ORIGINAL ARTICLE

Influence of Genes and Environment on Brain Volumes in Twin Pairs Concordant and Discordant for Bipolar Disorder

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Context: Structural neuroimaging studies suggest the presence of subtle abnormalities in the brains of patients with bipolar disorder. The influence of genetic and/or environmental factors on these brain abnormalities is unknown.

Objective: To investigate the contribution of genetic and environmental factors on brain volume in bipolar disorder.

Design: Magnetic resonance imaging (1.5 T) brain scans of monozygotic (MZ) or dizygotic (DZ) twins concordant and discordant for bipolar disorder were compared with healthy twin pairs.

Setting: Subjects were recruited from the population, the Netherlands Twin Register, and the twin pair cohort at the University Medical Center Utrecht, Utrecht, The Netherlands.

Participants: A total of 234 subjects including 50 affected twin pairs (9 MZ concordant; 15 MZ discordant; 4 DZ concordant; 22 DZ discordant) and 67 healthy twin pairs (39 MZ and 28 DZ) were included.

Main Outcome Measures: Volumes of the intracranium, cerebrum, cerebellum, lateral and third ventricle, and gray and white matter from the cerebrum and frontal, parietal, temporal, and occipital lobes, both with and without correction for lithium use. To estimate the influence of additive genetic, common, and unique environmental factors, structural equation modeling was applied.

Results: Bipolar disorder was associated with a decrease in total cortical volume. Decreases in white matter were related to the genetic risk of developing bipolar disorder (bivariate heritability, 77%; 95% confidence interval, 38% to 100%). Significant environmental correlations were found for cortical gray matter. These relationships all became more pronounced when data were corrected for lithium use.

Conclusions: Focusing on genes controlling white matter integrity may be a fruitful strategy in the quest to discover genes implicated in bipolar disorder. Elucidating the mechanism by which lithium attenuates brain matter loss may lead to the development of neuroprotective drugs.

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THE HIGH HERITABILITY (THE percentage of phenotypic variance explained by genetic factors) of bipolar disorder has been well documented.[1] However, environmental factors are likely to be involved as well because the concordance rate for monozygotic (MZ) twin pairs is only around 70%.[2]

The pathophysiology of bipolar disorder remains poorly understood, although findings from structural imaging studies suggest the presence of subtle abnormalities in the brains of patients with bipolar disorder. These abnormalities include decreases in cortical volume,[3-6] cerebral white matter,[7] cortical[5,7,8] and prefrontal gray matter, particularly in the subgenual and dorsolateral prefrontal cortex,[9] and increased ventricular volumes[10-14] compared with healthy subjects. However, these findings are not consistent; other studies fail to find changes in total brain[10,11,15] white[5,16] and gray matter volume,[6,12,16-19] while some studies even report increases in gray matter volume in bipolar disorder.[20-22] Some of the reported discrepancies may be owing to effects of medication, especially lithium,[22,23] or small sample sizes. Despite the pronounced genetic effects on both bipolar disorder[24] and brain volume,[25] the question of whether the genetic risk of developing bipolar disorder is associated with some of the reported brain abnormalities in this illness has hardly been addressed.

Examination of the unaffected relatives of patients is often used to study the relationship between increased genetic risk and brain

Table 1. Demographic Data

	Bipolar Twin Pairs (n=50)				Control Twin Pairs (n=67)			
	MZ[a] (n=24)		DZ[b] (n=26)		MZ (n=39)		DZ (n=28)	
Female, No.	34		34		46		31	
Mean (SD) age, y	37.4 (10.6)		43.8 (8.5)		39.0 (9.9)		39.0 (7.5)	
Mean (SD) parental education, y	10.9 (3.5)		11.2 (3.8)		11.3 (3.3)		11.5 (3.5)	
First-degree relative, No. (%)								
Bipolar disorder	8 (33)		4 (15)					
Depression	4 (17)		9 (35)					
Mood disorder	11 (48)		13 (50)					
	Bipolar Patient	Co-twin	Bipolar Patient	Co-twin	Twin 1	Twin 2	Twin 1	Twin 2
Mean (SD) education, y	11.9 (2.0)	12.0 (2.2)	13.6 (2.6)	12.3 (3.1)	13.5 (2.8)	13.8 (2.7)	13.3 (2.5)	12.6 (2.8)
First born, No. (%)	16 (48)		12 (40)					
Handedness (left/right/both), No.	6/24/3	4/10/1	1/25/4	1/20/1	4/34/1	8/30/1	6/21/1	1/26/1
Mean (SD) onset age, y[c]	26.5 (8.9)		31.3 (9.9)					
Lithium/no lithium on day of MRI, No.[d]	26/7		20/10					
Psychotic symptoms, No.	15		18					
Mean (SD) IDS score[e]	6.47 (6.7)	2.0 (2.5)	5.8 (8.3)	2.0 (2.5)	2.14 (2.9)	2.44 (2.7)	2.43 (3.9)	2.92 (2.7)
Mean (SD) YMRS score	1.1 (1.5)	.50 (.82)	.48 (.97)	.14 (.65)	.21 (.57)	.13 (.34)	.29 (.82)	.31 (.75)

Abbreviations: BD, bipolar disorder; DZ, dizygotic; IDS, inventory of depressive symptoms (both groups below score for depressive state); MRI, magnetic resonance imaging; MZ, monozygotic; YMRS, young mania rating scale.

[a] Concordant, 9; discordant, 15.

[b] Concordant, 4; discordant, 22.

[c] Significant difference between MZ and DZ ($F_{1,61}$=4.03; P=.05).

[d] Six patients in the bipolar patients who did not take lithium group took lithium in the past, 5 of whom had not taken lithium for at least 2 years (range, 2-8 years). One patient took lithium for 13 years and stopped 1 month before the MRI. Analyses excluding this patient did not change the results.

[e] Significant difference between patients who were taking lithium and those who were not ($F_{1,60}$=6.3; P=.01), but both groups were below the score for a depressive state.

abnormalities because these subjects carry the genetic risk for the disease but not the disease itself. However, these studies are limited by the fact that they cannot discriminate genetic from shared environmental influence. To date, one volumetric magnetic resonance imaging (MRI) study compared psychotic bipolar patients (n=38) and their unaffected relatives (n=52) with healthy subjects (n=54). No differences in volumes of the cerebrum, lateral and third ventricle, or hippocampus were reported.[26]

In contrast to studies in unaffected relatives, examining MZ and dizygotic (DZ) twin pairs with at least 1 twin affected by bipolar disorder is a powerful approach to determine the relative contribution of genetic and environmental influences. So far only 2 studies of twins have been conducted on bipolar disorder measuring brain volume with MRI. One study included 6 MZ discordant and 6 healthy MZ twin pairs measuring the basal ganglia, amygdala-hippocampus complex, and the cerebral hemispheres. The authors concluded that genetic factors may be associated with an increased left caudate nucleus volume.[27] The second study, examining volumes of (frontal and temporal) gray and white matter and ventricular cerebrospinal fluid in 16 twin subjects with bipolar I disorder, 15 healthy co-twins, and 27 control twins found decreased left white matter volume to be influenced by familiar, possibly genetic, factors.[18]

In larger twin samples, a genetic model–fitting approach, also called structural equation modeling, enables quantification of the relative contribution of genetic and environmental influences to the possible phenotypic correlation between bipolar disorder and brain volume. With this method, the extent to which common genes or environmental factors influence both bipolar disorder and brain volume can be estimated (bivariate heritability).[28]

To quantify the genetic and environmental effects on brain volume in bipolar disorder, we included 50 twin pairs of whom at least 1 had bipolar disorder and 67 healthy twin pairs (n=234), measuring global and regional (gray and white matter) brain volumes. Because several studies have suggested a neurotrophic or neuroprotective effect of lithium,[21,22] we also used genetic model fitting to estimate the genetic and environmental associations after controlling for the possible effect of lithium on brain volumes.

METHODS

SUBJECTS

A total of 50 twin pairs affected with bipolar disorder (9 MZ concordant; 15 MZ discordant; 4 DZ concordant; 22 DZ discordant) were included and compared with 67 (39 MZ and 28 DZ) healthy control twin pairs. All twins were raised together, except for one control pair who were separated at 12 years of age when both parents died. The subjects were between 18 and 60 years of age. Demographic information is presented in **Table 1**.

Clinical diagnosis of axis I psychiatric disorders was confirmed using the Structured Clinical Interview for *DSM-IV*,[29]

Table 2. Lifetime Psychiatric Diagnoses of the Bipolar Twin Pairs

	No.		
		Co-twins (n=50)	
	Index (n=50)	Concordant (n=13)	Discordant (n=37)
Diagnosis			
Bipolar I disorder	37	8	
Bipolar II disorder	1	3	
Bipolar disorder NOS		1	
Bipolar disorder NOS and schizophrenia, paranoid type		1	
Major depressive disorder			4
Depressive disorder NOS			3
Schizophrenia, paranoid type			3
Dissociative disorder NOS			1
Comorbid diagnosis			
Depressive disorder NOS			3
Mood disorder due to hyperthyroidism			1
Psychotic disorder NOS	1		
Psychotic disorder due to cannabis	1		
Agoraphobia without history of panic disorder	1		
Panic disorder without agoraphobia	1		1
Posttraumatic stress disorder	1		
Alcohol use disorder in full remission	2		1
Cannabis use disorder in full remission	1		
Sedative use disorder	1		
Sedative use disorder in full remission		1	
Anorexia nervosa	1		
Borderline personality disorder	5		1
Obsessive-compulsive disorder in full remission	1		
Obsessive-compulsive personality disorder			1
Personality disorder NOS		1	1
No diagnosis			26

Abbreviation: NOS, not otherwise specified.

for axis II personality disorders using the Structured Interview For *DSM-IV* Personality,[30] and for both through available medical records (**Table 2**). 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. Their current mood state was assessed using the Young Mania Rating Scale[31] and the Inventory for Depressive Symptomatology.[32] At the time of the study, all patients were euthymic, ie, were not in a depressive, manic, or hypomanic episode, or were in an episode in partial remission with a Young Mania Rating Scale score of 4 or less and an Inventory for Depressive Symptomatology score of 12 or less, except for 4 patients who met criteria for a depressive episode (Inventory for Depressive Symptomatology scores, 15, 20, 29, and 38, respectively).

The healthy control pairs were matched to the bipolar 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. The family histories of both the affected and control twins were obtained via the Family Interview Genetic Studies[33] performed with both the proband and co-twin. Zygosity was determined by DNA fingerprinting using high polymorphic microsatellite markers 9 to 11 in the laboratory of the Division Biomedical Genetics, University Medical Center Utrecht.

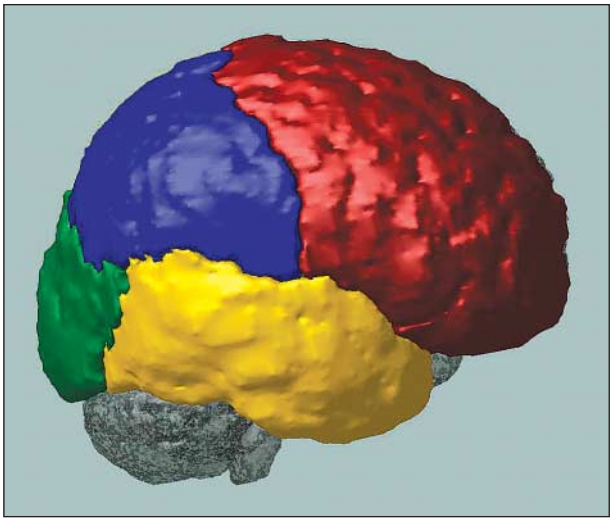

Figure 1. Segmentation of lobar volumes; frontal lobe (red), parietal lobe (blue), temporal lobe (yellow), and occipital lobe (green) (UMC Utrecht, Department of Psychiatry, Imaging Laboratory).

The study was approved by the medical ethics review board of the University Medical Center Utrecht and all participants gave written informed consent after full explanation of the study aims and procedures.

MRI ACQUISITION AND IMAGE ANALYSIS

Image acquisition and data processing have been described in previous studies from this group.[34] Quantitative assessments of the intracranium, cerebrum (total brain excluding cerebellum and stem), gray and white matter of the cerebrum, lateral and third ventricular volume, and cerebellum were performed based on histogram analyses and series of mathematical morphology operators to connect all voxels-of-interest.[35,36] All images were checked after measurement and corrected manually if necessary. To evaluate regional contributions, these gray- and white-matter segments from the individual images were used to identify gray and white matter for each individual lobe (frontal, parietal, temporal, and occipital). A fully automated warping technique was used (**Figure 1**). This technique uses nonlinear transformations to register every brain scan in the study to a model brain. The model brain was selected earlier from 200 brain images of subjects aged between 16 and 70 years.[37] Frontal, parietal, temporal, and occipital lobes were manually demarcated on this image. The borders have been described in detail previously.[38] In short, the cingulate gyrus and the insula were excluded from all cortical segments. The prefrontal segment excluded the precentral gyrus, although a frontal segment including the precentral gyrus was also defined. The parietal segment was separated from the frontal lobe by the central sulcus. The parietooccipital fissure defined the boundary with the occipital lobe. The boundary between the temporal and occipital segments was defined using the temporooccipital notch. Cortical volume is defined as the sum of the gray and white

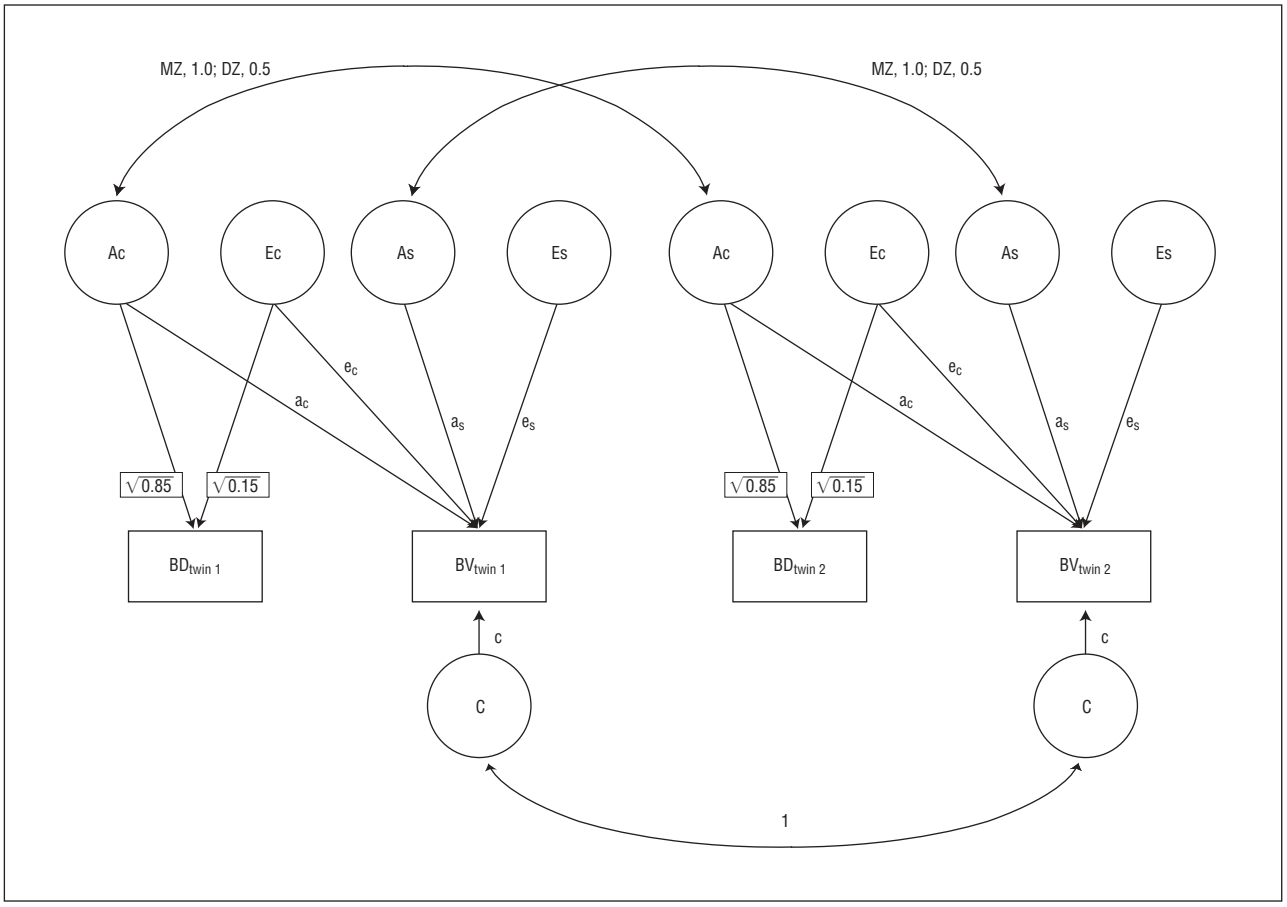

Figure 2. Example of a path diagram of the ACE genetic model for bipolar disorder (BD) and brain volume (BV). Bivariate twin model: genetic (A) and environmental (C/E) influences on BV and BD. The additive genetic factors (Ac and As) of monozygotic (MZ) twins are perfectly correlated (1.0), whereas those of dizygotic (DZ) twins are correlated at 0.5. Common environmental factors shared by twins from the same family (C) are correlated at 1 for both types of twins (only modeled for BV); the unique environmental influences (Ec and Es) are always uncorrelated between twins. Path coefficients (a_c and a_s) quantify the effects of genetic influences Ac and As on BV, where Ac represents genetic influences that also influence BD and As represents genetic influences that are unique for BV. Similarly, path coefficients e_c and e_s quantify the effect of unique environmental (Ec and Es) influences on BV. Path coefficient c quantifies the effect of common environmental influence on BV. Genetic and environmental variance of bipolar disorder is fixed on 0.85 and 0.15.

matter of the separate lobes, cortical gray matter as gray matter of all lobes, and lobar white matter as total white matter of all lobes. Brain images were registered to the model brain using the ANIMAL algorithm[39] to remove global differences in the sizes and shapes of the individual brains. The inverse of the transformation process registered the manual segmentations of the model brain to all subjects' brain images.

STATISTICAL ANALYSIS

The main aim of the bivariate genetic model–fitting analysis was to separate an expected correlation between bipolar disorder and brain volume into genetic and environmental components.[40,41]

To estimate the relative contributions of additive genetic (A), common environmental (C), and unique environmental (E) factors on individual differences in brain volume and the relationship with bipolar disorder, structural equation modeling was used. The extent to which A, C, and E explained the variance in brain volumes or covariance between brain volume and bipolar disorder was expressed as the percentage of the total covariance and variance, resulting in estimates of, respectively, h^2 (heritability), c^2 (common or shared environmentability), and e^2 (unique environmentability). The factor E also included measurement error (**Figure 2**).

Prior to structural equation modeling, phenotypic correlations (r_{ph}) between bipolar disorder and brain volumes and cross trait/cross twin correlations were calculated. A phenotypic correlation provides information on whether the specific volume is associated with bipolar disorder. It can result from a common set of genes or common set of environmental factors. Phenotypic correlations between bipolar disorder and brain volume were separated into genetic (r_g) and environmental components (r_e), thus providing information regarding the possible shared genetic and environmental influences of bipolar liability and brain volumes. Separation of these sources was based on the comparison of so-called cross-trait–cross-twin correlations for MZ and DZ twins. The cross-trait–cross-twin correlation is the correlation between a trait (ie, bipolar disorder) of twin 1 with another trait of twin 2 (brain volume), where twin 1 and twin 2 represent a twin pair. If the absolute value of the correlation between brain volume of twin 1 and bipolar disorder liability of twin 2 is larger in MZ twins than in DZ twins; this indicates that genes influencing brain volume (partly) overlap with genes that influence bipolar disorder. The extent of the overlap is reflected by the magnitude of the genetic correlation (r_g).

To implement these models, data were examined for outliers, and subsequently the residuals of the brain volumes, after regression on intracranial volume, sex, and age (SPSS ver-

Table 3. Brain Volumes of Bipolar Patients, Their Co-twins, and Healthy Comparison Subjects

	Mean (SD) Volume, mL[a]			Increase, %[b]		
	BP (n=63)[c]	Co-twins[d] (n=37)	HC (n=134)	BP vs HC	Co-twins[d] vs HC	Difference Between L⁻ and L⁺, %[e]
Intracranium	1420 (174)	1451 (179)	1428 (129)	+1.18	+2.62	+2.8
Cerebrum	1063 (128)	1089 (129)	1086 (111)	–1.37	–0.64	**–3.30**[f]
Gray matter	607 (69)	615 (71)	619 (70)	–1.13	–0.80	–3.64
White matter	456 (77)	474 (79)	467 (66)	–1.97	–0.78	–2.77
Lateral ventricle	17.1 (9.7)	16.6 (8.6)	15.2 (7.7)	+8.70	+4.48	**+12.49**[f]
Third ventricle	.89 (.53)	.84 (.41)	.79 (.41)	+7.7	–2.56	**+17.18**[f]
Cerebellum	138 (15)	138 (13)	141 (13)	–0.72	–2.17	–2.32
Cortical volume[g]	745 (92)	766 (92)	764 (80)	–.47	–0.54	**–3.26**[f]
Cortical gray matter[h]	447 (50)	456 (53)	458 (51)	–1.45	–0.47	–3.4
Lobar white matter[i]	297 (52)	310 (55)	306 (39)	–2.44	–1.25	–3.05
Gray matter						
Prefrontal lobe	153 (18)	155 (18)	156 (18)	–0.89	–0.58	–2.80
Temporal lobe	133 (14)	136 (16)	136 (14)	–1.35	–0.08	–2.92
Parietal lobe	109 (12)	110 (13)	111 (13)	–1.51	–1.14	–3.73
Occipital lobe	53 (8)	55 (8)	55 (8)	–3.07	–0.14	–5.60
White matter						
Prefrontal lobe	108 (18)	112 (19)	110 (14)	–1.16	–0.23	–3.08
Temporal lobe	66 (13)	69 (14)	68 (10)	–2.0	–0.97	–2.52
Parietal lobe	78 (14)	81 (14)	81 (10)	–3.25	–2.56	–4.89
Occipital lobe	45 (9)	48 (10)	46 (7)	–2.63	–0.04	–0.54

Abbreviations: BP, patients with bipolar disorder; HC, healthy control subjects (twin and co-twin); L⁺, bipolar patients who are taking lithium (n=46); L⁻, bipolar patients who did not take lithium (n=17).

[a] Uncorrected for age, sex, or intracranial volume.

[b] Corrected for age, sex, and intracranial volume; based on a mean age of 39.04 years, mean intracranial volume of 1430 mL, and female sex.

[c] Including 26 patients from concordant pairs (9 monozygotic; 4 dizigotic); for one patient, no separation of gray and white matter volume was possible.

[d] Co-twin without bipolar disorder

[e] Difference obtained by subtracting L⁺ from L⁻.

[f] Values in bold face are significant at $\alpha = .05$.

[g] Sum of the volumes of the prefrontal, parietal, temporal, and occipital lobes.

[h] Sum of the volumes of the gray matter of separate lobes.

[i] Sum of the volumes of the white matter of separate lobes.

sion 12.0; SPSS Inc, Chicago, Illinois) were used to calculate a 5-category ordinal scale. This allowed for a bivariate (bipolar disorder and brain volume) ordinal genetic data analysis using the statistical package Mx[42] (www.psy.vu.nl/mxbib). For ordinal genetic model fitting, the dichotomous variable "bipolar disorder" was assumed to represent an underlying continuous liability with a mean (SD) of 0 (1). A person with a high value on the liability scale crossing a certain threshold would be scored "patient" on our dichotomous variable, and in all other cases considered to be healthy (discordant co-twin of patient of healthy comparison twin pairs), thus receiving the alternative score. The critical threshold and heritability for the underlying bipolar disorder liability was not based on our sample because we included approximately equal numbers of concordant, discordant, and healthy twin pairs. We fixed prevalence and heritability of bipolar disorder to the population values; prevalence was set to 1%[43,44] and heritability was set to 85%.[1]

Effects of genes and familial background (C) were tested by fitting different models to the data. Parameters A, C, or both can be removed from the basic ACE model to generate submodels (ie, AE, CE, and E) that can be tested via likelihood ratio tests. This likelihood ratio test statistic follows a χ^2 distribution. A χ^2_1 larger than 3.84 indicates a significant difference at $\alpha = .05$ and indicates that the discarded effect (eg, the effect of C on brain volume) cannot be left out of the model without seriously deteriorating the goodness of fit. The most restrictive model was accepted as the best fitting one in case the difference between the two models was not significant.[42] For relevant estimates, 95% confidence intervals (CI) were obtained.[45] For bipolar disorder, the influence of C was not implemented into the model because the literature showed no evidence of family-related (common) environmental influences on bipolar disorder.[1]

The first likelihood ratio test for brain volume was whether the influence of C on brain volumes could be discarded from the model (see results). For the best-fitting model heritabilities and environmentabilities (ie, percentage of total variance accounted for by unique environmental influences, 1 hour[2]) of brain volumes, bivariate heritabilities (the percentage of covariance between bipolar disorder and brain volume that is accounted for by a common genetic factor: $h^2_{BV/BD} = |cov_A| / (|cov_A| + |cov_E|)$, where BV is brain volume, BD is bipolar disorder, and cov is covariance) and genetic and environmental correlations between bipolar disorder and brain volumes were obtained.

EFFECTS OF LITHIUM

Multiple univariate analyses of variance were used to determine if the patients who did not take lithium differ from the patients who did take lithium in age, age at onset, educational level, manic and depressive symptoms, number of depressive and manic episodes, number of hospitalizations, and all brain volumes, with age, sex, and intracranial volume as covariates. A χ^2 test was used for the differences in sex and zygosity. A Pearson correlation was used for all brain volumes and duration of lithium use.

After regression on intracranial volume, age, and sex, the differences in means for the separate brain volumes between patients who did not take lithium (L⁻; n=17 [for 1 patient, no gray/white matter separation was possible]) and the patients who took lithium (L⁺; n=46) were calculated (**Table 3**). This

difference was subtracted from the values of the lithium-using patients, resulting in an estimate of their volumes when no lithium would have been used. After this correction, structural equation modeling was performed including all subjects, as described in the previous paragraph. This correction for the effects of lithium is believed to yield better estimates of the true genetic and environmental effects on the relationship between brain volume and bipolar disorder.

EFFECTS OF PSYCHOTIC SYMPTOMS

Multiple univariate analyses of variance were used to determine if patients with psychotic symptoms (lifetime) differ from patients without psychotic symptoms in age, age of onset, educational level, manic and depressive symptoms, number of depressive and manic episodes, or number of hospitalizations. After genetic model fitting was performed, the volumes that were significantly associated with bipolar disorder (r_{ph}; eTable 1 and eTable 2; http://www.archgenpsychiatry.com) were analyzed post hoc using multiple univariate analyses of covariance to determine if these volumes were significantly different in patients with or without psychotic symptoms. Intracranial volume, age, and sex were used as covariates.

RESULTS

The demographic and clinical characteristics of all twin pairs are presented in Table 1. Bipolar patients who were taking lithium (L^+; n=46) were not significantly different from the bipolar patients who did not take lithium (L^-; n=17) on all clinical parameters (except for current depressive symptoms, $F_{1,61}=6.3$; $P=.01$); when correcting for multiple comparisons (Bonferroni correction), this effect was no longer significant. In Table 3, raw mean volumes and differences in brain volumes (in percentages) are presented for bipolar patients, co-twins of patients, and healthy comparison subjects. The differences between the volumes of L^- and L^+ bipolar patients are presented in Table 3. Multiple univariate analyses of covariance showed a significant difference in cerebral ($F_{1,58}=6.8$; $P=.01$), cortical ($F_{1,58}=6.8$; $P=.01$), and ventricular volumes ($F_{1,58}=5,4$; $P=.02$ for lateral ventricle and $F_{1,58}=6.8$; $P=.01$ for third ventricle).

There were no significant correlations between brain volume and duration of lithium use (lithium and cerebral volume $r=-0.04$; $P=.78$; cerebral gray matter $r=-0.23$; $P=.10$).

Bipolar patients without psychotic symptoms differed from bipolar patients with psychotic symptoms in number of depressive episodes (4.25 vs 3.0 episodes; $F_{1,56}=5.53$; $P=.02$). All other clinical variables were not significantly different. Brain volumes were not significantly different between patients with and without psychotic symptoms.

COMMON ENVIRONMENTAL INFLUENCE

The influence of common environment was not significant for brain volumes. There was one exception; for third ventricular volume, either a model containing common environmental influences or a model containing genetic influences explained the data best. The effects (common environment/genetic influence) could not be discarded simultaneously from the models without significantly reducing the goodness of fit ($\chi^2_3=26.514$) and there was not enough power to distinguish between them. We therefore report on the AE model for all brain volumes.

ASSOCIATION OF BRAIN VOLUME WITH BIPOLAR DISORDER

Bipolar disorder was significantly and negatively associated with cortical volume (the sum of the gray and white matter of all cortical lobes; phenotypic correlation, $r_{ph}=-0.14$), indicating a smaller cortical volume in bipolar patients. Adjusted for the effect of prescribed lithium, all brain volumes except for the cerebellum and occipital white matter were significantly associated with bipolar disorder; ventricular volumes (lateral ventricle $r_{ph}=0.24$; third ventricle $r_{ph}=0.29$) and intracranial volume ($r_{ph}=0.15$) were positively correlated, indicating an increase in these volumes in bipolar patients while all other volumes were negatively correlated (ranging from $r_{ph}=-0.15$ for temporal white matter volume to $r_{ph}=-0.37$ for total cortical volume) suggesting decreases of these volumes in bipolar patients (eTable 1).

COMMON GENETIC INFLUENCE ON BIPOLAR DISORDER AND BRAIN VOLUME

Irrespective of bipolar disorder, significant moderate to high heritabilities (h^2_{BV}) were found for brain volumes, ranging from 54% for third ventricle volume to 93% for intracranial volume (**Table 4**).

Bipolar disorder showed a genetically mediated association with lobar white matter. This was indicated by a significant negative MZ cross-trait/cross-twin correlation with bipolar disorder (–0.16) and a lower and nonsignificant DZ cross-trait–cross-twin correlation. Common genes appear to be involved because the genetic correlation with lobar white matter was significant ($r_g=-0.20$), as evidenced by the bivariate heritability ($h^2_{BV/BD}$). Additive genetic factors (A) were estimated to account for 77% of the covariance (CI, 38% to 100%), indicating that at least 38% (ie, the lower end of the CI range) of the covariance between lobar white matter and bipolar disorder liability can be explained by common genetic factors.

After correcting for the effects of lithium, the (common) genetic influence on white matter volumes and the risk for bipolar disorder became more pronounced; all white matter volumes showed significant MZ cross-trait–cross-twin correlations (eTable 2). Significant genetic correlations reflecting involvement of common genes were found for all white matter volumes (except for the occipital lobe), cerebral and total cortical volume, occipital gray matter, and third ventricular volume (r_g; eTable 2). The extent to which additive genetic factors (A) explain the covariance between bipolar disorder and brain volume was 68% for cerebral volume, 99% for lobar white matter, and 85% for cerebral white matter. The white matter of the separate cortical lobes contributed in almost equal measure to this high percentage ($h^2_{BV/BD}$ [CI]; eTable 2). Gray matter volumes did not show a significant common genetic influence.

Table 4. Estimated Influences of Additive Genetic (h^2) and Unique Environmental (e^2) Factors on Brain Volume, Irrespective of Disease[a]

Brain Volumes	h^2_{BV}, % (95% CI)	e^2_{BV}, % (95% CI)	$h^2_{BV\_L}$,[b] % (95% CI)	$e^2_{BV\_L}$,[b] % (95% CI)
Intracranium	93 (87-96)	7 (4-13)	91 (84-95)	9 (5-16)
Cerebrum	65 (46-78)	35 (22-54)	64 (45-77)	36 (23-55)
Cerebral GM	60 (39-75)	40 (25-61)	50 (29-67)	50 (33-71)
Cerebral WM	74 (58-84)	26 (16-42)	80 (66-88)	20 (22-34)
Lateral ventricle[c]	65 (47-78)	35 (22-53)	65 (47-78)	35 (22-53)
Third ventricle[c]	54 (35-70)	46 (30-65)	60 (43-73)	40 (27-57)
Cerebellum	83 (72-90)	17 (10-18)	84 (73-90)	26 (10-27)
Total cortical volume[d]	70 (53-82)	30 (18-47)	69 (49-70)	31 (30-51)
Cortical GM	74 (57-84)	26 (16-43)	64 (57-84)	36 (16-43)
Lobar WM	76 (61-85)	24 (15-39)	82 (70-90)	18 (10-30)

Abbreviations: BV, brain volume; CI, confidence interval; e^2, unique environmentability; GM, gray matter; h^2, heritability; WM, white matter.
[a] All analyses were corrected for intracranial volume, age, and sex.
[b] $h^2_{BV\_L}$ and $e^2_{BV\_L}$ are estimates after correction on the values of the patients who were taking lithium.
[c] Ventricular volumes were log-transformed.
[d] The sum of the volumes of the prefrontal, parietal, temporal, and occipital lobes.

UNIQUE ENVIRONMENTAL INFLUENCE ON BIPOLAR DISORDER AND BRAIN VOLUME

First it must be noted that because the heritability of bipolar disorder was set to 85%, only 15% of the variance in the underlying liability can be explained by unique environmental factors. Irrespective of disease, brain volumes showed unique environmental influences ranging from 7% for intracranial volume to 46% for third ventricular volume (Table 4). Environmental correlations represent unique environmental factors associated with both brain volume and bipolar disorder. For cortical gray matter, a significant environmental correlation was found (r_e=–0.46). The bivariate environmentability (the proportion of the correlation between bipolar disorder and brain volume associated with unique environmental factors) was significant for cortical gray matter; environmental influence explained 87% of the covariance between gray matter volume and bipolar disorder (CI, 34% to 100%).

After correcting for the effects of lithium use, significant negative environmental correlations were found for all gray matter volumes, cerebral and cortical volume, and cerebellar volume. Ventricular volumes were positively correlated with bipolar disorder (r_e; eTable 2). The eTable 2 ($e^2_{BV/BD}$) shows the extent to which unique environmental factors influence both brain volume and bipolar disorder (ranging from 32% for cerebral volume to 76% for prefrontal gray matter ($e^2_{BV/BD}$ [CI]; eTable 2). White matter volumes in bipolar disorder showed no significant environmental influences.

COMMENT

We examined the relative contributions of genetic and environmental influences on brain volume in bipolar disorder. Gray and white matter and ventricular volumes were measured in 50 twin pairs with bipolar disorder and 67 healthy control twin pairs. To our knowledge, this is the first MRI study using genetic model fitting in twin pairs discordant and concordant for bipolar disorder. The main finding is that a decrease in white matter is related to the genetic risk of developing bipolar disorder, while unique environmental factors are related to a decrease in (cortical) gray matter volume in patients with bipolar disorder.

By applying structural equation modeling, it was demonstrated that at least 38% of the covariance between white matter volume and bipolar disorder could be explained by genetic factors that influence both the volume of white matter and (the risk for developing) bipolar disorder. This indicates that genes involved in the etiology of bipolar disorder may contribute to the white matter decreases found in bipolar patients and in their co-twins.

In addition, a significant environmental correlation between the bipolar phenotype and cortical gray matter volume was found, with at least 34% of the covariance explained by unique environmental factors that are common to bipolar disorder and cortical gray matter brain volume. This suggests that environmental factors unique for each individual influence both bipolar disorder and gray matter volume, most likely in relation to the effects of the illness itself. Finally, lithium showed considerable effects on the brain changes found in this study, attenuating the decrease in both gray and white matter. As a consequence, findings became more pronounced, but did not change fundamentally, when analyses were corrected for lithium.

Our finding that a decrease in white matter is related to the genetic risk of developing bipolar disorder is consistent with that of a previous study in 16 bipolar twin pairs and 15 healthy co-twins. Those results provided evidence suggesting that the white matter decrease in bipolar disorder is genetically mediated, but owing to the smaller number of subjects and participation of incomplete twin pairs, familial and genetic effects could not be separated in that study.[18]

Our results build on several other lines of evidence, such as those derived from gene expression and genetic association studies, suggesting involvement of white matter pathology in bipolar illness. For instance, reductions in the number, size, and density of glial cells[46-49] as well as downregulation of key oligodendrocyte and myelination genes (including transcription factors that regu-

late these genes) have been reported in postmortem studies in bipolar disorder.[50,51] White matter abnormalities in the risk of developing bipolar disorder, as found in our study, are also consistent with several of the genetic association studies reporting changes in oligodendroglia-related genes in patients with bipolar disorder.[46,52]

Interestingly, white matter pathology has also been suggested to be central to the genetic risk of developing schizophrenia.[53] Indeed, in an earlier MRI study in twins discordant for schizophrenia, we reported that white matter decrease was associated with the increased genetic risk of developing schizophrenia.[34] Similarly, a voxel-based morphometry study that included patients with schizophrenia, bipolar patients, and their unaffected relatives found the genetic risk for both disorders to be associated with a white matter decrease in the left frontal and temporoparietal regions.[54] Results from brain imaging studies of schizophrenia are consistent with those from postmortem studies reporting reductions in number, size, and density of glial cells and downregulation of oligodendrocyte and myelination genes in schizophrenia.[47,55-58]

Taken together, white matter pathology may constitute a common genetic risk factor for bipolar disorder and schizophrenia. Indeed, findings from genetic association studies suggest considerable overlap in risk genes for bipolar disorder and schizophrenia, particularly regarding oligodendrocyte- and myelin-related genes.[50,52,55]

Our study also revealed a significant environmental correlation between bipolar disorder and decrease in cortical gray matter volume. A decrease in gray matter in bipolar disorder has been reported earlier,[5,7,59] but findings have been inconsistent.[18,26] In a recent meta-analysis of volumetric studies, a relative preservation of almost all volumes in bipolar disorder was reported; only the right lateral ventricle was found to be enlarged.[10] Strong heterogeneity for several brain regions, heterogeneous samples, different imaging methods, and medication use were mentioned as possible explanatory factors for the variable results. Indeed, the fact that gray matter decrease in bipolar disorder is an inconsistent finding may be owing to the use of lithium in these patients. Several reports have suggested a neurotrophic and neuroprotective effect of lithium; its use in bipolar patients has been associated with increases in cortical gray matter[21,22] and hippocampal volume.[23] Interestingly, after chronic administration of lithium, a doubling of Bcl-2 (one of the major neuroprotective proteins) levels in cortical layers II and III of the prefrontal cortex was demonstrated in rats.[60] It is these layers that have also been reported to show changes in neuronal and glial cells in postmortem studies in bipolar disorder. In vivo magnetic spectroscopy studies also support a neurotrophic effect of lithium, finding increases of N-acetyl-aspartate levels, a putative marker for neuronal viability and function, in all brain regions investigated.[61] Furthermore, a striking 0.97 correlation between lithium-induced N-acetyl-aspartate increases and regional voxel gray matter content was observed in bipolar patients after 4 weeks of lithium use.[61] The increases in both Bcl-2 and N-acetyl-aspartate in bipolar disorder have been interpreted as neuroprotective effects of lithium in response to malfunctioning frontal neurons.

Our findings must be viewed in light of several methodological limitations. Genetic models as used in this study cannot determine if these findings were present premorbidly or acquired with the passage of time. Although we realize that in bipolar disorder there is some evidence for progressive brain changes,[62-64] this cross-sectional study is not designed to address this question. Also, this twin sample is not a population-based sample but a selected subgroup of bipolar twins and healthy control twins in The Netherlands. Nevertheless, the whole sample of affected twins can be considered representative, with probandwise concordance rates for bipolar disorder of 54% for MZ twins and 26% for DZ twins.[1] This study found no significant shared environment contribution to liability to the disorder.[1] By constraining the familial environmental effect to zero, it is not possible to estimate a shared environmental correlation. It could be argued that our results may have optimized the genetic correlation. However, the MZ cross-trait–cross-twin correlations were more than twice as large as those for DZ twins in this study, suggesting that shared environmental effects are unlikely to contribute to the phenotypic correlations. Because two-thirds of our bipolar patients used lithium, it cannot be ruled out that this is a good compliance sample, having structural brain correlates of their own.

Finally, this study only analyzed global brain structures in twin pairs with bipolar disorder. Future studies should examine focal brain structures.

In conclusion, we found that white matter volume decrease is related to the genetic risk of developing bipolar disorder, while environmental factors, including the effects of illness, lead to decreased cortical gray matter volume. These findings mirror those reported in studies of schizophrenia and support the notion that the disorders share pathophysiological processes as well as vulnerability genes that are related to deficient myelination or abnormal white matter integrity. Interestingly, lithium greatly attenuated the brain volume changes, suggesting that its use may, in fact, obscure similarities in brain pathology between bipolar disorder and schizophrenia. Our results suggest that focusing on genes controlling white matter integrity and function may be a fruitful strategy in the quest to discover vulnerability genes for bipolar disorder. Elucidating the mechanisms by which lithium attenuates brain matter loss may lead to new drugs with neuroprotective properties.

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Correction

Error in Text. In the Original Article by King et al titled "Development and Validation of an International Risk Prediction Algorithm for Episodes of Major Depression in General Practice Attendees: The PredictD Study," published in the December issue of the *Archives* (2008; 65[12]:1368-1376), an incorrect URL was given in the "Results" and "Comment" sections for the predictD algorithm. The algorithm can be found at http://www.ucl.ac.uk/predict-depression.