Distinct and shared contributions of diagnosis and symptom domains to cognitive performance in severe mental illness

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ABSTRACT

Objective

Neurocognitive impairment is prominent in severe mental illness (SMI). We assessed relationships among diagnosis, symptom domains and neurocognitive performance in EMR-ascertained, diagnosis-naïve recruited SMI cases, investigated with healthy controls, from the genetically and culturally homogenous “Paisa” population of Colombia.

Methods

1,772 participants (1,220 cases, 552 controls; mean age 42 years, 59% female) were assessed for speed and accuracy across nine tests of the Penn Computerized Neurocognitive Battery (CNB). Cases carried diagnoses of schizophrenia (SCZ, n=141), bipolar-I (BP-I, n=453), bipolar-II (BP-II, n=137) and major depressive disorder (MDD, n=489) based on structured diagnostic interviews. Exploratory factor analysis applied to symptom data produced factor scores. Residualized z-scores were modeled as a function of diagnosis, sex, and all interactions using linear mixed models, with CNB tests as repeated measures. Analyses were repeated in cases, additionally modeling symptom factor scores as main effects.

Results

BP-I and SCZ displayed nearly identical impairment patterns on CNB tasks for both accuracy and speed. BP-II or MDD, however, performed similarly to controls with more subtle deficits in specific domains. A four-factor model (psychosis, mania, depression, and suicidality) represented symptom data. Controlling for diagnosis, high psychosis factor scores associated with reduced accuracy and slower speeds.

Conclusions

Severity of neurocognitive impairment separates SMI into two profiles (BP-I/SCZ and BP-II/MDD), and associates with lifetime psychotic symptoms across diagnoses. These findings suggest partially independent contributions of psychiatric diagnosis and lifetime symptomatology to cognitive functioning. Genetic investigations may help identify common risk factors predisposing to both psychosis and impaired cognition across SMI categories.

KEYWORDS: severe mental illness, cognition, psychosis, depression, bipolar disorder, transdiagnostic

Introduction

The disorders that together constitute severe mental illness (SMI) are among the largest contributors to the global burden of disease (1). The splitting of SMI into diagnostic categories based on symptoms and classical disease trajectories has long dominated psychiatric research and clinical practice. Recent evidence has increasingly challenged these dichotomies, and has stimulated efforts to re-orient psychiatric research around dimensional systems rather than categorical diagnoses. For example, the Research Domain Criteria (RDoC) initiative seeks to advance the mechanistic understanding of mental illness by encouraging the application to clinical research of a matrix for classifying cognition, emotion, motivation, and social behavior across dimensional domains (2, 3).

Because genetic studies offer unique information on the biological underpinnings of disease, a major motivation for large-scale introduction of dimensional phenotyping approaches within psychiatric research is that these measures may provide a clearer understanding of the genetic relationships among different forms of SMI than has been obtained through meta-analyses of categorical diagnoses only. On one hand, genome-wide association studies (GWAS) have identified dozens of loci that are associated at a genome-wide significance threshold with schizophrenia (SCZ), bipolar disorder (BPD), or major depressive disorder (MDD) but that do not show such significant association for the other diagnoses (4-6). On the other hand, statistical methods that evaluate the totality of the polygenic contribution to variation in these datasets indicate substantial cross-category genetic correlations; for example, BPD shows significant correlations with both SCZ and MDD (7). Yet even at this level of analysis diagnostic categories provide structure to the genetic profiles: BPD with severe mania (BP-I) shows a stronger genetic correlation with SCZ than with MDD, while BPD with hypomania only (BP-II) displays a stronger correlation with MDD than with SCZ (4). Taken together, the above observations indicate the need for analyses that both include and extend beyond categorical diagnoses to advance our understanding of the genetic architecture of SMI; specifically, to identify phenotypic features that are distinct to subtypes of SMI and those that are shared across them.

Two main classes of phenotype have been proposed for such analyses: (1) symptoms, such as those grouped under the rubric “psychosis,” which are components of specific diagnostic categories, but may be present across multiple categories, and (2) quantitative measures that assess behavioral domains, such as cognitive function, that are outside of the current diagnostic framework and yet characterize SMI. Analysis of both types of phenotypes has been limited by the heterogeneity across study samples in the approaches used for both ascertainment of participants and their phenotypic assessment. Additionally, large psychiatric case samples have typically obtained few if any of the measures needed to test hypotheses relating dimensional domains to SMI. Notably, most of the genetic evidence for cognitive function obtained to date in clinical populations has focused only on general intelligence (‘g’) or educational attainment (8-10).

Here, we investigate the association of both SMI diagnoses and symptom-based factors with cognitive performance in a large set of SMI cases and controls ascertained and phenotypically assessed in a uniform manner. Cognition was assessed across multiple domains (executive function, memory, complex cognition, social cognition, and motor speed) linkable to specific brain systems. The assessment allowed us to test the hypothesis that trans-diagnostic symptoms are associated with neurocognitive deficits, particularly in the domains of executive and social cognition (11). Using high-quality electronic medical records (EMR) from two large hospital systems in the Paisa region of Colombia, we ascertained, agnostic to specific diagnosis, cases with recorded diagnoses of either mood or psychotic disorders. This sample derives from a single population that is relatively homogenous in both genetic background and environmental exposure, thereby minimizing confounds due to inter-population variability in the prevalence of SMI categories or their component features (12-15). Additionally, the Paisa, like other Latin American populations, represents admixture between European and Native American founders; as such, findings from this study may be particularly informative for this large and rapidly growing ethnicity.

Methods

Sample Ascertainment and procedures

Cases with SMI were ascertained through Electronic Medical Records (EMR) at two hospitals in the Paisa Region of Colombia: Clínica San Juan de Dios de Manizales (CSJDM) in Manizales, Caldas and the Hospital Universitario San Vicente Fundación (HUSVF) in Medellín, Antioquía. Individuals were invited to participate in the project based on the following criteria: (1) EMR diagnosis of a mood or psychosis spectrum disorder of sufficient severity to have had a history of at least one inpatient hospitalization or treatment in the emergency department for symptoms considered sufficiently severe by a referring psychiatrist to warrant such hospitalization; (2) presenting symptoms were not clearly caused by a substance use disorder, in the judgment of an evaluating clinician; (3) have two Paisa surnames identified in anthropological and genetic analyses (13, 16, 17) (Supplementary Information); (4) aged 18 or above; (5) understand and sign an informed consent document; (6) no intellectual disability, and (7) no history of serious brain trauma or neurological disorder (e.g., seizure disorder. From among the overall participants, analyses reported here include individuals with a primary diagnosis of SCZ, BP-I, BP-II, or MDD based on structured diagnostic interview (see Study Measures).

Healthy controls were ascertained from the same communities as the cases, using the following criteria: (1) no (current or lifetime) SMI, as evaluated through the overview screening module of the NetSCID (2) no current substance use disorder, and (3) fulfillment of criteria 3-7 described for cases.

Cases were evaluated in the inpatient unit or during their outpatient visits to the two institutions. Controls were evaluated in the outpatient units. Before performing any assessment and after verifying inclusion and exclusion criteria, all participants (cases and controls) signed an

informed consent form electronically; a printed copy of the form was given to each participant. All procedures were approved by the IRB committees of the University of Antioquia (Comité de Ética del Instituto de Investigaciones Médicas de la Universidad de Antioquía), the Hospital San Vicente Fundación, the CSJD, UCLA and Penn.

Study Measures

Data collected on cases included parental socioeconomic status (SES) and education level, prior psychiatric contacts and hospitalizations, and medication history. Data collected on all participants included demographic information, medication use, substance use, the 45-question Symptom Assessment Questionnaire (SA-45) (18), a brief assessment of current severity of a range of psychiatric symptomatology, the Penn Computerized Neurocognitive Battery (19), and a blood sample.

NetSCID: To obtain lifetime DSM-5 diagnoses and cross-diagnosis symptom-level data, we performed a structured interview with all cases, using a Spanish translation of NetSCID, the first computerized version of the Structured Interview for DSM-5 (20, 21). This instrument, with built-in algorithms and decision trees for determining diagnosis, helped increase reliability and substantially reduce branching errors that could lead to misdiagnosis. The NetSCID modules for case assessment included: overview, screener of major psychopathology, mood disorders, psychotic disorders, and trauma and stressor-related disorders. To screen for major psychopathology in potential control participants, we used an overview screen module incorporated in the NetSCID.

Penn-CNB: To assess speed and accuracy of neurocognitive performance across five domains related to specific brain systems hypothesized to be most strongly associated with SMI (executive function, memory, complex cognition, social cognition, and motor speed), we used nine tests from the Penn Computerized Neurocognitive Battery (CNB), a psychometrically well-validated online battery (Supplementary Table 1) with standardized automated QA and scoring procedures. The Penn CNB has been validated across a wide age range, in both community samples and psychiatric populations (22-26). Data for speed were multiplied by -1 so that poorer performance (slower speed) would result in a lower value. All evaluators were trained by the University of Pennsylvania team to guarantee quality standards. It is well established that age and education have strong effects on neurocognitive performance, therefore as is standard for CNB analyses (27), the raw data for each test were regressed on age, age^2, age^3, education, and an age by education interaction, and residuals used for further analyses (see Regression Models, below). Residuals were winsorized at the top and bottom 1% level to reduce the influence of extreme outliers, and transformed to z-scores based on the mean and SD in control participants.

Regression Models of CNB Accuracy and Speed

Z-scores were modeled as a function of diagnosis, sex, test domain and all interactions using linear mixed models (LMM), with individual CNB tests as repeated measures, as in (27). Separate analyses were conducted for accuracy and speed, because they show a different

factorial structure (28), and to reduce the dimensionality of the analyses, as we did not have hypotheses involving accuracy by speed interactions. Significant main effects were further dissected with separate models for each test. Analyses were done using the R function lme() in the nmle package (29, 30).

Assessment of Possible Confounding Effects of Medication Use

Self-report medication data were collected on all participants for 30 psychiatric medications and grouped into three categories (Supplementary Table 2): antidepressants (15 medications), antipsychotics (11 medications) and mood stabilizers (four medications). In each category, a binary indicator of medication use was constructed for each participant. The LMM analysis of z-scores were repeated including these three covariates to assess robustness of conclusions to medication use effects.

Factor Analysis of Symptom Data in Cases

Symptom data for cases were obtained from the NetSCID interview, and from seven supplementary questions about specific symptoms of fatigue, grandiosity, decreased need for sleep, flight of ideas, hypersomnia, apathy and anhedonia. Symptoms are considered present in cases if they are endorsed at any point in the NetSCID (i.e., lifetime) or in additional queries, and considered absent if they were never endorsed, and confirmed as absent at least once. A total of 40 symptoms were evaluated. Missing symptom data for cases from the NetSCID were imputed a single time using bootstrapped expectation-maximization (EMB) by the amelia() function in the R Amelia package (31).

We conducted a factor analysis on all symptoms endorsed by at least 10% of cases (before imputation). We first ran exploratory item-factor analysis (32, 33) on the matrix of tetrachoric inter-item correlations using least-squares extraction and oblimin rotation. The number of factors to retain was determined by a combination of the minimum average partial (MAP) method (34), parallel analysis (35) with Glorfeld correction (36), visual examination of the scree plot, and theory. MAP was implemented by the nfactors() function in the psych package (37) in R; corrected parallel analysis was implemented by the fa.parallel() function (also in psych). 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.

Results

A total of 2,259 participants were recruited into the study and administered the Penn CNB. Data for 370 participants (284 cases and 23 controls) were excluded because they were unable to complete the cognitive testing. Among the remaining 1,889 participants (N= 1,337 cases and 552 controls), 117 cases did not qualify for a primary lifetime diagnosis on the NetSCID of SCZ, BP-I, BP-II, or MDD and were excluded from analysis. A summary of basic demographic

information for each diagnostic category for the remaining 1,772 participants is in Table 1; controls are significantly younger, and have significantly higher education levels, than cases.

Associations between Diagnosis and Cognitive Performance

A schematic of the cognitive performance LMM analysis pipeline and results is presented in Supplementary Figure 1. Both accuracy and speed showed significant interactions of diagnosis and cognitive test domain, indicating that the diagnostic groups differed in their profile of deficits (Supplementary Table 3A). As can be seen in Figure 1, for both accuracy and speed the four patient groups bifurcated into two profiles, with SCZ and BP-I showing greater deficits than BP-II and MDD. The pattern of deficits was nearly identical for SCZ and BP-I, with greater deficits across executive (where effect sizes neared and exceeded 1 SD), social cognition and motor speed tests relative to memory and complex cognition. BP-II and MDD groups likewise had similar profiles, with more subtle deficits in executive functions (effect sizes 0.5 SDs), social cognition and motor speed while other domains were performed at normative levels.

Additionally, speed showed a significant three-way interaction among sex, diagnosis and test domain, indicating that the effect of sex on the speed of cognitive performance, depended on diagnosis and test domain (Supplementary Table 3A, Supplementary Figures 1 and 2). This interaction was apparently generated by the differentially slower performance of SCZ and BP-I females on attention and working memory tests.

The high cognitive performance in participants with MDD/BP-II relative to those with BP-I/SCZ (Figure 1) could not be accounted for by reduced symptom severity in the former group; the distribution of the SA45 Global Severity Index was similar in the four diagnostic groups, with MDD and BP-II both having higher mean severity (Table 1). The largest deficits in cases overall, relative to controls, were seen in executive function speed and accuracy, especially attention and working memory; in social cognition, particularly emotion identification and in motor speed. While most participants were taking medications (Table 1), conclusions in the above analyses were robust to inclusion of medication use as a covariate (Supplementary Table 3B).

Associations among Symptom Factors and Cognitive Performance

To analyze the relationship between cognitive performance and psychiatric symptoms, across diagnoses, we first performed a factor analysis of the binary symptom data from the 1,220 cases diagnosed with SCZ, BP-I, BP-II, and MDD; by doing so we could represent dozens of categorical, and collinear items by a smaller number of continuous scores. We determined that a four-factor model was most appropriate for the data, as indicated by a combination of theoretical, empirical, and common subjective methods for determining the number of factors (34-36) (see Methods). The four symptom factors can be grouped as Psychosis (loading positively on hallucinations, delusions, and disorganized speech/behavior), Mania (loading positively on decreased need for sleep, flight of ideas and grandiosity), Depression (loading positively on anhedonia, fatigue, depressed mood, avolition and hypersomnia) and Suicidality (loading

positively on suicide attempt and suicidal thoughts) (Table 3). This method was applied in prior research to reduce dimensionality of symptom ratings (38).

Using only cases, we repeated the LMM analysis including factor scores on Psychosis, Mania, Depression, and Suicidality as covariates (Supplementary Table 3C). Controlling for diagnosis, high Psychosis factor score was significantly associated with reduced accuracy and slower speeds (accuracy: $F=21.67$, $df=1, 1208$; $p<0.0001$; speed: $F=15.33$; $df=1, 1208$; $p=0.0001$). Mania and Suicidality factor scores were not significantly associated with accuracy/speed, after controlling for diagnosis, and Depression factor score was only weakly related to accuracy. The three-way interaction among diagnosis, sex, and test domain was not significant for either speed or accuracy; however, both speed and accuracy had significant two-way interactions of test domain with sex and with diagnosis. These interactions prompted us to analyze test domains separately, including main effects of diagnosis and sex. Additionally, as only the Psychosis factor score was strongly associated with cognitive function, we do not present results of individual test domains in relation to the other three factor scores (Supplementary Figure 1).

At the neurocognitive domain level, after controlling for diagnosis, higher scores on the Psychosis factor were related to lower accuracy and slower speed in both executive function and social cognition, and to slower motor speed (Table 4). To visualize the effect of the Psychosis factor on cognition, we first regressed the effect of diagnosis out of raw CNB scores, prior to generating z-scores. We then categorized cases as being above or below the median of the Psychosis factor, irrespective of diagnosis (Table 1), transformed to z-scores based on the mean and SD in cases in the low Psychosis group, and plotted the cognition profiles for these two Psychosis groups (Figure 2). After removing the effect of diagnosis, we see that cases in the upper half of the distribution of Psychosis factor score have poorer performance on both speed and accuracy than do cases in the lower half of the distribution. Note that no SCZ participants are below the median on the Psychosis factor (Table 1).

Discussion

To our knowledge, this is the first study to examine performance across major neurocognitive domains in a large cohort of uniformly ascertained SMI-affected individuals, examined together with healthy controls from the same genetically and culturally homogeneous population. This investigation provides new insights on the magnitude and profile of neurocognitive impairment in SMI by diagnosis, ranging from MDD to BPD subtypes to SCZ, and empirically-derived symptom factors. The profile of deficits across domains was broadly consistent with that reported in prior, smaller studies from US and European populations (39-42).

Notably, speed of emotion identification was impaired in all diagnostic groups relative to controls, and may therefore be a hallmark of SMI across diagnostic categories. Regarding episodic memory, while face memory was impaired in BP-I and SCZ, associative memory (digit symbol recall) was relatively spared. This finding needs further replication as, to our knowledge,

this measure of associative memory has not been used in other studies. The large trans-diagnostic sample investigated here also enabled us to identify significant interactions between test domain, diagnosis and sex, specifically finding that females with SCZ were slower than males with SCZ in measures of executive speed (43, 44).

Results of the exploratory item-factor analysis of clinical symptoms indicated a clear psychosis factor, two mood-related factors, and a suicidality factor. Previous factor analysis of data from a broad psychopathology scale in a community sample identified four factors: Mood-anxiety ("anxious misery"), specific phobias, externalizing behavior, and psychosis (43). We did not expect to replicate these factors in the current sample ascertained for adult SMI; however, the other two symptom domains (Psychosis and Mood-anxiety) are well-represented by the symptoms analyzed here. This factor structure allowed us to evaluate broad symptom domains, but a higher level of granularity may be needed to identify specific biological pathways underlying particular traits (e.g., auditory vs. visual hallucinations).

The heterogeneity of neurocognitive function within BPD is a topic now receiving considerable attention (45); we found marked distinctions in this respect between BP-I and BP-II. Individuals with BP-I displayed impairments in both accuracy and speed which were nearly identical to those seen in SCZ in terms of both severity and profile. In contrast, individuals diagnosed with BP-II, like those diagnosed with MDD, showed only minimal impairments in neurocognitive performance, with similar profiles across domains. Recent studies have demonstrated strong genetic correlations between BP-I and SCZ and between BP-II and MDD (4), generating interest in efforts to identify specific phenotypic features that correspond to this clustering, as ours do. Our results therefore provide an empirical, large-scale demonstration of the utility of the RDoC approach to ascertainment and characterization of neurocognitive domains for identifying possible trans-diagnostic subtypes of SMI (46, 47). These findings also motivate efforts to delineate specific BP features that are associated with impairment in these domains; the most striking such association in our data is to the symptoms constituting the Psychosis factor that we identified.

Even after adjusting for effects of diagnosis, increasing scores on the Psychosis factor were associated with slower motor speed and significant impairments (lower accuracy and slower speed) in both executive function and social cognition. Previous studies have shown similar associations but have not examined such a broad range of SMI diagnoses, or such a uniformly ascertained study population. Notably, the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) consortium identified cognitive impairment among individuals with psychosis compared to controls, along a gradient of severity that increased along a spectrum from BP-I to schizoaffective disorder to SCZ (48); this study recruited participants from across the U.S. by advertising for individuals who carried these diagnoses.

Our results suggest either that lifetime psychotic symptomatology has deleterious effects on specific cognitive domains which transcend diagnostic categories, or that a common set of risk

factors may predispose to both psychotic symptoms and impaired cognition across SMI categories. Several studies have attempted to address this issue, either through examination of course of illness or from a developmental perspective. Although it is now well-accepted that premorbid cognitive impairment is a common feature of SCZ (49, 50), data indicating such premorbid impairment in BPD are sparse (51). Population cohort studies have suggested that psychotic symptoms are associated with progressively declining neurocognitive function across development, but typically with sample sizes of diagnosed SMI cases that are too small to draw strong conclusions. For example, such findings in the ALSPAC birth cohort (39) reflect analyses of only 19 individuals with psychotic disorder (of > 4,700 participants in the overall study), and the Dunedin Birth Cohort includes only 31 individuals who developed psychotic illness (52).

Independent studies have shown that the specific cognitive domains measured here are heritable in both children and adults, in European-derived and African-American populations (41, 42, 53), while studies of more limited sets of cognitive measures have demonstrated their genetic correlation with schizophrenia (9, 54, 55). Moreover, in an ethnically diverse cohort of youth in Philadelphia that were administered the Penn CNB, greater schizophrenia polygenic risk was associated with reduced speed of emotion identification; this finding was replicated in an adult cohort (56). Future genome-wide genotyping studies of the Paisa cohort described here will enable the examination of genetic correlations for the neurocognitive battery from the current study across SMI diagnoses and symptom factors, broadly, as well as GWAS of neurocognitive phenotypes across multiple domains.

Certain limitations of this study should be noted. First, although SMI case and control participants were recruited from the same communities, we cannot rule out subtle effects of demographic differences between these groups, although we adjusted for such effects statistically. Second, while most earlier studies of SCZ have highlighted deficits in verbal memory (57, 58), we did not assess this domain due to lack of normative data on word frequency in the Paisa population.

This large cohort of uniformly ascertained individuals provides unique opportunities for the phenotypic and genetic characterization of SMI that may ultimately lead to novel approaches for disease classification. Moreover, our project represents a step towards achieving an equitable representation of major world populations in SMI datasets, a crucial objective for reducing health disparities. Collectively, these findings provide the first characterization of domain-specific cognitive performance across a uniformly ascertained and phenotyped SMI cohort in the genetically homogeneous Paisa population.

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Table 1. Demographic and medication information for 1,772 participants

	Schizophrenia	Bipolar Disorder I	Bipolar Disorder II	Major Depressive Disorder	Controls	P-value comparing Cases to Controls
N	141	453	137	489	552	
Mean (SD) Age	37.7 (12.59)	44.6 (13.41)	40.79 (14.22)	40.291 (14.11)	36.1 (14.16)	1.68E-14
Mean (SD) Years of Education	10.49 (3.32)	10.84 (4.24)	12.12 (3.85)	11.65 (3.75)	11.68 (3.35)	0.035
Percent Female (N)	19% (27)	62% (281)	74% (101)	73% (357)	67% (370)	0.108
Percent on Antipsychotics	89%	68%	53%	34%	0%	
Percent on Antidepressants	27%	23%	45%	72%	0%	
Percent on Mood Stabilizers	25%	70%	67%	20%	1%	
Mean (SD) on SA45 Global Severity Index	36.99 (33.49)	29.39 (30.34)	48.18 (38.12)	48.66 (37.99)	11.75 (13.11)	<2e-16*
Mean (SD) on psychosis factor score	1.8 (0.8)	0.2 (0.9)	-0.5 (0.6)	-0.6 (0.4)	NA	
Mean (SD) on mania factor score	-0.7 (0.8)	0.9 (0.5)	0.5 (0.5)	-0.8 (0.6)	NA	
Mean (SD) on depression factor score	-1.1 (1)	-0.3 (1.1)	0.5 (0.5)	0.5 (0.4)	NA	
Mean (SD) on suicidality factor score	-1 (1.1)	-0.2 (1)	0.2 (0.8)	0.4 (0.7)	NA	
Bottom half of psychosis factor score (N)	0	123	96	398	NA	
Top half of psychosis factor score (N)	141	330	41	91	NA	
Bottom half of mania factor score (N)	116	33	26	438	NA	
Top half of mania factor score (N)	25	420	111	51	NA	
Bottom half of depression factor score (N)	118	281	55	161	NA	
Top half of depression factor score (N)	23	172	82	328	NA	
Bottom half of suicidality factor score (N)	111	243	57	219	NA	
Top half of suicidality factor score (N)	30	210	80	270	NA	

*This p-value reflects the comparison of mean GSI between SCZ/BP-I and BP-II/MDD

Table 2. Separate analyses of accuracy (A) and speed (B) z-scores for each test. 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. The reference category is control-females

A	Executive Function						Episodic Memory				Complex Cognition		Social Cognition			
	ATT		WM		PS		FMEM		AM		NVR		EID		EDI	
Coefficient	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**
Intercept	-0.028	6.71E-01	-0.056	3.44E-01	-0.030	5.35E-01	-0.011	8.18E-01	-0.022	6.30E-01	-0.076	1.02E-01	0.084	1.16E-01	0.021	6.90E-01
MDD	-0.440	1.47E-06	-0.219	6.55E-03	-0.207	1.66E-03	-0.146	2.23E-02	-0.152	1.62E-02	0.007	9.07E-01	-0.105	1.48E-01	-0.218	2.16E-03
BP2	-0.570	4.52E-05	-0.276	2.74E-02	-0.339	8.30E-04	-0.139	1.59E-01	-0.120	2.20E-01	-0.005	9.57E-01	-0.269	1.58E-02	-0.345	1.64E-03
BP1	-0.844	5.50E-19	-0.691	1.10E-15	-0.829	2.03E-32	-0.397	1.74E-09	-0.398	1.98E-09	-0.212	1.47E-03	-0.530	1.64E-12	-0.437	2.39E-09
SCZ	-1.454	2.05E-22	-0.856	1.61E-10	-1.127	7.78E-26	-0.523	2.62E-07	-0.563	3.36E-08	-0.363	3.80E-04	-0.764	2.89E-11	-0.612	5.21E-08
Male	0.084	2.69E-01	0.166	1.57E-02	0.089	1.08E-01	0.032	5.43E-01	0.067	2.12E-01	0.225	2.62E-05	-0.251	3.31E-05	-0.062	2.90E-01

B	Executive Function						Episodic Memory				Complex Cognition		Social Cognition				Motor	
	ATT		WM		PS		FMEM		AM		NVR		EID		EDI		SM	
Coefficient	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**
Intercept	-0.036	5.83E-01	-0.029	6.58E-01	-0.013	8.49E-01	0.031	6.21E-01	-0.045	4.41E-01	0.062	2.87E-01	0.064	3.74E-01	0.024	7.09E-01	-0.050	4.80E-01
MDD	-0.322	6.39E-04	-0.416	8.29E-06	-0.152	1.36E-01	-0.220	1.45E-02	0.133	1.17E-01	-0.142	9.56E-02	-0.293	4.61E-03	-0.019	8.39E-01	-0.373	2.67E-04
BP2	-0.509	3.35E-04	-0.069	6.27E-01	-0.515	8.53E-04	-0.274	4.33E-02	-0.055	6.70E-01	-0.280	3.15E-02	-0.494	1.55E-03	-0.187	1.78E-01	-0.543	4.04E-04
BP1	-0.845	1.33E-16	-0.619	2.52E-09	-0.923	1.33E-16	-0.472	9.66E-07	-0.017	8.55E-01	-0.244	8.93E-03	-0.917	1.89E-16	-0.474	1.56E-06	-1.053	1.14E-21
SCZ	-1.834	1.27E-10	-1.435	3.05E-07	-1.314	1.70E-05	-0.519	3.48E-02	0.334	1.87E-01	-0.068	7.87E-01	-1.828	2.76E-11	-0.491	4.78E-02	-1.264	3.29E-06
Male	0.106	3.43E-01	0.085	4.47E-01	0.040	7.43E-01	-0.093	3.91E-01	0.134	1.83E-01	-0.186	6.57E-02	-0.191	1.24E-01	-0.072	5.18E-01	0.162	1.89E-01
MDD:Male	0.142	4.04E-01	0.294	8.25E-02	-0.089	6.28E-01	0.080	6.20E-01	-0.004	9.80E-01	0.285	6.27E-02	0.023	9.03E-01	0.081	6.25E-01	0.026	8.89E-01
BP2:Male	0.446	9.64E-02	-0.052	8.48E-01	0.124	6.71E-01	0.370	1.51E-01	-0.100	6.80E-01	0.252	2.99E-01	0.236	4.25E-01	0.254	3.38E-01	0.375	2.02E-01
BP1:Male	0.228	1.74E-01	0.363	3.36E-02	-0.016	9.32E-01	0.097	5.43E-01	-0.052	7.36E-01	0.090	5.60E-01	-0.055	7.65E-01	-0.035	8.30E-01	0.136	4.57E-01
SCZ:Male	1.127	4.57E-04	0.878	5.87E-03	0.216	5.31E-01	0.268	3.47E-01	-0.521	6.95E-02	0.006	9.84E-01	0.541	9.03E-02	-0.066	8.19E-01	0.119	7.08E-01

Table 3. Factor loadings on 18 binary symptoms for the 4-factor model, and summary of missing data and endorsement by diagnosis of each symptom. "Uni" is the uniqueness for each symptom. Factor correlations are presented below the loadings

						MDD			BP2			BP1			SCZ		
	Psychosis	Mania	Depression	Suicidality	Uni	Percent Missing	Percent endorsed before imputation	Percent endorsed after imputation	Percent Missing	Percent endorsed before imputation	Percent endorsed after imputation	Percent Missing	Percent endorsed before imputation	Percent endorsed after imputation	Percent Missing	Percent endorsed before imputation	Percent endorsed after imputation
Auditory Hallucinations	0.87	0.14	-0.06	0.12	0.206	0.00%	14.11%	14.11%	0.73%	16.06%	16.79%	1.55%	49.67%	50.33%	1.42%	88.65%	89.36%
Visual Hallucinations	0.81	0.08	-0.02	0.16	0.373	1.23%	7.36%	7.77%	1.46%	12.41%	13.14%	2.43%	27.81%	29.14%	5.67%	53.90%	57.45%
Bizarre Delusion	0.79	-0.24	-0.08	0	0.287	0.41%	1.43%	1.43%	0.00%	2.92%	2.92%	2.87%	7.73%	7.95%	4.26%	55.32%	55.32%
Delusion of Reference	0.76	0.15	-0.02	-0.05	0.325	0.41%	3.48%	3.48%	0.73%	10.95%	11.68%	4.19%	33.55%	36.20%	2.13%	75.18%	76.60%
Persecutory Delusion	0.75	0.21	-0.15	-0.04	0.21	0.00%	4.70%	4.70%	0.00%	13.14%	13.14%	1.77%	49.23%	49.45%	0.00%	89.36%	89.36%
Grossly Disorganized Behavior	0.66	-0.19	-0.14	-0.3	0.214	0.20%	0.00%	0.20%	0.00%	0.73%	0.73%	1.10%	11.48%	11.92%	3.55%	60.99%	63.12%
Disorganized Speech	0.63	-0.01	-0.07	-0.3	0.32	0.00%	0.41%	0.41%	0.00%	0.00%	0.00%	0.22%	14.79%	14.79%	6.38%	42.55%	46.81%
Religious Delusion	0.48	0.37	-0.11	-0.04	0.508	0.20%	0.61%	0.61%	0.73%	0.73%	1.46%	1.99%	27.15%	27.37%	4.96%	26.24%	27.66%
Decreased Need for Sleep	-0.04	0.97	-0.03	-0.03	0.049	27.20%	4.09%	17.59%	0.00%	75.18%	75.18%	0.44%	94.48%	94.48%	51.06%	6.38%	23.40%
Grandiosity	0.13	0.89	0.08	-0.1	0.18	10.84%	3.89%	8.79%	0.00%	90.51%	90.51%	0.00%	90.95%	90.95%	30.50%	15.60%	31.21%
Flight of Ideas	0.13	0.88	0.05	-0.01	0.214	27.20%	5.93%	15.54%	0.00%	83.94%	83.94%	1.99%	88.96%	90.07%	51.06%	6.38%	33.33%
Anhedonia	-0.13	0.03	0.88	0.07	0.056	0.00%	97.55%	97.55%	0.00%	97.08%	97.08%	7.73%	71.74%	73.95%	27.66%	34.75%	44.68%
Fatigue	-0.12	0.09	0.86	0.04	0.145	0.00%	93.05%	93.05%	0.00%	92.70%	92.70%	14.57%	64.46%	67.11%	42.55%	24.82%	32.62%
Depressed Mood	-0.24	0.06	0.72	0.23	0.042	0.00%	99.80%	99.80%	0.00%	97.08%	97.08%	0.00%	71.52%	71.52%	0.00%	20.57%	20.57%
Avolition	0.35	-0.49	0.62	-0.14	0.387	0.00%	66.26%	66.26%	0.00%	54.74%	54.74%	0.00%	34.00%	34.00%	1.42%	71.63%	71.63%
Hypersomnia	-0.14	0.1	0.19	-0.16	0.934	0.20%	24.95%	25.15%	0.00%	32.85%	32.85%	14.57%	19.43%	24.72%	42.55%	7.09%	13.48%
Suicide attempt	0.09	-0.1	-0.05	0.83	0.374	0.82%	43.76%	43.97%	1.46%	33.58%	33.58%	1.55%	24.72%	25.61%	0.71%	18.44%	18.44%
Suicidal thoughts lifetime	-0.01	-0.09	0.34	0.72	0.097	1.23%	93.46%	94.27%	1.46%	87.59%	88.32%	1.55%	65.78%	66.45%	0.71%	38.30%	38.30%

Correlations among factors	**Psychosis**	**Mania**	**Depression**	**Suicidality**
Psychosis	1	0.09	-0.45	-0.32
Mania	0.09	1.0	-0.21	-0.05
Depression	-0.45	-0.21	1	0.45
Suicidality	-0.32	-0.05	0.45	1

Table 4. Separate analyses of accuracy (A) and speed (B) z-scores for each test, including four factor scores as covariates. 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.

A	Executive Function						Episodic Memory				Complex Cognition		Social Cognition			
	ATT		WM		PS		FMEM		AM		NVR		EID		EDI	
Coefficient	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**
MDD	-0.57	3.93E-10	-0.32	5.77E-05	-0.34	1.53E-08	-0.20	4.18E-04	-0.22	9.95E-05	-0.13	2.52E-02	-0.10	1.49E-01	-0.26	5.78E-05
BP2	-0.67	4.34E-06	-0.36	4.96E-03	-0.45	3.72E-06	-0.18	4.90E-02	-0.18	5.25E-02	-0.12	1.84E-01	-0.24	2.83E-02	-0.37	4.94E-04
BP1	-0.81	1.11E-18	-0.71	4.36E-18	-0.81	8.60E-40	-0.38	1.28E-11	-0.40	1.27E-12	-0.24	2.13E-05	-0.37	3.70E-08	-0.37	1.01E-08
SCZ	-1.06	5.07E-07	-0.71	1.71E-04	-0.78	1.80E-08	-0.36	5.75E-03	-0.43	9.52E-04	-0.15	2.42E-01	-0.26	9.21E-02	-0.32	3.60E-02
Psychosis	-0.21	3.44E-03	-0.09	1.47E-01	-0.19	4.93E-05	-0.09	5.57E-02	-0.08	7.01E-02	-0.13	3.92E-03	-0.18	4.32E-04	-0.13	9.10E-03
Male	0.01	8.95E-01	0.11	2.24E-01	0.04	5.20E-01	0.01	8.97E-01	0.06	3.88E-01	0.16	1.49E-02	-0.37	2.46E-06	-0.11	1.50E-01

B	Executive Function						Episodic Memory				Complex Cognition		Social Cognition				Motor	
	ATT		WM		PS		FMEM		AM		NVR		EID		EDI		SM	
Coefficient	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**	**Estimate**	**P**
MDD	-0.44	5.65E-09	-0.53	2.08E-12	-0.33	7.59E-05	-0.22	1.36E-03	0.09	1.89E-01	-0.02	7.72E-01	-0.30	3.22E-04	-0.11	1.36E-01	-0.60	2.65E-13
BP2	-0.54	1.21E-05	-0.26	3.37E-02	-0.60	7.95E-06	-0.20	8.61E-02	-0.12	2.48E-01	-0.18	1.04E-01	-0.43	1.64E-03	-0.20	8.36E-02	-0.64	1.42E-06
BP1	-0.89	2.43E-30	-0.61	4.75E-15	-0.90	6.64E-26	-0.45	1.70E-10	-0.05	4.70E-01	-0.23	7.85E-04	-0.87	5.49E-25	-0.43	1.80E-09	-1.03	2.58E-35
SCZ	-1.02	8.81E-09	-0.77	1.60E-05	-0.69	3.89E-04	-0.31	5.45E-02	-0.02	8.81E-01	-0.25	1.11E-01	-1.18	1.04E-09	-0.15	3.68E-01	-0.82	1.23E-05
Psychosis	-0.08	1.79E-01	-0.13	3.08E-02	-0.25	1.80E-04	-0.04	5.07E-01	-0.04	4.89E-01	0.05	3.25E-01	-0.11	1.01E-01	-0.22	9.91E-05	-0.27	2.22E-05
Male	0.39	1.23E-05	0.41	4.62E-06	0.02	8.69E-01	0.04	6.31E-01	0.06	4.37E-01	0.00	9.74E-01	-0.14	1.49E-01	-0.05	5.63E-01	0.26	6.41E-03

Figure Legends

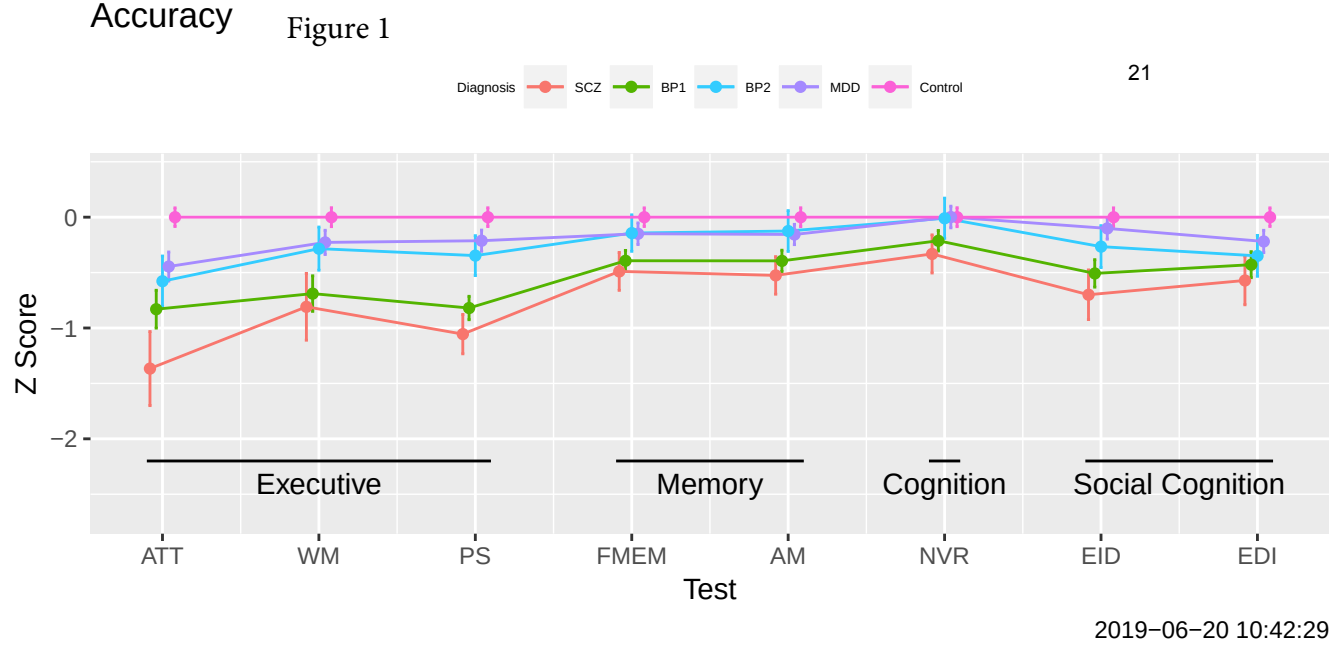
Figure 1. Z-scores on Accuracy (top) and Speed (bottom) profiles for tests assessing Executive Function, Memory, (Complex) Cognition, Social Cognition, and Motor Speed. Data for Speed were multiplied by -1 so that poorer performance (slower speed), would result in a lower value. Z-scores were generated relative to Controls. SCZ: schizophrenia BP1: bipolar disorder I, BP2: bipolar disorder II, MDD: major depressive disorder. Test abbreviations: 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 Recognition test; EDI = Measured Emotion Differentiation test; SM = Motor Praxis test. Error bars are the 95% confidence intervals.

Figure 2. Z-scores on Accuracy (top) and Speed (bottom) profiles for tests assessing Executive Function, Memory, (Complex) Cognition, Social Cognition, and Motor Speed, stratified by Psychosis factor scores. Data for speed were multiplied by -1 so that poorer performance (slower speed), would result in a lower value. In order to focus on the effect of Psychosis factor score, diagnosis was regressed out of raw test data, and SMI cases were categorized as being above or below the median on the Psychosis factor score. Z-scores were generated relative to the low Psychosis group. Test abbreviations: 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. High Psychosis=SMI cases with Psychosis factor scores above the median; Low Psychosis=SMI cases with Psychosis factor score below the median. Error bars are the 95% confidence intervals. The number of subjects in each Psychosis group is presented in Table 1.

Supplementary Figure 1. Schematic of linear mixed model analysis procedures and overview of results.

Supplementary Figure 2. Mean Speed Z-scores stratified by test domain, diagnosis and sex. Z-scores were generated relative to Controls. Error bars are the 95% confidence intervals. Data for Speed were multiplied by -1 so that poorer performance (slower speed), would result in a lower value. F=female, M=male. Test abbreviations: 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.

Figure 1


Accuracy
Diagnosis
SCZ
BP1
BP2
MDD
Control
Z Score
0
−1
−2
Executive
Memory
Cognition
Social Cognition
ATT
WM
PS
FMEM
AM
NVR
EID
EDI
Test
2019−06−20 10:42:29

Speed [x(−1)]
Diagnosis
SCZ
BP1
BP2
MDD
Control
Z Score
0
−1
−2
Executive
Memory
Cognition
Social Cognition
Motor
ATT
WM
PS
FMEM
AM
NVR
EID
EDI
SM
Test
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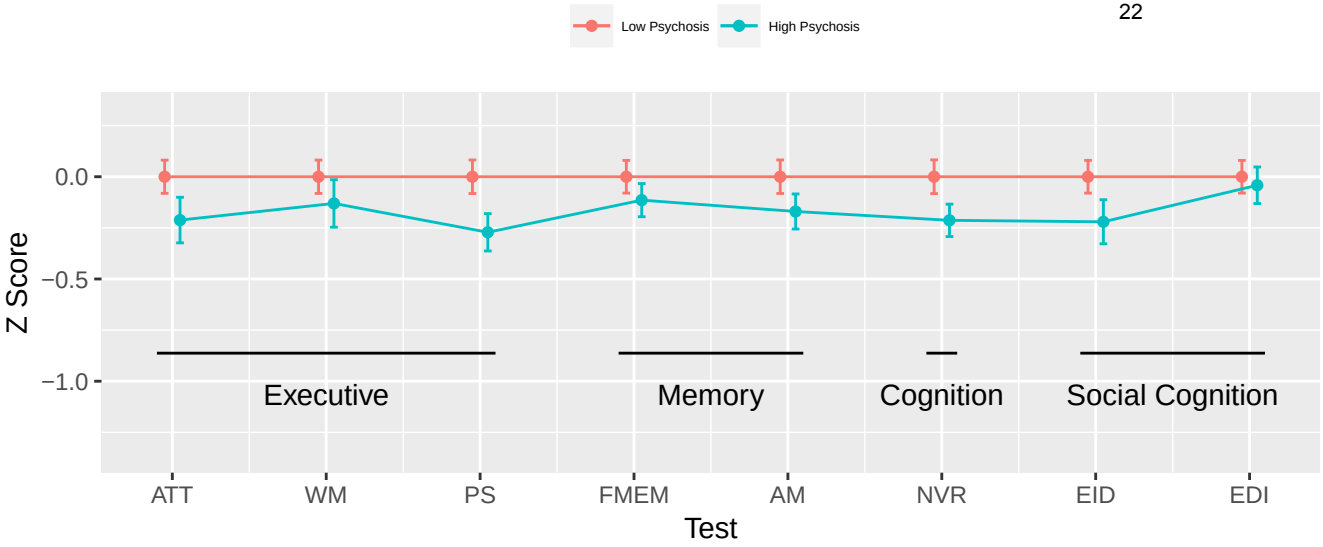
Accuracy

Figure 2



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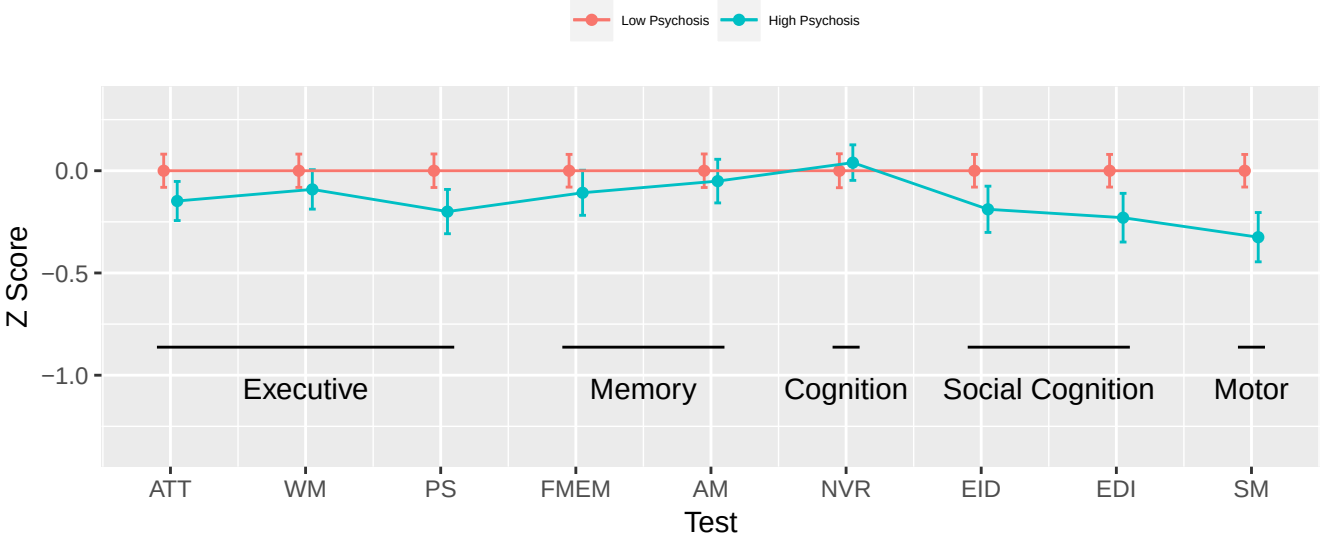
Speed [x(−1)]



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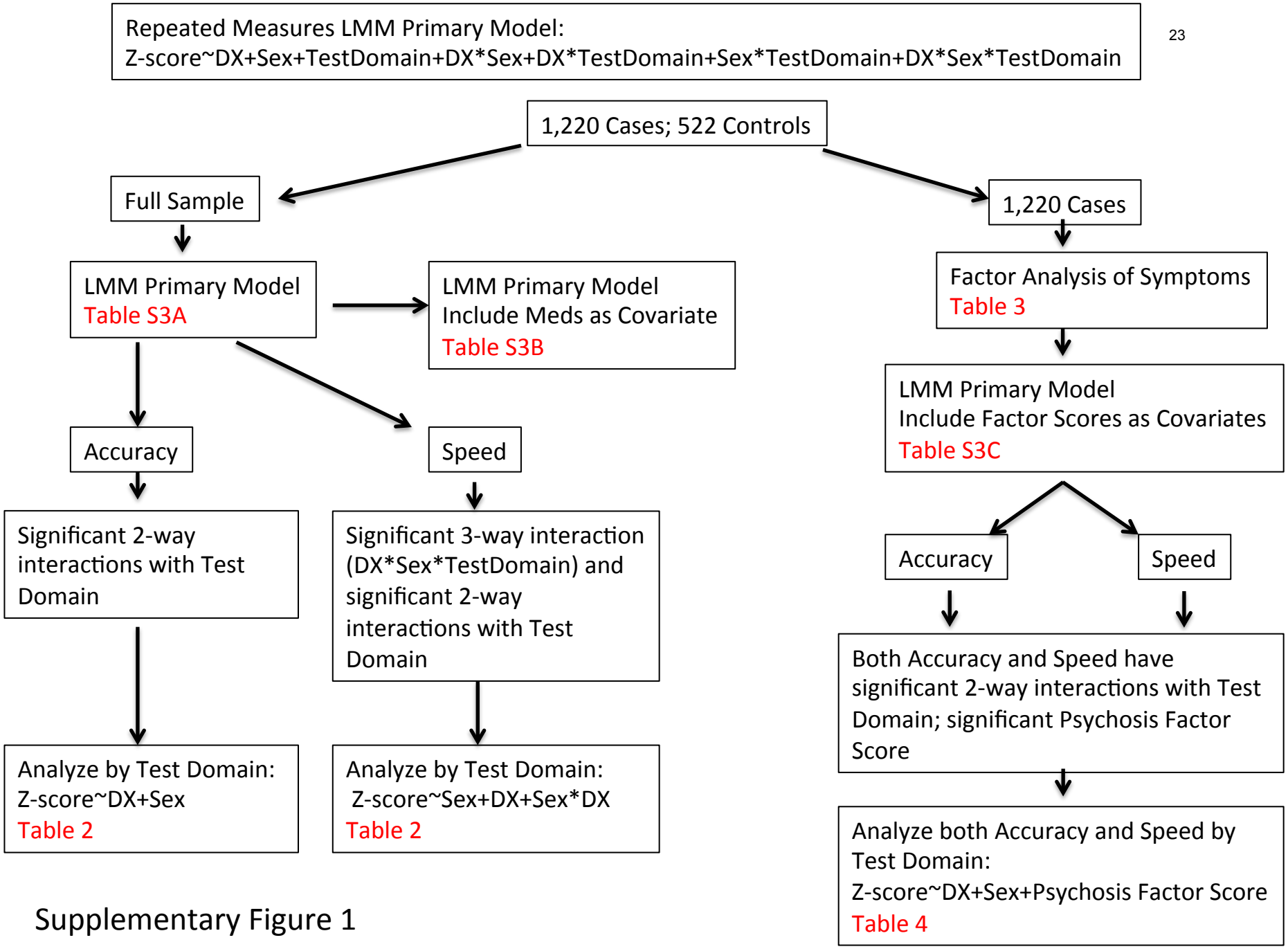
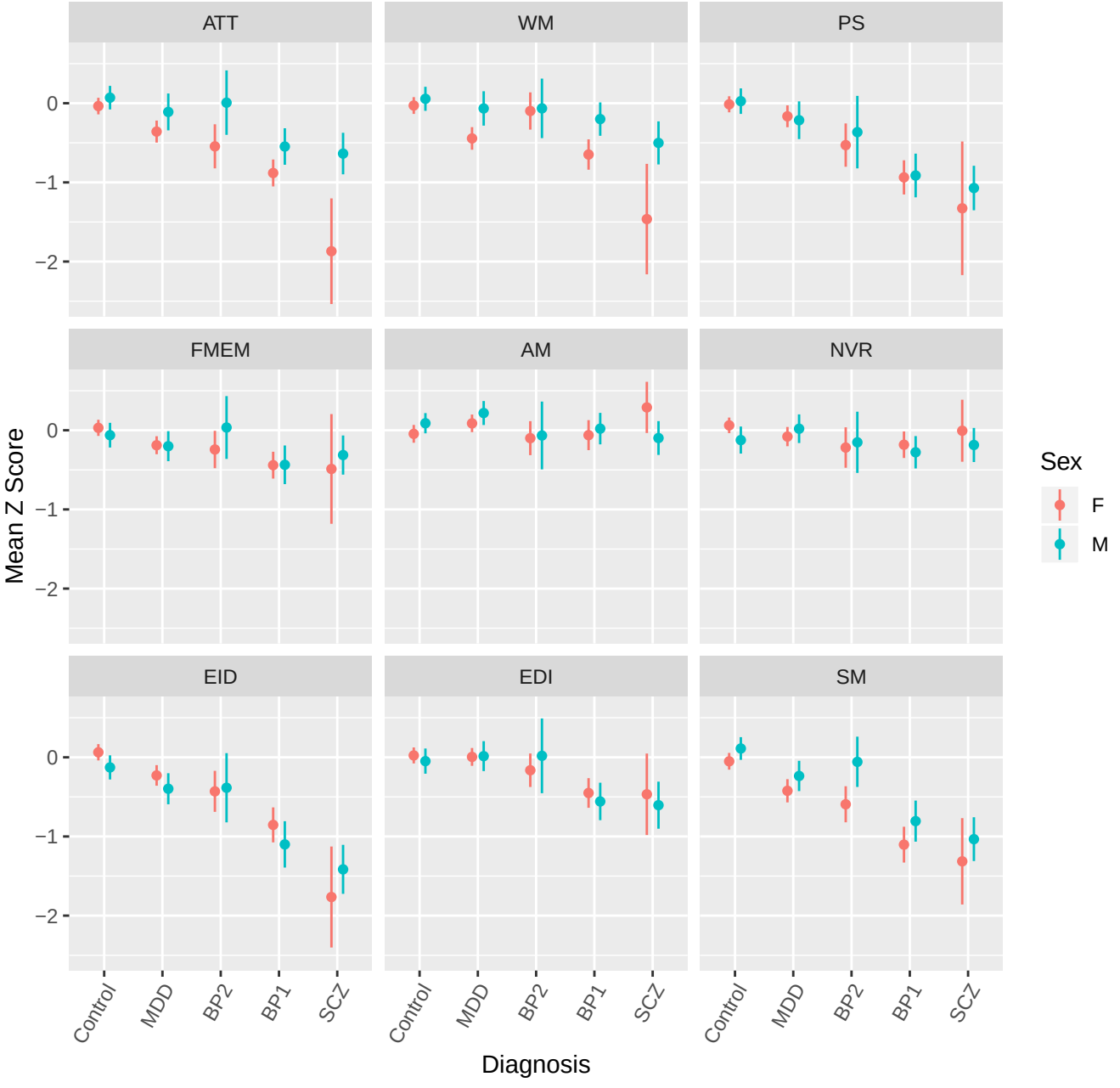


Supplementary Figure 1

Speed

Supplementary Figure 2