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Neurocognitive Endophenotypes for Bipolar Disorder Identified in Multiplex Multigenerational Families

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Abstract

Context—Although genetic influences on bipolar disorder are well established, localization of genes that predispose to the illness has proven difficult. Given that genes predisposing to bipolar disorder may be transmitted without expression of the categorical clinical phenotype, one strategy for identifying risk genes is the use of quantitative endophenotypes.

Objective—The goal of the current study is to adjudicate neurocognitive endophenotypes for bipolar disorder.

Design, Setting, and Participants—709 Latino individuals from the central valley of Costa Rica, Mexico City, Mexico, or San Antonio, Texas participated in the study. 660 of these persons were members of extended pedigrees with at least two siblings diagnosed with bipolar disorder (n=230). The remaining subjects were community controls drawn from each site and without personal or family history of bipolar disorder or schizophrenia. All subjects received psychodiagnostic interviews and comprehensive neurocognitive evaluations. Neurocognitive measures found to be heritable were entered into analyses designed to determine which tests are impaired in affected individuals, sensitive to genetic liability for the illness and genetically correlated with affection status.

Main Outcome Measures—The main outcome measure was neurocognitive test performance.

Results—Two of the 21 neurocognitive variables were not significantly heritable and were excluded from subsequent analyses. Patients with bipolar disorder were impaired on 6 of these

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cognitive measures compared to non-related healthy subjects. Non-bipolar first-degree relatives were impaired on five of these and three tests were genetically correlated with affection status: digit symbol coding, object delayed response, and immediate facial memory.

Conclusions—This large-scale extended pedigree study of cognitive functioning in bipolar disorder identified measures of processing speed, working memory and declarative (facial) memory as candidate endophenotypes for bipolar disorder.

Keywords

bipolar disorder; endophenotype; genetics; family studies; neurocognitive; neuropsychological

Introduction

Despite considerable evidence that risk for bipolar disorder is inherited, the molecular genetic basis for this illness remains elusive. A recent genome wide association analysis with over 5,000 cases and 6,000 controls implicated two risk genes for the illness, ANK3 and CACNA1C[1]. As these genes regulate voltage-gated sodium or calcium channels, respectively, the findings suggest that ion channel dysfunction may play an important role in the pathophysiology of bipolar disorder. However, as noted by the authors, theses genes (SNPs) have relatively small risk-ratios, explaining little of the genetic contribution of the illness. Given the high heritability and familial relative risk of bipolar disorder, there is little doubt that additional genes are involved in the etiology of bipolar disorder. The identification of these genes is of paramount importance as they hold the potential for spurring novel treatments for this common and debilitating illness.

Given that genes predisposing bipolar disorder may be transmitted without expression of the clinical phenotype, one strategy for identifying risk genes is the use of quantitative intermediate phenotypes or endophenotypes for the illness[2]. Indeed, a National Institute of Mental Health workgroup charged with improving research on genetics of affective disorders called for the widespread implementation of endophenotypic markers in the search for genes predisposing to bipolar disorder[3]. However, relatively few endophenotypes have been proposed for the illness[4], and fewer still have been validated in large-scale studies. Findings that asymptomatic individuals with bipolar disorder have neuropsychological impairments[5, 6], that these deficits appear to be stable over time[7] and that unaffected first-degree relatives of bipolar probands have similar, though less pronounced, impairments[8], suggest that neurocognitive measures may be candidate endophenotypes for the illness[9]. The goal of the current study is to test the hypothesis that neurocognitive tests are candidate endophenotypes for bipolar disorder.

Quantitative neurocognitive endophenotypes can be assessed in both affected and unaffected individuals, providing much greater statistical power to localize and identify disease-related genes than affection status alone[10, 11]. However, establishing a particular measure as an endophenotype requires that the trait be heritable, sensitive to affection status, and genetically correlated or associated with the illness (e.g. [2, 12]). While neurocognitive endophenotypes are appropriate for various linkage and association experimental designs, the establishment of a particular trait as a intermediate phenotype is most efficient with large extended pedigrees (e.g. [13]), as these families provide a single sample where all of the criteria for effective endophenotypes can be assessed simultaneously (e.g. heritability, sensitivity to the illness, genetic correlation).

In the current study, comprehensive neurocognitive assessments were conducted on large multigenerational pedigrees selected for sibling pairs concordant for bipolar I disorder or schizoaffective disorder, bipolar subtype, and community controls. The focus on multiplex

families reduces the potential of spurious or non-genetic forms of the illness and increases the potential that identified intermediate phenotypes reflect genetic factors that influence risk for bipolar disorder. To determine if a neurocognitive measure is a candidate endophenotype for bipolar disorder, we document its heritability, demonstrate that patients and their unaffected first-degree relatives are impaired on the measure, and establish genetic correlation between the measure and affection status.

Methods

Participants

709 Latino individuals from the central valley of Costa Rica (n=328, 46% of the sample), Mexico City, Mexico (n=139, 20%), or San Antonio, Texas (n=242, 34%) participated in the study. 660 of these persons were members of 45 families (average family size 14.67±10.56 members, range: 3-37) with at least two siblings diagnosed with bipolar disorder. Probands were recruited through systematic screening of outpatient and inpatient facilities. Inclusion and exclusion criteria were the same across sites and required a previous hospital diagnosis of bipolar I disorder in probands and at least one sibling with bipolar I disorder or schizoaffective disorder, bipolar type. In the current study, affected individuals were excluded if they did not provide written consent to contact family members, had history of mental retardation, a neurological disorder, or severe head trauma. Once an affected sibling pair provided informed consent, attempts were made to recruit all 1st, 2nd and 3rd degree relatives. Inclusion and exclusion criteria were identical for family members, with the exception of requiring a personal history of bipolar disorder. The remaining 49 subjects were community controls drawn in equal numbers from each site and without personal or family history (1st degree relatives) of bipolar disorder or schizophrenia. Community controls were recruited through advertisements in local newspapers and via fliers placed in medical clinics and had the same inclusion and exclusion criteria as family members.

All subjects proved written informed consent on forms in the language of their choice (Spanish or English) approved by the review boards of all participating study sites.

Diagnostic Assessment

All participants, regardless of diagnostic or family status, received the Diagnostic Interview for Genetic Studies[14] and the Family Interview for Genetic Studies[15]. Interviews were conducted by psychiatrists with established reliability (kappa = 0.85). Final diagnoses were determined through a best estimation processes[16] where two independent psychiatrists review all available records, arrive at independent diagnoses and reach a consensus diagnoses. If consensus could not be reached, a third best estimator reviewed the case independently (this occurred once in this sample).

Neurocognitive Assessment

Each participant received the South Texas Assessment of Neurocognition (STAN), a 90-min neuropsychological evaluation consisting of standard and computerized measures[13]. Tests were selected on evidence of heritability, sensitivity to bipolar disorder, and minimizing the effects of language (culture) or the availability of parallel English and Spanish forms. Instructions for computerized neuropsychological tests were translated to Spanish by bilingual psychologists and translated back into English by professional translators. Other tests (e.g. the California Verbal Learning Test) have published English[17] and Spanish[18] editions. All subjects received the same battery of tests, in the language of their choice, in a fixed order and were allowed breaks as needed.

The STAN battery included 16 tests with 21 separate measures (see Table 1). The computerized digit-symbol coding task required subjects to indicate, via button press, if a centrally presented digit-symbol pair was identical to one of the nine digit-symbol pairs in the reference list at the top of the screen[13]. During the identical pairs continuous performance test, subjects viewed a series of numbers presented briefly on the screen, pressing the space bar whenever the same number appeared twice in a row (e.g.[19]). During the manual Stroop test, subjects pressed arrow keys that faced in the same direction (congruent) or in the opposite direction (incongruent) as an arrow on the screen (e.g. [20]). The spatial delayed response task involved subjects remembering where a set of yellow circles appeared and indicating, via button press, if a green circle was presented in the same location[21]. During the object delayed response task, subjects remembered three abstract shapes (presented serially) and, after a delay, selected one of four shapes not part previously presented. The Penn facial memory test involved the presentation of 20 target faces and then immediate and delayed recognition (indicated by button press) of these faces mixed with an equal number of foils[22]. During the Penn conditional exclusion test (PCET), subjects choose stimuli based upon inferred rules and are provided feedback[23]. On each trial of the PCET, subjects choose which one of four objects (that vary in shape, height or width), do not belong with the other three stimuli[23].

Quantitative Genetic Analyses

Analyses were performed to determine which neurocognitive measures were (1) heritable, (2) sensitive to liability for bipolar disorder, and (3) genetically correlated with bipolar disorder. To ensure that the neuropsychological traits conform to the assumptions of normality, an inverse normal transformation was applied. All analyses were conducted with Sequential Oligogenic Linkage Analysis Routines (SOLAR[24]). The algorithms in SOLAR employ maximum likelihood variance decomposition methods to determine the relative importance of familial and environmental influences on a measure by modeling the covariance among family members as a function of genetic proximity (kinship).

Heritability Analyses—Heritability (h^2) represents the portion of the phenotypic variance accounted for by the total additive genetic variance ($h^2 = \sigma^2_g/\sigma^2_p$). Indices with stronger covariance between genetically more similar individuals than between genetically less similar individuals have higher heritability. Within SOLAR, this is assessed by contrasting the observed covariance matrices for a neuropsychological measure with the covariance matrix predicted by kinship and a likelihood ratio test is performed to test the hypothesis that the heritability is > 0. Heritability analyses were conducted twice: without demographic covariates and again with age, sex, age × sex interaction, age^2, age^2 x sex interaction, education level (years), and location of assessment included as covariates in the model. While the second h^2 estimates are critical for the current investigation, the raw estimates were included for comparability to other published data. Only neuropsychological variables with significant heritability, corrected for multiple comparison at a 5% false discovery rate (FDR[25]) were included in subsequent analyses.

Sensitivity to Bipolar Disorder—Heritable neuropsychological variables were examined to determine which measures differentiate individuals with bipolar disorder from unrelated, unaffected individuals. Within SOLAR, these analyses were conducted by including a variable that identified individuals in specific liability groups (e.g. bipolar vs. unrelated) and testing whether the mean of these groups differed within the context of the known pedigree structure and covariates (χ^2 test). Evidence that a particular neurocognitive measure was sensitive to bipolar disorder was provided if the grouping variable explained a significant proportion of trait variance at 5% FDR. Effect size estimates (standardized mean differences) were derived using the following equation: effect size = $((4*\chi)/(n-\chi))^{-1/2}$,

where n is the number of individuals included in the analyses. Given the non-independence of participants, this effect size estimate is conservative.

Neurocognitive measures sensitive to bipolar disorder were examined in analogous analyses in unaffected (non-bipolar) 1st degree relatives to confirm that the candidate endophenotype reflected underlying genetic vulnerability. An individual's liability for bipolar disorder was defined as the shortest genetic distance to an affected individual.

Bivariate Analyses—To determine if neurocognitive measures sensitive to bipolar disorder are influenced by the same genetic factors that influence risk for the illness, genetic correlation analyses were conducted. More formally, bivariate polygenic analyses were performed to estimate genetic (ρ_g) and environmental (ρ_e) correlations between affection status (bipolar or not bipolar) and cognitive measures sensitive to the illness. The significance of these correlations were tested by comparing the *In* likelihood for two restricted models (with either ρ_g or ρ_e constrained to equal 0.0) against the *In* likelihood for the model in which these parameters were estimated. The *In* likelihood values of the general and restricted models were compared using the likelihood ratio test and significance was set at 5% FDR. A significant genetic correlation is evidence for pleiotropy, that a gene or set of genes influences both phenotypes[26]. In the context of this study, a significant genetic correlation suggests that the same genetic factor or factors may influence risk for bipolar disorder and neurocognitive performance.

Finally, multivariate analyses were performed on those neurocognitive traits genetically correlated with bipolar disorder to determine if these traits represent independent risk factors. Significant genetic correlation between neurocognitive traits correlated with bipolar disorder raises the possibility that a single genetic factor (gene or set of genes) influences multiple endophenotypes, implying that these endophenotypes may not represent independent genetic paths to the illness.

Results

Sample Characteristics

Of the 660 subjects from extended pedigrees, 230 had a best estimate consensus DSM-IV diagnosis of bipolar disorder (161 Type I; 51 Type II; 6 Not Otherwise Specified) or schizoaffective disorder bipolar subtype (n=12) and are considered part of a "broad bipolar phenotype" (Table 2). Six individuals were diagnosed with schizophrenia or schizoaffective depressive subtype and were excluded from all analyses. Among family members without major psychosis, 243 were unaffected (non-bipolar spectrum) 1st degree, 86 were unaffected 2nd degree and 42 were unaffected 3rd degree relatives of affected individuals. 108 subjects were not biologically related to affected individuals and were used to form a genetic "unrelated" control sample: 59 were subjects who had married into selected families and 49 were unaffected subjects with no biologic or familial ties to the other subjects. Liability groups differed in average age ($F[3,704]=34.57$, $p<0.0001$) and in gender distributions ($\chi=7.15$, $p=0.05$), but not in education level ($F[3,704]=0.89$, $p=0.44$). Individuals with the broad bipolar phenotype had significantly higher rates of anxiety disorders ($\chi=32.34$, $p>0.0001$) and past alcohol abuse/dependence ($\chi=63.52$, $p>0.0001$) than their non-bipolar family members and unrelated participants. 56% of the individuals with the broad bipolar phenotype were prescribed psychotropic medications at the time of assessment: 66 were taking antidepressants, 16 were on lithium, 41 were on mood stabilizers, 30 were on anticonvulsants, 57 were on sedatives, 37 were on atypical antipsychotics, 23 were on typical antipsychotics, and 11 were on stimulants.

Heritability

Estimated heritability for 21 neurocognitive variables are presented in Table 3. Although demographic covariates were fixed for all analyses, those covariates that reached significance for a specific neurocognitive measure are included in the far right column. Two measures failed to reach significant levels of heritability: CVLT Semantic Clustering and CVLT Delay Recall. Performance on these measures was significantly correlated with education and differed by location. When these covariates were omitted from analyses, these indices were significantly heritable.

Location of Assessment

Location of assessment significantly influenced performance on many neurocognitive measures (see Table 3). Examining differences between individual sites indicated that the effect sizes for these differences were generally small. Indeed the average effect size for neurocognitive performance differences between San Antonio and Costa Rica was 0.32, between San Antonio and Mexico City was 0.20, and between Mexico City and Costa Rica was 0.17. In contrast, the effect size for formal education was 0.61. This pattern of results is consistent with our prior work in these locations[13].

Sensitivity to Liability for Bipolar Disorder

Results from the analyses determining the sensitivity of individual neurocognitive measures to liability for bipolar disorder are given in Table 4. Individuals with the broad bipolar phenotype were statically impaired on 6 of the 19 heritable cognitive measures compared to unrelated, unaffected subjects, after controlling FDR. To examine diagnostic specificity, analyses were repeated after constraining the affected group to bipolar I disorder patients alone. Bipolar I patients were impaired on all of the measures identified in the broad phenotype group, and were additional deficit on semantic fluency.

Given that individuals with bipolar disorder have increased rates of comorbid anxiety and alcohol use disorders (e.g. Table 2), it is unclear if neurocognitive impairments are due to these co-occurring illnesses or bipolar disorder *per se*. Hence, analyses were repeated with lifetime history of anxiety disorders and alcoholism included as covariates. Although anxiety disorders were associated with fewer hits on the CPT ($p=9.8\times10^{-3}$) and alcoholism was linked to deficits on the CPT (hits, $p=1.3\times10^{-4}$) and the trail making test (Trails A $p=0.043$; Trails B $p=3.2\times10^{-3}$), the addition of these covariates did not substantially alter the pattern of results in Table 4.

As psychotropic medications may influence neurocognitive performance, use of psychotropic medications at the time of assessment was entered as a covariate into the model. However, individuals with the broad bipolar phenotype remained significantly impaired on measures sensitive to bipolar disorder when controlling for medication usage (data not shown). Furthermore, unaffected 1st degree relatives, who do not typically use psychotropic medications, were impaired on five of these measures relative to unrelated control subjects: digit symbol coding, letter-number span, object delayed response, and immediate and delayed facial memory.

Bivariate Analyses

Estimates of genetic and environmental correlations performed on the neurocognitive measures impaired in bipolar disorder and the broad bipolar phenotype are given in Table 5. Of these measures, three were significantly negatively correlated with affection status: digit symbol coding, object delayed response and immediate facial memory, indicating that worse cognitive performance on these measures is related to increasing genetic risk for bipolar disorder. None of the environmental correlations were significant, given the false discovery

rate. Similar correlations were observed when affection status was defined as bipolar I disorder (digit symbol coding: $\rho_g \pm SE = -0.511 \pm 0.21$, p=0.037; object delayed response: −0.531±0.17, p=0.009; immediate facial memory = −0.442±0.19, p=0.034).

In the full sample, digit symbol coding performance was significantly genetically correlated with object delayed response performance ($\rho_g \pm SE = 0.784 \pm .09$, $p=3.3\times10^{-03}$) and immediate facial memory (0.593±0.16, p=0.001). Similarly, object delayed response performance was significantly correlated with immediate facial memory (0.619±0.12, $p=9.9\times10^{-5}$). This suggests that these traits were influenced by the same genetic factors.

Discussion

Measures of processing speed, working memory and declarative (facial) memory are candidate endophenotypes for bipolar disorder. Each of these measures was heritable, impaired in individuals with the illness and their non-bipolar relatives, and genetically correlated with affection status. Although a number of investigators have demonstrated that healthy first-degree relatives of bipolar probands have memory or executive functioning impairments, this is the first large-scale family-based study to provide evidence that the neurocognitive deficits found in bipolar disorder are related to genetic liability for the illness and, thus, can be considered intermediate phenotypes for bipolar disorder. While there are various definitions for intermediate phenotypes or endophenotypes[2, 12], there is universal agreement that these measures must be associated with genetic liability for the illness under investigation. An implicit assumption about endophenotypes is that the same gene or genes that convey risk for disease also influence the intermediate phenotype. More formally, there is an assumption of pleiotropy for illness status and the intermediate phenotype. In quantitative genetic methodology, pleiotropy can be demonstrated through estimation of genetic correlation[26]. Unfortunately, in non-twin designs, genetic correlation requires relatively large samples (n>300-500) of related individuals and, hence, is rarely applied in psychiatric genetics investigations. However, without formally demonstrating pleiotropy, one of the primary criteria of an intermediate phenotype is left untested. Each of the candidate endophenotypes identified in this study meet the necessary and sufficient criteria for a viable intermediate phenotype, providing testable hypotheses about brain systems implicated in the pathophysiology of bipolar disorder. Indeed, the delineation of three neurocognitive endophenotypes for bipolar disorder should spur a series of neuropsychological, neuroimaging and molecular genetic studies designed to refine the traits in question and determine their neural and genetic correlates.

Digit-symbol coding performance is an index of speed of processing, or the time needed to execute simple cognitive operations. Although speed of processing has not been localized to a single brain region, cognitive neuroscience emphasizes the integration of information across spatially distinct brain regions[27, 28], suggesting that cognitive slowing as indexed by processing rate is related to neuronal efficiency[29]. Several investigators have reported that euthymic individuals with bipolar disorder have moderate to severe digit-symbol impairments[6, 30, 31]. Although, speed of processing measures like the digit-symbol may be negatively influenced by psychotropic medications, a recent meta analysis in schizophrenia suggested that medication status had little effect on patient performance[32]. Furthermore, at least two previous studies have reported poor digit-symbol performance in unaffected family members of bipolar disorder probands[33, 34]. Our results further these findings by showing a significant negative genetic correlation between bipolar disorder and digit-symbol coding performance.

The object delayed response task[35] includes the maintenance and manipulation of memory for complex visual objects and was modeled after measures used in electrophysiological

studies of non-human primates[36]. Functional MRI experiments indicate that task performance engages a complex network of brain areas associated with working memory (e.g. prefrontal, temporal and parietal regions)[37]. Furthermore, patients with bipolar disorder showed relative hyperactivation in the right prefrontal and anterior cingulate regions and relative hypoactivation in medial temporal and visual processing regions compared to healthy subjects[37]. While relatively few investigators have used delayed response tasks in bipolar disorder, working memory deficits, particularly when manipulation of information is critical, have been consistently reported in remitted patients[5]. In contrast, there is little prior evidence for working memory dysfunction in unaffected bipolar relatives (e.g. [8]). The current findings suggest that the application of working memory or executive measures specifically designed for use in affective disorders could improve sensitivity of these measures to liability for bipolar disorder[38]. Nonetheless, the current findings should be confirmed in an independent sample.

Declarative memory impairments are among the most commonly reported cognitive deficits in bipolar disorder. Although most investigators report verbal memory impairments, visuospatial and facial memory deficits have also been observed in euthymic bipolar patients[5, 8]. Indeed, in an early investigation of monozygotic twin-pairs discordant for bipolar disorder, Gourovitch and colleagues[39] reported facial memory impairment in unaffected co-twins of bipolar probands. In the current study, verbal declarative memory was assessed with the California Verbal Learning Test[17, 18]. While CVLT performance was heritable and impaired in individuals with bipolar disorder, non-bipolar first-degree relatives were not statically different from healthy subjects. Our findings are similar to those reported in a recent meta analysis of cognitive performance in unaffected 1st degree relatives of bipolar probands[8]. Hence, while the current study nominates a facial declarative memory task as a candidate endophenotype for bipolar disorder, verbal declarative memory measures can not be excluded and may represent important risk factors for the illness. More generally, while findings from the current study are encouraging, they are limited by the families studied and the neurocognitive tests employed. Additional studies in different samples and with overlapping test batteries are warranted.

Significant heritability estimates indicate that a phenotype is more strongly influenced by genetic than environmental factors. However, heritability estimates do not provide information concerning the underling genetic architecture of a phenotype and are subject to a number of assumptions[40]. Indeed, phenotypes with high heritable estimates are not necessarily influenced by fewer genes or by genes with larger effects. For example, normal variation in adult height is highly heritable (h^2=0.89-0.93[41]), but current estimates suggest that up to 44 independent loci are associated with normal stature[42, 43]. In contrast, phenotypes with somewhat lower heritability estimates may have less complex genetic architectures. For example, the estimated heritability of the neuregulin 1 transcript was 0.50, but linkage analysis indicated a single locus (lod=15.8) on chromosome 8[44, 45]. Thus, while an intermediate phenotype should be heritable, the strength of the heritability estimate may be less critical. Heritability estimates for bipolar disorder are typically higher than those reported here for neurocognitive traits. Yet, it remains to be seen if the genetic architectures of these neurocognitive endophenotypes are less complex than for the illness itself. Furthermore, simulation studies indicate that quantitative intermediate phenotypes should be significantly more powerful for identifying genes than qualitative diagnoses[46].

Intermediate phenotypes can inform psychiatric noseology. Although bipolar disorder is considered a discreet psychiatric illness with a unique etiology, there is growing evidence that the illness may have some common genetic roots with schizophrenia[47]. Each of the neurocognitive endophenotypes nominated for bipolar disorder have also been found in schizophrenia. Indeed, the digit-symbol task applied here was the most sensitive cognitive

measure of genetic liability for schizophrenia in our extended pedigree study[13]. Similarly, the facial declarative memory measure has previously been found sensitive risk for schizophrenia[48]. Although the object delayed response task[35] employed here has not been used in schizophrenia family studies, similar measures have been proposed as intermediate phenotypes for the illness[48]. Although the spatial delayed response task applied in the current study was previously shown to be sensitive to genetic liability for schizophrenia[49, 50], individuals with the broad bipolar phenotype were not impaired on this measure, implying some level of diagnostic specificity. However, we have shown in two separate samples that bipolar patients with lifetime history of psychotic symptoms are impaired on this test, while patients without formal psychosis are not[38, 51], suggesting that the manifestation of psychosis may be linked to spatial working memory deficits rather than a specific diagnostic category. It is possible that by using a broad bipolar phenotype, where few individuals manifest psychosis, we obscured deficits on this test. Indeed, when affection status was limited to bipolar I disorder alone, impairments on this test were more pronounced, though still below the FDR requirement. These findings raise questions about the specificity of these intermediate phenotypes for bipolar disorder alone, rather than psychotic illness more generally. However, it is unlikely that these questions will be fully addressed until the genetic factors that influence both these neurocognitive endophenotypes and bipolar disorder are identified and found to also confer risk for schizophrenia.

A number of the neurocognitive measures impaired in individuals with bipolar disorder were not impaired in non-bipolar 1st degree relatives. Performance on these measures may be sensitive to the environmental factors necessary for the diathesis of the illness and thus impairment in affected individuals is not associated with genetic risk for bipolar disorder. Alternately, these tests may be influenced by affective or psychotic symptoms, psychotropic medication, sleep disturbances or other sequella of the illness. Indeed, current symptomatology and psychotropic medications used to treat bipolar disorder have been shown to impair performance on specific neurocognitive tests[6, 52]. Although 56% of the patients included in the study were medicated at the time of assessment, inclusion of a single covariate coding psychotropic medication usage did not significantly alter the observed of results. While this analysis was coarse and did not account for potentially important factors (e.g. lifetime history of medication usage, specific class of medication), each of the proposed intermediate phenotypes was also impaired in non-symptomatic and unmedicated unaffected 1st degree relatives. Hence, it is unlikely that the candidate endophenotypes identified here are explained by patient mood symptoms or medication usage.

Although the pattern of results did not significantly differ when affection status was constrained to bipolar I disorder, it is difficult to make conclusions about diagnostic specificity from this sample. Seventy percent of affected individuals were bipolar type I and those individuals with type II, NOS or schizoaffective disorder were genetically related to bipolar I patients. In order to draw inferences about the utility of these cognitive endophenotypes for genetic investigation of non-bipolar type I illnesses, family with these illnesses without bipolar I should be studied. Similar conclusions can be drawn about psychiatric co-morbidities like alcohol abuse and anxiety disorders.

One potential advantage of quantitative neurocognitive endophenotypes is that they may be less genetically complex than psychiatric diagnoses[12, 53]. While this potential has yet to be empirically demonstrated[54], it is possible to examine multiple endophenotypic markers simultaneously, focusing on the gene or genes common to all traits. Such a strategy could reduce the numbers of candidate genes nominated for functional genomic studies, but is only possible in situations where there is a reasonable potential that the various traits share at least part of their genetic makeup. Given that each of the neurocognitive measures elucidated in the current experiment were genetically correlated with each other, it is

unknown if these measures represent independent risk factors for bipolar disorder or are sensitive to a single "cognitive" liability factor. Although this potential genetic overlap facilitates the strategy for prioritizing genes for additional study as described above, additional studies examining the co-segregation of cognitive deficits over multiple generations should be examined.

As demonstrated here and elsewhere[13, 48], computerized neurocognitive measures can be efficiently and reliably administered to large numbers of individuals, a requirement for effective endophenotypes[55]. Indeed, each of the tests sensitive to risk for bipolar disorder was developed specifically for large-scale studies of psychopathology. These tests are currently being applied in a multi-site family-based linkage study of bipolar disorder and in a molecular genetics study of randomly ascertained individuals in large extended pedigrees. Together, these studies should provide clues into the genetic architecture of the neurocognitive endophenotypes identified in the current study and should facilitate localization and identification of specific genes that contribute to these endophenotypes. These genes, in turn, should be examined for association to bipolar disorder. This iterative process should provide a window into the causal neurobiological pathways involved in the illness. The ultimate promise of these measures is the discovery of causal pathway for mental illness and the potential to develop biomarkers for psychiatric disorders.

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Table 1

Neurocognitive Dependant Measures

Neurocognitive Task	Dependant Measure
Letter Fluency[56]	Number of words, beginning with a specific letter, generated in 60-seconds
Semantic Fluency[56]	Number of animal names generated in 60-seconds
Digit-Symbol Coding[13]	Number of correctly identified digit-symbol pairs in 90-seconds
Trail Making Test, Part A[56]	Time needed to connect letters in ascending order
CPT Hits[13]	Number of hits during a 6-minute identical pairs continues performance test (CPT)
CPT Catch Trials[13]	Number of false alarms during a 6-minute identical pairs continues performance test (CPT)
Digit Span Forward[57]	Number of correctly recalled digit strings in their original order of presentation
Stroop Reaction Time[20]	Reaction time difference between incongruent and congruent trials of a manual Stroop test (e.g.20)
Digit Span Backward[57]	Number of correctly recalled digit strings in reverse order of presentation
Letter-Number Span[58]	Number of correctly recalled number-letter strings in numeric and alphabetical order
Spatial Delayed Response[21]	Number of correct responses on a simple spatial delayed-response test
Object Delayed Response[35]	Number of correct trials an object delayed non-match to sample task
CVLT Learning[17]	Number of items recalled over 5 exposures of the 16-word list of the California Verbal Learning Test (CVLT)
CVLT Semantic Cluster[17]	Proximal recall of semantically related list items over 5 repeated exposures of the 16-word list
CVLT Delayed Recall[17]	Number of list item recalled after a 20 min delay
Digit-Symbol Recall[13]	Number of digits recalled when presented with the corresponding symbols from the Digit-Symbol Coding task
Facial Memory Immediate[22]	Number of faces recognized during the initial condition of the Penn Facial Memory test
Facial Memory Delay[22]	Number of faces recognized during the 20-minute delay condition on the Penn Facial Memory test[22]
Matrix Reasoning[59]	Number of correctly completed progressive matrices
PCET[23]	Number correctly matched shapes on the Penn Conditional Exclusion Test (PCET)
Trail Making Test, Part B[56]	Time needed to connect alternating letters and numbers

Table 2

Demographic Characteristics of Extended Pedigree Sample

	n	Age[1]	Education[1]	%Female	% Anxiety	% Alcohol
Broad Bipolar Phenotype[2]	230	40.41 (14.1) [15-77]	10.48 (4.0) [0-24]	61%	35%	40%
Bipolar I Disorder	161	40.67 (13.7) [15-77]	10.32 (3.9) [0-20]	59%	41%	39%
Unaffected 1st Degree	243	44.14 (16.7) [15-85]	10.24 (4.3) [0-22]	63%	20%	21%
Unaffected 2nd & 3rd Degree	128	28.14 (13.5) [15-81]	10.95 (3.2) [3-19]	49%	16%	9%
Unrelated Subjects	108	42.76 (14.0) [16-79]	10.50 (4.2) [0-18]	63%	12%	10%

[1]Age and education expressed in years (standard deviations) [range]

[2]Bipolar I disorder and bipolar spectrum disorders (schizoaffective disorder, bipolar NOS, bipolar II disorder)

Table 3

Heritability of Neurocognitive Measures

Trait	n	Heritability[1]	Heritability[2]	p-values[3]	Significant Covariates[4]
Letter Fluency	685	0.644 (0.08)	0.464 (0.09)	6.9×10^{-11}	ed, loc
Semantic Fluency	685	0.363 (0.08)	0.211 (0.08)	4.7×10^{-04}	age, sex, ed, loc
Digit Symbol Coding	692	0.510 (0.07)	0.335 (0.09)	2.0×10^{-05}	age, age*sex, age^2, age^2*sex, ed, loc
Trails A	613	0.529 (0.08)	0.287 (0.08)	5.3×10^{-06}	age, sex, age*sex, age^2, age^2*sex, ed, loc
CPT Hits	548	0.261 (0.09)	0.265 (0.09)	4.5×10^{-04}	age, ed
CPT Catch Trials	548	0.237 (0.11)	0.335 (0.11)	1.4×10^{-04}	age, ed, loc
Digit Span Forward	670	0.487 (0.08)	0.511 (0.09)	7.0×10^{-11}	age, ed
Stroop Reaction Time	567	0.142 (0.08)	0.223 (0.09)	0.0012	age, sex, ed
Digit Span Backward	670	0.402 (0.07)	0.329 (0.08)	3.2×10^{-08}	age, ed, loc
Letter-Number Span	670	0.503 (0.07)	0.477 (0.09)	7.3×10^{-10}	age, ed
Spatial Delayed Response	624	0.346 (0.09)	0.202 (0.09)	0.0043	age, ed
Object Delayed Response	622	0.566 (0.07)	0.473 (0.10)	1.0×10^{-09}	age, ed, loc
CVLT Learning	692	0.297 (0.08)	0.141 (0.08)	0.0194	age, sex, age*sex, ed, loc
CVLT Semantic Clustering	692	0.316 (0.08)	0.090 (0.12)	0.2188	loc
CVLT Delay Recall	687	0.199 (0.07)	0.033 (0.07)	0.3128	age, sex, age*sex, ed, loc
Digit Symbol Recall	692	0.435 (0.08)	0.254 (0.10)	9.0×10^{-04}	age, age*sex, age^2, age^2*sex, ed, loc
Facial Memory Immediate	699	0.544 (0.08)	0.448 (0.09)	7.1×10^{-09}	age, sex, age^2*sex, ed
Facial Memory Delay	699	0.518 (0.08)	0.416 (0.09)	2.6×10^{-08}	age, sex, ed
Matrix Reasoning	694	0.448 (0.06)	0.331 (0.07)	9.7×10^{-09}	age, age*sex, ed, loc
PCET Correct	700	0.192 (0.07)	0.163 (0.07)	0.0028	age, ed, loc
Trails B	578	0.318 (0.10)	0.258 (0.09)	6.5×10^{-04}	age, sex, age*sex, age^2*sex, ed, loc

[1] Heritability estimate, h^2, and (standard error) without demographic covariates

[2] Heritability estimate, h^2, and (standard error) with demographic covariates

[3] p-values for heritability estimates including covariates

[4] ed = education, loc = location

Table 4

Group Differences for Heritable Neuropsychological Measures

	Broad Bipolar Phenotype			Bipolar I Disorder			1st Degree Relatives		
Trait[1]	**χ^2**	**p-value**	**Effect Size**	**χ^2**	**p-value**	**Effect Size**	**χ^2**	**p-value**	**Effect Size**
Letter Fluency	0.99	0.319	0.109	0.68	0.408	0.101			
Semantic Fluency	4.34	0.037	0.228	**5.83**	**0.016**	**0.298**	0.34	0.561	0.062
Digit Symbol Coding	**27.67**	**1.4×10^{-07}**	**0.597**	**30.74**	**3.0×10^{-08}**	**0.718**	**16.68**	**4.4×10^{-05}**	**0.447**
Trails A	5.05	0.025	0.246	3.01	0.083	0.213			
CPT Hits	0.76	0.384	0.095	0.22	0.637	0.058			
CPT Catch Trials	4.04	0.044	0.220	3.11	0.078	0.216			
Digit Span Forward	3.63	0.057	0.208	2.10	0.147	0.178			
Stroop	0.39	0.533	0.068	0.15	0.696	0.048			
Digit Span Backward	2.04	0.153	0.156	1.25	0.264	0.136			
Letter-Number Span	**17.87**	**2.4×10^{-05}**	**0.473**	**16.14**	**5.9×10^{-05}**	**0.505**	**13.05**	**3.0×10^{-04}**	**0.393**
Spatial Delayed Response	2.60	0.107	0.176	4.67	0.031	0.266			
Object Delayed Response	**46.29**	**1.0×10^{-11}**	**0.797**	**42.36**	**7.6×10^{-11}**	**0.865**	**27.15**	**1.9×10^{-07}**	**0.579**
CVLT Learning	**22.14**	**2.5×10^{-06}**	**0.529**	**26.13**	**3.2×10^{-07}**	**0.656**	2.46	0.117	0.168
Digit Symbol Recall	0.64	0.424	0.087	0.10	0.757	0.038			
Facial Memory Immediate	**44.36**	**2.7×10^{-11}**	**0.777**	**42.40**	**7.4×10^{-11}**	**0.865**	**44.42**	**2.7×10^{-11}**	**0.761**
Facial Memory Delay	**37.53**	**9.0×10^{-10}**	**0.707**	**37.89**	**7.5×10^{-10}**	**0.810**	**33.57**	**6.9×10^{-09}**	**0.650**
Matrix Reasoning	1.71	0.190	0.143	2.43	0.119	0.191			
PCET Correct	0.75	0.385	0.095	0.94	0.333	0.118			
Trails B	3.63	0.057	0.208	3.54	0.060	0.231			

[1] Statically significant group differences, after controlling the false discovery rate, are bolded

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Table 5

Bivaraite Analysis between Affection Status and Neurocognitive Measures

	Broad Bipolar Phenotype					
	Genetic Correlation			Environmental Correlation		
Trait[1]	ρ_g	SE	P	ρ_e	SE	P
Semantic Fluency	0.224	0.27	0.401	−0.169	0.07	0.023
Digit Symbol Coding	**−0.698**	**0.18**	**0.002**	−0.017	0.09	0.851
Letter-Number Span	−0.165	0.20	0.436	−0.110	0.09	0.250
Object Delay Response	**−0.629**	**0.16**	**0.002**	−0.042	0.10	0.688
CVLT Learning	−0.466	0.30	0.160	−0.180	0.07	0.016
Facial Memory Immediate	**−0.573**	**0.18**	**0.004**	0.032	0.10	0.731
Facial Memory Delay	−0.395	0.19	0.067	−0.070	0.09	0.457

[1]Statically significant correlations, after controlling the false discovery rate, are bolded