Title

Distinct and shared contributions of diagnosis and symptom domains to cognitive performance in severe mental illness in the Paisa population: a case-control study

Journal

The Lancet Psychiatry, 7(5)

ISSN

2215-0366

Authors

Service, Susan K
Upegui, Cristian Vargas
Ramírez, Mauricio Castaño
et al.

Publication Date

2020-05-01

DOI

10.1016/s2215-0366(20)30098-5

Peer reviewed

HHS Public Access

Author manuscript

Lancet Psychiatry. Author manuscript; available in PMC 2021 January 07.

Published in final edited form as:

Lancet Psychiatry. 2020 May ; 7(5): 411–419. doi:10.1016/S2215-0366(20)30098-5.

Distinct and shared contributions of diagnosis and symptom domains to cognitive performance in severe mental illness in the Paisa population: a case-control study

Susan K Service,
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Cristian Vargas Upegui,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

Mauricio Castaño Ramírez,
Department of Mental Health and Human Behavior, University of Caldas, Manizales, Colombia

Allison M Port,
Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Tyler M Moore,
Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Marfred Munoz Umanes,
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Luis Guillermo Agudelo Arango,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

Ana M Díaz-Zuluaga,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

Juanita Melo Espejo,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

María Cecilia López,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

Juan David Palacio,

Correspondence to: Prof Carrie E Bearden, Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, Semel Institute, University of California Los Angeles, Los Angeles, CA 90095, USA cbearden@mednet.ucla.edu.

Contributors

CVU, MCR, LGAA, AMD-Z, JME, MCL, JDP, SRS, and JV recruited and interviewed participants and administered test instruments. TMT, MMU, and AE designed databases, coordinated data transfers, and managed data downloads. LOL and JDHG provided EMR data. BBB modified NetSCID for our use. CS, SKS, and TMM were responsible for data analysis. AMP designed databases and was also responsible for data analysis. JIE, VIR, CLJ, RCG, CEB, and NBF designed the study. SKS, CEB, RCG, and NBF wrote the Article.

Declaration of interests

BBB owns stock in TeleSage, which created the NetSCID software using funding from the National Institutes of Health and licenses the SCID from the American Psychiatric Press. All other authors declare no competing interests.

See **Online** for appendix

Department of Psychiatry, University of Antioquía, Medellín, Colombia

Sergio Ruiz Sánchez,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

Johanna Valencia,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

Terri M Teshiba,
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Alesandra Espinoza,
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Loes Olde Loohuis,
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Juan De la Hoz Gomez,
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Benjamin B Brodey,
TeleSage, Chapel Hill, NC, USA

Chiara Sabatti,
Departments of Biomedical Data Science and Statistics, Stanford University, Stanford, CA, USA

Javier I Escobar,
Department of Psychiatry, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Victor I Reus,
Department of Psychiatry, University of California San Francisco, San Francisco, CA, USA

Carlos Lopez Jaramillo,
Department of Psychiatry, University of Antioquía, Medellín, Colombia

Ruben C Gur,
Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Carrie E Bearden,
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Nelson B Freimer
Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

Summary

Background—Severe mental illness diagnoses have overlapping symptomatology and shared genetic risk, motivating cross-diagnostic investigations of disease-relevant quantitative measures. We analysed relationships between neurocognitive performance, symptom domains, and diagnoses in a large sample of people with severe mental illness not ascertained for a specific diagnosis (cases), and people without mental illness (controls) from a single, homogeneous population.

Methods—In this case-control study, cases with severe mental illness were ascertained through electronic medical records at Clínica San Juan de Dios de Manizales (Manizales, Caldas, Colombia) and the Hospital Universitario San Vicente Fundación (Medellín, Antioquía, Colombia). Participants were assessed for speed and accuracy using the Penn Computerized Neurocognitive Battery (CNB). Cases had structured interview-based diagnoses of schizophrenia, bipolar 1, bipolar 2, or major depressive disorder. Linear mixed models, using CNB tests as repeated measures, modelled neurocognition as a function of diagnosis, sex, and all interactions. Follow-up analyses in cases included symptom factor scores obtained from exploratory factor analysis of symptom data as main effects.

Findings—Between Oct 1, 2017, and Nov 1, 2019, 2406 participants (1689 cases [schizophrenia n=160; bipolar 1 disorder n=519; bipolar 2 disorder n=204; and major depressive disorder n=806] and 717 controls; mean age 39 years (SD 14); and 1533 female) were assessed. Participants with bipolar 1 disorder and schizophrenia had similar impairments in accuracy and speed across cognitive domains. Participants with bipolar 2 disorder and major depressive disorder performed similarly to controls, with subtle deficits in executive and social cognition. A three-factor model (psychosis, mania, and depression) best represented symptom data. Controlling for diagnosis, premorbid IQ, and disease severity, high lifetime psychosis scores were associated with reduced accuracy and speed across cognitive domains, whereas high depression scores were associated with increased social cognition accuracy.

Interpretation—Cross-diagnostic investigations showed that neurocognitive function in severe mental illness is characterised by two distinct profiles (bipolar 1 disorder and schizophrenia, and bipolar 2 disorder and major depressive disorder), and is associated with specific symptom domains. These results suggest the utility of this design for elucidating severe mental illness causes and trajectories.

Funding—US National Institute of Mental Health.

Introduction

Schizophrenia, bipolar disorder, and major depressive disorder—the diagnoses that together constitute severe mental illness—are each among the largest contributors to the global burden of disease.[1] The splitting of severe mental illness into these diagnostic categories on the basis of symptoms and classical disease trajectories has long dominated psychiatric research and clinical practice. Research from across the behavioural sciences has increasingly challenged these dichotomies, and stimulated efforts to reorient psychiatric research around systems of dimensional phenotypes.[2,3]

Two main classes of dimensional phenotype have been proposed: symptoms (eg, psychosis), which are components of specific diagnostic categories, but might be present across multiple categories; and quantitative measures that assess neurobehavioural domains (eg, cognitive

function), which are outside the current diagnostic framework, and yet characterise severe mental illness. Cognitive function is impaired in people with severe mental illness overall, compared with people without mental illness, and work over the past decade has shown that symptom components (eg, depression and psychosis) and diagnosis have potentially additive effects on cognition.[4,5] Few large psychiatric case samples have obtained the measures needed to test hypotheses relating symptoms and cognition to severe mental illness, and analyses have been limited by the heterogeneity across study samples in the approaches used for both ascertainment of participants and their phenotypic assessment. Furthermore, going forward, how use of dimensional phenotypes would affect understanding of the biological underpinnings of severe mental illness (eg, through genetic studies) is unclear.

Genome-wide association studies (GWAS) have identified hundreds of loci that are unequivocally associated with severe mental illness,[6] and most of these associations are to a specific diagnosis. However, analyses of the totality of genetic variation represented in these GWAS datasets indicate that the overall polygenic contribution to disease risk has both cross-diagnostic and disorder-specific components.[7] Significant genetic correlations and pleiotropy exist between most major neuropsychiatric disorders, with the strongest correlations observed between schizophrenia and bipolar 1 disorder.[7] Taken together, these data indicate the need for study designs that both include and transcend categorical diagnoses, incorporating dimensional phenotypes that might be specific to severe mental illness subtypes and those that are shared across them.

In a large and uniformly assessed case-control sample, we report our test of the hypothesis that neurocognitive performance is associated with both severe mental illness diagnoses and cross-diagnostic symptoms. Four aspects of this study are, to our knowledge, unique. First, the availability of electronic medical records from two psychiatric hospital systems in the Paisa region of Colombia enabled us to ascertain severe mental illness cases across diagnostic categories, and to incorporate measures of lifetime disease severity in our analyses. Second, the sample included large numbers of cases from each of the major severe mental illness diagnostic categories. Third, we assessed, in all cases, a set of symptoms that would typically be probed, using structured interview branching logic, only in individuals who have responded positively to specific screening questions. We assessed, for example, symptoms associated with depression and mania that would not typically be queried of people with schizophrenia. Finally, the study sample derives from a single population that is homogeneous genetically and culturally, thereby minimising confounds due to interpopulation variability.

Methods

Sample ascertainment and procedures

Participants with severe mental illness (ie, cases) were ascertained through electronic medical records at Clínica San Juan de Dios de Manizales (CSJDM) in Manizales, Caldas, Colombia and the Hospital Universitario San Vicente Fundación (HUSVF) in Medellín, Antioquía, Colombia, beginning in 2017 (appendix p 1). Individuals were invited to participate in the project based on the following criteria: (1) electronic medical record diagnosis of a mood or psychosis spectrum disorder with a history of at least one hospital

admission or treatment for symptoms considered sufficiently severe by a referring psychiatrist to warrant such hospital admission; (2) presenting symptoms were not clearly caused by a substance use disorder, in the judgment of an evaluating clinician; (3) have two Paisa surnames;[8] (4) aged 18 years or older; (5) not a first-degree relative of another participant; (6) understand and sign an informed consent document; (7) no intellectual disability; and (8) no history of serious brain trauma or neurological disorder. Analyses reported here include individuals diagnosed with schizophrenia, bipolar 1, bipolar 2, or major depressive disorder on structured interviews.

Controls (ie, people without mental illness) were ascertained from the same communities as cases, and recruited from friends, neighbours, or in-laws of cases, or from university students and staff, and hospital staff. All controls met the following criteria: no (current or lifetime) severe mental illness, as evaluated through the overview screening module of the web-based version of the Structured Clinical Interview for DSM-5 (NetSCID); no current substance use disorder; and fulfilment of criteria (3) to (8) described for cases. Cases and controls were reimbursed for transportation costs but were not otherwise compensated.

Cases and controls were evaluated at CSJDM or HUSVF by LGAA, SRS, JME, CVU, or MCR. Before any assessment and after verifying inclusion and exclusion criteria, all participants signed an informed consent form. All procedures were approved by the institutional review board of the University of Antioquia (Comité de Ética del Instituto de Investigaciones Médicas de la Universidad de Antioquía), the Hospital San Vicente Fundación, the CSJDM, University of California Los Angeles (UCLA), University of California San Francisco, and the University of Pennsylvania.

Study measures

Data on previous psychiatric contacts and hospital admissions, and medication history were collected for cases. We obtained lifetime DSM-5 diagnoses and cross-diagnosis symptom-level data through structured interviews using a Spanish translation of NetSCID, a computerised version of the structured interview for DSM-5.[9,10] Use of this instrument, with built-in algorithms and decision trees for determining diagnosis, increases reliability and reduces branching errors that could lead to misdiagnosis. NetSCID modules for case assessment included overview, screener of major psychopathology, mood disorders, psychotic disorders, and trauma and stressor-related disorders. To assess cross-diagnostic symptomatology, we administered seven supplementary questions about specific symptoms of fatigue, grandiosity, decreased need for sleep, flight of ideas, hypersomnia, apathy, and anhedonia to cases.

To screen for psychopathology in potential control participants, we used the NetSCID overview module.

Data collected for all participants included demo graphic information, medication use, substance use, a brief assessment of current severity of a range of psychiatric symptomatology (the 45-question Symptom Assessment Questionnaire [SA-45][11]), and the Word Accentuation Test (WAT), which is a reading test for Spanish speakers, based on

irregular accentuation of words,[12] that has been validated in that group as a measure of premorbid IQ (sample size for each measure is given in the appendix p 2).

To assess speed and accuracy of neurocognitive performance across five domains related to specific brain systems hypothesised to be most strongly associated with severe mental illness (executive function, memory, complex cognition, social cognition, and motor speed), we used nine tests from the Penn Computerized Neurocognitive Battery (CNB),[13] a psychometrically well validated online battery (appendix p 3) with standardised automated quality assurance and scoring procedures. We excluded the larger CNB tests that use verbal stimuli requiring linguistic input for adaptation (ie, verbal memory and reasoning) and two tests of social cognition because of time limitations. The CNB has been validated across a wide age range, in both community samples and psychiatric populations.[14,15] Data for speed were multiplied by −1 so that poorer performance (ie, longer response time) would result in a lower value. All evaluators were extensively trained by RCG and AMP using web-based training modules, on-site training, and web-based supervision. Age and education strongly affect neurocognitive performance; therefore, as is standard for CNB analyses,[16] the raw data for each test were regressed on age, age^2, age^3, education, and an age by education interaction. The inclusion of squared and cubed terms of age accounted for potential non-linear changes in cognition with increasing age, and the age by education interaction accounted for differences in the effect of education level on cognition for different age groups. Residuals from this regression were used for further analyses. Residuals were winsorised at the top and bottom 1% to reduce the influence of extreme outliers and transformed to Z scores based on the mean (SD) in control participants.

All study data were collected and managed using REDCap electronic data capture tools hosted at UCLA.[17,18] All statistical analyses used R, version 3.4.0.[19]

Regression models of CNB accuracy and speed

Z scores were modelled as a function of diagnosis (reference category controls), sex (reference category females), test domain, and all interactions using linear mixed models (LMM), with individual CNB tests as repeated measures.[16] Separate analyses were done for accuracy and speed, which show different factorial structures,[20] to reduce the dimensionality of the analyses, because we had no hypotheses involving accuracy by speed interactions. The R function lme(), in version 3.1.137 of the nlme package, was used for analyses.[21]

The LMM analysis of Z scores was repeated including self-report medication use to assess robustness of conclusions to effects of medication. Self-report data were collected on all participants for usage of 30 psychiatric medications and grouped into three categories: antidepressants (15 medications), antipsychotics (11 medications), and mood stabilisers (four medications; appendix p 4). In each category, a binary indicator of medication use was constructed for each participant.

Factor analysis of symptom data in cases

Symptom data for cases were obtained from the NetSCID interview, and supplementary questions. Symptoms were considered present if they were endorsed at any point in the NetSCID (ie, lifetime) or in additional queries, and considered absent if they were never

endorsed, and confirmed as absent at least once. 40 symptoms were evaluated, and we retained for analysis symptoms endorsed by at least 2·5% of cases. Missing symptom data for cases from the NetSCID were imputed once using bootstrapped expectation-maximisation by the amelia() function in version 1.7.5 of the R Amelia package.[22]

We did an exploratory item-factor analysis[23] on the matrix of tetrachoric interitem correlations using weighted least-squares extraction and promax rotation. This method has been applied previously to reduce dimensionality of symptom ratings.[24] The number of factors to retain was determined by a combination of the minimum average partial (MAP) method,[25] parallel analysis[26] with Glorfeld correction,[27] visual examination of the scree plot, and theory. In version 1.8.12 of the psych package[28] in R, MAP was implemented by the nfactors() function and corrected parallel analysis was implemented by the fa.parallel() function. Visual examination of the scree plot involved subjective judgment of the point on the plot where the eigenvalues began to form an approximate linear trend. In an analysis that used only cases, we repeated the LMM described above, including symptom factor scores as covariates.

We evaluated the robustness of our conclusions regarding the effect of symptom factors on cognition by doing two additional LMM analyses in cases. In one analysis, we added the WAT score in the model as a covariate to control for effects of premorbid IQ on cognition. Before this analysis, raw CNB data were adjusted only for age, age^2, and age^3, and not education. In a second set of analyses, we controlled for effects of lifetime and current illness severity on cognition. We included two proxies for lifetime disease severity as covariates, both of which were extracted from available electronic medical record data obtained from CSJDM (complete electronic medical record data were not available from cases recruited at HUSVF). One proxy was the duration of illness, taken as the number of years since the first visit to CSJDM to recruitment in the study. The second proxy for lifetime disease severity was the sum of the number of visits of each participant to the emergency department or inpatient unit of the CSJDM; this variable was skewed and was quantile-normal transformed before use as covariate. As a measure of current illness severity, we used raw scores on the Global Severity Index of the SA-45.

Role of the funding source

The funders had no role in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the report for publication.

Results

3467 participants completed clinical assessments and were recruited into the study (appendix p 1). Patients were recruited between Oct 1, 2017, and Nov 1, 2019. CNB data for 901 participants (817 cases and 84 controls) were missing (appendix p 5). Among the remaining 2566 participants (1849 cases and 717 controls), 160 cases did not qualify for a NetSCID primary lifetime diagnosis of schizophrenia, bipolar 1, bipolar 2, or major depressive disorder, and were excluded from analysis. A summary of basic demo graphic information for each diagnostic category for the remaining 2406 participants (1553 women,

873 men) is given in table 1; controls did not differ from cases in terms of sex or years of education, but controls were significantly younger than cases.

Both accuracy and speed showed significant interactions of diagnosis and cognitive test domain, indicating that the diagnostic groups differed in their profile of cognitive deficits (appendix pp 6, 7). For both accuracy and speed, the four patient groups bifurcated into two profiles (appendix p 8; table 2), with schizophrenia and bipolar 1 disorder showing greater deficits than bipolar 2 disorder and major depressive disorder. The pattern of deficits was similar for schizophrenia and bipolar 1 disorder, with greater deficits across executive function (where effect sizes neared and exceeded 1 SD), social cognition, and motor speed tests compared with memory and complex cognition. Although participants with schizophrenia tended to have less education than those diagnosed with bipolar 1 disorder (table 1), the similarity of schizophrenia and bipolar 1 disorder profiles persisted when cognitive data were not adjusted for education (data not shown). Bipolar 2 disorder and major depressive disorder groups had similar profiles, with more subtle deficits in executive functions (effect sizes 0·5 SD), social cognition, and motor speed, whereas performance in other domains was at normative levels.

The largest deficits in cases, compared with controls, were seen in executive function speed and accuracy, especially attention and working memory; in social cognition, particularly emotion identification; and in motor speed. Although most participants were taking medications (table 1), conclusions in the above analyses were robust to inclusion of medication use as a covariate (appendix p 7).

21 symptoms were endorsed by at least 2·5% of cases (appendix p 9). All symptoms were present in participants with schizophrenia, whereas psychosis-associated symptoms were uncommon in participants with bipolar 2 disorder and major depressive disorder. Participants with bipolar 1 disorder endorsed psychosis-associated symptoms at a reduced level compared with participants with schizophrenia; however, religious delusions were nearly as common in bipolar 1 disorder as in schizophrenia. Depressed mood, anhedonia, fatigue, avolition, and suicidal thoughts were common across all diagnoses.

We determined that the 21 binary symptoms endorsed by at least 2·5% of cases were best represented by a three-factor model. The three symptom factors can be described as psychosis (positive loadings for hallucinations, delusions, disorganised speech, and disorganised behaviour), mania (positive loadings for decreased need for sleep, flight of ideas and grandiosity, and negative loadings for avolition), and depression (positive loadings for anhedonia, fatigue, depressed mood, hypersomnia, suicide attempt, and suicidal thoughts; appendix pp 10, 11). As expected, participants with schizophrenia scored more highly on the psychosis factor, participants with bipolar 2 disorder and major depressive disorder cases scored more on the depression factor, and participants with bipolar 1 disorder scored more on the mania factor; however, distributions of factor scores overlapped substantially across diagnostic categories (appendix p 12). Factor analysis results were stable when missing symptom data were not imputed—ie, when we included only participants with complete symptom data, correlation of factor scores with and without imputation in those

with complete symptom data were high (psychosis r=0·93, depression r=0·97, mania r=0·98).

Including only cases, we repeated the LMM analysis using factor scores on psychosis, mania, and depression as covariates (appendix p 7). Controlling for diagnosis, high psychosis factor score was significantly associated with reduced accuracy and slower speeds; high depression score was significantly associated with increased accuracy; and mania factor score was not significantly associated with accuracy or speed. Our results remained consistent when analyses were done using non-imputed data (appendix p 13) and when done separately by diagnosis (appendix p 14). Although premorbid IQ (WAT) and illness severity (both lifetime [duration of illness, number of hospital admissions and emergency room visits] and current [raw scores on SA-45 Global Severity Index]) were associated with both diagnosis and factor scores (appendix p 15), conclusions in the earlier analyses were robust to inclusion of these data as covariates (appendix p 16).

Both speed and accuracy had significant two-way interactions of test domain with sex and with diagnosis. These interactions prompted us to analyse neuro cognitive test domains individually, including main effects of diagnosis and sex. We included the factor scores that were significant in the combined LMM analyses as covariates in these analyses (appendix pp 6, 7): analysis of accuracy included psychosis and depression, whereas analysis of speed included only psychosis.

Higher psychosis scores were specifically associated with lower accuracy and slower speed in both executive function and social cognition, and with slower motor speed, whereas higher depression scores were specifically associated with improved social cognition accuracy (table 3). To visualise the effect of the psychosis and depression factors on cognition, we first regressed the effects of diagnosis and sex out of raw CNB scores, before generating Z scores. We then categorised cases as above or below the median of each factor, irrespective of diagnosis (table 1), transformed to Z scores based on the mean (SD) in cases in the lower group, and plotted the cognition profiles for both groups in each factor (appendix pp 17, 18). After removing the effect of diagnosis, we saw that cases in the upper half of the distribution of psychosis factor scores had poorer performance on both speed and accuracy than did cases in the lower half of the distribution. In contrast, cases in the upper half of the distribution of depression scores had improved social cognition accuracy.

Discussion

In this study we investigated a prospective sample that included large numbers of cases representing each of the three main severe mental illness diagnoses, schizophrenia, bipolar disorder, and major depressive disorder. The study design enabled cross-diagnostic analyses not possible in previous investigations, in that cases were not ascertained for a specific diagnosis, and were assessed uniformly across diagnoses, both for performance across major neurocognitive domains and for individual lifetime symptoms. These assessments provide new insight into the magnitude and profile of neurocognitive impairment in severe mental illness in relation to both diagnosis and empirically derived, cross-diagnostic symptom factors. Additional assessments, including evaluation of electronic medical records available

for most cases, allowed us to show that our findings were robust to lifetime and current illness severity, premorbid IQ, and medication usage.

The bifurcation of cognitive profiles was the most striking finding with respect to diagnoses: compared with controls, individuals with schizophrenia and bipolar 1 disorder showed pronounced deficits across executive function, social cognition, and motor speed tests compared with memory and complex cognition, whereas individuals with bipolar 2 disorder and major depressive disorder had mild cognitive impairment across domains, with intact non-verbal reasoning. This result aligns with a growing body of evidence indicating heterogeneity of neurocognitive function within bipolar disorder,[29] and provides a possible explanation for a similarly bifurcated pattern of genetic correlations between the severe mental illness diagnoses revealed in recent large-scale GWAS datasets.[30] It provides further evidence that the traditional dichotomy between mood and psychotic disorders does not provide an adequate framework for scientific investigation of the causes and trajectories of severe mental illness.

Although very few comparable studies involving uniform cross-diagnostic ascertainment have been done, our results generally align with those of recent work in European populations. In particular, Bowie and colleagues[4]—comparing people with bipolar 1 disorder with psychosis to people with bipolar 1 disorder without psychosis—showed a deficit in cognition in the order of 0·75 SD units. Our findings indicate that with every 1 unit increase in the psychosis factor score, cognition decreases by 0·15 to 0·18 SD units. The range of psychosis factor scores in bipolar 1 disorder cases is more than 5 units, which means that the effect of psychosis on cognition, above diagnosis, is similar to that seen by Bowie and colleagues. Likewise, Hill and colleagues[31] found that among psychotic probands, more prominent mood features and less persistent psychotic symptoms were associated with less cognitive impairment.

Because of the branching structure of diagnostic interviews, severe mental illness symptoms are usually assessed only in respondents who endorse screening questions for the diagnoses typically associated with those symptoms. By uniformly assessing lifetime symptomatology outside of the NetSCID, we found that a substantial number of symptoms (depressed mood, anhedonia, fatigue, avolition, and suicidal thoughts) occurred at a high frequency (>25%) across all diagnoses. Our study design is ideal for further investigation of such symptoms—eg, through analyses aimed at dissecting polygenic risk across severe mental illness diagnoses. At that same time, further explorations of the symptom data might shed light on the biology related to specific diagnoses. Although the lifetime frequencies of the overall set of psychosis symptoms aligned with the above-noted bifurcation of cognition profiles (high in schizophrenia and bipolar 1 disorder, and low in bipolar 2 disorder and major depressive disorder), this pattern reflects mainly a few symptoms that are nearly as prominent in bipolar 1 disorder as in schizophrenia (eg, religious delusions).

The exploratory item-factor analysis of clinical symptoms identified a clear psychosis factor and two mood-related factors, which enabled cross-diagnostic evaluations of symptomatology in relation to specific neurocognitive domains. Even after adjusting for effects of diagnosis, increasing scores on the psychosis factor were associated with slower

motor speed and reduced accuracy in both executive function and social cognition. Previous studies have shown similar associations,[3,32] but have not examined such a broad range of severe mental illness diagnoses, or such a uniformly ascertained study population. We also obtained the unexpected finding that higher scores on the depression factor were associated with improved social cognition accuracy, after adjusting for effects of diagnosis; our results suggest that the effect, cross-diagnostically, is larger for accuracy than speed. Although major depressive disorder is associated with significant deficits in a number of components of social cognition, participants who exhibit subthreshold depression or dysphoria have shown greater accuracy than controls on a variety of social cognition tasks.[33] Finally, previous work indicates that within diagnostic categories (eg, schizophrenia) higher trait depression was associated with better cognitive and global functioning.[5] For both symptom factors, effects persisted after controlling for disease severity and premorbid IQ.

It is now well accepted that premorbid cognitive impairment is a common feature of schizophrenia.[34] Although we found that the effects of the psychosis symptom factor persisted after controlling for premorbid IQ, our results cannot differentiate between two possible mechanisms: lifetime psychotic symptomatology has deleterious effects on specific cognitive domains and these effects transcend diagnostic categories; or a common set of risk factors predisposes to both psychotic symptoms and impaired cognition across severe mental illness categories. Longitudinal data, from a developmental perspective, could shed light on this mechanism; further investigation of the electronic medical records of the Paisa sample might provide such information.

We note three limitations of this study. First, although severe mental illness case and control participants were recruited from the same communities, we cannot rule out subtle effects of demographic differences between these groups. Second, although previous studies have highlighted deficits in verbal memory in schizophrenia,[34] we did not assess this domain because of a lack of normative data on word frequency in the Paisa population. Lastly, although our results were robust to medication class, the dose and efficacy of medication could also affect cognitive performance, but are difficult to compare and account for in analyses.

Independent studies have shown that the specific cognitive domains measured here are heritable,[35] while studies of more limited sets of cognitive measures have shown their genetic correlation with schizophrenia.[36,37] Future genome-wide genotyping studies of the Paisa sample described here will enable the examination of genetic correlations for neurocognitive measures from the current study across severe mental illness diagnoses and symptom factors, broadly, as well as GWAS of neuro cognitive phenotypes across multiple domains. This large sample of uniformly ascertained individuals thus provides unique opportunities for the phenotypic and genetic characterisation of severe mental illness that might ultimately lead to novel approaches for disease classification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was supported by NIMH grants: R01MH113078 to NBF, CEB, and CLJ; R01MH095454-02S1 to NBF; and K99MH116115 to LOL. Clinical and Translational Science Institute grant UL1TR001881 provided support for the data collection system REDCap. We thank the CSJDM and HUSVF and all study participants for making this work possible.

References

1. Vigo D, Thornicroft G, Atun R. Estimating the true global burden of mental illness. Lancet Psychiatry 2016; 3: 171–78. [PubMed: 26851330]
2. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am J Psychiatry 2010; 167: 748–51. [PubMed: 20595427]
3. Reininghaus U, Böhnke JR, Chavez-Baldini U, et al. Transdiagnostic dimensions of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). World Psychiatry 2019; 18: 67–76. [PubMed: 30600629]
4. Bowie CR, Best MW, Depp C, et al. Cognitive and functional deficits in bipolar disorder and schizophrenia as a function of the presence and history of psychosis. Bipolar Disord 2018; 20: 604–13. [PubMed: 29777563]
5. Chiappelli J, Kochunov P, DeRiso K, et al. Testing trait depression as a potential clinical domain in schizophrenia. Schizophr Res 2014; 159: 243–48. [PubMed: 25171855]
6. Bray NJ, O'Donovan MC. The genetics of neuropsychiatric disorders. Brain Neurosci Adv 2019; 2: 2.
7. Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 2019; 179: 1469–82. [PubMed: 31835028]
8. Bedoya G, Montoya P, García J, et al. Admixture dynamics in Hispanics: a shift in the nuclear genetic ancestry of a South American population isolate. Proc Natl Acad Sci USA 2006; 103: 7234–39. [PubMed: 16648268]
9. First MBW, Williams JB, Benjamin LS, Spitzer RL. Structured clinical interview for DSM-5–research version. Washington, DC: American Psychiatric Association, 2015.
10. Brodey BB, First M, Linthicum J, Haman K, Sasiela JW, Ayer D. Validation of the NetSCID: an automated web-based adaptive version of the SCID. Compr Psychiatry 2016; 66: 67–70. [PubMed: 26995238]
11. Maruish ME, Bershadsky B, Goldstein L. Reliability and validity of the SA-45: further evidence from a primary care setting. Assessment 1998; 5: 407–19. [PubMed: 9835664]
12. Krueger KR, Lam CS, Wilson RS. The word accentuation testChicago. J Clin Exp Neuropsychol 2006; 28: 1201–07. [PubMed: 16840245]
13. Gur RC, Richard J, Hughett P, et al. A cognitive neuroscience-based computerized battery for efficient measurement of individual differences: standardization and initial construct validation. J Neurosci Methods 2010; 187: 254–62. [PubMed: 19945485]
14. Irani F, Brensinger CM, Richard J, et al. Computerized neurocognitive test performance in schizophrenia: a lifespan analysis. Am J Geriatr Psychiatry 2012; 20: 41–52. [PubMed: 22183011]
15. Roalf DR, Gur RE, Ruparel K, et al. Within-individual variability in neurocognitive performance: age- and sex-related differences in children and youths from ages 8 to 21. Neuropsychology 2014; 28: 506–18. [PubMed: 24773417]
16. Gur RE, Moore TM, Rosen AFG, et al. Burden of environmental adversity associated with psychopathology, maturation, and brain behavior parameters in youths. JAMA Psychiatry 2019; published online May 29. DOI:10.1001/jamapsychiatry.2019.0943.
17. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42: 377–81. [PubMed: 18929686]

18. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform 2019; 95: 103208. [PubMed: 31078660]
19. Team RC. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing, 2017.
20. Moore TM, Reise SP, Gur RE, Hakonarson H, Gur RC. Psychometric properties of the Penn Computerized Neurocognitive Battery. Neuropsychology 2015; 29: 235–46. [PubMed: 25180981]
21. Pinheiro J, Bates D, DebRoy S, Sarkar D, R Core Team. Nlme: linear and nonlinear mixed effects models 2018. R package version 3.1–137. (accessed Aug 29, 2017).
22. Honaker J, King G, Blackwell M, Amelia II. A program for missing data. J Stat Softw 2011; 45: 1–47.
23. Takane Y, Deleeuw J. On the relationship between item response theory and factor-analysis of discretized variables. Psychometrika 1987; 52: 393–408.
24. Moore TM, Calkins ME, Satterthwaite TD, et al. Development of a computerized adaptive screening tool for overall psychopathology (“p”). J Psychiatr Res 2019; 116: 26–33. [PubMed: 31176109]
25. Velicer WF. Determining number of components from matrix of partial correlations. Psychometrika 1976; 41: 321–27.
26. Horn JL. A rationale and test for the number of factors in factor-analysis. Psychometrika 1965; 30: 179–85. [PubMed: 14306381]
27. Glorfeld LW. An Improvement on horns parallel analysis methodology for selecting the correct number of factors to retain. Educ Psychol Meas 1995; 55: 377–93.
28. Revelle WR. Psych: procedures for personality and psychological research. Illinois, USA: Northwestern University, 2017 (accessed March 6, 2019).
29. Lima IMM, Peckham AD, Johnson SL. Cognitive deficits in bipolar disorders: Implications for emotion. Clin Psychol Rev 2018; 59: 126–36. [PubMed: 29195773]
30. Stahl EA, Breen G, Forstner AJ, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. Nat Genet 2019; 51: 793–803. [PubMed: 31043756]
31. Hill SK, Reilly JL, Keefe RS, et al. Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. Am J Psychiatry 2013; 170: 1275–84. [PubMed: 23771174]
32. Tamminga CA, Ivleva EI, Keshavan MS, et al. Clinical phenotypes of psychosis in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP). Am J Psychiatry 2013; 170: 1263–74. [PubMed: 23846857]
33. Harkness KL, Washburn D, Theriault JE, Lee L, Sabbagh MA. Maternal history of depression is associated with enhanced theory of mind in depressed and nondepressed adult women. Psychiatry Res 2011; 189: 91–96. [PubMed: 21733579]
34. Seidman LJ, Shapiro DI, Stone WS, et al. Association of neurocognition with transition to psychosis: baseline functioning in the second phase of the North American Prodrome Longitudinal Study. JAMA Psychiatry 2016; 73: 1239–48. [PubMed: 27806157]
35. Swagerman SC, de Geus EJC, Kan KJ, et al. The computerized neurocognitive battery: validation, aging effects, and heritability across cognitive domains. Neuropsychology 2016; 30: 53–64. [PubMed: 26710096]
36. Anttila V, Bulik-Sullivan B, Finucan HK, et al. Analysis of shared heritability in common disorders of the brain. Science 2018; 360: eaap8757. [PubMed: 29930110]
37. Smeland OB, Bahrami S, Frei O, et al. Correction: genome-wide analysis reveals extensive genetic overlap between schizophrenia, bipolar disorder, and intelligence. Mol Psychiatry 2019; published online July 15. 10.1038/s41380-019-0456-7.

Research in context

Evidence before this study

Previous work has shown that certain classes of dimensional phenotype might have particular utility for cross-diagnostic investigations of severe mental illness (defined here as schizophrenia and other chronic psychoses, bipolar disorder, and severe major depressive disorder). In particular, impairment in indices of neurocognitive function has been shown in each of the above diagnostic groups compared with controls, whereas symptoms that are characteristic of specific diagnoses might also be present at substantial frequencies in individuals with other diagnoses. To evaluate the existing state of cross-diagnostic evidence regarding the relationship between neurocognitive function, symptoms, and specific severe mental illness diagnoses, we searched PubMed up to Jan 1, 2020, without applying any date or language restrictions. We did multiple searches using the following terms, in different combinations: cognition, cognitive function, neurocognition, neurocognitive battery, severe mental illness, cohort; diagnosis, schizophrenia, bipolar disorder, major depression, symptom domain, endophenotype; RDoC; psychosis, transdiagnostic, social cognition.

All of the previous studies that we found focused on populations of European descent, and most investigated small samples, focused on single diagnoses, and did not consider the relationship between cross-diagnostic symptoms on cognition.

Added value of this study

To our knowledge, this is the first study to examine performance across major neurocognitive domains in a large cohort of uniformly ascertained individuals with severe mental illness. Our investigation provides new insights into the magnitude and profile of neurocognitive impairment in severe mental illness by diagnosis, and shows that after controlling for diagnosis, symptom domains (psychosis and depression) exert additional effects on cognition. Furthermore, this is the first large-scale study of neurocognition in severe mental illness done in a Latin American population.

Implications of all the available evidence

This large cohort of uniformly ascertained individuals provides unique opportunities for the phenotypic characterisation of severe mental illness that might ultimately lead to novel approaches for disease classification. The study offers a template for the implementation of dimensional phenotyping in cohorts recruited for discovery research. Moreover, our project is a step towards achieving an equitable representation of major world populations in severe mental illness datasets, a crucial objective for reducing health disparities.

Table 1:

Demographic and medication information for 2406 participants

	Schizophrenia	Bipolar 1 disorder	Bipolar 2 disorder	Major depressive disorder	Controls	p value
Sex						
Female	28/160 (17%)	312/519 (60%)	148/204 (72%)	596/806 (74%)	449/717 (63%)	..
Male	132/160 (83%)	207/519 (40%)	56/204 (28%)	210/806 (26%)	268/717 (37%)	0·47
Age	37·4 (12·8)	44·1 (13·8)	38·7 (14·4)	39·3 (14·1)	36·7 (14·45)	$2{\cdot}71\times10^{-9}$
Education, years	10·4 (3·3)	11·1 (4·24)	12·3 (3·7)	11·9 (3·7)	11·7 (3·5)	0·370
Premorbid IQ, WAT score	27·13 (8·64)	29·90 (10·03)	31·85 (8·29)	31·06 (8·12)	29·93 (8·29)	0·210
Raw SA45 Global Severity Index	38·6 (34·6)	30·7 (31·0)	55·2 (39·8)	53 (37·9)	12·5 (13·8)	NA
Number of hospital admissions and emergency room visits	14·68 (16·34)	12·21 (12·58)	5·91 (9·00)	3·71 (6·02)	NA	NA
Duration of illness, years	8·2 (4·9)	8·8 (4·6)	5·9 (4·3)	4·4 (3·8)	NA	NA
Antipsychotic use	142/160 (89%)	353/519 (68%)	106/204 (52%)	264/806 (33%)	0/717 (0%)	NA
Antidepressant use	43/160 (27%)	119/519 (23%)	95/204 (47%)	577/806 (72%)	1/717 (<1%)	NA
Mood stabiliser use	37/160 (23%)	363/519 (70%)	138/204 (68%)	151/806 (19%)	5/717 (1%)	NA
In top half of psychosis factor score	160/160 (100%)	417/519 (80%)	94/204 (46%)	160/806 (20%)	NA	NA
In top half of mania factor score	57/160 (36%)	508/519 (98%)	187/204 (92%)	91/806 (11%)	NA	NA
In top half of depression factor score	11/160 (7%)	165/519 (32%)	137/204 (67%)	439/806 (54%)	NA	NA

Data are n/N (%) or mean (SD). The p value compares all cases to controls. WAT=word accentuation test. NA=not applicable.

Table 2:

Analyses of accuracy and speed Z scores for each Penn Computerized Neurocognitive Battery test

	Executive function			Episodic memory		Complex cognition (NVR)	Social cognition		Motor (SM)
	ATT	WM	PS	FMEM	AM		EID	EDI	
Accuracy									
Intercept									
Estimate	−0·019	−0·067	−0·023	0·004	−0·025	−0·093*	0·081	0·023	NA
p value	0·73	0·21	0·6	0·92	0·54	0·025*	0·091	0·62	NA
Major depressive disorder									
Estimate	−0·415*	−0·287*	−0·235*	−0·179*	−0·168*	0·002	−0·163*	−0·244*	NA
p value	$4{\cdot}4 \times 10^{-09}$*	$2{\cdot}5 \times 10^{-05}$*	$3{\cdot}3 \times 10^{-05}$*	0·00086*	0·0017*	0·98	0·0073*	$2{\cdot}8 \times 10^{-05}$*	NA
Bipolar 2 disorder									
Estimate	−0·428*	−0·276*	−0·292*	−0·109	−0·172*	0·058	−0·270*	−0·318*	NA
p value	9×10^{-05}*	0·0087*	0·00091*	0·19	0·038*	0·48	0·0041*	0·00043*	NA
Bipolar 1 disorder									
Estimate	−0·721*	−0·681*	−0·848*	−0·390*	−0·380*	−0·236*	−0·544*	−0·445*	NA
p value	$1{\cdot}7 \times 10^{-19}$*	$7{\cdot}2 \times 10^{-18}$*	$2{\cdot}3 \times 10^{-38}$*	$1{\cdot}6 \times 10^{-10}$	$4{\cdot}6 \times 10^{-10}$*	0·00011*	$2{\cdot}7 \times 10^{-15}$*	$1{\cdot}5 \times 10^{-11}$*	NA
Schizophrenia									
Estimate	−1·372*	−0·896*	−1·092*	−0·509*	−0·554*	−0·417*	−0·858*	−0·655*	NA
p value	$6{\cdot}6 \times 10^{-27}$*	$7{\cdot}2 \times 10^{-13}$*	$5{\cdot}5 \times 10^{-27}$*	$8{\cdot}2 \times 10^{-08}$*	$5{\cdot}6 \times 10^{-09}$*	$1{\cdot}2 \times 10^{-05}$*	$1{\cdot}1 \times 10^{-15}$*	$1{\cdot}9 \times 10^{-10}$*	NA
Male									
Estimate	0·051	0·180*	0·061	−0·011	0·068	0·249*	−0·218*	−0·062	NA
p value	0·4	0·0024*	0·21	0·81	0·14	$8{\cdot}2 \times 10^{-08}$*	$2{\cdot}9 \times 10^{-05}$*	0·22	NA
Speed									
Intercept									
Estimate	−0·105*	−0·113*	−0·016	−0·011	−0·024	0·038	0·063	0·028	−0·081
p value	0·039*	0·023*	0·76	0·82	0·6	0·39	0·24	0·56	0·13
Major depressive disorder									

	Executive function			Episodic memory		Complex cognition (NVR)	Social cognition		Motor (SM)
	ATT	WM	PS	FMEM	AM		EID	EDI	
Estimate	−0·3 *	−0·345 *	−0·214 *	−0·179 *	0·096	−0·006	−0·21 *	0·017	−0·378 *
p value	$4{\cdot}2 \times 10^{-06}$ *	$4{\cdot}3 \times 10^{-08}$ *	0·0018 *	0·0037 *	0·092	0·92	0·0018 *	0·78	$3{\cdot}4 \times 10^{-08}$ *
Bipolar 2 disorder									
Estimate	−0·293 *	−0·066	−0·461 *	−0·14	−0·051	−0·205 *	−0·345 *	−0·108	−0·449 *
p value	0·0037 *	0·5	$1{\cdot}6 \times 10^{-05}$ *	0·14	0·56	0·02 *	0·00094 *	0·25	$2{\cdot}2 \times 10^{-05}$ *
Bipolar 1 disorder									
Estimate	−0·777 *	−0·402 *	−0·971 *	−0·496 *	−0·064	−0·212 *	−0·857 *	−0·496 *	−0·996 *
p value	$6{\cdot}8 \times 10^{-26}$	$3{\cdot}2 \times 10^{-08}$ *	$2{\cdot}2 \times 10^{-34}$ *	1×10^{-12} *	0·32	0·0011 *	$5{\cdot}6 \times 10^{-29}$ *	1×10^{-12} *	$2{\cdot}8 \times 10^{-37}$ *
Schizophrenia									
Estimate	−1·007 *	−0·726 *	−1·148 *	−0·463 *	−0·087	−0·092	−1·352 *	−0·572 *	−1·204 *
p value	$1{\cdot}1 \times 10^{-17}$ *	3×10^{-10} *	$1{\cdot}1 \times 10^{-20}$ *	$1{\cdot}9 \times 10^{-05}$ *	0·39	0·36	$9{\cdot}6 \times 10^{-30}$ *	$1{\cdot}3 \times 10^{-07}$ *	$1{\cdot}7 \times 10^{-23}$ *
Male									
Estimate	0·28 *	0·301 *	0·044	0·03	0·064	−0·101 *	−0·169 *	−0·075	0·226 *
p value	$6{\cdot}5 \times 10^{-07}$ *	$4{\cdot}5 \times 10^{-08}$ *	0·46	0·57	0·2	0·039 *	0·0034 *	0·15	0·00012 *

ATT=Continuous Performance Test. WM=Letter-N-Back test. PS=Digit Symbol Test, matching trials. FMEM=Face Memory test. AM=Digit Symbol test, recall trials. NVR=Matrix Analysis test. EID=Emotion Identification test. EDI=Measured Emotion Differentiation test. SM=Motor Praxis test. NA=not applicable. The reference category is control females.

* Nominal p<0·05.

Table 3:

Analyses of accuracy and speed Z scores for each Penn Computerized Neurocognitive Battery test, including psychosis factor score as a covariate for speed, and psychosis and depression factor scores as covariates for accuracy

	Executive function			Episodic memory		Complex cognition (NVR)	Social cognition		Motor (SM)
	ATT	WM	PS	FMEM	AM		EID	EDI	
Accuracy									
Major depressive disorder									
Estimate	−0·494*	−0·386*	−0·307*	−0·204*	−0·229*	−0·114*	−0·209*	−0·273*	NA
p value	$9{\cdot}3 \times 10^{-14}$*	$8{\cdot}6 \times 10^{-10}$*	$5{\cdot}1 \times 10^{-10}$*	$7{\cdot}2 \times 10{\cdot}0^{-06}$*	$5{\cdot}6 \times 10^{-07}$*	0·012*	$6{\cdot}9 \times 10^{-05}$*	$6{\cdot}5 \times 10^{-08}$*	NA
Bipolar 2 disorder									
Estimate	−0·489*	−0·371*	−0·348*	−0·124	−0·226*	−0·048	−0·297*	−0·337*	NA
p value	$1{\cdot}1 \times 10^{-05}$*	0·00049*	$3{\cdot}2 \times 10^{-05}$*	0·11	0·0035*	0·53	0·00098*	0·00011*	NA
Bipolar 1 disorder									
Estimate	−0·689*	−0·695*	−0·809*	−0·343*	−0·375*	−0·272*	−0·294*	−0·368*	NA
p value	$1{\cdot}5 \times 10^{-18}$*	$3{\cdot}7 \times 10^{-19}$*	$6{\cdot}5 \times 10^{-41}$*	$3{\cdot}6 \times 10^{-10}$*	$7{\cdot}2 \times 10^{-12}$*	$7{\cdot}1 \times 10^{-07}$*	$3{\cdot}1 \times 10^{-06}$*	$1{\cdot}5 \times 10^{-09}$*	NA
Schizophrenia									
Estimate	−1·074*	−0·780**	−0·769*	−0·301*	−0·411*	−0·275*	−0·126	−0·386*	NA
p value	$3{\cdot}3 \times 10^{-09}$*	$1{\cdot}1 \times 10^{-05}$*	$1{\cdot}2 \times 10^{-08}$*	0·016*	0·00096*	0·028*	0·38	0·0057*	NA
Psychosis									
Estimate	−0·159*	−0·006	−0·158*	−0·080*	−0·062	−0·068	−0·096*	−0·066	NA
p value	0·0043*	0·92	0·00016*	0·038*	0·11	0·079	0·03*	0·12	NA
Depression									
Estimate	−0·016	0·088	−0·014	0·007	0·022	0·023	0·239*	0·061	NA
p value	0·75	0·076	0·72	0·84	0·52	0·52	$5{\cdot}8 \times 10^{-09}$*	0·12	NA
Male									
Estimate	0·009	0·134	−0·012	−0·058	0·051	0·169*	−0·327*	−0·091	NA
p value	0·91	0·094	0·84	0·31	0·38	0·0033*	$9{\cdot}2 \times 10^{-07}$*	0·16	NA
Speed									

	Executive function			Episodic memory		Complex cognition (NVR)	Social cognition		Motor (SM)
	ATT	WM	PS	FMEM	AM		EID	EDI	
Major depressive disorder									
Estimate	−0·484*	−0·516*	−0·293*	−0·213*	0·073	0·015	−0·186*	−0·037	−0·571*
p value	$5{\cdot}7 \times 10^{-17}$*	9×10^{-21}*	$1{\cdot}8 \times 10^{-06}$*	$4{\cdot}9 \times 10^{-05}$*	0·13	0·75	0·0015*	0·48	$1{\cdot}2 \times 10^{-21}$*
Bipolar 2 disorder									
Estimate	−0·464*	−0·230*	−0·524*	−0·168	−0·074	−0·187*	−0·310*	−0·143	−0·615*
p value	$3{\cdot}2 \times 10^{-06}$*	0·016*	$9{\cdot}9 \times 10^{-07}$*	0·068	0·38	0·024*	0·0026*	0·12	4×10^{-09}*
Bipolar 1 disorder									
Estimate	−0·878*	−0·531*	−0·933*	−0·488*	−0·088	−0·218*	−0·762*	−0·418*	−1·003*
p value	$2{\cdot}3 \times 10^{-35}$*	$1{\cdot}3 \times 10^{-14}$*	$3{\cdot}2 \times 10^{-34}$*	$3{\cdot}3 \times 10^{-14}$*	0·13	0·00021*	$1{\cdot}1 \times 10^{-25}$*	$7{\cdot}3 \times 10^{-11}$*	$1{\cdot}4 \times 10^{-41}$*
Schizophrenia									
Estimate	−0·928*	−0·765*	−0·831*	−0·361*	−0·114	−0·173	−1·097*	−0·196	−0·806*
p value	$7{\cdot}5 \times 10^{-09}$*	$9{\cdot}3 \times 10^{-07}$*	$9{\cdot}8 \times 10^{-07}$*	0·012*	0·39	0·19	$1{\cdot}7 \times 10^{-11}$*	0·18	$8{\cdot}3 \times 10^{-07}$*
Psychosis									
Estimate	−0·126*	−0·075	−0·154*	−0·054	0·002	0·019	−0·091	−0·176*	−0·243*
p value	0·0092*	0·11	0·0029*	0·22	0·96	0·65	0·062	$5{\cdot}9 \times 10^{-05}$*	$8{\cdot}3 \times 10^{-07}$*
Male									
Estimate	0·348*	0·383*	0·000	0·019	0·064	−0·006	−0·187*	−0·081	0·216*
p value	$3{\cdot}1 \times 10^{-06}$*	$1{\cdot}2 \times 10^{-07}$*	1	0·78	0·31	0·93	0·015*	0·23	0·0056*

ATT=Continuous Performance Test. WM=Letter-N-Back test. PS=Digit Symbol Test, matching trials. FMEM=Face Memory test. AM=Digit Symbol test, recall trials. NVR=Matrix Analysis test. EID=Emotion Identification test. EDI=Measured Emotion Differentiation test. SM=Motor Praxis test. NA=not applicable.

*Nominal p<0·05.