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Multi-system Component Phenotypes of Bipolar Disorder for Genetic Investigations of Extended Pedigrees

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Nelson B. Freimer and Carrie E. Bearden had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Abstract

IMPORTANCE—Genetic factors contribute to risk for bipolar disorder (BP), yet its pathogenesis remains poorly understood. A focus on measuring multi-system 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 impact on BP as well as its component phenotypes.

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

DESIGN—Multi-generational pedigree study in two closely related, genetically isolated populations: the Central Valley of Costa Rica (CVCR) and Antioquia, Colombia (ANT).

PARTICIPANTS—738 individuals, all from CVCR and ANT pedigrees, of whom 181 are affected with BP-I.

MAIN OUTCOME MEASURE—Familial aggregation (heritability) and association with BP-I of 169 quantitative neurocognitive, temperament, magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI) phenotypes.

RESULTS—Seventy-five percent (126) of the phenotypes investigated were significantly heritable, and 31% (53) were associated with BP-I. About 1/4 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 and microstructural integrity 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—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.

Introduction

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 (GWAS) 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 here our investigation, in 26 pedigrees selected for multiple cases of severe BP (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 BP-affected individuals, and values in non-BP individuals intermediate between those of their BP-relatives and control subjects. These phenotypes assay temperament[13–15]; perceptual creativity[16–18]; neurocognitive function[19–21]; and neuroanatomy (via structural magnetic resonance imaging [sMRI] 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 etiologic 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 here, 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 here 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, utilizing genealogic information to extend each pedigree. To prioritize pedigree branches for quantitative

phenotyping we recruited nuclear families including at least one member with known BP-I (based on the Diagnostic Interview for Genetics Studies, DIGS[37,38], and/or extensive medical records), available parents, and at least two non-BP-I siblings (see Supplementary Material, e1.1 for additional details). Families varied considerably in size (12 to 355 members, mean = 55), and in the number of individuals phenotyped in this study (three to 177, mean = 29; 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 (BE) process, modified from previous procedures[33](Supplementary Material, section e1.2), and including diagnostic interviews using Spanish versions of the Mini International Neuropsychiatric Interview[39]and the DIGS. Individuals designated as BP-I had a BE diagnosis of BP-I, unipolar mania, or schizoaffective disorder, bipolar type, as in previous studies[27,33,40]. The Young Mania Rating Scale (YMRS)[41]and the 17-item Hamilton Depression Rating Scale (HDRS)[42] administered at the time of assessment, identified individuals with significant mood symptoms (YMRS > 14 or HDRS ≥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 seven instruments (Supplementary Material, e1.3), included multiple dimensions categorized into four subdomains: affective temperament, impulsivity/risk-taking, perceptual creativity and delusion-proneness (Table 2). The neurocognitive battery (Supplementary Material, e1.4) included a computerized neuropsychological evaluation[43], and paper-and-pencil measures of verbal abilities, inhibitory control[44], and declarative memory[45].

Neuroimaging

We acquired T1-weighted structural neuroimages on 1.5 Tesla scanners, from 527 subjects (285 from CVCR and 242 from ANT) (Supplementary Material, e1.5), implementing protocols for acquisition of diffusion tensor images (DTI) in ANT only. We used Freesurfer software[46,47], with manual inspection of intermediate steps in the processing stream to correct common errors, to generate 96 sMRI phenotypes, including measures of volume, surface area, and cortical thickness (Table 2 and eTable2)[48,49].

We determined DTI phenotypes (Supplementary Material, e1.5) using FSL[50,51], employing the Johns Hopkins University probabilistic tractography atlas[52]to determine and customize ROIs, which we limited to tracts previously associated with BP[53–55]. In total we generated 18 DTI phenotypes across three categories, fractional anisotropy (FA), the degree of anisotropy; axial diffusivity (AD), diffusivity along the major axis of diffusion; and radial diffusivity (RD), an average of the diffusivities along the two minor axes[56–59] (Table 2, eTable2).

Statistical Analyses

We assessed familial aggregation of traits using SOLAR[60], 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 $Var(Y) = \sigma_g^2 + \sigma_e^2$, and the covariance between phenotype values of individuals *i* and *j* is $Cov(Y_i,Y_j)=2\ \phi_{ij}\ \sigma_g^2$, where ϕ_{ij} is the kinship between individuals *i* and *j*.

Variance components analysis is sensitive to outliers and non-normal trait distributions. To guard against potential statistical artifacts induced by skewed distributions, we used, prior to analysis, a rank-based procedure[61]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[62].

We regressed all phenotypes on three covariates (sex, age and country). Additional covariates included years of education (temperament and neurocognitive measures), body weight (T1-weighted and DTI variables), intracranial volume (ICV, volume measurements from T1-weighted images), and total cortical surface area (regional surface area measures). We implemented regressions in SOLAR, using pedigree structures, employing 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 family-wise error rate at the 0.05 level, using a Bonferroni-corrected threshold for each test (heritability and BP-I association; $p<2.96\times10^{-4}$). We used published 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 one-tailed test, eTable2.

We estimated phenotypic correlations for all trait pairs. Genetic correlations were estimated for all pairs in which both traits were significantly heritable using SOLAR[63]. Graphs of the estimated correlation structures used methods described in Supplementary Material, e1.6.

Results

Sample characteristics

Table 1 shows summary statistics for the sample, by family; eTable1 provides additional clinical characterization of the 181 subjects who met BE criteria for BP-I. We excluded five individuals with elevated YMRS or HDRS scores from analyses of neurocognitive and temperament data, and five additional individuals from BP-I association analyses (but not from heritability analyses) because a BP-I diagnosis could neither be confirmed nor excluded.

Heritability and Association with BP-I

Of the 169 traits examined, 126 (74.6%) were significantly heritable, 53 (31.3%) were significantly associated with BP-I, and 41 (24.3%) were both heritable and associated with BP-I (Figure 1 and eTable2). These results were robust with respect to phenotype variations across pedigrees and countries (data not shown) and to outliers (Supplementary Material, e2 and eFigure1); for secondary analyses of the effects of medications and duration of illness on trait values see Supplementary Material, e3. Results within each domain are described below.

Temperament—Six of the fifteen temperament measures demonstrated significant heritability, although overall this domain showed the lowest estimates of additive genetic influence (h^2~0.18–0.30). In contrast, three temperament traits displayed the strongest BP-I-associations of all 169 measures: TEMPS cyclothymia scale, BIS, and PDI. Delusion-proneness (PDI) and perceptual creativity (BWAS-Dislike) were both heritable and associated with BP-I, while risk-taking propensity (BART) 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 (13/19); within this heritable subset, most were associated with BP-I (9/13). Within working memory assessments, verbal but not spatial tasks showed evidence of heritability, and BP-I subjects showed significant impairment on measures of sustained attention (IP-CPT), spatial working memory (SCAP), and verbal working memory tasks (Letter-Number Sequencing). Measures of inhibitory control (Stroop Color-Word interference and SST) showed evidence for impairment in BP-I subjects, of which the Stroop measures (Color-Word interference trials, time and number of errors) were also heritable. Nonverbal abstract reasoning measures (AIM, TONI, Matrix Reasoning) were neither significantly heritable, nor associated with BP-I.

Neuroimaging—Most neuroimaging phenotypes (~88%) were significantly heritable, and a substantial number of these measures were significantly associated with BP-I. Several global measures differed between BP-I subjects and their non-BP-I relatives (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 hippocampus and ventral diencephalon (while amygdala and thalamus show a similar trend). The T1-weighted and DTI sequences provided convergent evidence for BP-I-related changes in the corpus callosum; BP-I subjects showed decreases in volume (total callosum and four of the five callosal subdivisions) and overall fractional anisotropy, while increased radial diffusivity in the splenium of the callosum indicated reduced white matter integrity.

Compared to non-BP-I relatives, BP-I subjects displayed widespread reduction of cortical thickness in heteromodal association regions in most of the prefrontal (PFC) and temporal cortex, including the superior temporal gyrus (STG), inferior temporal gyrus (IFG), fusiform and lingual regions (Figure 2, lower panel). Most lateral PFC regions, including all

subregions of the inferior frontal gyrus and lateral orbitofrontal cortex, were significantly thinner in BP-I subjects. 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 FDR methods we determined thresholds (*t*) for rejecting the null hypothesis of correlation=0; $t = 2.58$ standard errors (SE) from 0 for phenotypic correlations (rho_p), and 2.81 SE from 0 for genetic correlations (rho_g). About 20% (2117/10,585) of trait-pairs exceeded *t* for rho_p and 9.9% (539 of 5460) of heritable pairs exceeded *t* for rho_g. Schematic representations (Supplementary Material, e1.6) of the networks of phenotypic and genetic correlations (Figure 3) demonstrate the clustering of phenotypes by domain, showing no clear separation between heritable and non-heritable traits (circles and squares, respectively). Similarly, BP-I associated traits showed no distinct clustering (nodes with a red border). The 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 rostral middle frontal and inferior parietal surface area (Figure 3; nodes 34, 87, and 107, right panel).

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 potential informativeness of traits based on their heritability and association with BP-I, we can divide them into four 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[64]. Analyses at loci linked and/or associated to both BP-I and to 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[65], appear broadly characteristic of the major psychoses. Others, such as perceptual creativity, appear specific to BP predisposition[66–68]; individuals diagnosed with BP are over-represented in creative occupations compared to individuals diagnosed with other psychiatric disorders, or to the general population[67,68]. Many BP-affected individuals consider heightened creativity a positive aspect of their condition[69], 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[20,21,43,70–74]. Such phenotypes could contribute to the shared risk between these disorders suggested by recent GWAS[75].

Group 1 neuroimaging measures provide the first confirmation in families of BP-related anatomic variations previously identified through case-control studies[76–81]. Although generally in accord with sMRI 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 significant volume reduction and cortical thinning in two prefrontal systems implicated in BP pathogenesis; 1) a cortico-cognitive network anchored in the dorsolateral and ventrolateral PFC, including all subdivisions of the inferior frontal gyrus, which plays a role in attention, working memory and inhibitory control, and shows attenuated activation in fMRI studies of BP subjects[82–87], and; 2) a ventral-limbic system implicated in emotional reactivity, involving the hippocampus, amygdala and orbitofrontal cortex[76,78–80]. Further, the reduced corpus callosum volume and white matter integrity aligns with twin studies suggesting genetically influenced alterations of this structure in BP[88,89]. Gray matter reduction in temporal structures, including the superior temporal sulcus (STS) and the lingual and fusiform gyri, are noteworthy given the involvement of these structures in facial emotion identification, a process impaired in BP individuals and adolescents at high-risk[90–94].

Numerous phenotypes, including the majority of the neuroimaging measures, were heritable but not associated with BP-I (Group 2). The lack of difference in cortical surface area between BP-I subjects and their non-BP-I relatives supports previous evidence dissociating this measure from cortical thickness abnormalities characteristic of the disorder[81]. Similarly, neurocognitive traits in this category have consistently demonstrated heritability in twin and family samples[73,95–102] but have shown inconsistent association with BP-I[20,21,70,103].

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[104], 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 BP-I subjects.

Our results for neurocognitive traits are remarkably similar to those reported in the only previously published study of such traits in BP pedigrees[43], with three exceptions. First, we did not find significant heritability for face memory (which was impaired in BP-I subjects in both studies). Second, we observed significant impairment in BP-I individuals on measures of sustained attention and spatial working memory. As deficits in these domains may index psychotic symptoms, regardless of diagnosis[105], 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 to 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 (e.g. limbic regions with the pars opercularis of the inferior frontal gyrus[87]). This analysis also suggests shared genetic influence among select measures across domains, e.g. 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 subjects would tend to make them more similar to each other compared to 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: BP-I subjects may carry risk alleles with strong and/or non-additive phenotypic effects, and/or 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 non-random 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 employment of alternative measures could have yielded discrepant outcomes. While such discrepancies may reflect incompatibilities in the theoretical underpinnings of different instruments (e.g., for temperament scales), identification of genetic co-associations between BP-I and specific component measures will accelerate the standardization of phenotyping.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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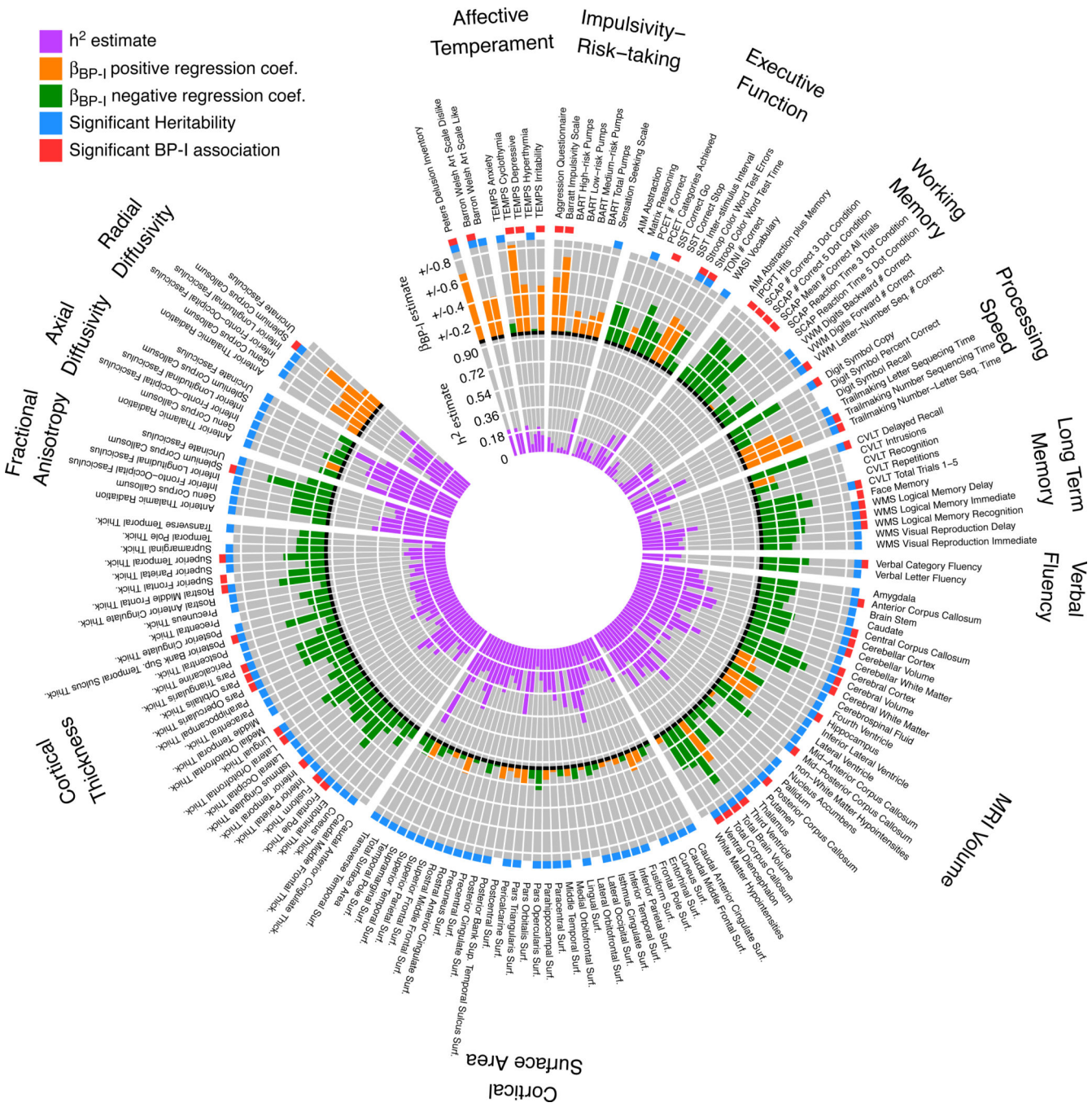

Figure 1. Summary of analyses of heritability and association with BP-I

The results of analyses of heritability and of association with BP-I are shown as two 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. In *orange are positive coefficients* representing traits that are higher in BP-I subjects compared to non-BP-I family members. *In green are negative coefficients*

representing traits that are lower in BP-I subjects. A red box at the outer edge of the circle indicates traits that exceeded the significance threshold for association with BP-I. Abbreviations; PCET; Penn Conditional Exclusion Test, SST; Stop Signal Task, TONI; Test of Nonverbal Intelligence, AIM; Abstraction Inhibition and Memory test, IPCPT; Identical Pairs Continuous Performance Test, VWM; verbal working memory, CVLT; California Verbal Learning Test, WMS; Wechsler Memory Scale, BART; Balloon Analog Risk Task; TEMPS, Temperament Evaluation of Memphis, Pisa, Paris and San Diego; WASI, Wechsler Abbreviated Scale of Intelligence; SCAP, Spatial Capacity Delayed Response Test.

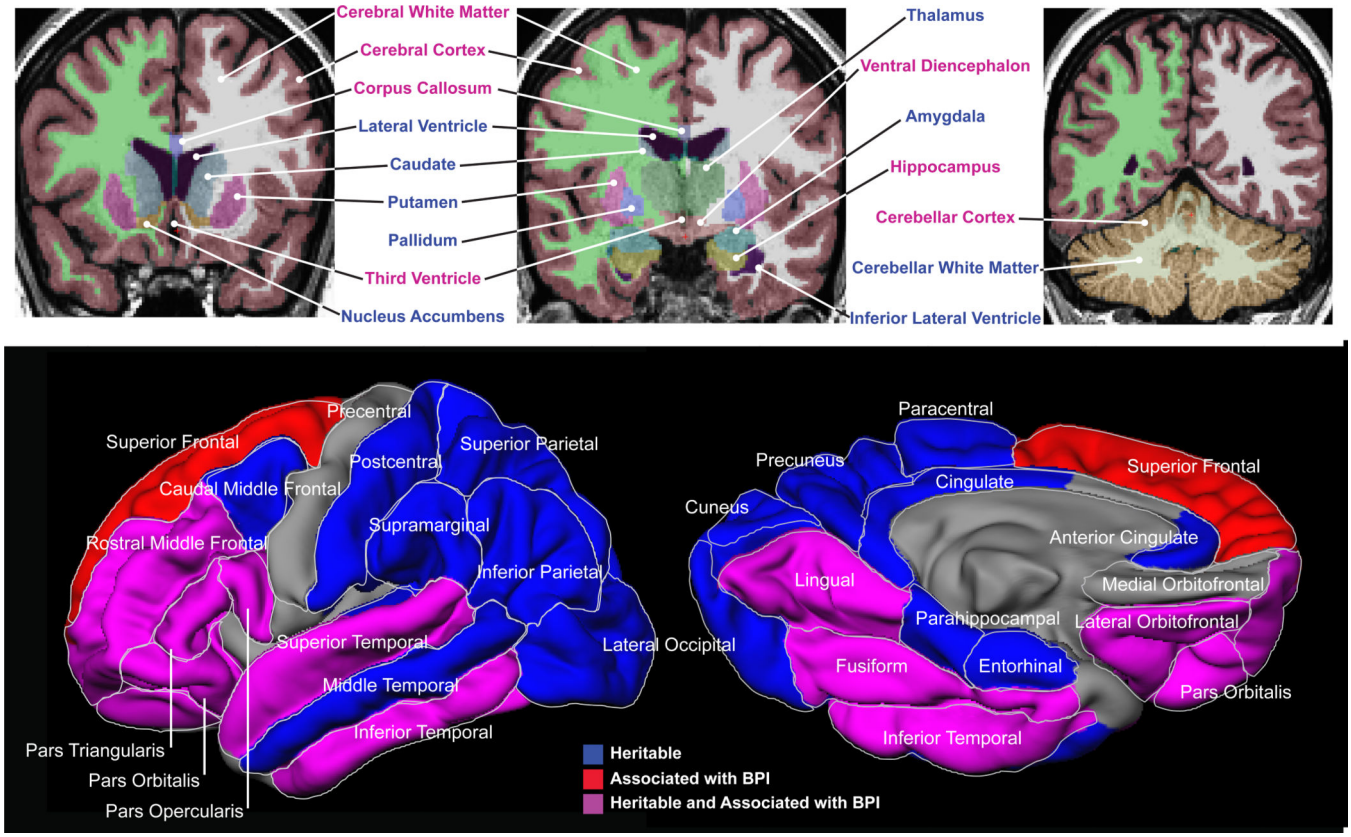

Figure 2. Structural neuroimaging phenotypes

Upper panel shows results of the heritability and BP-I association analyses of volumetric MRI phenotypes. The three representative T1-weighted MRI coronal 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).

Lower panel depicts cortical thickness phenotypes and shows the results of the heritability and BP-I association analysis for cortical gray matter thickness. Heritable cortical regions are colored in blue, BP-I-associated regions are shown in red and regions that were both heritable and associated with BP-I are colored in magenta. The medial surface is rotated upwards by 60° to provide a view of the ventral surface.

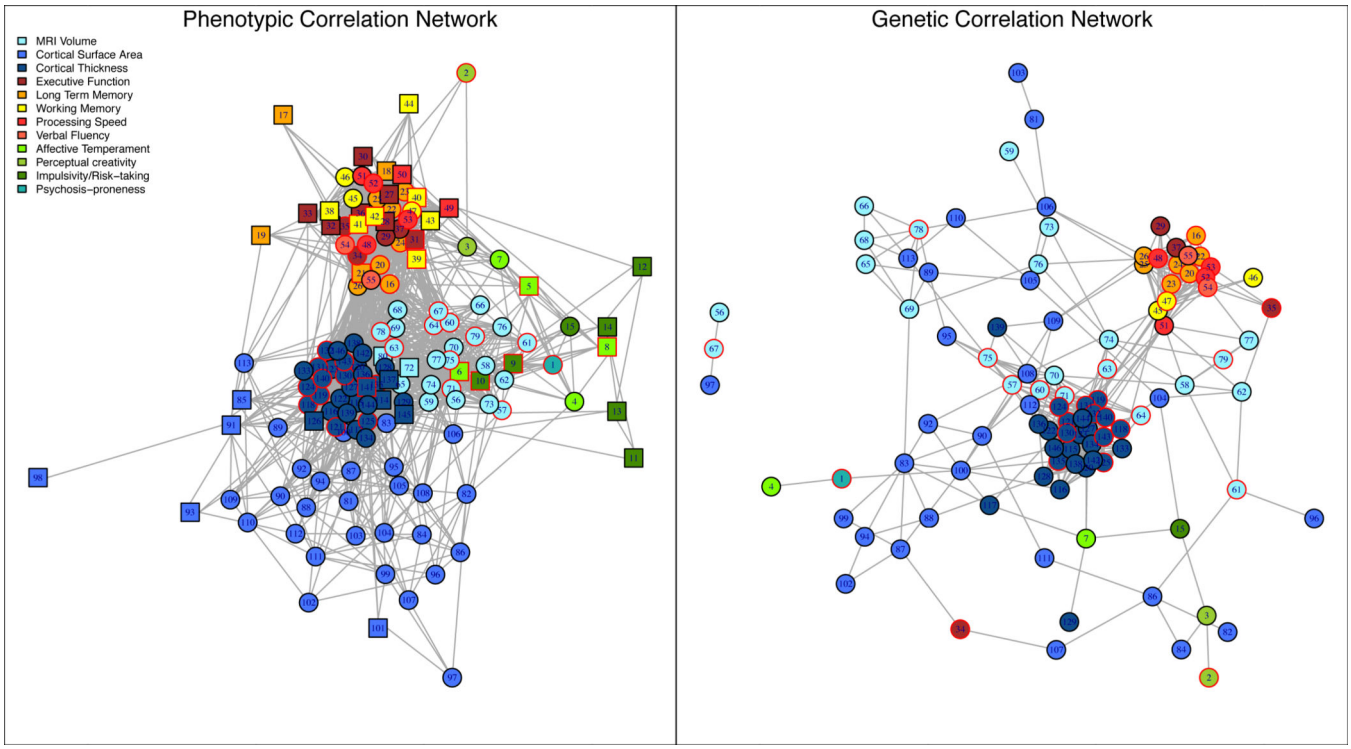

Figure 3. Network graph of correlations among phenotypes

Network representations of pairwise phenotypic correlations are drawn in the left panel and genetic correlations are shown in the right panel. 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 eTable2 in the Supplemental). Circular nodes represent significantly heritable phenotypes and square nodes represent non-heritable phenotypes. Traits that were significantly associated with BP-I are drawn with a red border. Nodes are connected with an edge when the hypothesis of correlation=0 was rejected using FDR-controlled thresholds. Numbers on the graph correspond to Plot ID's for phenotypes detailed in eTable2 in the Supplemental. Examples of genetically correlated traits mentioned in the main text can be seen in the right panel and include; 1) the hippocampus (#67), amygdala (#56) and surface area of the pars opercularis (#97); and 2) Stroop Color Word Test Errors (#34) with surface area measures from the inferior parietal (#87), and rostral middle frontal (#107) ROIs.

Table 1

Sample Characteristics by Country and Family

Summary statistics for each country are shown in the first two rows with the remaining rows providing information for each family. The second column shows total size and number of BP-I cases for each pedigree and the remaining columns show the summary statistics for individuals with phenotype data. Education was assessed in years. Abbreviations; ANT, Antioquia, Colombia; CVCR, Central Valley of Costa Rica.

Total Sample		Sample Assessed for Component Phenotypes				
Family	**n (BP-I cases)**	**n (BP-I cases)**	**MRI (DTI)**	**Female**	**Mean Age (SD) <range>**	**Mean Years of Education (SD) <range>**
ANT All	512 (96)	353 (86)	242 (225)	58%	47.7 (17.7) <18–85>	8.3 (4.7) <0–23>
CVCR All	918 (128)	386 (95)	285 (0)	55%	49.1 (15.6) <18–87>	7.8 (4.9) <0–24>
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) <18–85>	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>
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>

Total Sample		Sample Assessed for Component Phenotypes				
Family	**n (BP-I cases)**	**n (BP-I cases)**	**MRI (DTI)**	**Female**	**Mean Age (SD) <range>**	**Mean Years of Education (SD) <range>**
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>

Table 2
Behavioral and Neuroimaging Measures

Summary of methods used to generate phenotypes. The upper rows of the table list the instruments and measures used to assess temperament and neurocognitive phenotypes. The lower rows list the neuroimaging regions of interest (ROIs). ROIs highlighted in bold represent measures that were derived by summing sub-region measures that are also included as traits (e.g. total brain volume is the sum of total cerebral, total cerebellar and brain stem volumes). For each cortical surface ROI, two measures were determined; surface area and average gray matter thickness. Abbreviations; FA, fractional anisotropy; AD, axial diffusivity; RD radial diffusivity.

Subdomain	Instrument	Phenotype	Measure
Temperament			
Delusion-proneness	Peters Delusion Inventory[106]	Peters Delusion Inventory	Score on 40 items assessing delusional ideation and unusual perceptual experiences
Perceptual Creativity	Barron Welsh Art Scale[16,107]	Barron Welsh Art Scale Dislike	Preference rating on simple/ symmetric figures of 86 total
		Barron Welsh Art Scale Like	Preference rating on complex/ asymmetric figures of 86 total
Affective Temperament	TEMPS-A[108]	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[109]	Aggression Questionnaire	Score on 12 item Likert-scale of aggressive traits/behaviors
	Barratt Impulsivity Scale[110]	Barratt Impulsivity Scale	Score on 30 item Likert-scale assessing frequency of impulsive behaviors
	Sensation Seeking Scale[111,112]	Sensation Seeking Scale	Score on 40 items of sensory stimulation preferences
	Balloon Analog Risk Task[113]	BART Low-risk Pumps	Number of balloon pumps on Low-risk trials
		BART Medium-risk Pumps	Number of balloon pumps on Medium-risk trials
		BART High-risk Pumps	Number of balloon pumps on High-risk trials
		BART Total Pumps	Total number of balloon pumps on all trials
Neurocognition			
Long Term Memory	California Verbal Learning Test	CVLT Delayed Recall	Number of items out of 16 word list recalled after a 20 min. delay
		CVLT Intrusions	Number of intrusions during list recollection

Subdomain	Instrument	Phenotype	Measure
		CVLT Recognition	Number of items out of 16 word list recognized after a 20 min delay
		CVLT Repetitions	Number of repeated words during list recollection
		CVLT Total Trials 1–5	Number of items recalled over 5 repeated exposures of a 16 word list
	Miscellaneous[43]	Face Memory	Number of faces recalled from visual presentation after delay
	Wechsler Memory Scale[45]	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
Executive Function	Abstraction Inhibition and Working Memory[114]	AIM Abstraction	Number of correctly matched shapes presented simultaneously
	Wechsler Abbreviated Scale of Intelligence	Matrix Reasoning	Number of correctly completed patterns
		WASI Vocabulary	Number of correctly named/ defined objects/words
	Penn Conditional Exclusion Test[115]	PCET # Correct	Number of correctly identified non-matching objects
		PCET Categories Achieved	Number of categories of achieved
	Stop Signal Task	SST Correct Go	Number of correct go trials
		SST Correct Stop	Number correct stop trials
		SST Inter-stimulus Interval	Response time (ms) on correct stop trials
	Stroop Color-Word Interference Test[44]	Stroop Color Word Test Errors	Number of errors on Color-Word test
		Stroop Color Word Test Time	Time needed to complete test
	Test of Non-verbal Intelligence[116]	TONI # Correct	Number of correctly completed progressive matrices
Working Memory	Abstraction Inhibition and Working Memory[114]	AIM Abstraction plus Memory	Number of correctly matched shapes after delayed target presentation
	Identical Pairs Continuous Performance Test	IPCPT Hits	Number of correctly identified pairs on continuous performance test
	Spatial Capacity Delayed Response Test	SCAP # Correct 3 Dot Condition	Number of correct responses on 3-dot spatial delayed memory task
		SCAP Reaction Time 3 Dot Condition	Response time (ms) on 3-dot condition

Subdomain	Instrument	Phenotype	Measure
		SCAP # Correct 5 Dot Condition	Number of correct responses on 5-dot spatial delayed memory task
		SCAP Reaction Time 5 Dot Condition	Response time (ms) on 5-dot condition
		SCAP Mean # Correct All Trials	Mean number of correct responses on all trials
	Miscellaneous[43]	VWM Digits Forward # Correct	Correctly recalled digits strings in original order of presentation
		VWM Digits Backward # Correct	Correctly recalled digits strings in reverse order of presentation
		VWM Letter-Number Seq. # Correct	Correctly recalled number-letter strings, in alpha-numeric sequence
Processing Speed	Miscellaneous[43]	Digit Symbol Copy	Correctly identified digit-symbol pairs in 90 sec
		Digit Symbol Recall	Number of digits recalled when presented with corresponding symbols
		Digit Symbol Percent Correct	Percent correct on digit-symbol task
	Trail Making Test	Trailmaking Letter Sequencing Time	Time needed to connect letters in alphabetical order
		Trailmaking Number-Letter Seq. Time	Time needed to connect alternating sequence of numbers and letters
		Trailmaking Number Sequencing Time	Time needed to connect numbers in ascending order
Verbal Fluency	Miscellaneous[43]	Verbal Letter Fluency	Words starting with a specific letter generated in 60 sec.
		Verbal Category Fluency	Animal names generated in 60 sec.
Neuroimaging			
Measure	Analysis Package	Regions of Interest (ROIs)	
MRI Volume	FreeSurfer[46,47]T1-Weighted Images	Amygdala, Anterior Corpus Callosum, Brain Stem, 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, Mid-Anterior Corpus Callosum, Mid-Posterior 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 Area		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[50,51]DTI	Anterior Thalamic Radiation, Genu Corpus Callosum, Inferior Fronto-Occipital Fasciculus, Inferior Longitudinal Fasciculus, Splenium Corpus Callosum, Uncinate Fasciculus	