Cognitive endophenotypes of psychosis within dimension and diagnosis

Elena I. Ivleva[a,*], **David W. Morris**[a], **Julian Osuji**[a], **Amanda F. Moates**[a], **Thomas J. Carmody**[a], **Gunvant K. Thaker**[a,b], **Munro Cullum**[a], and **Carol A. Tamminga**[a]

[a]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

[b]Department of Psychiatry, Maryland Psychiatric Research Center, University of Maryland School of Medicine, Baltimore, MD 21228, USA

1. INTRODUCTION

Since biological criteria are not available to define objective phenotypes in psychiatric disorders, clinical phenomenology has been used to classify psychiatric diagnoses. In recent years, traditional diagnostic constructs have been increasingly challenged, especially in the cases where prominent symptom dimensions cut across diagnostic boundaries. This is particularly evident in schizophrenia (SZ) and bipolar disorder (BD) where an extensive overlap exists in many clinical characteristics, including psychosis, cognition, mood and behavioral symptoms. Moreover, recent genetic (Wellcome Trust Case Control Consortium, 2007) and neurophysiological (Thaker, 2008) studies have provided evidence for putative molecular and biological markers that overlap the two diagnoses. These observations challenge the traditional dichotomous model of SZ and BD and advocate for dimensional distinctions to enable studies of biological disease criteria.

One of the approaches that seeks to define biological markers which support valid diagnosis is the identification of endophenotypes: the specific heritable characteristics of brain anatomy, biochemistry or function that provide a direct measure of brain behavior, and, perhaps, more direct molecular underpinnings for disease definition than does the clinical syndrome (Gottesman and Shields, 1973). One of the broadly studied putative endophenotypes in psychiatric syndromes is cognitive dysfunction, as suggested by Burdick et al. (2006) and Bora et al. (2009). The established heritability of cognitive function and the described neural networks mediating specific aspects of cognition, as well as the availability of objective measurement tools to assess cognitive performance provide support for examining cognitive function as a promising endophenotype for SZ and BD (Ivleva et al., 2010). Several cognitive endophenotypes have been described in probands with SZ (SZP) and BD (BDP), with deficits in executive function, declarative memory and processing speed consistently found in both diagnoses (Schretlen et al., 2007; Hill et al., 2008; Arts et al., 2008; Smith et al., 2009; Stefanopoulou et al., 2009). Deficits in working memory and sustained attention are common in SZP (Braff, 1993; Keefe et al., 1995; Cornblatt and Malhotra, 2001), whereas are less consistently reported in BDP (Clark et al., 2002; Glahn et

*Corresponding author: Elena I. Ivleva, M.D., Ph.D., Department of Psychiatry, UT Southwestern Medical Center, 6363 Forest Park Road, BL6.633, Dallas, TX 75390, USA, Phone 214 648 0843, Fax 214 648 5321, ivlevaelena@hotmail.com.

al., 2010), with some describing them as state-dependent (Kumar et al., 2010). Cognition deficits in SZP are thought to be more severe and stable "trait" measures, while these deficits in BDP are described as less debilitating and partially state-dependent, although attenuated impairments remain during periods of euthymia (Ferrier et al., 1999; Rubinsztein et al., 2000; Thompson et al., 2005). In addition, deficits in executive function, working and declarative memory, and processing speed have been reported in biological relatives of SZP (SZR) (Faraone et al., 1995; Toomey et al., 1998; Cannon et al., 2000; Asarnow et al., 2002; Sitskoorn et al., 2004), as well as in relatives of BDP (BDR) (Glahn et al., 2004; Kieseppa et al., 2005; Hill et al., 2008; Glahn et al., 2010). Deficits in attention are well documented in SZR (Snitz et al., 2006; Sponheim et al., 2006), whereas reports in BDR are less consistent (Gourovitch et al., 1999; Bora et al., 2009; Kumar et al., 2010). Growing evidence suggests that BDP may have distinctive cognitive profiles depending on presence of lifetime psychosis; in that, probands with psychotic BD show deficits in domains of executive function, verbal and non-verbal declarative memory, working memory, processing speed and attention, similar to those found in SZP (Glahn et al., 2006; Glahn et al., 2007; Martinez-Aran et al., 2008; Reichenberg et al., 2009). Mild psychosis phenotypes (e.g., schizotypy) have been linked to poorer cognitive performance in SZR (Cannon et al., 1994; Niendam et al., 2007). Interestingly, a single study of BDR with lifetime subclinical psychotic-like symptoms showed better performance in motor speed, verbal declarative memory and attention compared to non-psychotic BDR (Jabben et al., 2009).

Overall, evidence suggests that psychosis may be a key clinical dimension associated with overlapping cognitive characteristics in SZ and BD. Therefore, in this study we examined putative cognitive endophenotypes within the SZ - psychotic BD boundary contrasting the two clinical paradigms: traditional dichotomous DSM-IV diagnoses (SZ, BD) and the psychosis dimension defined as manifestation of lifetime psychotic symptoms independent of the DSM-IV diagnoses. In accordance with the classic endophenotype criteria (Gottesman and Shields, 1973), we conducted this examination in a family sample of probands with SZ and psychotic BD, and in their first-degree biological relatives. Establishing similarities and differences in the endophenotypic signatures of SZ and BD families may provide important insights for future genetic studies, and may improve conceptualizations about the common and distinct aspects of pathophysiology, about clinical heterogeneity, and about clinical boundaries of the two psychotic disorders. We asked the question, whether there are aspects of cognitive dysfunction that distinguish the traditional diagnostic groups (SZ and BD), or whether cognitive dysfunction is common to probands and relatives across the SZ/BD psychosis dimension. We conducted two sets of analyses with the cognitive measures, one contrasting individuals with the two categorical diagnoses, and the other contrasting individuals with and without lifetime psychoses. The *traditional DSM-IV diagnosis analyses* examined cognitive performance in probands with SZ and BD, and their relatives in the four study groups: SZP, BDP, SZR and BDR. The *psychosis dimension analyses* examined cognitive performance in individuals with and without lifetime psychoses and contrasted the three study groups: 1) psychosis probands (SZP and BDP, combined), 2) relatives with psychosis spectrum disorders (defined in **Methods**), and 3) relatives without psychosis spectrum disorders. We hypothesized that: 1) within traditional diagnoses, SZP and BDP would show similar cognitive performance on measures of working memory, declarative memory, executive function and attention; SZR and BDR would show similar performance on these measures; whereas relatives would show higher cognitive performance than probands; and, 2) within the psychosis dimension, probands would show lower cognitive performance on the measures of working memory, declarative memory, executive function and attention compared to relatives without psychosis spectrum disorders; whereas relatives with psychosis spectrum disorders would show cognitive performance on these measures intermediate between probands and non-psychotic relatives. This is the first study to directly compare putative cognitive endophenotypes in probands and relatives from both diagnostic

groups (SZ and psychotic BD) using a psychosis "diagnosis vs. dimension" contrast. The proband groups included stable on medications out-patients, similar in age, education, IQ and socio-economic status, providing a common baseline of relevant characteristics for cognitive performance comparisons.

2. METHODS

2.1. Subjects

The study recruited probands who met the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) criteria for SZ or BD, type I with lifetime history of psychotic symptoms, and their eligible first-degree relatives with and without lifetime psychiatric diagnoses. All SZ and BD probands recruited into this study were clinically stable medicated out-patients with active psychosis and mood symptoms severity varying from remission/euthymic state to mild symptoms. Relatives who had lifetime psychiatric diagnoses were clinically stable and asymptomatic at the time of the study. Psychosis spectrum disorders in relatives were defined as lifetime psychotic DSM-IV Axis I diagnoses (e.g., major depressive disorder with psychotic features, substance-induced psychosis, etc.), or any SZ spectrum/Cluster A personality disorder. All volunteers were between ages 15 and 65 years, English-speaking, and had an IQ > 70. Probands were recruited through advertising and by referrals from community out-patient mental health centers within Dallas county and from the UT Southwestern out-patient psychiatric clinics; relatives were recruited with the probands' consents. Individuals with a history of major neurological or decompensated medical illness, mental retardation, traumatic brain injury with loss of consciousness, substance abuse within the last month or substance dependence within the last three months were excluded from the study. The study was approved by the institutional review board of the UT Southwestern Medical Center and was consistent with standards for the ethical conduct of human research. All volunteers provided written informed consent after the study procedures had been fully explained.

Initially, a total of 131 volunteers were recruited for the study, including 76 probands (44 SZP and 32 BDP) and 55 relatives (30 SZR and 25 BDR). The few relatives who had diagnoses of SZ (n=2) or psychotic BD (n=2) were moved to the proband groups for both the traditional DSM-IV diagnosis and the psychosis dimension analyses. Therefore, the traditional diagnosis analysis groups included 1) SZP (n=46), 2) BDP (n=34), 3) SZR (n=29) and, 4) BDR (n=22); and the psychosis dimension analyses groups included 1) probands (n=80, including SZP and BDP); 2) psychotic relatives (n=22, including SZR and BDR with lifetime psychosis spectrum disorders: SZR [n=16, including 6 with psychotic major depressive disorder, 9 with cluster A personality disorder, and 1 with bipolar disorder, type II, and cluster A personality disorder] and BDR [n=6, including 1 with psychotic major depressive disorder, 1 with psychotic disorder not otherwise specified, and 4 with cluster A personality disorder]; and 3) non-psychotic relatives (n=29, including SZR and BDR without lifetime psychosis spectrum disorders: SZR [n=13, including 4 with no identifiable Axis I or II diagnoses, 3 with non-psychotic major depressive disorder, 1 with anxiety disorder, 2 with non-psychotic major depressive disorder and anxiety disorder, and 3 with substance abuse/dependence] and BDR [n=16, including 3 with no identifiable Axis I or II diagnoses, 1 with non-psychotic bipolar disorder not otherwise specified, 1 with non-psychotic major depressive disorder, 3 with non-psychotic major depressive disorder and anxiety disorder, 6 with substance abuse/dependence, and 2 with cluster C personality disorder].

2.2. Clinical Assessments

DSM-IV Axis I diagnoses in probands and relatives were determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996). DSM-IV Axis II diagnoses of cluster A/"SZ spectrum personality disorders" in relatives were determined based on the Structured Interview for DSM-IV Personality Disorders (Zanarini et al., 1996). In this study, more liberal criteria for SZ spectrum personality disorders were used in order to increase sensitivity for detecting mild psychosis phenotypes (Thaker et al., 1993): three DSM-IV criteria for schizoid and paranoid, and four criteria for schizotypal personality disorders were sufficient for the personality disorder diagnoses. The Brief Psychiatric Rating Scale (Overall and Gorham, 1962) was used to evaluate active symptoms severity. The Hollingshead Index of Social Position (Hollingshead, 1975) was used to evaluate the highest lifetime occupational/socio-economic level. In addition, psychiatric and medication history were collected in all study volunteers. Clinical assessments were administered by trained research clinicians who maintained inter-rater reliability at > 0.85.

2.3. Neuropsychological Testing

Study volunteers completed ten standardized neuropsychological measures that tapped four cognitive domains known to be most affected in psychosis: 1) *working memory* - Letter Number Sequencing and Spatial Span subtests from the Wechsler Memory Scale – Third edition (Wechsler, 1997b), and Digit Symbol Coding subtest of the Wechsler Adult Intelligence Scale – Third edition (Wechsler, 1997a); 2) *declarative memory* - Logical Memory II (delayed story recall) from the Wechsler Memory Scale – Third edition, the Word Recognition and the Face Recognition subtests from the Warrington Recognition Memory Test (Warrington, 1984); 3) *executive function* - perseverative response score from the Wisconsin Card Sorting Test (Heaton et al., 1993), Letter Fluency (PRW) total score from the Controlled Oral Word Association Test (Benton et al., 1994), and the Trail Making Test, Part B (Reitan and Wolfson, 1985); 4) *attention* - Trail Making Test, Part A (Reitan and Wolfson, 1985). In addition, an estimate of general intellectual level was obtained from the Wechsler Test of Adult Reading (Wechsler, 2001). Demographically corrected T-scores, which have a mean of 50 and standard deviation of 10, were used for the Wisconsin Card Sorting Test, Trail Making Test, Letter and Category Fluency (Heaton et al., 2004), and age-corrected scaled scores from the Wechsler Adult Intelligence Scale – Third edition and Wechsler Memory Scale – Third edition subtests were transformed to T-scores. T-scores for the Warrington Recognition Memory Test were obtained from the test manual (Warrington, 1984). The Wechsler Test of Adult Reading IQ estimate has a mean of 100 and standard deviation of 15. In addition, composite scores for the four cognitive domains were calculated as the average of the individual T-scores within each domain; a global neuropsychological composite score was also calculated as an average of means T-scores for all individual tests.

2.4. Statistical Analysis

A one-way analysis of variance (ANOVA) with a subsequent post hoc Tukey HSD test and Yates corrected chi-square test were used as appropriate for demographic and clinical variables. To test the *a priori* hypotheses, the primary analyses compared working memory, declarative memory, executive function, attention composites, and the global neuropsychological composite scores between the traditional DSM-IV diagnostic groups (SZP, BDP, SZR, BDR), and between the psychosis dimension groups (probands, psychotic relatives, and non-psychotic relatives). Each outcome was analyzed using a mixed-effects repeated measures analysis (PROC MIXED in SAS, SAS, Cary, North Carolina), applying Kenward–Roger approximation to calculate the appropriate denominator degrees of freedom. Correlations between members of the same family were accounted for in the error structure by inclusion of a random family effect. Subsequent post hoc pair wise comparisons between the diagnosis and psychosis dimension groups were conducted using PROC

MIXED controlling the family-wise error rate by the simulation method of Edwards and Berry (Edwards and Berry, 1987). The magnitude of pair wise differences between the groups was also assessed using Cohen's *d*. The analyses of neuropsychological composites (working memory, declarative memory, executive function and attention) were corrected for multiple comparisons using the Holm method (Holm, 1979) which allows for a less stringent correction for non-independent outcomes. In addition, an exploratory analysis of individual neuropsychological tests in each cognitive domain was conducted. Uncorrected probability values below 0.05 were considered significant.

3. RESULTS

3.1. Demographic and Clinical Characteristics

Age, gender, handedness, years of education, the Wechsler Test of Adult Reading estimated IQ, and lifetime occupational/social position status did not differ across proband and relative groups (Table 1). There was a higher proportion of African-American volunteers in the SZP group than in the BDP and BDR groups. No differences in the Brief Psychiatric Rating Scale scores were found between SZP and BDP, whereas probands expectedly had higher scores than relatives. Based on volunteers report, the majority of SZ and BD probands and a proportion of relatives had a past history of psychotropic medication use of varying duration. Most probands (33/46 of SZP and 26/34 of BDP) were actively treated with a combination of psychotropic medications including antipsychotic agents, mood stabilizers, antidepressants, and anxiolytics; only 1/46 of SZP and 1/34 of BDP were medication–free. In the relatives, 10/29 of SZR and 7/22 of BDR were treated with psychotropic agents, among which antidepressants and anxiolytics were most common. Since SZ and BD proband and relative groups were comparable with respect to medication status, cognitive outcomes were not adjusted for medication use.

3.2. Cognitive Performance

The mean scores for all neuropsychological tests in the proband and relative groups fell within one standard deviation of the normative mean using demographically corrected T-scores, except for performance on the Warrington Face Recognition test in SZP (39.20 ± 11.03). Cognitive performance within the traditional diagnoses [SZP vs. BDP vs. SZR vs. BDR] failed to distinguish proband or relative diagnostic groups (Figure 1A). The diagnostic group contrasts showed differences in the global neuropsychological composite [$F(3,96) = 5.6$, $P = 0.002$], and in three of the four cognitive domain composites: working memory [$F(3,93) = 8.2$, $P < 0.001$], declarative memory [$F(3,86) = 2.9$, $P = 0.038$]), executive function [$F(3,103) = 2.8$, $P = 0.043$]), but not in attention [$F(3,93) = 2.1$, $P = 0.107$], with differences accounted for by probands vs. relatives performance. Differences in working memory remained significant after correction for multiple comparisons. Probands with SZ and BD did not differ on any composite measures (all P 0.95, $d = 0.05 – 0.08$ for pair wise comparisons) (Table 2) or individual tests (Supplementary Table 1). Similarly, SZ and BD relatives did not perform differently on any composite scores (all P 0.22, $d = 0.7 – 0.44$ for pair wise comparisons) or individual tests. Probands scored lower than relatives in the domains of working and declarative memory, on the global neuropsychological composite (all $P < 0.49$, $d = 0.59 – 0.89$ for pair wise comparisons), and on several individual tests.

Analyses of cognitive performance across the psychosis dimension groups [probands vs. psychotic relatives vs. non-psychotic relatives] showed differences in all neuropsychological composites: working memory [$F(2,83) = 10.0$, $P < 0.001$], declarative function [$F(2,102) = 4.5$, $P = 0.013$], executive function [$F(2,110) = 3.9$, $P = 0.022$], attention [$F(2,111) = 3.3$, $P = 0.041$], and in the global neuropsychological composite [$F(2,106) = 8.4$, $P < 0.001$] (Figure

1B). These differences remained significant after correction for multiple comparisons. Specifically, probands showed lower performance than non-psychotic relatives in working and declarative memory, attention, in the global neuropsychological composite (all $P < 0.4$, $d = 0.52 – 0.84$ for pair wise comparisons) (Table 2), and on several individual tests (Supplementary Table 1). No differences emerged between probands and psychotic relatives, except for working memory composite ($P = 0.3$, $d = 0.45$), the Trail Making Test/B ($P = 0.01$), and the global neuropsychological composite ($P = 0.50$, $d = 0.52$) scores. No differences were found between psychotic and non-psychotic relatives, however the effect sizes for the global neuropsychological composite, working and declarative memory, and attention composite scores were small to medium ($d = 0.20 – 0.38$), supporting better cognitive performance in non-psychotic relatives.

4. DISCUSSION

The overall goal of this study was to examine whether probands with SZ and psychotic BD and their first-degree relatives differ in cognitive performance when segmented by traditional diagnostic boundaries or by psychosis dimension. We anticipated that these outcomes will contribute to the discussion of the distinctiveness of SZ and BD diagnoses. To our knowledge, this is the first study to directly compare cognitive function across several domains known to be affected in psychosis (working and declarative memory, executive function, and attention) in concurrently recruited probands with SZ and psychotic BD, along with their biological relatives. Probands recruited into this study were moderately symptomatic, stable, treated out-patients, similar in age, education, socio-economic status, and IQ. The relative groups were highly heterogeneous, allowing an exploration of cognitive endophenotypes across the psychosis dimension. There was a higher proportion of African-American individuals in the SZ proband and relative groups, compared to the BD groups. Prior reports have not shown differences in cognitive performance in African-American vs. Caucasian SZP across numerous cognitive domains after correction for level of education (Lewine and Caudle, 2000). In this sample, there were no differences in education between African-American and Caucasian subjects across the study groups (results not shown).

Cognitive performance within the DSM-IV diagnoses failed to distinguish SZP and BDP, or SZR and BDR, thus lending support to our first hypothesis. Indeed, probands with SZ and psychotic BD showed strikingly similar performance in all cognitive domains evaluated including working memory, declarative memory, executive function and attention. Similarly, SZR and BDR did not differ in performance across the four cognitive domains. As predicted, relatives had higher scores than probands in all domains (effect sizes ranging from .35 to .89), with differences in working and declarative memory being statistically significant. The pattern of cognitive performance was similar in proband and relative groups, consistent with previous reports (Cannon et al., 1994; Gur et al., 2007; Arts et al., 2008). These cognition findings from the diagnosis analysis add to the growing body of evidence suggesting that the two psychotic diagnoses are not distinguished based on cognitive characteristics (Glahn et al., 2007; Martinez-Aran et al., 2008; Reichenberg et al., 2009). By contrast, the psychosis dimension analysis showed that probands had poorer cognitive performance in working and declarative memory, executive function and attention, compared to non-psychotic relatives, whereas the psychotic relatives showed intermediate performance for SZ spectrum personality disorders, similar to Thaker et al. (Thaker et al., 1993), in order to capture across all cognitive domains. In this study, we used modestly less stringent diagnostic criteria mild psychosis phenotypes in relatives. This approach increased the proportion of relatives with SZ spectrum personality disorders two-fold, with the schizotypal phenotype being most sensitive to the reduced diagnostic criteria (results not shown). Thus, the liberalized diagnostic strategy significantly increased sensitivity for identifying individuals near the diagnostic threshold, and may benefit future translational

and genetic studies in psychosis. Overall, our data suggest that individuals with lifetime psychosis, regardless of the formal DSM-IV diagnoses, manifest poorer cognitive function as defined by working memory, declarative memory, executive function and attention performance compared to their non-psychotic counterparts, lending support to the existence of a cognition endophenotype for psychosis, independent of diagnosis.

In this sample, SZP and BDP showed similar neuropsychological scores which challenges previous reports of more severe cognitive disturbance in SZP, compared to BDP (Seidman et al., 2002; Altshuler et al., 2004; Dickerson et al., 2004; Burdick et al., 2006). Characteristics of our sample may contribute to this finding, namely, this sample included only BDP with lifetime psychotic symptoms; whereas, the majority of previous studies combined psychotic and non-psychotic BD individuals (Pearlson et al., 1995; Potash, 2006; Glahn et al., 2006). This is consistent with previous reports of the negative effect of lifetime psychosis on cognitive function in BD (Glahn et al., 2007; Martinez-Aran et al., 2008). It is also worth noting that the estimated IQ scores for our groups were in the average range and did not differ across the groups. Therefore, this analysis compared SZP and BDP similar in overall intellectual functioning and was not affected by IQ differences. As such, our SZP sample may be less representative in general, but ideal for contrasting cognitive characteristics between diagnostic groups.

We should note several limitations of this study. First, the modest sample size limited statistical power of the cognitive analyses, despite our ability to show meaningful differences. Second, the specific neuropsychological battery chosen for this analysis could limit characterization of cognitive endophenotypes, although we selected measures commonly used in the literature that have good norms and psychometric properties to represent the cognitive domains of interest. Third, although probands and relatives included in this study were clinically stable and overall minimally symptomatic, the variation in the active symptom severity (e.i., higher BPRS scores in probands than in relatives) could have contributed to cognitive outcomes. Fourth, a significant proportion of relatives and most probands in this sample had a long history of medication use and were treated with a combination of various psychotropic agents while active in this study; therefore the effect of medication on cognitive performance cannot be ruled out. Future studies including larger samples of unaffected relatives could help to further characterize cognitive endophenotypes of psychosis free of illness and medication effect. Finally, our sample was delimited by the diagnostic boundaries of SZ and psychotic BD and thus does not reflect the full spectrum of psychotic disorders. As endophenotypes of psychosis become better characterized, it will be interesting to explore these measures in other psychoses.

4.1. Conclusions

Cognitive performance in the domains of working memory, declarative memory, executive function and attention was successful in distinguishing probands and relatives with and without lifetime psychosis (independent of their categorical diagnoses) but did not distinguish probands and their first-degree relatives within traditional SZ and psychotic BD diagnostic groups. These findings support the notion that the two disorders may present a clinical continuum with overlapping cognitive characteristics defining the psychosis phenotype. Future research examining cognitive and other endophenotypes and their genetic underpinnings in larger family psychosis samples may shed further light on a dimensional definition of psychosis and aid in the development of biology-based diagnostic classification and novel treatments.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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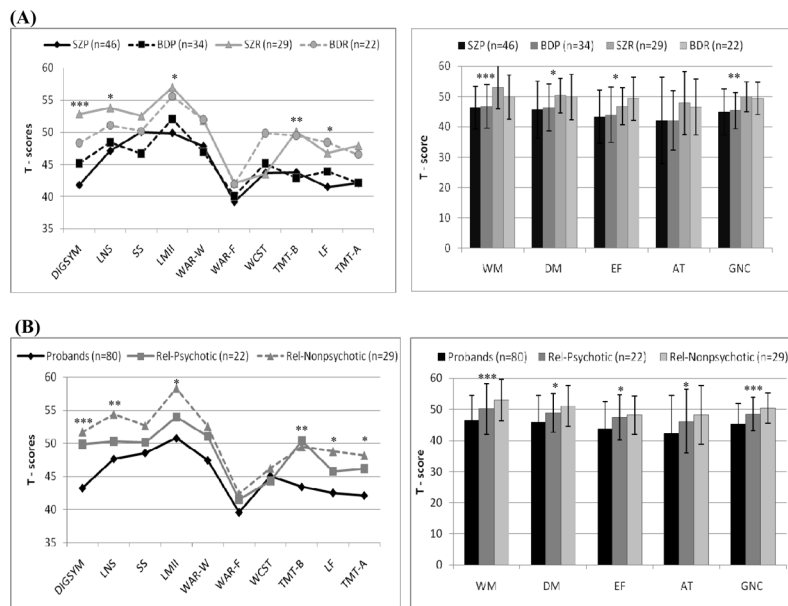
Figure 1. Cognitive Profiles of Probands with Schizophrenia and Psychotic Bipolar I Disorder, and their First - Degree Relatives by Traditional Diagnoses (A) and Psychosis Dimension (B)
Between group differences based on a mixed - effect repeated measure analysis (PROC MED): * $p < .05$, ** $p < .01$, *** $p < .001$

SZP – probands with schizophrenia, BDP – probands with psychotic bipolar I disorder, SZR – relatives of SZP, BDR – relatives of BDP, Rel-Psychotic – relatives with psychosis spectrum disorders, Rel-Nonpsychotic – relatives without psychosis spectrum disorders; DIGSYM – Digit Symbol Coding, LNS – Letter Number Sequencing, SS – Spatial Span, LM II – Logical Memory II, WAR-W – Warrington Word Recognition, WAR-F – Warrington Face Recognition, WCST – Wisconsin Card Sort Test – Perseverative Response, TMT-B – Trial Making Test B Time, LF – Letter Fluency, TMT-A – Trial Making Test A Time; WM – Working Memory Composite, DM – Declarative Memory Composite, EF – Executive Function Composite, AT – Attention, GNC – Global Neuropsychological Composite

Table 1

Demographic and Clinical Characteristics of Study Sample

Socio – demographic characteristics	SZP (*n*=46)	BDP (*n*=34)	SZR (*n*=29)	BDR (*n*=22)
Age, yrs; Mean (SD)	40.58 (10.75)	36.55 (10.68)	42.06 (10.9)	34.55 (14.29)
Gender/Male; n (%)	27 (58.69)	13 (38.23)	12 (41.37)	10 (45.45)
Left-handed; n (%)	7 (15.22)	4 (11.76)	2 (6.89)	2 (9.09)
Race; n (%) Black [a]	15 (32.61)	3 (8.82)	8 (28.58)	1 (4.54)
Education, yrs; Mean(SD)	13.54 (2.53)	13.35 (2.26)	14.48 (2.38)	13.68 (2.74)
WTAR IQ	98.92 (13.61)	101.35 (9.94)	100.38 (12.58)	101.50 (12.56)
Hollingshead occupational status; Mean (SD)	4.25 (1.71)	3.94 (1.38)	3.07 (1.29)	3.66 (1.82)
BPRS total scores; Mean (SD) [b]	48.04 (11.68)	44.06 (9.58)	31.35 (8.94)	28.4 (6.01)
Concomitant medications				
Off medications; n (%)	1 (2.17)	1 (2.95)	19 (65.52)	15 (68.18)
Typical antipsychotics; n (%)	10 (21.74)	1 (2.95)	-	-
Atypical antipsychotics; n (%)	36 (78.26)	19 (55.88)	2 (6.9)	2 (9.09)
Antidepressants; n (%)	24 (52.17)	17 (50.0)	9 (31.04)	3 (13.64)
Mood stabilizers; n (%)	6 (13.04)	26 (76.47)	3 (10.34)	1 (4.55)
Anxiolytics/Hypnotics; n (%)	13 (28.26)	14 (41.18)	5 (17.24)	4 (18.18)
Combined medications; n (%)	33 (71.74)	26 (76.47)	5 (17.24)	2 (9.09)

SZP – probands with schizophrenia, BDP – probands with psychotic bipolar I disorder, SZR – relatives of SZP,

BDR – relatives of BDP, WTAR IQ – Wechsler Test of Adult Reading general intelligence estimate,

BPRS - the Brief Psychiatric Rating Scale

[a]SZP vs. BDP, $\chi^2(1, N = 80) = 5.05$, $P = 0.024$; SZP vs. BDF, $\chi^2(1, N = 68) = 5.05$, $P = 0.024$

[b]$F(3,125) = 29.72$, $P < 0.001$; SZP vs. SZR, $P < 0.001$; SZP vs. BDR, $P < 0.001$; BDP vs. SZR, $P < 0.001$; BDP vs. BDR, $P < 0.001$

Table 2

Cognitive Performance in the Traditional Diagnoses and the Psychosis Dimension Proband and Relative Groups

Composites	T-score, Mean(SD)	PROC MIXED Primary Analyses	PROC MIXED Pair Wise Comparisons*	Cohen's d
		Diagnosis [SZP (n=46) vs. BDP (n=34) vs. SZR (n=29) vs. BDR (n=22)]		
WM	SZP, 46.30(8.71); BDP, 46.76(7.11); SZR, 53.10(7.19); BDR, 49.84(7.3)	$F(3,93) = 8.2, P < 0.001$[a]	**SZP/SZR, P<0.001; BDP/SZR, P=0.01;** SZP/BDP, P=0.95; SZR/BDR, P=0.33; BDP/BDR, P=0.50; SZP/SZR, P=0.33	SZP/SZR, d=0.84; BDP/SZR, d=0.89; SZP/BDP, d=0.05; SZR/BDR, d=0.44; BDP/BDR, d=0.43; SZP/SZR, d=0.43
DM	SZP, 45.62(9.42); BDP, 46.37(7.73); SZR, 50.30(5.69); BDR, 49.84(7.46)	$F(3,86) = 2.9, P = 0.038$	**SZP/SZR, P=0.049;** SZP/BDP, P=0.97; SZR/BDR, P=0.48; BDP/BDR, P=0.48; SZP/BDR, P=0.28; BDP/SZR, P=0.22	SZP/SZR, d=0.59; SZP/BDP, d=0.08; SZR/BDR, d=0.07; BDP/BDR, d=0.46; SZP/BDR, d=0.48; BDP/SZR, d=0.52
EF	SZP, 43.27(8.81); BDP, 44.01(9.14); SZR, 46.78(6.16); BDR, 49.27(7.16)	$F(3,103) = 2.8, P = 0.043$	SZP/BDP, P=0.98; SZR/BDR, P=0.90; SZP/SZR, P=0.22; BDP/BDR, P=0.17; SZP/BDR, P=0.08; BDP/SZR, P=0.51	SZP/BDP, d=0.08; SZR/BDR, d=0.37; SZP/SZR, d=0.45; BDP/BDR, d=0.63; SZP/BDR, d=0.72; BDP/SZR, d=0.36
AT	SZP, 42.10(14.23); BDP, 42.14(9.78); SZR, 47.89(10.31); BDR, 46.54(9.23)	$F(3,93) = 2.1, P = 0.107$	n/a	SZP/BDP, d=0.08; SZR/BDR, d=0.37; SZP/SZR, d=0.46; BDP/BDR, d=0.46; SZP/BDR, d=0.35; BDP/SZR, d=0.57
GNC	SZP, 44.88(7.63); BDP, 45.35(6.01); SZR, 49.84(4.93); BDR, 49.34(5.35)	$F(3,96) = 5.6, P = 0.002$	**SZP/SZR, P=0.003; BDP/SZR, P=0.03;** SZP/BDP, P=0.98; SZR/BDR, P=0.92; BDP/BDR, P=0.18; SZP/BDR, P=0.10	SZP/SZR, d=0.75; BDP/SZR, d=0.81; SZP/BDP, d=0.07; SZR/BDR, d=0.09; BDP/BDR, d=0.71; SZP/BDR, d=0.65
		Psychosis Dimension [Probands (n=80) vs. Psychotic Relatives (n=22) vs. Non-psychotic Relatives (n=29)]		
WM	Probands, 46.5(8.02) R-P, 50.10(8.11); R-NP, 52.91(6.6)	$F(2,83) = 10.0, P < 0.001$[a]	**Probands/R-NP, P<0.001; Probands/R-P, P=0.03;** R-P/R-NP, P=0.61	Probands/R-NP, d=0.84; Probands/R-P, d=0.45; R-P/R-NP, d=0.38
DM	Probands, 45.94 (8.7) R-P, 48.83(6.18); R-NP, 51.07(6.59)	$F(2,102) = 4.5, P = 0.013$[a]	**Probands/R-NP, P=0.01;** Probands/R-P, P=0.26; R-P/R-NP, P=0.67	Probands/R-NP, d=0.63; Probands/R-P, d=0.36; R-P/R-NP, d=0.35
EF	Probands, 43.59(8.91) R-P, 47.45(7.24); R-NP, 48.16(6.29)	$F(2,110) = 3.9, P = 0.022$[a]	Probands/R-NP, P=0.051; Probands/R-P, P=0.10; R-P/R-NP, P=0.99	Probands/R-NP, d=0.56; Probands/R-P, d=0.45; R-P/R-NP, d=0.11
AT	Probands, 42.12(9.78) R-P, 46.18(10.27); R-NP, 48.17(9.49)	$F(2,111) = 3.3, P = 0.041$[a]	**Probands/R-NP, P=0.04;** Probands/R-P, P=0.34; R-P/R-NP, P=0.78	Probands/R-NP, d=0.52; Probands/R-P, d=0.34; R-P/R-NP, d=0.20
GNC	Probands, 45.08(6.94) R-P, 48.53(5.35); R-NP, 50.46(4.76)	$F(2,106) = 8.4, P < 0.001$	**Probands/R-NP, P<0.001; Probands/R-P, P=0.050;** R-P/R-NP, P=0.63	Probands/R-NP, d=0.84; Probands/R-P, d=0.52; R-NP, d=0.38

*
Adjusted probability values based on a simulation method in PROC MIXED reported for post hoc pair wise comparisons analysis.

[a]
Significant after Holm correction for multiple comparisons.

Statistically significant results are listed in bold.

SZP – probands with schizophrenia, BDP – probands with psychotic bipolar I disorder, SZR – relatives of SZP, BDR – relatives of BDP, R-P – relatives with psychosis spectrum disorders, R-NP – relatives without psychosis spectrum disorders; WM – Working Memory Composite, DM – Declarative Memory Composite, EF – Executive Function Composite, AT – Attention, GNC – Global Neuropsychological Composite