Supplementary Online Content


eFigure 1. Genetic and environmental liability for disease and cortical thickness. Genetic (rph-A) and environmental (rph-E) correlations between liability for schizophrenia (SZ) and bipolar disorder (BD) with cortical thickness are shown in colored maps. Higher genetic (Figure 1A) or environmental (Figure 1C) liability for disease associated with a thinner cortex is represented by negative correlations (up to blue/purple), and higher genetic (A) or environmental (C) liability for disease associated with a thicker cortex is represented by positive correlations (up to orange/red). Significance levels are shown below $P<.05$; in dark red areas significantly below $P<.00008912$ (Bonferroni-corrected for multiple comparisons) (Figures 1B and 1D). Data are shown after corrections for age and sex in all subjects and after correction for lithium use in bipolar disorder patients.

eFigure 2. Cortical thickness in schizophrenia and bipolar disorder patients and their co-twins. Cortical thickness in the patients (Figure 2A) and their co-twins (Figure 2C) as expressed in mean difference (in mm) from normal. A thinner cortex in patients or co-twins as compared to normal is shown in blue, a thicker cortex is shown in orange/red. Significance levels are shown below $P<0.05$; in dark red areas significantly below $P<.00008912$ (Bonferroni corrected for multiple comparisons) Figures 2B and 2D). Data are shown after corrections for age and sex in all subjects and after correction for lithium use in bipolar disorder patients.

eText. Methods

This supplementary material has been provided by the authors to give readers additional information about their work.

eReferences
Fig 1A & B

Genetic correlations (rph-A)

LEFT  |  SZ  |  RIGHT
LATERAL | MEDIAL | MEDIAL | LATERAL

BD
0.25 (thicker with higher genetic liability)
0
-0.25 (thinner with higher genetic liability)

Genetic correlations (rph-A)

LEFT  |  SZ  |  RIGHT
LATERAL | MEDIAL | MEDIAL | LATERAL

BD

p<0.00008912 (corrected for multiple comparison)
p<0.05 (uncorrected)
Fig 2A and 2B

Patient - Healthy controls

LEFT  |  MEDIAL  |  MEDIAL  |  LATERAL
------|----------|----------|---------
SZ     |          |          |         

BD

0.10 (thicker in patients)
0.05
-0.05
-0.10 (thinner in patients)

Patient - Healthy controls

LEFT  |  MEDIAL  |  MEDIAL  |  LATERAL
------|----------|----------|---------
SZ     |          |          |         

BD

p<0.00008912 (corrected for multiple comparison)
p<0.05 (uncorrected)
Fig 2 C & D

Co-twins - Healthy controls

LEFT

LATERAL

MEDIAL

SZ

MEDIAL

RIGHT

LATERAL

BD

0.10 (thicker in cotwins)
0.05
-0.05
-0.10 (thinner in cotwins)

Co-twins - Healthy controls

LEFT

LATERAL

MEDIAL

SZ

MEDIAL

RIGHT

LATERAL

BD

p<0.00008912 (corrected for multiple comparison)
p<0.05 (uncorrected)
Methods
Participants

Twin pairs had been included based on national newspaper advertisements and through referrals. The selection criteria for the schizophrenia twins in the current study were all twins that were willing to participate and had one 1.5T MRI scan made at the UMC Utrecht according to our scan acquisition protocol. There were more twin-pairs included in the current sample as compared to and this was because in the current study only one scan was required while the follow-up study two scans per twin-pair were required. Since some twins with a baseline 1.5T scan did not return for the follow-up scan, these baseline data were not used in that study. Indeed, the remaining 9 and 10 pairs are identical (baseline) data and selection criteria were the same. Additional pairs were included from reference 2. Three cotwins with schizophrenia were discarded in the current study and 1 MZ discordant twin pair was left out of the analyses because of a poor GM/WM separation. The selection criteria for the bipolar twin sample were the same as for the schizophrenia twin sample and overlapped almost completely with the sample as discussed in references 3 and 4.

In the schizophrenia twin cohort, extensive psychiatric assessments using the Comprehensive Assessment of Symptoms and History were carried out. Outcome was assessed using the Global Assessment of Functioning (GAF). The Camberwell Assessment of Need (CAN) was used to evaluate the need for care of the patient in daily life functioning. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate severity of symptoms. In the co-twins of the SZ patients and the matched healthy twin pairs, the Schedule for Affective Disorders and Schizophrenia–Lifetime version and the Structured Interview for DSM-IV Personality were completed. The PANSS mean (SD) total score was 61.1 (25.3), the negative symptoms score was 15.5 (9.0), and the positive symptoms score was 14.5 (6.3).

In the bipolar disorder twin cohort, clinical diagnosis of axis I psychiatric disorders was confirmed using the Structured Clinical Interview for DSM-IV (SCID) for axis II personality disorders using the Structured Interview For DSM-IV Personality and for both through available medical records; Their current mood state was assessed using the Young Mania Rating Scale and the Inventory for Depressive Symptomatology. At the time of the study, all patients were euthymic with a Young Mania Rating Scale (YMRS) score of 4 or less and an Inventory for Depressive Symptomatology (IDS) score of 12 or less, except for 4 patients who met criteria for a depressive episode IDS scores, 15, 20, 29, and 38.

The family histories of both the affected and control twins were obtained via the Family Interview Genetic Studies performed with both the proband and co-twin. Zygosity was determined by DNA fingerprinting. All twins were raised together, except for one control twin pair who was separated at age 12 years when both parents died.

At the time of scanning, 7 schizophrenia patients were taking atypical antipsychotic medication (including clozapine, olanzapine, and risperidone) exclusively, 13 typical antipsychotic medication exclusively, and 1 both atypical (clozapine) and typical antipsychotic medication, 2 lithium; in 4 reliable antipsychotic medication information was unavailable. In addition, 5 patients with schizophrenia were taking antidepressants, and 5 benzodiazepines. At the time of scanning of the cotwins of the schizophrenia patients, 3 were taking antidepressants.

At the time of scanning, 46 patients with bipolar disorder were taking lithium. In addition, 7 patients with bipolar disorder were taking typical antipsychotics, 1 atypical antipsychotics, 17 antidepressants, 12 benzodiazepines, 6 thyroid medication, 6 other medications. At the time of
scanning of the cotwins of the bipolar disorder patients, 1 was taking antidepressants, 3 thyroid medication and 3 other medications.

The twin pairs had no history of drug or alcohol dependency for the last 6 months and no severe medical illness, verified with a medical history inventory.

Healthy control pairs were matched to the SZ and BD pairs for zygosity, sex, age, parental education, and birth order. Healthy control pairs had no history of axis I psychiatric disorder or axis II personality disorder according to DSM-IV criteria (confirmed with a Structured Clinical Interview for DSM-IV and a Structured Interview for DSM-IV Personality interview, respectively) and no history of severe medical illness. Furthermore, they had no first-degree relative with a history of a major axis I psychiatric disorder (DSM-IV), such as schizophrenia, psychotic disorder, mood disorder, anxiety disorder, or substance-related disorder.

There were more male than female schizophrenia twin pairs and more female than male bipolar disorder twin pairs in the study. The effect of sex reached statistical significance (P<0.05). The schizophrenia twin pairs were somewhat older than the bipolar twin pairs and this effect was on the verge of significance. Throughout the study, analyses were corrected for age and sex. There were no significant differences between any of the other demographic variables (except for medication). Throughout the study, analyses were corrected for lithium use in bipolar disorder patients.

Cortical thickness processing
Cortical thickness extraction included fitting of a 3D surface to the white matter/gray matter interface, which created the inner surface of the cortex which was then expanded out to fit the gray matter/cerebrospinal fluid interface, thereby creating the outer cortical surface. Cortical thickness was estimated by taking the distance between the two surfaces such that each polygon vertex on the outer surface had a counterpart vertex on the inner surface. A vertex-by-vertex analysis was carried out to evaluate the differences in cortical thickness change at each point. Each subject's thickness measurements were smoothed across the surface using a 20 mm (FWHM) surface-based blurring kernel. This method of blurring improves the chances of detecting population differences, but also follows the curvature of the surface to preserve any anatomical boundaries within the cortex. The surfaces of the subjects were registered to an average surface created from 152 subjects (International Consortium for Brain Mapping).16

Model fitting
In the genetic model Rph would depend on both genetic and environmental correlations, and thus be a two degrees of freedom test. In theory, in these models it is possible that an Rph=0 (ie, patients and healthy controls have the same values) could be significant, because rg and re would have opposite directions of effect (one increasing, one decreasing), and thus cancel out in a subject. For cortical thickness, we chose to also test the Rph in a simplified model, that tested the significance (df=1) of the within twin/between trait correlations (equated over zygosity and twin 1/twin 2, but allowed to differ over disease cohorts). In this model all other correlations were estimated without constraint. This made sure that significant phenotypic correlations would always reflect observed differences in thickness between patients and healthy controls.
eReferences


