ORIGINAL ARTICLE

Association of Genetic Risks for Schizophrenia and Bipolar Disorder With Specific and Generic Brain Structural Endophenotypes

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Context: For more than a century, it has been uncertain whether or not the major diagnostic categories of psychosis—schizophrenia and bipolar disorder—are distinct disease entities with specific genetic causes and neuroanatomical substrates.

Objective: To investigate the relationship between genetic risk and structural variation throughout the entire brain in patients and their unaffected relatives sampled from multiply affected families with schizophrenia or bipolar disorder.

Design: Analysis of the association between genetic risk and variation in tissue volume on magnetic resonance images.

Setting: Psychiatric research center.

Participants: Subjects comprised 25 patients with schizophrenia, 36 of their unaffected first-degree relatives, 37 patients with bipolar 1 disorder who experienced psychotic symptoms during illness exacerbation, and 50 of their unaffected first-degree relatives.

Main Outcome Measures: We used computational morphometric techniques to map significant associations between a continuous measure of genetic liability for each subject and variation in gray or white matter volume.

Results: Genetic risk for schizophrenia was specifically associated with distributed gray matter volume deficits in the bilateral fronto-striato-thalamic and left lateral temporal regions, whereas genetic risk for bipolar disorder was specifically associated with gray matter deficits only in the right anterior cingulate gyrus and ventral striatum. A generic association between genetic risk for both disorders and white matter volume reduction in the left frontal and temporoparietal regions was consistent with left frontotemporal disconnectivity as a genetically controlled brain structural abnormality common to both psychotic disorders.

Conclusions: Genetic risks for schizophrenia and bipolar disorder are associated with specific gray matter but generic white matter endophenotypes. Thus, Emil Kraepelin's pivotal distinction was neither wholly right nor wholly wrong: the 2 major psychoses show both distinctive and similar patterns of brain structural abnormality related to variable genetic risk.

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More than a century ago, Emil Kraepelin[1] divided psychotic illness into 2 diagnostic categories: dementia praecox and manic-depressive insanity. The distinction between these disorders, now known as schizophrenia and bipolar disorder, is embedded in the major diagnostic systems in current use. However, the line of demarcation between these clinical phenotypes is blurred, with many patients demonstrating features of both putative diseases. Consequently, there is continued controversy regarding whether or not the 2 disorders are indeed distinct disease entities caused by separable genetic and other risks.[2]

Twin and adoption studies have established that both disorders are highly heritable.[3-7] Susceptibility genes likely act by causing abnormalities in adult brain structure and function, perhaps as a result of aberrant early neurodevelopmental control.[8] It is clear that an inherited liability to develop psychosis reflects the combined effects of several susceptibility genes and their interactions with environmental risks such as perinatal complications and drug abuse.[9] Psychotic disorders lack well-defined, quantitative phenotypes (even postmortem), and therefore genetic research has relied on clinical syndromes with imprecise boundaries and heterogeneous constitutions. More valid phenotypes for genetic research into psychosis could be provided by endopheno-

types; for example, quantitative deviations in brain structure or function that underlie the clinical symptoms and are likely to represent more direct effects of the action of susceptibility genes.[10,11] The definition of such endophenotypes may also provide neurobiological substrates for more accurate diagnosis and classification of psychotic disorders than classical, clinical-syndromal phenotypes.[11]

Case-control studies of schizophrenia with magnetic resonance imaging (MRI) have demonstrated enlarged ventricles and subtle (<5.0%) volumetric deficits in multiple cortical and subcortical regions, including medial temporal lobe structures and the thalamus and frontal lobes, as well as volume deficits in white matter tracts.[12-15] Brain abnormalities in bipolar disorder have been less thoroughly investigated, but there is some imaging evidence of ventricular enlargement and increased rates of deep white-matter hyperintensities.[16-18] There are conflicting findings from the few studies that have compared patients who have schizophrenia or bipolar disorder with each other or the same control group, with some studies reporting gray matter or medial temporal lobe volume deficits only in schizophrenia[19-21] and others finding such deficits in both disorders.[22,23]

If the seminal Kraepelinian dichotomy of psychosis is correct, the neuroanatomical endophenotypes associated with genetic risks for schizophrenia and bipolar disorder should be distinct. To test this prediction, we conducted, to our knowledge, the first large-scale comparative MRI study of adult patients with schizophrenia or bipolar 1 disorder and their unaffected first-degree relatives, all from multiply affected families (N=148). We calculated a quantitative measure of genetic liability for each subject to model their likely exposure to genetic risk, and we used computational morphometric techniques to comprehensively and reliably map significant associations between genetic risk and variation in gray and white matter volume throughout the brain.

METHODS

SUBJECTS

We recruited subjects through voluntary support groups or by direct referral from their mental health services. We successfully performed MRI on 25 patients with schizophrenia, 36 of their first-degree relatives without psychosis, 37 patients with bipolar 1 disorder, and 50 of their first-degree relatives without psychosis. The patients with bipolar disorder had all experienced psychotic symptoms during episodes of illness exacerbation. Patients and relatives were assessed using the same clinical scales. Structured diagnostic interviews were performed using the Schedule for Affective Disorders and Schizophrenia–Lifetime Version,[24] and additional information regarding the timing and nature of symptoms was obtained to enable *DSM-IV* diagnoses. Information regarding history of psychiatric illness was obtained from the most reliable informants using the Family Interview for Genetic Studies[25] and from medical notes when available. The Schedule for Schizotypal Personalities[26] was used to assess relatives without psychosis and controls for schizotypal traits and to make *DSM-IV* diagnoses of schizotypal personality disorder.

The study sample was independent from that described previously by McDonald et al.[27] Subjects were not included if they had organic brain disease, had experienced head trauma resulting in loss of consciousness for more than 5 minutes, or fulfilled *DSM-IV* criteria for substance or alcohol dependence in the 12 months prior to assessment. No subjects were inpatients at the time of assessment. The study was approved by the relevant local ethical committees, and all subjects gave written informed consent to participate.

The patients with schizophrenia and their relatives were from 27 families (in some families the index patient did not successfully complete MRI), and in each family the index patient had at least 1 first- or second-degree relative affected with schizophrenia (20 families), another nonorganic psychotic disorder (3 families), or schizotypal disorder (4 families). Subjects with bipolar disorder and their relatives were from 32 families; in each family the index patient had at least 1 first- or second-degree relative affected with bipolar disorder accompanied by psychotic symptoms (24 families) or another nonorganic psychotic disorder (8 families).

GENETIC LIABILITY SCALE

We modeled the likely variation in the level of genetic risk among subjects using a continuous quantitative measure of genetic liability based on each individual's affection status and the number, affection status, and genetic relatedness of all adult members of each family as far as second degree from the index patient. The derivation of a similar measure for schizophrenia has been described previously.[28] Separate genetic liability scales were derived for schizophrenia and bipolar disorder. To calculate the scales, a polygenic multifactorial liability threshold model of illness was used[29] in which liability was assumed to be continuous in the population with a gaussian distribution. Patients were initially assumed to have an expected liability above a particular threshold, which was based on the population prevalence rates of the illnesses: 0.7% for schizophrenia and 0.5% for bipolar disorder.[30] Given these assumptions, the initial imputed liabilities were 2.78 for patients with schizophrenia and 2.89 for patients with bipolar disorder. Other subjects with psychotic disorders who were in families with schizophrenia or bipolar disorder were assumed to express the same phenotype as the index patient and were assigned the same initial liability. A second threshold was included for families with schizophrenia to categorize subjects with personality disorders related to schizophrenia, assumed to have a population prevalence of 3.3%,[31] which produced an initial expected liability of 2.08 for such individuals. Other relatives were considered unaffected and had an initial expected liability of –0.08 in families with schizophrenia and –0.07 in families with bipolar disorder.

For each family, we derived a vector of liabilities (L),which was initially imputed to each family member. These scores were then adjusted for each subject to account for family size and affection distribution. First, a correlation matrix for each family (R) was constructed describing the genetic interrelationships of all individuals older than 16 years and as far as second degree from the index patient (ie, self=1; first-degree relatives=0.5; second-degree relatives=0.25; spouse=0). Assuming that genes are the only source of familial resemblance (as has been demonstrated by twin studies[5,6]), a second correlation matrix of liabilities to illness in each family (V) was produced by multiplying the off-diagonal elements of R by an estimate of heritability, considered to be 0.7 for both schizophrenia and bipolar disorder. A vector of expected genetic risks (G) for each family is then given by the formula

$$G = RV^{-1}L,$$

with the assumptions of normal distribution theory.[32] These calculations produced estimates of continuously variable genetic risk (genetic liability score) for subjects in families with schizophrenia and bipolar disorder.

MRI DATA ACQUISITION AND PREPROCESSING

For each subject, a set of 1.5-mm-thick contiguous coronal T1-weighted MRI studies representing the whole brain was obtained using a 3-dimensional spoiled gradient recalled echo sequence with a 1.5-T scanner (N/Vi Signa System; General Electric, Milwaukee, Wis) and the following protocol: time to repeat = 13.1 milliseconds, inversion time = 450 milliseconds, echo time = 5.8 milliseconds, number of excitations = 1, flip angle = 20°, and acquisition matrix = 256×256×128. The scanning protocol was identical for all participants, who underwent scanning in random order with respect to affection status.

Optimized voxel-based morphometry[33,34] was used to segment MRI data and coregister probabilistic maps of gray matter and white matter volume density for each participant in standard anatomical space. This was implemented using Matlab version 6.0 (MathWorks, Natick, Mass) with SPM99 software (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, University College London, London, England).

Initially, customized gray, white, and cerebrospinal fluid template images in standard stereotactic space were created from a sample of 52 healthy control subjects, who had undergone scanning using identical parameters randomly throughout the study period, to minimize any scanner-specific bias and provide a template matched to the sample. These subjects were group matched to the combined samples of patients and relatives on the basis of age (mean ± SD, 39.3 ± 14.8 years; range, 19-69 years), sex (46.2% men; n = 24), and parental social class (38.5% I or II; ie, professional, managerial, or technical occupations; n = 20) and had no personal or family history of a psychotic, bipolar, or schizophrenia spectrum disorder. The MRI study of each control subject was segmented into gray, white, and cerebrospinal fluid tissue in native space. These images were smoothed using an isotropic gaussian kernel (8 mm full width at half maximum) and then spatially normalized using parameters derived from applying a 12-parameter affine transformation of each unsmoothed gray matter map to the standard SPM99 T1-weighted gray matter template and applying these to the smoothed segmented images. The images were then averaged to create customized gray, white, and cerebrospinal fluid tissue templates in standard stereotactic space.

Gray and white matter maps normalized to these customized tissue templates were produced for each subject included in the study as follows. Each subject's MRI study was segmented into gray, white, and cerebrospinal fluid tissue classes in native space. Parameters were derived from the spatial normalization of each subject's gray matter map to the customized gray matter template and iteratively applied to the original brain image to produce an image optimally normalized for gray matter segmentation. The images were resliced at a final voxel size of 1.5 mm^3 and resegmented using the customized tissue templates as prior probability maps, and the gray matter maps were retained. This procedure was repeated using parameters derived from normalizing each white matter map to the white matter template and iteratively applying them to the original image to derive white matter tissue maps for each subject. The gray and white matter images were then modulated by multiplying voxel values by the Jacobian determinants from the spatial normalization to correct for volume changes introduced at this step.[33,34] Finally all normalized, segmented, modulated gray and white matter tissue maps were smoothed using an isotropic gaussian kernel (4 mm full width at half maximum).

UNIVARIATE ANALYSIS OF MRI ENDOPHENOTYPES

Multiple regression models were specified to estimate the association between genetic liability and brain structural variation at each intracerebral voxel with gray or white matter volume density as dependent variables, genetic liability score as the key predictor variable, and age, sex, and affection status as covariates. Analyses were performed separately for the families with schizophrenia and bipolar disorder. A map of the standardized regression model coefficient of interest (β) coding the association between anatomical variation and genetic risk at each voxel was thresholded such that if $\beta > 1.96$ (probability of $\beta < 0.05$), the voxel value was set to $\beta - 1.96$; otherwise the voxel value was set to 0. This procedure generated a set of suprathreshold voxel clusters in 3 dimensions, each with a mass, or sum of suprathreshold voxel statistics. We tested the null hypotheses of no association between brain structure and genetic risk by permutation at cluster level, as described in detail elsewhere.[14,35,36] Stringent thresholds for statistical significance were derived from the permutation distribution so that the expected number of false-positive test results in each map was less than 1. Significant clusters were anatomically localized, and Brodmann areas were ascribed when relevant from the coordinates of the centroid voxel and the 2-dimensional spatial extent of each cluster in each axial slice in accordance with the standard atlas of Talairach and Tournoux.[37]

MULTIVARIATE ANALYSIS OF MRI ENDOPHENOTYPES

The mass of each significant cluster for each individual was transferred to a spreadsheet and, when multiple clusters were present, principal components (PC) analysis without rotation was performed to explore the extent of correlation between endophenotypic regions. In general, we found that anatomical variation was strongly correlated between brain regions associated with genetic risk; that is, the first PC always accounted for more than 70% of total variance. We therefore used individual scores for the first PC as summary measures of anatomical variation in endophenotypic systems comprising 2 or more correlated gray or white matter regions associated with genetic risks for schizophrenia or bipolar disorder.

MULTILEVEL MODELING OF MRI ENDOPHENOTYPES

We anticipated that variation in putative anatomical endophenotypes should be associated to the same extent with variable genetic risk in both patients and relatives and that endophenotypic variation might be specifically associated with genetic risk for 1 type of psychosis or generally associated with genetic risks for both types of psychosis. To explore these issues, we modeled the association between anatomical variation in endophenotypic systems (as defined by PC scores) and genetic liability using hierarchical observation models that accommodated the nonindependent clustering of some individuals within the same families. Multilevel modeling was implemented using Stata software version 6.0 (Stata Corporation, College Station, Tex), and a 2-tailed probability threshold for significance in these systems-level analyses was set at $P = .05$.

We first explored the association between genetic liability and related endophenotypic systems separately for groups of patients with schizophrenia or bipolar disorder and their relatives to test the hypothesis that genetic risk was associated with endophenotypic variation in relatives without psychosis as well as patients. Second, we explored the associations between endophenotypes, defined by prior analysis of families with that disorder, and genetic liability in unaffected relatives from both types of families. Disorder-specific endophenotypes are associated with genetic risk only in unaffected relatives of index patients with a diagnosis of that disorder, whereas disorder-generic endophenotypes are associated with genetic risk in unaffected relatives of patients with both types of disorder.

Table 1. Demographic Characteristics of Each Subject Group*

	Schizophrenia		Bipolar Disorder		Statistic	
	Patients (n = 25)	Relatives (n = 36)	Patients (n = 37)	Relatives (n = 50)	F or χ^2	*P* Value
Age, y	37.3 (10.2)	48.5 (13.0)	40.7 (11.6)	44.1 (15.7)	4.08	.008
Age range, y	24-55	16-68	22-64	17-68	NA	NA
Height, cm	174.8 (10.0)	169.8 (12.2)	171.2 (9.9)	169.9 (10.3)	1.37	.25
Education, y	13.8 (3.2)	14.1 (3.0)	14.2 (3.2)	14.4 (3.7)	0.24	.87
Male sex, No. (%)	18 (72.0)	14 (38.9)	15 (40.5)	24 (48.0)	7.79	.05
Left-handed, No. (%)	3 (12.0)	4 (11.1)	3 (8.1)	10 (20.0)	2.95	.40
Parental SES, No. (% I or II)†	12 (48.0)	15 (41.7)	16 (43.2)	23 (46.0)	0.31	.96

Abbreviations: NA, not applicable; SES, socioeconomic status.
*Data are presented as mean (SD) unless otherwise indicated.
†The SES is based on details of parental occupation at the subject's birth; SES I or II refers to professional, managerial, and technical occupations.

RESULTS

SUBJECTS

The demographic characteristics of the subjects are listed in **Table 1**. There was a significant age difference between patients with schizophrenia and their relatives because the relative groups included parents as well as siblings, and there was a greater proportion of men in the schizophrenia group. All subjects were of white ethnicity. All patients with schizophrenia were taking antipsychotic medication. Of the patients with bipolar disorder, 31 were taking mood stabilizers, 1 was taking olanzapine, and 5 were receiving no medication. Unaffected relatives had never experienced a psychotic illness, but 10 relatives of patients with schizophrenia and 9 relatives of patients with bipolar disorder had experienced another *DSM-IV* Axis 1 disorder at some point in their lives, mostly major depressive disorder. Four relatives of patients with schizophrenia also fulfilled the criteria for schizotypal personality disorder.

GRAY MATTER ENDOPHENOTYPES

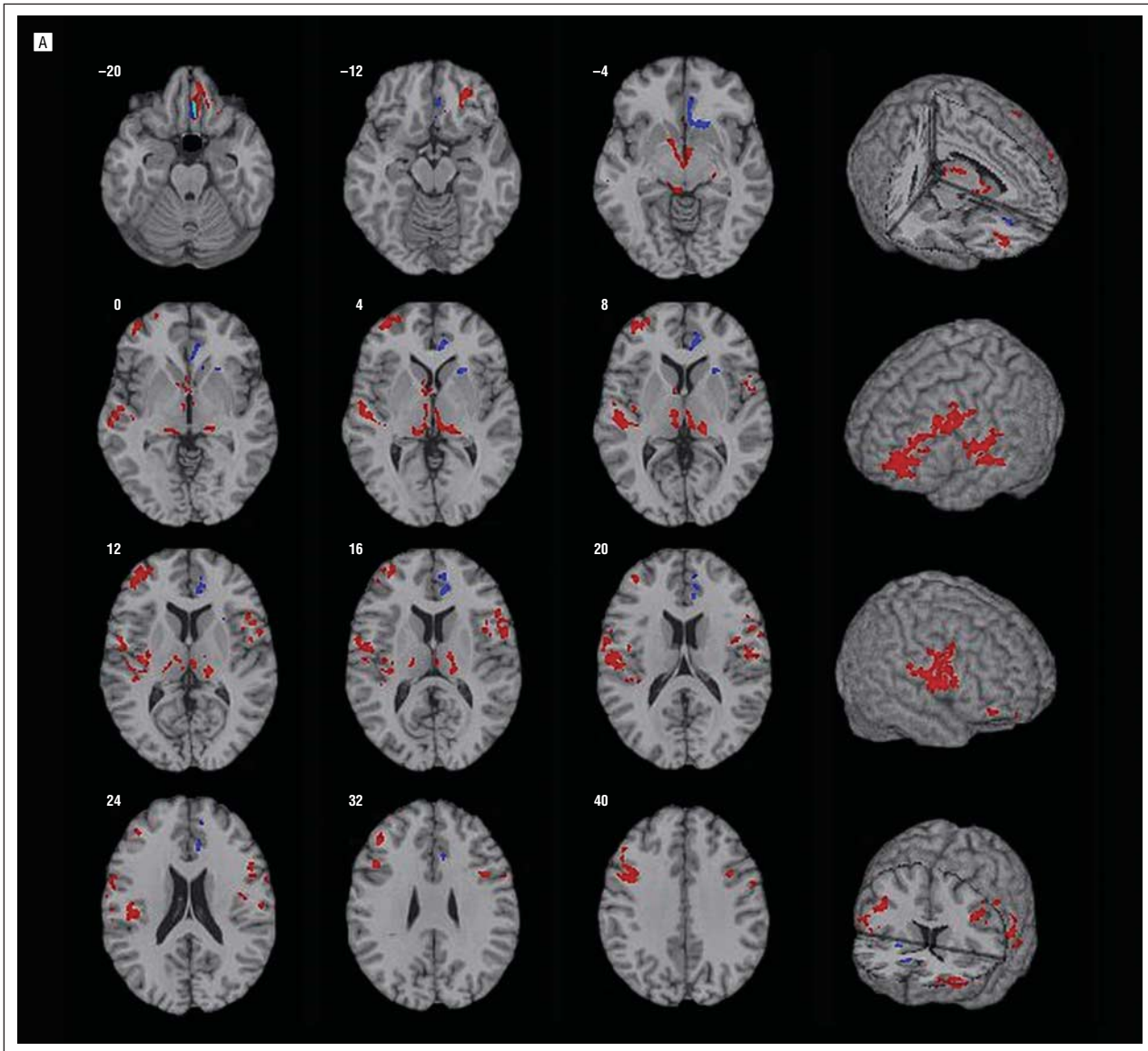
Genetic risk for schizophrenia was associated with distributed gray matter volume deficits in the orbital, prefrontal, and premotor parts of the frontal cortex, caudate nucleus, and bilateral thalamus as well as the left insula and lateral temporal cortex (**Figure 1**A and **Table 2**). The PC analysis showed that these gray matter deficits were highly correlated across regions, implying genetically determined effects on the volume of a cortical-subcortical network. All regions of gray matter volume deficit loaded positively for the first PC (Table 2), which explained 73.5% of the total variance in the group of patients with schizophrenia and their relatives. Scores for the first PC were strongly associated with genetic risk in patients with schizophrenia and their relatives without psychosis (**Table 3**). There was no significant interaction between subject group (patient vs relative) and genetic liability score, indicating that this pattern of gray matter deficit was not determined solely by abnormalities in the patients (Table 3 and Figure 1B). The relationship between increased genetic risk and greater gray matter volume deficits in this cortical-subcortical system remained significant when the analysis was confined to the 20 families in which the patient's family history consisted specifically of schizophrenia ($\beta = -1.49$; $P = .02$; 95% confidence interval, −2.63 to −0.31).

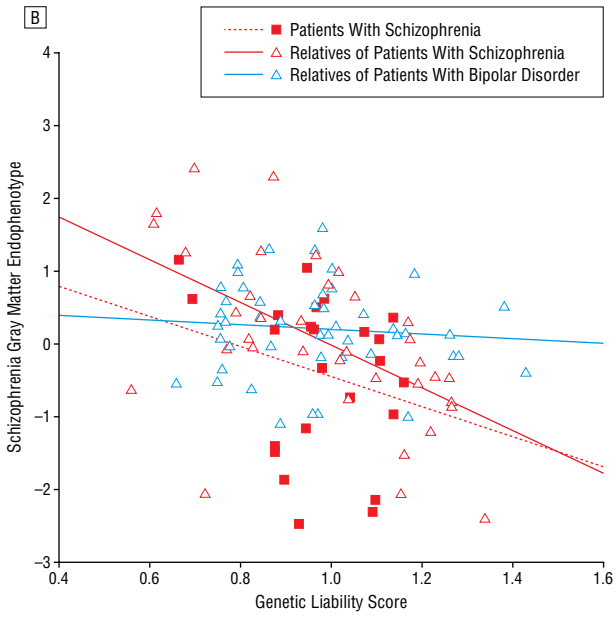
In contrast, genetic risk for bipolar disorder was associated with gray matter deficits in an almost completely separate and relatively circumscribed set of regions, principally the right anterior cingulate gyrus and ventral striatum (Figure 1A and Table 2). Regional analysis confirmed that genetic risk was associated with reduced gray matter volume of the anterior cingulate gyrus and striatum in patients with bipolar disorder and their relatives (Table 3); there was no significant interaction between subject group and genetic liability score, again indicating that this association was not determined solely by abnormalities in the patients (Table 3 and Figure 1C).

WHITE MATTER ENDOPHENOTYPES

We also found strong associations between genetic risk for each type of psychosis and anatomical variation in white matter. However, the white matter endophenotypes associated with genetic risk in the 2 groups were anatomically overlapping, in contrast to their anatomically distinct gray matter endophenotypes. Risk for schizophrenia was associated with white matter deficits in the posterior corpus callosum and left frontal and temporoparietal regions (**Figure 2**A and Table 2). Deficits in these regions were highly correlated, and all regions of white matter volume deficit loaded positively for the first PC (Table 2), which explains 82.5% of the total variance in the group of patients with schizophrenia and their relatives. First PC scores were significantly associated with genetic liability, and the interaction between subject group (patients vs relatives) and genetic liability score was not significant (Table 3 and Figure 2B).

Genetic risk for bipolar disorder was associated with white matter deficits in the anterior corpus callosum and bilateral frontal, left temporoparietal, and right parietal regions (Figure 2A and Table 2). All regions of white matter volume deficit loaded positively for the first PC, which explains 80.7% of the total variance. First PC scores were





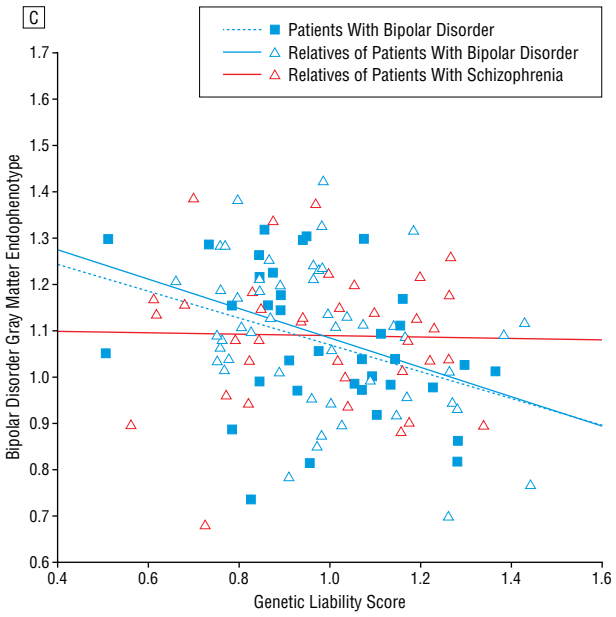


Table 2. Anatomical Location, Approximate Brodmann Areas, and Cluster Size and Loading Scores on First PC for Endophenotypic Regions of Gray and White Matter Significantly Associated With Genetic Liability for Schizophrenia and Bipolar Disorder

	Area*	Side	Brodmann Area	No. of Voxels in Cluster	Loading on First PC†
Families with schizophrenia					
Gray matter	Medial frontal gyrus, orbital gyrus, inferior/middle frontal gyri	R	11/47	402	0.86
	Inferior/middle frontal gyri, precentral/postcentral gyrus	R	6/9/40/43/44/45	602	0.88
	Middle/superior frontal gyri	L	9/10/46	423	0.78
	Middle frontal gyrus	L	6/8/9	333	0.86
	Thalamus, anterior cingulate gyrus, caudate nucleus, brainstem	L and R	NA/25	474	0.91
	Thalamus	R	NA	284	0.87
	Superior/middle temporal gyri, transtemporal gyrus, precentral/postcentral gyrus, insula	L	6/21/22/40/41/42/43	933	0.84
White matter	Lateral frontal lobe between middle and inferior frontal gyri, extending to the anterior insula and postcentral gyrus	L	NA	633	0.93
	Temporal lobe between middle temporal gyrus and hippocampus/parahippocampal gyrus, extending to the superior temporal gyrus and posterior insula	L	NA	645	0.91
	Splenium of corpus callosum	R and L	NA	515	0.88
Families with bipolar disorder					
Gray matter	Medial frontal gyrus, anterior cingulate gyrus, caudate nucleus, anterior putamen	R	9/11/24/25/32	689	NA
White matter	Medial frontal lobe between the anterior cingulate/medial frontal gyri and middle frontal gyrus, extending into the genu of the corpus callosum	R	NA	507	0.90
	Lateral frontal lobe between the inferior frontal gyrus, anterior insula, and caudate nucleus, anterior cingulate gyrus	L	NA	1112	0.90
	Temporal lobe between the superior/middle temporal gyri and hippocampus/parahippocampal gyrus, posterior cingulate gyrus	L	NA	1041	0.89
	Parietal lobe between the lateral ventricle, posterior cingulate gyrus, precuneus and inferior parietal lobule, supramarginal/angular gyri, extending to the postcentral gyrus	R	NA	1014	0.90

Abbreviations: L, left; NA, not applicable; PC, principal components; R, right.

*Anatomical localization of cluster extent and ascribed Brodmann areas were derived from the 2-dimensional centroid voxels (available from the authors on request) and spatial extent of the cluster in each axial slice.

†The PC analysis was used to reduce the dimensionality of data for further analyses at systems level when more than 1 cluster was present. In each analysis, there were strong positive loadings for every cluster on the first PC.

Figure 1. Gray matter endophenotypes associated with genetic risks for schizophrenia and bipolar disorder. A, Map of gray matter volume deficits associated with genetic risks for schizophrenia (red voxels) and bipolar disorder (blue voxels) superimposed onto a single brain in standard stereotactic space. Green indicates overlapping voxels. Clusterwise probability of type 1 error, $P = .004$ for both schizophrenia and bipolar disorder; that is, <1 false-positive test result.The z coordinate for each axial slice in the plane of the Talairach atlas is given in millimeters, and the right side of each panel represents the right side of the brain. B, Linear associations between systemic gray matter volume deficits in regions associated with genetic risk for schizophrenia (y-axis) and genetic liability score (x-axis) estimated separately for patients with schizophrenia, unaffected relatives of patients with schizophrenia, and unaffected relatives of patients with bipolar disorder. First principal component scores (y-axis) summarize correlated gray matter deficits in all frontal, temporal, and subcortical regions for each individual. C, Linear associations between gray matter volume deficits in regions associated with genetic risk for bipolar disorder (y-axis) and genetic liability score (x-axis) estimated separately for patients with bipolar disorder, unaffected relatives of patients with bipolar disorder, and unaffected relatives of patients with schizophrenia. Genetic liability scores are adjusted to the sample mean for age, sex, and subject group.

strongly associated with genetic liability, and there was no significant interaction between subject group (patients vs relatives) and genetic liability score (Table 3).

DISORDER SPECIFICITY OF GRAY AND WHITE MATTER ENDOPHENOTYPES

Genetic risk for bipolar disorder was not significantly associated with volume deficits in the gray matter endophenotype for schizophrenia, and there was a significant interaction between the 2 relative groups (relatives of patients with schizophrenia vs relatives of patients with bipolar disorder) and genetic liability on PC scores (Table 3 and Figure 1B). These results indicate that gray matter variation in this distributed frontostriatal and

Table 3. Genetic-Phenotypic Associations Between Genetic Liability Scores and Gray or White Matter Endophenotypic Systems*

	Gray Matter Endophenotypic Systems			White Matter Endophenotypic Systems		
	β	95% CI	*P* Value	β	95% CI	*P* Value
Schizophrenia endophenotypes						
Overall G-P association (pooling patients with schizophrenia and their relatives)	–1.75	(–2.88 to –0.61)	.004	–1.47	(–2.80 to –0.14)	.03
Test for difference in strength of G-P association between patients with schizophrenia and their relatives	–0.80	(–3.39 to 1.79)	.53	–2.33	(–5.02 to 0.35)	.09
Test for difference in strength of G-P association between relatives of patients with schizophrenia and relatives of patients with bipolar disorder	–0.95	(–1.65 to –0.25)	.009	–0.30	(–1.04 to 0.44)	.42
Bipolar endophenotypes						
Overall G-P association (pooling patients with bipolar disorder and their relatives)	–1.35	(–1.93 to –0.77)	<.001	–1.31	(–1.98 to –0.63)	<.001
Test for difference in strength of G-P association between patients with bipolar disorder and their relatives	–0.27	(–1.85 to 1.30)	.72	0.11	(–1.82 to 2.03)	.92
Test for difference in strength of G-P association between relatives of patients with schizophrenia and relatives of patients with bipolar disorder	0.66	(0.04 to 1.27)	.04	0.49	(–0.26 to 1.25)	.20

Abbreviations: CI, confidence interval; G-P, genetic-phenotypic.

*Overall G-P association results corroborate cluster-level mapping results at systems level, using multilevel modeling to accommodate intrafamilial correlation. Tests for difference in strength of G-P association between patients and relatives confirm that anatomical variation in these systems is not associated with genetic liability only in patients. Tests for difference in strength of G-P association between relatives of patients with schizophrenia and bipolar disorder indicate that gray matter endophenotypes are disorder specific, differentially associated with genetic liability for different types of psychosis, whereas white matter endophenotypes are disorder generic. Multiple linear regression analyses were performed with first principal components scores as dependent variables controlling for age, sex, and subject group. The regression model was also extended to include a quadratic function of age to model possible nonlinear effects of age on brain structure, but this did not materially affect the results.

temporal system is an endophenotypic marker specifically associated with genetic risk for schizophrenia.

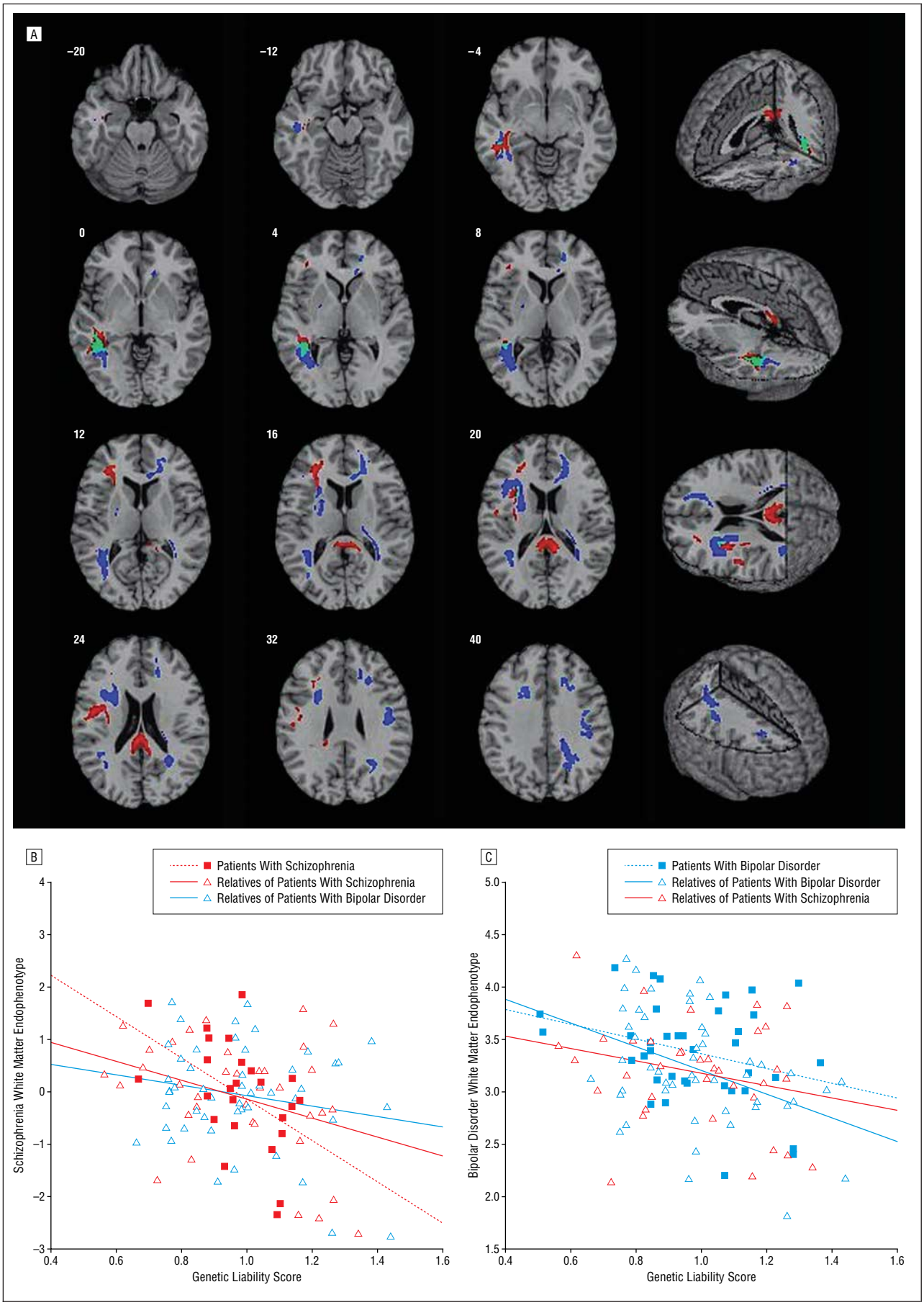
Likewise, genetic risk for schizophrenia was not significantly associated with volume deficits in the gray matter endophenotype for bipolar disorder, and there was a significant interaction between the 2 relative groups (relatives of patients with schizophrenia vs relatives of patients with bipolar disorder) and genetic liability on PC scores (Table 3 and Figure 1C). These results indicate that gray matter variation in this relatively circumscribed cingulate and striatal system is an endophenotypic marker specifically associated with genetic risk for bipolar disorder.

Genetic liability for bipolar disorder was associated with anatomical deficits in the white matter endophenotype defined by univariate analysis of the schizophrenia group; similarly, genetic liability for schizophrenia was associated with anatomical deficits in the white matter endophenotype defined by analysis of the bipolar disorder group (Table 3). A finer-grained analysis of genetic risk and endophenotypic association for the white matter systems showed that genetic liability score was generally associated with variation in the left hemispheric parts of both schizophrenia and bipolar disorder endophenotypes (Figure 2C) but that genetic risk for bipolar disorder was specifically associated with the right hemispheric parts of the bipolar disorder white matter endophenoype (further details are available from us on request). There was no material change in the results of the analyses of the combined relatives group after excluding the 24 relatives who had a previous diagnosis of any Axis 1 disorder, schizotypal personality disorder, or alcohol or substance dependence or were taking any psychotropic medications. These results indicate that white matter variation in the left frontal and temporoparietal regions is an endophenotypic marker generically associated with genetic risk for both schizophrenia and bipolar disorder.

COMMENT

These results provide support for the Kraepelinian dichotomy of psychosis to the extent that we have demonstrated markedly different gray matter endophenotypes associated with the genetic risks for schizophrenia and psychotic bipolar disorder. Genetic risk for schizophrenia was associated with a relatively extensive system of frontal, temporal, and subcortical gray matter deficits. These regions are compatible with regions of structural deficit identified by prior case-control studies of patients with schizophrenia.[12-14] However, interregionally correlated anatomical variation in this gray matter system was associ-

Figure 2. White matter endophenotypes associated with genetic risks for schizophrenia and bipolar disorder. A, Map of white matter volume deficits associated with genetic risks for schizophrenia (red voxels) and bipolar disorder (blue voxels) superimposed onto a single brain in standard stereotactic space. Green indicates overlapping voxels. Clusterwise probability of type 1 error, *P*=.01 for both schizophrenia and bipolar disorder; that is, <1 false-positive test result.The *z* coordinate for each axial slice in the plane of the Talairach atlas is given in millimeters, and the right side of each panel represents the right side of the brain. B, Linear associations between systemic white matter volume deficits in regions associated with genetic risk for schizophrenia (y-axis) and genetic liability score (x-axis) estimated separately for patients with schizophrenia, unaffected relatives of patients with schizophrenia, and unaffected relatives of patients with bipolar disorder. First principal component scores (y-axis) summarize correlated white matter deficits in all regions for each individual. C, Linear associations between white matter volume deficits in the left temporoparietal region identified as endophenotypic for bipolar disorder (y-axis) and genetic liability score (x-axis), estimated separately for patients with bipolar disorder, unaffected relatives of patients with bipolar disorder, and unaffected relatives of patients with schizophrenia. Genetic liability scores are adjusted to the sample mean for age, sex, and subject group.



ated with variable genetic risk in relatives without psychosis as well as patients with schizophrenia (suggesting that anatomical variation in this system is a marker for genetic risk rather than for caseness) but was not significantly associated with genetic risk among unaffected relatives of patients with bipolar disorder (suggesting that this endophenotypic brain system is indicative of genetic risk specifically for schizophrenia).

In contrast, risk for bipolar disorder was associated with more local gray matter deficits in the right anterior cingulate gyrus and ventral striatum, both of which are components of brain circuits for emotional processing[38] and have been identified as exhibiting abnormalities in previous case-control studies of patients with familial bipolar disorder using structural and functional neuroimaging.[39] However, in this article we have clarified that anatomical variation in these regions is a marker for genetic risk even among relatives without psychosis, not merely a marker for the presence of bipolar disorder in patients, and we have shown that this endophenotypic brain system is indicative of genetic risk specifically for bipolar disorder.

Studies examining unaffected relatives or discordant twins of patients with schizophrenia have previously linked genetic risk to volumetric reduction of the thalamus[40,41] and prefrontal and temporal cortical gray matter,[42,43] especially the dorsolateral prefrontal cortex,[43] but there was no evidence of gray matter reduction with genetic risk in a recent twin study of bipolar disorder.[44] Some studies comparing unaffected relatives of patients with schizophrenia with controls have reported that genetic risk is related to volume reduction of the hippocampus,[41,45,46] which did not emerge in this study. However, the effect of genetic risk on this structure remains to be fully elucidated because other studies failed to find hippocampal volume reduction in unaffected relatives[47,48]; evidence also suggests that hypoxic birth complications and the transition to psychosis influence medial temporal lobe volume deficits in schizophrenia.[46,48-50] In relation to these prior data, the distinctive value of our results is that they provide a more comprehensive map of the gray matter endophenotype in schizophrenia throughout the brain, and they allow an unprecedented direct comparison with the gray matter endophenotype in bipolar disorder.

The unique comparative design of this study also draws attention to aspects of the brain phenotype that are expressed in common between the 2 forms of psychosis. Genetic risk for both disorders was associated with distributed white matter volume deficits that were anatomically coincident in the left prefrontal and temporoparietal regions. White matter abnormalities have been reported in case-control studies of both schizophrenia[14,51,52] and bipolar disorder.[16,17,53] Studies of discordant twins have reported a genetic effect on global white matter volume reduction in schizophrenia[54] and left hemispheric white matter volume reduction in bipolar disorder,[44] although other studies assessing unaffected relatives of subjects with schizophrenia have failed to find a genetic effect on global white matter volume.[42,55,56] Our data map the white matter endophenotype for psychosis more precisely to territories normally occupied by major intrahemispheric tracts: the left superior longitudinal fasciculus, which connects the frontal lobe to the temporal, parietal, and occipital lobes; and the left inferior longitudinal fasciculus, which connects the temporal pole to the occipital lobe.

We surmise that risk for psychosis in general is associated with a pattern of white matter abnormality that is likely to compromise intrahemispheric anatomical connectivity between the left prefrontal and temporoparietal cortex. This conjecture is compatible with a substantial body of case-control data and theory implicating disintegration or disconnectivity of large-scale neurocognitive networks, especially frontotemporal disconnectivity, as a critical substrate for the generation of psychotic symptoms.[57-60] We acknowledge that the neuropathological substrate of these white matter changes is incompletely determined by the magnetic resonance signal changes reported in this article. For example, it is possible that the white matter changes we have described as deficits could reflect changes in the magnetic resonance signal owing to abnormal myelination rather than reduction in the number of axons. There is prior evidence from case-control studies of gene expression in the frontal cortex for the down-regulation of genes related to myelination and oligodendrocyte function in both schizophrenia and bipolar disorder.[61,62] In future studies, we will directly investigate associations between allelic variation in candidate genes and structural variation in the gray and white matter endophenotypes defined in this article. Such studies are expected to improve the power to detect pathogenetically relevant genes for psychotic disorders and to enhance understanding of the cellular substrates of MRI endophenotypes.

Some methodological aspects of our study deserve comment. The patients participating in this study were carefully diagnosed according to operationalized criteria and were drawn exclusively from multiply affected families. We treated genetic risk as continuously variable among relatives without psychosis rather than assuming that all relatives shared the same level of risk. We suggest that this is a more realistic assumption, in light of the likely variation between families in their exposure to multiple susceptibility genes, that may have conferred greater statistical power to detect brain endophenotypes with our regression analysis of anatomical variation and continuous genetic liability scores than would have been attainable by, for example, an analysis of variance treating patients and relatives as 2 discrete levels of genetic risk. We also used a customized, computerized "pipeline" for computational morphometry of the whole brain structure that incorporated software sourced from several laboratories for optimized nonlinear image registration and nonparametric hypothesis testing of spatially informed cluster-level statistics. All images were registered to a single template image constructed for this purpose from MRI studies acquired using the same scanner and pulse sequence of a group of healthy comparison subjects demographically matched to the patient and relative groups.

Enduring controversy often indicates that more than one view is reasonably tenable. We suggest that the long-standing dialectic between categorical and dimensional accounts of major mental illness is related to the main

implication of these data: genetic risks for schizophrenia and bipolar disorder are associated with both specific and generic brain structural endophenotypes. The anatomically segregated expression of specific and generic genetic effects that, to our knowledge, we have demonstrated for the first time is consistent with morphometric deviations linked to the clinical phenotypes of schizophrenia and bipolar disorder. These results also provide an important basis for future studies seeking to more powerfully identify susceptibility genes for psychosis by association with neuroimaging endophenotypes. We conclude that Kraepelin's pivotal distinction was neither wholly right nor wholly wrong. It is more apt, perhaps, to think of psychosis as a sibling pair of neurogenetic syndromes than as 1 or 2 discrete disease entities.

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