Original Investigation

Multisystem Component Phenotypes of Bipolar Disorder for Genetic Investigations of Extended Pedigrees

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IMPORTANCE Genetic factors contribute to risk for bipolar disorder (BP), but its pathogenesis remains poorly understood. A focus on measuring multisystem quantitative traits that may be components of BP psychopathology may enable genetic dissection of this complex disorder, and investigation of extended pedigrees from genetically isolated populations may facilitate the detection of specific genetic variants that affect BP as well as its component phenotypes.

OBJECTIVE To identify quantitative neurocognitive, temperament-related, and neuroanatomical phenotypes that appear heritable and associated with severe BP (bipolar I disorder [BP-I]) and therefore suitable for genetic linkage and association studies aimed at identifying variants contributing to BP-I risk.

DESIGN, SETTING, AND PARTICIPANTS Multigenerational pedigree study in 2 closely related, genetically isolated populations: the Central Valley of Costa Rica and Antioquia, Colombia. A total of 738 individuals, all from Central Valley of Costa Rica and Antioquia pedigrees, participated; among them, 181 have BP-I.

MAIN OUTCOMES AND MEASURES Familial aggregation (heritability) and association with BP-I of 169 quantitative neurocognitive, temperament, magnetic resonance imaging, and diffusion tensor imaging phenotypes.

RESULTS Of 169 phenotypes investigated, 119 (70%) were significantly heritable and 51 (30%) were associated with BP-I. About one-quarter of the phenotypes, including measures from each phenotype domain, were both heritable and associated with BP-I. Neuroimaging phenotypes, particularly cortical thickness in prefrontal and temporal regions and volume of the corpus callosum, represented the most promising candidate traits for genetic mapping related to BP based on strong heritability and association with disease. Analyses of phenotypic and genetic covariation identified substantial correlations among the traits, at least some of which share a common underlying genetic architecture.

CONCLUSIONS AND RELEVANCE To our knowledge, this is the most extensive investigation of BP-relevant component phenotypes to date. Our results identify brain and behavioral quantitative traits that appear to be genetically influenced and show a pattern of BP-I association within families that is consistent with expectations from case-control studies. Together, these phenotypes provide a basis for identifying loci contributing to BP-I risk and for genetic dissection of the disorder.

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Bipolar disorder (BP) encompasses a broad range of phenotypic features. However, most research into its etiology has focused on the overall syndrome[1-6] rather than on its components. Although genome-wide association studies have identified the first replicated loci contributing to BP susceptibility,[3-6] the small relative risk attributed to these loci may reflect the complex genetic nature of the disorder. This possibility motivates efforts to identify heritable BP-associated quantitative traits for which the genetic basis is simpler and for which higher-impact variants may be detected.[7-12]

We describe our investigation, in 26 pedigrees selected for multiple cases of severe BP (bipolar I disorder [BP-I]), of quantitative traits hypothesized to represent components of the biology underlying BP. Previous studies of these measures demonstrated association with BP, deficits in euthymic individuals with BP, and values in family members without BP that are intermediate between those of their relatives with BP and control participants. These phenotypes assay temperament,[13-15] perceptual creativity,[16-18] neurocognitive function,[19-21] and neuroanatomy (via structural magnetic resonance imaging [MRI] and diffusion tensor imaging [DTI]).[22-24] We also measured sleep, activity, and circadian rhythms, analyses of which are ongoing and will be reported separately.

Previously described pedigrees, including many of those evaluated here,[25-28] show BP segregation patterns suggesting the transmission of high-impact risk alleles. However, linkage studies of such pedigrees have yielded equivocal results, presumably because BP is genetically complex even within these families.[3] The feasibility of identifying rare, high-impact variants through next-generation sequencing has stimulated renewed interest in pedigree studies; however, even with this technology, the etiological complexity of BP hinders the identification of risk variants. We hypothesize that BP results from the confluence of multiple etiological processes, each of which alone may be simpler to unravel. Investigation of quantitative component phenotypes in pedigrees from population isolates such as the genetically related isolates of the Central Valley of Costa Rica (CVCR) and Antioquia, Colombia (ANT),[29-31] from which we recruited the pedigrees investigated herein, may lead to a better understanding of the heritable components of the disorder and at the same time simplify the search for specific genetic risk factors.

We report results from evaluations of the most extensive set of putative BP component phenotypes yet assessed within any study sample. For each measure, we describe its degree of familial aggregation (an indicator of heritability [h^2]) and of association with BP-I. These results suggest multiple phenotypes for genetic investigations of BP-I across the domains of temperament, neurocognition, and neuroanatomy.

Methods

Sample

We investigated pedigrees from ANT (11) and CVCR (15), ascertained in previous genetic studies[25-28,32-36] through hospitals and clinics in each country, using genealogic information to extend each pedigree. To prioritize pedigree branches for quantitative phenotyping, we recruited nuclear families including at least 1 member with known BP-I (based on the Diagnostic Interview for Genetics Studies[37,38] and/or extensive medical records), available parents, and at least 2 siblings without BP-I (eAppendix 1 in Supplement). Families varied considerably in size (12-355 members; mean, 55 members) and in the number of individuals phenotyped in this study (3-177 individuals; mean, 29 individuals) (**Table 1**). Written informed consent was obtained from each participant. Institutional review boards at participating institutions approved all study procedures.

Clinical Assessments

To establish *DSM-IV* diagnoses, we used a best-estimate process modified from previous procedures[33] (eAppendix 1 in Supplement) and including diagnostic interviews using Spanish versions of the Mini International Neuropsychiatric Interview[39] and the Diagnostic Interview for Genetics Studies. Individuals designated as having BP-I had a best-estimate diagnosis of BP-I, unipolar mania, or schizoaffective disorder, bipolar type, as in previous studies.[27,33,40] The Young Mania Rating Scale[41] and the 17-item Hamilton Depression Rating Scale[42] were administered at the time of assessment and identified individuals with significant mood symptoms (Young Mania Rating Scale Score >14 or Hamilton Depression Rating Scale score >14), whom we excluded from analyses of temperament and neurocognitive measures.

Temperament and Neurocognitive Assessment

Temperament and neurocognitive measures, assessed in 738 subjects, had previously demonstrated heritability and association to BP[13-16,22-24] (**Table 2**). The temperament battery, 15 measures generated from 7 instruments (eAppendix 1 in Supplement), included multiple dimensions categorized into 4 subdomains: affective temperament, impulsivity/risk taking, perceptual creativity, and delusion proneness (Table 2). The neurocognitive battery (eAppendix 1 in Supplement) included a computerized neuropsychological evaluation[51] and paper-and-pencil measures of verbal abilities, inhibitory control,[55] and declarative memory.[52]

Neuroimaging

We acquired T1-weighted structural neuroimages on 1.5-T scanners from 527 subjects (285 from CVCR and 242 from ANT) (eAppendix 1 in Supplement), implementing protocols for acquisition of DTIs in ANT only. We used Freesurfer software,[57,58] with manual inspection of intermediate steps in the processing stream to correct common errors, to generate 96 structural MRI phenotypes, including measures of volume, surface area, and cortical thickness (**Table 3**, eTable 1 in Supplement).[61,62]

We determined DTI phenotypes (eAppendix 1 in Supplement) with Functional MRI of the Brain (FMRIB) Software Library software[59,60] using the Johns Hopkins University probabilistic tractography atlas[63] to determine and customize regions of interest, which we limited to tracts previously associated with BP.[64-66] In total, we generated 18 DTI phenotypes across 3 categories: fractional anisotropy, indicating the degree of anisotropy; axial diffusivity, or diffusivity along the major axis of dif-

Table 1. Sample Characteristics by Country and Family

Family	Total Sample, No. (BP-I Cases, No.)	Sample Assessed for Component Phenotypes				
		Participants, No. (BP-I Cases, No.)	MRI, No. (DTI, No.)	Female, %	Age, Mean (SD) [Range], y	Education, Mean (SD) [Range], y
ANT						
All	512 (96)	353 (86)	242 (225)	58	47.7 (17.7) [18-85]	8.3 (4.7) [0-23]
ANT10	38 (6)	24 (5)	19 (18)	75	52 (15.4) [29-75]	11.2 (5.1) [3-19]
ANT13	24 (5)	19 (4)	15 (15)	58	47.5 (20) [18-85]	12.2 (3.9) [2-19]
ANT14	29 (8)	22 (7)	19 (19)	50	46.8 (16.6) [20-78]	7.3 (3.7) [3-16]
ANT15	27 (5)	21 (5)	14 (13)	57	46 (19) [8-85]	10.4 (3.6) [2-15]
ANT18	37 (6)	25 (6)	23 (21)	56	56 (16) [30-81]	8.2 (4.7) [2-18]
ANT23	48 (9)	31 (8)	16 (16)	68	47 (17.4) [18-82]	7.5 (4.8) [0-16]
ANT25	15 (4)	13 (4)	11 (11)	54	58 (14.1) [43-82]	3.5 (1.8) [1-6]
ANT27	58 (9)	35 (6)	22 (21)	57	50.5 (18.6) [18-84]	8.5 (4.7) [1-18]
ANT4	71 (10)	43 (9)	28 (26)	58	43.3 (18.6) [18-81]	6.5 (4.2) [1-16]
ANT7	149 (29)	112 (27)	71 (63)	52	44.8 (16.8) [18-82]	8 (4.4) [0-16]
ANT8	16 (5)	8 (5)	4 (2)	75	53.1 (21.3) [25-85]	13.2 (5.6) [3-23]
CVCR						
All	918 (128)	386 (95)	285 (0)	55	49.1 (15.6) [18-87]	7.8 (4.9) [0-24]
CVCR001	45 (8)	7 (3)	4 (0)	43	55.3 (9.6) [44-68]	14.9 (3.5) [11-20]
CVCR004	186 (23)	45 (10)	33 (0)	53	55.2 (13) [28-83]	8.3 (4.5) [0-18]
CVCR006	35 (4)	8 (2)	8 (0)	38	50 (14.2) [28-67]	13.1 (3.1) [8-17]
CVCR007	11 (2)	6 (2)	6 (0)	50	53.2 (13.3) [39-78]	13.3 (3.9) [6-17]
CVCR008	29 (7)	13 (5)	9 (0)	46	42.6 (13.8) [20-66]	7.2 (3.3) [3-14]
CVCR009	44 (9)	34 (9)	21 (0)	68	40.6 (14.9) [20-74]	8 (4.4) [0-17]
CVCR010	30 (4)	12 (3)	12 (0)	58	43.8 (15.5) [22-74]	12.2 (6) [5-24]
CVCR011	16 (3)	12 (3)	10 (0)	67	50 (23.2) [21-87]	11.8 (3.6) [6-18]
CVCR012	34 (5)	22 (5)	8 (0)	64	42.6 (15) [21-68]	8.1 (4.8) [0-16]
CVCR013	39 (4)	8 (3)	5 (0)	75	53 (17.8) [35-76]	13.9 (4.9) [6-19]
CVCR014	26 (5)	3 (1)	3 (0)	67	50.3 (8.5) [44-60]	5.7 (0.6) [5-6]
CVCR015	19 (2)	10 (2)	8 (0)	70	52.1 (14.4) [38-72]	6.4 (2.5) [3-13]
CVCR016	24 (4)	19 (4)	12 (0)	47	52.2 (15.3) [20-81]	3.6 (5) [0-20]
CVCR201	355 (44)	177 (40)	137 (0)	51	49.6 (15.7) [18-87]	6.5 (4.3) [0-19]
CVCR277	25 (4)	10 (3)	9 (0)	60	49.4 (11) [37-71]	10.8 (4.4) [4-17]

Abbreviations: ANT, Antioquia, Colombia; CVCR, Central Valley of Costa Rica; DTI, diffusion tensor imaging; MRI, magnetic resonance imaging.

fusion; and radial diffusivity, an average of the diffusivities along the 2 minor axes[67-70] (Table 3, eTable 1 in Supplement).

Statistical Analysis

We assessed familial aggregation of traits using SOLAR version 6.3.6 software,[71] which implements a variance component method to estimate the proportion of phenotypic variance due to additive genetic factors (narrow-sense heritability). This model partitions total variability into polygenic and environmental components. The environmental component is unique to individuals, while the polygenic component is shared between individuals as a function of their pedigree kinship. If the variance in phenotype Y due to the polygenic component is designated as σ_g^2 and the environmental component as σ_e^2, then in this model $\mathrm{Var}(Y) = \sigma_g^2 + \sigma_e^2$, and the covariance between phenotype values of individuals i and j is $\mathrm{Cov}(Y_i, Y_j) = 2(\varphi_{ij})(\sigma_g^2)$, where φ_{ij} is the kinship between individuals i and j.

Variance components analysis is sensitive to outliers and nonnormal trait distributions. To guard against potential statistical artifacts induced by skewed distributions, we used, prior to analysis, a rank-based procedure[72] to inverse normal transform all phenotypes. This transformation, implemented within SOLAR, is standard in variance component analyses as it does not induce correlations between relatives or lead to inflated estimates of heritability.[73]

We regressed all phenotypes on 3 covariates (sex, age, and country). Additional covariates included years of education (temperament and neurocognitive measures), body weight (T1-weighted and DTI variables), intracranial volume (volume measurements from T1-weighted images), and total cortical surface area (regional surface area measures). We implemented regressions in SOLAR with pedigree structures using residuals from these models in all further analyses.

We tested for difference in trait means between individuals with and without a diagnosis of BP-I (BP-I association analyses), using SOLAR to account for dependencies among relatives. We controlled the family-wise error rate at the 0.05 level, using a Bonferroni-corrected threshold for each test (heritability and BP-I association; $P < 2.96 \times 10^{-4}$). We used pub-

Table 2. Behavioral Measures to Generate Phenotypes

Subdomain	Instrument	Phenotype	Measure
Temperament			
Delusion proneness	Peters et al Delusions Inventory[43]	Peters et al Delusions Inventory	Score on 40 items assessing delusional ideation and unusual perceptual experiences
Perceptual creativity	Barron-Welsh Art Scale[16,44]	Barron-Welsh Art Scale dislike subscale	Preference rating on simple or symmetric figures of 86 total
		Barron-Welsh Art Scale like subscale	Preference rating on complex or asymmetric figures of 86 total
Affective temperament	TEMPS-Autoquestionnaire[45]	TEMPS anxiety	Total score on 3 anxiety items
		TEMPS cyclothymia	Total score on 12 cyclothymia items
		TEMPS depressive	Total score on 8 depressive items
		TEMPS hyperthymia	Total score on 8 hyperthymia items
		TEMPS irritability	Total score on 8 irritability items
Impulsivity/risk taking	Aggression Questionnaire[46]	Aggression Questionnaire	Score on 12-item Likert scale of aggressive traits and behaviors
	Barratt Impulsiveness Scale[47]	Barratt Impulsiveness Scale	Score on 30-item Likert scale assessing frequency of impulsive behaviors
	Sensation Seeking Scale[48,49]	Sensation Seeking Scale	Score on 40 items of sensory stimulation preferences
	BART[50]	BART low-risk pumps	No. of balloon pumps on low-risk trials
		BART medium-risk pumps	No. of balloon pumps on medium-risk trials
		BART high-risk pumps	No. of balloon pumps on high-risk trials
		BART total pumps	Total No. of balloon pumps on all trials
Neurocognition			
Long-term memory	CVLT	CVLT delayed recall	No. of items from 16-word list recalled after 20-min delay
		CVLT intrusions	No. of intrusions during list recollection
		CVLT recognition	No. of items from 16-word list recognized after 20-min delay
		CVLT repetitions	No. of repeated words during list recollection
		CVLT total trials 1-5	No. of items recalled over 5 repeated exposures of a 16-word list
	Miscellaneous[51]	Face memory	No. of faces recalled from visual presentation after delay
	WMS[52]	WMS logical memory delay	Memory score for auditory story after 20-min delay
		WMS logical memory immediate	Memory score for auditory story immediately after presentation
		WMS logical memory recognition	Recognition score for auditory story after 20-min delay
		WMS visual reproduction immediate	Score for visuospatial memory immediately after figure presentation
		WMS visual reproduction delay	Score for visuospatial memory after delay

(continued)

lished evidence to assign each trait an expected a priori direction of change, designating them as BP-I associated only if the difference was in the a priori assigned direction, therefore using a 1-tailed test (eTable 1 in Supplement).

We estimated phenotypic correlations for all trait pairs. Genetic correlations were estimated for all pairs in which both traits were significantly heritable using SOLAR.[74] Graphs of the estimated correlation structures used methods described in eAppendix 1 in the Supplement.

Results

Sample Characteristics

Table 1 shows summary statistics for the sample by family; eTable 2 in the Supplement provides additional clinical characterization of the 181 participants who met best-estimate criteria for BP-I. We excluded 5 individuals with elevated Young Mania Rating Scale or Hamilton Depression Rating Scale scores

Table 2. Behavioral Measures to Generate Phenotypes (continued)

Subdomain	Instrument	Phenotype	Measure
Executive function	AIM[53]	AIM abstraction	No. of correctly matched shapes presented simultaneously
	WASI	Matrix reasoning	No. of correctly completed patterns
		WASI vocabulary	No. of correctly named or defined objects or words
	PCET[54]	PCET No. correct	No. of correctly identified nonmatching objects
		PCET categories achieved	No. of categories achieved
	SST	SST correct go	No. of correct go trials
		SST correct stop	No. of correct stop trials
		SST interstimulus interval	Response time (in ms) on correct stop trials
	Stroop Color-Word Interference Test[55]	Stroop Color-Word Interference Test errors	No. of errors on color-word test
		Stroop Color-Word Interference Test time	Time needed to complete test
	TONI[56]	TONI No. correct	No. of correctly completed progressive matrices
Working memory	AIM[53]	AIM abstraction plus memory	No. of correctly matched shapes after delayed target presentation
	IP-CPT	IP-CPT hits	No. of correctly identified pairs on continuous performance test
	SCAP	SCAP No. correct, 3-dot condition	No. of correct responses on 3-dot spatial delayed memory task
		SCAP reaction time, 3-dot condition	Response time (in ms) on 3-dot condition
		SCAP No. correct, 5-dot condition	No. of correct responses on 5-dot spatial delayed memory task
		SCAP reaction time, 5-dot condition	Response time (in ms) on 5-dot condition
		SCAP mean No. correct, all trials	Mean No. of correct responses on all trials
	Miscellaneous[51]	VWM digits forward No. correct	Correctly recalled digits strings in original order of presentation
		VWM digits backward No. correct	Correctly recalled digits strings in reverse order of presentation
		VWM letter-number sequence No. correct	Correctly recalled letter-number strings, in alphanumeric sequence
Processing speed	Miscellaneous[51]	Digit symbol copy	Correctly identified digit-symbol pairs in 90 s
		Digit symbol recall	No. of digits recalled when presented with corresponding symbols
		Digit symbol % correct	% Correct on digit-symbol task
	Trail Making Test	Trail Making Test letter-sequencing time	Time needed to connect letters in alphabetical order
		Trail Making Test number-Letter-sequencing time	Time needed to connect alternating sequence of numbers and letters
		Trail Making Test number-sequencing time	Time needed to connect numbers in ascending order
Verbal fluency	Miscellaneous[51]	Verbal letter fluency	Words starting with a specific letter generated in 60 s
		Verbal category fluency	Animal names generated in 60 s

Abbreviations: AIM, Abstraction, Inhibition, and Working Memory Task; BART, Balloon Analogue Risk Task; CVLT, California Verbal Learning Test; IP-CPT, Identical Pairs Continuous Performance Test; PCET, Penn Conditional Exclusion Test; SCAP, Spatial Capacity Delayed Response Test; SST, Stop Signal Task; TEMPS, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego; TONI, Test of Nonverbal Intelligence; VWM, verbal working memory; WASI, Wechsler Abbreviated Scale of Intelligence; WMS, Wechsler Memory Scale.

from analyses of neurocognitive and temperament data, and we excluded 5 additional individuals from BP-I association analyses (but not from heritability analyses) because a BP-I diagnosis could be neither confirmed nor excluded.

Heritability and Association With BP-I

Of the 169 traits examined, 119 (70%) were significantly heritable, 51 (30%) were significantly associated with BP-I, and 38 (22%) were both heritable and associated with BP-I (**Figure 1**, eTable 1 in Supplement). These results were robust with respect to phenotype variations across pedigrees and countries (data not shown) and to outliers (eAppendix 2 and eFigure in Supplement); for secondary analyses of the effects of medications and duration of illness on trait values, see eAppendix 3 in the Supplement. Results within each domain are described here.

Table 3. Neuroimaging Measures to Generate Phenotypes

Measure	Analysis Package	Regions of Interest[a]
MRI volume	FreeSurfer,[57,58] T1-weighted images	Amygdala, anterior corpus callosum, brainstem, caudate, central corpus callosum, cerebellar cortex, **cerebellar volume**, cerebellar white matter, cerebral cortex, **cerebral volume**, cerebral white matter, cerebrospinal fluid, fourth ventricle, hippocampus, inferior lateral ventricle, lateral ventricle, midanterior corpus callosum, midposterior corpus callosum, non–white matter hypointensities, nucleus accumbens, pallidum, posterior corpus callosum, putamen, thalamus, third ventricle, **total brain volume**, **total corpus callosum**, ventral diencephalon, white matter hypointensities
Cortical surface[b]	FreeSurfer,[57,58] T1-weighted images	Caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, frontal pole, fusiform, inferior parietal, inferior temporal, isthmus cingulate, lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, paracentral, parahippocampal, pars opercularis, pars orbitalis, pars triangularis, pericalcarine, postcentral, posterior bank of superior temporal sulcus, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, temporal pole, transverse temporal
FA, AD, RD	FSL TBSS,[59,60] DTI	Anterior thalamic radiation, genu corpus callosum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, splenium corpus callosum, uncinate fasciculus

Abbreviations: AD, axial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; FSL, Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library; MRI, magnetic resonance imaging; RD, radial diffusivity; TBSS, Tract-Based Spatial Statistics.

[a] Regions of interest in bold indicate measures derived by summing subregion measures that are also included as traits (eg, total brain volume is the sum of total cerebral, total cerebellar, and brainstem volumes).

[b] For each cortical surface region of interest, 2 measures were determined: surface area and average gray matter thickness.

Temperament

Six of the 15 temperament measures demonstrated significant heritability, although overall this domain showed the lowest estimates of additive genetic influence (h^2 of approximately 0.18-0.30). In contrast, 3 temperament traits displayed the strongest BP-I associations of all 169 measures: Temperament Evaluation of Memphis, Pisa, Paris, and San Diego cyclothymia scale, Barratt Impulsiveness Scale, and Peters et al Delusions Inventory. Delusion proneness (Peters et al Delusions Inventory) and perceptual creativity (Barron-Welsh Art Scale dislike subscale) were both heritable and associated with BP-I, while risk-taking propensity (Balloon Analogue Risk Task) was neither heritable nor associated with BP-I.

Neurocognition

Some measures from all domains assessed showed significant heritability and BP-I associations. Most measures of processing speed, long-term memory, and verbal fluency were significantly heritable (13 of 19); within this heritable subset, most were associated with BP-I (9 of 13). Within working memory assessments, verbal but not spatial tasks showed evidence of heritability, and participants with BP-I showed significant impairment on measures of sustained attention (Identical Pairs Continuous Performance Test), spatial working memory (Spatial Capacity Delayed Response Test), and verbal working memory tasks (letter-number sequencing). Measures of inhibitory control (Stroop Color-Word Interference Test and Stop Signal Task) showed evidence for impairment in participants with BP-I; among these measures, the Stroop measures (Stroop Color-Word Interference Test trials, time, and number of errors) were also heritable. Nonverbal abstract reasoning measures (Abstraction, Inhibition, and Working Memory Task, Test of Nonverbal Intelligence, matrix reasoning) were neither significantly heritable nor associated with BP-I.

Neuroimaging

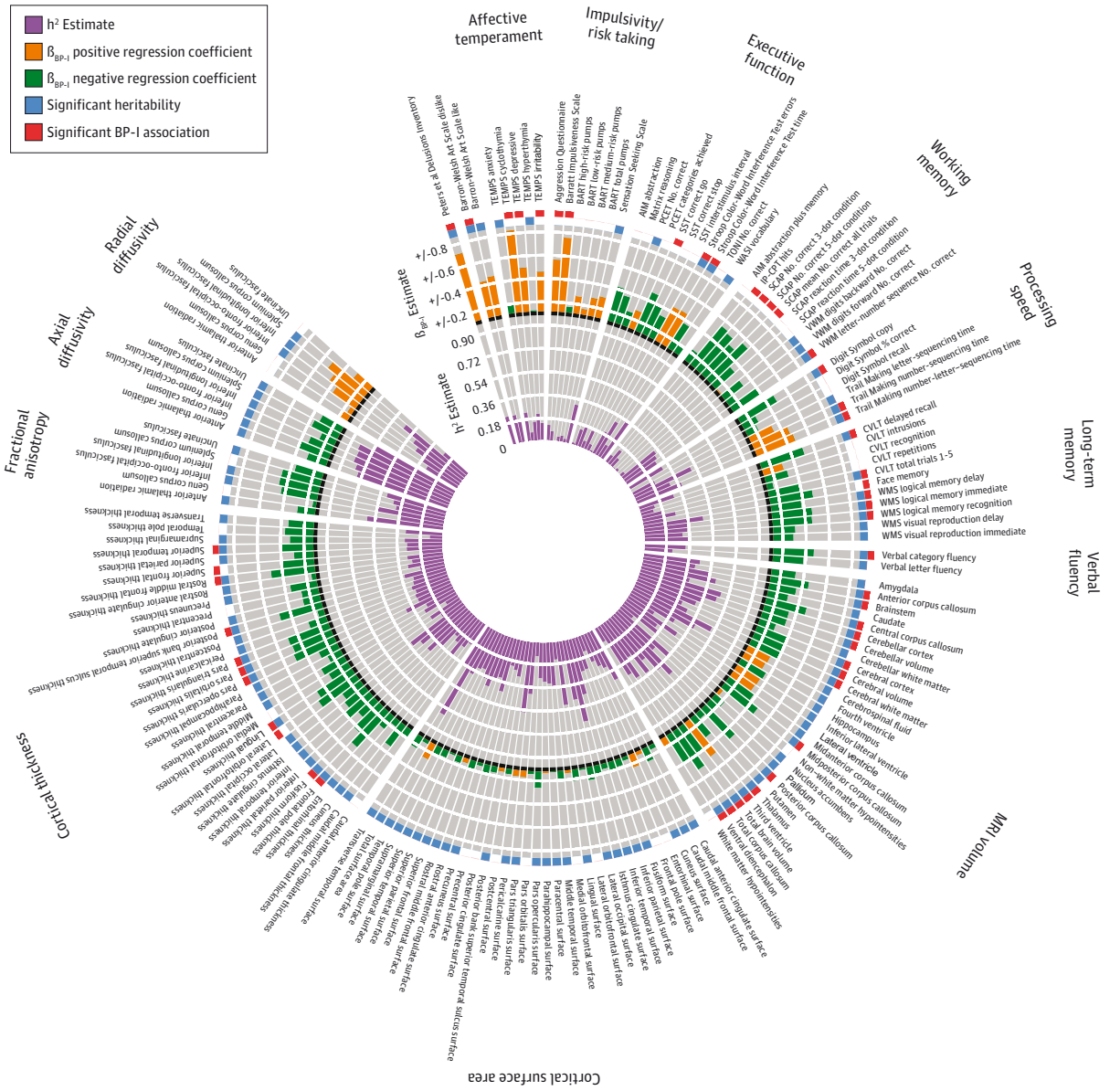
Most neuroimaging phenotypes (approximately 82%) were significantly heritable, and a substantial number of these measures were significantly associated with BP-I. Several global measures differed between participants with BP-I and their relatives without BP-I (decreased total cerebral gray and white matter and cerebellar volumes, with corresponding increases in third-ventricle volume). Localized reductions were also observed in several structures (**Figure 2**), including thalamus and ventral diencephalon (while amygdala and hippocampus showed a similar trend). The T1-weighted sequences also provided evidence for BP-I–related changes in white matter; participants with BP-I showed overall volumetric decreases in the corpus callosum and 4 of the 5 corpus callosum subdivisions.

Compared with relatives without BP-I, participants with BP-I displayed widespread reduction of cortical thickness in heteromodal association regions in most of the prefrontal and temporal cortex, including the superior temporal gyrus, fusiform, and lingual regions (Figure 2B). Most lateral prefrontal cortex regions, including all subregions of the inferior frontal gyrus, were significantly thinner in participants with BP-I. In contrast, the medial orbitofrontal region was neither heritable nor associated with BP-I. Another exception to the overall pattern of findings was the superior frontal gyrus, which showed BP-I–associated gray matter reduction but was not significantly heritable. Most measures of regional surface area were heritable but were not significantly associated with BP-I.

Evaluation of Between-Trait Phenotypic and Genetic Correlations

Using false discovery rate methods, we determined thresholds (t) for rejecting the null hypothesis of correlation = 0; t = 2.59 SEs from 0 for phenotypic correlations (ρ_p) and 2.86 SEs from 0 for genetic correlations (ρ_g). About 19% of trait pairs (2024 of 10 585) exceeded t for ρ_p and 8% of heritable pairs (407 of 5050) exceeded t for ρ_g. Schematic representations (eAppendix 1 in Supplement) of the networks of phenotypic and genetic correlations (**Figure 3**) demonstrate the clustering of phenotypes by domain, showing no clear separation between heritable and nonheritable traits (circles and squares, respectively). Similarly, BP-I–associated traits showed no distinct clustering (nodes with a red border). The

Figure 1. Summary of Analyses of Heritability and Association With Bipolar I Disorder



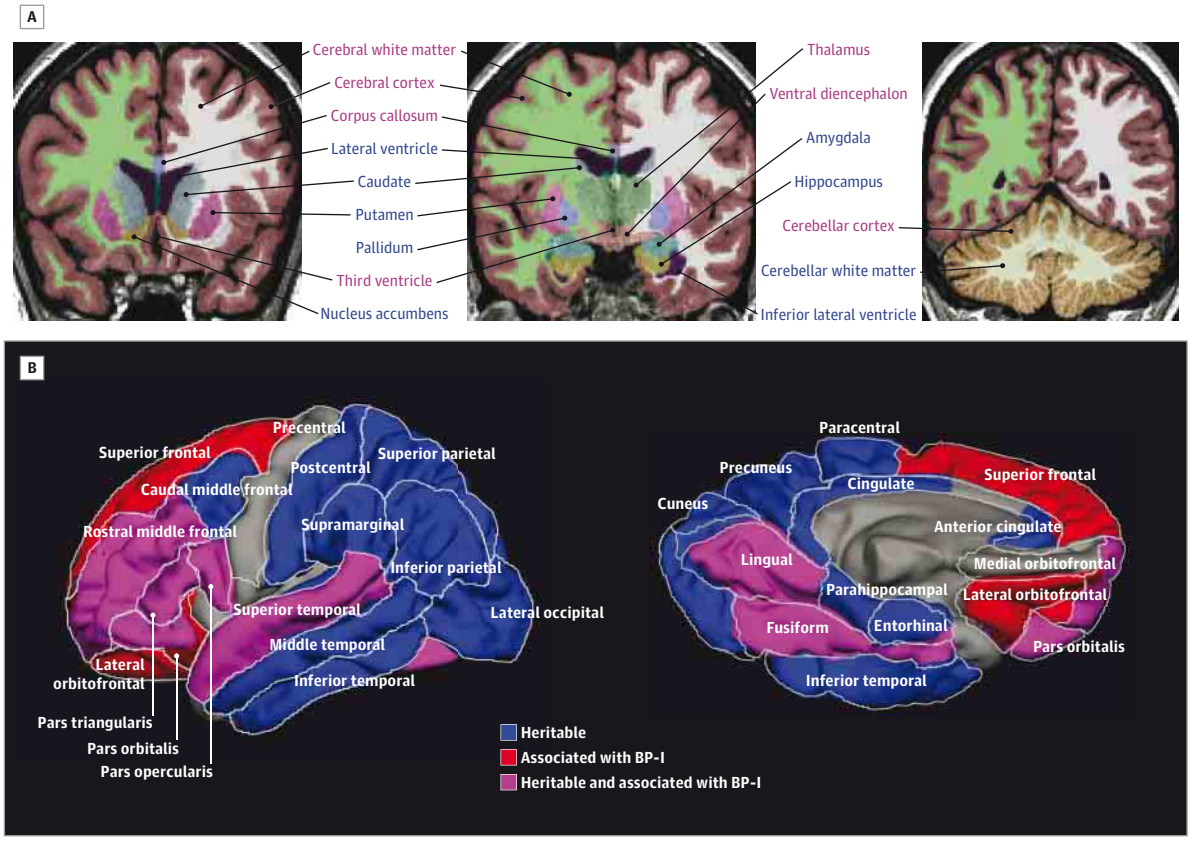
The results of analyses of heritability and of association with bipolar I disorder (BP-I) are shown as 2 histograms stacked on top of each other. Inner histogram purple bars show the magnitude of the heritability estimate for each component phenotype, and the blue box next to the trait name at the outer edge of the plot indicates estimates that passed the significance threshold. Outer histogram shows the magnitude of the estimated regression coefficient for the BP-I association test. Orange bars show positive coefficients representing traits that are higher in participants with BP-I compared with family members without BP-I. Green bars show negative coefficients representing traits that are lower in participants with BP-I. A red box at the outer edge of the circle indicates traits that exceeded the significance threshold for association with BP-I. AIM indicates Abstraction, Inhibition, and Working Memory Task; BART, Balloon Analogue Risk Task; CVLT, California Verbal Learning Test; IP-CPT, Identical Pairs Continuous Performance Test; MRI, magnetic resonance imaging; PCET, Penn Conditional Exclusion Test; SCAP, Spatial Capacity Delayed Response Test; SST, Stop Signal Task; TEMPS, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego; TONI, Test of Nonverbal Intelligence; VWM, verbal working memory; WASI, Wechsler Abbreviated Scale of Intelligence; and WMS, Wechsler Memory Scale.

network structure of the genetic correlations was sparser than, but qualitatively similar to, that of phenotypic correlations. Traits mainly clustered within phenotypic domains, but some genetic correlations across domains were observed, such as Stroop errors with inferior parietal surface area (Figure 3B; nodes 34 and 87).

Discussion

Through the most comprehensive evaluation to date of BP component phenotypes, we delineated measures that may help elucidate the genetic contribution to BP-I risk. Gauging the po-

Figure 2. Structural Neuroimaging Phenotypes



A, Results of the heritability and bipolar I disorder (BP-I) association analyses of volumetric magnetic resonance imaging phenotypes. The 3 representative T1-weighted coronal magnetic resonance images depict the results of the Freesurfer segmentation overlaid as colored masks selected to better distinguish the anatomy. Mask colors are not related to the results. The colors of the text labels indicate structures that showed significant evidence of familial aggregation (blue) and structures that were both heritable and associated with BP-I (magenta). B, Cortical thickness phenotypes and results of the heritability and BP-I association analysis for cortical gray matter thickness. The medial surface is rotated upward by 60° to provide a view of the ventral surface.

tential informativeness of traits based on their heritability and association with BP-I, we can divide them into 4 groups.

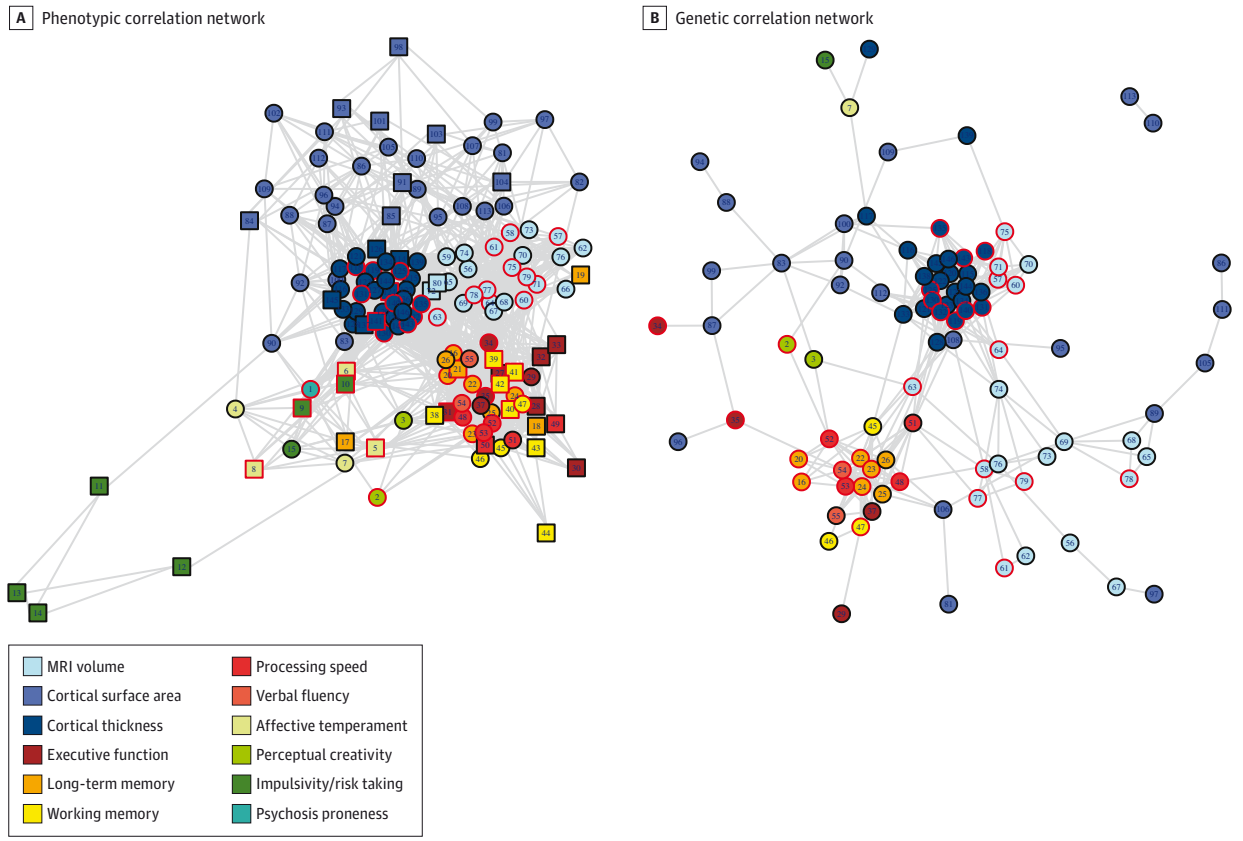
Measures that demonstrate both heritability and association with BP-I (group 1) are the most promising phenotypes for identifying loci contributing to disease risk, as shown for other neuropsychiatric disorders.[75] Analyses at loci linked to and/or associated with both BP-I and a group 1 phenotype will suggest the degree of BP-I genetic risk directly attributable to that measure; some loci may, of course, contribute to trait variability but not to disease risk.

All domains that we assessed include group 1 phenotypes. Some phenotypes in this group, such as delusion proneness,[76] appear broadly characteristic of the major psychoses. Others, such as perceptual creativity, appear specific to BP predisposition[77-79]; individuals diagnosed as having BP are overrepresented in creative occupations compared with individuals diagnosed as having other psychiatric disorders or with the general population.[78,79] Many individuals with BP consider heightened creativity a positive aspect of their condition,[80] which should fuel efforts to elucidate the mechanisms underlying this association.

Among the neurocognitive processes in group 1, the BP-I associations reflect impairments in processing speed, verbal learning and memory, category fluency, and inhibitory control, mirroring findings from previous BP and schizophrenia case-control, family, and pedigree studies.[20,21,51,81-85] Such phenotypes could contribute to the shared risk between these disorders suggested by recent genome-wide association studies.[86]

Group 1 neuroimaging measures provide the first confirmation in families of BP-related anatomical variations previously identified through case-control studies.[87-92] Although generally in accord with structural MRI findings from prior studies, our results identified larger zones of BP-I-associated gray matter reduction, which may reflect the greater size and reduced ethnic heterogeneity of the sample. We identified volume reduction and cortical thinning in 2 prefrontal systems implicated in BP pathogenesis: (1) a corticocognitive network anchored in the dorsolateral and ventrolateral prefrontal cortex, including most subdivisions of the inferior frontal gyrus, which plays a role in attention, working memory, and inhibitory control and shows attenuated activation in functional MRI studies of individuals with BP[93-98]; and (2) a ventral-limbic system implicated in emotional reactivity, involving the hippocampus, amygdala, and orbitofrontal cortex.[87,89-91] Further, the reduced corpus callosum volume aligns with twin studies suggesting genetically influenced alterations of this structure

Figure 3. Network Graph of Correlations Among Phenotypes



Network representations of pairwise phenotypic correlations (A) and genetic correlations (B). All trait pairs were included in the phenotypic correlation analysis, and only pairs in which both traits were heritable were included in the genetic correlation analysis. Nodes are colored according to their assigned subdomain (see Subdomain column in eTable 1 in Supplement). Circular nodes indicate significantly heritable phenotypes; square nodes, nonheritable phenotypes. Traits that were significantly associated with bipolar I disorder have a red border. Nodes are connected with an edge when the hypothesis of correlation = 0 was rejected using false discovery rate–controlled thresholds. Numbers correspond to plot identification numbers for phenotypes detailed in eTable 1 in the Supplement. MRI indicates magnetic resonance imaging. B, Examples of genetically correlated traits mentioned in the text include the hippocampus (67), amygdala (56), and surface area of the pars opercularis (97) as well as Stroop Color-Word Interference Test errors (34) with surface area measures from the inferior parietal region of interest (87).

in BP.[99,100] Gray matter reduction in temporal structures, including the superior temporal, lingual, and fusiform gyri, is noteworthy given the involvement of these structures in facial emotion identification, a process impaired in individuals with BP and adolescents at high risk.[101-105]

Numerous phenotypes, including most of the neuroimaging measures, were heritable but not associated with BP-I (group 2). The lack of difference in cortical surface area between participants with BP-I and their relatives without BP-I supports previous evidence dissociating this measure from cortical thickness abnormalities characteristic of the disorder.[92] Similarly, neurocognitive traits in this category have consistently demonstrated heritability in twin and family samples[84,106-113] but have shown inconsistent association with BP-I.[20,21,81,114]

A third set of phenotypes showed BP-I association but were not heritable (group 3), suggesting they may be predominantly influenced by environmental or disease-specific factors. Previous studies have proposed that temperament is a key contributor to BP genetic risk,[115] but we found little evidence for heritability of several measures associated with emotional reactivity (cyclothymic, irritable, and depressive temperament, aggression, and impulsivity) that were elevated in our participants with BP-I.

Our results for neurocognitive traits are remarkably similar to those reported in the only previously published study of such traits in BP pedigrees,[51] with 3 exceptions. First, we did not find significant heritability for face memory (which was impaired in participants with BP-I in both studies). Second, we observed significant impairment in participants with BP-I on measures of sustained attention and spatial working memory. As deficits in these domains may index psychotic symptoms, regardless of diagnosis,[116] this discordance may reflect the larger percentage of patients in our sample with a lifetime history of psychosis. Finally, we found lower heritability for nonverbal abstract reasoning. As we report heritability estimates corrected for demographic variables, comparisons with the prior study are with its similarly corrected estimates.

We identified extensive correlation among measures within each phenotypic domain, including phenotype clusters consistently implicated in BP pathology. Some such clusters also showed evidence of shared genetic influence (eg, limbic regions with the pars opercularis of the inferior frontal gyrus[98]). This analysis also suggests shared genetic influence among select measures across domains, eg, that between Stroop test performance and surface area MRI measures.

Our ascertainment strategy emphasized close family relationships, enhancing the power for quantitative genetic analyses; however, the shared genetic and environmental backgrounds of our participants would tend to make them more similar to each other compared with cases and independently ascertained controls and reduce power to identify phenotypic associations with BP-I. Two scenarios may explain group differences observed for some phenotypes: participants with BP-I may carry risk alleles with strong and/or nonadditive phenotypic effects, and/or they may have experienced different environmental exposures, either prior to illness onset or as a consequence of the disorder. As the ascertainment of the pedigrees themselves and of the specific individuals evaluated within them were nonrandom with respect to clinical diagnosis, our data are not suitable for assessing the genetic relationship between these phenotypes and BP-I.

Although prior evidence supported the selection of each measure that we evaluated, the use of alternative measures could have yielded discrepant outcomes. While such discrepancies may reflect incompatibilities in the theoretical underpinnings of different instruments (eg, for temperament scales), identification of genetic coassociations between BP-I and specific component measures will accelerate the standardization of phenotyping.

Conclusions

Our findings establish a core set of measures across multiple domains as component phenotypes for identifying the genetic basis of BP-I risk. Overall, the profile of brain and behavioral impairments in these pedigrees is similar to those identified previously in case-control samples. We therefore anticipate that while specific genetic variants contributing to these phenotypes and to BP-I risk may be distinct to the CVCR and ANT population isolates, they could suggest genes that also influence disease risk in other populations.

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