

Overlapping and Segregating Structural Brain Abnormalities in Twins With Schizophrenia or Bipolar Disorder

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Context: The nosologic dichotomy between schizophrenia and bipolar disorder (BD) as formulated by Kraepelin is currently being questioned, stimulated by the finding that schizophrenia and BD partly share a common genetic origin. Although both disorders are characterized by changes in brain structure, family studies suggest more segregating than overlapping neuroanatomical abnormalities in both disorders.

Objectives: To investigate whether patients with schizophrenia and patients with BD display overlapping abnormalities in brain volumes and cortical thickness and whether these are caused by shared genetic or environmental influences.

Design: Magnetic resonance imaging findings of monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for schizophrenia, twin pairs concordant and discordant for BD, and healthy twin pairs were compared using structural equation modeling.

Setting: The Netherlands Twin Register and University Medical Center Utrecht.

Participants: A total of 310 individuals from 158 (152 complete and 6 incomplete) twin pairs were included: 26 pairs discordant for schizophrenia (13 MZ and 13 DZ),

49 pairs with BD (9 MZ and 4 DZ concordant; 14 MZ and 22 DZ discordant), and 83 healthy twin pairs (44 MZ and 39 DZ).

Main Outcome Measures: Estimates of additive genetic and unique environmental associations between schizophrenia and BD with overlapping and nonoverlapping volumes and cortical thickness.

Results: Higher genetic liabilities for schizophrenia and BD were associated with smaller white matter volume, thinner right (and left) parahippocampus, thinner right orbitofrontal cortex, and thicker temporoparietal and left superior motor cortices; higher environmental liabilities were associated with thinner right medial occipital cortex. Genetic liability for schizophrenia was associated with thicker right parietal cortex; for BD, with larger intracranial volume.

Conclusions: Brain structures reflect overlapping and segregating genetic liabilities for schizophrenia and BD. The overlapping smaller white matter volume and common areas of thinner cortex suggest that both disorders share genetic (neurodevelopmental) roots.

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THE DISTINCTION BETWEEN schizophrenia and bipolar disorder (BD) as formulated by Kraepelin¹ is being challenged,² stimulated by the finding that schizophrenia and BD partly share a common genetic origin.³ The extent to which heritable traits are implicated in both disorders may aid in understanding what is genetically shared by both illnesses or, in contrast, what features segregate them. Schizophrenia and BD are characterized by structural brain abnormalities that are at least partially genetic in origin.⁴⁻⁶ However, whether (shared) genetic liabilities for schizophrenia and BD

are expressed in overlapping brain abnormalities is unknown.

In schizophrenia, brain volumes have consistently been found to be decreased, particularly in the frontal and temporal lobes, including the hippocampus, thalamus, and striatum, with increases in the lateral and third ventricles (see meta-analyses⁷⁻⁹). In BD, a meta-analysis¹⁰ of 98 studies revealed lateral ventricle enlargement with gray matter volume increases in patients using lithium, expanding on an earlier meta-analysis¹¹ in which lateral ventricle enlargement was reported. Three meta-analyses^{10,12,13} compared brain volumes in schizophrenia and BD. Lat-

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Table 1. Overview of MRI Studies Comparing Patients With Schizophrenia (Sz) and Bipolar Disorder (BD) and Their Unaffected Family Members

| Source | Sz, No. | | BD, No. | | Controls, No. | Brain MRI | Sz Findings | | BD Findings | |
|-------------------------------------|-----------------------------|--|---|--|---------------|---|---|----------------|--|----------------|
| | Patients | Unaffected Family | Patients | Unaffected Family | | | Patients | Family Members | Patients | Family Members |
| McDonald et al, 2004 ²³ | 25 | 36 ^a | 37 | 50 ^a | NC | VBM of gray and white matter | Shared in Sz and BD white matter volume reduction in the left frontal and temporoparietal regions | | Shared bilateral frontostriathalamic and left lateral temporal volume deficits | |
| McIntosh et al, 2004 ²⁴ | 26 | 24 ^{a,b} | 26 From BD family; 19 from mixed family | 22 From BD family; 26 from mixed family ^{a,b} | 49 | VBM of gray matter | Shared in Sz and BD anterior thalamic gray matter reduction | | Shared right anterior cingulate gyrus and ventral striatum volume deficits | |
| Connor et al, 2004 ^{25c} | 58 Familial; 50 nonfamilial | 91 Familial ^a ; 61 nonfamilial ^a | 39 Familial | 54 Familial ^a | 219 | Hippocampal shape analysis | Increase in prevalence of moderate to severe hippocampal shape anomalies | | None | |
| McIntosh et al, 2005 ^{26d} | 26 | 24 ^{a,b} | 26 From BD family; 19 from mixed family | 22 From BD family; 26 from mixed family ^{a,b} | NC | VBM of white matter | White matter reductions in frontal subgyral and anterior limb internal capsule | | White matter reductions in anterior limb internal capsule | |
| McIntosh et al, 2006 ^{27d} | 26 | 24 ^{a,b} | 26 From BD family; 19 from mixed family | 22 From BD family; 26 from mixed family ^{a,b} | NC | VBM of gray and white matter | Shared prefrontal gray (and white) matter loss in DLPFC and VLPFC | | None | |
| McDonald et al, 2006 ^{28c} | 42 | 57 ^a | 38 | 52 ^a | 54 | Cerebrum, lateral and third ventricles, hippocampus | Shared increased lateral and third ventricle volumes | | None | |
| Mondelli et al, 2008 ^{29c} | 26 | 22 Familial ^a ; 22 nonfamilial ^a | 29 | 38 Familial ^a | 46 | Pituitary volume | Reduced hippocampal volume | | None | |
| | | | | | | | Increased pituitary volume in relatives; in Sz, only in those taking prolactin-elevating antipsychotics | | None | |

Abbreviations: DLPFC, dorsolateral prefrontal cortex; NC, no controls were included in the study; MRI, magnetic resonance imaging; VBM, voxel-based morphometry; VLPFC, ventrolateral prefrontal cortex.

^aFirst-degree relatives.

^bSecond-degree relatives.

^cIndividuals are considerably overlapping with those in the study by McDonald et al.²³

^dIndividuals are considerably overlapping with those in the study by McIntosh et al.²⁴

eral^{10,12} and third¹⁰ ventricle volumes were enlarged in both disorders, although more so in schizophrenia than in BD. Moreover, regions of gray matter reduction were less extensive in BD than in schizophrenia^{12,13} but were substantially overlapping in the paralimbic regions, including the anterior cingulate cortex and insula.¹³ In contrast, cortical and limbic gray matter abnormalities¹³ were more pronounced in schizophrenia. Specifically, hippocampus volume was smaller in schizophrenia compared with BD.¹⁰ A distinct region of pregenual cingulate cortex (anterior Brodmann area 4) revealed gray matter reductions in only BD.¹³ Indeed, studies directly comparing brain structures between patients with schizophrenia and those with BD revealed shared loss in gray matter¹⁴⁻¹⁶ (although see McDonald et al¹⁷) and white matter.¹⁷⁻¹⁹ Thus, overall, the ventricular enlargement (and possibly white matter loss) is shared in patients with schizophrenia and patients with BD. However, there is no consensus about whether, and to what extent, gray matter loss in schizophrenia is mirrored in BD and what is the effect of medication. Studies in family members of patients who share the risk of the disease but not the con-

foundings factors, such as medication use, may help elucidate whether abnormalities in brain structures are shared by both illnesses.

Some of the structural brain abnormalities in schizophrenia and BD have been linked to the genetic liabilities to develop these disorders.^{4-6,20-22} Brain changes found in family members of patients with schizophrenia include decreases in whole brain and hippocampus volumes (see the meta-analysis by Boos et al²⁰) and progressive loss of gray matter.⁴ In family members of patients with BD, decreases in gray and white matter and increases in caudate nucleus volumes have been reported.^{5,6,21,22} These findings suggest that patients with schizophrenia and those with BD show overlapping brain changes, with some of these also present in their (unaffected) family members. However, whether (shared) genetic liabilities in schizophrenia and BD are expressed in overlapping brain abnormalities requires direct comparison between their family members.

A few studies²³⁻²⁹ have directly compared patients with schizophrenia, patients with BD, and their first- and second-degree relatives (**Table 1**). Increased familial risk of schizophrenia and BD was reported for white matter volume re-

ductions in the left frontal and temporoparietal regions²³ and has been suggested as a marker for psychosis in general.²⁴ Increased familial risk of schizophrenia but not of BD was associated with increased lateral and third ventricle volumes,²⁸ increased pituitary volume,²⁹ loss of gray (and white) matter in the dorsolateral and ventrolateral prefrontal cortices²⁷ and thalamus,²⁴ and distributed gray matter volume deficits in the frontal, temporal, and thalamic brain areas.²³ Increased familial risk of BD but not of schizophrenia was associated with gray matter loss in the right anterior cingulate gyrus and ventral striatum.²³ Patients with schizophrenia and patients with BD but not their family members shared white matter reductions in the anterior limb of the internal capsule.²⁶ Finally, an abnormal shape of the hippocampus was found in patients with schizophrenia but not in their family members and in patients with BD or their family members.²⁵ It was suggested that the familial risk of both disorders was due, at least in part, to increased genetic liabilities for these diseases based on comparisons of first- with second-degree family members and on the family history.^{24,28} Thus, whereas some family studies imply that the increased genetic risk of schizophrenia and BD is reflected in overlapping brain structure changes,^{23,24} most of the studies suggest that the neuroanatomical abnormalities segregate the 2 disorders.

However, there are several reasons why the conclusion that neuroanatomical abnormalities segregate schizophrenia and BD may be premature. First, the 2 cohorts on which the 7 family studies²³⁻²⁹ are based include only first- and second-degree singleton unaffected family members; therefore, their genetic risk may have been too low to detect some of the brain abnormalities. Moreover, 3 of these studies did not include a control group; therefore, the unaffected family members could not be compared with controls. Also, some studies show considerable participant overlap, decreasing the overall power of the findings. Finally, brain measures included volumes (1 study), gray and white matter density based on voxel-based morphometry (4 studies), hippocampal shape (1 study), and pituitary volume (1 study), but none of the studies focused on cortical changes. Therefore, we set out to study twins concordant and discordant for schizophrenia or BD to examine whether the genetic risk of these disorders is reflected in brain volumes and cortical thickness.

METHODS

DESIGN

In the twin model, monozygotic (MZ) twins, who share (nearly) all their DNA sequence, can be compared with dizygotic (DZ) twins, who, similar to singleton siblings, share on average 50% of their segregating genes.³⁰ The twin model is a powerful approach for determining the contributions of genetic influences on complex phenotypes such as brain volumes and on the common origin of brain volumes with disease liability.³¹

PARTICIPANTS

The following participants were recruited from the Netherlands Twin Register and University Medical Center Utrecht: (1) twin pairs discordant for schizophrenia and their matched con-

trol twin pairs (schizophrenia cohort)^{4,32} and (2) twin pairs discordant and concordant for BD and their matched control twin pairs (BD cohort).^{5,6}

A total of 310 individuals from 158 (152 complete and 6 incomplete) twin pairs were included, consisting of 13 MZ (1 incomplete, with only the co-twin) and 13 DZ twin pairs discordant for schizophrenia and 23 MZ and 26 DZ twin pairs (3 incomplete, with the proband from whom the co-twins with schizophrenia were excluded from the analysis) affected with BD (9 MZ concordant, 14 MZ discordant, 4 DZ concordant, and 22 DZ discordant), and were compared with 44 MZ (1 incomplete) and 39 DZ (1 incomplete) control twin pairs (**Table 2**) (eText; <http://www.archgenpsychiatry.com>).

All the twins participated after providing written informed consent. The study was approved by the medical ethics committee for research in humans of the University Medical Center Utrecht and was performed according to the directives of the Declaration of Helsinki (amendment of Edinburgh, 2000).

BRAIN IMAGING

Magnetic resonance brain imaging was performed using a Philips NT scanner (Philips Medical Systems, Best, the Netherlands) operating at 1.5 T in all the participants as applied previously.^{4,6,33} T1-weighted, 3-dimensional, fast-field echo scans with 160 to 180 contiguous coronal slices (individually adjusted so that the head would fit in the image) (echo time=4.6 milliseconds, repetition time=30 milliseconds, flip angle=30°, 1 × 1 × 1.2 mm³) and T2-weighted, dual echo-turbo-spin-echo scans with 120 contiguous coronal slices (echo time 1 = 14 milliseconds, echo time 2 = 80 milliseconds, repetition time = 6350 milliseconds, flip angle = 90°, 1 × 1 × 1.6 mm³) of the whole head were used for quantitative measurements. Head size or, more precisely, head length did not differ between the groups.

Processing was performed using the neuroimaging computer network of the Department of Psychiatry, University Medical Center Utrecht. All the images were coded to ensure blinding for participant identification and diagnoses, were manually put into a Talairach frame (no scaling) for segmentation purposes, and were corrected for inhomogeneities in the magnetic field.³⁴

Segments of gray and white matter of the cerebrum (total brain excluding cerebellum and stem) were based on histogram analyses.^{35,36} All the images were checked after measurement and were corrected manually where necessary. There was no difference among groups in the extent to which scans needed manual correction. The interrater reliabilities of (the editing of) volume measurements were determined on a set of 10 images that were checked and edited by different raters; the intraclass correlation coefficients of these measurements were 0.95 and higher.

Cortical thickness was based on a custom implementation of the CLASP (Constrained Laplacian Anatomic Segmentation using Proximity) algorithm in CIVET, an image-processing environment designed at the McConnell Brain Imaging Centre,³⁷⁻³⁹ as applied previously.³³ The original CLASP algorithm was used, but gray matter, white matter, and cerebrospinal fluid segments from our own segmentation algorithm, as described previously herein, were used as inputs instead of taking these segments from the CIVET pipeline. Cortical thickness extraction was conducted by hemisphere; each surface consisted of 81 920 polygons and 40 962 vertices. The surfaces are modeled as nets of polygons (triangles), with vertices being the points where the polygons meet, that is, the angular points of the nets (eText).

MODEL FITTING

Brain volume and cortical thickness data were prepared for model fitting using regression analyses to control for the effects of sex,

Table 2. Demographic Characteristics of 310 Patients With Schizophrenia (Sz), Patients With Bipolar Disorder (BD), Their Co-Twins, and Control Twin Pairs

| Characteristic | Patients | | Co-twins | | Controls (n=164) |
|---------------------------------------|-------------|------------------------|-------------|-------------|------------------|
| | Sz (n=25) | BD ^a (n=62) | Sz (n=26) | BD (n=33) | |
| Zygosity, MZ/DZ, No. | 12/13 | 32/30 | 13/13 | 13/20 | 87/77 |
| Sex, M/F, No. | 14/11 | 18/44 | 14/12 | 11/22 | 72/92 |
| Age, mean (SD), y | 36.2 (11.0) | 40.1 (10.0) | 37.4 (11.4) | 41.8 (10.4) | 37.6 (9.5) |
| Handedness, R/L, No. | 22/3 | 48/14 | 23/3 | 26/7 | 134/30 |
| Education, mean (SD), y | | | | | |
| Patients | 11.4 (2.9) | 12.8 (2.5) | 12.3 (3.1) | 12.2 (2.9) | 13.2 (2.8) |
| Parents | 12.0 (2.4) | 11.2 (3.6) | 11.8 (2.7) | 10.6 (3.7) | 11.4 (3.3) |
| Age at illness onset, mean (SD), y | 21.5 (5.7) | 28.7 (9.7) | NC | NC | NC |
| Duration of illness, mean (SD), y | 14.9 (9.5) | 11.3 (8.2) | NC | NC | NC |
| Brain volumes, mean (SD) ^b | | | | | |
| Intracranial | 1416 (150) | 1418 (174) | 1431 (148) | 1434 (172) | 1428 (128) |
| Total brain | 1221 (151) | 1215 (143) | 1237 (122) | 1229 (139) | 1244 (115) |
| Cerebral gray matter | 615 (80) | 607 (69) | 632 (70) | 610 (72) | 621 (66) |
| Cerebral white matter | 454 (71) | 456 (77) | 451 (55) | 468 (79) | 469 (57) |
| Lateral ventricle ^a | 17.3 (6.1) | 16.9 (9.7) | 14.8 (8.8) | 16.7 (9.0) | 14.7 (7.6) |
| Third ventricle ^a | 0.94 (0.49) | 0.89 (0.54) | 0.85 (0.36) | 0.85 (0.40) | 0.79 (0.45) |
| Mean cortical thickness | 2.95 (0.13) | 2.95 (0.09) | 3.01 (0.13) | 2.96 (0.15) | 2.95 (0.11) |

Abbreviations: DZ, dizygotic; MZ, monozygotic; NC, no controls were included in the study; R/L, right/left or ambidexterous.

^aOf these patients, 44 had BD I and 18 had BD II; 31 with psychosis and 31 without psychosis.

^bIntracranial volume was not available for 3 participants; gray and white matter volumes were not available for 1 participant. Participants were aged 18 to 62 years. Brain volumes represent raw values.

age, and lithium use (and intracranial volume for brain volumes only).^{5,6,40,41} For correction of lithium use, the differences in mean volume/cortical thickness between patients who did not take lithium (n=16 with BD) and patients who took lithium (n=46) were calculated. This difference was subtracted from the values of the lithium-using patients, resulting in an estimate of their volumes had no lithium been used. The standardized residuals of the regressions were then used to calculate a 5-category ordinal scale. This scale allowed for a multigroup with a 2-level (cohort, ie, schizophrenia and BD; and zygosity, ie, MZ and DZ), bivariate (disease status and brain volume/cortical thickness), ordinal genetic twin analysis using the statistical package Mx⁴² as applied previously.^{4,5}

For genetic model fitting, the dichotomous variable “disease status” was assumed to represent an underlying continuous liability with a mean (SD) of 0 (1). A patient will have a high value on the liability scale, thereby crossing a certain threshold (patient status=1). All other individuals will have lower liability scores and will not cross the threshold (discordant co-twin of patient or control twin pairs, patient status=0). The critical threshold and heritability for the underlying liability for BD or schizophrenia was not based on this sample because we included approximately equal numbers of concordant, discordant, and healthy twin pairs. We fixed the prevalence and heritability (the relative contribution of genetic variance to total variance) of the disorder to the population values; prevalence was set to 1%,⁴³⁻⁴⁵ and heritability was set to 81% for schizophrenia^{30,46} and to 85% for BD.⁴⁷ In addition, influences of shared environment on schizophrenia liability were set to 11%.⁴⁶

Genetic model fitting consisted of a bivariate ordinal genetic Cholesky decomposition with additive genetic (A) and unique environmental (E) influences (Figure 1 and eText). Common environmental influences (C) were discarded from all the analyses (although influences of shared environment on schizophrenia liability set to 11% were taken into account) since after initial analyses, testing for influences on volume/thickness shared within twin pairs regardless of zygosity had not shown any significant effects. Calculation of phenotypic associations (R_{ph}) was

based on within-twin/within-trait correlations. Calculation of heritability (h²) and disentangling genetic (r_g) and environmental (r_e) correlations between volume/thickness and disease liability (for each disease separately) was based on the polychoric correlations within MZ and DZ groups, that is, MZ and DZ cross-twin/within-trait and cross-twin/cross-trait correlations.^{4,5,48} Calculation of phenotypic associations (r_{ph}) was based on within-twin/between-trait correlations. The following tests were performed on the phenotypic correlations: is r_{ph}(schizophrenia) equal to r_{ph}(BD); if so, is r_{ph}(combined) equal to 0; if not, is r_{ph}(schizophrenia) or r_{ph}(BD) equal to 0? These criteria were then used as a mask for the genetic analyses.

The significance of additive genetic (A) and unique environmental (E) effects on volume/thickness and on their association with disease liability was tested by fitting different nested submodels to the data and comparing their goodness of fit via likelihood ratio tests (Figure 1 and eText). A likelihood ratio test statistic (twice the difference between the respective log-likelihoods of the models) follows a χ^2 distribution. Critical values at $\alpha = .05$ are 3.84 for r_{ph}, r_g, and r_e and 2.71 for h². For cortical thickness, the uncorrected $\alpha = .05$ was corrected for multiple comparisons using Bonferroni correction. This was done by dividing the alpha value by the number of independent statistical tests performed over the cortex, that is, dividing the number of vertices by the number that are effectively dependent due to the applied blurring of 20 mm in 2 dimensions. This resulted in the following critical level for significance: the average total cerebral surface area (as determined from the control subjects of the schizophrenia sample) was divided by the blurring area: 1764 cm²/3.1416 cm²=561. So, the corrected α value is .05/561 = .00008912, and the corresponding critical χ^2 value is 15.35.

All the analyses were rerun with data uncorrected for lithium use. Because the results of both sets of analyses led to the same conclusions, we chose to report on the lithium-corrected data. Setting the prevalences and heritabilities for schizophrenia and BD on the values reported in the study by Lichtenstein et al³ or equating them for schizophrenia and BD did not alter the findings.

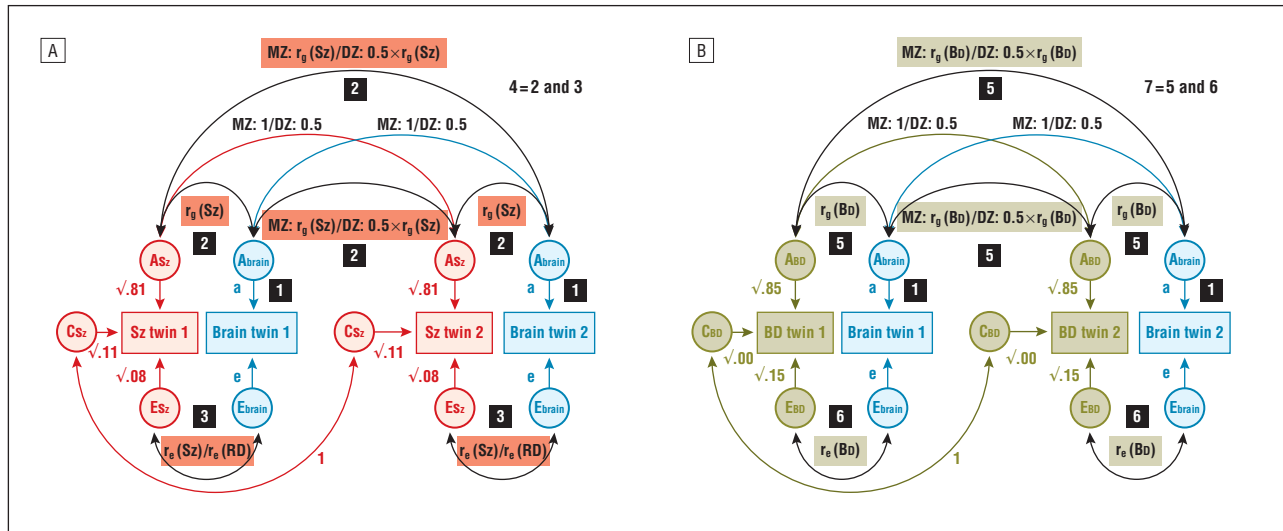


Figure 1. Path diagram of model fitting. Four data groups were defined: 2 (monozygotic [MZ] and dizygotic [DZ]) for the schizophrenia (Sz) cohort (A) and 2 (MZ and DZ) for the bipolar disorder (BD) cohort (B). The 4 rectangles represent dependent variables, linked to the observed ordinal variables through a probit link function: disease liability (Sz [red] or BD [green]) and brain (blue, ie, volume or vertex) for twins 1 and 2. Circles represent latent factors that influence these variables: additive genetic (A_{Sz} or A_{BD}), common environmental (C_{Sz} or C_{BD}), and unique environmental (E_{Sz} or E_{BD}) factors influence disease liabilities for Sz (red) or BD (green), and additive genetic (A_{brain}) and unique environmental (E_{brain}) factors influence the brain (blue). Factor loadings were fixed to population values for disease liability ($\sqrt{.81}$, $\sqrt{.11}$, and $\sqrt{.08}$ for A_{Sz} , C_{Sz} , and E_{Sz} ; $\sqrt{.85}$, $\sqrt{.00}$, and $\sqrt{.15}$ for A_{BD} , C_{BD} , and E_{BD}). Factor loadings for brain variables were estimated in the model (a and e for influences of A and E, respectively). Following the assumptions of the twin design, correlations between the additive genetic factors within a trait are 1 for MZ and 0.5 for DZ twin pairs, and correlations between common environmental factors within a trait are 1 for both types of twin pairs. In the base model, disease liability and brain index within a twin were correlated through a genetic path (via the “genetic” correlations r_{gSz}/r_{gBD}) and an environmental path (via the “environmental” correlations r_{eSz}/r_{eBD}). The cross-trait/cross-twin correlations (eg, BD twin 1 with brain twin 2) are a function of the genetic correlations (r_{gSz}/r_{gBD} for MZ twins and $0.5 \times r_{gSz}/0.5 \times r_{gBD}$ for DZ twins) but not of the environmental correlations. Five parameters (a, r_{gSz} , r_{gBD} , r_{eSz} , and r_{eBD}) are estimated. Note that e is not estimated because $a^2 + e^2$ is constrained to be 1 (the distribution of an underlying liability of an ordinal variable is not known and is, therefore, set to a standard normal distribution). From these estimated parameters, a variety of other parameters are derived:

1. Heritability of the brain variable: $h^2_{brain} = h^2_{brain}/(a^2_{brain} + e^2_{brain})$.
2. The phenotypic correlation due to additive genetic factors $r_{ph}(genetic)$. This parameter reflects the correlation between disease liability and brain volume or cortical thickness that would arise if influences of environmental factors could be kept constant and is a function of heritability of both traits and of the genetic correlation between them: $r_{ph}(genetic,Sz) = \sqrt{.81} \times r_{gSz} \times \sqrt{h^2_{brain}}$ for schizophrenia and $r_{ph}(genetic,BD) = \sqrt{.85} \times r_{gBD} \times \sqrt{h^2_{brain}}$ for BD.
3. Likewise, we calculated the phenotypic correlation due to environmental factors $r_{ph}(environmental)$ for both disease liabilities ($r_{ph}(environmental,Sz) = \sqrt{.08} \times r_{eSz} \times \sqrt{e^2_{brain}}$ and $r_{ph}(environmental,BD) = \sqrt{.15} \times r_{eBD} \times \sqrt{e^2_{brain}}$).
4. The sum of $r_{ph}(genetic)$ and $r_{ph}(environmental)$ is referred to as the total phenotypic correlation (calculated separately for Sz and BD in the base model). Note that if either $r_{ph}(genetic)$ or $r_{ph}(environmental)$ is negative and the other is positive, the resulting r_{ph} could become zero. This would reflect a situation in which patients do not show deviant brain volume or cortical thickness but co-twins do.

In the base model, heritability of volume/thickness was constrained to be the same for both cohorts, but the correlation between volume/thickness and disease status was allowed to differ. Thus, in the base model, we estimated the heritability of volume/thickness and genetic and environmental correlations between volume/thickness and Sz liability and between volume/thickness and BD liability. A variety of tests were performed to assess overlapping and segregating influences of genes and environmental factors contributing to Sz and BD as reflected in brain structure. It was tested whether r_g and r_e could be equated across diseases (ie, whether it was the same across disease cohorts, which implies that deviant volume/cortical thickness in patients with Sz is the same as in patients with BD in that volume/vertex). Depending on the outcome of this test, the models were further reduced. If equating r_g and r_e across diseases did not significantly deteriorate the model, this reduced submodel now served as a new baseline for testing the third submodel. In the third submodel, it was tested whether the combined r_g (2, $df=1$), r_e (3, $df=1$), or r_{ph} (2 and 3, $df=2$) could be set to zero. If, however, equating r_g and r_e across diseases resulted in significant loss of goodness of fit, then in a fourth submodel these 3 tests were performed separately for each disease while leaving the parameters of the other disease cohort intact. The likelihoods of these models were tested against the likelihood of the base model.

RESULTS

Irrespective of group status (schizophrenia, BD, or control), the heritability for brain structures varied from 44% (gray matter) to 90% (cerebellum) (**Table 3**) and for cortical thickness varied from 12% to 74%.

GLOBAL BRAIN VOLUMES AND LIABILITY FOR DISEASE

Abnormalities in brain volumes associated with schizophrenia and BD were not significantly different in type (genetic or environmental) or direction and size of effect except for intracranial volume (Tables 2 and 3 and **Figure 2**). The larger intracranial volume was associated with genetic liability for BD (phenotypic correlation=0.15, explained by genes involved in BD) but not

for schizophrenia. All brain volumes were subsequently corrected for intracranial volume. The smaller white matter volume was associated with genetic factors in both illnesses (phenotypic correlation=-0.23, explained for 96% by genes involved in schizophrenia and BD with white matter volume). The smaller gray matter volume was due to environmental factors for 72% in both illnesses, but this finding did not reach significance according to our decision criterion (Table 3).

CORTICAL THICKNESS AND LIABILITY FOR DISEASE

Phenotypic correlations that overlapped between schizophrenia and BD liabilities were found in shared thinner left and right parahippocampi and right orbitofrontal and right medial occipital (calcarine) cortices (**Table 4**,

Table 3. Brain Volumes and Disease Liabilities for Schizophrenia (Sz) and Bipolar Disorder (BD)^a

| Volume | h ² BV, % | Sz or BD | Separate | | | | | Combined | | | | | |
|--------------------------------|----------------------|----------|--------------------|--------------------|--------------------|--------------------------|--------------------------------|------------------------|--------------------|--------------------|--------------------|--------------------------|--------------------------------|
| | | | r _{ph} | r _g | r _e | r _{ph(Genetic)} | r _{ph(Environmental)} | χ ² Sz ≠ BD | r _{ph} | r _g | r _e | r _{ph(Genetic)} | r _{ph(Environmental)} |
| Intracranial | 91 ^b | Sz | -0.08 | -0.08 | -0.22 | -0.07 | -0.02 | 6.272 ^c | 0.08 | 0.09 | 0.03 | 0.08 | 0 |
| | | BD | 0.15 ^c | 0.16 ^c | 0.20 | 0.14 ^c | .02 | | | | | | |
| Total brain | 65 ^c | Sz | -0.20 ^c | -0.15 | -0.52 | -0.11 | -0.09 | 1.252 | -0.26 ^c | -0.26 ^c | -0.41 ^c | -0.19 ^c | -0.07 ^c |
| | | BD | -0.29 ^c | -0.31 ^c | -0.37 | -0.22 ^b | -0.06 | | | | | | |
| Gray matter | 44 ^c | Sz | -0.06 | 0.14 | -0.68 ^c | 0.08 | -0.15 ^c | 3.645 | -0.18 ^c | -0.08 | -0.61 ^c | -0.05 | -0.13 ^c |
| | | BD | -0.22 ^c | -0.17 | -0.56 ^c | -0.10 | -0.12 ^c | | | | | | |
| White matter | 78 ^c | Sz | -0.24 ^c | -0.31 ^c | 0.09 | -0.25 ^c | 0.01 | 0.556 | -0.23 ^c | -0.27 ^c | -0.07 | -0.22 ^c | -0.01 |
| | | BD | -0.22 ^c | -0.25 ^c | -0.16 | -0.20 ^c | -0.01 | | | | | | |
| Lateral ventricle ^d | 69 ^c | Sz | 0.21 | 0.13 | 0.74 ^c | 0.10 | 0.12 ^c | 1.562 | 0.23 ^c | 0.20 ^c | 0.51 ^c | 0.15 ^c | 0.08 ^c |
| | | BD | 0.24 | 0.24 ^c | 0.35 | 0.18 ^c | 0.06 | | | | | | |
| Third ventricle ^d | 61 ^c | Sz | 0.17 | 0.14 | 0.42 | 0.10 | 0.07 | 1.121 | 0.23 ^c | 0.19 ^c | 0.56 ^c | 0.13 ^c | 0.10 ^c |
| | | BD | 0.26 ^c | 0.20 ^c | 0.64 ^c | 0.14 ^c | 0.11 ^c | | | | | | |

^aHeritabilities of brain volumes (h² BV); phenotypic (r_{ph}), genetic (r_g), and environmental (r_e) correlations between disease liabilities and brain volumes for both diseases separately and combined are presented, as are phenotypic correlations when only genetic (r_{ph(Genetic)}) or environmental (r_{ph(Environmental)}) sources are considered. The phenotypic correlation provides information on whether brain volume is associated with the disorder(s). The correlation can be decomposed into a part that is attributable to genes, r_{ph(Genetic)}, and a part that is attributable to nongenetic influences, r_{ph(Environmental)}. These 2 entities indicate the correlations between 2 traits that would arise if the other source of variance could be kept constant (r_{ph(Genetic)} is a function of the heritabilities of both traits and the genetic correlation between them, r_g: r_{ph(Genetic)} = √ h² brain × √ h² disease × r_g, and likewise for r_{ph(Environmental)}). Based on structural equation modeling with correction for intracranial volume, age, sex, and lithium use (patients with BD only). For a significant association between a volume with overlapping genetic liabilities between both disorders, the decision criterion was: R_{ph_combined} > 3.84, r_{ph(Sz)} > 3.84, and r_{ph(BD)} > 3.84; r_{g(combined)} > 3.84, r_{g(Sz)} > 3.84, and r_{g(BD)} > 3.84; with segregating genetic liabilities: r_{ph(Sz) ≠ BD} > 3.84, r_{ph(separate genetic)} > 3.84, r_{ph(Sz)} or r_{ph(BD)} > 3.84, and r_{g(Sz)} or r_{g(BD)} > 3.84. The same holds for environmental liabilities (e instead of g).

^bSignificant effect; critical χ² r_{g(Sz) ≠ r_{g(BD)}: 3.845, df=1.}

^cCritical χ² Sz ≠ BD > 5.99, df=2. This indicates whether the phenotypic correlations between brain volume with Sz liability is the same as with BD.

^dLog transformed.

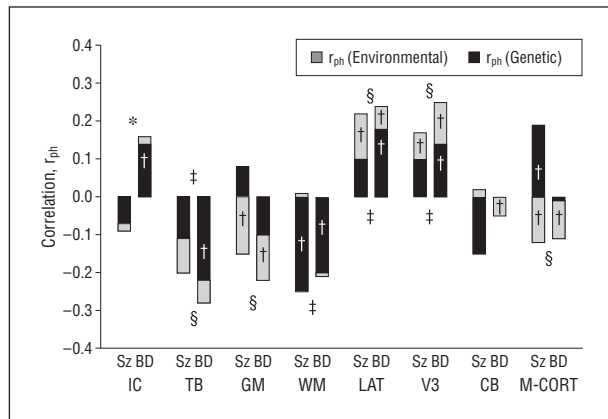


Figure 2. Brain volume and disease liability. Genetic and environmental contributions to the phenotypic correlations (r_{ph}) between disease liability and brain volume are plotted for schizophrenia (Sz) and bipolar disorder (BD). Columns indicate genetic and environmental contributions to the phenotypic correlations (r_{ph}). The r_{ph} between disease liability and brain volume is the sum of the genetic and environmental correlations. Data are shown after corrections for age, sex, and intracranial (IC) volume in all the participants and for lithium use in patients with BD. CB indicates cerebellum; GM, cerebral gray matter; LAT, lateral ventricle; M-CORT, mean cortical thickness; TB total brain; V3, third ventricle; and WM, cerebral white matter. *Significantly different correlations between IC volume and the 2 disease liabilities at α = .05. †Significant contribution to the correlation within the disease group. ‡Significant contribution of genetic influences to the correlation between liability for Sz and BD and brain volume. §Significant contribution of environmental influences to the correlation between liability for Sz and BD and brain volume.

Figure 3, eFigure 1, and eFigure 2) and in shared thicker left temporal-parietal supramarginal (Wernicke area), left precentral/paracentral lobule, left fusiform, and right post-central/rolandic operculum cortices. These effects were

largely influenced by genetic factors implicated for both diseases except for the occipital cortex, which was largely influenced by environmental factors implicated for both diseases. Phenotypic correlations that segregated between schizophrenia and BD liabilities were found in the right superior-parietal and right postcentral cortices, where a thicker cortex was associated with schizophrenia liability due to genetic influences but not with BD liability.

COMMENT

In this twin study of 310 individuals, we found that overlapping genetic liabilities for schizophrenia and BD are reflected in shared abnormalities in cortical gray and white matter. Specifically, the elevated genetic risk of schizophrenia and BD is most prominently reflected in a global decrease in white matter volume and in specific thinner and thicker cortex locally, such as with thinner parahippocampus and orbitofrontal cortex and thicker temporo-parietal (including Wernicke area) and superior motor cortices. Increased liabilities for these disorders separately could be best differentiated by changes in intracranial volume and right parietal cortical thickness. Specifically, increased genetic liability for BD but not for schizophrenia was associated with enlarged intracranial volume, whereas increased genetic liability for schizophrenia but not for BD was associated with a thicker right parietal cortex. Environmental influences on the risk of BD and schizophrenia were found to be associated with a thinner right medial occipital cortex. Taken together, these findings indicate that increased (and possibly shared) genetic risk of schizophrenia and BD is reflected in loss

Table 4. Cortical Thickness and Disease Liabilities for Schizophrenia (Sz) and Bipolar Disorder (BD)^a

| Area | h ² _{CT} , % | Separate | | | | χ ² _{Sz ≠ BD^b} | Combined | | |
|--------------------------------------|----------------------------------|----------|--------------------|--------------------|--------------------|---|--------------------|--------------------|--------------------|
| | | Sz or BD | r _{ph} | r _g | r _e | | r _{ph} | r _g | r _e |
| Same effects in both disorders | | | | | | | | | |
| Supramarginal left | 32 ^c | Sz | 0.19 ^d | 0.61 ^d | -0.52 ^d | 6.657 | 0.22 ^c | 0.48 ^b | -0.13 |
| | | BD | 0.25 ^c | 0.35 ^d | 0.28 | | | | |
| Precentral/paracentral lobule left | 38 ^c | Sz | 0.22 ^d | 0.39 ^d | 0 | 2.990 | 0.21 ^c | 0.27 ^d | 0.27 |
| | | BD | 0.22 ^c | 0.18 | 0.53 ^d | | | | |
| Fusiform left | 30 ^c | Sz | 0.25 ^d | 0.78 ^c | -0.56 ^d | 1.945 | 0.24 ^c | 0.65 ^c | -0.35 ^d |
| | | BD | 0.24 ^c | 0.57 ^c | -0.17 | | | | |
| Parahippocampus left | 14 | Sz | -0.26 ^d | -0.37 | -0.52 ^d | 1.075 | -0.23 ^c | -0.38 ^d | -0.38 ^d |
| | | BD | -0.21 ^c | -0.43 ^d | -0.24 | | | | |
| Parahippocampus right | 32 ^c | Sz | -0.30 ^c | -0.67 ^c | 0.15 | 2.838 | -0.29 ^c | -0.52 ^c | -0.11 |
| | | BD | -0.30 ^c | -0.42 ^c | -0.36 | | | | |
| Postcentral/rolandic operculum right | 27 ^c | Sz | 0.17 ^d | 0.48 ^d | -0.23 | 3.626 | 0.25 ^c | 0.54 ^c | -0.01 |
| | | BD | 0.30 ^c | 0.54 ^c | 0.21 | | | | |
| Orbitofrontal superior right | 12 | Sz | -0.33 ^c | -0.70 ^d | -0.42 ^d | 5.496 | -0.20 ^c | -0.43 ^d | -0.25 |
| | | BD | -0.14 ^d | -0.39 ^d | -0.05 | | | | |
| Calcarine right | 57 ^c | Sz | -0.10 ^d | 0.13 | -0.95 ^d | 3.604 | -0.21 ^c | -0.05 | -0.80 ^c |
| | | BD | -0.27 ^c | -0.14 | -0.59 ^d | | | | |
| Sz only | | | | | | | | | |
| Parietal superior right | 23 ^c | Sz | 0.37 ^c | 1.00 ^c | -0.24 | 20.006 | 0.10 ^c | 0.42 ^d | -0.31 |
| | | BD | -0.01 | 0.22 | -0.41 | | | | |
| Postcentral right | 22 ^c | Sz | 0.37 ^c | 1.00 ^c | -0.22 | 19.591 | 0.10 ^c | 0.34 ^c | -0.16 |
| | | BD | 0.00 | 0.09 | -0.15 | | | | |

^aHeritabilities of cortical thickness (h²_{CT}); phenotypic (r_{ph}), genetic (r_g), and environmental (r_e) correlations between disease liabilities and cortical thickness for both diseases separately and combined are presented. Based on structural equation modeling with correction for age, sex, and lithium use (patients with BD only). χ² Sz ≠ BD indicates whether the phenotypic correlation between cortical thickness with Sz liability differs from that with BD (corrected for multiple comparisons, χ² > 15.35). For a significant association between a vertex with overlapping genetic liabilities between both disorders, the following findings had to be present: r_{ph}(combined) > 15.35, r_{ph}(Sz) and r_{ph}(BD) > 3.84, r_{ph}(Sz) or r_{ph}(BD) > 15.35, and r_g(combined) > 3.84; with segregating genetic liabilities: r_{ph}(Sz) ≠ BD > 15.35, r_{ph}(Sz) or r_{ph}(BD) > 15.35, and r_g(Sz) or r_g(BD) > 15.35. The same holds for environmental liabilities (e instead of g).

^bχ² Sz ≠ BD indicates whether the phenotypic correlation between brain volume and SZ liability differs from that with BD (corrected for multiple comparisons, χ² > 15.35).

^cSignificant effect corrected for multiple comparisons at χ² > 15.35.

^dχ² > 3.84, P < .05 uncorrected.

of white matter volume and in specific abnormalities in (frontotemporal) cortical mantle thickness.

The change in brain volume that most prominently reflected the (shared) genetic risk of schizophrenia and BD in this study was expressed as decreased white matter volume. This is consistent with an earlier study²³ in first-degree family members (although not co-twins) of patients with schizophrenia and BD linking reductions in left frontal and temporoparietal white matter to increased familial risk to both disorders (but see the article by McIntosh et al²⁶). Although we measured only global white matter, the regions where other researchers²³ found loss of white matter to be linked to increased familial risk of schizophrenia and BD partly overlap with the local thinner and thicker cortex that we find to be associated with a shared genetic risk of both disorders, that is, the left superior motor, right orbitofrontal, and temporoparietal regions. That white matter loss is implicated in the liability for both illnesses is also corroborated by studies comparing brain images of patients with schizophrenia and patients with BD using voxel-based morphometry¹⁷ and diffusion tensor imaging.^{18,19} However, meta-analyses in schizophrenia⁷ and BD¹⁰ separately have failed to detect significantly reduced white matter volume in either of these disorders. Possibly, in the present study, the correction for overall head size has

decreased variance and increased statistical power, particularly in patients with BD. Moreover, the inclusion of co-twins who share the genetic risk of the disorder but not the environmental influences may have contributed to finding an association between decreased white matter volume and genetic liability for both illnesses.

Some abnormalities in cortical thickness were shared by patients with schizophrenia and patients with BD and by their co-twins, suggesting that these abnormalities are related to the increased (genetic) risk common to both disorders. We found increased genetic risk of both illnesses to be associated with a thinner orbitofrontal cortex, thinner parahippocampal gyri, and thicker lateral temporoparietal cortices. In the few earlier studies directly comparing familial risk of schizophrenia and BD, no shared associations between gray matter and increased genetic risk for both disorders were found, instead, only segregating familial influences on gray matter densities were found.^{23,27,29} That we do find some areas of overlap may be due to the inclusion of co-twins. The twin model is a powerful approach for determining the relative contributions of genetic and environmental influences on variation in brain volumes and their common origin with disease liability.³¹ Thus, including co-twins with a high (up to 100%) genetic risk of schizophrenia and BD reveals areas of cortical gray matter common to increased

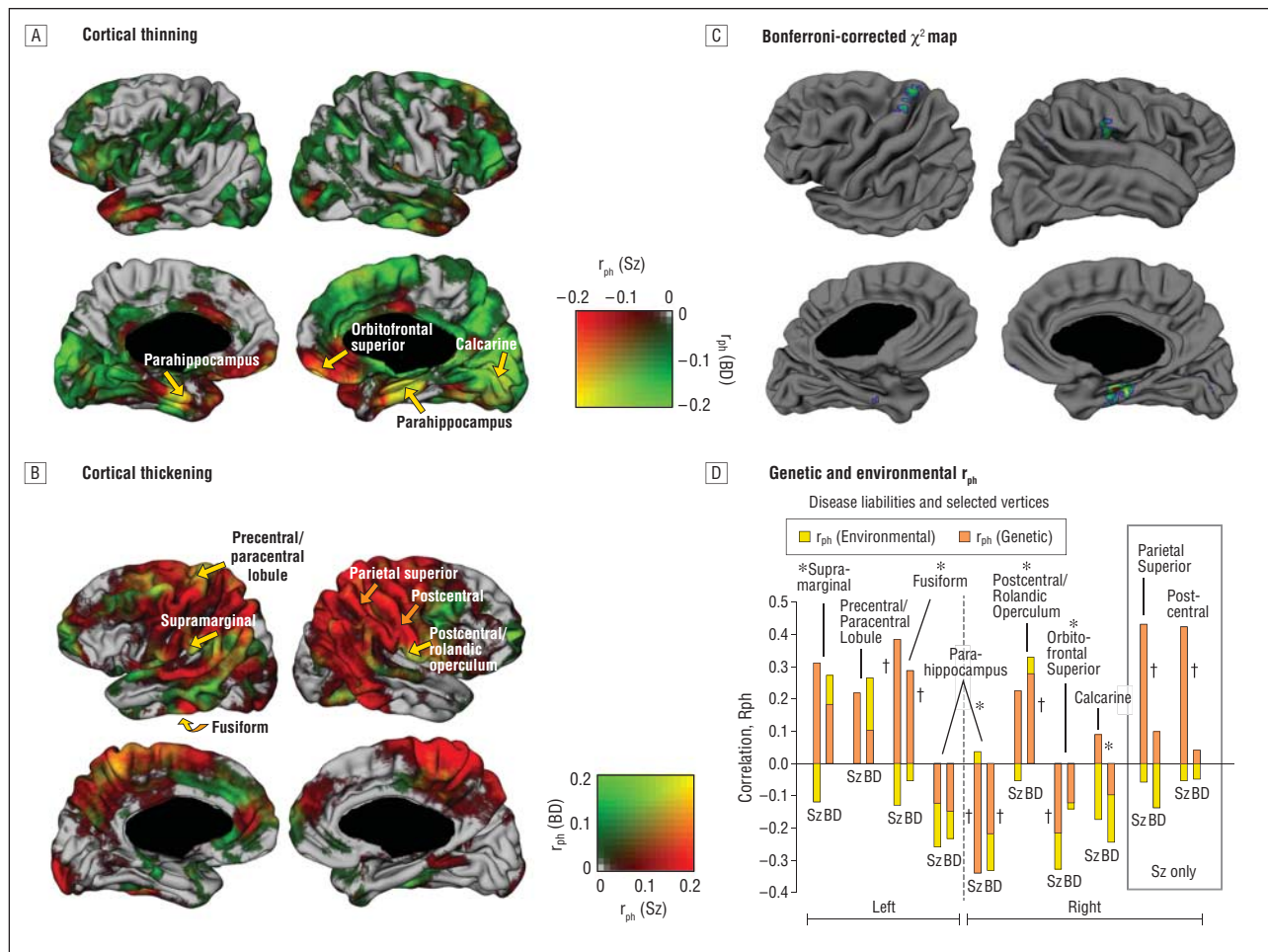


Figure 3. Disease liability and cortical thickness. Thinner (A) and thicker (B) cortical thickness shown as phenotypic correlations (r_{ph}) with liability for schizophrenia (Sz) and bipolar disorder (BD) expressed in colored vertices and arrows. Cortical thinning associated with higher disease liability for Sz ($r_{ph}[Sz]$) is shown in red, for BD ($r_{ph}[BD]$) in green, and for their overlap in yellow. For visual purposes, r_{ph} values have been clamped to lie between -0.2 and 0 , that is, values below -0.2 are the same color as -0.2 . C, Bonferroni-corrected χ^2 values ($\chi^2 > 15.35$) are shown for thinner and thicker cortical thickness. D, Higher genetic liabilities for Sz and BD simultaneously were associated with thinner right (and left) parahippocampal and right orbitofrontal cortices and with thicker left supramarginal, left fusiform, left precentral/paracentral, and right postcentral/rolandic operculum cortices. Higher environmental liabilities for Sz and BD were associated with thinner right medial occipital (calcarine) cortex (*). Genetic liability for Sz was associated with thicker right parietal superior and postcentral cortices. Data are shown after correction for age and sex in all the participants and for lithium use in patients with BD. †Significant contribution of genetic influences to the correlation within the disease group.

genetic risk of both disorders that may otherwise remain concealed.

Another possibility is that cortical thickness represents a more sensitive measure of local gray matter than does measurement of gray matter density using voxel-based morphometry, as was applied in family studies comparing both disorders.^{23,27} Recent studies measuring cortical thickness in schizophrenia and BD suggest that this may, indeed, be the case. Comparing the present cortical thickness findings in patients with schizophrenia and BD and their co-twins with findings in studies that have assessed cortical thickness in both disorders,^{15,16} we found them to be consistent with the thinner orbitofrontal cortex reported in patients with schizophrenia and patients with BD.¹⁶ In addition, the present finding of a thicker temporoparietal cortex associated with increased genetic risk of both disorders is in agreement with the thicker cortex found in the temporoparietal junction in an earlier study¹⁵ directly comparing schizophrenia and BD (but see the article by Rimol et al¹⁶). A thicker temporopari-

etal cortex associated with liability for schizophrenia may seem implausible in light of the overall gray matter tissue loss in these patients. However, several earlier studies⁴⁹⁻⁵² report local areas of increased thickness in schizophrenia, particularly in the parietal cortex (but see the article by Narr et al⁵³). Thus, the areas of thinner and thicker cortex that we find to be associated with increased genetic risk of both disorders seems largely consistent with those reported in patients with schizophrenia and BD.

In contrast, other areas of the cortical mantle differentiated (genetic) liabilities for schizophrenia from those for BD, with those in the right parietal cortex showing the largest effect. Nonoverlapping gray matter changes in families affected with schizophrenia and BD have been reported earlier but mostly in frontal brain areas.^{23,26,27} The right parietal cortex may, therefore, serve as a potential target for distinguishing liabilities for schizophrenia from those for BD when searching for disease-specific markers. However, we cannot exclude antipsychotic medica-

tion use as a disease-related (nongenetic) factor, but it has not been associated before with a thicker cortex, only with less prominent thinning.⁴⁹ Of the global structures, intracranial volume best differentiated between genetic risks of schizophrenia and BD: intracranial volume was related to an increased genetic risk in BD but not in schizophrenia. Since intracranial volume is stable from late childhood, this volume may represent a potential early developmental marker for BD. It was recently found that individuals with excellent school performance had a nearly 4-fold increased risk of later BD compared with those with average grades, whereas this was not the case in schizophrenia.⁵⁴ Since head size and intelligence are positively associated through common genes,⁵⁵ we could argue that genes associated with larger head size and higher intelligence may be implicated in BD, whereas the opposite (lower intelligence and associated lower brain volume) may be true for schizophrenia.⁵⁶

What does the local thinner and thicker cortex in schizophrenia and BD represent? The thinner frontal and medial temporal cortices in patients with schizophrenia, patients with BD, and their genetically related, but mostly unaffected, family members suggest that incomplete early development, or more pronounced shrinkage, of the cortex is an expression of the increased genetic risks of these 2 disorders. The latter explanation would be consistent with earlier findings of progressive brain volume loss in patients with schizophrenia,^{9,57,58} a process that was also found to occur to some extent in their discordant co-twins⁴ and in siblings of patients with childhood-onset schizophrenia.⁵⁹ It would also be consistent with aberrant brain growth since we found that these cortical areas increase in thickness during normal adulthood, a process that we found to be heritable.³³ Similarly, the decreased white matter volume in patients with schizophrenia, patients with BD, and their genetically related family members may represent developmental stagnation of white matter growth during normal development.⁶⁰⁻⁶²

In addition to thinning in the frontal and medial temporal cortices, we find a thicker temporoparietal cortex to be related to increased genetic risk of both disorders. This thickening may reflect abnormal or incomplete maturation of the cortex during adolescence, since cortical thinning occurs normally during that period of brain development.⁶³ These considerations also hold for the structural brain abnormalities segregating (the risk of) schizophrenia and BD. Indeed, the increased intracranial volume in patients with BD may represent aberrant (excessive) early brain growth not found in schizophrenia. Future studies in younger individuals at risk who are observed throughout adolescence may shed more light on causal relationships between structural brain abnormalities and liabilities for schizophrenia⁶⁴ and BD.

This study has several limitations that should be taken into consideration when interpreting its results. First, we did not include twin pairs in which one had the diagnosis of schizophrenia and the other the diagnosis of BD. Adding such pairs would have allowed us to make a stronger argument for associations of overlapping genetic risk for both diseases with the phenotype. However, the segregating risks for schizophrenia and BD with the phenotype were substantial, and considering the relatively large number

of participants (n=310), these findings can be interpreted with a reasonable degree of confidence. Second, we measured cortical thickness and overall gray and white matter volumes; therefore, no statements can be made regarding volumes of cortical subregions,¹⁴ subcortical nuclei,¹⁶ and white matter tracks,²² which have all been associated with both disorders in earlier studies. Third, although we corrected for lithium use in patients with BD, we did not correct for the use of antipsychotic agents or other medications, such as antidepressants or anticonvulsants, in these patients. This may have resulted in some bias in the findings. However, because not correcting for lithium therapy did not alter the findings and because co-twins of both patient groups did not use these medications, the associations with genetic risk are unlikely to be significantly influenced by medication intake. Fourth, there were significantly more male than female discordant-for-schizophrenia twin pairs and more female than male BD twin pairs. Moreover, BD twin pairs were somewhat older than schizophrenia twin pairs, an effect that was on the verge of significance. This may have resulted in some bias in the findings. However, since we corrected all the measurements for sex and age, it is unlikely that they significantly influenced the findings. Fifth, we included twins concordant for BD but not concordant schizophrenia twin pairs, introducing an asymmetry to the model. Excluding the concordant BD pairs from the analyses resulted in similar or somewhat lower parameter estimates with slightly larger CIs (probably due to a lower total number), which was most pronounced for white matter (genetic correlation for BD liability, -0.19 ; 95% CI, -0.40 to 0.01). Thus, overall findings were not driven by this asymmetry in the model. Sixth, the "dichotomous" genetic model was used, with a priori prevalence, heritability, and environmental liability for schizophrenia and BD separately. However, although this currently may represent the best possible estimate, it may not entirely reflect the complexity of the disorders. Seventh, this study applied an additive model to genetic and environmental influences to liabilities for schizophrenia and BD; therefore, possible gene \times environment interactions may have remained unnoticed.

In conclusion, we found decreased white matter volume, thinner orbitofrontal and medial temporal cortices, and a thicker temporoparietal cortex to be markers for genetic risk factors that are shared between schizophrenia and BD. Right parietal cortical thickness best differentiated disease liabilities for schizophrenia and BD: a thicker cortex was associated with increased genetic liability for schizophrenia. Thus, while there is some degree of genetic specificity, the overlapping smaller white matter and common areas of thinner cortex suggest that both disorders share genetic (neurodevelopmental) roots.

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