-504.16.2.el6.x86_64
PHHR	1	1.5T GE Signa	We acquired T1-weighted SPGR (Spoiled Gradient Recalled) scans: flip angle=40°, TE=5 ms, TR=25 ms, FOV=24 cm x18 cm, matrix=256x160 pixels, NEX=1, no inter-slice gap, 124 coronal, 1.5 mm thick slices.	Coronal	v5.3.0	macOS: Darwin kernel 15.6.0
SydneyBipolarGroup	1	Philips Achieva 3T	180 T1-weighted 3D turbo field-echo images were acquired sagitally (TR=5.5msec, TE=2.5ms, flip angle=8°, field of view=256x256x180mm, voxel size=1x1x1mm, scan time=371s).	Sagittal	v5.3.0	Linux: 2.6.32-504.3.3.el6.x86_64
STAR (Swedish) twin cohort	1	GE 1.5T Signa	T1 - sagittal irSPGR sequence, 1mm3 isotropic voxels, 256mm FOV, TR/TE = 25/6 msec, 35 degree flip	Sagittal	v5.3.0	3.10.0-693.43.1.el7.x86_64
UMCG – GROUP	1	3T Philips Intera	8-SENSE head coil, and anatomic images were obtained using a sagittal 3D T1-weighted sequence (176 slices, repetition time 9 ms, echo time 3.5 ms, field of view 256 mm, voxel size 1 x 1 x 1 mm, slice thickness 1.0 mm).	Sagittal	v6.0.0	3.10.0-693.2.2.el7.x86_64

Sample	# of Scanners	Scanner Vendor & Type	Imaging Protocols	Slice Orientation	FreeSurfer Version	Operating System/Linux Kernel Version
UMCU – BD twins	1	1.5T Philips NT	The acquired scans were T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%).	Coronal	v5.1.0	2.6.32-358.6.2.el6.x86_64
UMCU – DBSOS	1	3T Philips Achieva	The T1-weighted 3-dimensional fast-field echo scans were acquired with the following parameters: 220 0.8 mm contiguous slices, echo time = 4.6 ms, repetition time = 10 ms, flip angle = 8°, in-plane voxel size 0.75x0.75 mm2.		v5.3.0	2.6.32-358.6.2.el6.x86_64
UMCU – GROUP	1	1.5T Philips Achieva	The acquired scans were T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%).	Coronal	v5.1.0	2.6.32-358.6.2.el6.x86_64
UMCU – Parents	1	1.5T Philips NT	The acquired scans were T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%).	Coronal	v5.3.0	2.6.32-358.6.2.el6.x86_64
UMCU – UTWINS	2	1.5T Philips NT/3T Philips Achieva	1.5T: T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%). 3T: The T1-weighted 3-dimensional fast-field echo scans were acquired with the following parameters: 220 0.8 mm contiguous slices, echo time = 4.6 ms, repetition time = 10 ms, flip angle = 8°, in-plane voxel size 0.75x0.75 mm2.		v5.3.0	2.6.32-358.6.2.el6.x86_64
UNIBA	1	GE 3T	124 1.3-mm slices using 3D T1-weighted gradient echo fast SPGR sequence (TE=min full; flip angle, 6°; prep time, 725; field of view, 250 mm; bandwidth, 31.25; matrix, 256 x 256)		v5.3.0	4.4.0-116-generic

Table S3. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and (from left to right) FDRs-BD, patients with bipolar disorder, FDRs-SZ, patients with schizophrenia. Last column displays whether the effect sizes differed significantly between FDRs-BD and FDRs-SZ and between BD and SZ patients.

	BIPOLAR DISORDER		SCHIZOPHRENIA		
	Relatives ES ± 95% CI	Patients# ES ± 95% CI	Relatives ES ± 95% CI	Patients ES ± 95% CI	*Significant differences*
Global measures					
ICV	0.16 [0.06 , 0.27]**	0.04 [-0.12 , 0.20]	-0.01 [-0.11 , 0.09]	-0.12 [-0.30 , 0.06]	BD rel>SZ rel; BD pt>SZ pt
Total brain	0.11 [0.00 , 0.22]*	-0.13 [-0.30 , 0.04]	-0.10 [-0.20 , -0.00]*	-0.40 [-0.59 , -0.21]**	BD rel>SZ rel; BD pt>SZ pt
Surface area	0.15 [0.03 , 0.27]*	0.08 [-0.10 , 0.25]	-0.01 [-0.12 , 0.10]	-0.21 [-0.45 , 0.03]	BD rel>SZ rel; BD pt>SZ pt
Cortical thickness	-0.01 [-0.11 , 0.09]	-0.35 [-0.60 , -0.11]**	-0.13 [-0.24 , -0.02]*	-0.62 [-0.76 , -0.48]**	BD rel>SZ rel; BD pt>SZ pt
Cortical GM	0.15 [0.04 , 0.27]*	-0.08 [-0.25 , 0.10]	-0.08 [-0.19 , 0.04]	-0.48 [-0.65 , -0.31]**	BD rel>SZ rel; BD pt>SZ pt
Cerebral WM	0.06 [-0.05 , 0.17]	-0.10 [-0.27 , 0.07]	-0.09 [-0.17 , -0.01]*	-0.27 [-0.43 , -0.10]**	BD rel>SZ rel; BD pt>SZ pt
Cerebellum GM†	0.13 [0.01 , 0.25]*	-0.19 [-0.35 , -0.02]*	-0.10 [-0.17 , -0.02]*	-0.26 [-0.40 , -0.13]**	BD rel>SZ rel
Cerebellum WM†	0.00 [-0.13 , 0.14]	-0.13 [-0.25 , -0.01]*	-0.10 [-0.17 , -0.02]*	-0.18 [-0.34 , -0.02]**	
Third ventricle	-0.01 [-0.11 , 0.10]	0.32 [0.06 , 0.58]*	0.14 [0.03 , 0.25]*	0.51 [0.38 , 0.65]**	BD rel<SZ rel; BD pt<SZ pt
Lateral ventricles	0.14 [0.04 , 0.23]*	0.31 [0.03 , 0.60]*	0.07 [-0.01 , 0.15]	0.33 [0.17 , 0.49]**	
Subcortical volumes					
Thalamus	0.02 [-0.08 , 0.12]	-0.33 [-0.54 , -0.12]**	-0.12 [-0.19 , -0.04]**	-0.32 [-0.45 , -0.18]**	BD rel>SZ rel
Caudate	0.08 [-0.01 , 0.17]	-0.07 [-0.23 , 0.10]	-0.04 [-0.12 , 0.04]	0.16 [0.00 , 0.31]**	BD rel>SZ rel; BD pt<SZ pt
Putamen	0.01 [-0.09 , 0.12]	-0.08 [-0.35 , 0.18]	-0.07 [-0.15 , -0.00]*	0.25 [0.12 , 0.38]**	BD pt<SZ pt
Pallidum	0.05 [-0.06 , 0.15]	0.09 [-0.07 , 0.26]	-0.05 [-0.12 , 0.02]	0.40 [0.25 , 0.55]**	BD pt<SZ pt
Hippocampus	0.02 [-0.07 , 0.11]	-0.20 [-0.37 , -0.02]*	-0.07 [-0.15 , 0.00]	-0.49 [-0.57 , -0.40]**	BD pt>SZ pt
Amygdala	0.07 [-0.02 , 0.16]	-0.13 [-0.33 , 0.08]	-0.01 [-0.12 , 0.11]	-0.33 [-0.41 , -0.24]**	BD pt>SZ pt
Accumbens	0.07 [-0.05 , 0.19]	-0.20 [-0.45 , 0.06]	-0.07 [-0.15 , 0.01]	-0.25 [-0.38 , -0.13]**	BD rel>SZ rel

*$p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | # lithium corrected

Table S4. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and (from left to right) FDRs-BD, patients with bipolar disorder, FDRs-SZ, patients with schizophrenia, controlling for intracranial volume (ICV). Last column displays whether the effect sizes differed significantly between FDRs-BD and FDRs-SZ and between BD and SZ patients.

	BIPOLAR DISORDER		SCHIZOPHRENIA		
	Relatives	Patients#	Relatives	Patients	
	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI	Significant differences
Global measures					
ICV	-	-	-	-	
Total brain	0.00 [-0.11 , 0.11]	-0.36 [-0.54 , -0.18]**	-0.16 [-0.23 , -0.09]**	-0.57 [-0.74 , -0.39]**	BD rel>SZ rel; BD pt>SZ pt; SZ rel>SZ pt
Surface area	0.06 [-0.05 , 0.16]	0.03 [-0.17 , 0.23]	-0.03 [-0.11 , 0.06]	-0.22 [-0.41 , -0.03]**	BD pt>SZ pt
Cortical thickness	0.00 [-0.10 , 0.09]	-0.37 [-0.62 , -0.12]**	-0.13 [-0.25 , -0.02]**	-0.63 [-0.77 , -0.49]**	BD rel>SZ rel; BD pt>SZ pt
Cortical GM	0.06 [-0.04 , 0.16]	-0.22 [-0.41 , -0.04]**	-0.11 [-0.21 , -0.02]**	-0.62 [-0.76 , -0.47]**	BD rel>SZ rel; BD pt>SZ pt
Cerebral WM	-0.07 [-0.18 , 0.04]	-0.25 [-0.41 , -0.10]**	-0.12 [-0.19 , -0.04]**	-0.29 [-0.45 , -0.13]**	
Cerebellum GM†	0.07 [-0.04 , 0.18]	-0.26 [-0.40 , -0.13]**	-0.09 [-0.16 , -0.02]**	-0.25 [-0.37 , -0.13]**	BD rel>SZ rel
Cerebellum WM†	-0.08 [-0.22 , 0.06]	-0.21 [-0.33 , -0.09]**	-0.09 [-0.17 , -0.02]**	-0.16 [-0.29 , -0.04]**	
Third ventricle	-0.06 [-0.15 , 0.03]	0.29 [0.00 , 0.58]*	0.15 [0.04 , 0.26]**	0.56 [0.43 , 0.70]**	BD rel<SZ rel; BD pt<SZ pt; SZ rel<SZ pt
Lateral ventricles	0.08 [-0.03 , 0.19]	0.29 [-0.04 , 0.61]	0.09 [0.00 , 0.18]*	0.38 [0.21 , 0.55]**	
Subcortical volumes					
Thalamus	-0.07 [-0.18 , 0.03]	-0.45 [-0.66 , -0.25]**	-0.13 [-0.23 , -0.03]**	-0.32 [-0.41 , -0.23]**	
Caudate	0.01 [-0.09 , 0.10]	-0.12 [-0.29 , 0.04]	-0.03 [-0.11 , 0.04]	0.22 [0.10 , 0.35]**	BD pt<SZ pt
Putamen	-0.04 [-0.13 , 0.05]	-0.12 [-0.37 , 0.12]	-0.07 [-0.14 , 0.01]	0.33 [0.22 , 0.44]**	BD pt<SZ pt
Pallidum	-0.01 [-0.12 , 0.09]	0.06 [-0.10 , 0.22]	-0.05 [-0.12 , 0.02]	0.47 [0.32 , 0.61]**	BD pt<SZ pt
Hippocampus	-0.04 [-0.15 , 0.07]	-0.26 [-0.43 , -0.09]**	-0.06 [-0.14 , 0.01]	-0.49 [-0.57 , -0.40]**	BD pt>SZ pt
Amygdala	0.01 [-0.08 , 0.10]	-0.22 [-0.47 , 0.03]	0.00 [-0.11 , 0.11]	-0.32 [-0.40 , -0.23]**	
Accumbens	0.02 [-0.09 , 0.14]	-0.24 [-0.47 , -0.01]*	-0.05 [-0.13 , 0.02]	-0.21 [-0.32 , -0.11]**	

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | # lithium corrected

Table S5. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and FDRs-BD and FDRs-SZ, controlling for psychopathology in relatives and/or controls by i) adding the presence of a diagnosis (not BD or SZ) as a covariate, ii) comparing only the *healthy* relatives with the *healthy* controls.

	BIPOLAR DISORDER		SCHIZOPHRENIA	
	i) Covariate ES ± 95% CI	ii) Healthy only ES ± 95% CI	i) Covariate ES ± 95% CI	ii) Healthy only ES ± 95% CI
Global measures				
ICV	0.18 [0.07 , 0.28]**	0.16 [0.05 , 0.27]**	0.00 [-0.10 , 0.10]	0.00 [-0.11 , 0.12]
Total brain	0.13 [0.02 , 0.24]*	0.13 [0.01 , 0.25]*	-0.08 [-0.17 , 0.01]	-0.07 [-0.17 , 0.04]
Surface area	0.17 [0.05 , 0.28]**	0.18 [0.06 , 0.31]**	0.01 [-0.10 , 0.11]	0.01 [-0.11 , 0.13]
Cortical thickness	0.00 [-0.09 , 0.10]	-0.02 [-0.13 , 0.09]	-0.12 [-0.23 , -0.02]*	-0.12 [-0.22 , -0.02]*
Cortical GM	0.17 [0.06 , 0.28]**	0.18 [0.06 , 0.30]**	-0.06 [-0.17 , 0.05]	-0.05 [-0.16 , 0.06]
Cerebral WM	0.07 [-0.04 , 0.18]	0.08 [-0.04 , 0.19]	-0.07 [-0.14 , 0.01]	-0.07 [-0.16 , 0.03]
Cerebellum GM†	0.15 [0.03 , 0.28]*	0.15 [0.01 , 0.29]*	-0.09 [-0.16 , -0.01]*	-0.07 [-0.15 , 0.02]
Cerebellum WM†	0.01 [-0.12 , 0.13]	0.01 [-0.13 , 0.15]	-0.09 [-0.17 , -0.02]*	-0.08 [-0.17 , -0.00]*
Third ventricle	0.00 [-0.11 , 0.10]	0.00 [-0.13 , 0.13]	0.15 [0.03 , 0.27]*	0.16 [0.03 , 0.28]*
Lateral ventricles	0.13 [0.03 , 0.23]*	0.11 [0.00 , 0.21]*	0.08 [-0.01 , 0.17]	0.08 [-0.03 , 0.18]
Subcortical volumes				
Thalamus	0.03 [-0.07 , 0.13]	0.04 [-0.08 , 0.15]	-0.11 [-0.18 , -0.03]*	-0.11 [-0.19 , -0.03]*
Caudate	0.09 [-0.00 , 0.18]	0.04 [-0.06 , 0.15]	-0.02 [-0.10 , 0.06]	-0.04 [-0.13 , 0.05]
Putamen	0.02 [-0.09 , 0.13]	0.00 [-0.11 , 0.11]	-0.06 [-0.14 , 0.01]	-0.07 [-0.15 , 0.01]
Pallidum	0.06 [-0.05 , 0.17]	0.06 [-0.06 , 0.19]	-0.04 [-0.11 , 0.03]	-0.04 [-0.13 , 0.05]
Hippocampus	0.01 [-0.08 , 0.10]	0.02 [-0.08 , 0.12]	-0.07 [-0.14 , 0.00]	-0.08 [-0.16 , -0.00]*
Amygdala	0.08 [-0.01 , 0.17]	0.09 [-0.01 , 0.19]	0.00 [-0.11 , 0.10]	-0.01 [-0.12 , 0.10]
Accumbens	0.08 [-0.03 , 0.19]	0.09 [-0.04 , 0.22]	-0.07 [-0.17 , 0.02]	-0.07 [-0.17 , 0.02]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses

Table S6. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and FDRs-BD and FDRs-SZ, controlling for intracranial volume (ICV) and psychopathology in relatives and/or controls by i) adding the presence of a diagnosis (not BD or SZ) as a covariate, ii) comparing only the *healthy* relatives with the *healthy* controls.

	BIPOLAR DISORDER		SCHIZOPHRENIA	
	i) Covariate ES ± 95% CI	ii) Healthy only ES ± 95% CI	i) Covariate ES ± 95% CI	ii) Healthy only ES ± 95% CI
Global measures				
ICV	-	-	-	-
Total brain	0.01 [-0.10 , 0.13]	0.05 [-0.07 , 0.16]	-0.13 [-0.21 , -0.06]**	-0.14 [-0.22 , -0.06]**
Surface area	0.07 [-0.04 , 0.18]	0.11 [-0.00 , 0.22]	-0.01 [-0.10 , 0.08]	-0.01 [-0.11 , 0.08]
Cortical thickness	0.00 [-0.09 , 0.09]	-0.01 [-0.11 , 0.10]	-0.13 [-0.24 , -0.02]**	-0.12 [-0.22 , -0.01]*
Cortical GM	0.08 [-0.01 , 0.17]	0.12 [0.01 , 0.22]*	-0.09 [-0.19 , -0.00]*	-0.09 [-0.17 , 0.00]
Cerebral WM	-0.07 [-0.19 , 0.05]	-0.05 [-0.16 , 0.06]	-0.09 [-0.17 , -0.02]**	-0.11 [-0.19 , -0.03]*
Cerebellum GM†	0.09 [-0.03 , 0.21]	0.09 [-0.05 , 0.22]	-0.09 [-0.16 , -0.01]**	-0.07 [-0.15 , 0.01]
Cerebellum WM†	-0.09 [-0.22 , 0.04]	-0.07 [-0.22 , 0.07]	-0.09 [-0.17 , -0.02]**	-0.09 [-0.17 , -0.01]*
Third ventricle	-0.06 [-0.16 , 0.04]	-0.06 [-0.18 , 0.06]	0.16 [0.05 , 0.28]**	0.16 [0.05 , 0.28]**
Lateral ventricles	0.07 [-0.04 , 0.19]	0.05 [-0.07 , 0.17]	0.09 [0.01 , 0.18]*	0.09 [-0.00 , 0.18]
Subcortical volumes				
Thalamus	-0.06 [-0.16 , 0.03]	-0.04 [-0.15 , 0.08]	-0.13 [-0.23 , -0.03]**	-0.13 [-0.25 , -0.02]*
Caudate	0.02 [-0.08 , 0.11]	-0.02 [-0.13 , 0.09]	-0.02 [-0.09 , 0.05]	-0.05 [-0.13 , 0.03]
Putamen	-0.04 [-0.13 , 0.05]	-0.05 [-0.16 , 0.05]	-0.06 [-0.13 , 0.01]	-0.07 [-0.16 , 0.01]
Pallidum	0.00 [-0.11 , 0.11]	0.02 [-0.12 , 0.15]	-0.04 [-0.12 , 0.03]	-0.06 [-0.14 , 0.02]
Hippocampus	-0.06 [-0.18 , 0.06]	-0.04 [-0.16 , 0.08]	-0.06 [-0.13 , 0.01]	-0.08 [-0.16 , 0.00]
Amygdala	0.01 [-0.08 , 0.10]	0.03 [-0.07 , 0.14]	0.01 [-0.10 , 0.11]	-0.01 [-0.12 , 0.10]
Accumbens	0.03 [-0.08 , 0.14]	0.04 [-0.08 , 0.16]	-0.06 [-0.15 , 0.03]	-0.06 [-0.14 , 0.02]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses

Table S7a. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-BD, i.e. MZ co-twins, DZ co-twins, offspring, siblings, and parents. Last column displays whether the effect sizes differ significantly from each other, pairwise.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings† ES ± 95%CI	Parents[1] ES ± 95%CI	Significant differences
Global measures						
ICV	0.21 [-0.12 , 0.54]	0.15 [-0.16 , 0.45]	0.19 [-0.00 , 0.39]	0.10 [-0.05 , 0.26]	0.10 [-0.44 , 0.63]	
Total brain	0.07 [-0.26 , 0.40]	0.04 [-0.27 , 0.35]	0.11 [-0.11 , 0.33]	0.13 [-0.04 , 0.31]	-0.07 [-0.61 , 0.46]	
Surface area	0.04 [-0.29 , 0.37]	0.05 [-0.26 , 0.35]	0.15 [-0.08 , 0.39]	0.18 [-0.02 , 0.39]	0.22 [-0.31 , 0.76]	
Cortical thickness	0.12 [-0.27 , 0.51]	-0.03 [-0.34 , 0.28]	-0.07 [-0.30 , 0.16]	-0.02 [-0.17 , 0.13]	0.13 [-0.41 , 0.66]	
Cortical GM	0.19 [-0.14 , 0.52]	0.03 [-0.28 , 0.34]	0.14 [-0.09 , 0.37]	0.17 [-0.03 , 0.37]	0.30 [-0.23 , 0.84]	
Cerebral WM	-0.03 [-0.36 , 0.30]	0.04 [-0.26 , 0.35]	0.08 [-0.12 , 0.27]	0.08 [-0.10 , 0.27]	-0.22 [-0.75 , 0.32]	
Cerebellum GM†	0.09 [-0.24 , 0.42]	0.08 [-0.23 , 0.38]	0.10 [-0.19 , 0.39]	0.13 [-0.03 , 0.30]	-0.18 [-0.71 , 0.36]	
Cerebellum WM†	0.00 [-0.34 , 0.35]	-0.10 [-0.66 , 0.45]	-0.04 [-0.34 , 0.25]	0.05 [-0.12 , 0.22]	-0.10 [-0.63 , 0.44]	
Third ventricle	0.19 [-0.42 , 0.80]	0.05 [-0.26 , 0.35]	-0.05 [-0.28 , 0.17]	-0.05 [-0.20 , 0.10]	0.38 [-0.16 , 0.92]	
Lateral ventricles	0.26 [-0.29 , 0.82]	0.16 [-0.15 , 0.47]	0.20 [0.06 , 0.33]*	0.00 [-0.15 , 0.15]	0.76 [0.21 , 1.30]*	OFF>SIB
Subcortical volumes						
Thalamus	-0.18 [-0.54 , 0.18]	-0.01 [-0.32 , 0.30]	0.06 [-0.11 , 0.23]	0.04 [-0.11 , 0.19]	-0.47 [-1.01 , 0.07]	
Caudate	0.18 [-0.16 , 0.51]	0.17 [-0.14 , 0.48]	0.09 [-0.05 , 0.24]	0.05 [-0.11 , 0.21]	-0.30 [-0.84 , 0.23]	
Putamen	0.07 [-0.30 , 0.45]	0.11 [-0.39 , 0.61]	0.05 [-0.12 , 0.22]	-0.04 [-0.22 , 0.14]	-0.08 [-0.61 , 0.46]	
Pallidum	0.03 [-0.31 , 0.37]	0.09 [-0.36 , 0.53]	0.06 [-0.12 , 0.24]	0.09 [-0.06 , 0.24]	-0.75 [-1.30 , -0.20]*	
Hippocampus	0.02 [-0.32 , 0.35]	-0.03 [-0.33 , 0.28]	-0.04 [-0.19 , 0.12]	0.14 [-0.01 , 0.29]	-0.46 [-1.00 , 0.08]	OFF<SIB
Amygdala	0.18 [-0.15 , 0.51]	0.05 [-0.26 , 0.35]	0.04 [-0.10 , 0.18]	0.10 [-0.05 , 0.25]	-0.01 [-0.54 , 0.52]	
Accumbens	-0.20 [-0.61 , 0.21]	0.07 [-0.23 , 0.38]	0.11 [-0.10 , 0.32]	0.11 [-0.09 , 0.31]	-0.09 [-0.62 , 0.45]	

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | [1] Parents only 1 cohort; no meta-analysis

Table S7b. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-SZ, i.e. MZ co-twins, DZ co-twins, offspring, siblings, and parents. Last column displays whether the effect sizes differ significantly from each other, pairwise.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI	Significant differences
Global measures						
ICV	-0.12 [-0.42 , 0.18]	-0.03 [-0.31 , 0.24]	-0.20 [-0.52 , 0.11]	0.09 [-0.08 , 0.26]	-0.04 [-0.30 , 0.22]	OFF< SIB
Total brain	-0.25 [-0.56 , 0.06]	-0.14 [-0.41 , 0.14]	-0.33 [-0.67 , 0.01]	-0.01 [-0.13 , 0.11]	-0.10 [-0.46 , 0.27]	OFF< SIB
Surface area	-0.20 [-0.6 , 0.20]	-0.04 [-0.32 , 0.24]	-0.27 [-0.57 , 0.02]	0.10 [-0.06 , 0.26]	0.03 [-0.25 , 0.30]	OFF< SIB; OFF<PAR
Cortical thickness	-0.29 [-0.71 , 0.14]	-0.52 [-1.39 , 0.34]	-0.07 [-0.49 , 0.35]	-0.11 [-0.22 , 0.00]	0.01 [-0.39 , 0.41]	DZ< OFF; DZ<SIB; DZ<PAR
Cortical GM	-0.32 [-0.62 , -0.02]*	-0.17 [-0.44 , 0.11]	-0.30 [-0.68 , 0.08]	0.01 [-0.11 , 0.13]	0.06 [-0.33 , 0.45]	MZ< SIB,PAR; OFF<SIB,PAR
Cerebral WM	-0.22 [-0.53 , 0.08]	-0.12 [-0.40 , 0.15]	-0.27 [-0.54 , -0.00]*	-0.01 [-0.12 , 0.09]	-0.17 [-0.44 , 0.11]	OFF<SIB
Cerebellum GM	0.03 [-0.27 , 0.33]	0.06 [-0.31 , 0.43]	-0.17 [-0.37 , 0.02]	-0.10 [-0.20 , 0.00]	-0.15 [-0.40 , 0.10]	
Cerebellum WM	0.10 [-0.20 , 0.40]	-0.07 [-0.35 , 0.20]	-0.16 [-0.35 , 0.04]	-0.06 [-0.17 , 0.05]	-0.34 [-0.61 , -0.07]*	MZ>PAR; SIB>PAR
Third ventricle	0.29 [-0.01 , 0.59]	0.18 [-0.09 , 0.46]	0.10 [-0.10 , 0.29]	0.16 [-0.03 , 0.35]	0.01 [-0.34 , 0.36]	
Lateral ventricles	0.17 [-0.13 , 0.47]	0.02 [-0.35 , 0.40]	0.08 [-0.11 , 0.28]	0.04 [-0.05 , 0.13]	0.00 [-0.64 , 0.63]	
Subcortical volumes						
Thalamus	-0.13 [-0.44 , 0.18]	-0.23 [-0.55 , 0.09]	-0.29 [-0.55 , -0.04]*	-0.05 [-0.14 , 0.04]	-0.24 [-0.50 , 0.01]	OFF<SIB
Caudate	0.12 [-0.18 , 0.43]	-0.13 [-0.42 , 0.15]	-0.21 [-0.41 , -0.02]*	0.02 [-0.11 , 0.16]	0.03 [-0.22 , 0.28]	OFF<MZ; OFF<SIB
Putamen	0.02 [-0.30 , 0.33]	-0.15 [-0.44 , 0.14]	-0.32 [-0.64 , 0.01]	-0.02 [-0.11 , 0.07]	-0.18 [-0.46 , 0.10]	OFF<SIB
Pallidum	0.15 [-0.17 , 0.47]	0.01 [-0.28 , 0.30]	-0.35 [-0.63 , -0.06]*	-0.03 [-0.12 , 0.06]	0.03 [-0.22 , 0.28]	OFF<MZ,DZ,SIB,PAR
Hippocampus	-0.14 [-0.46 , 0.19]	0.03 [-0.26 , 0.32]	-0.25 [-0.51 , -0.00]*	-0.04 [-0.13 , 0.05]	-0.09 [-0.39 , 0.21]	OFF<SIB
Amygdala	-0.20 [-0.62 , 0.23]	0.01 [-0.28 , 0.29]	-0.27 [-0.51 , -0.03]*	0.04 [-0.12 , 0.20]	0.36 [0.03 , 0.70]*	MZ,DZ,OFF,SIB<PAR; OFF<SIB
Accumbens	-0.24 [-0.63 , 0.15]	0.03 [-0.25 , 0.30]	-0.22 [-0.50 , 0.07]	-0.04 [-0.13 , 0.05]	0.01 [-0.39 , 0.42]	OFF<SIB

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected

Table S8a. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-BD, i.e. MZ co-twins, DZ co-twins, offspring, siblings, parents, controlling for intracranial volume (ICV). Last column displays whether the effect sizes differ significantly from each other, pairwise.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings† ES ± 95%CI	Parents[1] ES ± 95%CI	Significant differences
Global measures						
ICV	-	-	-	-	-	
Total brain	-0.12 [-0.45 , 0.21]	-0.05 [-0.45 , 0.35]	-0.06 [-0.27 , 0.16]	0.09 [-0.07 , 0.25]	-0.21 [-0.75 , 0.32]	
Surface area	-0.15 [-0.67 , 0.36]	-0.03 [-0.34 , 0.27]	0.03 [-0.16 , 0.21]	0.14 [-0.03 , 0.32]	0.20 [-0.34 , 0.73]	
Cortical thickness	0.11 [-0.26 , 0.48]	-0.07 [-0.37 , 0.24]	-0.06 [-0.28 , 0.17]	-0.01 [-0.16 , 0.14]	0.15 [-0.39 , 0.68]	
Cortical GM	0.07 [-0.26 , 0.40]	-0.08 [-0.38 , 0.23]	0.02 [-0.17 , 0.21]	0.13 [-0.04 , 0.29]	0.29 [-0.24 , 0.83]	
Cerebral WM	-0.23 [-0.56 , 0.10]	0.02 [-0.48 , 0.51]	-0.11 [-0.31 , 0.08]	0.02 [-0.17 , 0.20]	-0.37 [-0.91 , 0.17]	
Cerebellum GM†	0.02 [-0.31 , 0.35]	0.03 [-0.27 , 0.34]	0.05 [-0.21 , 0.31]	0.06 [-0.10 , 0.23]	-0.21 [-0.75 , 0.32]	
Cerebellum WM†	-0.11 [-0.50 , 0.28]	-0.17 [-0.78 , 0.44]	-0.13 [-0.44 , 0.17]	-0.03 [-0.20 , 0.13]	-0.14 [-0.67 , 0.40]	
Third ventricle	0.18 [-0.37 , 0.73]	-0.05 [-0.35 , 0.26]	-0.11 [-0.33 , 0.10]	-0.07 [-0.22 , 0.08]	0.37 [-0.17 , 0.91]	
Lateral ventricles	0.32 [-0.13 , 0.77]	0.06 [-0.25 , 0.37]	0.11 [-0.07 , 0.29]	-0.06 [-0.21 , 0.09]	0.80 [0.25 , 1.35]*	MZ>SIB
Subcortical volumes						
Thalamus	-0.52 [-1.19 , 0.14]	0.12 [-0.53 , 0.77]	-0.04 [-0.17 , 0.10]	0.00 [-0.17 , 0.18]	-0.52 [-1.06 , 0.02]	MZ<DZ,OFF,SIB
Caudate	0.09 [-0.25 , 0.43]	0.14 [-0.17 , 0.45]	-0.02 [-0.18 , 0.13]	0.01 [-0.17 , 0.18]	-0.34 [-0.88 , 0.19]	
Putamen	-0.03 [-0.55 , 0.49]	0.06 [-0.45 , 0.58]	-0.03 [-0.17 , 0.11]	-0.05 [-0.21 , 0.11]	-0.13 [-0.66 , 0.41]	
Pallidum	-0.06 [-0.46 , 0.33]	0.02 [-0.40 , 0.45]	-0.02 [-0.16 , 0.12]	0.07 [-0.08 , 0.22]	-0.81 [-1.36 , -0.26]*	
Hippocampus	-0.08 [-0.47 , 0.32]	-0.08 [-0.42 , 0.26]	-0.18 [-0.32 , -0.04]*	0.15 [-0.00 , 0.30]	-0.54 [-1.08 , -0.00]*	OFF<SIB
Amygdala	0.12 [-0.21 , 0.45]	0.00 [-0.30 , 0.31]	-0.05 [-0.19 , 0.08]	0.08 [-0.07 , 0.23]	-0.06 [-0.60 , 0.47]	
Accumbens	-0.27 [-0.76 , 0.22]	0.07 [-0.24 , 0.37]	0.03 [-0.16 , 0.23]	0.08 [-0.12 , 0.27]	-0.10 [-0.63 , 0.44]	MZ<SIB

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | [1] Parents only 1 cohort; no meta-analysis

Table S8b. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-SZ, i.e. MZ co-twins, DZ co-twins, offspring, siblings, parents, controlling for intracranial volume (ICV). Last column displays whether the effect sizes differ significantly from each other, pairwise.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI	Significant differences
Global measures						
ICV	-	-	-	-	-	
Total brain	-0.30 [-0.83 , 0.23]	-0.21 [-0.59 , 0.16]	-0.23 [-0.51 , 0.05]	-0.13 [-0.22 , -0.04]*	-0.14 [-0.58 , 0.31]	
Surface area	-0.19 [-0.72 , 0.34]	-0.05 [-0.33 , 0.22]	-0.18 [-0.50 , 0.14]	0.02 [-0.09 , 0.13]	0.07 [-0.18 , 0.33]	OFF<SIB,PAR
Cortical thickness	-0.28 [-0.71 , 0.15]	-0.51 [-1.43 , 0.41]	-0.08 [-0.50 , 0.34]	-0.12 [-0.24 , 0.00]	-0.01 [-0.39 , 0.37]	DZ<OFF,SIB,PAR
Cortical GM	-0.32 [-0.66 , 0.02]	-0.50 [-1.45 , 0.45]	-0.24 [-0.63 , 0.15]	-0.06 [-0.15 , 0.03]	0.07 [-0.28 , 0.43]	MZ,DZ,OFF<PAR; DZ<SIB
Cerebral WM	-0.21 [-0.70 , 0.27]	-0.17 [-0.44 , 0.11]	-0.12 [-0.31 , 0.08]	-0.10 [-0.19 , -0.00]*	-0.18 [-0.43 , 0.07]	
Cerebellum GM	0.10 [-0.21 , 0.41]	0.06 [-0.29 , 0.40]	-0.10 [-0.29 , 0.10]	-0.12 [-0.21 , -0.03]*	-0.12 [-0.37 , 0.13]	
Cerebellum WM	0.21 [-0.15 , 0.58]	-0.09 [-0.37 , 0.18]	-0.12 [-0.32 , 0.07]	-0.08 [-0.18 , 0.01]	-0.34 [-0.60 , -0.07]*	MZ>OFF,SIB,PAR; SIB>PAR
Third ventricle	0.34 [0.04 , 0.64]*	0.21 [-0.06 , 0.49]	0.21 [-0.08 , 0.51]	0.13 [-0.04 , 0.30]	0.02 [-0.32 , 0.37]	
Lateral ventricles	0.24 [-0.07 , 0.55]	0.09 [-0.26 , 0.43]	0.20 [-0.09 , 0.49]	0.03 [-0.06 , 0.12]	-0.02 [-0.70 , 0.65]	
Subcortical volumes						
Thalamus	-0.12 [-0.43 , 0.19]	-0.28 [-0.77 , 0.21]	-0.16 [-0.52 , 0.21]	-0.09 [-0.23 , 0.04]	-0.23 [-0.48 , 0.02]	
Caudate	0.26 [-0.04 , 0.56]	-0.16 [-0.44 , 0.13]	-0.14 [-0.33 , 0.05]	-0.04 [-0.13 , 0.05]	0.07 [-0.18 , 0.32]	MZ>DZ,OFF,SIB
Putamen	0.07 [-0.25 , 0.38]	-0.32 [-0.94 , 0.29]	-0.18 [-0.38 , 0.01]	-0.03 [-0.12 , 0.06]	-0.17 [-0.46 , 0.12]	DZ<SIB
Pallidum	0.20 [-0.12 , 0.51]	-0.10 [-0.59 , 0.40]	-0.24 [-0.43 , -0.04]*	-0.05 [-0.14 , 0.04]	0.07 [-0.18 , 0.32]	OFF<MZ,SIB,PAR
Hippocampus	-0.08 [-0.38 , 0.23]	0.04 [-0.25 , 0.32]	-0.16 [-0.35 , 0.04]	-0.05 [-0.15 , 0.06]	-0.07 [-0.32 , 0.19]	
Amygdala	-0.15 [-0.58 , 0.29]	-0.01 [-0.39 , 0.37]	-0.17 [-0.37 , 0.02]	-0.01 [-0.17 , 0.14]	0.41 [0.15 , 0.67]**	MZ,DZ,OFF,SIB<PAR
Accumbens	-0.20 [-0.60 , 0.21]	-0.20 [-0.98 , 0.58]	-0.14 [-0.40 , 0.12]	-0.04 [-0.13 , 0.05]	0.00 [-0.35 , 0.36]	

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected

Table S9a. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-BD, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents, controlling for psychopathology in relatives and/or controls by adding the presence of a diagnosis as a covariate.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings† ES ± 95%CI	Parents[1] ES ± 95%CI
Global measures					
ICV	0.25 [-0.08 , 0.58]	0.16 [-0.15 , 0.47]	0.22 [0.04 , 0.40]*	0.10 [-0.05 , 0.26]	0.10 [-0.44 , 0.63]
Total brain	0.06 [-0.27 , 0.39]	0.03 [-0.27 , 0.34]	0.15 [-0.06 , 0.36]	0.15 [-0.04 , 0.33]	-0.07 [-0.61 , 0.46]
Surface area	0.05 [-0.28 , 0.38]	0.04 [-0.27 , 0.34]	0.20 [-0.03 , 0.43]	0.19 [-0.02 , 0.40]	0.22 [-0.31 , 0.76]
Cortical thickness	0.07 [-0.35 , 0.48]	-0.02 [-0.33 , 0.29]	-0.05 [-0.26 , 0.16]	0.01 [-0.14 , 0.15]	0.13 [-0.41 , 0.66]
Cortical GM	0.17 [-0.16 , 0.50]	0.02 [-0.29 , 0.32]	0.19 [-0.02 , 0.40]	0.18 [-0.02 , 0.37]	0.30 [-0.23 , 0.84]
Cerebral WM	-0.01 [-0.34 , 0.32]	0.04 [-0.27 , 0.35]	0.10 [-0.10 , 0.30]	0.09 [-0.10 , 0.28]	-0.22 [-0.75 , 0.32]
Cerebellum GM†	0.08 [-0.25 , 0.41]	0.06 [-0.25 , 0.37]	0.13 [-0.17 , 0.44]	0.17 [0.00 , 0.33]*	-0.18 [-0.71 , 0.36]
Cerebellum WM†	-0.02 [-0.39 , 0.34]	-0.11 [-0.66 , 0.45]	-0.03 [-0.30 , 0.25]	0.05 [-0.11 , 0.22]	-0.10 [-0.63 , 0.44]
Third ventricle	0.18 [-0.34 , 0.70]	0.09 [-0.22 , 0.40]	-0.05 [-0.26 , 0.16]	-0.07 [-0.22 , 0.08]	0.38 [-0.16 , 0.92]
Lateral ventricles	0.28 [-0.24 , 0.80]	0.19 [-0.12 , 0.50]	0.18 [0.05 , 0.32]*	-0.02 [-0.17 , 0.13]	0.76 [0.21 , 1.30]*
Subcortical volumes					
Thalamus	-0.14 [-0.51 , 0.24]	0.00 [-0.31 , 0.31]	0.08 [-0.09 , 0.24]	0.04 [-0.11 , 0.19]	-0.47 [-1.01 , 0.07]
Caudate	0.21 [-0.13 , 0.55]	0.19 [-0.12 , 0.5]	0.12 [-0.02 , 0.25]	0.04 [-0.10 , 0.19]	-0.30 [-0.84 , 0.23]
Putamen	0.08 [-0.26 , 0.41]	0.11 [-0.40 , 0.62]	0.06 [-0.10 , 0.23]	-0.04 [-0.22 , 0.15]	-0.08 [-0.61 , 0.46]
Pallidum	0.08 [-0.25 , 0.42]	0.04 [-0.28 , 0.37]	0.09 [-0.10 , 0.27]	0.08 [-0.07 , 0.23]	-0.75 [-1.30 , -0.20]*
Hippocampus	-0.05 [-0.38 , 0.28]	-0.08 [-0.39 , 0.23]	-0.04 [-0.17 , 0.10]	0.15 [-0.02 , 0.32]	-0.46 [-1.00 , 0.08]
Amygdala	0.14 [-0.19 , 0.47]	0.04 [-0.27 , 0.34]	0.06 [-0.08 , 0.19]	0.10 [-0.04 , 0.25]	-0.01 [-0.54 , 0.52]
Accumbens	-0.15 [-0.51 , 0.21]	0.07 [-0.23 , 0.38]	0.13 [-0.06 , 0.32]	0.10 [-0.09 , 0.29]	-0.09 [-0.62 , 0.45]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | [1] Parents only 1 cohort; no meta-analysis

Table S9b. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-SZ, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents, controlling for psychopathology in relatives and/or controls by adding the presence of a diagnosis as a covariate.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
Global measures					
ICV	-0.09 [-0.39 , 0.21]	-0.01 [-0.29 , 0.27]	-0.16 [-0.45 , 0.12]	0.09 [-0.08 , 0.26]	-0.04 [-0.30 , 0.22]
Total brain	-0.18 [-0.48 , 0.12]	-0.13 [-0.40 , 0.15]	-0.29 [-0.59 , 0.01]	0.01 [-0.12 , 0.13]	-0.09 [-0.44 , 0.25]
Surface area	-0.15 [-0.59 , 0.30]	-0.02 [-0.30 , 0.25]	-0.22 [-0.47 , 0.03]	0.11 [-0.05 , 0.27]	0.04 [-0.21 , 0.29]
Cortical thickness	-0.24 [-0.66 , 0.18]	-0.50 [-1.28 , 0.29]	-0.07 [-0.49 , 0.35]	-0.10 [-0.21 , 0.01]	0.01 [-0.41 , 0.43]
Cortical GM	-0.27 [-0.57 , 0.03]	-0.17 [-0.45 , 0.10]	-0.26 [-0.60 , 0.09]	0.03 [-0.10 , 0.15]	0.06 [-0.32 , 0.45]
Cerebral WM	-0.17 [-0.48 , 0.15]	-0.10 [-0.37 , 0.18]	-0.23 [-0.46 , -0.00]*	0.00 [-0.11 , 0.11]	-0.15 [-0.40 , 0.10]
Cerebellum GM	0.15 [-0.15 , 0.45]	0.08 [-0.27 , 0.43]	-0.17 [-0.36 , 0.03]	-0.09 [-0.19 , 0.00]	-0.17 [-0.46 , 0.11]
Cerebellum WM	0.13 [-0.17 , 0.43]	-0.09 [-0.36 , 0.19]	-0.15 [-0.34 , 0.05]	-0.06 [-0.17 , 0.04]	-0.35 [-0.63 , -0.08]*
Third ventricle	0.36 [0.06 , 0.67]*	0.27 [-0.01 , 0.54]	0.12 [-0.07 , 0.32]	0.15 [-0.05 , 0.36]	-0.02 [-0.41 , 0.37]
Lateral ventricles	0.19 [-0.13 , 0.52]	0.04 [-0.33 , 0.41]	0.08 [-0.11 , 0.27]	0.06 [-0.06 , 0.17]	0.01 [-0.62 , 0.64]
Subcortical volumes					
Thalamus	-0.10 [-0.41 , 0.21]	-0.23 [-0.51 , 0.05]	-0.28 [-0.54 , -0.01]*	-0.04 [-0.13 , 0.05]	-0.25 [-0.50 , 0.00]
Caudate	0.15 [-0.15 , 0.46]	-0.12 [-0.40 , 0.16]	-0.19 [-0.38 , 0.01]	0.04 [-0.10 , 0.18]	0.04 [-0.21 , 0.29]
Putamen	0.05 [-0.27 , 0.36]	-0.14 [-0.45 , 0.16]	-0.27 [-0.53 , -0.00]*	-0.01 [-0.10 , 0.08]	-0.17 [-0.45 , 0.11]
Pallidum	0.19 [-0.13 , 0.51]	0.05 [-0.24 , 0.34]	-0.34 [-0.62 , -0.06]*	-0.02 [-0.12 , 0.07]	0.03 [-0.22 , 0.28]
Hippocampus	-0.13 [-0.43 , 0.18]	0.00 [-0.29 , 0.28]	-0.21 [-0.40 , -0.01]*	-0.04 [-0.13 , 0.06]	-0.09 [-0.38 , 0.21]
Amygdala	-0.22 [-0.69 , 0.26]	-0.02 [-0.30 , 0.26]	-0.20 [-0.39 , -0.00]*	0.04 [-0.11 , 0.20]	0.36 [0.04 , 0.68]*
Accumbens	-0.31 [-0.75 , 0.13]	0.01 [-0.27 , 0.29]	-0.20 [-0.46 , 0.06]	-0.02 [-0.13 , 0.10]	0.02 [-0.39 , 0.42]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected

Table S10a. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-BD, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents, controlling for intracranial volume (ICV) and psychopathology in relatives and/or controls by adding the presence of a diagnosis as a covariate.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings† ES ± 95%CI	Parents[1] ES ± 95%CI
Global measures					
ICV	-	-	-	-	-
Total brain	-0.19 [-0.52 , 0.15]	-0.08 [-0.53 , 0.37]	-0.01 [-0.25 , 0.22]	0.12 [-0.05 , 0.29]	-0.21 [-0.75 , 0.32]
Surface area	-0.20 [-0.74 , 0.34]	-0.09 [-0.39 , 0.22]	0.08 [-0.13 , 0.28]	0.15 [-0.02 , 0.33]	0.20 [-0.34 , 0.73]
Cortical thickness	0.06 [-0.34 , 0.45]	-0.05 [-0.36 , 0.25]	-0.05 [-0.24 , 0.14]	0.02 [-0.13 , 0.17]	0.15 [-0.39 , 0.68]
Cortical GM	0.00 [-0.33 , 0.33]	-0.11 [-0.42 , 0.19	0.07 [-0.12 , 0.25]	0.14 [-0.01 , 0.29]	0.29 [-0.24 , 0.83]
Cerebral WM	-0.26 [-0.59 , 0.07]	0.00 [-0.52 , 0.52]	-0.10 [-0.32 , 0.12]	0.03 [-0.17 , 0.23]	-0.37 [-0.91 , 0.17]
Cerebellum GM†	-0.02 [-0.35 , 0.31]	0.01 [-0.30 , 0.31]	0.07 [-0.23 , 0.37]	0.11 [-0.05 , 0.28]	-0.21 [-0.75 , 0.32]
Cerebellum WM†	-0.16 [-0.52 , 0.21]	-0.18 [-0.81 , 0.45]	-0.13 [-0.42 , 0.16]	-0.03 [-0.19 , 0.14]	-0.14 [-0.67 , 0.40]
Third ventricle	0.16 [-0.31 , 0.63]	0.00 [-0.31 , 0.30]	-0.11 [-0.32 , 0.10]	-0.09 [-0.24 , 0.06]	0.37 [-0.17 , 0.91]
Lateral ventricles	0.31 [-0.06 , 0.68]	0.09 [-0.21 , 0.40]	0.09 [-0.09 , 0.27]	-0.07 [-0.24 , 0.09]	0.80 [0.25 , 1.35]*
Subcortical volumes					
Thalamus	-0.48 [-1.09 , 0.13]	0.05 [-0.45 , 0.56]	-0.04 [-0.18 , 0.09]	0.02 [-0.15 , 0.18]	-0.52 [-1.06 , 0.02]
Caudate	0.11 [-0.23 , 0.45]	0.16 [-0.15 , 0.47]	-0.01 [-0.17 , 0.15]	0.02 [-0.13 , 0.16]	-0.34 [-0.88 , 0.19]
Putamen	-0.04 [-0.57 , 0.49]	0.07 [-0.47 , 0.60]	-0.02 [-0.16 , 0.12]	-0.04 [-0.22 , 0.13]	-0.13 [-0.66 , 0.41]
Pallidum	-0.02 [-0.40 , 0.35]	0.01 [-0.39 , 0.41]	-0.01 [-0.16 , 0.15]	0.07 [-0.10 , 0.23]	-0.81 [-1.36 , -0.26]*
Hippocampus	-0.18 [-0.67 , 0.31]	-0.16 [-0.57 , 0.25]	-0.20 [-0.34 , -0.06]	0.16 [-0.01 , 0.33]	-0.54 [-1.08 , -0.00]*
Amygdala	0.05 [-0.28 , 0.38]	-0.02 [-0.33 , 0.29]	-0.05 [-0.19 , 0.08]	0.10 [-0.07 , 0.26]	-0.06 [-0.60 , 0.47]
Accumbens	-0.24 [-0.70 , 0.22]	0.06 [-0.25 , 0.37]	0.05 [-0.13 , 0.22]	0.07 [-0.11 , 0.25]	-0.10 [-0.63 , 0.44]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | [1] Parents only 1 cohort; no meta-analysis

Table S10b. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between controls and the different types of FDRs-SZ, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents, controlling for intracranial volume (ICV) and psychopathology in relatives and/or controls by adding the presence of a diagnosis as a covariate.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
Global measures					
ICV	-	-	-	-	-
Total brain	-0.23 [-0.67 , 0.20]	-0.20 [-0.48 , 0.07]	-0.22 [-0.49 , 0.05]	-0.09 [-0.18 , 0.00]	-0.12 [-0.54 , 0.30]
Surface area	-0.16 [-0.68 , 0.36]	-0.09 [-0.36 , 0.19]	-0.16 [-0.47 , 0.15]	0.04 [-0.08 , 0.16]	0.11 [-0.14 , 0.37]
Cortical thickness	-0.22 [-0.65 , 0.21]	-0.47 [-1.33 , 0.39]	-0.12 [-0.51 , 0.26]	-0.10 [-0.22 , 0.02]	-0.01 [-0.42 , 0.39]
Cortical GM	-0.26 [-0.56 , 0.04]	-0.49 [-1.37 , 0.38]	-0.21 [-0.58 , 0.16]	-0.03 [-0.12 , 0.06]	0.07 [-0.28 , 0.43]
Cerebral WM	-0.16 [-0.58 , 0.26]	-0.17 [-0.45 , 0.10]	-0.12 [-0.31 , 0.08]	-0.07 [-0.16 , 0.02]	-0.14 [-0.39 , 0.11]
Cerebellum GM	0.21 [-0.09 , 0.51]	0.07 [-0.25 , 0.39]	-0.11 [-0.30 , 0.09]	-0.12 [-0.21 , -0.02]*	-0.16 [-0.44 , 0.12]
Cerebellum WM	0.21 [-0.09 , 0.51]	-0.13 [-0.40 , 0.15]	-0.12 [-0.31 , 0.08]	-0.08 [-0.17 , 0.01]	-0.35 [-0.63 , -0.08]*
Third ventricle	0.42 [0.12 , 0.72]*	0.30 [0.03 , 0.58]*	0.23 [-0.07 , 0.52]	0.12 [-0.06 , 0.30]	-0.01 [-0.40 , 0.38]
Lateral ventricles	0.25 [-0.09 , 0.60]	0.10 [-0.24 , 0.44]	0.16 [-0.06 , 0.39]	0.04 [-0.05 , 0.13]	-0.01 [-0.68 , 0.66]
Subcortical volumes					
Thalamus	-0.09 [-0.40 , 0.22]	-0.25 [-0.56 , 0.07]	-0.17 [-0.53 , 0.20]	-0.09 [-0.24 , 0.06]	-0.24 [-0.49 , 0.01]
Caudate	0.28 [-0.03 , 0.58]	-0.15 [-0.43 , 0.13]	-0.13 [-0.32 , 0.07]	-0.02 [-0.11 , 0.07]	0.07 [-0.18 , 0.32]
Putamen	0.08 [-0.23 , 0.40]	-0.33 [-0.97 , 0.30]	-0.17 [-0.37 , 0.02]	-0.02 [-0.11 , 0.07]	-0.16 [-0.45 , 0.13]
Pallidum	0.23 [-0.09 , 0.55]	-0.08 [-0.59 , 0.44]	-0.25 [-0.45 , -0.06]*	-0.04 [-0.13 , 0.05]	0.06 [-0.19 , 0.31]
Hippocampus	-0.08 [-0.38 , 0.23]	-0.01 [-0.30 , 0.28]	-0.14 [-0.33 , 0.06]	-0.04 [-0.15 , 0.07]	-0.06 [-0.31 , 0.19]
Amygdala	-0.17 [-0.63 , 0.29]	-0.02 [-0.30 , 0.26]	-0.14 [-0.33 , 0.05]	0.00 [-0.16 , 0.15]	0.43 [0.16 , 0.70]**
Accumbens	-0.27 [-0.70 , 0.16]	-0.22 [-0.99 , 0.55]	-0.14 [-0.38 , 0.10]	-0.01 [-0.11 , 0.09]	0.00 [-0.37 , 0.37]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected

Table S11a. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between *healthy* controls and the different types of *healthy* FDRs-BD, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings† ES ± 95%CI	Parents[1] ES ± 95%CI
Global measures					
ICV	0.26 [-0.16 , 0.68]	0.23 [-0.11 , 0.58]	0.18 [-0.00 , 0.37]	0.08 [-0.08 , 0.25]	0.10 [-0.44 , 0.63]
Total brain	0.11 [-0.30 , 0.52]	0.09 [-0.26 , 0.44]	0.13 [-0.07 , 0.34]	0.17 [-0.04 , 0.39]	-0.07 [-0.61 , 0.46]
Surface area	0.17 [-0.25 , 0.58]	0.09 [-0.26 , 0.43]	0.19 [-0.03 , 0.42]	0.21 [-0.02 , 0.45]	0.22 [-0.31 , 0.76]
Cortical thickness	0.00 [-0.57 , 0.57]	-0.01 [-0.35 , 0.34]	-0.06 [-0.29 , 0.18]	-0.03 [-0.20 , 0.13]	0.13 [-0.41 , 0.66]
Cortical GM	0.21 [-0.20 , 0.62]	0.08 [-0.27 , 0.42]	0.21 [0.03 , 0.39]	0.18 [-0.05 , 0.40]	0.30 [-0.23 , 0.84]
Cerebral WM	0.04 [-0.37 , 0.45]	0.10 [-0.24 , 0.45]	0.07 [-0.13 , 0.26]	0.13 [-0.09 , 0.35]	-0.22 [-0.75 , 0.32]
Cerebellum GM†	0.10 [-0.31 , 0.51]	0.05 [-0.30 , 0.39]	0.08 [-0.23 , 0.40]	0.22 [0.02 , 0.41]*	-0.18 [-0.71 , 0.36]
Cerebellum WM†	0.00 [-0.42 , 0.41]	-0.13 [-0.62 , 0.37]	-0.04 [-0.34 , 0.26]	0.08 [-0.10 , 0.26]	-0.10 [-0.63 , 0.44]
Third ventricle	0.04 [-0.41 , 0.49]	0.12 [-0.23 , 0.46]	-0.03 [-0.36 , 0.29]	-0.07 [-0.24 , 0.11]	0.38 [-0.16 , 0.92]
Lateral ventricles	0.14 [-0.50 , 0.78]	0.12 [-0.23 , 0.46]	0.16 [-0.00 , 0.31]	0.00 [-0.16 , 0.16]	0.76 [0.21 , 1.30]*
Subcortical volumes					
Thalamus	-0.02 [-0.45 , 0.40]	0.00 [-0.35 , 0.35]	0.04 [-0.17 , 0.24]	0.07 [-0.09 , 0.23]	-0.47 [-1.01 , 0.07]
Caudate	0.22 [-0.20 , 0.63]	0.20 [-0.15 , 0.55]	0.07 [-0.09 , 0.24]	-0.02 [-0.18 , 0.15]	-0.30 [-0.84 , 0.23]
Putamen	0.17 [-0.25 , 0.59]	0.13 [-0.33 , 0.59]	0.04 [-0.12 , 0.20]	-0.09 [-0.28 , 0.11]	-0.08 [-0.61 , 0.46]
Pallidum	0.13 [-0.32 , 0.58]	0.19 [-0.24 , 0.61]	0.09 [-0.11 , 0.28]	0.07 [-0.09 , 0.24]	-0.75 [-1.30 , -0.20]*
Hippocampus	0.04 [-0.38 , 0.45]	-0.02 [-0.36 , 0.33]	-0.05 [-0.21 , 0.11]	0.17 [-0.02 , 0.36]	-0.46 [-1.00 , 0.08]
Amygdala	0.16 [-0.26 , 0.57]	0.15 [-0.28 , 0.57]	0.03 [-0.13 , 0.19]	0.16 [-0.02 , 0.35]	-0.01 [-0.54 , 0.52]
Accumbens	-0.21 [-0.82 , 0.39]	0.02 [-0.32 , 0.37]	0.17 [-0.05 , 0.39]	0.09 [-0.13 , 0.32]	-0.09 [-0.62 , 0.45]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | [1] Parents only 1 cohort; no meta-analysis

Table S11b. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between *healthy* controls and the different types of *healthy* FDRs-SZ, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents.

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
Global measures					
ICV	-0.05 [-0.42 , 0.32]	0.04 [-0.25 , 0.34]	-0.32 [-0.77 , 0.14]	0.09 [-0.08 , 0.27]	-0.05 [-0.31 , 0.21]
Total brain	-0.15 [-0.52 , 0.22]	-0.05 [-0.35 , 0.24]	-0.45 [-0.92 , 0.02]	0.02 [-0.12 , 0.16]	-0.09 [-0.43 , 0.25]
Surface area	-0.19 [-0.56 , 0.18]	0.00 [-0.29 , 0.30]	-0.33 [-0.72 , 0.06]	0.13 [-0.06 , 0.31]	0.07 [-0.20 , 0.33]
Cortical thickness	-0.08 [-0.66 , 0.50]	-0.43 [-1.22 , 0.36]	-0.12 [-0.47 , 0.23]	-0.11 [-0.26 , 0.03]	-0.14 [-0.40 , 0.12]
Cortical GM	-0.22 [-0.59 , 0.15]	-0.13 [-0.42 , 0.17]	-0.36 [-0.85 , 0.12]	0.03 [-0.10 , 0.16]	0.05 [-0.32 , 0.42]
Cerebral WM	-0.14 [-0.51 , 0.23]	-0.05 [-0.35 , 0.24]	-0.41 [-0.81 , -0.00]*	0.02 [-0.11 , 0.15]	-0.13 [-0.39 , 0.13]
Cerebellum GM	0.14 [-0.23 , 0.51]	0.26 [-0.04 , 0.55]	-0.15 [-0.37 , 0.06]	-0.08 [-0.19 , 0.03]	-0.20 [-0.48 , 0.07]
Cerebellum WM	0.16 [-0.21 , 0.53]	0.08 [-0.22 , 0.37]	-0.16 [-0.38 , 0.05]	-0.07 [-0.18 , 0.04]	-0.29 [-0.56 , -0.03]*
Third ventricle	0.44 [0.07 , 0.81]*	0.29 [-0.00 , 0.59]	0.09 [-0.12 , 0.31]	0.16 [-0.05 , 0.36]	0.02 [-0.33 , 0.38]
Lateral ventricles	0.23 [-0.29 , 0.74]	-0.02 [-0.55 , 0.51]	0.02 [-0.20 , 0.23]	0.07 [-0.05 , 0.19]	0.00 [-0.66 , 0.66]
Subcortical volumes					
Thalamus	-0.04 [-0.41 , 0.34]	-0.24 [-0.55 , 0.07]	-0.38 [-0.70 , -0.05]*	-0.03 [-0.13 , 0.07]	-0.27 [-0.53 , -0.01]*
Caudate	0.15 [-0.22 , 0.52]	-0.13 [-0.43 , 0.17]	-0.28 [-0.54 , -0.03]*	0.02 [-0.12 , 0.16]	0.02 [-0.24 , 0.28]
Putamen	0.08 [-0.31 , 0.46]	-0.07 [-0.38 , 0.24]	-0.49 [-0.95 , -0.03]*	-0.01 [-0.11 , 0.09]	-0.16 [-0.47 , 0.14]
Pallidum	0.25 [-0.14 , 0.64]	0.03 [-0.28 , 0.33]	-0.46 [-0.83 , -0.08]*	-0.01 [-0.13 , 0.11]	0.03 [-0.23 , 0.30]
Hippocampus	-0.19 [-0.57 , 0.18]	-0.08 [-0.38 , 0.23]	-0.28 [-0.57 , 0.02]	-0.04 [-0.14 , 0.06]	-0.10 [-0.39 , 0.18]
Amygdala	-0.26 [-0.77 , 0.26]	-0.01 [-0.31 , 0.29]	-0.26 [-0.53 , 0.01]	0.02 [-0.14 , 0.18]	0.40 [0.04 , 0.75]*
Accumbens	-0.20 [-0.64 , 0.23]	0.01 [-0.29 , 0.31]	-0.26 [-0.48 , -0.03]*	-0.03 [-0.15 , 0.10]	-0.03 [-0.39 , 0.32]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected

Table S12a. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between *healthy* controls and the different types of *healthy* FDRs-BD, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents, controlling for intracranial volume (ICV).

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings† ES ± 95%CI	Parents[1] ES ± 95%CI
Global measures					
ICV	-	-	-	-	-
Total brain	-0.01 [-0.42 , 0.40]	-0.14 [-0.48 , 0.21]	0.01 [-0.20 , 0.21]	0.16 [-0.03 , 0.34]	-0.21 [-0.75 , 0.32]
Surface area	0.00 [-0.54 , 0.54]	-0.11 [-0.46 , 0.23]	0.10 [-0.08 , 0.29]	0.18 [-0.01 , 0.37]	0.20 [-0.34 , 0.73]
Cortical thickness	0.02 [-0.51 , 0.54]	-0.02 [-0.36 , 0.33]	-0.04 [-0.26 , 0.18]	-0.02 [-0.18 , 0.14]	0.15 [-0.39 , 0.68]
Cortical GM	0.12 [-0.29 , 0.53]	-0.10 [-0.44 , 0.25]	0.13 [-0.02 , 0.29]	0.14 [-0.04 , 0.32]	0.29 [-0.24 , 0.83]
Cerebral WM	-0.13 [-0.54 , 0.28]	-0.06 [-0.49 , 0.37]	-0.10 [-0.26 , 0.05]	0.08 [-0.12 , 0.29]	-0.37 [-0.91 , 0.17]
Cerebellum GM†	0.03 [-0.39 , 0.44]	-0.03 [-0.38 , 0.31]	0.03 [-0.28 , 0.34]	0.17 [-0.01 , 0.35]	-0.21 [-0.75 , 0.32]
Cerebellum WM†	-0.13 [-0.54 , 0.28]	-0.24 [-0.76 , 0.29]	-0.13 [-0.44 , 0.18]	0.01 [-0.18 , 0.19]	-0.14 [-0.67 , 0.40]
Third ventricle	0.03 [-0.38 , 0.45]	-0.01 [-0.35 , 0.34]	-0.10 [-0.41 , 0.21]	-0.09 [-0.25 , 0.07]	0.37 [-0.17 , 0.91]
Lateral ventricles	0.15 [-0.26 , 0.56]	-0.01 [-0.35 , 0.34]	0.08 [-0.13 , 0.29]	-0.04 [-0.20 , 0.12]	0.80 [0.25 , 1.35]*
Subcortical volumes					
Thalamus	-0.27 [-0.69 , 0.15]	0.03 [-0.68 , 0.75]	-0.02 [-0.18 , 0.14]	0.07 [-0.11 , 0.26]	-0.52 [-1.06 , 0.02]
Caudate	0.15 [-0.27 , 0.57]	0.12 [-0.23 , 0.47]	-0.03 [-0.25 , 0.2]	-0.04 [-0.20 , 0.13]	-0.34 [-0.88 , 0.19]
Putamen	0.04 [-0.53 , 0.60]	0.07 [-0.48 , 0.61]	-0.04 [-0.20 , 0.12]	-0.09 [-0.28 , 0.10]	-0.13 [-0.66 , 0.41]
Pallidum	-0.03 [-0.73 , 0.68]	0.11 [-0.36 , 0.59]	0.01 [-0.18 , 0.19]	0.07 [-0.10 , 0.24]	-0.81 [-1.36 , -0.26]*
Hippocampus	-0.05 [-0.46 , 0.36]	-0.11 [-0.46 , 0.23]	-0.19 [-0.35 , -0.03]*	0.18 [0.02 , 0.35]*	-0.54 [-1.08 , -0.00]*
Amygdala	0.10 [-0.31 , 0.51]	0.08 [-0.39 , 0.54]	-0.06 [-0.22 , 0.09]	0.15 [-0.04 , 0.34]	-0.06 [-0.60 , 0.47]
Accumbens	-0.30 [-0.96 , 0.37]	-0.03 [-0.37 , 0.32]	0.11 [-0.09 , 0.31]	0.05 [-0.16 , 0.26]	-0.10 [-0.63 , 0.44]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | [1] Parents only 1 cohort; no meta-analysis

Table S12b. Global and subcortical brain measures differences (Cohen's *d* effect sizes [± 95% CI]) between *healthy* controls and the different types of *healthy* FDRs-SZ, i.e. MZ co-twins, DZ co-twins, offspring, siblings and parents, controlling for intracranial volume (ICV).

	MZ co-twins ES ± 95%CI	DZ co-twins ES ± 95%CI	Offspring ES ± 95%CI	Siblings ES ± 95%CI	Parents ES ± 95%CI
Global measures					
ICV	-	-	-	-	-
Total brain	-0.20 [-0.57 , 0.17]	-0.16 [-0.46 , 0.13]	-0.28 [-0.63 , 0.07]	-0.10 [-0.21 , -0.00]*	-0.11 [-0.54 , 0.31]
Surface area	-0.26 [-0.66 , 0.14]	-0.11 [-0.40 , 0.19]	-0.15 [-0.44 , 0.14]	0.04 [-0.10 , 0.18]	0.13 [-0.13 , 0.40]
Cortical thickness	-0.07 [-0.66 , 0.53]	-0.41 [-1.29 , 0.46]	-0.13 [-0.47 , 0.22]	-0.12 [-0.27 , 0.04]	-0.15 [-0.41 , 0.11]
Cortical GM	-0.23 [-0.60 , 0.14]	-0.53 [-1.51 , 0.45]	-0.23 [-0.65 , 0.18]	-0.04 [-0.14 , 0.06]	0.04 [-0.27 , 0.35]
Cerebral WM	-0.14 [-0.53 , 0.26]	-0.17 [-0.46 , 0.13]	-0.18 [-0.39 , 0.03]	-0.08 [-0.18 , 0.02]	-0.13 [-0.39 , 0.14]
Cerebellum GM	0.19 [-0.18 , 0.56]	0.24 [-0.05 , 0.54]	-0.08 [-0.29 , 0.14]	-0.11 [-0.21 , -0.01]*	-0.18 [-0.46 , 0.10]
Cerebellum WM	0.23 [-0.14 , 0.60]	0.02 [-0.28 , 0.32]	-0.13 [-0.34 , 0.09]	-0.09 [-0.19 , 0.01]	-0.29 [-0.55 , -0.02]*
Third ventricle	0.49 [0.12 , 0.86]*	0.32 [0.02 , 0.61]*	0.15 [-0.06 , 0.37]	0.12 [-0.06 , 0.29]	0.04 [-0.31 , 0.39]
Lateral ventricles	0.29 [-0.25 , 0.83]	0.01 [-0.50 , 0.53]	0.16 [-0.09 , 0.42]	0.04 [-0.06 , 0.14]	-0.02 [-0.73 , 0.68]
Subcortical volumes					
Thalamus	-0.04 [-0.42 , 0.33]	-0.40 [-0.97 , 0.17]	-0.17 [-0.52 , 0.18]	-0.08 [-0.25 , 0.08]	-0.26 [-0.52 , 0.00]
Caudate	0.27 [-0.10 , 0.64]	-0.20 [-0.50 , 0.11]	-0.19 [-0.40 , 0.03]	-0.04 [-0.14 , 0.06]	0.04 [-0.22 , 0.31]
Putamen	0.12 [-0.27 , 0.50]	-0.16 [-0.59 , 0.26]	-0.27 [-0.54 , -0.00]*	-0.03 [-0.13 , 0.07]	-0.15 [-0.47 , 0.17]
Pallidum	0.28 [-0.11 , 0.67]	-0.01 [-0.31 , 0.30]	-0.30 [-0.51 , -0.08]*	-0.05 [-0.15 , 0.05]	0.07 [-0.20 , 0.33]
Hippocampus	-0.17 [-0.55 , 0.21]	-0.11 [-0.41 , 0.20]	-0.14 [-0.36 , 0.07]	-0.06 [-0.16 , 0.04]	-0.07 [-0.34 , 0.19]
Amygdala	-0.22 [-0.73 , 0.28]	-0.02 [-0.33 , 0.28]	-0.15 [-0.36 , 0.07]	-0.04 [-0.19 , 0.11]	0.48 [0.15 , 0.80]*
Accumbens	-0.16 [-0.59 , 0.27]	-0.01 [-0.34 , 0.32]	-0.19 [-0.40 , 0.03]	-0.03 [-0.14 , 0.07]	-0.06 [-0.33 , 0.22]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected

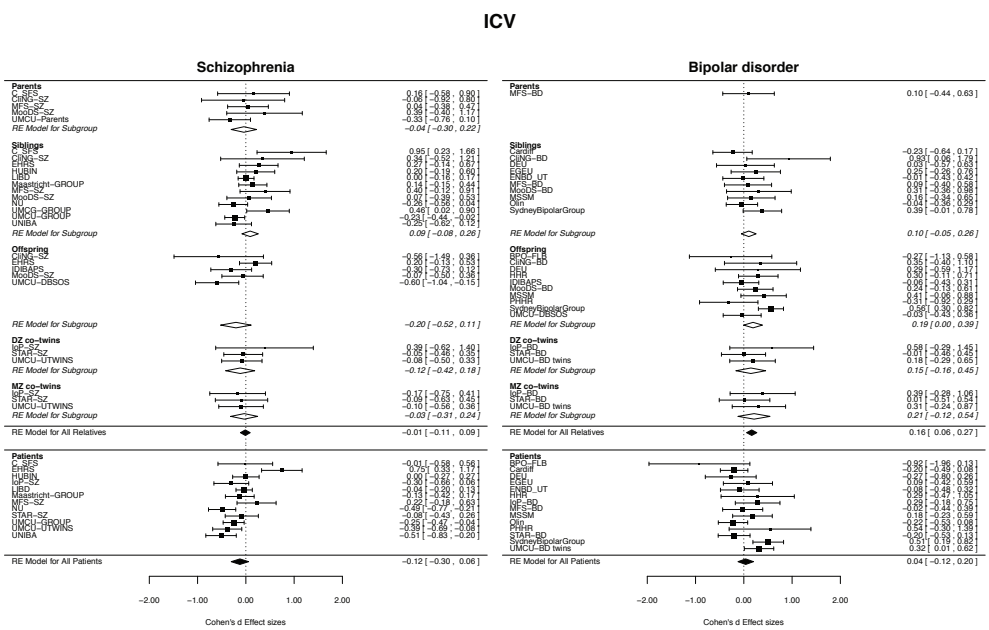
Table S13. Meta-regression results for relationship between FDRs-BD (left) and FDRs-SZ (right) compared with controls and mean age.

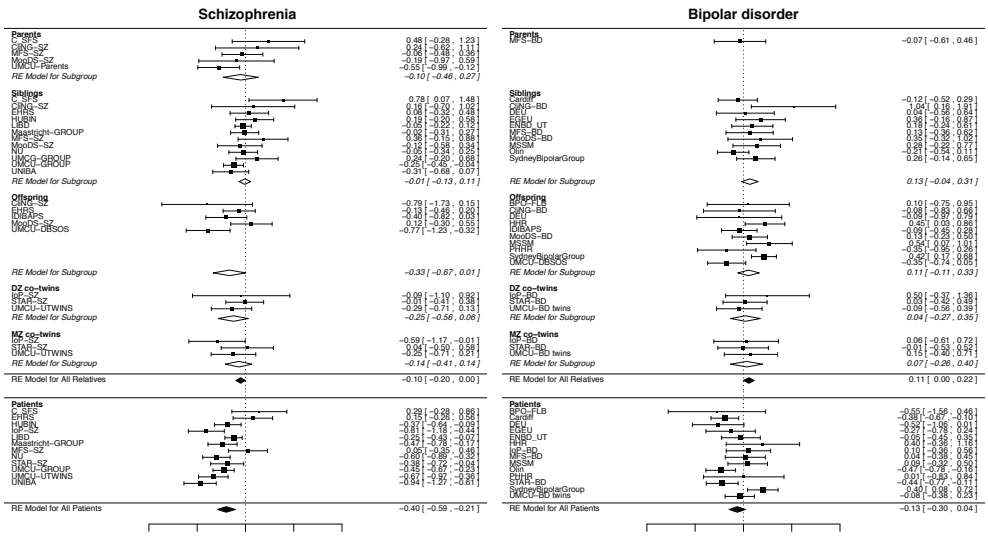
	BIPOLAR DISORDER				SCHIZOPHRENIA			
	Beta	*p*-value	SE	95% CI	Beta	*p*-value	SE	95% CI
Global measures								
ICV	-0.003	0.535	0.004	-0.011 – 0.006	0.005	0.310	0.005	-0.004 – 0.013
Total brain	0.000	0.965	0.004	-0.009 – 0.009	0.006	0.202	0.004	-0.003 – 0.014
Surface area	0.001	0.907	0.005	-0.009 – 0.010	0.008	0.086	0.005	-0.001 – 0.017
Cortical thickness	0.000	0.906	0.004	-0.008 – 0.007	0.001	0.846	0.005	-0.009 – 0.011
Cortical GM	0.001	0.892	0.005	-0.009 – 0.010	0.009	0.067	0.005	-0.001 – 0.018
Cerebral WM	-0.001	0.868	0.004	-0.009 – 0.008	0.003	0.432	0.004	-0.004 – 0.010
Cerebellum GM†	0.000	0.989	0.005	-0.009 – 0.009	0.005	0.185	0.004	-0.002 – 0.012
Cerebellum WM†	0.002	0.711	0.005	-0.009 – 0.012	-0.001	0.851	0.004	-0.008 – 0.007
Third ventricle	0.006	0.175	0.004	-0.003 – 0.014	-0.001	0.780	0.005	-0.011 – 0.008
Lateral ventricles	0.000	0.926	0.004	-0.008 – 0.008	-0.001	0.852	0.004	-0.009 – 0.007
Subcortical volumes								
Thalamus	-0.005	0.172	0.004	-0.013 – 0.002	0.002	0.572	0.004	-0.005 – 0.009
Caudate	-0.005	0.182	0.004	-0.012 – 0.002	0.004	0.255	0.004	-0.003 – 0.012
Putamen	-0.002	0.701	0.004	-0.010 – 0.007	0.001	0.828	0.004	-0.006 – 0.008
Pallidum	-0.003	0.436	0.004	-0.012 – 0.005	0.004	0.316	0.004	-0.003 – 0.011
Hippocampus	0.003	0.423	0.004	-0.004 – 0.010	0.005	0.153	0.004	-0.002 – 0.012
Amygdala	0.003	0.424	0.004	-0.004 – 0.010	0.013	0.008*	0.005	0.003 – 0.022
Accumbens	-0.005	0.280	0.005	-0.014 – 0.004	0.004	0.347	0.004	-0.004 – 0.011

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses

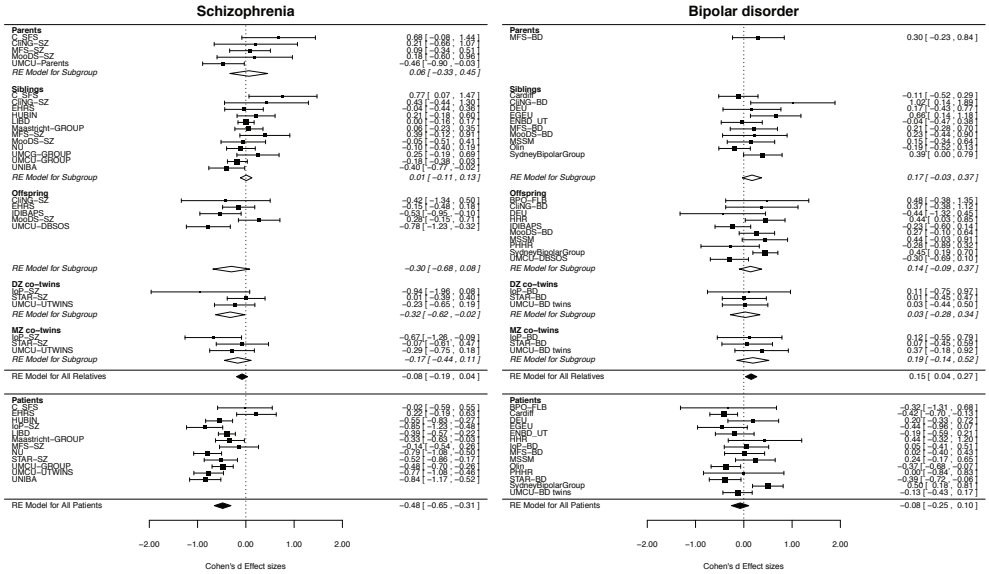
SUPPLEMENTARY FIGURES

Figure S1i-xvii. Forest plots per region of interest

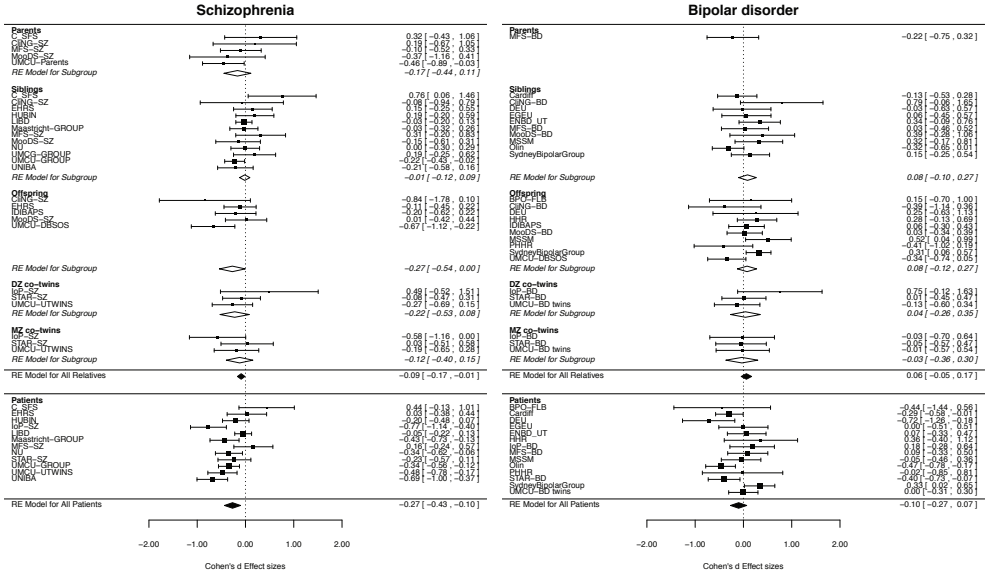




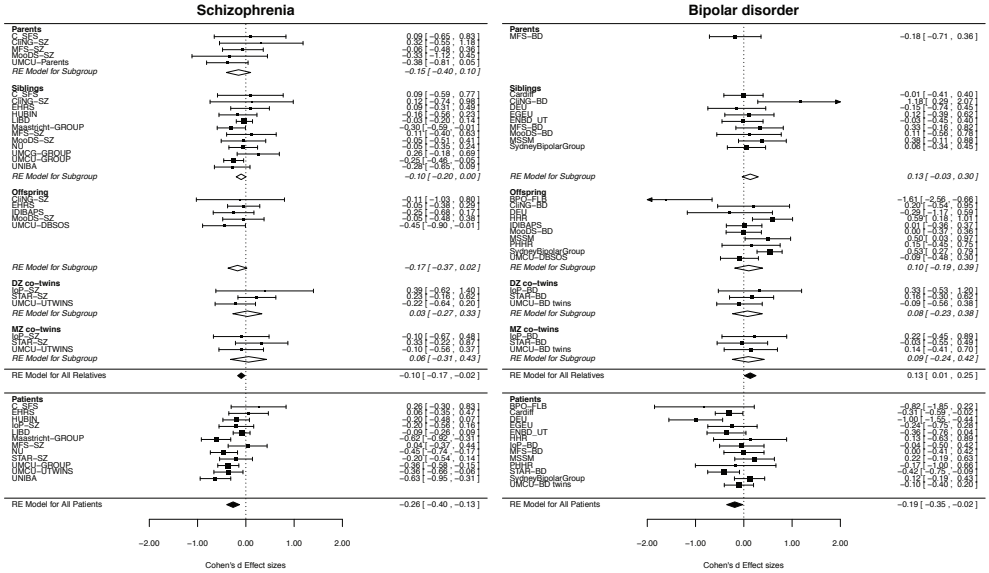
cortical gray matter



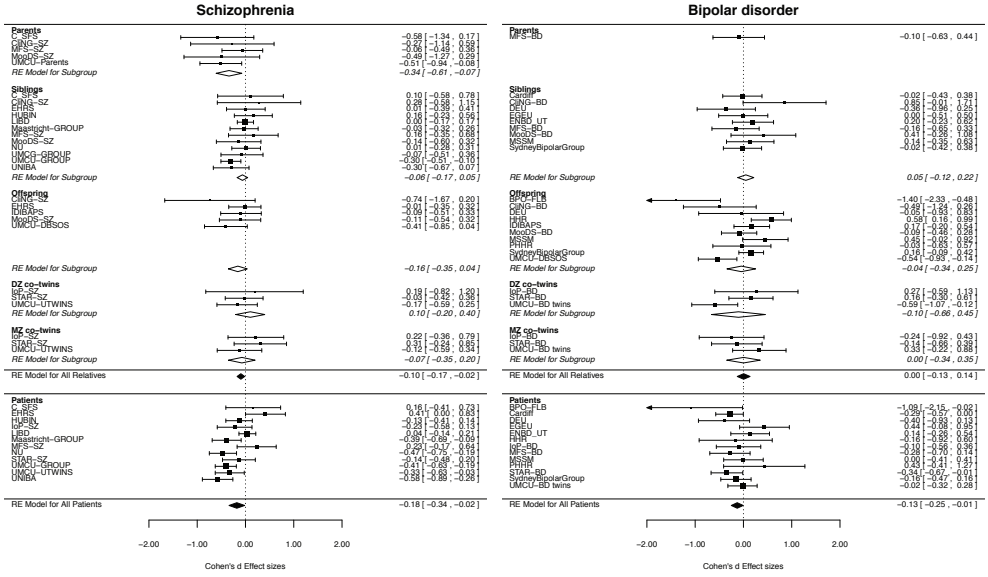
cerebral white matter



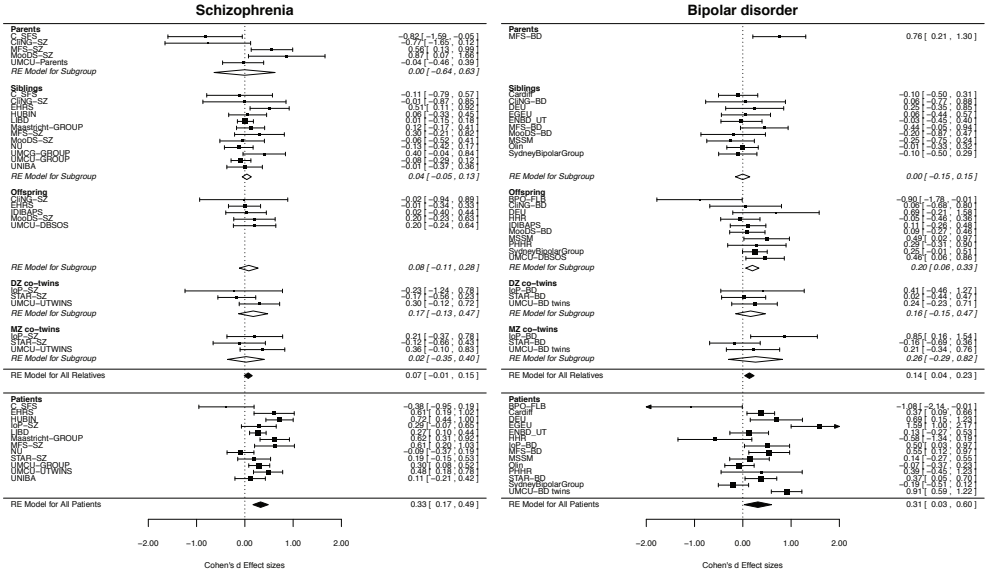
cerebellum gray matter



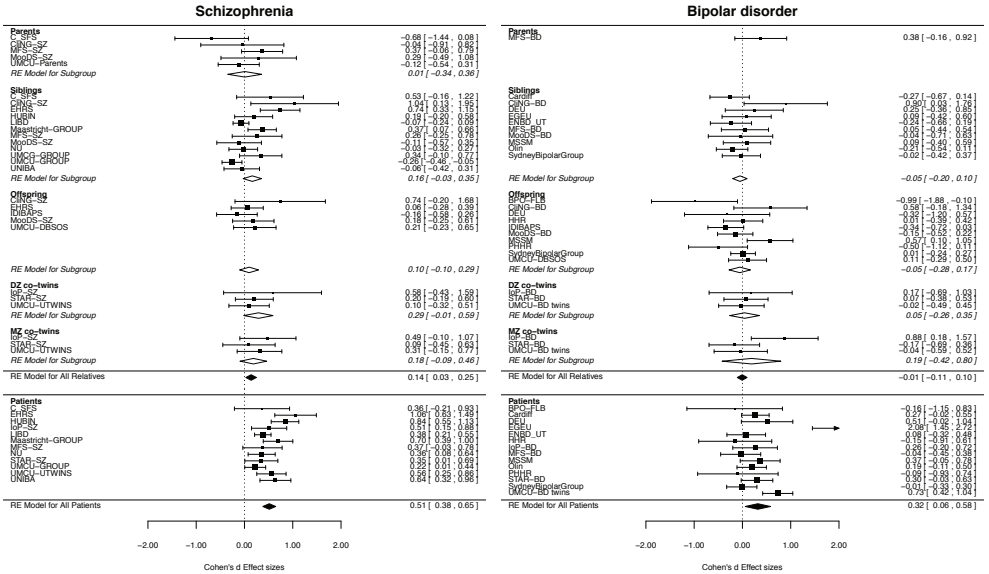
cerebellum white matter



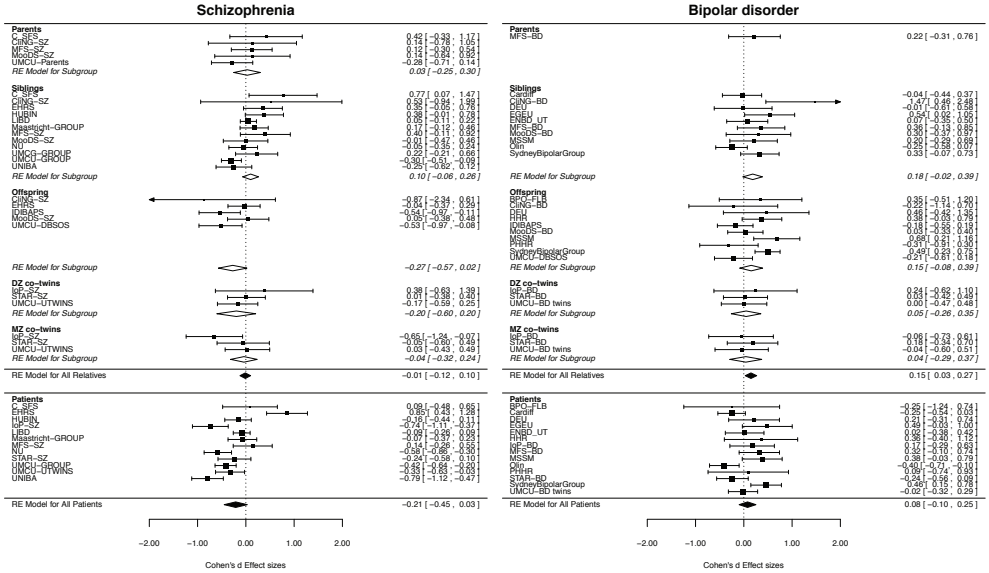
lateral ventricles



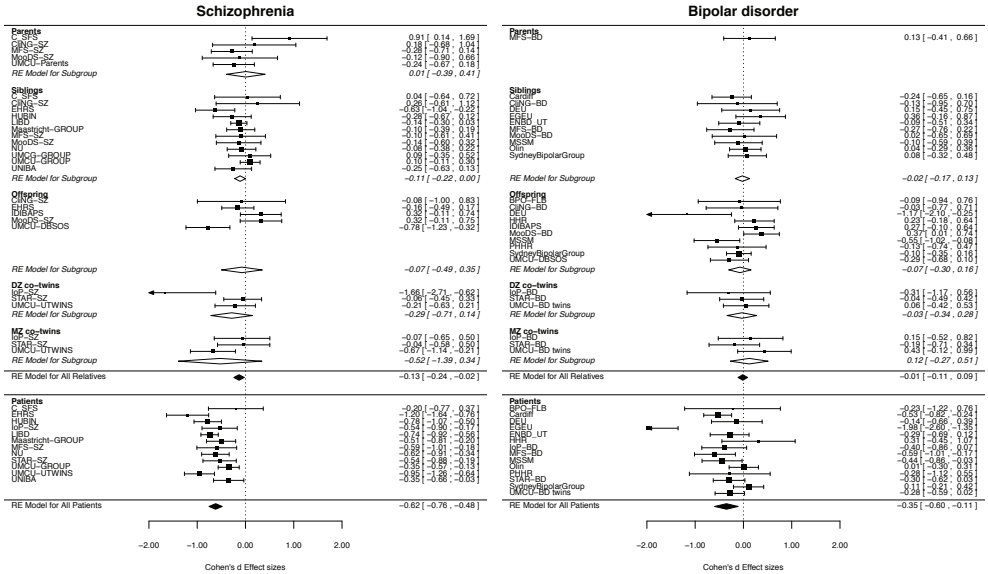
third ventricle



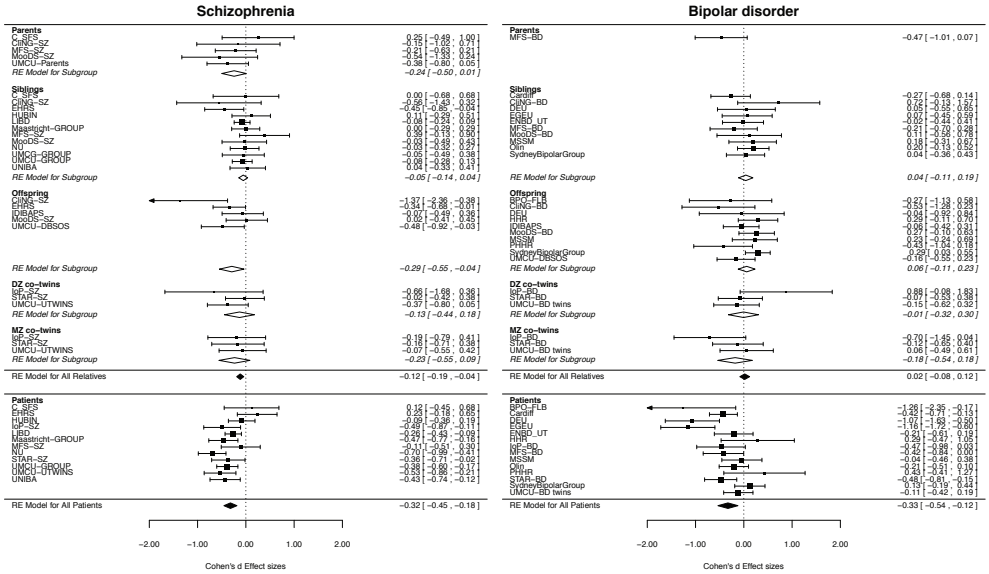
surface area



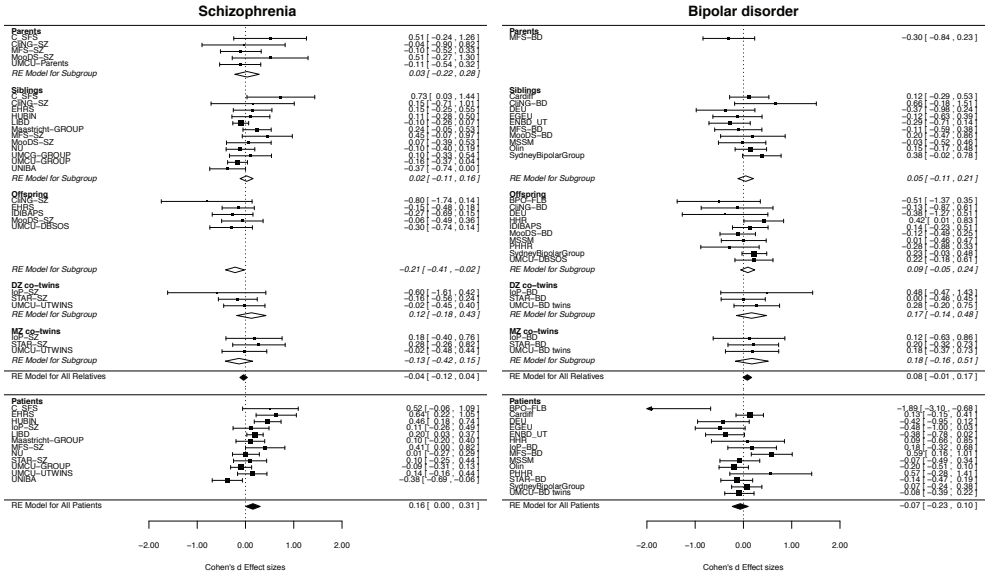
cortical thickness



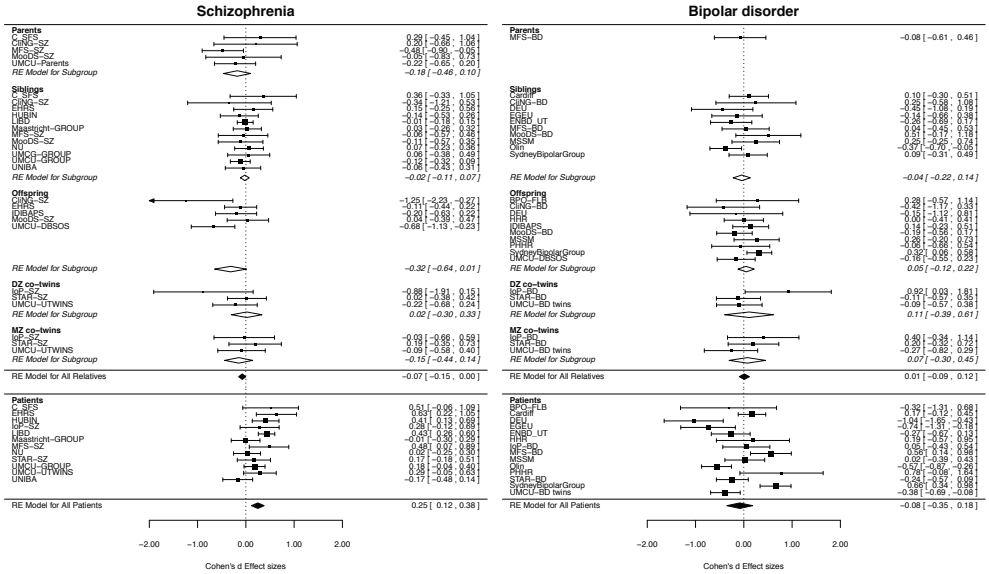
thalamus



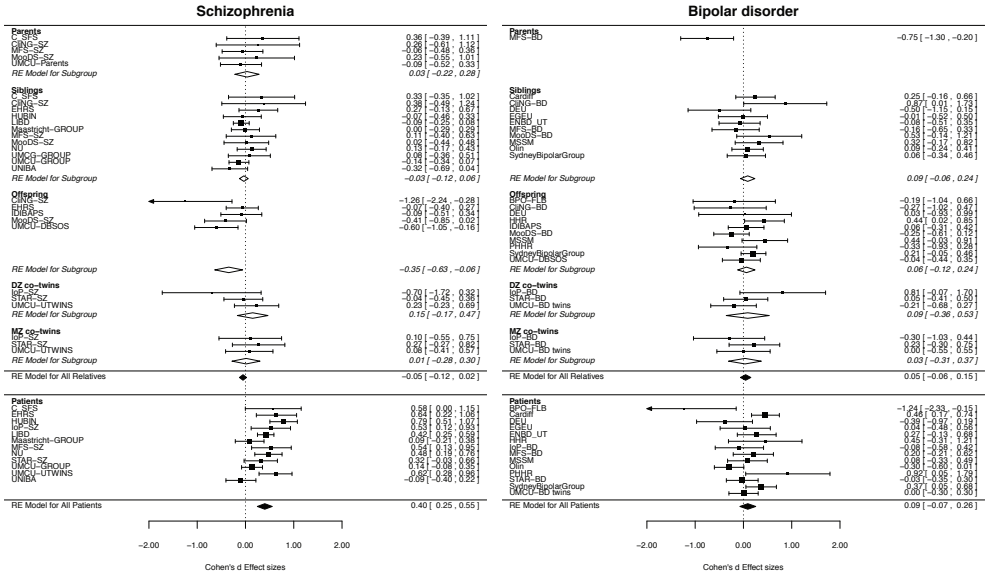
caudate



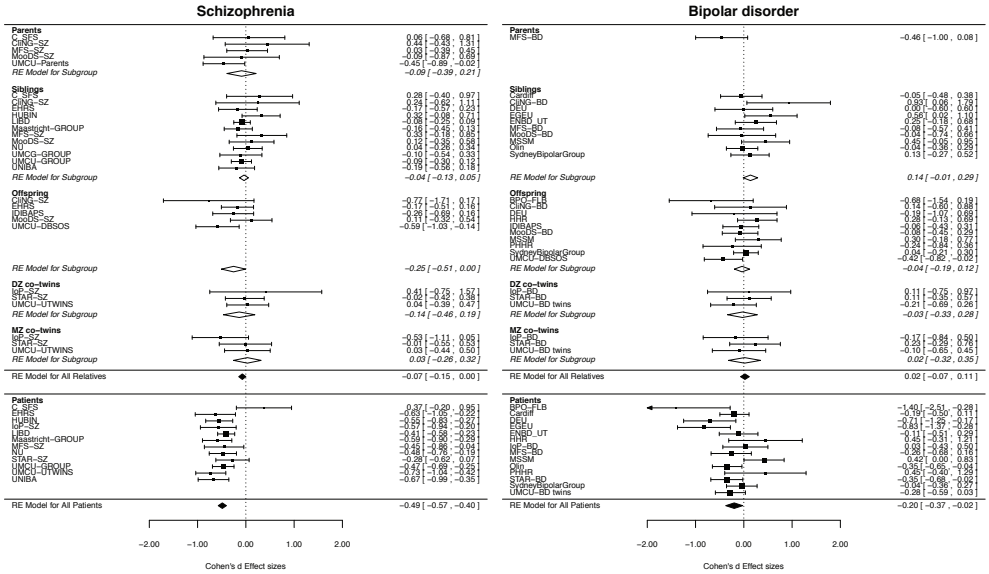
putamen



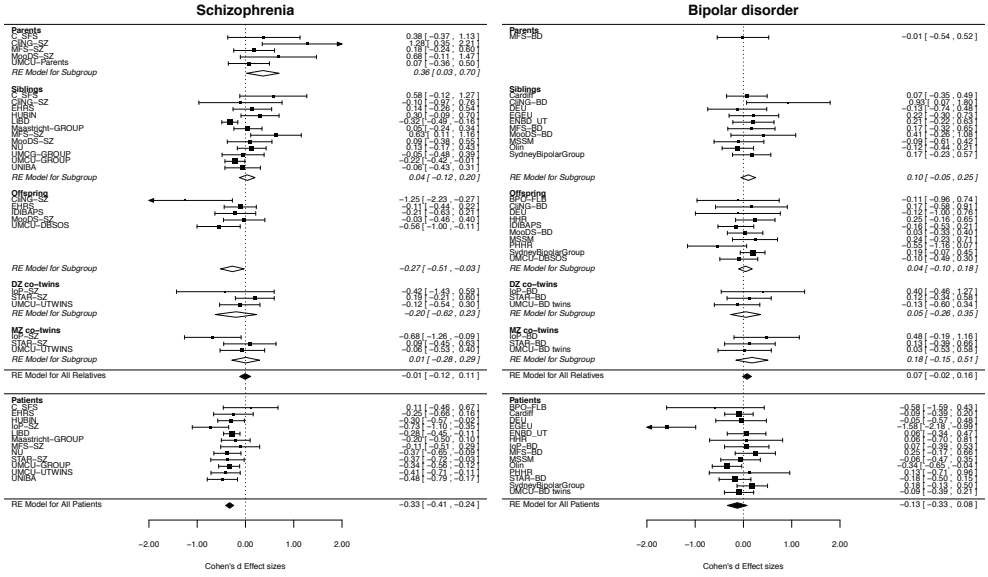
pallidum



hippocampus



amygdala



accumbens

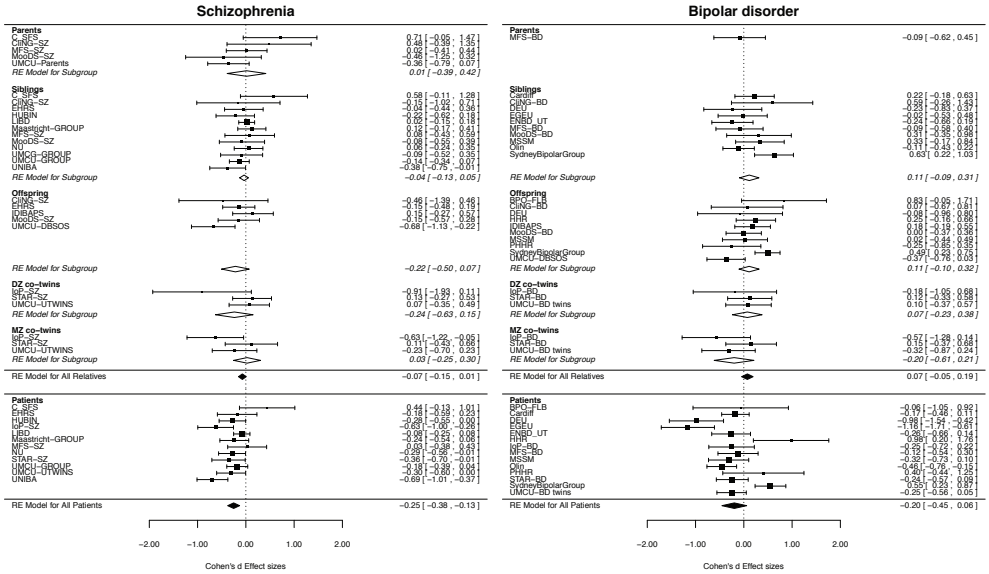
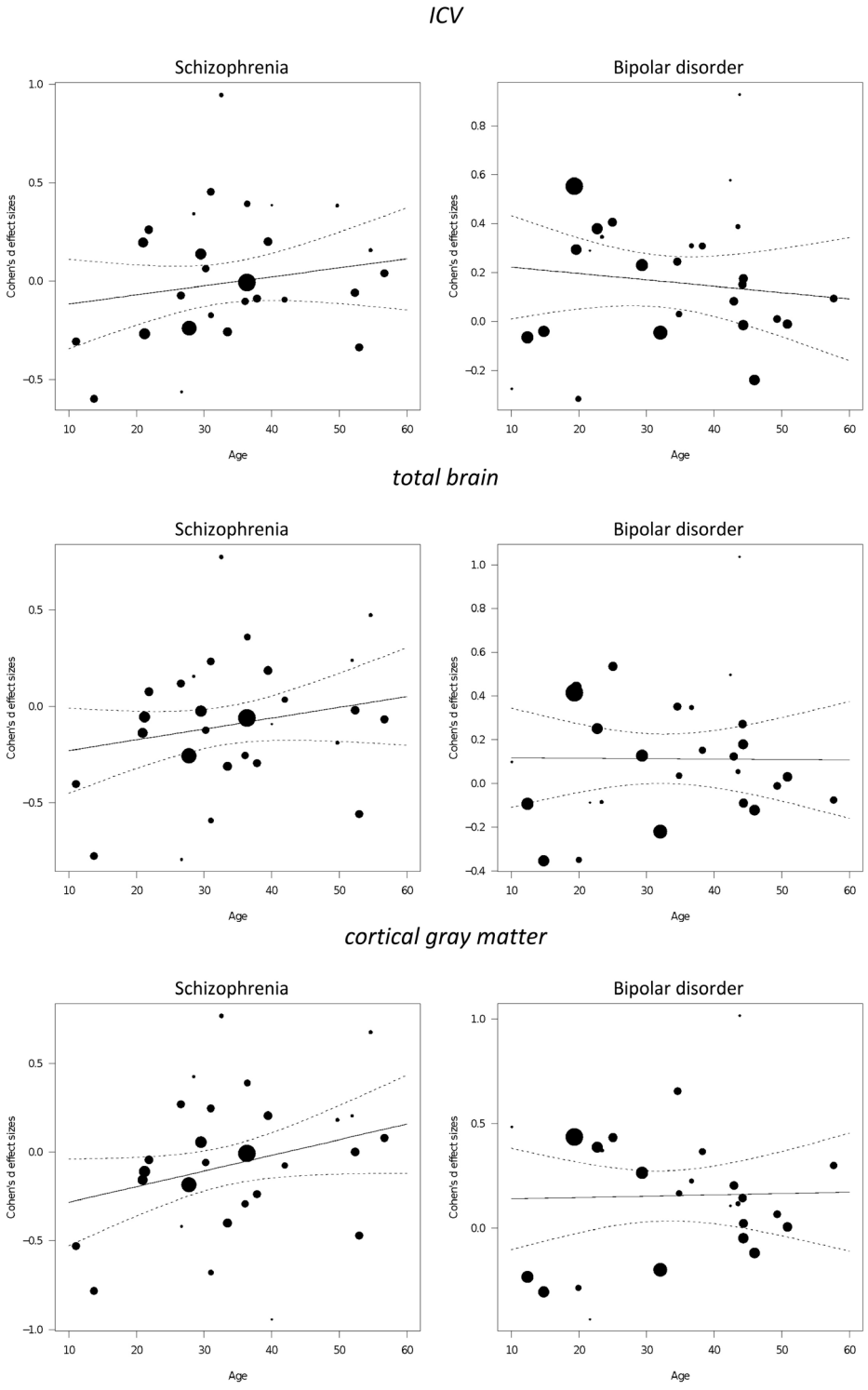
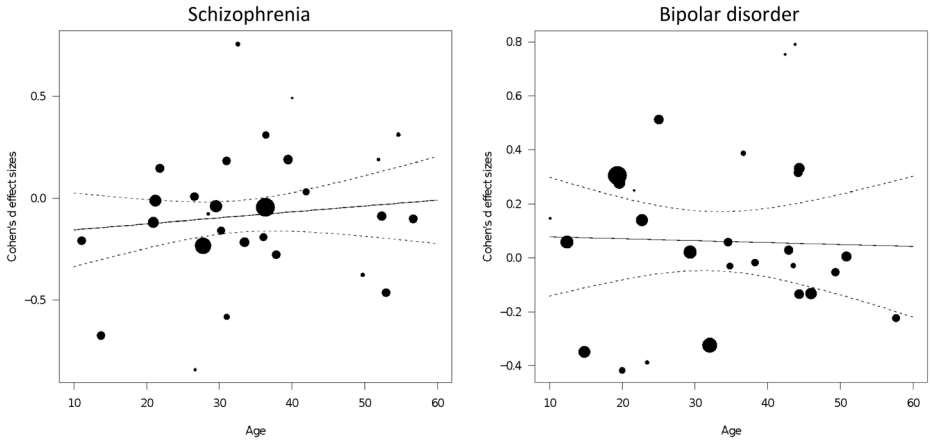

Schizophrenia
Parents
C_SFS 0.71 [−0.05 , 1.47]
CliNG−SZ 0.48 [−0.39 , 1.35]
MFS−SZ 0.02 [−0.41 , 0.44]
MooDS−SZ −0.48 [−1.25 , 0.32]
UMCU−Parents −0.36 [−0.79 , 0.07]
RE Model for Subgroup 0.01 [−0.39 , 0.42]
Siblings
C_SFS 0.58 [−0.11 , 1.28]
CliNG−SZ −0.15 [−1.02 , 0.71]
EHRS −0.04 [−0.44 , 0.36]
HUBIN −0.22 [−0.62 , 0.18]
LIBD 0.02 [−0.15 , 0.18]
Maastricht−GROUP 0.12 [−0.17 , 0.41]
MFS−SZ 0.08 [−0.43 , 0.59]
MooDS−SZ −0.08 [−0.52 , 0.39]
NU −0.09 [−0.54 , 0.35]
UMCG−GROUP −0.09 [−0.52 , 0.35]
UMCU−GROUP −0.14 [−0.54 , 0.27]
UNIBA −0.38 [−0.75 , −0.01]
RE Model for Subgroup −0.04 [−0.13 , 0.05]
Offspring
CliNG−SZ −0.46 [−1.39 , 0.46]
EHRS −0.15 [−0.48 , 0.19]
IDIBAPS 0.15 [−0.27 , 0.57]
MooDS−SZ −0.15 [−0.57 , 0.28]
UMCU−DBSOS −0.68 [−1.13 , −0.22]
RE Model for Subgroup −0.22 [−0.50 , 0.07]
DZ co−twins
IoP−SZ −0.91 [−1.93 , 0.11]
STAR−SZ 0.13 [−0.27 , 0.53]
UMCU−UTWINS 0.07 [−0.35 , 0.49]
RE Model for Subgroup −0.24 [−0.63 , 0.15]
MZ co−twins
IoP−SZ −0.63 [−1.22 , −0.05]
STAR−SZ 0.11 [−0.43 , 0.66]
UMCU−UTWINS −0.23 [−0.70 , 0.23]
RE Model for Subgroup 0.03 [−0.25 , 0.30]
RE Model for All Relatives −0.07 [−0.15 , 0.01]
Patients
C_SFS 0.44 [−0.13 , 1.01]
EHRS −0.18 [−0.59 , 0.23]
HUBIN −0.23 [−0.50 , 0.05]
IoP−SZ −0.61 [−1.30 , 0.08]
LIBD −0.02 [−0.17 , 0.13]
Maastricht−GROUP −0.22 [−0.52 , 0.08]
MFS−SZ 0.03 [−0.38 , 0.43]
NU −0.29 [−0.58 , −0.01]
STAR−SZ −0.36 [−0.70 , −0.01]
UMCU−GROUP −0.18 [−0.39 , 0.04]
UMCU−UTWINS −0.30 [−0.60 , 0.00]
UNIBA −0.69 [−1.01 , −0.37]
RE Model for All Patients −0.25 [−0.38 , −0.13]
−2.00 −1.00 0.00 1.00 2.00
Cohen's d Effect sizes
Bipolar disorder
Parents
MFS−BD −0.09 [−0.62 , 0.45]
Siblings
Cardiff 0.22 [−0.18 , 0.63]
CliNG−BD 0.59 [−0.26 , 1.43]
DEU −0.23 [−0.83 , 0.37]
EGEU −0.02 [−0.53 , 0.48]
ENBD_UT 0.24 [−0.06 , 0.53]
MFS−BD −0.09 [−0.58 , 0.40]
MooDS−BD 0.31 [−0.35 , 0.98]
MSSM 0.33 [−0.17 , 0.84]
Olin −0.11 [−0.43 , 0.22]
SydneyBipolarGroup 0.63 [0.22 , 1.03]
RE Model for Subgroup 0.11 [−0.09 , 0.31]
Offspring
BPO−FLB 0.83 [−0.05 , 1.71]
CliNG−BD 0.07 [−0.67 , 0.81]
DEU −0.08 [−0.96 , 0.80]
EHR 0.25 [−0.16 , 0.66]
IDIBAES 0.18 [−0.19 , 0.55]
MooDS−BD 0.00 [−0.37 , 0.36]
MSSM 0.02 [−0.44 , 0.48]
PHHR −0.25 [−0.85 , 0.35]
SydneyBipolarGroup 0.49 [0.03 , 0.95]
UMCU−DBSOS −0.37 [−0.76 , 0.03]
RE Model for Subgroup 0.11 [−0.10 , 0.32]
DZ co−twins
IoP−BD −0.18 [−1.05 , 0.68]
STAR−BD 0.15 [−0.33 , 0.58]
UMCU−BD twins 0.10 [−0.37 , 0.57]
RE Model for Subgroup 0.07 [−0.23 , 0.38]
MZ co−twins
IoP−BD −0.57 [−1.28 , 0.14]
STAR−BD 0.15 [−0.37 , 0.66]
UMCU−BD twins −0.32 [−0.87 , 0.24]
RE Model for Subgroup −0.20 [−0.61 , 0.21]
RE Model for All Relatives 0.07 [−0.05 , 0.19]
Patients
BPO−FLB −0.06 [−1.05 , 0.92]
Cardiff −0.07 [−0.48 , 0.33]
DEU −0.98 [−1.54 , −0.42]
EGEU −1.18 [−1.77 , −0.61]
ENBD_UT −0.07 [−0.35 , 0.21]
EHR 0.38 [−0.08 , 0.84]
IoP−BD −0.26 [−0.72 , 0.20]
MFS−BD −0.13 [−0.54 , 0.30]
MSSM −0.32 [−0.73 , 0.10]
Olin −0.46 [−0.76 , −0.15]
PHHR 0.40 [−0.44 , 1.25]
STAR−BD −0.24 [−0.57 , 0.09]
SydneyBipolarGroup 0.55 [0.23 , 0.87]
UMCU−BD twins −0.25 [−0.56 , 0.05]
RE Model for All Patients −0.20 [−0.45 , 0.06]
−2.00 −1.00 0.00 1.00 2.00
Cohen's d Effect sizes

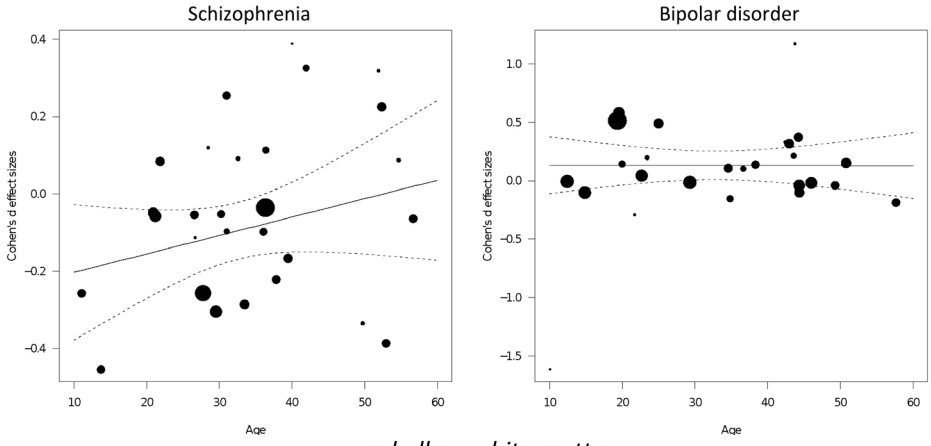
Figure S2i-xvii. Meta-regression plots per region of interest



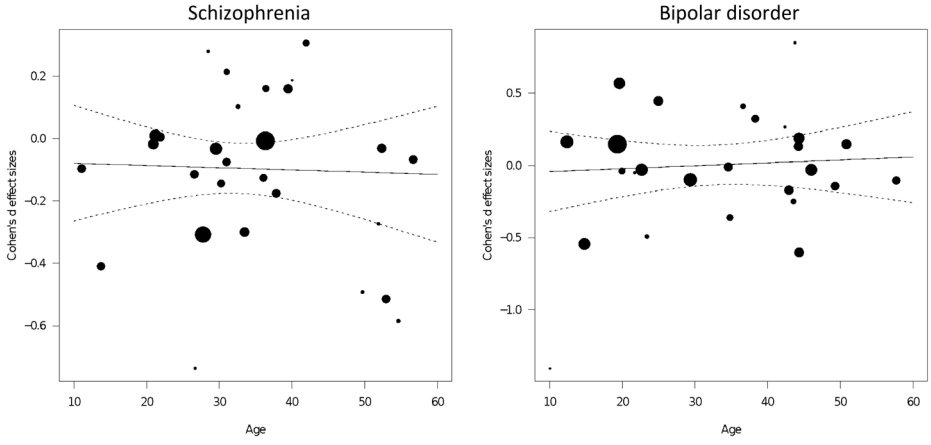
cerebral white matter



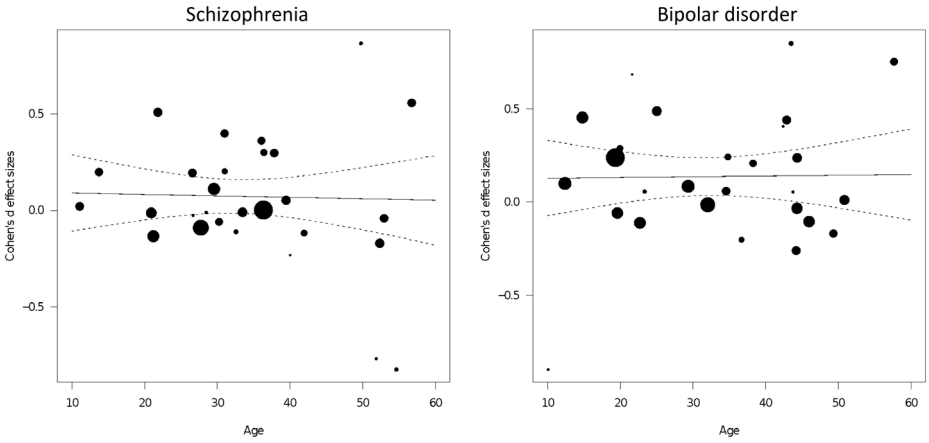
cerebellum gray matter



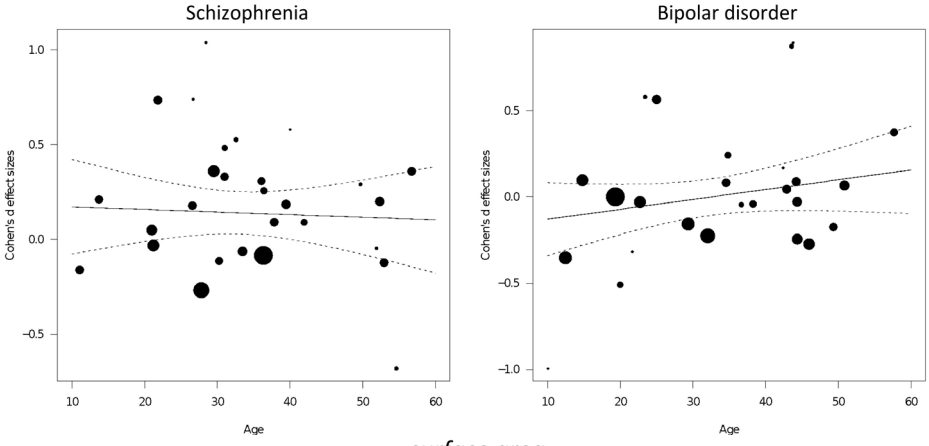
cerebellum white matter



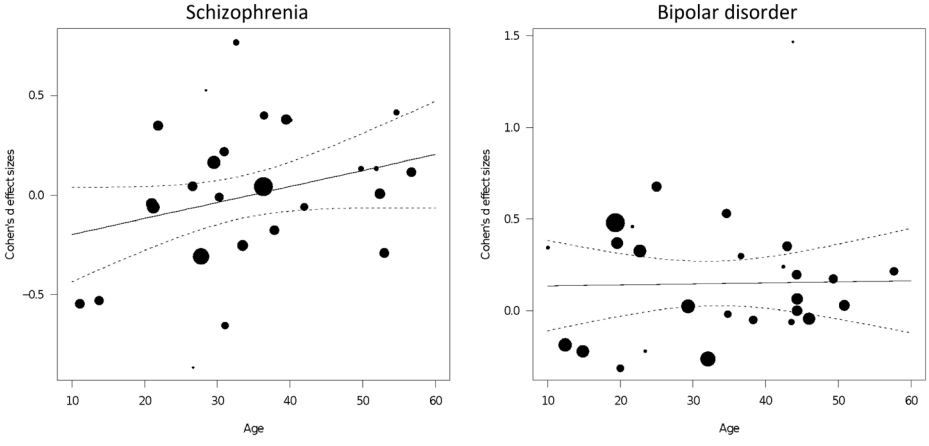
lateral ventricles



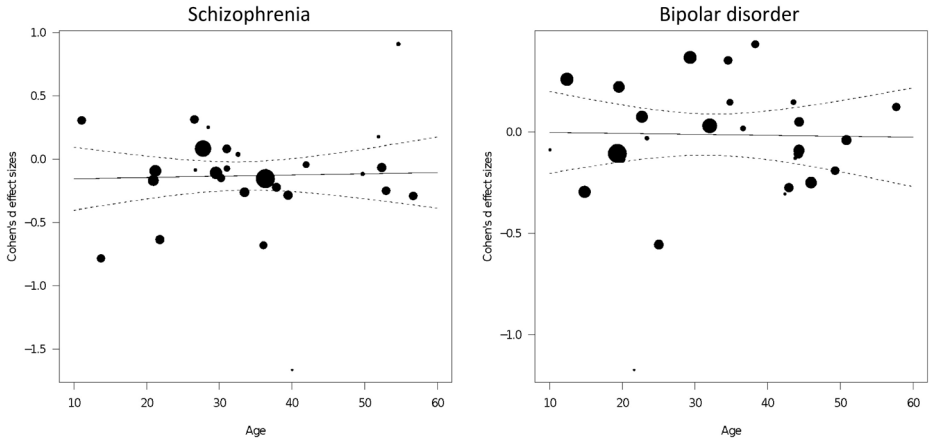
third ventricle



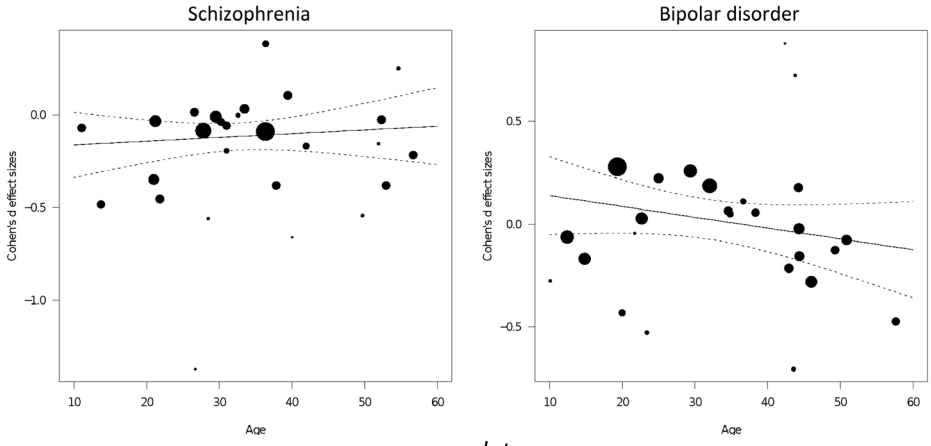
surface area



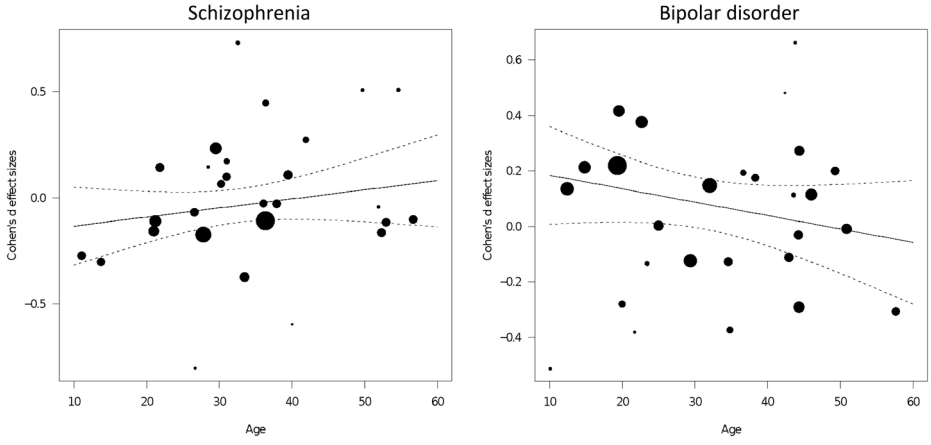
cortical thickness

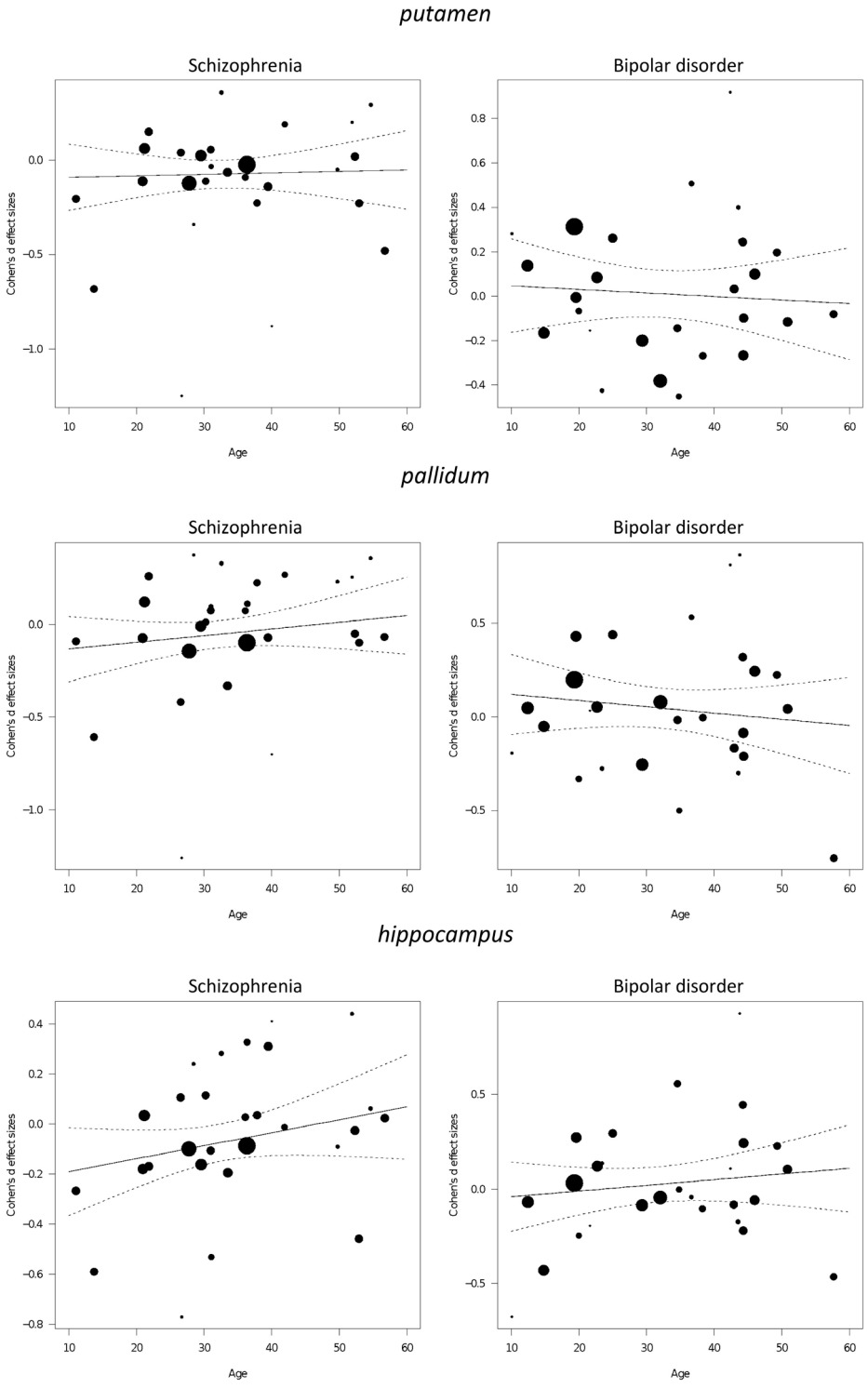


thalamus

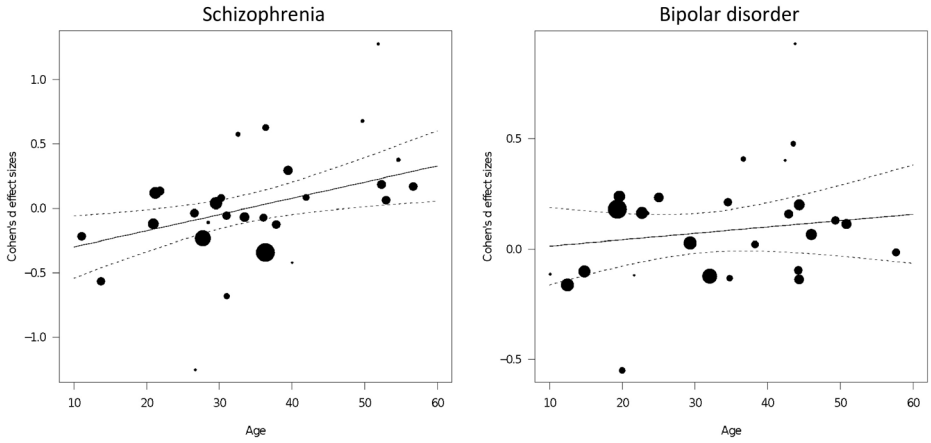


caudate

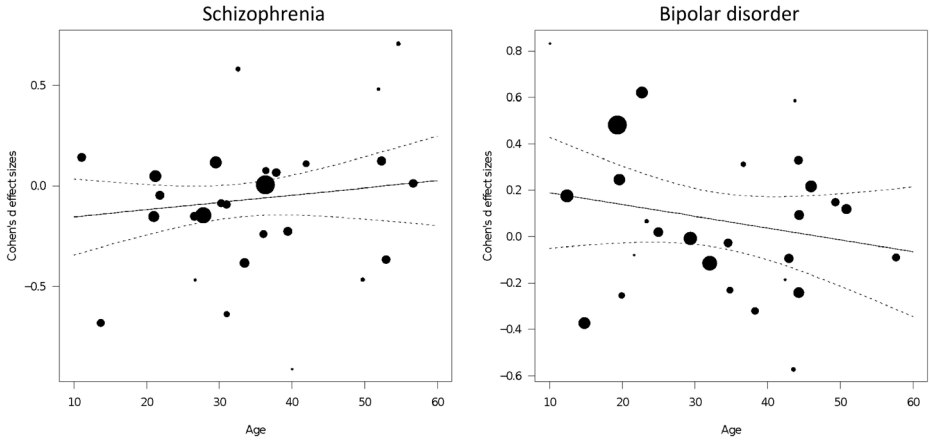



putamen
Schizophrenia
Bipolar disorder
Cohen's d effect sizes
Age
pallidum
Schizophrenia
Bipolar disorder
Cohen's d effect sizes
Age
hippocampus
Schizophrenia
Bipolar disorder
Cohen's d effect sizes
Age

amygdala



accumbens



PRESS RELEASE *BIOLOGICAL PSYCHIATRY*

Risk of psychotic disorders has disease-specific brain effects

Relatives of patients with schizophrenia or bipolar disorder have distinct brain abnormalities

Philadelphia, August 20, 2019

Brain abnormalities in people at familial risk of schizophrenia and bipolar disorder emerge in unique patterns, despite the symptom and genetic overlap of the disorders, according to a study in *Biological Psychiatry*, published by Elsevier. Similarities between schizophrenia and bipolar disorder have led to the diagnoses being increasingly combined in studies of psychosis, but the findings highlight that risk for the disorders has distinct effects on the brain.

Schizophrenia and bipolar disorder tend to run in families, as relatives share genetic risk factors and exposure to life events that can increase risk of the disease, referred to as environmental risk factors. "We were interested in the relationship between this increased risk for schizophrenia or bipolar disorder and brain development," said first author Sonja M.C. de Zwarte, MSc, University Medical Center Utrecht, The Netherlands.

Relatives of bipolar disorder patients had larger intracranial volumes—a measure that includes total brain tissue and cerebrospinal fluid—and relatives of schizophrenia patients had smaller brain volumes when compared with people without family history of these disorders.

"The size of intracranial volume is considered a marker for early brain development. Thus, our findings suggest that the familial risk for these disorders is influencing brain development already early in life, and in a different manner," said Ms. de Zwarte.

The differences in brain development between the disorders will be an important consideration for future brain imaging studies of psychiatric disorders. "Recent focus on dimensional cross-diagnostic features of psychiatric disorders has deemphasized important complementary categorical distinctions. This imaging genomics study reminds us of the potential importance of these categorical distinctions," said John Krystal, MD, Editor of *Biological Psychiatry*.

The researchers also found differences in brain anomalies when the participants were separated by their relationship with the patients, though no clear pattern developed based on relative type. First-degree relatives share about 50 percent of their genes, so the variation between the types of first-degree relatives suggests that environmental risk factors also contribute to the brain anomalies in family members.

The international collaborative study by researchers of the ENIGMA consortium was the largest examination of first-degree relatives of patients with schizophrenia or bipolar disor-

der, including over 6,000 brain imaging datasets in a meta-analysis. The study emphasizes the usefulness of studying family members of people with psychiatric disorders to better understand how risk of the illnesses affects the brain, an approach that avoids the disease or medication effects that complicate studies of patients.

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Sonja M.C. de Zwarte, Rachel M. Brouwer, Ingrid Agartz, Martin Alda, Silvia Alonso-Lana, Carrie E. Bearden, Alessandro Bertolino, Aurora Bonvino, Elvira Bramon, Elizabeth E.L. Buimer, Wiepke Cahn, Erick J. Canales-Rodríguez, Dara M. Cannon, Tyrone D. Cannon, Xavier Caseras, Josefina Castro-Fornieles, Qiang Chen, Yoonho Chung, Elena De la Serna, Caterina del Mar Bonnin, Caroline Demro, Annabella Di Giorgio, Gaelle E. Doucet, Mehmet Cagdas Eker, Susanne Erk, Mar Fatjó-Vilas, Scott C. Fears, Sonya F. Foley, Sophia Frangou, Janice M. Fullerton, David C. Glahn, Vina M. Goghari, Jose M. Goikolea, Aaron L. Goldman, Ali Saffet Gonul, Oliver Gruber, Tomas Hajek, Emma L. Hawkins, Andreas Heinz, Ceren Hidiroglu Ongun, Manon H.J. Hillegers, Josselin Houenou, Hilleke E. Hulshoff Pol, Christina M. Hultman, Martin Ingvar, Viktoria Johansson, Erik G. Jönsson, Fergus Kane, Matthew J. Kempton, Marinka M.G. Koenis, Miloslav Kopecek, Bernd Krämer, Stephen M. Lawrie, Rhoshel K. Lenroot, Machteld Marcelis, Venkata S. Mattay, Colm McDonald, Andreas Meyer-Lindenberg, Stijn Michielse, Philip B. Mitchell, Dolores Moreno, Robin M. Murray, Benson Mwangi, Leila Nabulsi, Jason Newport, Cheryl A. Olman, Jim van Os, Bronwyn J. Overs, Aysegul Ozerdem, Giulio Pergola, Marco M. Picchioni, Camille Piguet, Edith Pomarol-Clotet, Joaquim Radua, Ian S. Ramsay, Anja Richter, Gloria Roberts, Raymond Salvador, Aybala Saricicek Aydogan, Salvador Sarró, Peter R. Schofield, Esma M. Simsek, Fatma Simsek, Jair C. Soares, Scott R. Sponheim, Gisela Sugranyes, Timothea Toulopoulou, Giulia Tronchin, Eduard Vieta, Henrik Walter, Daniel R. Weinberger, Heather C. Whalley, Mon-Ju Wu, Nefize Yalin, Ole A. Andreassen, Christopher R.K. Ching, Sophia I. Thomopoulos, Theo G.M. van Erp, Neda Jahanshad, Paul M. Thompson, René S. Kahn, Neeltje E.M. van Haren

Intelligence, educational attainment and brain structure in those at familial high-risk for schizophrenia or bipolar disorder

Submitted

ABSTRACT

First-degree relatives of patients diagnosed with schizophrenia (FDRs-SZ) show similar patterns of brain abnormalities and cognitive alterations to patients, albeit with smaller effect sizes. First-degree relatives of patients diagnosed with bipolar disorder (FDRs-BD) show divergent patterns; on average, intracranial volume is larger compared to controls, and findings on cognitive alterations in FDRs-BD are inconsistent. Here, we performed a meta-analysis of global and regional brain measures (cortical and subcortical), current IQ, and educational attainment in 5,795 individuals (1,103 FDRs-SZ, 867 FDRs-BD, 2,190 controls, 942 schizophrenia patients, 693 bipolar patients) from 36 schizophrenia and/or bipolar disorder family cohorts, with standardized methods. Compared to controls, FDRs-SZ showed a pattern of widespread thinner cortex, while FDRs-BD had widespread larger cortical surface area. IQ was lower in FDRs-SZ ($d = -0.42$, $p = 3 \times 10^{-5}$), with weak evidence of IQ reductions amongst FDRs-BD ($d = -0.23$, $p = 0.045$). Both relative groups had similar educational attainment compared to controls. When adjusting for IQ or educational attainment, the group-effects on brain measures changed, albeit modestly. Changes were in the expected direction, with less pronounced brain abnormalities in FDRs-SZ and more pronounced effects in FDRs-BD. To conclude, FDRs-SZ and FDRs-BD show a differential pattern of structural brain abnormalities. In contrast, both had lower IQ scores and similar school achievements compared to controls. Given that brain differences between FDRs-SZ and FDRs-BD remain after adjusting for IQ or educational attainment, we suggest that differential brain developmental processes underlying predisposition for schizophrenia or bipolar disorder are likely independent of general cognitive impairment.

INTRODUCTION

Schizophrenia and bipolar disorder are highly heritable disorders with a shared genetic architecture (Anttila et al., 2018; Lee et al., 2013; Lichtenstein et al., 2009). Both patient groups are characterized by overlapping patterns of structural brain abnormalities (Arnone et al., 2009; Ellison-Wright & Bullmore, 2010; Haijma et al., 2013; Hibar et al., 2017, 2016; Ivleva et al., 2017; McDonald et al., 2004; Okada et al., 2016; Van Erp et al., 2015, 2018). In contrast, our recent ENIGMA–Relatives meta-analysis showed that their family members — who share the risk for the disorder but generally are not confounded by medication use or other illness related factors — show divergent patterns of global brain measures (De Zwarte et al., 2019b). That study found that first-degree relatives of patients diagnosed with bipolar disorder (FDRs-BD) had a larger intracranial volume (ICV) which was not present in first-degree relatives of patients diagnosed with schizophrenia (FDRs-SZ). When we adjusted for ICV, no differences were found between FDRs-BD and controls but FDRs-SZ still showed significantly smaller brain volumes, diminished cortical thickness and larger ventricle volume compared to controls. These findings suggest that individuals at familial risk for either bipolar disorder or schizophrenia may show disease-specific deviations during early brain development.

Differential neurodevelopmental trajectories in schizophrenia and bipolar disorder have also been linked to intelligence quotient (IQ) development and school performance (Parellada et al., 2017). Schizophrenia has been associated with poorer cognitive performance, as well as decreases in cognitive performance over time, years before onset (Agnew-Blais & Seidman, 2013; Dickson et al., 2012; Hochberger et al., 2018; Kendler et al., 2015; Khandaker et al., 2011; Reichenberg et al., 2005; Woodberry et al., 2008), while premorbid IQ or educational attainment are often not affected or are even higher in individuals who later develop bipolar disorder (MacCabe et al., 2010; Smith et al., 2015; Tiihonen et al., 2005; Zammit et al., 2004).

Both IQ and educational attainment are highly heritable (Devlin et al., 1997; Heath et al., 1985; Tambs et al., 1989). Consequently, similar patterns of cognitive performance and educational attainment are often found among relatives. Indeed, cognitive alterations have been reported in FDRs-SZ compared to controls (Hughes et al., 2005; Kremen et al., 1998; McIntosh et al., 2005; Niendam et al., 2003; Sitskoorn et al., 2004; Van Haren et al., 2019; Vreeker et al., 2016) and in FDRs-BD compared to controls (Vonk et al., 2012; Vreeker et al., 2016). Vreeker et al. (2016) showed, in a direct comparison, a discrepancy between IQ and educational attainment in FDRs-SZ and FDRs-BD: both groups showed lower IQ but similar educational attainment compared to controls. These findings suggest that, despite the high genetic and phenotypic overlap between intelligence and educational attainment in the general population (Sniekers et al., 2017; Strenze, 2007), it is important to differentiate between these two measures when investigating individuals at familial risk for mental illness.

Intelligence has consistently been associated with brain structure (McDaniel, 2005) and our recent schizophrenia family study reported that IQ was intertwined with most of the brain abnormalities in FDRs-SZ (De Zwarte et al., 2019a). However, in FDRs-BD, it remains unknown how IQ and risk for bipolar disorder interact with the brain. In particular, the relationship between IQ and the familial predisposition for a larger ICV in FDRs-BD is unclear.

Here, through the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA)—Relatives Working Group, we performed meta-analyses of magnetic resonance imaging data sets consisting of FDRs-SZ and/or FDRs-BD, probands, and matched control participants. There were three main aims. First, we extended our findings of group differences in global brain measures between relatives and controls (and patients) for both disorders (De Zwarte et al., 2019b) by adding local cortical measures. Previous ENIGMA meta-analyses have shown that patients with schizophrenia have widespread attenuation of cortical thickness and surface area (with largest effects in frontal and temporal lobe regions), with evidence for regional specificity only in the thickness findings (Van Erp et al., 2018). In contrast, patients with bipolar disorder have shown thinner cortex in frontal, temporal and parietal regions, but no differences in surface area, compared to controls (Hibar et al., 2017). Based on the patient findings and our previous ENIGMA—Relatives findings for global brain measures – showing globally thinner cortex in FDRs-SZ and larger surface area in FDRs-BD – we expected to find subtle regional differences in these measures in the relatives. In particular, we predicted locally thinner cortex in FDRs-SZ with a similar pattern to previous observations in patients but with smaller effect sizes (Van Erp et al., 2018). Based on the larger ICV and global surface area reported in our previous study, locally larger surface area in FDRs-BD was expected in contrast to previous bipolar patient findings (Hibar et al., 2017). Second, in cohorts that had information on IQ and/or educational attainment (the latter is defined as years of education completed), we meta-analyzed the group effects of IQ and educational attainment between relatives and controls (and patients) for both disorders. We hypothesized that both FDRs-SZ and FDRs-BD would have, on average, lower current IQ than controls. Educational attainment findings in relatives have been inconsistent, with findings of both lower educational attainment and no detectable differences between relatives and controls; therefore, we expected subtle but significant differences between both FDRs-SZ and FDRs-BD and controls. Thirdly, we investigated the influence of IQ and educational attainment on global and local brain differences between relatives and controls. We hypothesized that IQ will account for most of the brain abnormalities found in FDRs-SZ, while a lower IQ most likely would not explain our previously reported larger ICV in FDRs-BD because of the well- established positive relationship between overall head size and IQ (McDaniel, 2005). The moderating effect of educational attainment on brain abnormalities is expected to be less pronounced than that of IQ, as we are only expecting modest group differences in educational attainment between relatives and controls.

Table 1. Sample demographics bipolar disorder family cohorts

	Total									IQ scores						Educational attainment					
	Controls			Patients			Relatives			Controls		Patients		Relatives		Controls		Patients		Relatives	
Sample	N	M/F	Age	N	M/F	Age	N	M/F	Age	N	IQ	N	IQ	N	IQ	N	EA	N	EA	N	EA
BPO-FLB	7	3/4	12.9 (1.3)	9	5/4	13.3 (2.6)	22	10/12	10.0 (3.5)	7	91.0 (10.2)	5	91.2 (16.1)	7	95.4 (17.3)	-		-		-	
Cardiff	79	28/51	39.8 (8.7)	120	42/78	41.9 (8.1)	33	13/20	45.9 (6.9)	-		-		-		-		-		-	
CliNG – BD*	19	6/13	30.9 (9.6)	-			19	6/13	31.9 (5.0)	-		-		-		12	14.9 (3.3)	-		10	15.2 (3.2)
DEU	27	11/16	32.9 (8.8)	27	10/17	36.3 (9.5)	23	11/12	31.3 (8.9)	-		-		-		21	13.1 (4.1)	24	12.9 (2.9)	14	11.6 (3.1)
EGEU	33	13/20	33.6 (7.8)	27	16/11	36.7 (7.8)	27	10/17	34.5 (9.5)	-		-		-		28	11.6 (3.8)	26	10.8 (4.2)	23	10.8 (4.4)
ENBD-UT	36	13/23	34.8 (11.7)	72	23/49	36.9 (12.4)	52	10/42	44.3 (13.6)	27	101.0 (14.5)	40	97.0 (12.0)	19	99.2 (14.4)	26	15.2 (3.0)	55	14.7 (2.3)	46	15.1 (2.3)
FIDMAG-Clinic	61	12/49	41.1 (10.1)	18	3/15	42.6 (8.8)	18	5/13	45.1 (10.0)	61	112.9 (13.6)	14	101.9 (13.1)	16	105.8 (16.7)	-		-		-	
Geneva	19	10/9	20.1 (2.7)	-			18	9/9	19.4 (3.1)	-		-		-		-		-		-	
IDIBAPS*	53	21/32	12.3 (3.6)	-			61	31/30	12.4 (3.4)	53	106.1 (12.4)	-		61	107.0 (13.0)	-		-		-	
IoP – BD	39	9/30	35.4 (11.2)	34	15/19	40.6 (13.1)	17	4/13	43.1 (14.6)	-		-		-		31	15.2 (2.6)	26	15.4 (3.2)	14	16.4 (2.6)
MFS – BD*	54	25/29	40.2 (15.3)	38	15/23	41.0 (11.7)	41	17/24	49.3 (9.6)	39	110.8 (16.1)	31	97.4 (11.7)	34	100.0 (10.3)	35	14.1 (3.9)	35	13.9 (3.3)	31	14.6 (4.0)
MooDS – BD*	63	25/38	30.3 (9.5)	-			63	25/38	30.4 (9.4)	62	99.4 (5.5)	-		62	101.5 (5.8)	33	15.4 (2.4)	-		34	17.2 (2.8)
MSSM	52	25/27	35.2 (13.0)	41	21/20	44.3 (11.9)	50	26/24	33.8 (8.3)	-		-		-		-		-		-	
Olin	68	25/43	32.2 (11.7)	108	34/74	34.5 (12.3)	78	30/48	32.0 (13.0)	54	107.0 (15.0)	95	102.9 (15.6)	68	105.6 (15.1)	40	15.2 (2.4)	74	14.6 (2.2)	40	14.6 (2.2)
ORBIS-I	32	12/20	20.7 (3.3)	6	0/6	22.9 (4.0)	39	13/26	19.8 (3.2)	-		-		-		-		-		-	
ORBIS-II	18	7/11	23.0 (3.5)	8	3/5	24.0 (5.0)	26	10/16	19.9 (4.0)	-		-		-		-		-		-	
PENS – BD*	16	6/10	45.9 (10.1)	20	14/6	46.9 (10.4)	9	5/4	40.4 (6.3)	16	115.7 (13.8)	20	103.7 (15.8)	9	101.3 (18.0)	16	16.0 (1.3)	19	14.8 (2.7)	9	15.0 (1.6)
PHCP – BD*	38	21/17	38.4 (13.7)	29	7/22	32.2 (11.6)	7	2/5	51.0 (6.1)	38	106.3 (11.8)	29	101.8 (8.8)	7	100.6 (9.1)	29	16.0 (2.5)	18	14.8 (1.8)	7	15.4 (1.5)
STAR – BD*	83	39/44	49.0 (10.4)	25	7/18	45.8 (10.1)	21	6/15	47.9 (11.3)	-		-		-		81	11.9 (2.9)	25	12.9 (3.6)	21	11.5 (2.5)
SydneyBipolarGroup	117	54/63	22.2 (3.9)	59	17/42	25.1 (3.6)	150	65/85	19.9 (5.4)	116	117.6 (10.3)	57	116.2 (12.3)	147	114.5 (10.6)	24	17.1 (3.2)	32	16.4 (2.3)	30	15.9 (2.2)
UMCU – BD twins*	110	40/70	39.3 (9.2)	52	13/39	39.6 (9.7)	27	9/18	41.7 (9.3)	48	98.0 (13.5)	22	92.4 (13.2)	14	95.4 (14.1)	108	13.4 (2.7)	47	12.7 (2.6)	26	12.1 (2.6)
UMCU – DBSOS*	40	21/19	12.7 (2.1)	-			66	37/29	14.7 (2.7)	40	117.1 (13.0)	-		63	106.7 (18.3)	-		-		-	

* overlapping controls with schizophrenia sample from the same site, i.e. with CliNG-SZ (n=10), IDIBAPS (n=53), MFS-SZ (n=54), MooDS-SZ (n=36), PENS-SZ (n=16), PHCP-SZ (n=38), STAR-SZ (n=73), UMCU-UTWINS (n=19), UMCU-DBSOS (n=40)

Table 2. Sample demographics schizophrenia family cohorts

	Total									IQ scores						Educational attainment					
	Controls			Patients			Relatives			Controls		Patients		Relatives		Controls		Patients		Relatives	
Sample	N	M/F	Age	N	M/F	Age	N	M/F	Age	N	IQ	N	IQ	N	IQ	N	EA	N	EA	N	EA
C–SFS	23	11/12	40.2 (11.1)	25	13/12	40.8 (10.8)	23	8/15	42.1 (11.9)	-		-		-		20	15.2 (2.4)	23	14.2 (3.1)	19	16.1 (2.7)
CliNG – SZ*	20	11/9	35.7 (12.2)	-			20	11/9	36.1 (6.4)	-		-		-		14	15.1 (2.1)	-		14	14.0 (2.6)
EHRS	89	44/45	21.0 (2.5)	31	19/12	21.8 (3.7)	90	44/46	21.2 (3.1)	82	101.9 (12.9)	22	87.9 (14.5)	90	97.6 (13.5)	-		-		-	
HUBIN	102	69/33	41.9 (8.9)	104	78/26	41.3 (7.7)	33	23/10	39.4 (7.8)	69	102.0 (16.5)	73	89.1 (20.4)	19	106.6 (12.4)	90	14.3 (3.0)	93	12.5 (2.7)	30	12.9 (2.3)
IDIBAPS*	53	21/32	12.3 (3.6)	-			37	21/16	11.0 (3.3)	53	106.1 (12.4)	-		37	97.6 (14.2)	-		-		-	
IoP – SZ	67	35/32	40.8 (12.2)	54	39/15	34.8 (10.8)	18	8/10	33.0 (12.4)	41	119.6 (13.9)	37	91.5 (15.8)	12	102.2 (12.6)	57	14.1 (2.4)	41	13.3 (3.1)	14	13.5 (2.9)
LIBD	361	162/199	32.5 (9.9)	211	161/50	35.2 (10.2)	240	99/141	36.2 (9.6)	361	109.6 (9.2)	211	95.4 (11.6)	240	107.3 (10.8)	259	17.5 (2.7)	165	14.8 (2.4)	201	16.3 (2.4)
Maastricht – GROUP	87	33/54	30.8 (10.8)	88	59/29	28.2 (7.0)	96	50/46	29.5 (8.7)	87	111.3 (15.0)	87	96.7 (14.3)	96	108.9 (16.2)	-		-		-	
MFS – SZ*	54	25/29	40.2 (15.3)	42	31/11	36.4 (9.8)	56	21/35	49.4 (8.4)	35	107.8 (14.1)	39	106.4 (16.1)	35	107.9 (16.8)	35	14.1 (3.9)	39	13.9 (3.2)	41	14.1 (3.0)
MooDS – SZ*	65	26/39	30.6 (10.1)	-			63	24/39	30.6 (8.2)	63	100.0 (5.0)	-		61	97.5 (12.3)	37	15.1 (2.3)	-		35	16.1 (2.5)
PENS – SZ*	16	6/10	45.9 (10.1)	20	13/7	47.4 (9.5)	11	4/7	48.3 (8.9)	16	115.7 (13.8)	20	102.9 (15.3)	11	105.0 (14.8)	16	16.0 (1.3)	19	12.7 (1.6)	11	14.5 (1.8)
PHCP – SZ*	38	21/17	38.4 (13.7)	41	30/11	42.2 (11.6)	13	4/9	45.4 (11.4)	38	106.3 (11.8)	41	93.3 (11.7)	13	99.5 (10.5)	29	16.0 (2.5)	38	13.8 (2.3)	12	15.8 (3.0)
STAR – SZ*	73	33/40	49.0 (10.4)	31	18/13	49.7 (8.9)	29	17/12	49.8 (9.6)	-		-		-		73	12.0 (3.0)	31	12.9 (3.4)	28	12.0 (3.8)
UMCU – DBSOS*	40	21/19	12.7 (2.1)	-			40	12/28	13.7 (3.0)	40	117.1 (13.0)	-		40	100.6 (19.2)	-		-		-	
UMCU – GROUP	167	83/84	27.7 (8.2)	162	130/32	27.0 (5.8)	201	95/106	27.7 (7.1)	164	111.9 (14.8)	153	93.5 (15.5)	199	101.4 (14.3)	83	14.0 (2.1)	83	11.2 (3.0)	119	13.5 (2.7)
UMCU – Parents	41	14/27	52.8 (4.6)	-			44	13/31	52.9 (4.3)	41	119.0 (13.1)	-		44	116.9 (14.7)	41	12.5 (3.1)	-		43	12.1 (3.8)
UMCU – UTWINS*	184	84/100	31.8 (13.0)	56	33/23	35.6 (10.6)	45	29/16	37.0 (11.9)	168	106.0 (13.3)	45	96.7 (15.0)	38	107.2 (15.1)	94	13.9 (2.4)	39	11.4 (3.4)	34	13.1 (2.9)
UNIBA	78	52/26	31.4 (8.6)	77	58/19	33.9 (8.2)	44	23/21	33.8 (8.9)	64	108.1 (12.7)	60	74.5 (17.0)	33	94.6 (17.2)	22	15.7 (3.3)	45	11.4 (3.3)	13	13.0 (4.4)

* overlapping controls with bipolar sample from the same site, i.e. with CliNG-BD (n=10), IDIBAPS (n=53), MFS-BD (n=54), MooDS-BD (n=36), PENS-BD (n=16), PHCP-BD (n=38), STAR-BD (n=73), UMCU-BD twins (n=19), UMCU-DBSOS (n=40)

METHODS

Study Samples

This study included 5,795 participants from 36 family cohorts (age range 6 – 72 years). In total, 1,103 FDRs-SZ (42 monozygotic co-twins, 50 dizygotic co-twins, 171 offspring, 728 siblings, 112 parents), 867 FDRs-BD (32 monozygotic co-twins, 33 dizygotic co-twins, 453 offspring, 331 siblings, 18 parents), 942 patients diagnosed with schizophrenia, 693 patients diagnosed with bipolar disorder, and 2,190 controls were included (Tables 1 and 2). All family cohorts included their own control participants. Controls did not have a family history of schizophrenia or bipolar disorder. FDRs-SZ or FDRs-BD were defined by having a first-degree family member with schizophrenia or bipolar disorder, respectively, and not having experienced (hypo)mania and/or psychosis themselves. Demographic characteristics for each cohort and their inclusion criteria are summarized in Tables 1 and 2 and Supplementary Table S1. The cohorts in the current meta-analysis overlap largely, but not completely with those in our previous meta-analysis (De Zwarte et al., 2019b). All study centers obtained approval from their respective ethics committee for research, following the Declaration of Helsinki. Informed consent was obtained from all participants and/or parents, in the case of minors.

Intelligence Quotient

Twenty-five family cohorts had either full scale IQ scores or estimated IQ scores available for most of their participants. In total, 4,095 participants with a measure of IQ were included; 968 FDRs-SZ, 507 FDRs-BD, 788 patients diagnosed with schizophrenia, 313 patients diagnosed with bipolar disorder and 1,549 controls (Table 1 and 2; Supplementary Table S2 for IQ test battery description).

Educational Attainment

Educational attainment was measured as years of completed education. These data were available in 27 family cohorts. Subjects were included if they were at least 25 years old to avoid the bias of including participants still in school. In total, 3,056 participants were included; 614 FDRs-SZ, 306 FDRs-BD, 616 patients diagnosed with schizophrenia, 381 patients diagnosed with bipolar disorder and 1,139 controls (Table 1 and 2; Supplementary Table S3 for educational attainment description).

Image Acquisition and Processing

Structural T1-weighted brain magnetic resonance imaging scans were acquired at each research center (Supplementary Table S4). Cortical and subcortical reconstruction and volumetric segmentations were performed with the FreeSurfer pipeline (Supplementary Table S4) (http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/) (Fischl, 2012). The segmentations were quality checked according to the ENIGMA quality control protocol for subcortical volumes, cortical thickness and surface area (http://enigma.ini.usc.edu/protocols/

imaging-protocols/). Global brain measures, regional cortical thickness and surface area measures and subcortical volumes were extracted from individual images (Fischl & Dale, 2000; Fischl et al., 1999).

Statistical Meta-analyses

All statistical analyses were performed using R (http://www.rproject.org). Linear mixed model analyses were performed within each cohort for bipolar disorder and schizophrenia separately, comparing relatives (per relative type) with controls and, if present, patients with controls, while taking family relatedness into account (http://CRAN.R-project.org/package=nlme) (Pinheiro & Bates, 2000). Patients were analyzed as a sanity check as effects in patients are not the main focus of the study; for differences between patients and controls we refer to the Supplementary Material. Mean centered age, age squared, and sex were included as covariates. Brain measures were corrected for lithium use at time of scan in patients with bipolar disorder by adding a covariate (yes=1/no=0). All global brain measures and subcortical volume analyses were performed both with and without adjusting for ICV by including ICV as covariate. All regional cortical thickness analyses were performed with and without correction for mean cortical thickness and all regional cortical surface areas with and without correction for total surface area to assess regional specificity. Analyses of multiscanner studies included binary dummy covariates for n – 1 scanners. Cohen's d effect sizes and 95% confidence intervals were calculated within each cohort separately and pooled per disorder for all relatives combined, and for patients as a group, using an inverse variance-weighted random-effects meta-analysis. All random-effects models were fitted using the restricted maximum likelihood method. False discovery rate ($q < 0.05$) thresholding across all global and subcortical phenotypes, and separately per regional phenotype, was used to control for multiple comparisons for the analyses between relatives and controls, and between patients and controls (Hochberg, 1995). Correlations between brain measures and IQ, brain measures and educational attainment, and between IQ and educational attainment were estimated by performing linear mixed model analyses in the overall sample and in the relative groups only, based on the gathered statistics of the local analyses. The resulting *t*-statistics were converted to correlation *r* with R package 'esc' (http://CRAN.R-project.org/package=esc). Analyses were generally performed locally by the research center that contributed the cohort, using code created within the ENIGMA-Relatives Working Group (scripts available upon request). For some cohorts, data were sent to the main site for analysis.

RESULTS

Cortical Thickness

FDRs-SZ had a thinner cortex in most cortical regions, compared to controls, with a thinner bilateral pars orbitalis surviving correction for multiple testing (left $d = -0.17$, right $d = -0.16$, $q < 0.05$ corrected) (Figure 1a). There were no significant differences in regional cortical thickness in FDRs-BD compared to controls. To investigate whether findings were

driven by a global effect we corrected for mean cortical thickness. None of the findings survived correction for multiple testing in FDRs-SZ. FDRs-BD had a significantly thicker right caudal middle frontal cortex (d = +0.21, q < 0.05 corrected) (Figure 1b). For all regional cortical thickness effect sizes, and for the patient findings, see Figure 1, and Supplementary Figures S1 and S2.

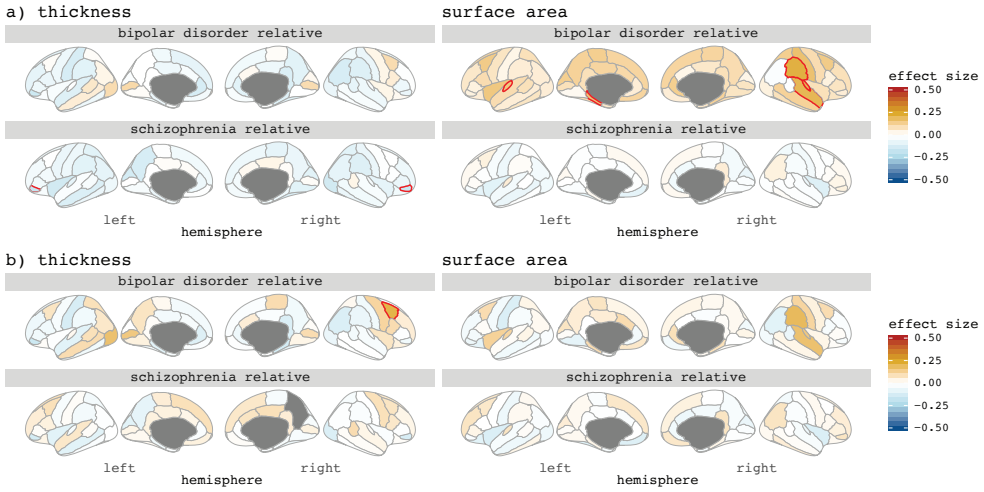

Figure 1. Cohen's d effect sizes comparing bipolar relatives and schizophrenia relatives to controls on a) regional cortical thickness (left) and cortical surface area (right), b) corrected for mean cortical thickness (left) and total surface area (right). Red lined regions survive false discovery rate correction for multiple testing (q < 0.05)

Cortical Surface Area

Differences between FDRs-SZ and controls were subtle and none were statistically significant. FDRs-BD had larger cortical surface areas in many cortical areas compared to controls, with a significantly larger cortical surface area in the left transverse temporal, left parahippocampal, right superior temporal, right supramarginal and right transverse temporal regions surviving correction for multiple testing (ds > +0.15, q < 0.05 corrected) (Figure 1a). When controlling for total surface area to investigate regional specificity, none of the findings survived (Figure 1b). For all regional cortical surface area effect sizes, and for the patient findings see Figure 1, and Supplementary Figures S3 and S4.

Intelligence Quotient

FDRs-SZ had significantly lower IQ compared to controls with a medium effect size d = –0.42 (p = 3 x 10^{-5}). FDRs-BD showed mild IQ reductions compared to controls and of borderline significance with effect size d = –0.23 (p = 0.045) (Figure 2). These findings translate to an average of 6.3 IQ points lower in FDRs-SZ and 3.5 IQ points lower in FDRs-BD compared to controls. In FDRs-SZ, most effect sizes of the global brain measures were slightly smaller after controlling for IQ; none of them survived correction for multiple testing (Figure 3c, Supplementary Table S5, Supplementary Figures S5 and S6). After controlling

for IQ, most effect sizes of the global brain measures were slightly larger in FDRs-BD; however, after correction for multiple testing only larger caudate volume survived (d = +0.23; q < 0.05 corrected) (Figure 3c, Supplementary Table S5, Supplementary Figures S5 and S6). For all effect sizes and the effects in patients, see Supplementary Tables S5–S8, and Supplementary Figures S5 and S6.

Educational Attainment

Both FDRs-SZ and FDRs-BD did not differ from controls on years of education completed (Figure 2). After adjusting for educational attainment, the effect sizes in most global brain measures were slightly smaller in FDRs-SZ (none of which survived correction for multiple testing), while the effect sizes of the global brain measures were slightly larger in FDRs-BD, with a significantly larger ICV (d = +0.25, q < 0.05 corrected) (Figure 3d, Supplementary Table S5, Supplementary Figures S5 and S6). For all effect sizes and the effects in patients, see Supplementary Tables S5–S8, and Supplementary Figures S5 and S6.

Correlations Between IQ, Educational Attainment and Brain Measures

The correlation between IQ and educational attainment in the total sample was r = 0.40 ($p = 4 \times 10^{-22}$). All correlations between IQ and global and subcortical brain measures were positive (ranging from r = 0.06 and r = 0.22 (q < 0.05 corrected), except for the third [r = –0.04] and lateral ventricles [r = –0.01]; Supplementary Table S9; for the results in the FDRs-SZ or FDRs-BD subgroups see Supplementary Table S10). A significant positive correlation was found between educational attainment and total brain, cortical gray matter, cerebellar gray and white matter, and hippocampal volume (r = 0.06 to r = 0.08, q < 0.05 corrected; Supplementary Table S9).

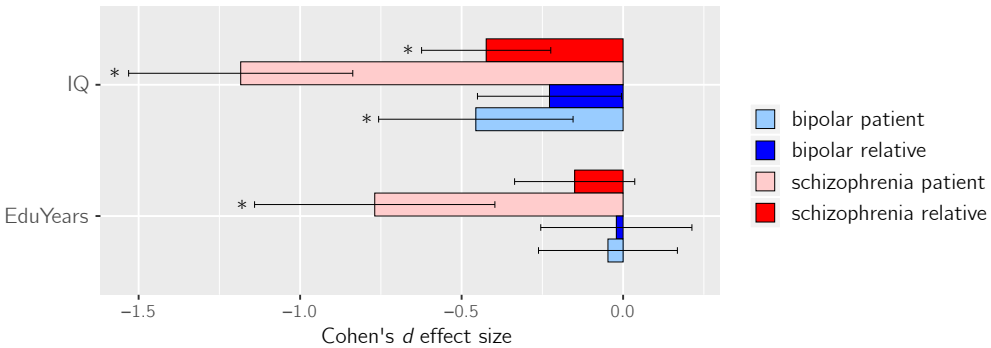

Figure 2. Cohen's d effect sizes comparing bipolar disorder patients (light blue), bipolar disorder relatives (blue), schizophrenia patients (pink), and schizophrenia relatives (red) to controls for intelligence quotient scores (IQ; top) and educational attainment (EduYears; bottom). The error bars depict the lower and upper 95% confidence intervals (CIs). *p < 0.001

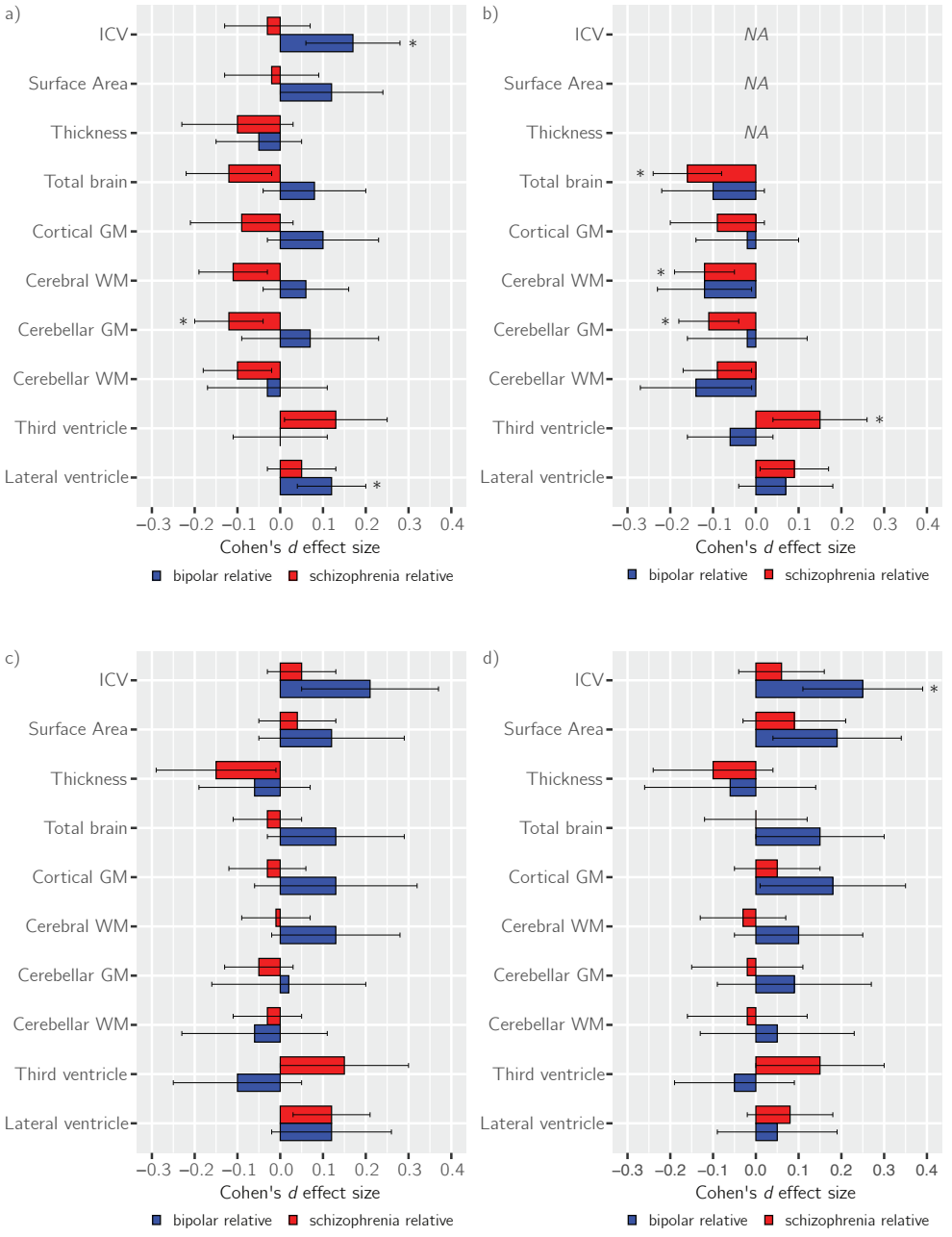

Figure 3. Cohen's *d* effect sizes comparing schizophrenia relatives (red), and bipolar disorder relatives (blue) to controls on a) global brain measures, corrected for b) intracranial volume (ICV), c) intelligent quotient (IQ), d) educational attainment. Analyses displayed in a) and b) have been presented in our previous study, but were for completeness repeated here, albeit with slightly different cohorts (de Zwarte et al., 2019b). Error bars depict the lower and upper 95% confidence intervals (CIs). *$q < 0.05$, corrected. GM = gray matter; WM = white matter; NA = not corrected for ICV

DISCUSSION

In previous work from the ENIGMA–Relatives Working Group we showed that FDRs-BD had a larger ICV which was not found in FDRs-SZ; when we adjusted for ICV, no differences in global brain measures were found between FDRs-BD and controls, while FDRs-SZ had significantly smaller brain volumes, diminished cortical thickness and larger ventricle volume compared to controls (De Zwarte et al., 2019b). In this study we extended the investigation to compare local cortical ROIs, IQ and educational attainment in FDRs-SZ and FDRs-BD with controls and investigated the effect of IQ and educational attainment on global and local brain measures in the relatives.

The main findings in the current study were that: 1) FDRs-SZ had a thinner cortex in most cortical regions, compared to controls, with a thinner bilateral pars orbitalis surviving correction for multiple testing. However, these findings may reflect a global effect rather than regionally specific effect. In contrast, FDRs-BD had a significantly thicker caudal middle frontal cortex when compared to controls that was only present when statistically controlling for global thickness and may thus reflect regionally specific sparing; 2) only FDRs-BD (and not FDRs-SZ) had larger cortical surface area in the temporal lobe, which was no longer present after statistically controlling for total surface area; 3) IQ was lower in both FDRs-BD and FDRs-SZ, while educational attainment did not differ between the relatives and controls; 4) there was a modest yet significant correlation between IQ and most brain measures in the full sample; however, statistically controlling for individual differences in IQ and educational attainment only minimally changed the group effects on the brain measures the expected direction, i.e., effect sizes of brain measure differences between groups decreased for FDRs-SZ and increased for FDRs-BD after adjusting for IQ or educational attainment.

Cortical Thickness and Surface Area in the Relatives

FDRs-SZ had a thinner cortex in most brain areas. This pattern of findings is comparable to that in the included patient sample (Supplementary Figure S1) as well as in the much larger sample of patients diagnosed with schizophrenia in an earlier ENIGMA study (Van Erp et al., 2018). However, effect sizes are lower in FDRs-SZ. The most pronounced effect was observed in the bilateral *pars orbitalis*. This region has previously been associated with language function in those at familial risk for schizophrenia (Francis et al., 2012) and in individuals with non-clinical auditory verbal hallucinations (Van Lutterveld et al., 2014). When statistically controlling for mean cortical thickness this finding was no longer significant, suggesting that thinner cortex in FDRs-SZ is a global effect. In contrast, the pattern in FDRs-BD was diffuse with both thicker and thinner cortical regions, whereas patients with bipolar disorder showed globally thinner cortex (Supplementary Figure S1), consistent with previous findings (Hibar et al., 2017). After correction for mean cortical thickness the right *caudal middle frontal cortex* was significantly thicker when compared to controls, suggesting regionally specific cortical thickness abnormalities in FDRs-BD.

Regional cortical surface area findings showed, on the one hand, that where the patients with schizophrenia had overall smaller surface area (Supplementary Figure S3) (Van Erp et al., 2018), the effects in FDRs-SZ were even more subtle, and in both directions, compared to controls. On the other hand, FDRs-BD had widespread larger regional cortical surface area when compared to controls, in accord with our previous findings of larger total surface area in FDRs-BD (De Zwarte et al., 2019b). While total surface area in patients with bipolar disorder was not significantly larger, we did see a pattern of mostly larger regional cortical surface area in the bipolar patients as well (Supplementary Figure 3). This finding was not reported in the large ENIGMA bipolar disorder meta-analysis (Hibar et al., 2017); however, findings in that study were all corrected for ICV which most likely reduced the global surface area differences.

Cortical thickness and surface area are highly heritable and largely influenced by independent genetic factors (Grasby et al., 2018; Strike et al., 2019). The latest cortical thickness and surface area genome-wide association study (GWAS) showed that the effects of genetic variants associated with surface area are more likely to be prenatal, while cortical thickness effects are more likely postnatal (Grasby et al., 2018), supporting the radial unit hypothesis that cortical thickness and surface area originate from two distinct processes in early brain development (Rakic, 1988). That FDRs-BD and FDRs-SZ show different patterns of abnormal cortical thickness and surface area, strengthens the notion that genetic predisposition may underlie distinct neurodevelopmental trajectories for these disorders early in life.

Discrepancy Between IQ and Educational Attainment

Given the high genetic (r_g = 0.7 (Sniekers et al., 2017)) and phenotypic (r = ~0.5 (Strenze, 2007)) correlation between intelligence and educational attainment, educational attainment is often considered a proxy for IQ. In the current study, we found a phenotypic correlation of r = 0.4 between IQ and educational attainment. This implies that educational attainment is at most a weak proxy for IQ; it only explains 16% of the variance. We showed that IQ and educational attainment act differently in relatives, i.e. lower IQ in FDRs-SZ and FDRs-BD than in controls, with larger alterations in FDRs-SZ, but no differences in educational attainment between FDRs-SZ and FDRs-BD as compared to controls. These findings are in line with an earlier study – of which a subset of the participants is included in the present study – investigating IQ and educational attainment in FDRs-SZ and FDRs-BD (Vreeker et al., 2016), suggesting that even though relatives have a lower IQ on average, gross school performance and engagement is not necessarily affected. It has previously been shown that differentiating intelligence from educational performance is important, as other factors besides intelligence are predictive of educational performance (Chamorro-Premuzic & Furnham, 2003; Deary et al., 2007). In addition, completing a level of education gives little insight into the level of academic performance (e.g., grades). In fact, those measures are only partly correlated (Strenze, 2007). Perhaps, the modest cognitive alterations in the relatives cannot be picked up by a categorical measure such as educational attainment or the

cognitive alterations must reach a certain threshold to lead to a lower level of school performance, which may be the case in patients with schizophrenia (who have the largest negative effect size for IQ and are significantly different from controls in educational attainment).

IQ, Educational Attainment and the Brain

IQ and educational attainment both share genetic variance with ICV (r_g = +0.29 and r_g = +0.34, respectively (Okbay et al., 2016; Sniekers et al., 2017). Therefore, we speculated previously that the larger ICV reported in FDRs-BD could potentially be confounded by higher cognitive functioning (De Zwarte et al., 2019b). Here, we showed that in the total sample ICV and all global brain measures were significantly correlated with IQ, except the ventricles, while correlations between the brain measures and educational attainment were much smaller. Adding to that, IQ was significantly lower in the relatives while this was not the case for educational attainment. Based on these findings, we propose that IQ is a more informative measure than educational attainment to explain variation in brain measures or group differences in brain measures.

As mentioned, only small-to-modest effects of IQ in relation to brain abnormalities in those at familial risk were reported, but these were in the expected direction. In FDRs-SZ, adjusting for IQ explained part of the effect of familial risk for schizophrenia in total brain, gray and white matter volumes (i.e. effect sizes decreased). This was previously shown in two twin studies (both included in this study; Bohlken et al., 2016; Toulopoulou et al., 2015) and a study that included a subset of the present participants using a mega-analysis (De Zwarte et al., 2019a). Interestingly, adjusting for IQ resulted in an even larger ICV difference in FDRs-BD as compared to controls. Given that a larger ICV is associated with a higher IQ in healthy individuals, these findings suggest that the larger ICV in FDRs-BD is unrelated to differences in IQ (which was non-significantly lower in FDRs-BD compared to controls). Taken together, the study findings provide suggestive evidence for different genetic influences on neurodevelopmental processes in FDRs-SZ and FDRs-BD, leading to larger ICV and lower IQ in those at familial risk for bipolar disorder and lower IQ and but similar ICV in those at familial risk for schizophrenia compared to controls.

Limitations

A few limitations to this study should be taken into account. This study is a meta-analysis of multiple cohorts from research centers around the world, with heterogeneity across samples (e.g., in acquisition protocols, scanner field strength, FreeSurfer version, IQ test battery, schooling systems, inclusion and exclusion criteria). Meta-analysis approaches find consistent effects despite this variance but cannot account for all sources of heterogeneity. One source of heterogeneity might also be the substantial age differences between the different cohorts. Both adult and children/adolescent cohorts were included in the analyses, and considering that the brains of the children and adolescents have not reached its adults size and that they have not yet reached the average age-at-onset, might have influenced the findings

of the overall effects. In addition, the FDR groups consist of multiple first-degree relative types (parents, siblings, offspring, co-twins). We decided not analyze each relative type separately, as our prior study showed insufficient power to detect group differences between the different relatives subtypes (De Zwarte et al., 2019b). Importantly, the composition of the FDRs-SZ and FDRs-BD groups differed. More FDRs-SZ were included, of whom a larger proportion were siblings, whereas there were more offspring in the FDRs-BD group. This indicates an overall systematic difference in the way bipolar and schizophrenia families were recruited and highlights that these are not epidemiologically acquired samples representing the entire population of relatives. This could confound the differences reported in the FDRs-SZ and FDRs-BD. Finally, we only analyzed current IQ and educational attainment as cognitive measures in relation to brain structure. Little to no information was available in the participating cohorts on some demographic features, such as parental socioeconomic status (SES), longitudinal cognitive performance (to address cognitive development over time) and other environmental factors that are potentially related to brain structure and to risk for schizophrenia and/or bipolar disorder.

CONCLUSIONS

In summary, investigating family members of patients with schizophrenia and bipolar disorder can provide insight into the effect of familial risk of these disorders on the brain and cognition. This study showed differential global cortical thickness and surface area abnormalities in FDRs-SZ and FDRs-BD. While present in both relative groups, cognitive alterations were more pronounced in FDRs-SZ, adding to the evidence that cognition is more affected in (risk for) schizophrenia than in (risk for) bipolar disorder. Brain differences in the relatives were related to cognitive alterations, as expected based on the well-established positive relationship between intelligence and brain. However, we found no evidence that the larger ICV in FDRs-BD was related to IQ, nor were differences in other brain measures between relatives and controls explained by IQ. This suggests that differential brain developmental trajectories underlying predisposition to schizophrenia or bipolar disorder are only minimally related to IQ. This study of schizophrenia and bipolar disorder relatives further disentangles the biological underpinnings of both disorders. The resulting findings may also inform the ongoing debate on whether schizophrenia and bipolar disorder should be conceptualized as different categories or whether they are part of a continuum of symptoms.

SUPPLEMENTARY TABLES

Table S1. Sample inclusion criteria

Sample	Inclusion criteria
BPO_FLB	BD patients were diagnosed with either type I or type II BD (BD I and BD II), or BD not otherwise specified (BD NOS) according to DSM-IV. Patients exclusion criteria included substance use within the past six months and general medical problems. Inclusion criteria for offspring of BD patients included diagnosis of BD in biological father and or mother according to SCID. Inclusion criteria for healthy controls included those without a history of any psychiatric/neurological disorders or mood disorders in first-degree relatives. Exclusion criteria for patient, healthy control and offspring groups included head injury with loss of consciousness, presence of metallic objects in the body, family history of hereditary neurological disorders, and pregnancy.
C_SFS	Schizophrenia and schizoaffective patients participated. Inclusion criteria for all participants included: 1) age 18-65; 2) minimum intelligence quotient (IQ) of 70 as measured by Wechsler Abbreviated Scale of Intelligence; 3) no current diagnosis of drug or alcohol dependence or abuse; 4) no history of head injury or being unconscious for more than 20 minutes; 5) no history of electroconvulsive therapy; and 6) no history of a neurological condition. Further criteria for inclusion of relatives and controls were no lifetime diagnosis of a psychotic or bipolar disorder, Axis II Cluster A disorder, or history of anti-psychotic medication use. Further criterion for inclusion of community controls was no family history of a psychotic or bipolar disorder.
Cardiff	All participants were age 35 years or older and included: 1) individuals with confirmed diagnosis of bipolar disorder type I or type II, euthymic at time of recruitment and reporting mood stability and no-change in medication for one month prior scanning; 2) unaffected relatives of bipolar participants with no personal history of mood disorders or psychosis; 3) healthy controls with no personal or first-degree family history of mental disorders. All DSM-IV diagnoses were confirmed through the Mini-international neuropsychiatric interview (1). Patients were recruited through the Bipolar Disorder Research Network (BDRN) and the National Centre for Mental Health (NCMH) both at Cardiff University, non-affected siblings were recruited via BD participants, and healthy controls from the community via advertisement.
CLiNG – BD	Inclusion criteria for participants were a) age between 18 and 60 years, b) parents, siblings or offspring of index patients with bipolar disorder, c) no own diagnosis of a mental disorder and d) right-handedness. Diagnosis of bipolar disorder in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, unless a medical report confirming diagnosis of bipolar disorder was provided. Exclusion criteria included history of neurological and severe medical disorders, current or past psychopathology as well as substance dependence and substance abuse.
CLiNG – SZ	Inclusion criteria for participants were a) age between 18 and 60 years, b) parents, siblings or offspring of index patients with schizophrenia, c) no own diagnosis of a mental disorder and d) right-handedness. Diagnosis of schizophrenia in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, unless a medical report confirming diagnosis of schizophrenia was provided. Exclusion criteria included history of neurological and severe medical disorders, current or past psychopathology as well as substance dependence and substance abuse.
DEU	The inclusion criteria for patient group were having a diagnosis of bipolar disorder type I according to DSM-IV, aging between 18 and 65 years, being in euthymic state (according to DSM-IV and scoring ≤ 7 on both Young Mania Rating Scale and Hamilton Rating Scale for Depression) for at least six months and having no axis I comorbidity. The inclusion criteria for first degree relatives of bipolar disorder patients were having no lifetime axis I diagnosis, and for healthy controls, having no lifetime axis I diagnosis and family history for psychiatric disorders at the time of recruitment. The following exclusion criteria were applied to all groups: presence of auditory or visual impairment, history of neurosurgical intervention, being pregnant or breastfeeding, diagnosis of neurocognitive illness or substance use during the preceding six weeks before participating in the study. All participants were evaluated using the Structured Clinical Interview for Diagnostic Statistical Manual-IV (DSM-IV) (SCID-I).
EGEU	All participants were aged between 20 and 55 years old and included: 1) patients with bipolar disorder type 1, euthymic at the time of recruitment (defined as scoring less than five on the Young Mania Rating Scale (YMRS), and less than 11 on the Hamilton Depression Rating Scale-17 item (HAM-D-17) for at least three months prior to and during the MRI scanning); 2) healthy siblings of bipolar participants, never diagnosed with mental illness; 3) unrelated healthy controls, no personal or family history of mental illness. All patients were recruited from the Ege University School of Medicine's Department of Psychiatry, where the patients had been receiving follow-up care with monthly assessments for at least three years, healthy siblings were recruited via BD patients, and unrelated healthy controls from community via local advertisement.
EHRS	All participants were aged between 16 and 25 years old and recruited across Scotland. High-risk individuals were included if they had no history of serious psychiatric problems and had at least two first- or second-degree relatives affected with schizophrenia. Participants for the control group were recruited from the social network of the high-risk individuals themselves; they had no personal or family history of other psychotic illness, but could have a family history of other psychiatric illness and otherwise were similar to the high-risk participants as possible. First-episode individuals were recruited from local hospitals, were balanced group-wise for age with the high-risk individuals and had no family history of schizophrenia.

Sample	Inclusion criteria
ENBD_UT	Specific inclusion criteria for the BD sibling pairs are: a) BD proband with diagnosis of BD I or II, based on DSM-IV criteria, b) having a same-gender sibling not affected by BD; c) ages 18-65 years old; d) BD proband and unaffected sibling no more than 10 years apart in age; e) BD proband at any current mood state at the time of the study; f) BD proband preferably off pharmacological treatment at the time of study, but if not feasible, being on antidepressants and mood stabilizers (including anticonvulsants, typical and atypical antipsychotics, and lithium will be allowed; g) BD proband and unaffected sibling brought up together in the same family. Exclusion criteria for the BD sibling pairs: a) diagnosis of Bipolar Disorder, Schizoaffective Disorder or Schizophrenia is not allowed. Alcohol and substance abuse/ dependence (if in remission in the past 6 months) and anxiety disorders are allowed; b) being on a regular dose of benzodiazepines within two weeks of study participation; c) pregnancy d) ineligibility or inability of one of the members of the sibling pair to participate in the study. Exclusion criteria for controls: a) a lifetime psychiatric diagnosis, b) family history of psychiatric illness in a first-degree relative.
FIDMAG-Clinic	The patients met DSM-IV criteria for bipolar disorder, based on interview and review of case notes, and were euthymic at the time of scanning. The unaffected siblings and healthy controls were excluded if they reported a history of mental illness and/or treatment with psychotropic medication as assessed using the Computerized Diagnostic Interview Schedule for the DSM-IV. Healthy controls were also excluded if they had a first-degree relative with a major psychiatric disorder. Patients, siblings and controls were also excluded if: (a) they were younger than 18 or older than 65 years; (b) they had a history of brain trauma or neurological disease; (c) they had shown alcohol/substance abuse within 12 months prior to participation; or (d) they had undergone electroconvulsive therapy in the previous 12 months.
Geneva	The offspring were aged between 15 and 25 years old at inclusion. Proband parent were outpatients from the Geneva University Hospital, followed in the Mood Disorder Unit. BD diagnostic in the proband was established with the Mini-International Neuropsychiatric Interview (MINI) as part of the standard evaluation. Offspring of BD patients were recruited after their parents gave formal consent to contact their children.Participants younger than 18 years of age were assessed with the French version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). Participants older than 18 years of age were assessed with the French version of the Diagnostic Interview for Genetic Studies (DIGS).Control subjects were matched for age, gender, laterality, and years of education, and were recruited through advertisements placed at the University of Geneva and on classified web sites. Inclusion criteria for controls were age, no history of psychiatric or neurological treatment for the subjects, and no reported history of a psychiatric disorder for their parents, as assessed during the interview of the subject. All participants gave written informed consent before assessment. The research was conducted according to the principles of the Declaration of Helsinki and was approved by the University of Geneva research ethics committee (CER 13–081).
HUBIN	Patients diagnosed with long term psychotic disorder were recruited from outpatient clinics in the North-Western part of Stockholm County. The patients were diagnosed according to DSM-III-R and DSM-IV based on information from interviews and medical records. Non-psychotic siblings of patients with psychosis were asked to participate when their relative with a psychotic disorder had agreed to their participation. Control subjects were recruited among students, hospital staff members or from a population register. All controls with the exception of those recruited from a population register had earlier attended in biological research at the Karolinska Institute. The controls consisted of non-psychotic individuals unrelated to the patients. Neither the siblings, nor the controls received any psychotic diagnosis according to DSM-III-R and DSM-IV.
IDIBAPS	The study was conducted in the Child and Adolescent Psychiatry Department of the Hospital Clinic of Barcelona, Spain. The protocol was approved by the local ethics review board. Patients with a diagnosis of schizophrenia or bipolar disorder from adult psychiatry units with offspring 6 to 17 years old were identified and invited to participate in the study. The exclusion criteria for proband parents were intellectual disability and drug or medically induced psychosis or mania. Exclusion criteria for offspring included intellectual disability, head injury with loss of consciousness, or severe neurological conditions. Community control parents were recruited through advertisements posted in primary health care centers and other community locations within the same geographic area as the patients. The exclusion criteria were intellectual disability, severe neurological conditions and personal or first-degree family history of schizophrenia or bipolar spectrum disorders. All 6- to 17-year-old offspring of community control parents were invited to participate in the study; exclusion criteria were the same as those for high-risk offspring. To decrease selection bias, parents who stated they were specifically motivated to participate because of concerns about school performance or emotional or behavioral problems in their offspring were excluded.
IoP – BD	Twins were recruited using a variety of methods; 1. Direct contact with health professionals; 2. Advertising; 3. Talks were given by team members at service user and professional conferences. Control subjects were recruited primarily via advertising in the national media, with further recruitment from a pool of research participants obtained for previous studies conducted at the Institute of Psychiatry (IoP, now IoPPN), with a smaller group being referred by members of staff at the Bethlem and Maudsley Hospital Trust and word of mouth. Exclusion criteria for all participants were a history of neurologic illness or of systemic illness with known neurologic complication, history of head injury with loss of consciousness, and current substance misuse or dependence. Controls had no personal or family history of psychotic illness. Controls and unaffected relatives with a nonpsychotic psychiatric diagnosis were included. All participants were between 16 and 65 years-old at the time of participation. All the studies were approved by institutional review boards, and all the participants gave written informed consent before participating.

Sample	Inclusion criteria
IoP – SZ	Twins were referred from across the United Kingdom by their treating psychiatrists. Control twins were recruited from the Institute of Psychiatry Volunteer Twin Register and by national media advertisements. Families were referred from clinics and voluntary organizations across the United Kingdom. Control subjects were ascertained from a pool of research participants obtained for previous studies conducted at the Institute of Psychiatry, from members of staff at the Bethlem and Maudsley Hospital Trust, and through advertisements in the press. Exclusion criteria for all participants were a history of neurologic illness or of systemic illness with known neurologic complication, history of head injury with loss of consciousness, and current substance misuse or dependence. Controls had no personal or family history of psychotic illness. Controls and unaffected relatives with a nonpsychotic psychiatric diagnosis were included. All the studies were approved by institutional review boards, and all the participants gave written informed consent before participating. Demographic information including years of education was collected using a standardised interview. With regard to educational achievement, both total years of completed education and highest completed academic qualification were recorded.
LIBD	Participants were recruited nationwide as part of a study at the National Institute of Mental Health, Bethesda, MD. Samples used in this study were under a standard procedure including a structured diagnostic interview (Structured Clinical Interview for DSM-IV) and a formal neurological examination. All patients met DSM-IV criteria for schizophrenia or related diagnoses including schizoaffective disorder, psychosis (not otherwise specified), and schizoid, paranoid, and schizotypal personality disorders. The majority of patients were taking antipsychotic medication at the time of scan, and a minority had a lifetime history of comorbid mental illness or substance abuse/dependence (including alcohol). Exclusion criteria for normal controls included a current or past history of neurological or psychiatric disorders, hypertension or drug abuse. A minority of siblings had a past lifetime history of a non-psychotic mental illness and/or substance abuse and/or dependence (39.7%), but none met criteria at the time of evaluation. No subjects in any group had a current history of alcohol or substance abuse within 6 months of being scanned. All subjects provided written informed consent, and participated according to the guidelines of the National Institute of Mental Health Institutional Review Board.
Maastricht – GROUP	Participants were recruited in selected representative geographical areas in the Netherlands and Belgium, patients were identified through representative clinicians providing health care for patients with psychotic disorder. Siblings were contacted through participating patients. Mailings and advertisements were effectuated in local newspapers of the same geographical area in order to recruit control participants. Inclusion criteria were; age range 16-50 years, fluent in Dutch language and for patients: a diagnosis of non-affective psychotic disorder with illness duration of <10 years. Siblings and controls were excluded if they had a lifetime diagnosis of any non-affective psychotic disorder. In addition, controls were excluded if they had a first-degree relative with a lifetime diagnosis of any psychotic disorder. This was assessed using the Family Interview for Genetic Studies (FIGS). Diagnosis was based on the Diagnostic and Statistical Manual of Mental Disorder-IV (DSM-IV) criteria, measured with the Comprehensive Assessment of Symptoms and History (CASH) interview. All participants were screened before MRI scanning and excluded based on the following: brain injury with unconsciousness of > than 1 hour, meningitis or other neurological diseases with possible impact on brain structure or function, cardiac arrhythmia requiring medical treatment and severe claustrophobia. Participants with metal corpora aliena were excluded from the study, as were women with intrauterine device status and (suspected) pregnancy.
MFS	All individuals were aged 16-70. Participant groups included (i) patients with DSM-IV confirmed diagnoses of schizophrenia or bipolar 1 disorder; (ii) unaffected first-degree relatives of these patients including parents, siblings and offspring; (iii) healthy volunteers with no personal or family history of psychotic illness. Families were recruited through voluntary organizations or by direct psychiatric referral and on the basis of either being multiply affected, where the index patient had one or more first- or second- degree relatives with a psychotic disorder, or singly-affected where there was no known family history of psychotic disorder. All of the bipolar disorder patients and relatives were from multiply affected families. Exclusion criteria for all participants included organic brain disease, head trauma resulting in loss of consciousness for more than 5 minutes, or DSM-IV substance or alcohol dependence in the 12 months before the assessment.
MooDS – BD	Participants were aged between 18 and 53 years. First degree relatives were offspring or siblings of index patients with BPD. Diagnosis of BPD in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, or the patients provided a medical report confirming diagnosis of BPD. All participants had no history of any neurologic disorder or current psychiatric Axis I disorder including drug or alcohol dependence as verified by the nonpatient version of the Structured Clinical Interview for DSM-IV and had no MRI contraindications.
MooDS – SZ	Participants were aged between 18 and 55 years. First degree relatives were parents, offspring or siblings of index patients with SCZ. Diagnosis of SCZ in index patients was made by an experienced clinician using the German version of the Structured Clinical Interview for DSM-IV, or the patients provided a medical report confirming diagnosis of SCZ. All participants had no history of any neurologic disorder or current psychiatric Axis I disorder including drug or alcohol dependence as verified by the nonpatient version of the Structured Clinical Interview for DSM-IV and had no MRI contraindications.
MSSM	All participants were aged 18 to 67 years. The eligibility criteria for all participants were (a) IQ>70; (b) no history of head trauma or loss of consciousness; (c) no current or lifetime history of medical or neurological disorders; (d) no lifetime history of substance use disorder; (e) no MRI contraindications (e.g. metal implants, claustrophobia). Patients were required to fulfil diagnostic DSM-IV criteria for BD type-1 or type II, while healthy volunteers were included if they had no lifetime personal history of mental disorders and no family history (up to second-degree relatives) of BD. Unaffected relatives of bipolar participants were included if they had no personal history of bipolar disorder or psychosis.

Sample	Inclusion criteria
Olin	Patients with bipolar I disorder, their unaffected siblings, and unrelated healthy volunteers were recruited from psychiatric facilities and community advertisements in Hartford, Conn. Patients were included if they met DSM-IV criteria for bipolar I disorder based on the Structured Clinical Interview for DSM-IV disorders; had no history of major medical or neurological conditions (e.g. epilepsy, migraine, head trauma with loss of consciousness); had an IQ > 80 (based on WASI); and had a sibling willing to participate in the study. Eligibility criteria for siblings and unrelated healthy volunteers were identical to those for patients, with the exception of a personal lifetime diagnosis of bipolar or psychosis spectrum disorders (having a DSM-IV diagnosis other than bipolar or psychosis spectrum disorders was not an exclusion criterium). In addition, unrelated healthy volunteers could not have a family history of mood or psychotic disorders. All participants provided informed consent as approved by the institutional review board at Hartford Hospital and Yale University.
ORBIS I	Participants were recruited from an ongoing Offspring Risk for BD Imaging Study–ORBIS. We recruited offspring from families of well-characterized adult BD probands who had participated in previous genetic and HR studies in Halifax, Nova Scotia. The inclusion criterion was 15–30 years of age. We included participants with BD type I or type II. The offspring from BD probands were divided into two subgroups. (1) The unaffected HR group, which included offspring without a personal history of Axis I psychiatric disorders. These individuals were considered HR because they came from multiplex families (more than one member affected with BD) and had one parent affected with a primary mood disorder. (2) The affected familial group, which included offspring meeting criteria for a lifetime Axis I diagnosis of mood disorders (i.e. a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria) and had one parent affected with a primary mood disorder. Depressive episodes were included because unipolar depression is characteristically the first manifestation of illness in patients who later develop BD. Lastly, we recruited control participants free of personal or family history of DSM-IV Axis I psychiatric disorders. Common exclusion criteria for all groups were a personal history of (1) any serious medical or neurologic disorders, (2) substance abuse/dependence during the previous 6 months, or (3) magnetic resonance imaging (MRI) exclusion criteria.
ORBIS II	Families were identified through adult probands with BD, who had participated in the Czech Bipolar Disorder Case Registry. Only the offspring from these families, not the probands, were a part of the MRI study. The inclusion criterion was 15–30 years of age. We included participants with BD type I or type II, but not with BD NOS. The offspring from BD parents were divided into two subgroups: 1) the Unaffected HR group, which consisted of offspring with no lifetime history of psychiatric disorders. These individuals were at an increased risk for BD because they had one parent affected with a primary mood disorder. 2) The Affected Familial group, which consisted of offspring who met criteria for a lifetime Axis I diagnosis of mood disorders (i.e., a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria). Also, we recruited control participants free of personal or family history of DSM-IV Axis I psychiatric disorders. Common exclusion criteria for all groups were a personal history of (1) any serious medical or neurologic disorders, (2) substance abuse/dependence during the previous 6 months, or (3) magnetic resonance imaging (MRI) exclusion criteria.
PENS	Participants with schizophrenia, schizoaffective disorder, or BD I, as well as first-degree relatives of individuals with schizophrenia, schizoaffective disorder, or BD, and a group of healthy controls were recruited through the Minneapolis VA, Craigslist, and the community. All participants were aged 18 to 59 years old and underwent a SCID interview to screen for DSM-IV-TR diagnostic criteria, with final diagnostic decisions made through consensus of two trained staff members. For relatives, the diagnosis of the family member with a psychosis spectrum or BD was established by our research staff. Psychosis subjects were required to be stable outpatients. Participants without a primary psychotic or BD (i.e., relatives and controls) additionally completed the Structured Interview for Schizotypy to rule out Cluster A personality disorders. Exclusion criteria for all subjects included English as a second language, mental retardation (WAIS IQ<70), current alcohol or drug dependence, current or past central nervous system condition, history of electroconvulsive therapy, history of stroke, history of head injury with skull fracture or substantial loss of consciousness (>30 minutes), and all standard MRI contraindications.
PHCP	Participants with schizophrenia, schizoaffective disorder, or bipolar disorder I with psychotic features, as well as first-degree relatives of individuals with schizophrenia, schizoaffective disorder, or bipolar disorder, and a group of healthy controls were recruited through the Minneapolis VA, University of Minnesota, and the community. All participants were aged 18 to 69 years old and underwent a SCID interview to screen for DSM-IV-TR diagnostic criteria, with final diagnostic decisions made through consensus of two trained staff members. For relatives, the diagnosis of the family member with a psychosis spectrum disorder was established by our research staff. Psychosis subjects were required to be stable outpatients. Participants without a primary psychotic disorder (i.e., relatives and controls) additionally completed the Structured Interview for Schizotypy to rule out Cluster A personality disorders.
STAR (Swedish) BD twin cohort	Subjects were identified on a nation-wide basis through the Sweden Twin Registry. Twin pairs were eligible for inclusion if they were same sex, between the ages of 25 and 65, and born in Sweden between 1940 and 1985 (inclusive). To ascertain twin pairs comprising at least one twin with a diagnosis of schizophrenia or bipolar disorder, this set of twins was screened using hospital admission and discharge diagnosis information from the Swedish National Patient Registry. Monozygotic and dizygotic pairs were recruited from all counties in Sweden and invited to Karolinska Institute for structured diagnostic interviews and additional evaluations, including neuroimaging. Final diagnoses were determined by a consensus procedure. Zygosity was determined for nearly all twin pairs using DNA testing or a well-validated screening measure for those without DNA available on both co-twins. Exclusion criteria were presence of a neurological disorder, history of significant head injury with loss of consciousness, mental retardation, history of substance dependence within 6 months of the screening interview, or inability to read or comprehend spoken and written Swedish. Healthy control pairs were recruited to match proband pairs on age, sex, and zygosity. Healthy controls were excluded if they had a family history of schizophrenia or bipolar disorder according to medical records or self-report.

Sample	Inclusion criteria
STAR (Swedish) SZ twin cohort	Subjects were identified on a nation-wide basis through the Sweden Twin Registry. Twin pairs were eligible for inclusion if they were same sex, between the ages of 25 and 65, and born in Sweden between 1940 and 1985 (inclusive). To ascertain twin pairs comprising at least one twin with a diagnosis of schizophrenia or bipolar disorder, this set of twins was screened using hospital admission and discharge diagnosis information from the Swedish National Patient Registry. Monozygotic and dizygotic pairs were recruited from all counties in Sweden and invited to Karolinska Institute for structured diagnostic interviews and additional evaluations, including neuroimaging. Final diagnoses were determined by a consensus procedure. Zygosity was determined for nearly all twin pairs using DNA testing or a well-validated screening measure for those without DNA available on both co-twins. Exclusion criteria were presence of a neurological disorder, history of significant head injury with loss of consciousness, mental retardation, history of substance dependence within 6 months of the screening interview, or inability to read or comprehend spoken and written Swedish. Healthy control pairs were recruited to match proband pairs on age, sex, and zygosity. Healthy controls were excluded if they had a family history of schizophrenia or bipolar disorder according to medical records or self-report.
SydneyBipolar-Group	All participants were aged between 12 and 30 years and included: (1) individuals with a confirmed diagnosis of bipolar disorder I, II, or schizoaffective disorder; (2) the offspring or siblings of a proband with a confirm DSM-IV diagnosis of bipolar disorder I, II, or schizoaffective disorder; (3) control subjects with no family history of bipolar disorder I or II, schizoaffective disorder, schizophrenia, recurrent major depression, recurrent substance abuse, or psychiatric hospitalisation, and no personal history of bipolar disorder I, II, or schizoaffective disorder. Current or lifetime diagnoses of psychiatric disorders other than bipolar disorder were not considered an exclusion factor for controls or bipolar relatives. All DSM-IV diagnoses were confirmed by two independent raters using Best Estimate Methodology and the K-SADS-BP or DIGS Version 4, the FIGS, and available medical records. Participants were recruited from bipolar research clinics, mental health organizations, families participating in alternate bipolar research projects, electronic and printed media, and public notice boards.
UMCU – BD twins	All twins were raised together, except for one control pair where twins were separated at 12 years of age when both parents died. Subjects were between 18 and 60 years of age at the time of enrolment in the study. Clinical diagnosis of Axis I psychiatric disorders and Axis II personality disorders was confirmed using the SCID and SIDP, respectively, and through available medical records. Patients were also interviewed on their medication history. The twin pairs had no history of drug or alcohol dependency for the last 6 months prior to inclusion in the study, for this was an exclusion criterion. Moreover, none had severe medical illness, verified with a medical history inventory. The current mood state of BD patients was assessed using the YMRS and the IDS. Upon inclusion, all patients were euthymic with a YMRS score of 4 or less and an IDS score of 12 or less, except for nine BD patients who were mildly to severely depressed or hypomanic. Healthy control pairs were matched to the bipolar pairs for zygosity, gender, age and parental education. Control pairs had no history of severe medical illness and had no first-degree relative with a history of a major Axis I psychiatric disorder (DSM-IV). Family histories of all twins were obtained via the Family Interview Genetic Studies, performed with both twins of each pair. Zygosity was determined with DNA fingerprinting using high polymorphic microsatellite markers 9 to 11. The medical ethics review board of the University Medical Center Utrecht approved the study and all participants gave written informed consent after full explanation of the study aims and procedures.
UMCU – DBSOS	This study includes participants between 8 and 18 years of age, including offspring of a patient with schizophrenia, offspring of a patient with bipolar disorder, and community control subjects. None met DSM-V criteria for schizophrenia or a related psychotic disorder at the time of baseline assessment (present and lifetime). For each family, all offspring in the appropriate age range entered our study to prevent a biased selection of participants within the family, as offspring with (subthreshold) symptoms may otherwise be more likely to be signed up for study participation than offspring with no (subthreshold) symptoms. Clinical diagnoses of parents were confirmed using the SCID-I. Control parents were screened for psychopathology using the mini-SCAN. The medical ethics committee of the University Medical Center Utrecht approved the study, and all participating children and their parents provided written informed consent. The K-SADS-PL was used to evaluate symptoms and DSM-V diagnoses of all participants. The majority of the offspring were naïve to psychotropic medication.
UMCU – GROUP	Patients had to fulfil the following criteria: (1) age between 16 and 50 years, (2) meeting DSM-IV criteria for a nonaffective psychotic disorder (including schizophrenia, schizophreniform disorder, and schizoaffective disorder), (3) fluent in Dutch, and (4) able and willing to give written informed consent. Eligible siblings had to fulfil the criteria of (1) age between 16 and 50 years, (2) fluent in Dutch, and (3) able and willing to give written informed consent. Eligible healthy control subjects had to fulfil the criteria of (1) age between 16 and 50 years, (2) no lifetime psychotic disorder and/or use of lithium medication (in the past), (3) no first- or second-degree family member with a lifetime psychotic disorder, (4) fluent in Dutch, and (5) able and willing to give written informed consent. Presence or absence of psychopathology was established by using the CASH. Diagnosis was based on the DSM-IV criteria. Of all subjects, urine was screened for cocaine, amphetamines, and for cannabis. Subjects with substance dependence/abuse (based on the criteria of the CIDI [sections B, J, and L]) and a major medical or neurological illness were excluded.
UMCU – Parents	Both parents of patients with schizophrenia were recruited at the University Medical Center Utrecht, as well as healthy control couples. The CASH, SADS-L, SIDP-IV, and the FIGS were obtained from all participants. Psychiatric diagnosis was established according to DSM-IV criteria. At least one of the children of the parents met DSM-IV criteria for schizophrenia on the basis of the CASH. Parents of patients were excluded if they had a history of psychotic illness. For control couples, exclusion followed in case of any axis-I DSM-IV diagnosis, or diagnosis of depression, manic depression, or psychotic disorder in first-degree family, or psychotic disorder in second-degree family. In both groups all participants were physically healthy and had no history of neurological illness, or drug or alcohol abuse.

Sample	Inclusion criteria
UMCU – UTWINS	1.5T: Twin pairs discordant for schizophrenia, and healthy control twins were pairwise matched on zygosity, sex, age, and birth order took part in the study. Subjects were recruited in collaboration with psychiatric services and by advertisements in national newspapers. All subjects gave written informed consent to participate in the study. Zygosity was determined by DNA fingerprinting. Except for 1 control twin pair, all twins were reared together. The 1 control twin pair was separated at age 12 years when both their parents died. All subjects underwent extensive psychiatric assessment procedures using the CASH interview, the SADS-L, the Structured Interviews for DSM-III-R and DSM-IV, the FIGS, and a medical history inventory. Psychiatric diagnosis was established according to criteria of DSM- IV. The following subtypes were diagnosed in the twins with schizophrenia: paranoid, disorganized, undifferentiated, residual, and catatonic. Diagnoses in non-schizophrenic co-twins included paranoid personality disorder, schizotypal personality disorder, schizoid personality disorder, major depressive disorder, avoidant personality disorder, generalized anxiety disorder with a dependent personality disorder, and no psychiatric diagnoses. Moreover, some patients and co-twins had histories of substance or alcohol abuse. Healthy control twins had no schizophrenic spectrum disorders, no first-degree relatives with a history of psychiatric illness, and no second-degree relatives with a psychotic disorder. Two patients had never been on antipsychotic medication. 3T: U-TWIN consists of twins with discordance for schizophrenia and control twins. The control twins were selected to match the discordant twins on age, handedness, and parental educational level. There were more males in the discordant twin group compared with the control twins, which was corrected for statistically. Control twins were excluded if they ever met criteria for a psychotic or manic disorder or substance dependence, had a first-degree relative with schizophrenia, or were diagnosed as having a neurologic disorder. Zygosity of all twins was determined through testing polygenic genetic markers. The zygosity of incomplete pairs was known from participation in earlier studies. All subjects underwent psychiatric assessment by means of the CASH interview, symptom severity in the patients was assessed using the PANSS. Diagnoses were established using DSM-IV criteria. All but one patient received antipsychotic medication. The twins were recruited through the UMC Utrecht twin database, the participant database of the GROUP cohort, 3 national newspaper advertisement and local psychiatry clinics. All subjects from the previous cohort agreed to participate again in this new 3T MRI study; no data from previous measurements was used. The Medical Ethical Committee of the University Medical Center Utrecht approved this study, and the experiments were in accordance with the Declaration of Helsinki. All participants gave their written informed consent. The subject overlap with our previous twin cohort is 30.5% (and in case of overlap, only the 3T measurement was included).
UNIBA	Participants included patients with schizophrenia, unaffected siblings and healthy subjects. All individuals were white Caucasian, from the Apulia region, and they were aged 18 to 65 years. The eligibility criteria for all participants were (a) no history of head trauma or loss of consciousness; (b) no current or lifetime history of medical or neurological disorders; (c) no lifetime history of substance use disorder; (d) no MRI contraindications (e.g. metal implants). Patients were required to fulfil diagnostic DSM-IV criteria for Schizophrenia, while unaffected relatives of patients and healthy volunteers were included if they had no lifetime history of psychiatric disorders.

Table S2. IQ test battery description, NA = not applicable

Sample	Inclusion criteria
BPO_FLB	BD patients were diagnosed with either type I or type II BD (BD I and BD II), or BD not otherwise specified (BD NOS) according to DSM-IV. Patients exclusion criteria included substance use within the past six months and general medical problems. Inclusion criteria for offspring of BD patients included diagnosis of BD in biological father and or mother according to SCID. Inclusion criteria for healthy controls included those without a history of any psychiatric/neurological disorders or mood disorders in first-degree relatives. Exclusion criteria for patient, healthy control and offspring groups included head injury with loss of consciousness, presence of metallic objects in the body, family history of hereditary neurological disorders, and pregnancy.
C_SFS	NA
Cardiff	NA
CLiNG – BD	NA
CLiNG – SZ	NA
DEU	NA
EGEU	NA
EHRS	Total IQ was measured by using the verbal (Information, Comprehension, Arithmetic, Digit Span, Similarities, and Vocabulary) and performance (Picture Arrangement, Picture Completion, Block Design, Object Assembly, and Digit Symbol) subtests of the Wechsler Adult Intelligence Scale—Revised (WAIS-R)
ENBD_UT	The neuropsychological battery includes the Wechsler Abbreviated Scale of Intelligence (WASI; four subtests: vocabulary, similarities, block design, and matrix reasoning)
FIDMAG-Clinic	Total IQ was measured using four subtests of the Wechsler Adult Intelligence Scale III (WAIS-III) (vocabulary, similarities, block design, and matrix reasoning)
Geneva	NA
HUBIN	WAIS Vocabulary was used as a proxy for IQ
IDIBAPS	Intelligence quotient (IQ) was assessed using the Spanish version of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) which evaluates intellectual abilities in children and adolescents aged between 6 and 16 years old. The General Ability Index (GAI), derived from the VCI and PRI, was used as an index of intelligence level.
IoP – BD	NA
IoP – SZ	Current IQ was assessed with the Wechsler Adult Intelligence Scale–Third Edition
LIBD	The WAIS-R short-form full-scale IQ was used for estimating IQ
Maastricht – GROUP	For estimating the IQ the Wechsler Adult Intelligence Scale (WAIS; including subscales symbol, calculation, block design and information) was used. Based on the WAIS an estimated total IQ was be provided.
MFS	Total IQ was measured using a five sub-tests of the short form (vocabulary, similarities, comprehension, block design, object assembly) of the Wechsler Adult Intelligence Scale–Revised (WAIS–R)
MooDS – BD	Total IQ was meaured using the MWT B (Mehrfach Wortschatz Test), a multiple choice vocabulary test that roughly measures verbal cristalline intelligence. Test results were translated to IQ values and mean corrected.
MooDS – SZ	Total IQ was meaured using the MWT B (Mehrfach Wortschatz Test), a multiple choice vocabulary test that roughly measures verbal cristalline intelligence. Test results were translated to IQ values and mean corrected.
MSSM	NA
Olin	Total IQ was estimated based on vocabulary and matrix reasoning from the Wechsler Abbreviated Scale of Intelligence (WASI).
ORBIS I	NA
ORBIS II	NA
PENS	Total IQ was estimated using the Vocabulary and Block Design subtests from the WAIS-III.
PHCP	Total IQ was estimated using the Similarities and Matrix Reasoning subtests from the WAIS-IV.

Sample	Inclusion criteria
STAR (Swedish) BD twin cohort	NA
STAR (Swedish) SZ twin cohort	NA
SydneyBipolar-Group	For the majority of participants total IQ was estimated based on vocabulary and matrix reasoning from the Wechsler Abbreviated Scale of Intelligence (WASI). A small number of participants did not have a usable MRI scan at the first testing time point (baseline) so we used their data from the next timepoint that involved an MRI scan (follow-up 2). Whilst participants completed a WASI IQ test at baseline, participants at follow-up 2 completed the Wechsler Test of Adult Reading (WTAR) instead.
UMCU – BD twins	Four subtests of the Dutch version of the WAIS were used as a proxy for IQ, i.e. vocabulary, block design, picture arrangement and comprehension. The four subtests were used to calculate a proxy measure for the full-scale IQ.
UMCU – DBSOS	The total IQ score for each study group was estimated based on the performance of four subtests, Picture Arrangement, Block Design, Vocabulary and Information, of the Dutch version of the WAIS III in participants older than 16 years old4, or the Dutch version of the Wechsler Intelligence Scale for Children-Revised Wechsler Intelligence Scale for Children (WISC) III in the case of younger offspring.
UMCU – GROUP	The IQ scores were based on four subtests of the Dutch version of the WAIS III, digit-symbol coding, information, arithmetic, and block design4. The four subtests were used to calculate a proxy measure for the full-scale IQ.
UMCU – Parents	Current IQ was estimated using a short form of the Groningen Intelligence Test.
UMCU – UTWINS	Cohort I: An evaluation of intellectual ability was obtained by a shortened version of the Wechsler Adult Intelligence Scale (WAIS) III general intelligence test, consisting of five subtests: Digit Symbol-Coding, Block Design, Arithmetic, Digit Span, and Information. The five subtests were used to calculate a proxy measure for the full-scale IQ. Cohort II: Four subtests of the Dutch version of the WAIS were used as a proxy for IQ, i.e. vocabulary, block design, picture arrangement and comprehension. The four subtests were used to calculate a proxy measure for the full-scale IQ.
UNIBA	We estimated IQ using the Wechsler Adult Intelligence Scale-Revised. Furthermore, the Italian version of the Wide Reading Achievement Test was administered to obtain a measure of premorbid IQ for each participant.

Table S3. Educational attainment (i.e. years of education completed) criteria description, NA = not applicable

Sample	Inclusion criteria
BPO_FLB	NA
C_SFS	Years of Education Completed
Cardiff	NA
CLiNG – BD	What is your highest finished secondary school qualification? 0) No education finished, 1) Lower Secondary education, 2) O-Level, 3) Higher school certificate (A level) What is your highest professional qualification? 0) No professional qualification, 1) Vocational education, 2) University, 3) Doctorate This was converted to years of education
CLiNG – SZ	What is your highest finished secondary school qualification? 0) No education finished, 1) Lower Secondary education, 2) O-Level, 3) Higher school certificate (A level) What is your highest professional qualification? 0) No professional qualification, 1) Vocational education, 2) University, 3) Doctorate This was converted to years of education
DEU	Years of Education Completed
EGEU	Years of Education Completed
EHRS	Age individuals left school, which was used to calculate years of education completed (age left school minus 5; based on the average age that children start school in Scotland)
ENBD_UT	Years of Education Completed
FIDMAG-Clinic	NA
Geneva	NA
HUBIN	Years of Education Completed
IDIBAPS	Intelligence quotient (IQ) was assessed using the Spanish version of the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) which evaluates intellectual abilities in children and adolescents aged between 6 and 16 years old. The General Ability Index (GAI), derived from the VCI and PRI, was used as an index of intelligence level.
IoP – BD	Demographic information including years of education was collected using a standardised interview. Both total years of completed education and highest completed academic qualification were recorded.
IoP – SZ	Demographic information including years of education was collected using a standardised interview. Both total years of completed education and highest completed academic qualification were recorded.
LIBD	The WAIS-R short-form full-scale IQ was used for estimating IQ
Maastricht – GROUP	NA
MFS	Education was measured by asking individuals the number of years they have been in education as well as highest completed academic qualification.
MooDS – BD	Education was measured by asking individuals the number of years they have been in education.
MooDS – SZ	Education was measured by asking individuals the number of years they have been in education.
MSSM	NA
Olin	Education was measured by asking individuals the number of years they have been in education, regardless of graduation
ORBIS I	NA
ORBIS II	NA
PENS	We ask for the subject's highest completed grade or degree in years (with 12 being completion of High School or Equivalent).
PHCP	We ask for the subject's highest completed grade or degree in years (with 12 being completion of High School or Equivalent).

Sample	Inclusion criteria
STAR (Swedish) BD twin cohort	Highest Education? 1 = Elementary school (9 years in school) 2 = Realskola (similar to elementary school between the years 1905 to 1962 – the older twins attended this school) -> 9 years (approximately) 3 = High school 2 years 4 = High school 3 years 5 = University 6 = Other 7 = Don't know 8 = Do not want to answer
STAR (Swedish) SZ twin cohort	Highest Education? 1 = Elementary school (9 years in school) 2 = Realskola (similar to elementary school between the years 1905 to 1962 – the older twins attended this school) -> 9 years (approximately) 3 = High school 2 years 4 = High school 3 years 5 = University 6 = Other 7 = Don't know 8 = Do not want to answer
SydneyBipolar-Group	Years of Education Completed
UMCU – BD twins	What is your highest finished education with a diploma? 0) No education finished, 1) Primary school only, 2) Lower vocational education (LB0), 3) General secondary education (LAVO, MAVO), 4) Higher secondary education (HAVO), 5) Higher secondary education (VWO), 6) Intermediate vocational education (MBO), 7) Higher vocational education (HBO) 8) University This was converted to years of educational completed
UMCU – DBSOS	NA
UMCU – GROUP	What is your highest finished education with a diploma? 0) No education finished, 1) Primary school only, 2) Lower vocational education (LB0), 3) General secondary education (LAVO, MAVO), 4) Higher secondary education (HAVO), 5) Higher secondary education (VWO), 6) Intermediate vocational education (MBO), 7) Higher vocational education (HBO) 8) University This was converted to years of educational completed
UMCU – Parents	What is your highest finished education with a diploma? 0) No education finished, 1) Primary school only, 2) Lower vocational education (LB0), 3) General secondary education (LAVO, MAVO), 4) Higher secondary education (HAVO), 5) Higher secondary education (VWO), 6) Intermediate vocational education (MBO), 7) Higher vocational education (HBO) 8) University This was converted to years of educational completed
UMCU – UTWINS	What is your highest finished education with a diploma? 0) No education finished, 1) Primary school only, 2) Lower vocational education (LB0), 3) General secondary education (LAVO, MAVO), 4) Higher secondary education (HAVO), 5) Higher secondary education (VWO), 6) Intermediate vocational education (MBO), 7) Higher vocational education (HBO) 8) University This was converted to years of educational completed
UNIBA	Years of Education Completed, including graduate school and medical specialization

Table S4. Sample image acquisition and image processing details

Sample	# of Scanners	Scanner Vendor & Type	Imaging Protocols	Slice Orientation	FreeSurfer Version	Operating System/Linux Kernel Version
BPO_FLB	1	3.0T Siemens Allegra	T1-weighted scans were acquired using a three-dimensional magnetization prepared rapid gradient echo (3DMPRAGE) protocol with the following parameters. Repetition time (TR) = 1750 ms, echo time (TE) = 4.38 ms, flip angle = 8°, Slice thickness = 1mm, matrix size = 256 x 208 and voxel size = 1 mm.		v5.3.0	
C_SFS	1	3T General Electric Discovery MR750	Each scan consisted of a whole-brain T1-weighted 3D magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with the following parameters: echo time (TE)=3.1ms, inversion time (TI)=650ms, repetition time (TR)=7.4ms, flip angle=11°, field of view (FOV)=25.6, matrix=256 x 256, slice thickness=1mm, 236 coronal slices.		v6.0.0	
Cardiff	1	GE HDx 3T scanner	T1 - axial 3D fast spoiled gradient recalled (FSPGR) sequence (TR/TE/TI = 8/3/ 450 ms; Flip Angle = 200; acquisition matrix= 256(AP) x192(LR)x172(SI), 1mm isotropic voxels)		v5.3.0	3.0.80-0.7-default
CLiNG	1	3T Magnetom TIM Trio	MRI scanning was performed on a 3.0-Tesla Magnetom TIM Trio (Siemens, Erlangen, Germany). A T1-weighted, 3D magnetization prepared rapid gradient echo sequence (MPRAGE) (TR/TE/TI/FA=2250 ms/3.26 ms/900 ms/9°; image matrix = 256 x 256; duration 8 min and 26 sec) was acquired generating 192 sagittal slices with a voxel size of 1 mm^3.	Sagittal	v5.3.0	Ubuntu 12.04: 2.6.32-431.17.1.el6.x86_64
DEU	1	1.5 T Philips Tesla Achieva MRI	3D T1-fast field echo (FFE) axial images were acquired with the following parameters: repetition time (TR) =8.7 ms, echo time (TE) =4 ms, flip angle=8 o, field of view (FOV) =230 mm x 220 mm, slice thickness=1 mm, number of signal averages (NSA) =1, matrix=192		v5.3.0	2.6.32-573.12.1.el6.x86_64
EGEU	1	Siemens 3T Magnetom Verio	T1-weighted anatomical 3D (MP-RAGE) 1 mm3 isotropic (FoV=256, TR=1600 msec, TE=221 msec, TI= 900 msec, FA=9°), matrix 256X256		v5.3.0	2.6.32-431.17.1.el6.x86_64
EHRS	1	1T Siemens	Scanned with a 1T 42 SPE Siemens MRI scanner (Siemens, Erlangen, Germany). 128 contiguous coronal T1-weighted slices (thickness 1.88 mm, field-of-view 250 x 250 mm) were obtained using a Magnetisation Prepared Rapid Acquisition of Gradient Echo (MPRAGE) sequence (TR=10ms, TE=4ms, TI=200ms, relaxation time 500ms).	Coronal	v5.3.0	Linux: 2.6.32-754.2.1.e16.x86_64
ENBD_UT	1	Philips 3 T	T1-weighted, 25.6cmx25.6cm square field-of-view (1.0mm slice, Tr=1750msec, Te=4.4msec, Ti=900msec, flip=80, data acquisition matrix-=256(phase)x256(frequency)x(160 slice).	Axial	v5.3.0	
FIDMAG-Clinic	1	1.5 T GE Signa	T1-weighted MRI data were acquired using 180 contiguous slices with thickness of 1 mm. The images were collected in a 256 x 224 acquisition matrix and were zero-filled in the k-space by the scanner to yield an image of 512 x 512 pixels with reconstruction diameter of 240 mm, resulting in an effective in-plane voxel size of 0.47 x 0.47 mm2. The echo (TE), repetition (TR) and inversion (TI) times were equal to (TE/TR/TI) = 3.93 ms/2000 ms/710 ms respectively. The flip angle was 15 degrees.	Axial	v6.0.0	Ubuntu 18.04 x86_64
Geneva	1	3T Siemens Trio	32 channels head-coil, 3D T1-weighted images, 192 sagittal slices, TR 1900 ms, TE: 2.27 ms, Voxel size: 1.0x1.0x1.0 mm, 9° flip angle, Field of view 256mm, Acquisition Matrix 256x256 mm	Sagittal	v6.0.0	Ubuntu 16.04

Sample	# of Scanners	Scanner Vendor & Type	Imaging Protocols	Slice Orientation	FreeSurfer Version	Operating System/Linux Kernel Version
HUBIN	1	1.5T GE Signa	3D spoiled gradient recalled pulse sequence for T1-weighted images: 1.5 mm coronal slices, no gap, 35° flip angle, repetition time 24 ms, echo time 6.0 ms, number of excitations 2, field of view 24 cm, acquisition matrix 256x192.		v5.3.0	3.13.0-79-generic
IDIBAPS	1	Siemens Trio 3T	240 sagittal slices, 2,300-ms repetition time, 3.01-ms echo time, 1-mm slice thickness, 900-ms inversion time, 394x240 field of view, 256x256 matrix size, and 9 degrees flip angle.		v5.3.0	2.6.32.12-0.7; 3.0.76-0.11
IoP – BD	1	1.5 Tesla GE N/Vi Signa System	Coronal FSPGR. Matrix: 256 x 256, 124 slices with 1.5mm slice thickness. FOV: 220x160. Flip angle: 20°. Number of excitations: 1. No gap. RT=13.1ms echo time = 5.8ms TI=450ms. Matched to MFS.	Coronal	v5.3.0	2.6.32-358.6.2.el6.x86_64
IoP – SZ	1	1.5 Tesla GE N/Vi Signa System	3D T1-weighted, spoiled gradient (SPGR) (TE=5ms, TR=35ms, flip angle=30°, NEX=1, FOV=200x200mm, voxel dimensions=1x1x1.5mm), yielding 124 contiguous slices 1.5mm thick.	Coronal	v5.3.0	2.6.32-358.6.2.el6.x86_64
LIBD	1	1.5T GE	T1-weighted spoiled gradient recalled sequence (spgr). Repetition time, 24ms; echo time, 5ms; number of excitations, 1; flip angle, 45 degrees; matrix size 256 x 256; field of view, 24 x 24cm; 124 sagittal slices (0.94 x 0.94 x 1.5mm).	Sagittal	v5.0.0	Linux: 2.6.32-696.23.1.e16.x86_64
Maastricht–GROUP	1	3T Siemens Magnetom Allegra	Modified Driven Equilibrium Fourier Transform sequence (MDEFT); TR=7.92ms, TE=2.4ms, IR=910ms, flip angle=15°, FOV=256x240. Acquisition Matrix=256x240x176 (1x1x1mm). Magnetisation Prepared Rapid Acquisition of Gradient Echo (MPRAGE); TR=2250ms, TE=2.6ms, IR=900ms, flip angle=9°, FOV=256x256. Acquisition Matrix=256x256x192 (1x1x1mm).		v5.3.0	macOS: 10.8.0
MFS	1	1.5T GE N/Vi Signa System	3D T1-weighted spoiled gradient recall echo sequence (SPGR). TR=13.1 ms, TI=450 ms, TE=5.8 ms, number of excitations=1, flip angle=20°, acquisition matrix=256x256x128, 1.5mm thick contiguous coronal slices.	Coronal	v5.3.0	3.0.0-21-generic
MooDS	1	Siemens Trio 3T	T1-weighted 3D (MP-RAGE) 1 mm3 isotropic (FoV=192, TR=1.57 s, TE=2.74 ms, FA=15°)		v5.3.0	4.4.0-142-generic
MSSM	1	1.5T GE Signa	3D T1-weighted spoiled gradient recalled acquisition in steady state; Voxel Size: 0.9375x0.9375x1.5mm3, TR/TE/TI=5.1/18/450ms, Flip Angle:20°	Axial	v5.3.0	2.6.32-358.6.2.el6.x86_64
Olin	1	Siemens Magnetom Allegra 3T	3D magnetization-prepared rapid gradient-echo (MPRage) sequence: TI=766; TR=2200; TE=4.13; flip angle 13 deg; FOV 256 mm; 0.8mm iso; axial slices parallel to the AC-PC line. To increase signal-to-noise ratio, four volumes were acquired per subject.		v5.3.0	Linux: 2.6.32-504.16.2.el6.x86_64
ORBIS I	1	1.5T GE Signa	T1-weighted SPGR (Spoiled Gradient Recalled) scans: flip angle=40°, TE=5ms, TR=25ms, FOV=24cmx18cm, matrix=256x160 pixels, NEX=1, no inter-slice gap, 124 coronal, 1.5mm thick slices.	Coronal	v5.3.0	macOS: Darwin kernel 15.6.0
ORBIS II	1	1.5T GE Signa	T1-weighted SPGR (Spoiled Gradient Recalled) scans: flip angle=40°, TE=5ms, TR=25ms, FOV=24cmx18cm, matrix=256x160 pixels, NEX=1, no inter-slice gap, 124 coronal, 1.5mm thick slices.	Coronal	v5.3.0	macOS: Darwin kernel 15.6.0

Sample	# of Scanners	Scanner Vendor & Type	Imaging Protocols	Slice Orientation	FreeSurfer Version	Operating System/Linux Kernel Version
PENS	1	3T Siemens Trio	32 channels head-coil, 3D T1-weighted MP-RAGE images, 239 sagittal slices, TR 2400 ms, TE: 2.12 ms, Voxel size: 1.0x1.0x1.0 mm, 8° flip angle, Inversion time 1060 ms, Field of view 256 x 240 mm, Acquisition Matrix 256 x 240	double oblique Sagittal	v5.3.0	Linux 2.6.32-74-generic x86_64
PHPC	1	3T Siemens Prisma	32 channels head-coil, 3D T1-weighted multi-echo MP-RAGE images, 208 double oblique sagittal slices, TR 2500 ms, TE: 1.81/3.6/5.39/7.18 ms, Voxel size: 0.8x0.8x0.8 mm, 8° flip angle, Inversion time 1000 ms, Field of view 256 x 240 mm, Acquisition Matrix 320 x300	double oblique Sagittal	v5.3.0	Linux cn0456 3.10.0-957.27.2.e17.x68_64
STAR (Swedish) BD twin cohort	1	GE 1.5T Signa	T1 - sagittal irSPGR sequence, 1mm3 isotropic voxels, 256mm FOV, TR/TE = 25/6 msec, 35 degree flip		v5.3.0	Linux: 3.10.0-693.43.1.el7.x86_64
STAR (Swedish) SZ twin cohort	1	GE 1.5T Signa	T1 - sagittal irSPGR sequence, 1mm3 isotropic voxels, 256mm FOV, TR/TE = 25/6 msec, 35 degree flip		v5.3.0	Linux: 3.10.0-693.43.1.el7.x86_64
SydneyBipolarGroup	1	Philips Achieva 3T	180 T1-weighted 3D turbo field-echo images were acquired sagitally (TR=5.5msec, TE=2.5ms, flip angle=8°, field of view=256x256x180mm, voxel size=1x1x1mm, scan time=371s).	Sagittal	v5.3.0	Linux : 2.6.32-504.3.3.el6.x86_64
UMCU – BD twins	1	1.5T Philips NT	The acquired scans were T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%).	Coronal	v5.1.0	2.6.32-358.6.2.el6.x86_64
UMCU – DBSOS	1	3T Philips Achieva	The T1-weighted 3-dimensional fast-field echo scans were acquired with the following parameters: 220 0.8 mm contiguous slices, echo time = 4.6 ms, repetition time = 10 ms, flip angle = 8°, in-plane voxel size 0.75x0.75 mm2.		v5.3.0	2.6.32-358.6.2.el6.x86_64
UMCU – GROUP	1	1.5T Philips Achieva	The acquired scans were T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%).	Coronal	v5.1.0	2.6.32-358.6.2.el6.x86_64
UMCU – Parents	1	1.5T Philips NT	The acquired scans were T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%).	Coronal	v5.3.0	2.6.32-358.6.2.el6.x86_64
UMCU – UTWINS	2	1.5T Philips NT/3T Philips Achieva	1.5T: T1-weighted, 3-dimensional, fast-field echo scans with 160-180 contiguous coronal slices (256x256 matrix, echo time = 4.6ms, repetition time = 30ms, flip angle = 30°, 1x1x1.2 mm3 voxels, field of view = 256mm/70%). 3T: The T1-weighted 3-dimensional fast-field echo scans were acquired with the following parameters: 220 0.8 mm contiguous slices, echo time = 4.6 ms, repetition time = 10 ms, flip angle = 8°, in-plane voxel size 0.75x0.75 mm2.		v5.3.0	2.6.32-358.6.2.el6.x86_64
UNIBA	1	GE 3T	124 1.3-mm slices using 3D T1-weighted gradient echo fast SPGR sequence (TE=min full; flip angle, 6°; prep time, 725; field of view, 250 mm; bandwidth, 31.25; matrix, 256 x 256)		v5.3.0	4.4.0-116-generic

Table S5. Cohen's *d* effect size bipolar and schizophrenia relatives compared to controls, controlled for IQ (middle column) and controlled for educational attainment (EA; right column)

	BIPOLAR DISORDER RELATIVE			SCHIZOPHRENIA RELATIVE		
	ES ± 95% CI	IQ ES ± 95% CI	EA ES ± 95% CI	ES ± 95% CI	IQ ES ± 95% CI	EA ES ± 95% CI
Global measures						
ICV	0.17 [0.06 0.28]**	0.21 [0.05 0.36]*	0.25 [0.11 0.4]**	-0.03 [-0.13 0.06]	0.05 [-0.03 0.13]	0.06 [-0.04 0.16]
Surface area	0.12 [-0.00 0.24]	0.12 [-0.05 0.29]	0.19 [0.04 0.34]*	-0.02 [-0.13 0.09]	0.04 [-0.05 0.13]	0.09 [-0.03 0.21]
Cortical thickness	-0.05 [-0.15 0.06]	-0.06 [-0.19 0.07]	-0.06 [-0.26 0.13]	-0.10 [-0.23 0.03]	-0.15 [-0.29 -0.01]*	-0.1 [-0.24 0.04]
Total brain	0.08 [-0.04 0.2]	0.13 [-0.03 0.3]	0.15 [-0 0.29]	-0.12 [-0.22 -0.02]*	-0.03 [-0.11 0.05]	0 [-0.12 0.11]
Cortical GM	0.1 [-0.03 0.23]	0.13 [-0.06 0.33]	0.18 [0.01 0.36]*	-0.09 [-0.21 0.03]	-0.03 [-0.12 0.07]	0.05 [-0.05 0.15]
Cerebral WM	0.06 [-0.04 0.17]	0.13 [-0.02 0.28]	0.1 [-0.05 0.25]	-0.11 [-0.19 -0.02]*	-0.01 [-0.09 0.07]	-0.03 [-0.13 0.08]
Cerebellum GM†	0.07 [-0.09 0.22]	0.02 [-0.16 0.2]	0.09 [-0.09 0.27]	-0.12 [-0.2 -0.04]**	-0.05 [-0.13 0.03]	-0.02 [-0.15 0.1]
Cerebellum WM†	-0.03 [-0.17 0.11]	-0.06 [-0.23 0.11]	0.05 [-0.13 0.23]	-0.1 [-0.18 -0.01]*	-0.03 [-0.11 0.05]	-0.02 [-0.16 0.11]
Third ventricle	0 [-0.11 0.1]	-0.1 [-0.25 0.04]	-0.05 [-0.19 0.09]	0.13 [0.01 0.25]*	0.15 [0 0.29]*	0.15 [0 0.31]*
Lateral ventricles	0.12 [0.04 0.21]**	0.12 [-0.02 0.27]	0.05 [-0.09 0.19]	0.05 [-0.03 0.13]	0.12 [0.03 0.21]*	0.08 [-0.02 0.19]
Subcortical volumes						
Thalamus	0.02 [-0.09 0.13]	0.14 [0.02 0.26]*	0.02 [-0.12 0.17]	-0.09 [-0.19 -0]*	-0.03 [-0.16 0.09]	0.01 [-0.12 0.14]
Caudate	0.18 [0.09 0.26]**	0.23 [0.12 0.35]**	0.11 [-0.03 0.26]	0 [-0.1 0.1]	0.03 [-0.06 0.13]	0.06 [-0.05 0.16]
Putamen	0.05 [-0.06 0.15]	0.11 [-0.05 0.27]	0.04 [-0.1 0.18]	-0.02 [-0.13 0.09]	0.04 [-0.07 0.15]	0.01 [-0.11 0.13]
Pallidum	0.04 [-0.07 0.15]	0.14 [-0.01 0.28]	0.06 [-0.11 0.22]	0.02 [-0.1 0.13]	0.07 [-0.06 0.19]	0.07 [-0.05 0.19]
Hippocampus	0 [-0.1 0.11]	0.02 [-0.1 0.13]	-0.01 [-0.16 0.13]	-0.11 [-0.19 -0.03]**	-0.05 [-0.14 0.03]	0 [-0.12 0.11]
Amygdala	0.01 [-0.08 0.1]	0.06 [-0.06 0.19]	-0.01 [-0.16 0.13]	-0.04 [-0.13 0.06]	0.02 [-0.08 0.12]	0.08 [-0.02 0.18]
Accumbens	0.08 [-0.05 0.2]	0.19 [0.01 0.37]*	0.02 [-0.13 0.16]	-0.08 [-0.19 0.02]	-0.08 [-0.17 0.01]	-0.04 [-0.17 0.08]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses

Table S6. Cohen's *d* effect size bipolar and schizophrenia patients compared to controls, controlled for IQ (middle column) and controlled for educational attainment (EA; right column)

	BIPOLAR DISORDER PATIENT#			SCHIZOPHRENIA PATIENT		
	ES ± 95% CI	IQ ES ± 95% CI	EA ES ± 95% CI	ES ± 95% CI	IQ ES ± 95% CI	EA ES ± 95% CI
Global measures						
ICV	0.05 [-0.12 0.21]	0.04 [-0.38 0.45]	0.16 [-0.05 0.37]	-0.15 [-0.32 0.02]	0.04 [-0.12 0.19]	-0.07 [-0.23 0.08]
Surface area	0.02 [-0.17 0.21]	0.03 [-0.24 0.29]	0.08 [-0.20 0.36]	-0.14 [-0.34 0.07]	0.03 [-0.15 0.21]	-0.16 [-0.34 0.02]
Cortical thickness	-0.31 [-0.55 -0.07]*	-0.28 [-0.52 -0.03]*	-0.31 [-0.57 -0.04]*	-0.52 [-0.74 -0.31]**	-0.56 [-0.86 -0.25]**	-0.54 [-0.74 -0.34]**
Total brain	-0.19 [-0.36 -0.01]*	-0.11 [-0.41 0.2]	-0.11 [-0.37 0.14]	-0.39 [-0.59 -0.2]**	-0.16 [-0.27 -0.05]**	-0.34 [-0.53 -0.15]**
Cortical GM	-0.13 [-0.33 0.06]	-0.08 [-0.37 0.22]	-0.05 [-0.26 0.16]	-0.45 [-0.65 -0.24]**	-0.24 [-0.39 -0.09]**	-0.41 [-0.62 -0.2]**
Cerebral WM	-0.16 [-0.32 -0]*	-0.03 [-0.3 0.24]	-0.1 [-0.38 0.19]	-0.29 [-0.46 -0.12]**	-0.05 [-0.16 0.06]	-0.23 [-0.4 -0.06]**
Cerebellum GM†	-0.17 [-0.34 -0.01]*	-0.08 [-0.28 0.12]	-0.14 [-0.37 0.09]	-0.27 [-0.42 -0.12]**	-0.11 [-0.3 0.07]	-0.14 [-0.26 -0.03]**
Cerebellum WM†	-0.06 [-0.21 0.08]	-0.14 [-0.31 0.04]	0.02 [-0.2 0.25]	-0.2 [-0.36 -0.04]**	-0.05 [-0.2 0.09]	-0.11 [-0.25 0.04]
Third ventricle	0.39 [0.18 0.6]**	0.27 [-0.21 0.75]	0.44 [0.09 0.79]*	0.51 [0.38 0.64]**	0.5 [0.28 0.72]**	0.51 [0.37 0.65]**
Lateral ventricles	0.39 [0.18 0.59]**	0.35 [-0.07 0.77]	0.44 [0.15 0.72]**	0.34 [0.22 0.46]**	0.42 [0.32 0.52]**	0.37 [0.24 0.5]**
Subcortical volumes						
Thalamus	-0.21 [-0.39 -0.03]*	-0.08 [-0.37 0.21]	-0.17 [-0.4 0.07]	-0.14 [-0.31 0.03]	0.01 [-0.14 0.16]	-0.11 [-0.31 0.09]
Caudate	-0.02 [-0.15 0.11]*	-0.02 [-0.28 0.25]	0.01 [-0.16 0.18]	0.11 [-0.03 0.25]	0.19 [0.09 0.28]**	0.13 [-0.01 0.27]
Putamen	-0.1 [-0.33 0.13]	0 [-0.41 0.42]	-0.1 [-0.4 0.2]	0.16 [0.05 0.27]**	0.21 [0.1 0.32]**	0.19 [0.06 0.33]**
Pallidum	0.05 [-0.12 0.22]	0.07 [-0.2 0.35]	0.05 [-0.13 0.22]	0.28 [0.13 0.43]**	0.35 [0.18 0.52]**	0.32 [0.12 0.52]**
Hippocampus	-0.17 [-0.32 -0.01]*	-0.09 [-0.48 0.29]	-0.12 [-0.26 0.03]	-0.33 [-0.54 -0.12]**	-0.25 [-0.46 -0.04]**	-0.24 [-0.45 -0.03]**
Amygdala	-0.06 [-0.2 0.08]	0.1 [-0.13 0.33]	-0.12 [-0.33 0.1]	-0.18 [-0.36 -0.01]*	-0.02 [-0.21 0.17]	-0.11 [-0.32 0.1]
Accumbens	-0.13 [-0.36 0.1]	-0.08 [-0.37 0.21]	-0.24 [-0.56 0.07]	-0.14 [-0.3 0.02]	-0.11 [-0.34 0.1]	-0.19 [-0.36 -0.02]**

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | # lithium corrected

Table S7. Cohen's *d* effect size bipolar and schizophrenia relatives compared to controls corrected for ICV (except ICV, surface area and cortical thickness), controlled for IQ (middle column) and controlled for educational attainment (EA; right column)

	BIPOLAR DISORDER RELATIVE			SCHIZOPHRENIA RELATIVE		
		IQ	EA		IQ	EA
	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI
Global measures						
ICV	0.17 [0.06 0.28]**	0.21 [0.05 0.36]*	0.25 [0.11 0.4]**	-0.03 [-0.13 0.06]	0.05 [-0.03 0.13]	0.06 [-0.04 0.16]
Surface area	0.12 [-0.00 0.24]	0.12 [-0.05 0.29]	0.19 [0.04 0.34]*	-0.02 [-0.13 0.09]	0.04 [-0.05 0.13]	0.09 [-0.03 0.21]
Cortical thickness	-0.05 [-0.15 0.06]	-0.06 [-0.19 0.07]	-0.06 [-0.26 0.13]	-0.10 [-0.23 0.03]	-0.15 [-0.29 -0.01]*	-0.1 [-0.24 0.04]
Total brain	-0.10 [-0.22 0.03]	-0.06 [-0.22 0.09]	-0.08 [-0.23 0.07]	-0.16 [-0.24 -0.08]**	-0.14 [-0.22 -0.05]**	-0.13 [-0.28 0.01]
Cortical GM	-0.02 [-0.14 0.10]	-0.01 [-0.17 0.16]	0.04 [-0.11 0.2]	-0.09 [-0.20 0.02]	-0.1 [-0.2 -0.00]*	-0.02 [-0.15 0.1]
Cerebral WM	-0.12 [-0.23 -0.00]*	-0.05 [-0.23 0.12]	-0.12 [-0.31 0.07]	-0.12 [-0.19 -0.04]**	-0.09 [-0.17 -0.01]*	-0.16 [-0.26 -0.05]**
Cerebellum GM†	-0.02 [-0.16 0.13]	-0.09 [-0.26 0.08]	-0.06 [-0.25 0.13]	-0.11 [-0.18 -0.03]**	-0.07 [-0.15 0.02]	-0.06 [-0.17 0.05]*
Cerebellum WM†	-0.14 [-0.27 -0.00]*	-0.2 [-0.38 -0.02]*	-0.08 [-0.27 0.11]	-0.09 [-0.17 -0.02]*	-0.06 [-0.14 0.02]	-0.08 [-0.21 0.05]
Third ventricle	-0.06 [-0.16 0.04]	-0.16 [-0.28 -0.04]*	-0.10 [-0.25 0.04]	0.15 [0.04 0.27]**	0.14 [-0.00 0.27]	0.12 [-0.02 0.26]
Lateral ventricles	0.07 [-0.04 0.17]	0.06 [-0.09 0.21]	-0.03 [-0.17 0.11]	0.09 [0.01 0.17]*	0.14 [0.04 0.25]*	0.06 [-0.04 0.17]
Subcortical volumes						
Thalamus	-0.05 [-0.17 0.07]	0.06 [-0.06 0.18]	-0.07 [-0.22 0.08]	-0.05 [-0.16 0.06]	-0.02 [-0.18 0.13]	0.03 [-0.1 0.17]
Caudate	0.13 [0.03 0.23]*	0.18 [0.05 0.31]*	0.08 [-0.06 0.22]	0.03 [-0.06 0.12]	0.03 [-0.07 0.14]	0.06 [-0.06 0.18]
Putamen	0 [-0.09 0.1]	0.07 [-0.05 0.19]	0.01 [-0.16 0.17]	0.02 [-0.08 0.12]	0.04 [-0.07 0.15]	0.02 [-0.1 0.14]
Pallidum	-0.01 [-0.11 0.1]	0.05 [-0.11 0.21]	0.02 [-0.14 0.18]	0.04 [-0.07 0.14]	0.03 [-0.09 0.15]	0.07 [-0.05 0.19]
Hippocampus	-0.04 [-0.17 0.09]	-0.05 [-0.21 0.1]	-0.08 [-0.25 0.1]	-0.09 [-0.16 -0.01]*	-0.07 [-0.16 0.02]	0 [-0.12 0.11]
Amygdala	-0.03 [-0.12 0.06]	0 [-0.11 0.12]	-0.05 [-0.19 0.09]	-0.01 [-0.09 0.08]	0.01 [-0.12 0.13]	0.09 [-0.01 0.2]
Accumbens	0.05 [-0.07 0.17]	0.14 [-0.05 0.32]	0 [-0.14 0.14]	-0.06 [-0.14 0.02]	-0.1 [-0.2 0]	-0.04 [-0.17 0.1]

* p < 0.05, uncorrected | ** q < 0.05, corrected | † excluded Olin in cerebellum analyses | # lithium corrected

Table S8. Cohen's *d* effect size bipolar and schizophrenia patients compared to controls corrected for ICV (except ICV, surface area and cortical thickness), controlled for IQ (middle column) and controlled for educational attainment (EA; right column)

	BIPOLAR DISORDER PATIENT#			SCHIZOPHRENIA PATIENT		
		IQ	EA		IQ	EA
	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI	ES ± 95% CI		
Global measures						
ICV	0.05 [-0.12 0.21]	0.04 [-0.38 0.45]	0.16 [-0.05 0.37]	-0.15 [-0.32 0.02]	0.04 [-0.12 0.19]	-0.07 [-0.23 0.08]
Surface area	0.02 [-0.17 0.21]	0.03 [-0.24 0.29]	0.08 [-0.20 0.36]	-0.14 [-0.34 0.07]	0.03 [-0.15 0.21]	-0.16 [-0.34 0.02]
Cortical thickness	-0.31 [-0.55 -0.07]**	-0.28 [-0.52 -0.03]*	-0.31 [-0.57 -0.04]*	-0.52 [-0.74 -0.31]**	-0.56 [-0.86 -0.25]**	-0.54 [-0.74 -0.34]**
Total brain	-0.41 [-0.58 -0.24]**	-0.22 [-0.53 0.10]	-0.41 [-0.69 -0.13]*	-0.49 [-0.69 -0.29]**	-0.37 [-0.46 -0.27]**	-0.49 [-0.77 -0.22]**
Cortical GM	-0.25 [-0.44 -0.06]**	-0.19 [-0.47 0.10]	-0.22 [-0.40 -0.04]*	-0.50 [-0.69 -0.31]**	-0.39 [-0.6 -0.18]**	-0.52 [-0.79 -0.26]**
Cerebral WM	-0.32 [-0.50 -0.13]**	-0.14 [-0.41 0.13]	-0.34 [-0.64 -0.04]*	-0.28 [-0.44 -0.11]**	-0.14 [-0.24 -0.05]**	-0.26 [-0.47 -0.05]**
Cerebellum GM†	-0.24 [-0.39 -0.10]**	-0.19 [-0.36 -0.01]*	-0.28 [-0.51 -0.04]*	-0.23 [-0.36 -0.10]**	-0.14 [-0.32 0.05]	-0.15 [-0.26 -0.04]**
Cerebellum WM†	-0.13 [-0.29 0.02]	-0.27 [-0.44 -0.09]*	-0.08 [-0.33 0.17]	-0.14 [-0.27 -0.02]**	-0.08 [-0.21 0.06]	-0.09 [-0.22 0.04]
Third ventricle	0.36 [0.15 0.56]**	0.28 [-0.16 0.73]	0.36 [0.02 0.71]*	0.57 [0.44 0.71]**	0.53 [0.31 0.76]**	0.55 [0.38 0.71]**
Lateral ventricles	0.34 [0.12 0.56]**	0.36 [-0.06 0.78]	0.34 [0.02 0.66]*	0.41 [0.27 0.55]**	0.44 [0.31 0.57]**	0.44 [0.28 0.59]**
Subcortical volumes						
Thalamus	-0.3 [-0.51 -0.09]**	-0.11 [-0.31 0.09]	-0.33 [-0.63 -0.02]*	-0.07 [-0.20 0.06]	0.01 [-0.15 0.18]	-0.07 [-0.26 0.13]
Caudate	-0.08 [-0.25 0.09]	-0.06 [-0.22 0.09]	-0.09 [-0.31 0.12]	0.17 [0.05 0.30]**	0.19 [0.08 0.3]**	0.22 [0.04 0.4]**
Putamen	-0.13 [-0.37 0.10]	-0.04 [-0.38 0.3]	-0.19 [-0.52 0.15]*	0.23 [0.11 0.35]**	0.21 [0.07 0.34]**	0.25 [0.08 0.43]**
Pallidum	0.02 [-0.14 0.17]	0 [-0.21 0.21]	-0.03 [-0.18 0.12]	0.34 [0.17 0.50]**	0.35 [0.15 0.56]**	0.39 [0.15 0.63]**
Hippocampus	-0.23 [-0.42 -0.05]**	-0.15 [-0.44 0.14]	-0.24 [-0.45 -0.03]*	-0.31 [-0.52 -0.10]**	-0.3 [-0.54 -0.06]**	-0.22 [-0.41 -0.03]**
Amygdala	-0.14 [-0.33 0.05]	0 [-0.2 0.21]	-0.23 [-0.54 0.09]	-0.15 [-0.31 0.01]	-0.06 [-0.31 0.19]	-0.1 [-0.3 0.1]
Accumbens	-0.16 [-0.40 0.08]	-0.19 [-0.53 0.15]	-0.3 [-0.64 0.04]	-0.10 [-0.25 0.05]	-0.14 [-0.38 0.11]	-0.19 [-0.37 -0.01]*

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses | # lithium corrected

Table S9. Correlations brain and IQ (left), and educational attainment (right); across all subjects

	IQ		Educational attainment	
		ICV corrected		ICV corrected
	r ± 95% CI	r ± 95% CI	r ± 95% CI	r ± 95% CI
Global measures				
ICV	0.15 [0.11 0.2]**	*NA*	0.05 [-0 0.1]	*NA*
Surface area	0.16 [0.11 0.21]**	*NA*	0.04 [-0.01 0.08]	*NA*
Cortical thickness	0.09 [0.04 0.14]**	*NA*	0.03 [-0.03 0.09]	*NA*
Total brain	0.22 [0.18 0.26]**	0.17 [0.12 0.22]**	0.07 [0.01 0.12]**	0.06 [0.01 0.11]**
Cortical GM	0.22 [0.17 0.27]**	0.17 [0.11 0.22]**	0.08 [0.02 0.14]**	0.08 [0.03 0.13]**
Cerebral WM	0.18 [0.14 0.23]**	0.1 [0.05 0.15]**	0.04 [-0.01 0.08]	0.02 [-0.03 0.07]
Cerebellum GM†	0.15 [0.11 0.19]**	0.1 [0.06 0.14]**	0.08 [0.03 0.13]**	0.07 [0.03 0.11]**
Cerebellum WM†	0.13 [0.09 0.16]**	0.08 [0.04 0.12]**	0.06 [0.01 0.11]**	0.05 [0.01 0.09]**
Third ventricle	-0.04 [-0.09 0.02]	-0.08 [-0.13 -0.03]**	0.01 [-0.04 0.07]	-0.01 [-0.06 0.04]
Lateral ventricles	-0.01 [-0.05 0.04]	-0.06 [-0.11 -0.02]**	-0.01 [-0.04 0.02]	-0.02 [-0.08 0.03]
Subcortical volumes				
Thalamus	0.13 [0.08 0.17]**	0.07 [0.03 0.1]**	0.03 [-0 0.07]	0.02 [-0.02 0.05]
Caudate	0.08 [0.04 0.11]**	0.03 [-0 0.06]	0.01 [-0.02 0.05]	0 [-0.04 0.03]
Putamen	0.06 [0.02 0.09]**	0.01 [-0.03 0.05]	0.01 [-0.02 0.05]	0 [-0.03 0.04]
Pallidum	0.08 [0.04 0.12]**	0.03 [-0.01 0.08]	0.03 [-0.01 0.06]	0.02 [-0.02 0.06]
Hippocampus	0.16 [0.12 0.21]**	0.11 [0.07 0.15]**	0.07 [0.02 0.12]**	0.05 [0.01 0.1]**
Amygdala	0.14 [0.09 0.18]**	0.08 [0.05 0.12]**	0.03 [-0.02 0.08]	0.01 [-0.03 0.05]
Accumbens	0.09 [0.06 0.12]**	0.05 [0.02 0.08]**	0.01 [-0.03 0.06]	0.01 [-0.03 0.05]

* $p < 0.05$, uncorrected | ** $q < 0.05$, corrected | † excluded Olin in cerebellum analyses

Table S10. Correlations brain and IQ; in the bipolar (left column) and schizophrenia (right column) relatives subject groups only.

	BD relatives	SZ relatives
	r ± 95% CI	r ± 95% CI
Global measures		
ICV	0.17 [0.06 0.27]**	0.21 [0.15 0.28]**
Surface area	0.2 [0.1 0.29]**	0.18 [0.12 0.25]**
Cortical thickness	0.04 [-0.09 0.17]	-0.01 [-0.07 0.06]
Total brain	0.2 [0.1 0.29]**	0.2 [0.13 0.27]**
Cortical GM	0.21 [0.12 0.31]**	0.17 [0.1 0.23]**
Cerebral WM	0.14 [0.05 0.23]**	0.18 [0.1 0.26]**
Cerebellum GM†	0.15 [0.05 0.26]**	0.19 [0.11 0.27]**
Cerebellum WM†	0.08 [-0.02 0.19]	0.16 [0.09 0.24]**
Third ventricle	0.04 [-0.07 0.14]	0.09 [0.02 0.16]**
Lateral ventricles	0.02 [-0.07 0.12]	0.12 [0.04 0.2]**
Subcortical volumes		
Thalamus	0.17 [0.07 0.26]**	0.09 [0.01 0.17]**
Caudate	0.12 [0.02 0.21]**	0.06 [-0 0.13]
Putamen	0.12 [0.02 0.22]**	0.03 [-0.03 0.1]
Pallidum	0.11 [0.02 0.21]**	0.05 [-0.02 0.11]
Hippocampus	0.15 [0.06 0.24]**	0.07 [-0 0.13]
Amygdala	0.12 [0.03 0.22]**	0.09 [0.01 0.18]**
Accumbens	0.16 [0.07 0.26]**	0.07 [0 0.13]*

* p < 0.05, uncorrected | ** q < 0.05, corrected |
† excluded Olin in cerebellum analyses | # lithium corrected

SUPPLEMENTARY FIGURES

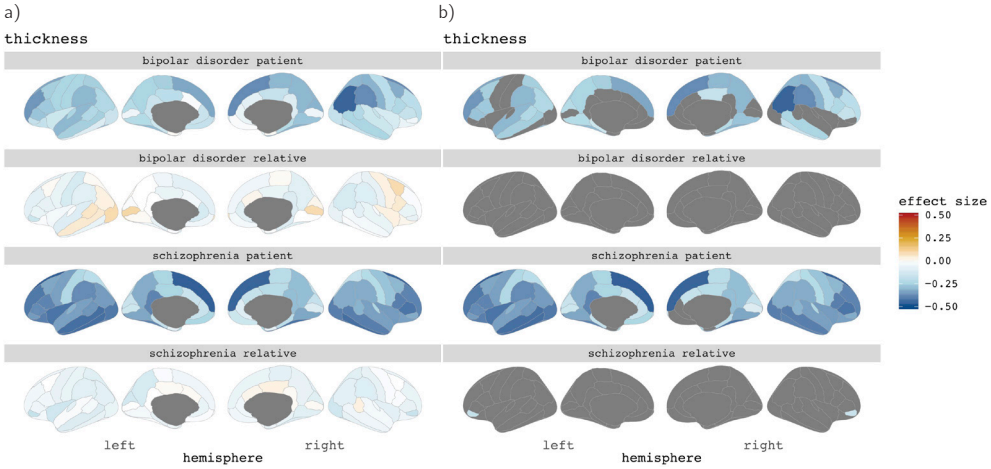

Figure S1. Cohen's *d* effect sizes comparing bipolar patients, bipolar relatives, schizophrenia patients, and schizophrenia relatives to controls on a) regional cortical thickness, b) only cortical thickness regions surviving false discovery rate correction for multiple testing ($q < 0.05$)

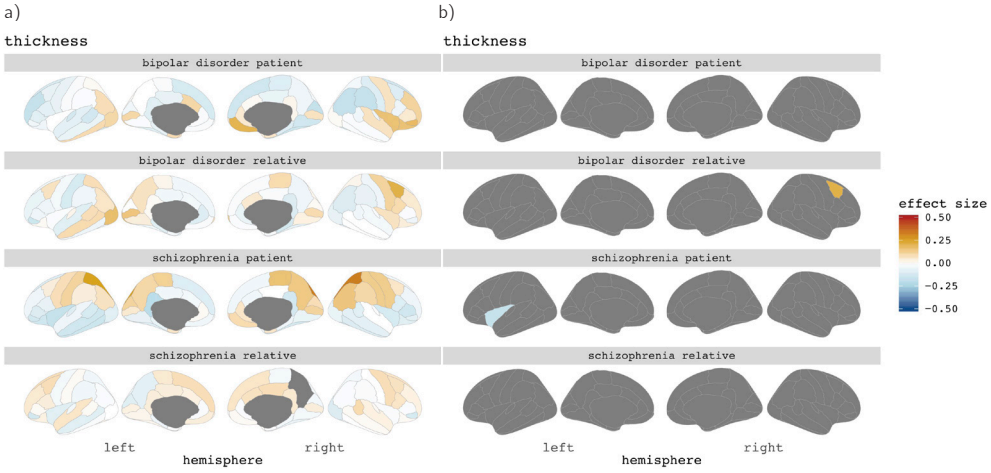

Figure S2. Cohen's *d* effect sizes comparing bipolar patients, bipolar relatives, schizophrenia patients, and schizophrenia relatives to controls on a) regional cortical thickness corrected for mean thickness, b) only cortical thickness regions corrected for mean thickness surviving false discovery rate correction for multiple testing ($q < 0.05$)

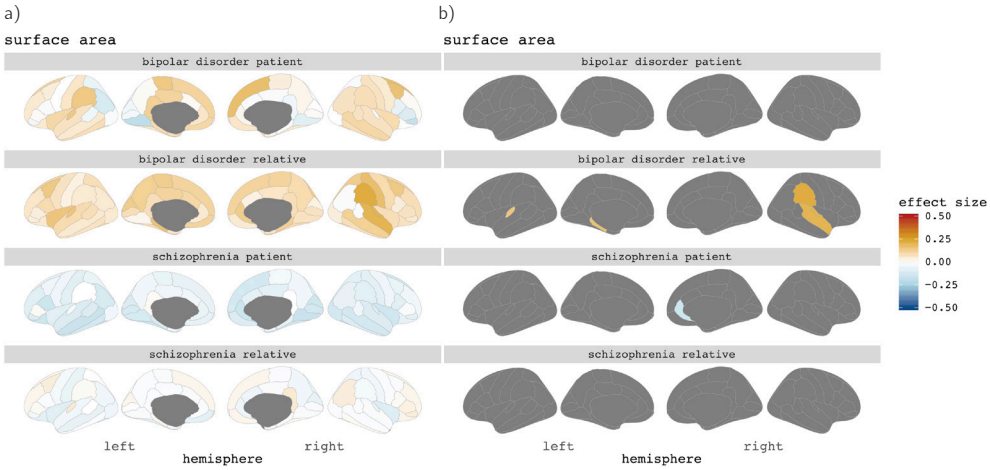

Figure S3. Cohen's *d* effect sizes comparing bipolar patients, bipolar relatives, schizophrenia patients, and schizophrenia relatives to controls on a) regional cortical surface area, b) only cortical surface area regions surviving false discovery rate correction for multiple testing ($q < 0.05$)

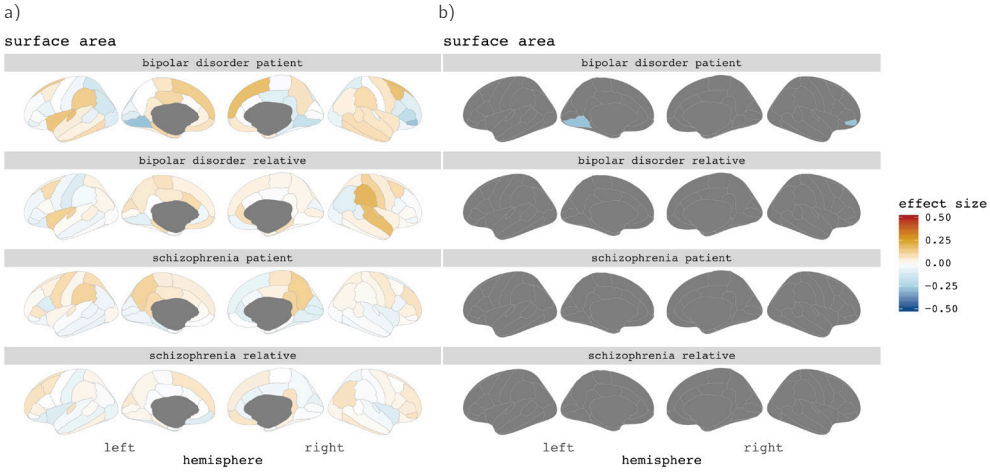

Figure S4. Cohen's *d* effect sizes comparing bipolar patients, bipolar relatives, schizophrenia patients, and schizophrenia relatives to controls on a) regional cortical surface area corrected for total surface area, b) only cortical surface area regions corrected for total surface area surviving false discovery rate correction for multiple testing ($q < 0.05$)

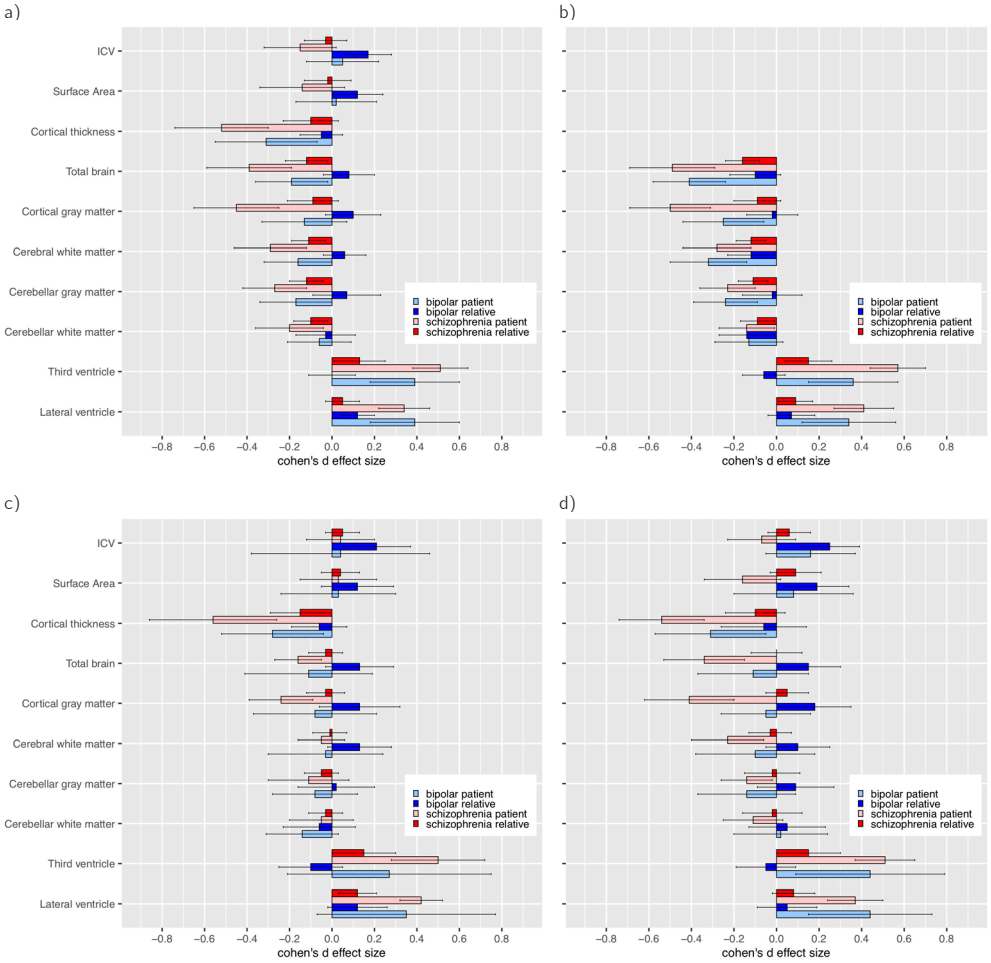

Figure S5. Cohen's *d* effect sizes comparing bipolar patients (light blue), bipolar relatives (blue), schizophrenia patients (pink), and schizophrenia relatives (red) to controls on a) global brain measures, corrected for b) intracranial volume (ICV), c) intelligent quotient (IQ), d) educational attainment. The error bars depict the lower and upper 95% confidence intervals (CIs).

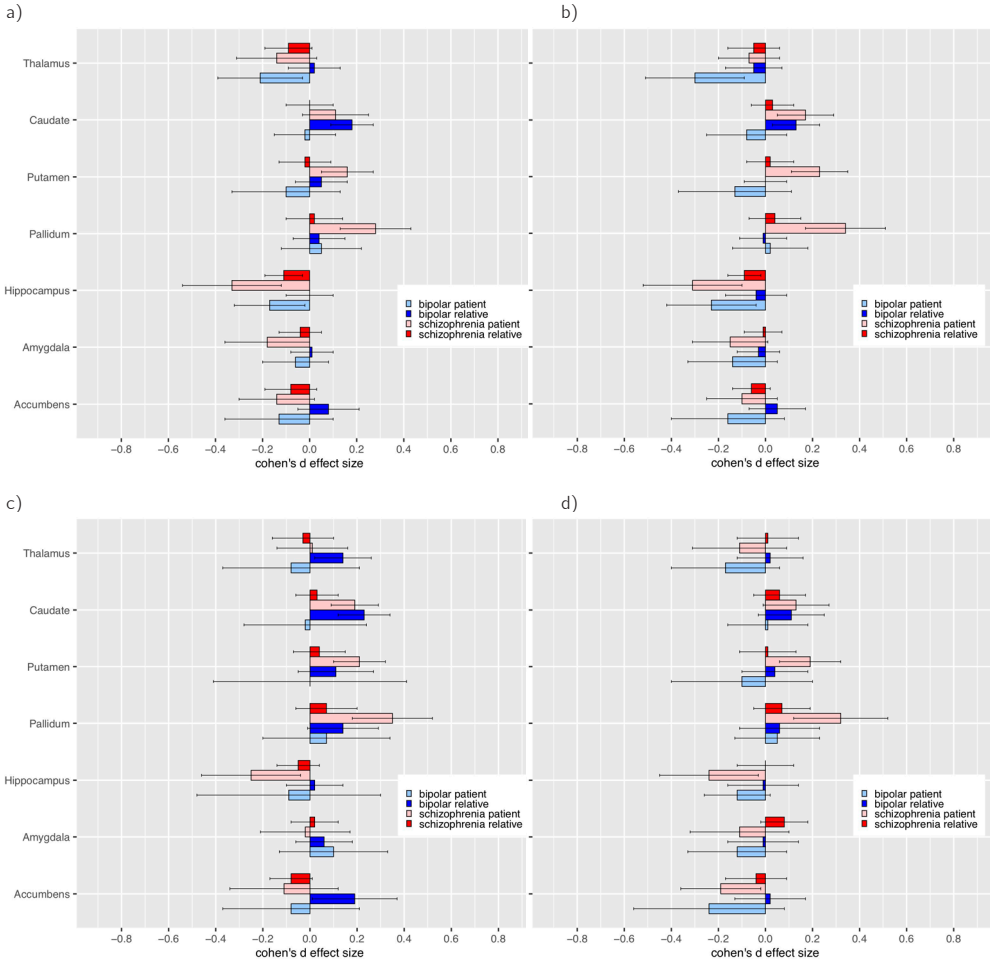

Figure S6. Cohen's *d* effect sizes comparing bipolar patients (light blue), bipolar relatives (blue), schizophrenia patients (pink), and schizophrenia relatives (red) to controls on a) subcortical volumes, corrected for b) intracranial volume (ICV), c) intelligent quotient (IQ), d) educational attainment. The error bars depict the lower and upper 95% confidence intervals (CIs).

5

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The genetic relationship between schizophrenia, bipolar disorder and intracranial volume through polygenic scoring

In preparation

ABSTRACT

There is a discrepancy between being at-risk for or being diagnosed with schizophrenia or bipolar disorder in relation to intracranial volume (ICV). Imaging studies have shown that as compared to controls, patients with schizophrenia, but not patients with bipolar disorder, have smaller ICV. In contrast, relatives of patients with bipolar disorder, but not relatives of patients with schizophrenia, have larger ICV compared to controls. To investigate whether the relationship between the disorders and ICV may have genetic origin we examined if and to what degree the relationships between schizophrenia and bipolar disorder risk genes with ICV are present in healthy individuals, and whether these relationships can be measured on an individual level through polygenic scoring. Polygenic scores for schizophrenia (SZ-PGS), bipolar disorder (BD-PGS), and ICV (ICV-PGS) were computed for each individual, and we investigated whether these were related to each other and to the phenotype ICV, using the UK Biobank (n = 459,250 participants; with MRI scan n = 9,074). ICV-PGS was significantly correlated with BD-PGS (r = 0.05, P < 0.005), SZ-PGS (r = 0.02, P < 0.005), and phenotype ICV (r = 0.09, P < 0.005). In contrast, phenotype ICV was not associated with BD-PGS and showed a significant negative correlation with SZ-PGS (r = –0.02, P < 0.005). Despite the effects being small, we showed a positive relationship of risk for both bipolar disorder and schizophrenia with the genetic predisposition for larger ICV on an individual level in the general population, with suggestive evidence for a greater effect in bipolar disorder. The discrepancy between ICV-PGS and phenotype ICV in their association with SZ-PGS and BD-PGS may imply that other factors lead to smaller ICV in those at-risk for the disorder, such as environment or gene-by-environment interactions.

INTRODUCTION

Schizophrenia and bipolar disorder are heritable neurodevelopmental disorders with overlapping symptoms. A marker of neurodevelopment is intracranial volume (ICV); it only reaches its maximum size at the age of 15 years (Courchesne et al., 2000; Sgouros et al. 1999). Meta-analyses of structural brain imaging studies have shown that ICV is smaller in patients with schizophrenia compared to controls (Haijma et al., 2013; Okada et al., 2016; Van Erp et al., 2015), but this effect was not found in patients with bipolar disorder (Hibar et al., 2016).

ICV is highly heritable (Baare et al., 2001; Pfefferbaum et al., 2000), and twin studies have shown that a larger ICV is associated with genetic liability for bipolar disorder but not for schizophrenia (Hulshoff Pol et al., 2012). This was confirmed by a recent meta-analysis in over six thousand subjects, where first-degree relatives of patients with bipolar disorder had a larger ICV than controls, but no differences were reported between schizophrenia relatives and controls (de Zwarte et al., 2019b). These imaging findings suggest that there is a discrepancy between schizophrenia and bipolar disorder with regard to ICV, both between the patient groups (i.e., smaller volume in schizophrenia patients but no differences in bipolar patients as compared to controls) as well between their unaffected family members (i.e., no differences in schizophrenia relatives but larger volumes in bipolar relatives as compared to controls). While the findings in relatives suggest that familial factors underlie the difference in ICV in bipolar disorder and schizophrenia; the within-disorder discrepancy between the proband and his/her family member suggests that possibly also disease- or environment related influences lead to smaller ICV in patients as compared to their non-ill relatives.

To what degree this differential effect of ICV in schizophrenia or bipolar disorder relatives is of genetic origin remains unclear. Genome wide association studies (GWASs) have shown that bipolar disorder and schizophrenia are genetically highly correlated (Anttila et al., 2018; Lee et al., 2013). However, the degree and direction of the genetic relationships between the disorders and ICV is less established (Franke et al., 2016; Lee et al., 2016; Smeland et al., 2017b; Stahl et al., 2019). Given that we observed disease-specific differences in ICV of patients and their relatives, it is of interest to investigate whether ICV associates with schizophrenia or bipolar disorder risk differently on a genotypic or phenotypic level, and therefore investigating genetic correlations only may not be sufficient.

Polygenic scoring allows to investigate the genetic relationships at an individual level, and to link genetic risk to a phenotype. The genetic liability for disorders, such as schizophrenia (SZ-PGS) and bipolar disorder (BD-PGS) polygenic scores, can be calculated within each individual from GWAS summary statistics. Similarly, one can estimate the genetic predisposition for traits, such as a polygenic score for ICV (ICV-PGS). As expected based on the strong genetic correlation between schizophrenia and bipolar disorder (Anttila et al., 2018; Lee et al., 2013), there is a highly significant overlap between BD-PGS and SZ-PGS

(Smoller et al., 2013). Additionally, numerous studies have linked SZ-PGS and/or BD-PGS to other traits or symptoms, including brain structure and cognitive functioning with mixed findings (Abé et al., 2019; Alnæs et al., 2019; Córdova-Palomera et al., 2018; Hubbard et al., 2016; Mistry et al., 2019; Neilson et al., 2019; Ranlund et al., 2018; Van Os et al., 2017). To date there is only limited evidence that risk genes for schizophrenia or bipolar disorder are linked to ICV or its polygenic score.

Here, we investigated to what degree the polygenic scores of schizophrenia, bipolar disorder, and ICV are related and whether these polygenic scores are associated with the phenotype ICV in healthy individuals from a large population-based cohort (UK Biobank). Based on our earlier finding on ICV in relatives of patients, we hypothesized that there is i) a positive relationship between BD-PGS with both phenotype ICV and ICV-PGS (based on larger ICV in relatives of patient with bipolar disorder but not in the patients), ii) no relationship between SZ-PGS with both phenotype ICV and ICV-PGS (based on only smaller ICV in patients with schizophrenia but not their relatives), iii) a small positive relationship between phenotype ICV and ICV-PGS, as previously reported (Luciano et al., 2015). We used the latest ICV-GWAS summary statistics tailored for this current study and to investigate whether the PGS relationships are in line with genetic correlations we calculated through LD score regression (Bulik-Sullivan et al., 2015a, 2015b).

METHODS

Study Sample

The UK Biobank dataset is a large prospective population-based cohort (https://www.ukbiobank.ac.uk) (Bycroft et al., 2018) and a total of 459,250 participants with self-reported white ethnicity — i.e., white British, white Irish, and other white background — were included in the current study.

Image Acquisition and Processing

Structural MRI scans were acquired in a subset of the participants (n = 20,196; 63.2 ± 7.4 years old [age range 45.2 – 80.7]; 52.5% female) scanned at three different sites. FreeSurfer version 6.0 was used to obtain measures for estimated Total Intracranial Volume (eTIV) in each individual (Fischl, 2012) (http://surfer.nmr.mgh.harvard.edu/fswiki/recon-all/). Part of the participants was included in the ICV-GWAS (see below) and a cut-off date of February 3, 2017 was used in the ICV-PGS (n = 446,375) and phenotype ICV analyses to prevent overlap between the participants in the GWAS and those for which we calculated the ICV-PGS (n = 9,074; 63.9 ± 7.4 years old [age range 47.0 – 80.7]; 52.8% female) (see below).

Polygenic Scoring and Genetic Correlations

Polygenic scores were calculated using schizophrenia-, bipolar disorder- and ICV-associated alleles and effect sizes reported in the GWAS summary statistics (Ripke et al., 2014; Stahl

et al., 2019) (unpublished ICV GWAS data; courtesy of Sarah Medland). Overlapping SNPs between the GWAS (training dataset), 1000 reference Genome (reference dataset), and dataset of interest (target dataset) were selected. Then the following SNPs were excluded: 1) insertion or deletion, ambiguous SNPs; 2) SNPs with MAF < 0.01 and SNPs with imputation quality (R^2) < 0.8; and 3) SNPs located in complex-LD regions (Price et al., 2008). The remaining SNPs were clumped in two rounds using PLINK; round 1 with the default parameters (physical distance threshold 250 kb and LD threshold (R^2) < 0.5; round 2 with a physical distance threshold of 5,000 kb and LD threshold (R^2) < 0.2; the resulting SNPs were used for polygenic score calculation. Odds ratios and Z-scores for autosomal SNPs reported in the summary statistics were log-converted to beta values. Polygenic scores were calculated using PLINK's score function for 12 GWAS *P*-value thresholds (P_T): 5 x 10^{-8}, 5 x 10^{-7}, 5 x 10^{-6}, 5 x 10^{-5}, 5 x 10^{-4}, 0.005, 0.05, 0.1, 0.2, 0.3, 0.4 and 0.5. For comparison between PGS-level associations and genetic correlations from the GWAS statistics, we computed genetic correlations between the unpublished ICV-GWAS summary statistics (courtesy of Sarah Medland) and the published schizophrenia and bipolar disorder summary statistics (Ripke et al., 2014; Stahl et al., 2019)(unpublished ICV GWAS data; courtesy of Sarah Medland), using LD score regression (Bulik-Sullivan et al., 2015a, 2015b). In addition, SNP heritability for ICV was calculated to investigate genetic signal captured by the ICV-GWAS.

Statistical Analyses

All statistical analyses were conducted using R version 3.5.0 (http://www.r-project.org). The first 3 principle components, provided by the UK Biobank, were regressed out of each of the polygenic scores. Age, sex and cohort site were regressed out for the ICV measures. The residuals were used to perform Pearson correlations between SZ-PGS, BD-PGS, ICV-PGS for each PT, and phenotype ICV. To estimate the explained variance of ICV-PGS on the phenotype ICV, a baseline linear relationship including only sex, age and the first 3 PCs as variables was modelled first. Subsequently, a linear model including polygenic scores for each ICV-GWAS PT was calculated. An explained variance R^2 value was obtained for every model and the baseline R^2 value was subtracted, resulting in a Δ explained variance that describes the contribution of ICV-based PGS to the phenotype ICV. In the current study we focused on the findings of P_T = 0.05 for SZ-PGS and BD-PGS, based on the consensus in the literature, and the P_T that explained most variance in ICV. Partial correlations were performed to investigate whether the genetic overlap between schizophrenia and bipolar disorder risk influences relationship between ICV and its polygenic score and the polygenic scores of bipolar disorder and schizophrenia. Significance threshold was set at $P < (0.05 / 10 =) 0.005$ (6 pairwise correlations between SZ-PGS, BD-PGS, ICV-PGS and phenotype ICV, and 4 partial correlations).

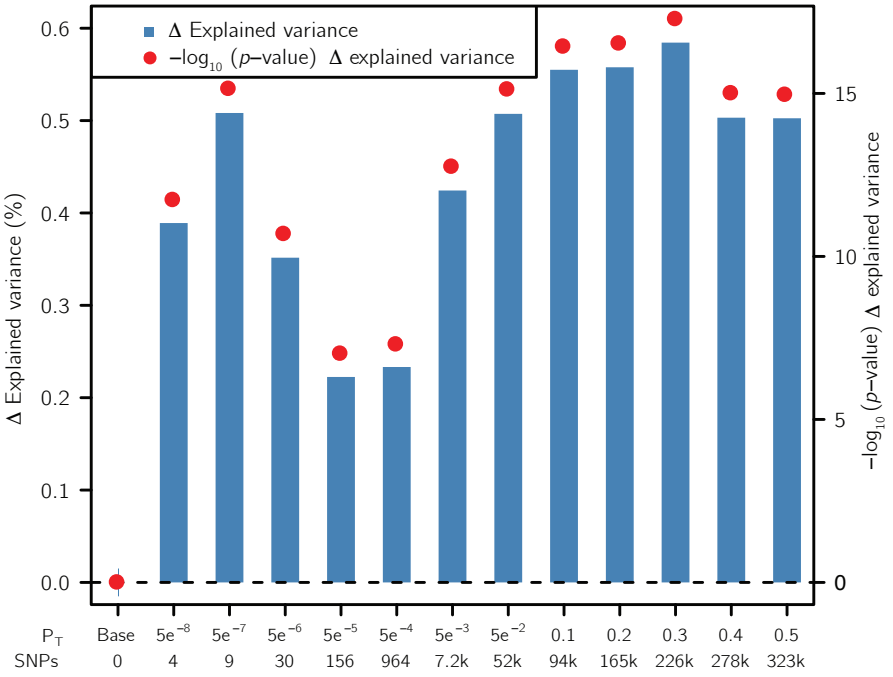

Figure 1. Analysis of polygenic scores (PGS) for intracranial volume (ICV) in a target sample of 9,074 participants from the UK Biobank. *P*-value thresholds (P_T) for intracranial volume SNPs are shown on the x-axis, where the number of SNPs increases with a more lenient P_T. Delta (Δ) explained variances (%) of a linear model including ICV-based PGS versus a baseline model without PGS (blue bars) are shown for each P_T. Log_{10} *P*-values of Δ explained variance per P_T (red dots) represent *P*-values from the linear model of phenotype intracranial volume on ICV-PGS, including sex, age, scanner site and first 3 principal components as covariates. Based on these findings we present in the current paper the findings for ICV-PGS at $P_T = 0.03$.

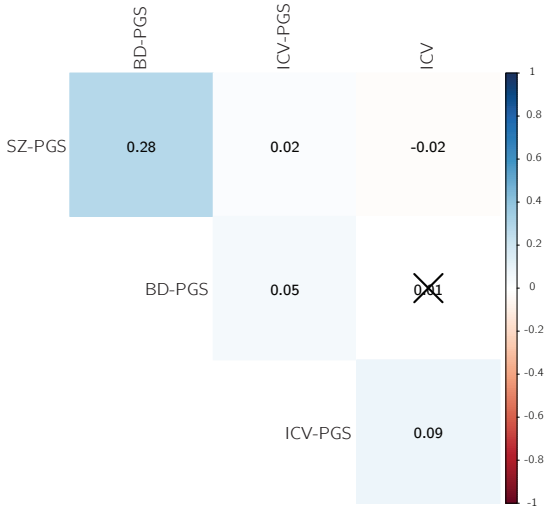

Figure 2. Correlations between the polygenic scores of schizophrenia (SZ-PGS) at genome wide association study (GWAS) P-value threshold (P_T) of 0.05, bipolar disorder (BD-PGS) at $P_T = 0.05$, intracranial volume (ICV-PGS) at $P_T = 0.3$ and phenotype intracranial volume (ICV). Significance threshold was set at $P < 0.005$. Non-significant correlations were crossed out.

RESULTS

Intracranial Volume and its Polygenic Score

The explained variance that describes the contribution of ICV-PGS to the phenotype ICV was very low with a maximum of 0.6% at GWAS *P*-value threshold (P_T) of 0.03 (Figure 1). ICV and the ICV-PGS showed a small significant positive correlation of $r = 0.09$ at $P_T = 0.03$ (95% confidence interval (CI) = 0.07 - 0.11, $T = 8.49$, $P < 0.005$) (Figure 2). An overview of the contribution at each P_T can be found in Figure 3.

Polygenic Scores of Schizophrenia and Bipolar Disorder

The BD-PGS and SZ-PGS had a significant positive relationship with a correlation of $r = 0.28$ (95% CI = 0.28 - 0.29, $T = 200.15$, $P < 0.005$) (Figure 2). Correlations for all other P_T can be found in Figure 3.

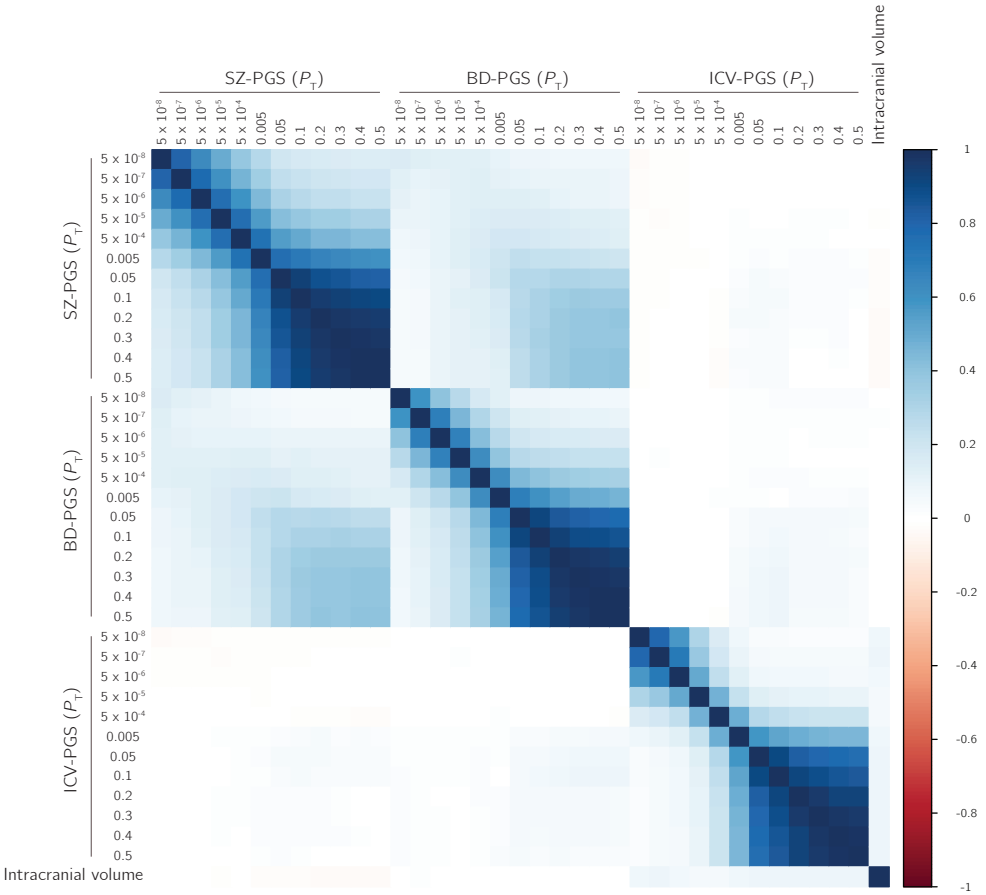

Figure 3. Correlations between the polygenic scores for schizophrenia (SZ-PGS), bipolar disorder (BD-PGS), intracranial volume (ICV-PGS) at 12 GWAS P-value thresholds (P_T): 5 x 10^{-8}, 5 x 10^{-7}, 5 x 10^{-6}, 5 x 10^{-5}, 5 x 10^{-4}, 0.005, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and phenotype intracranial volume.

Relationships Between BD-PGS, Intracranial Volume and its Polygenic Score

There was a small positive correlation of $r = 0.05$ between BD-PGS and ICV-PGS (95% CI = 0.05 - 0.06, $T = 36.48$, $P < 0.005$) (Figure 2). No significant correlation was found between BD-PGS and the phenotype ICV ($r = 0.01$, 95% CI = –0.00 - 0.02, $T = 1.34$, $P = 0.18$) (Figure 2). Correlations for all other P_T can be found in Figure 3.

Partial correlation analyses showed that when accounting for SZ-PGS, the correlation between BD-PGS and ICV-PGS remained similar ($r = 0.05$; $T = 33.14$, $P < 0.005$), and that the correlation between BD-PGS and phenotype ICV after correcting for SZ-PGS also remained similar ($r = 0.02$, $T = 2.35$, $P = 0.02$).

Relationships Between SZ-PGS, Intracranial Volume and its Polygenic Score

SZ-PGS and ICV-PGS were positively correlated ($r = 0.02$, 95% CI = 0.02 - 0.03, $T = 16.59$, $P < 0.005$) (Figure 2), while SZ-PGS and the phenotype ICV were negatively correlated ($r = –0.02$, 95% CI = –0.04 - –0.01, $T = –3.18$, $P < 0.005$) (Figure 2). Correlations for all other PT can be found in Figure 3.

Partial correlation analyses showed that when accounting for BD-PGS, the correlation between SZ-PGS and ICV-PGS still reaches significance ($r = 0.01$; $T = 6.56$, $P < 0.005$) as did the negative correlation between SZ-PGS and phenotype ICV after correcting for BD-PGS ($r = –0.03$; $T = –3.72$, $P < 0.005$).

LD Score Regression: Genetic Correlations and SNP Heritability of Intracranial Volume

The SNP heritability (h^2) of ICV was 0.16 ± 0.03. LD score regression analyses showed that ICV was not significant genetically correlated with schizophrenia ($r_g = 0.02$; $Z = 0.36$, $P = 0.72$) or bipolar disorder ($r_g = 0.09$; $Z = 1.52$, $P = 0.13$) (Figure 4). For completeness, we recalculated the genetic correlation between schizophrenia and bipolar disorder ($r_g = 0.69$) (in line with Anttila et al., 2018; Lee et al., 2013).

DISCUSSION

In this study we aimed to investigate the genetic underpinnings of the discrepancy of ICV in relation to schizophrenia and bipolar disorder. Patients with schizophrenia (but not bipolar disorder) have smaller ICV than controls, while we recently reported that relatives of patients with bipolar disorder (but not schizophrenia) have larger ICV. To address this issue in a manner which could potentially be meaningful for the individual, we investigated associations between polygenic scores of schizophrenia, bipolar disorder and ICV in a large population sample of the UK Biobank. The main findings were 1) a positive relationship between ICV-PGS, and both BD-PGS and SZ-PGS, with the largest effect between BD-PGS and ICV-PGS; 2) correlations between the polygenic scores were in the same direction as genetic

correlations calculated through LD score regression, albeit smaller; 3) a discrepancy between the genotype and phenotype ICV in relation to SZ-PGS (positive and negative respectively) and BD-PGS (positive and non-significant respectively).

ICV-PGS was positively related to both SZ-PGS and BD-PGS, albeit with small correlations of respectively $r = 0.02$ and $r = 0.05$. This suggests that risk genes for both disorders, but more so in bipolar disorder, are related to a genetic predisposition for a larger ICV. That risk for bipolar disorder is related with larger ICV is in line with our finding in the ENIGMA-Relatives study in which first-degree relatives of patients with bipolar disorder (i.e. individuals at familial (thus partly genetic) high-risk for the disorder but who themselves are not ill) had significantly larger ICV (De Zwarte et al., 2019b). Although very modestly, we also found a positive relationship between risk for schizophrenia and larger ICV based on the polygenic scores. In our ENIGMA-Relative study we did not find this positive relationship based on structure imaging data in schizophrenia relatives (De Zwarte et al., 2019b). Genetic overlap between schizophrenia and ICV has been suggested through conditional false discovery rate analysis which identified shared loci (Smeland et al., 2017b) and partitioning heritability analysis (Lee et al., 2016), suggesting that the genetic architectures of schizophrenia and ICV are not completely independent. However, based on genetic correlations reported previously (Franke et al., 2016; Stahl et al., 2019) there is no direct evidence that common risk genes for schizophrenia would be related to predisposition for the size of the ICV (neither was this the case for bipolar disorder). A new ICV-GWAS was performed for the current study, with reasonable polygenic signal given the SNP heritability of 16%, and we confirmed, through LD score regression, that there was no significant relationship between genetic predisposition for ICV and genetic risk for schizophrenia or bipolar disorder (Figure 4). However, while not significant, we did see a trend towards a positive relationship between genetic risk for both disorders and ICV, in particular for bipolar disorder ($r_g = 0.09$). This is in line with the correlations reported between the polygenic scores in the current study, suggesting that there is a very modest yet positive relationship between the common genetic variants leading to larger ICV and increased genetic risk for the disorders, in particular for bipolar disorder.

The relationship between *phenotype* ICV and SZ-PGS or BD-PGS differed from the *genotype* ICV as estimated through ICV-PGS. In contrast to the positive relationship between ICV-PGS and both SZ-PGS and BD-PGS, we found no significant correlation between BD-PGS and ICV and a small negative correlation between SZ-PGS and ICV in a healthy population. This implies that we are capturing a differential relationship when we relate the ICV-PGS or the phenotype ICV itself to schizophrenia or bipolar risk genes. Interestingly, the negative relationship between ICV and schizophrenia and no relationship between bipolar disorder and ICV is confirming the effects that are consistently found in patients with these disorders, i.e. a smaller ICV in patients with schizophrenia than controls and no differences in ICV between patients with bipolar disorder and controls (Haijma et al., 2013; Hibar et al., 2016; Okada et al., 2016; Van Erp et al., 2015). That the relationship between ICV measured through MRI and ICV-PGS is different may imply that factors other than common

genetic variation influence ICV as an outcome measure in relation to risk for either schizophrenia or bipolar disorder, such as environmental factors, gene-by-environment interactions or rare genetic variants not captured by GWASs. For instance, copy number variants (CNVs) studies have shown a dose response on ICV of CNVs more common in schizophrenia than the general population, (Lin et al., 2017; Sønderby et al., 2018).

ICV and its polygenic score (ICV-PGS) were positively correlated (r = 0.09 at P_T = 0.03). This was in line with a study by Luciano et al. (2015) in which they showed correlations ranged 0.08 – 0.10 in a sample of 624 older individuals. The amount of variance explained by these polygenic effects in ICV in our sample was small (~0.6%), although it has been argued that the variance explained will increase with larger GWASs on which predicti on is based (Dudbridge, 2013). In contrast, the SNP heritability of ICV (i.e. the proportion or phenotypic variance explained by additive effects from SNPs) was ~16%, suggesting that at least part of the genetic signal is captured by common genetic variation. The low explained variance and modest SNP heritability suggest that (currently) the ICV-PGS is poorly powered to investigate an individuals' genetic predisposition for this trait as comparison with SZ-PGS and BD-PGS, and we have to be careful with drawing definite conclusions based solely on the current ICV-PGS.

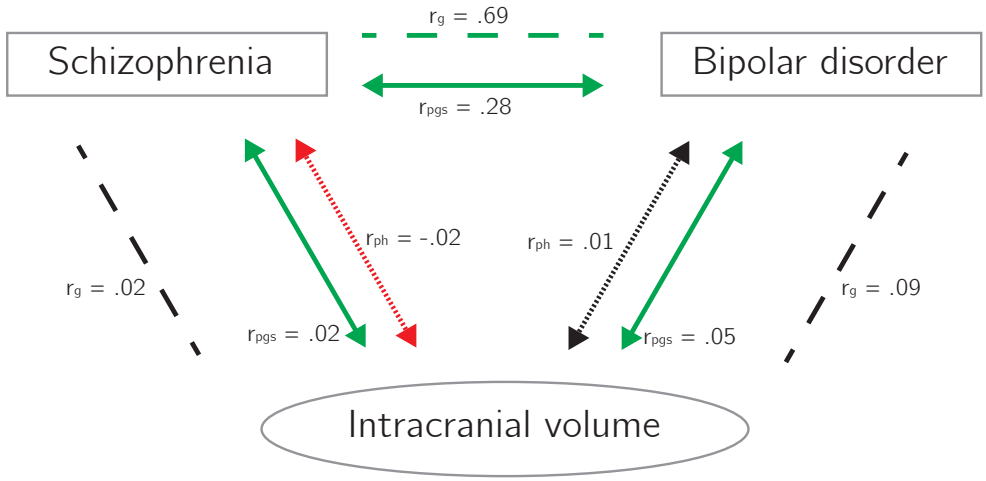

Figure 4. Overview of the correlations between intracranial volume, genetic predisposition for schizophrenia and genetic predisposition for bipolar disorder. The genetic correlation calculated through LD score regression (r_g; dashed lines), correlation between the polygenic scores of schizophrenia, bipolar disorder and intracranial volume (r_{pgs}; solid lines), and the correlation between phenotype intracranial volume and the polygenic score of schizophrenia or bipolar disorder (r_{ph}; dotted lines) are displayed here. Red lines are significant negative correlations, green lines are significant positive correlations, black lines not significant.

A few limitations to the current study should be noted. First, the correlations between the traits represent small effects and we have to bear this in mind when interpreting the results and replication is essential before we can draw definite conclusions. In addition, these small effects confirm that we are still far from using polygenic scores as a tool to understand underlying biological measures at the level of the individual. Second, while still of considerable sample size, the group with an MRI scan (n = ~9k) was much smaller than the total UK Biobank sample (n = ~460k). Consequently, we have to be careful with drawing conclusions regarding the difference between genotype and phenotype of ICV. Finally, the UK Biobank is a large prospective cohort established to primarily investigated the genetic and lifestyle determinants of a wide range of diseases and aging in middle and later life (Sudlow et al., 2015). At the time of the MRI scan, the average age was 63 years old. A recent longitudinal study has shown that ICV does not stay constant during adulthood but instead shows small increases during young adulthood and decreases from the fourth decade of life (Caspi et al., 2019). Therefore, we have to be careful with drawing conclusions on the differential effect between the phenotype ICV and ICV-PGS. It is possible that the relationship between ICV and the SZ-PGS and BD-PGS was more pronounced earlier in life before ageing effects took place. An important next step should include looking at the development of ICV during childhood and adolescence in relation to genetic risk for schizophrenia and bipolar disorder.

Polygenic scoring is to date one of the few methods to assess, within the individual, risk genes and/or genetic predisposition for traits. Although the effects are very small, we showed that there is suggestive evidence of a positive genetic relationship between bipolar disorder and ICV. This relationship is also present between schizophrenia and ICV, albeit less pronounced. Investigating the relationships between the traits through polygenic score allowed for a direct comparison within the individual between ICV-PGS and the phenotype ICV. Risk genes for bipolar disorder, and to a lesser extent schizophrenia, are related to genetic predisposition for larger ICV. There is less evidence for an association between the bipolar risk genes and phenotype ICV, while in contrast, there is a small negative association between SZ-PGS and phenotype ICV. The discrepancy between ICV-PGS and phenotype ICV in their association with SZ-PGS and BD-PGS suggests that other factors, such as environmental influences, gene-by-environment interactions or rare genetic variations, may lead to smaller ICV in those at-risk.

6

Summary and general discussion

The research described in this thesis explored the relationships between risk for schizophrenia and bipolar disorder, brain structure, and cognition. This chapter summarizes the main findings, provides a discussion in light of relevant literature, and proposes methodological considerations and future directions.

In **Chapter 2**, I investigated whether first-degree relatives of patients with schizophrenia share brain abnormalities with their ill family member in five schizophrenia family cohorts. In this study, I showed that first-degree relatives of patients with schizophrenia have structural brain abnormalities, including smaller intracranial volume (ICV), surface area, total brain, cortical gray matter, cerebral white matter, cerebellar gray and white matter, thalamus, putamen, amygdala, and nucleus accumbens volumes compared to control individuals. However, the effect sizes were much smaller than those found for patients with schizophrenia (**Chapter 2**; Haijma et al., 2013; Okada et al., 2016; Van Erp et al., 2015). The abnormalities were most pronounced in the offspring group. Since first-degree relatives (except for monozygotic twins) share on average 50% of their genes with the proband, the finding that effect sizes appear larger for offspring may suggest the existence of an environmental component that contributes to brain abnormalities in individuals at familial risk for schizophrenia. It must be noted, however, that the differences among the different types of relatives were modest at most. IQ was significantly lower in the monozygotic co-twins, offspring, and siblings compared to controls, and this study showed that IQ was strongly related to the brain abnormalities reported in relatives. In other words, when we account for the IQ scores most of the brain structure differences between the relatives and controls disappear. These findings were not influenced by the presence of nonpsychotic diagnoses in the relatives. Together, these findings suggest that the familial risk to develop schizophrenia explains, at least partly, the brain abnormalities seen in patients, and that there is an overlap between familial risk factors leading to low IQ and risk for schizophrenia.

In **Chapter 3**, I meta-analyzed harmonized global and subcortical brain measures of 1,228 relatives of patients with schizophrenia and 852 relatives of patients with bipolar disorder in the largest examination of first-degree relatives to date. The ENIGMA—Relatives Working Group was initiated to investigate brain structure in family members of psychiatric patients at an unprecedented scale. By joining forces with 34 research groups around the world, I was able to answer the question whether our findings in the first-degree relatives of patients with schizophrenia in **Chapter 2** would replicate and how they compare to findings in first-degree relatives of patients with bipolar disorder. I showed that the two relative groups (schizophrenia and bipolar disorder) have differential brain abnormalities compared to control subjects. The main finding was that relatives of patients with bipolar disorder have larger ICV compared to the control group, which was not found in relatives of patients with schizophrenia. When we account for ICV, no differences were found between relatives of patients with bipolar disorder and controls, while, by contrast, relatives of patients with schizophrenia had significantly smaller brain volumes, mean cortical thickness, and larger ventricle volume than controls. Furthermore, I replicated our findings of **Chapter 2** in a larger

sample: subtle differences were apparent between the different relative types but no evidence of a clear pattern was detected. Finally, in line with the findings from **Chapter 2**, this study confirmed that psychopathology in relatives and controls did not influence the extent of the brain abnormalities. These findings suggest that brain structure in individuals at familial risk for either bipolar disorder or schizophrenia may deviate during early-brain development in a disease-specific manner.

The discovery of differential ICV in relatives of patients with bipolar disorder and schizophrenia led to two follow-up studies, which were described in **Chapters 4** and **5**. Building on the positive relationship between intelligence and brain size (McDaniel, 2005), in **Chapter 4** I investigated whether the larger ICV in relatives of patients with bipolar disorder was potentially confounded by higher IQ and/or higher educational attainment. I investigated the level of IQ and/or educational attainment in first-degree relatives of patients with schizophrenia or bipolar disorder, and to what degree these measures influenced the brain abnormalities, through prospective harmonized meta-analysis through the ENIGMA—Relatives collaboration. First, I extended the global and subcortical brain analyses from **Chapter 3**, by investigating regional cortical thickness and surface area. The first-degree relatives of patients with schizophrenia showed an overall pattern of thinner cortex, while the relatives of patients with bipolar disorder predominantly showed a pattern of larger surface area. I also found that both relatives of patients with schizophrenia and bipolar disorder had a lower IQ, which was more pronounced in relatives of patients with schizophrenia than in relatives of patients with bipolar disorder. Educational attainment did not differ between the relatives and controls. Controlling for IQ or educational attainment also had minimal effect on brain differences between relatives and controls. However, the present effects were in the expected direction, namely that effect sizes of brain measure differences between groups decreased for first-degree relatives of patients with schizophrenia (similar to findings in **Chapter 2**) and increased for first-degree relatives of bipolar disorder patients after correction for IQ or educational attainment. Hence, the larger ICV in relatives of patients with bipolar disorder seems unrelated to differences in IQ and/or educational attainment.

In **Chapter 5**, I investigated whether a genetic component is underlying the discrepancy in ICV findings between schizophrenia and bipolar disorder. I addressed this issue in a manner that could potentially be meaningful for the individual. More specifically, I investigated associations between polygenic scores for schizophrenia (SZ-PGS), bipolar disorder (BD-PGS), and ICV (ICV-PGS) in a large population sample of almost half a million individuals recruited through the UK Biobank. I found a small positive relationship between ICV-PGS, and both BD-PGS and SZ-PGS, with the largest effect between BD-PGS and ICV-PGS. In a subgroup of individuals (n = 9,074) who underwent brain imaging, a discrepancy between the *genotype* and *phenotype* ICV in relation to SZ-PGS (positive and negative respectively) and BD-PGS (positive and non-significant respectively) was found. With this study, I provide suggestive evidence that the positive relationship between bipolar disorder and ICV has, at least in part, a genetic basis. Furthermore, this study also provides preliminary evidence

for environmental or gene-by-environment factors related to risk for the disorder, which ultimately leads to smaller ICV in the general population than what they are genetically predisposed for. An example of environmental factors related to schizophrenia that might influence ICV is smoking: genetic risk for schizophrenia is positively related to risk for smoking behaviors (Hartz et al., 2018). Moreover, infants with a smoking mother have a smaller head circumference at birth (Källén, 2000). This may imply that similar mechanisms play a role in patients with schizophrenia (and bipolar disorder). Patients possibly have a genetic risk for a larger ICV, but due to environmental or gene-by-environmental influences related to disease onset, in reality ICV is smaller.

GENERAL DISCUSSION

DIFFERENTIAL NEURODEVELOPMENTAL TRAJECTORIES

The studies described in this thesis demonstrate that even though the clinical representation and genetic underpinnings of schizophrenia and bipolar disorder are strongly overlapping, risk for schizophrenia and bipolar disorder may be differentially related to brain development.

Previous meta-analyses of MRI studies showed that patients with schizophrenia (but not bipolar disorder) have smaller ICV than controls (Haijma et al., 2013; Hibar et al., 2016; Okada et al., 2016; Van Erp et al., 2015), while in this thesis I demonstrated that relatives of patients with bipolar disorder (but not schizophrenia) have larger ICV (**Chapters 3** and **4**). ICV is an accurate measure of overall head size, which combines gray and white matter of the brain and the cerebrospinal fluid inside the dura, and represents a proxy for the maximal brain growth during development and maturation. While most of the development of ICV happens prenatally and in the first years of life, ICV reaches its maximum size at the age of 15 years (Courchesne et al., 2000; Sgouros et al., 1999). Therefore, changes in ICV may represent a possible indicator of neurodevelopmental abnormality. The discrepancy in ICV between those at familial risk for schizophrenia or bipolar disorder suggests that different neurodevelopment trajectories in relatives of patients with bipolar disorder and schizophrenia may play a role in developing the disease.

SCHIZOPHRENIA

Head size has long been implicated (as a neurodevelopmental aspect) in schizophrenia; babies who later develop schizophrenia already have smaller head circumference at time of birth (Kunugi et al., 1996; McNeil et al. 1993). This finding is in line with the smaller ICV reported in patients with schizophrenia (Haijma et al., 2013; Okada et al., 2016; Van Erp et al., 2015), suggesting that the trajectory for smaller ICV in patients with schizophrenia perhaps already occurs prenatally. In **Chapter 2**, I showed that relatives of patients with schizophrenia also had smaller ICV; however, this finding was not replicated in a much larger sample (**Chapters 3** and **4**). This implies that familial risk for developing schizophrenia, which is shared between the proband and non-ill family member, is likely not related to ICV.

The evidence for a genetic relationship between ICV and schizophrenia is indeed not strong: using the established LD score regression approach (Franke et al., 2016) (which I confirmed using the updated ICV-GWAS summary statistics in **Chapter 5**), there is no significant genetic correlation between schizophrenia and ICV. However, through partitioning heritability analysis (Lee et al., 2016) and through conditional false discovery rate analysis (Smeland, et al., 2017b), evidence for a genetic overlap was suggested. The latter study identified two shared loci. Indeed, the relationship between the polygenic scores, i.e. SZ-PGS and ICV-PGS, showed a small but positive correlation (**Chapter 5**). By contrast, risk for schizophrenia (SZ-PGS) was negatively related to the phenotype ICV, i.e., the higher the polygenic score for schizophrenia comes with a lower volume of the intracranium. This opposite pattern between the correlations of SZ-PGS and either *phenotype* or *genotype* ICV is remarkable; however, we have to be cautious with drawing conclusions from these very small effects. Both polygenic scores and genetic correlations are based on common genetic variation. That risk genes for schizophrenia are positively related to the genetic predisposition for ICV but negatively related to phenotype ICV might imply that even though a genetically at-risk individual is on a genetic trajectory of developing a larger ICV, other (non-common genetic) factors, such as environment, gene-by-environment interactions, or rare genetic variation related to the risk of developing schizophrenia may eventually lead to a smaller ICV.

Cognitive deficits are also a hallmark of schizophrenia (Kahn & Keefe, 2013). In this thesis, I confirmed the presence of cognitive deficits in their family members, albeit to a lesser extent (**Chapters 2** and **4**). With a genetic correlation of r_g = –0.20 (Sniekers et al., 2017) and many shared loci between IQ and schizophrenia (most of the schizophrenia risk alleles were associated with poorer cognitive performance) (Smeland et al., 2017a, 2019), this relationship between schizophrenia and cognition is likely of genetic origin. A gene set analysis of the loci shared between schizophrenia and intelligence implicated biological processes related to neurodevelopment, synaptic integrity, and neurotransmission (Smeland et al., 2019), which makes it likely that this association explains (part of) the brain deficits in schizophrenia. Patients with schizophrenia in the studies described in this thesis consistently showed smaller ICV (*d*s = –0.12 to –0.30), albeit not all reached significance, with effect sizes comparable to those described in the existing literature (*d*s = –0.10 to –0.17) (**Chapters 2 – 4**) (Haijma et al., 2013; Okada et al., 2016; Van Erp et al., 2015). After controlling for IQ in patients with schizophrenia, the effect of smaller ICV disappears, resulting in no significant differences in ICV between patients, relatives and controls (**Chapters 2** and **4**). These findings suggest that ICV, IQ and (risk for) schizophrenia are intertwined. This adds to twin study findings that showed that IQ shares a substantial genetic origin with global brain deficits seen in schizophrenia (Bohlken et al., 2016; Toulopoulou et al., 2015).

In general, brain abnormalities in first-degree relatives of patients with schizophrenia showed a similar pattern as in patients but with smaller effect sizes (**Chapters 2 – 4**). While many of these abnormalities disappeared when correcting for IQ, this seemed not the case of cortical thickness in both the patients and their relatives (**Chapters 2 – 4**). During early-brain

development, cortical thickness develops independently from cortical surface area (Rakic, 1988) (which is highly genetically related to ICV r_g = 0.86) (Grasby et al., 2018). A twin study reported that IQ and cortical thickness show significant and independent shared genetic variance with schizophrenia liability, indicating that measuring brain-imaging phenotypes helps explain genetic variance in schizophrenia liability that is not captured by variation in IQ (Bohlken et al., 2016). Together, this suggest that another genetic risk factor that is unrelated to IQ might influence the cortical thickness anomalies reported in patients and their family members.

BIPOLAR DISORDER

Findings of differential brain structure development in relation to the development of bipolar disorder have been inconsistent, which is possibly due to the heterogeneity of the samples and medication use (Sanches et al., 2008). I showed in the largest harmonized investigation to date, that relatives of patients with bipolar disorder have a larger ICV than control individuals (**Chapters 3** and **4**), which suggests that abnormal brain development is related to familial risk to the disorder. However, ICV in patients with bipolar disorder does not deviate from controls (**Chapters 3** and **4**) (Hibar et al., 2016). This discrepancy between patients with bipolar disorder and their family members could indicate that the fact that patients have a smaller ICV than their family members reflects a disease effect. It could also suggest that larger ICV in the non-ill relatives is some kind a compensatory mechanism, i.e., does a larger ICV prevents them from becoming ill? There is suggestive evidence that the positive relationship between ICV and risk for bipolar disorder has a genetic origin (**Chapter 5**). However, while genetic risk for bipolar disorder and the genetic predisposition for ICV were positively related, this relationship was not present between genetic risk for bipolar disorder (as measured by BD-PGS) and phenotype ICV (**Chapter 5**). This may imply that illness related environmental or gene-by-environmental factors lead to a smaller ICV than the expected ICV based on genetic predisposition alone. This corroborates with the imaging findings in the relatives and patients: although bipolar risk genes put one on trajectory for larger ICV, the exposure to (already in early life when ICV is still developing) environmental or gene-by-environmental factors lead to a 'normal' ICV in patients with bipolar disorder while the relatives without exposure to these factors do show larger ICV.

All types of first-degree relatives of patients with bipolar disorder had larger ICV compared to their own control groups (**Chapter 3**). This very consistent pattern, even in the young (still developing) offspring, suggests that the brain development of first-degree relatives already deviate from the control participants without a family history of psychiatric illness early in life (before illness onset). Related to the larger ICV, relatives of patients with bipolar disorder showed widespread increases of cortical surface area (**Chapters 3** and **4**). The recent surface area GWAS also showed that the effects of genetic variants associated with surface area are more likely to be prenatal (Grasby et al., 2018), which is in line with the radial unit hypothesis (Rakic, 1988). This hypothesis postulates that the size of cortical surface

area is driven by neurogenesis — a process that is largely completed within the first weeks of postnatal life (Clowry et al., 2010; Hill et al., 2010; Rakic, 2009). This could imply that relatives of patients with bipolar disorder may already deviate from a healthy developing brain trajectory prenatally. On the other hand, surface area and ICV continue to grow until later in childhood (until the ages of 8 and 15 years respectively) (Courchesne et al., 2000; Raznahan et al., 2011; Sgouros et al., 1999); therefore, it remains unclear exactly when in brain development the relatives start to deviate.

The finding of larger ICV in relatives of bipolar disorder patients was not explained by a higher IQ and/or better school performance (**Chapter 4**). Both relatives and patients with bipolar disorder had a lower IQ, but did not differ on years of education completed from the control subjects. In fact, accounting for IQ and/or educational attainment led to an even greater effect size of ICV in the relatives (**Chapter 4**). Lower IQ scores in both relatives and patients have previously been reported (Vreeker et al., 2016), although they are somewhat remarkable in the light of findings from population studies. Such studies show that premorbid IQ and school performance is often not affected or are even higher in individuals who later develop bipolar disorder (MacCabe et al., 2010; Smith et al., 2015; Tiihonen et al., 2005; Zammit et al., 2004). In this thesis, there was no data available on premorbid IQ scores in patients or IQ development in relatives, and therefore it remains unclear whether different patterns of IQ were present earlier in life. On a genetic level, there is no clear evidence for a shared genetic background between bipolar disorder and IQ. A small and non-significant genetic correlation is reported (Sniekers et al., 2017); however, a recent genetic study did show shared loci between bipolar risk genes and intelligence, of which the majority of the bipolar risk alleles were associated with better cognitive performance (Smeland et al., 2019). It thus remains unclear to what extent, and which direction (positively or negatively) risk for bipolar disorder and IQ are related to each other.

METHODOLOGICAL CONSIDERATIONS AND FUTURE DIRECTIONS

ENVIRONMENT

One important component that still remains to be investigated in light of the risk of developing schizophrenia or bipolar disorder are the environmental risk factors. When investigating brain structure and cognition in first-degree relatives, effects of shared environmental component cannot be distinguished from those of genetic risk. The genetic risk component is clear (i.e., relatives share on average half of their genes with the ill family member); however, it is extremely complicated to quantify the degree to which family members are exposed to shared environmental risk factors, let alone to investigate the potential interactions between genes and the environment. The common way of investigating the role of specific environmental risk factors is through large population studies. These studies have shown that many environmental factors are associated to disease (which are often shared between proband and family member), including adverse life events, childhood trauma, extensive cannabis use, urbanicity, immigration, (McDonald & Murray, 2000; Rowland & Marwaha, 2018). However,

the effect sizes for most of these environmental risk factors are much smaller than the effect size for a family history of psychiatric illness.

Each study in this thesis indicates that environmental factors play a role in the findings of brain abnormalities in both patients and their relatives. In **Chapter 2**, the offspring group showed the largest effects. One could argue that children who grow up with an ill parent, are exposed to a more stressful environment early in life than the other first-degree relatives, which suggests that an environmental component contributes to brain abnormalities in those at-risk for schizophrenia. However, this offspring effect was not so much present in **Chapter 3**. Here, offspring group(s) included in this study were more heterogenic; for example, the average age was higher and inclusion criteria differed among the different cohorts. In **Chapter 5**, there was a difference in the relationship of genetic risk for bipolar disorder or schizophrenia with *genotype* ICV (as measured by ICV-PGS) and *phenotype* ICV (as measured via MRI); even though one is genetically predisposed for a larger ICV, in reality their ICV is not larger. This discrepancy may imply that environmental factors influence the developmental trajectory and final outcome of ICV. **Chapters 2**, **3** and **4** also showed that monozygotic co-twins were not more affected than the other family members. As they share all their genes with the ill proband and the other first-degree relatives share on average only half of their genes, one would expect that the monozygotic co-twins have more pronounced brain abnormalities in case the underlying mechanism is purely genetic. The fact that they did not differ significantly from the other family members implies that the shared family environment is also important for the development of brain abnormalities. Indeed, twin studies have shown that common environment substantially accounts for brain volume differences in schizophrenia (Picchioni et al., 2017). An interesting and necessary next step would be to incorporate (shared) environmental components and to investigate how they interact with the genetic risk for each disorder.

CLINICAL IMPLICATIONS

The effect sizes reported in this thesis — in relation to risk for the disorder and measures such as brain structure and cognition — are all very small. Therefore, these findings have no direct implications for clinical work. Nonetheless, these findings may inform the debate on whether schizophrenia and bipolar disorder are on the mood-psychosis continuum or whether they are two distinct disorders. It is of great clinical importance to know who is at risk of developing what illness, as this may inform early detection and prevention strategies. A decade ago, the National Institute of Mental Health (NIHM) started the Research Domain Criteria (RDoC) initiative to provide us with new ways of classifying mental illnesses, which are based on dimensions of observable behavior and neurobiological measures rather than based solely on the clinical presentation (Insel et al., 2010). Indeed, future work should focus on researching specific symptoms (across specific diagnoses) in order to better understand the underlying biological mechanisms. However, the findings presented in this thesis suggest that we might have to be careful to only conceptualize schizophrenia and bipolar disorder as

expressions within the mood-psychosis continuum, as my studies strengthen the notion that different neurodevelopmental trajectories are at play in either disorder.

Another important next step should include looking at the development of ICV and brain structure during childhood and adolescence in relation to risk for schizophrenia and bipolar disorder. Brain abnormalities described in this thesis were all measured at one time point; however, the brain is dynamic and develops throughout life, driven by genetic and environmental factors, as well as their interactions. In particular, it would be very insightful to see exactly when individuals who develop schizophrenia or bipolar disorder deviate in brain structure trajectories from their family members (who do not become ill). This would give more insight in whether relatives of patients with bipolar disorder indeed have some kind of compensatory mechanism. Hopefully, we will be able further disentangle who is on a path to become ill and who is not, and eventually discover whether it is possible to halt development of the disease at an early stage.

CONCLUDING REMARKS

Schizophrenia and bipolar disorder are two severe psychiatric disorders with shared symptoms and a strong genetic component; however, which factors lead to the illness is mostly still unknown. Through investigating their first-degree relatives, and using a cross-disorder approach, I showed that schizophrenia and bipolar disorder have differential neurodevelopmental trajectories based on divergent findings of ICV. There is suggestive evidence for a genetic component for the positive relationship between bipolar disorder and ICV, which is independent of IQ. These studies provide further evidence that early life brain development is different in those at risk for the disorders. Important next steps should be longitudinal studies and to investigate the effect of the environment on the risk of developing a disorder. The ultimate goal is to correctly identify who is at risk of developing the disorder, thereby allowing for early intervention or even preventing someone from becoming ill in the first place.

7

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A

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NEDERLANDSE SAMENVATTING

Schizofrenie en bipolaire stoornis zijn twee ernstige psychiatrische aandoeningen die met een prevalentie van respectievelijk ~0,5% en ~1% relatief vaak voorkomen. De gevolgen voor de patiënt zelf, alsook voor familie en vrienden, maar ook de bredere gevolgen voor de samenleving in de vorm van zorgtaken en -kosten zijn substantieel. Schizofrenie wordt gekenmerkt door langdurige psychoses en cognitieve problematiek, terwijl bipolaire stoornis gekarakteriseerd wordt door afwisselende periodes van manie en depressie. Het klinische onderscheid tussen beide stoornissen is echter niet altijd duidelijk, aangezien de ziektebeelden overlappende symptomen vertonen. Schizofrenie, en in mindere mate ook bipolaire stoornis, wordt geduid als een hersenontwikkelingsstoornis. Dit houdt in dat een verstoring in de hersenontwikkeling, soms al prenataal, kan leiden tot klinische symptomen in de late adolescentie of op volwassen leeftijd. Ondanks deze vergaande gevolgen, is het nog steeds grotendeels onbekend welke factoren daadwerkelijk leiden tot het ziek worden van deze patiënten.

Een grote uitdaging in het bestuderen van psychiatrische aandoeningen zoals schizofrenie en bipolaire stoornis zijn ziekte-gerelateerde factoren die het beeld van de stoornis beïnvloeden, zoals medicatiegebruik of een langdurige periode van verminderde activiteit. Hierdoor is het vaak onduidelijk of men de ziekte zelf onderzoekt of bijvoorbeeld de effecten van het langdurig gebruik van antipsychotica. Familiestudies en grote bevolkingsstudies hebben aangetoond dat zowel schizofrenie als bipolaire stoornis erfelijke ziektes zijn: wanneer je een familielid hebt die ziek is, heb je een verhoogt risico om zelf ziek te worden. Eerstegraadsfamilieleden – kinderen, ouders, een-/twee-eiige tweelingen, broers of zussen – delen ongeveer de helft van hun genen met hun zieke familielid (met uitzondering van eeneiige tweelingen; zij delen alle genen), maar hebben zelf geen diagnose schizofrenie of bipolaire stoornis. Daarmee zijn eerstegraadsfamilieleden een relevante groep om de oorzaken van psychiatrische stoornissen te onderzoeken.

In dit proefschrift worden drie belangrijke componenten van hersenontwikkeling onderzocht: i) hersenstructuur, ii) informatieverwerking, iii) risicogenen. Er wordt gekeken of en in welke mate deze factoren gerelateerd zijn aan het risico op het ontwikkelen van schizofrenie of bipolaire stoornis, en in hoeverre deze componenten overlappen of uniek zijn voor deze ziektes. Het beter begrijpen van de samenhang tussen deze componenten helpt ons te identificeren wie een verhoogd risico heeft om ziek te worden. Dit begrip is van cruciaal belang om detectie- en preventiestrategieën te ontwikkelen en verbeteren.

Hoofdstuk 2 laat zien dat eerstegraadsfamilieleden van patiënten met schizofrenie – die zelf niet de diagnoses hebben – hersenafwijkingen vertonen in vergelijking met een gezonde controlegroep. Deze hersenafwijkingen zijn echter veel subtieler dan aanwezig in de patiëntengroep. In dit onderzoek is voor het eerst gekeken of er verschillen zijn tussen de verschillende groepen eerstegraadsfamilieleden. Hieruit komt naar voren dat kinderen van de

patiënten de grootste afwijkingen vertonen ten opzichte van gezonde vrijwilligers. Aangezien eerstegraadsfamilieleden ongeveer 50% van hun genen met hun zieke familielid delen, kan deze bevinding erop wijzen dat er naast een genetisch component er ook een omgevingsfactor is die bijdraagt aan hersenafwijkingen in familieleden, die er voor zorgt dat kinderen van patiënten (die opgroeien in een stressvolle omgeving en waarbij de hersenen zich nog steeds ontwikkelen) grotere hersenafwijkingen laten zien in vergelijking met de andere soort eerstegraadsfamilieleden. Aangezien de verschillen tussen de soorten eerstegraadsfamilieleden klein zijn, moeten we wel voorzichtig zijn conclusies te trekken. Hiernaast toonde het onderzoek dat IQ significant lager was in de eeneiige tweelingen, kinderen, broers en zussen van patiënten. Deze studie laat zien dat IQ sterk samenhangt met de hersenafwijkingen in de familieleden: wanneer de hersenmaten gecorrigeerd werden voor de IQ-scores, verdwenen de meeste verschillen in hersenstructuur tussen de familieleden en de controlegroep. De studie demonstreerde ook dat afwijkingen in hersenstructuur in de familieleden niet beïnvloed zijn door de aanwezigheid van eventuele andere psychiatrische aandoeningen in de familieleden. Tezamen suggereren de bevindingen in **hoofdstuk 2** dat familiair risico op schizofrenie, in ieder geval gedeeltelijk, leidt tot hersenafwijkingen in de patiënten, en dat er een overlap is tussen familiaire risicofactoren die leiden tot een lager IQ en risico op schizofrenie.

Hoofstuk 3 beschrijft een meta-analyse studie van globale en subcorticale hersenstructuren van 1.228 eerstegraadsfamilieleden van patiënten met schizofrenie en 852 eerstegraadsfamilieleden van patiënten met bipolaire stoornis; de grootste studie in zijn soort tot op heden. Deze omvangrijke aantallen zijn mogelijk gemaakt door het ENIGMA-consortium. Dit consortium is ruim 10 jaar geleden opgericht om MRI- en genetische data, expertise en middelen te bundelen met onderzoeksgroepen wereldwijd om fundamentele vragen te antwoorden in de neurowetenschappen, psychiatrie, neurologie en genetica. Ik initieerde mede het ENIGMA—Relatives-initiatief, een nieuwe werkgroep binnen ENIGMA. Dit initiatief heeft een samenwerking bewerkstelligd met 34 familiestudies verspreid over de wereld. Deze studie laat zien dat de twee onderzochte groepen (familieleden van patiënten met schizofrenie en bipolaire stoornis) een ander patroon van hersenafwijkingen vertonen. De belangrijkste bevinding had betrekking op het intracraniaal volume (ICV). ICV is een maat voor de totale inhoud van het hoofd – een combinatie van de volumes van grijze en witte stof van de hersenen, en het hersenvocht. Familieleden van patiënten met bipolaire stoornis hebben een groter ICV in vergelijking met de controlegroep. Hierbij zijn er geen aantoonbare verschillen tussen de familieleden van patiënten met schizofrenie en de controlegroep. Na een correctie voor ICV in de overige hersenstructuren blijken er geen verschillen tussen de familieleden van patiënten met bipolaire stoornis en de controlegroep. Familieleden van patiënten met schizofrenie hebben daarentegen na correctie van ICV juist significant kleinere hersenvolumes, dunnere cortex en een groter ventrikel volume dan de controlegroep. Deze bevindingen suggereren dat de hersenen van personen met een familiar risico voor bipolaire stoornis zich al vroeg in het leven anders ontwikkelen dan personen met een familiar risico voor schizofrenie.

De bevinding dat ICV anders is in familieleden van patiënten met schizofrenie en bipolaire stoornis is aanleiding geweest voor twee vervolgstudies, die beschreven staan in **hoofstukken 4** en **5**. Voortbouwend op de consensus dat er een positieve relatie is tussen intelligentie en hersenvolume, wordt in **hoofdstuk 4** onderzocht wat de relatie is tussen hersenafwijkingen in de familieleden en IQ of aantal jaren opleiding dat iemand genoten heeft. Immers, indien familieleden een lager IQ hebben dan gezonde vrijwilligers zouden de hersenafwijkingen (tenminste voor een deel) hierdoor verklaard kunnen worden. Er was gekozen om naast IQ ook aantal jaren opleiding te onderzoeken aangezien deze maat vaak wordt gezien als een schatting voor iemands intelligentie en makkelijker meetbaar is dan IQ. Opnieuw komt deze studie voort uit een groot samenwerkingsverband met de onderzoeksgroepen van ENIGMA—Relatives. Deze studie toont aan dat IQ lager is in de familieleden van patiënten met schizofrenie dan in de controlegroep. In mindere mate was dit ook het geval voor de familieleden van patiënten met bipolaire stoornis. Het aantal jaren opleidingen die beide groepen familieleden hebben genoten verschilde echter niet significant van de controlegroep. Een correctie voor IQ-score of jaren opleiding had dan ook weinig effect op de hersenmaatverschillen tussen de twee groepen familieleden en controlegroep. De effecten die we zagen, waren in lijn met onze hypothese: de verschillen in hersenvolume tussen familieleden van patiënten met schizofrenie en de controlegroep namen af terwijl deze tussen de familieleden van patiënten met bipolaire stoornis en de controlegroep toenam na een correctie voor IQ of opleidingsjaren. Hieruit blijkt dat de grotere ICV in de familieleden van patiënten met bipolaire stoornis waarschijnlijk niet gerelateerd is aan intelligentie.

In **hoofdstuk 5** wordt de genetische component die mogelijk aan de basis ligt van de verschillen in ICV tussen schizofrenie en bipolaire stoornis verder onderzocht. Om deze relaties op een niveau te onderzoeken dat mogelijk waardevol kan zijn voor het individu, en niet alleen op groepsniveau, is er gekeken naar de relaties tussen de polygenetische scores. Polygenetische scores kunnen berekend worden voor ieder individu om informatie te verschaffen over hoeveel risicogenen iemand heeft die gelinkt zijn aan een bepaalde (erfelijke) ziekte of in hoeverre iemand aanleg heeft voor een (erfelijke) eigenschap. In deze studie zijn de relatie tussen de polygenetische scores van schizofrenie (SZ-PGS), bipolaire stoornis (BD-PGS) en ICV (ICV-PGS) onderzocht in een grote bevolkingscohort afkomstig uit het Verenigd Koninkrijk (UK Biobank) van bijna een half miljoen deelnemers. De studie toont een kleine positieve correlatie tussen ICV-PGS en zowel BD-PGS als (in mindere mate) SZ-PGS. Dit betekent dat mensen met een verhoogd genetisch risico op bipolaire stoornis en schizofrenie hebben ook een genetische aanleg voor een groter ICV. Bij een subgroep van de deelnemers (n = 9.074) is ook MRI-scan afgenomen en werd het ICV bepaald. Er werd discrepantie zichtbaar tussen het genetisch risico op schizofrenie (SZ-PGS) en bipolaire stoornis (BD-PGS) in hun relaties met het *genotype* ICV (oftewel ICV-PGS) en het *fenotype* ICV (de hersenmaat gemeten op basis van de MRI-scan). Het genetisch risico op schizofrenie was positief gerelateerd aan ICV-PGS maar negatief gerelateerd aan het fenotype ICV. Het genetisch risico op bipolaire stoornis was positief gerelateerd aan

ICV-PGS maar het bleek niet gerelateerd aan het fenotype ICV. Vanwege het vergrote ICV in eerstegraadsfamilieleden van patiënten met bipolaire stoornis, beschreven in **hoofdstukken 3** en **4**, werd in **hoofdstuk 5** verder onderzocht of en in hoeverre deze relatie mogelijk genetische bepaald is. Deze studie laat zien dat de positieve relatie tussen bipolaire stoornis en ICV, hetzij een heel kleine, tot op zekere hoogte mogelijk een genetische basis heeft. Aangezien ICV in werkelijkheid kleiner is dan dat genetisch bepaald lijkt te zijn (hetgeen blijkt uit de discrepantie tussen het genotype en fenotype), geeft ruimte om te speculeren dat omgevingsfactoren gerelateerd aan schizofrenie en bipolaire stoornis (hierbij kunnen we denken aan bijvoorbeeld trauma in de kindertijd of een moeder die rookte tijdens de zwangerschap), of mogelijk gen-omgevingsfactoren (de interactie van genetische aanleg en invloeden uit de omgeving) ook invloed hebben op ICV in de algemene bevolking.

Hoofdstuk 6 vormt de samenvatting en discussie van de belangrijkste bevindingen uit de **hoofdstukken 2 – 5**. In dit proefschrift is trans-diagnostisch onderzoek gedaan naar de relatie tussen hersenstructuur, cognitie en risicogenen. Familieleden van patiënten met schizofrenie of bipolaire stoornis (die zelf de diagnose niet hebben) speelden een belangrijke rol in het aantonen dat schizofrenie en bipolaire stoornis een afwijkend hersenontwikkelingspatroon vertonen. Hierbij is de bevinding dat ICV niet afwijkt bij familieleden van patiënten met schizofrenie maar vergroot is bij familieleden van patiënten met bipolaire stoornis van doorslaggevend belang. Er zijn belangrijke aanwijzingen dat een genetisch component ten grondslag ligt aan de positieve relatie tussen bipolaire stoornis en ICV (oftewel het vergrote ICV bij familieleden van patiënten met bipolaire stoornis), die onafhankelijk is van de hoogte van het IQ. Deze studies bieden bovendien bewijs dat het brein van mensen met een risico voor schizofrenie of bipolaire stoornis zich al vroeg in het leven anders ontwikkeld. Belangrijke vervolgstappen voor toekomstig onderzoek zijn om mensen over de tijd te volgen door middel van longitudinale studies, indien mogelijk al vanaf de baarmoeder, en het effect van omgevingsfactoren die al dan niet samenhangen met het risico op schizofrenie en bipolaire stoornis te analyseren. Het ultieme doel hiervan is om uiteindelijk nauwkeurig te kunnen identificeren wie een verhoogd risico heeft om ziek te worden, zodat er tijdig en adequaat kan worden gehandeld of zelfs kan worden voorkomen dat iemand de ziekte gaat ontwikkelen.

DANKWOORD

Tot slot wil ik graag iedereen bedanken die door de jaren heen, zowel direct als indirect, heeft bijgedragen aan de totstandkoming van dit proefschrift.

Mijn dank gaat allereerst uit naar alle deelnemers – patiënten, hun familieleden en alle gezonde vrijwilligers – die onbaatzuchtig aan de verschillende studies hebben deelgenomen. Zij waren essentieel voor de studies die in dit proefschrift beschreven staan. Zelfs jaren na dato is de informatie die zij ons gaven nog steeds ontzettend waardevol.

Natuurlijk bijzondere dank voor mijn (co-)promotoren, prof. dr. René Kahn, prof. dr. Neeltje van Haren, dr. Rachel Brouwer. Mijn onderzoek zou onmogelijk geweest zijn zonder jullie hulp en steun. Bedankt voor het eindeloze vertrouwen dat jullie in mij hebben en voor de vrijheid die jullie me gaven om mijn eigen pad te kiezen.

René, ik waardeer je eerlijke en ongenuanceerde commentaren, onuitputtelijke kennis en humor. Ook veel dank voor alle mogelijkheden die je me bood; van een jaar extra promoveren, toegang tot de UK Biobank data, het mogelijk maken dat ik mijn werk mocht presenteren op internationale congressen, tot een bezoek aan Mount Sinai. Ik kijk ernaar uit dat we ook in de toekomst blijven samenwerken.

Neeltje, toen ik jouw vacature online zag staan had ik niet verwacht dat er een baan zou zijn die zo aansloot bij mijn wensen. Eigenlijk dacht ik destijds dat promoveren niet iets voor mij was, maar ik heb uiteindelijk echt (nou ja vooruit, bijna) nooit spijt gehad van de beslissing om dit avontuur met jou aan te gaan. Ik bewonder al je ideeën en de kunst om die goed te verwoorden, je aanstekelijke optimisme en je onvermoeibaarheid. Het was zo fijn dat je dag en nacht voor me klaarstond. Ook jij verliet mijn team fysiek voor een nieuwe uitdaging in Rotterdam, maar ik ben super trots dat ik je daardoor mijn promotor mag noemen.

Rachel, mijn wetenschappelijke rots in de branding. Een klein jaar na de start van mijn promotie werd je officieel onderdeel van mijn begeleidingsteam en daar ben ik nog steeds heel dankbaar voor. Ik waardeer enorm dat ik te allen tijde bij je binnen kon lopen voor hulp of advies, en je hielp ons ook altijd de focus te bewaren als we weer aan het afdwalen waren. Waar was ik geweest zonder al jouw hulp? Erg leuk dat je straks weer mijn collega wordt. Iederéén zou een Rachel in z'n team moeten hebben.

Graag wil ik ook de leden van lees- en promotiecommissie bedanken, prof. dr. Chantal Kemner, prof. dr. Sarah Durston, prof. dr. Jan Veldink, prof. dr. Steven Kushner, dr. Emma Sprooten, dank dat jullie de tijd en de moeite hebben genomen om mijn werk te lezen en te beoordelen. Prof. dr. David Glahn, thank you for taking the time in your busy schedule to attend my PhD defence ceremony.

On the other side of the pond there are a couple of people that contributed to my thesis as well who I would like to thank.

First of all, Hilary, personally I think it all started with you. It was you that introduced me to the world of psychiatry. Thank you for being my mentor for life and I am proud to be a part of the MDRP family.

I am really grateful that I had the opportunity to visit two research labs during my PhD: Elvira Bramon (UCL) and Roel Ophoff (UCLA). Elvira, thank you for hosting me in London, it was great working with you and still is, through all the collaborative studies we work on together. Roel, thank you for hosting me in Los Angeles, I think I learned more in those 5 months with you than ever before – I am a genetics fan for life! Also, many thanks to the entire Ophoff lab – Anil, Tim, Yoon, Loes, Catharine, Anouk, Niamh – for welcoming me from the get-go. I still consider my UCLA visit as one of the highlights during my PhD.

Last but not least, thanks to the ENIGMA consortium. Paul, thank you for your kind leadership, your always encouraging words and enthusiasm. To the entire extended ENIGMA team, thank you for your collaboration. I really enjoyed the projects we worked on together and the many meetings we attended. I am sure that we will meet again.

Verder wil ik naast mijn (co-)promotoren ook alle overige co-auteurs – Hilleke, Wiepke, Manon, Ada en alle (100+) ENIGMA collega's – die hebben bijgedragen aan mijn publicaties ontzettend bedanken. Natuurlijk ook alle stagiaires, bedankt voor jullie inzet. Dank voor jullie hulp bij de vreselijke taak van het cleanen van alle FreeSurfer data, vooral Elizabeth, jouw bijdrage hieraan was onmisbaar. Jurjen, Kristel en Bochao, dank voor jullie hulp tijdens mijn genetica avontuur. De vaste staf, Tjen, Mirjam, Janneke, ena, Yumas, Thijs, René M en Hugo, jullie waren essentieel om alles op rolletjes te laten lopen. Joyce en Zimbo, ontzettend bedankt voor alle databaseondersteuning en zo veel meer.

En dan de mensen die ervoor zorgden dat ik echt elke dag met plezier naar Utrecht ging: mijn getalenteerde en lieve kantoorgenoten. Op alfabetische volgorde: Bart, Elise, Herm, Jalmar, Jasper, Jessica, Judith, Manabu, Marc, Marinka, Martijn, Merel, Mireille, Pascal, Thalia, Xiao – bedankt voor alle gezelligheid, lunches, wandelingen, uitjes, koffie, pizza's, borrels, sinterklaasvieringen, kerstontbijt, discussies, kennis, hulp, kantoordecoratie en natuurlijk een immer volle snoeptrommel. Ik had het niet zonder jullie willen doen.

Nu ga ik zeker mensen vergeten, maar Annabel, Marieke, Maya, Lucija, Mascha, Sanne V, Sanne K, Elizabeth, Nikita, Caitlyn, Branko, Dienke, Chantal, Jan, Dorinde, Ania, Natascha, Yaron, Gijsje, het connectomics lab en natuurlijk de eerdergenoemde collega's, zo leuk dat ik allerlei (semi-)wetenschappelijke avonturen met jullie mocht beleven. Congressen, wintersport, Zandvoort, borrels, summer schools, etc. Hard werken, dat promoveren!

Lena, Jolanda en Martijn, mijn neuroclubje, mijn lotgenoten, (promotie) steun en toeverlaat, reis- en vierdaagsebuddy's. Samen gestudeerd en daarna praktisch allemaal tegelijkertijd begonnen met ons promotieonderzoek. Zo fijn dat ik dit met jullie kon delen. Lena, our many Sunday-funday drinks, spontaneous get-togethers, our Ireland trip, I am so glad we met that very first day of the masters. Who would have thought we would be doctors eight years later. Jolanda, het afgelopen jaar hebben we vele uren met frisse tegenzin samen gewerkt aan ons proefschrift – ook voor jou is de finishlijn nu echt in zicht en er liggen fantastische nieuwe avonturen voor jou in het verschiet. En Martijn, vriend en collega van begin tot eind, dank dat jij mijn paranimf wilt zijn.

Tot slot al mijn lieve vrienden buiten mijn wetenschappelijke bubbel en mijn (schoon)familie, dank voor jullie steun en vriendschap. Naast al het werken zorgden jullie voor veel plezier (en de noodzakelijke afleiding) in mijn leven.

Ingrid, mijn geweldige, talentvolle en lieve zus, het was zo fijn om al het promotie lief en leed met je te kunnen delen – hoe bijzonder dat we elkaars paranimf mogen zijn. Tim, ik had geen betere zwager kunnen wensen, een heerlijk geschiedenis-powerkoppel zijn jullie.

Papa & mama, mijn lieve en fantastische ouders, zonder jullie had ik hier zeker niet gestaan. Jullie waren er altijd voor me en hebben me altijd onvoorwaardelijk gesteund in al mijn keuzes. Ontzettend bedankt voor alles!

En lieve Bas, nu is ie echt klaar, beloofd. Dankjewel dat je deze promotieperiode met mij hebt meegeleefd en hebt overleefd, en dat je me hielp om uiteindelijk alles te kunnen relativeren. Het leven is gewoon leuker met jou!

LIST OF PUBLICATIONS

De Zwarte SMC, Brouwer RM, Agartz I, Alda M, Aleman A, Alpert KI, ... , Kahn RS, van Haren NEM (2019). The association between familial risk and brain abnormalities is disease specific: an ENIGMA–Relatives study of schizophrenia and bipolar disorder. Biol Psychiatry 86:545-556.

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FORTHCOMING

De Zwarte SMC, Brouwer RM, Agartz I, Alda M, Alonso-Lana S, Bearden CE, ... , Kahn RS, van Haren NEM. Intelligence, educational attainment and brain structure in those at familial high-risk for schizophrenia or bipolar disorder. *Submitted*

De Zwarte SMC, Brouwer RM, Kahn RS, van Haren NEM. The genetic relationship between schizophrenia, bipolar disorder and intracranial volume through polygenic scoring. *In preparation*

CURRICULUM VITAE

Sonja de Zwarte was born on November 28th 1986 in Hillegom, the Netherlands. In 2005, she graduated high school (Christelijke Scholengemeenschap Walcheren, Middelburg). She obtained a Bachelor of Science degree in Physics and Astronomy at the Utrecht University and a Research Master of Science degree in Neurosciences at the Vrije Universiteit Amsterdam. As part of her master's program, she went to Yale University (New Haven, CT, USA) for an 8 month internship, where she studied brain structure in adolescents at familial risk for bipolar disorder under the supervision of prof. dr. Hilary Blumberg. This internship resulted in her first peer-review first authorship but also was the introduction into psychiatric research. After graduating in 2014, she started her PhD project at the University Medical Center Utrecht (UMCU) in the Department of Psychiatry under the supervision of prof. dr. Neeltje van Haren, prof. dr. René Kahn and dr. Rachel Brouwer. She studied multiple family datasets consisting of patients with schizophrenia or bipolar disorder, their unaffected first-degree relatives and healthy volunteers to investigate the relationships between brain structure, cognition and risk genes. As part of the project, she co-chaired the ENIGMA—Relatives working group within the ENIGMA consortium, a large collaboration of researchers worldwide. She also had the opportunity to visit prof. dr. Elvira Bramon at the Division of Psychiatry, University College London (London, UK) for 2.5 months and the Human Genetics lab of prof. dr. Roel Ophoff at the University of California, Los Angeles (Los Angeles, CA, USA) for 5 months. As of April 2020, she will continue her academic career as a post-doctoral researcher at the UMCU in the lab of prof. dr. Hilleke Hulshoff Pol.