Latent Profiles of Cognitive Control, Episodic Memory, and Visual Perception Across Psychiatric Disorders Reveal a Dimensional Structure

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Although meta-analyses suggest that schizophrenia (SZ) is associated with a more severe neurocognitive phenotype than mood disorders such as bipolar disorder, considerable between-subject heterogeneity exists in the phenotypic presentation of these deficits across mental illnesses. Indeed, it is unclear whether the processes that underlie cognitive dysfunction in these disorders are unique to each disease or represent a common neurobiological process that varies in severity. Here we used latent profile analysis (LPA) across 3 distinct cognitive domains (cognitive control, episodic memory, and visual integration; using data from the CNTRACS consortium) to identify distinct profiles of patients across psychotic illnesses. LPA was performed on a sample of 223 psychosis patients (59 with Type I bipolar disorder, 88 with SZ, and 76 with schizoaffective disorder). Seventy-three healthy control participants were included for comparison but were not included in sample LPA. Three latent profiles ("Low," "Moderate," and "High" ability) were identified as the underlying covariance across the 3 domains. The 3-profile solution provided highly similar fit to a single continuous factor extracted by confirmatory factor analysis, supporting a unidimensional structure. Diagnostic ratios did not significantly differ between profiles, suggesting that these profiles cross diagnostic boundaries (an exception being the Low ability profile, which had only one bipolar patient). Profile membership predicted Brief Psychiatric Rating Scale and Young Mania Rating Scale symptom severity as well as everyday communication skills independent of diagnosis. Biological, clinical and methodological implications of these findings are discussed.

Key words: schizophrenia/bipolar disorder/cluster analysis/schizoaffective disorder

Introduction

The comorbidity, heterogeneity, and potentially shared mechanisms that characterize psychiatric illnesses complicate efforts to understand their etiology. Cognitive deficits, eg, are characteristic of many psychiatric disorders including schizophrenia (SZ), schizoaffective disorder (SZ-A), and bipolar disorder (BD). These deficits vary in severity depending on the disease, with SZ patients often presenting with the worst dysfunction.[1,2] Nonetheless, considerable heterogeneity and diagnostic overlap exist in these deficits. One study, eg, found that the majority of SZ and BD patients in a middle aged (~35 years) sample were neurocognitively indistinct from one another.[3] Related to this point, a key question in psychiatry is the degree to which cognitive deficits in mental illness can be characterized as dysfunction in shared processes that vary in severity depending on the disorder. In support of this idea, the relative severity of cognitive impairment is often similar across domains in different disorders (reviewed by Barch, Sheffield[4]; eg, study by Reichenberg, Harvey, Bowie, Mojtabai, Rabinowitz, Heaton, Bromet[5] showing the most impairment in verbal memory and least impairment in visual processing across illnesses). Conclusive evidence for a shared neurocognitive process would have major clinical implications as it would suggest a common treatment for cognitive symptoms independent of primary diagnosis. Alternatively, patterns of cognitive performance may be domain-independent and/or diagnosis-specific, suggesting a treatment targeting one domain may not effectively modulate another (depending on the disorder).

If they exist, how can shared neurocognitive processes be identified? One fruitful approach is use data-driven analyses to partition datasets into "clusters," "classes,"

or "profiles" based on the distance of each data point to the cluster mean (among other metrics). If these profiles share similar levels of performance across all features examined in the analysis, it suggests common dysfunctional mechanism that varies in severity. On the other hand, if a profile is abnormal in one feature but normal (or even enhanced) in another, it may suggest a unique mechanism that underlies pathology in that particular subset of patients.

As an illustrative example, a recent study Bora, Veznedaroglu, Vahip[3] used latent class analysis (ie, latent profile analysis [LPA] as applied to continuous data) across a sample of patients with SZ or BD using data from 2 executive function tasks and 2 theory of mind (ToM) tasks as features. A 4-profile solution best fit the data, in which one profile performed at healthy levels, a second profile showed moderately impaired ToM but intact executive function, a third profile showed moderately impaired ToM and executive function, and a fourth profile showed severely impaired ToM and executive function. Substantial diagnostic overlap was observed between profiles. The finding that impaired ToM is dissociable from executive function in one profile suggests a separate mechanism for ToM deficits in this group that may persist independent of primary DSM diagnosis. The finding, however, that a dimensional structure was observed in 2 of the profiles (with moderate or severe deficits in both domains) suggests a common mechanism that may also contribute across domains in cases of moderate or greater executive dysfunction. Nonetheless, latent group-based analyses that incorporate cognitive data from across psychiatric disorders remain underutilized tools, and the extent to which dimensional and dissociable deficits exist across cognitive domains is still poorly understood.

To that end, the goal of this study was to perform LPA across a range of psychotic disorders using data from 3 cognitive domains: cognitive control, episodic memory, and visual integration (visual perception). These data were collected as part of a 5-site consortium using psychometrically optimized tasks from validated experimental cognitive paradigms.[6] Healthy controls (HCs) were analyzed for comparison but not included in the clustering as we were exclusively concerned with heterogeneity in patient populations. Clinical between-profile comparisons were also performed. We also performed confirmatory factor analysis (CFA) to evaluate fit of a purely dimensional, single-factor solution relative to that of the multi-profile solutions extracted by LPA. As LPA and CFA are data-driven techniques, we did not hypothesize any particular clustering solution.

Materials and Methods

Participants

Participants were recruited as part of the CNTRACS consortium (http://cntracs.ucdavis.edu). The consortium consists of 5 sites: The University of California—Davis, The Maryland Psychiatric Research Center at the University of Maryland, Rutgers University –Robert Wood Johnson Medical School, The University of Minnesota—Twin Cities, and Washington University. The respective institutional review boards for each site approved study procedures, and informed consent was acquired for all subjects. Additional details regarding the consortium are provided in refs.[6,7].

Two hundred ninety-six participants (ages 18–56) were included in the study sample—59 patients with Type I BD with a history of psychosis, 88 patients with SZ, 76 patients with SZ-A, and 73 HC participants. Exclusion criteria included head trauma, diagnosis of mental retardation or a pervasive developmental disorder, substance dependence in the past 6 months or substance abuse in the past month, and failed drug and alcohol urine screen on the day of testing. All patients were medication stable in the month leading up to test day and were either stable outpatients or had partial hospital status. All HCs had no history of SZ, SZ-A, BD, depression, or any other psychotic disorder and were not taking psychotropic or cognitive-enhancing drugs. Clinical assessments were performed or supervised by Master's level clinicians and all raters achieved agreement with "gold" standard ratings (see ref.[7] for details). Clinical ratings scales included the Schizo-Bipolar Scale (a continuous scale that measures the extent to which symptoms are BD-like [low scores] or SZ-like [high scores]).[8] Young Mania Rating Scale (YMRS),[9] the 24-item Brief Psychiatric Rating Scale (BPRS) (which includes subscales for negative, positive, disorganization, mania, and depressed mood symptoms[10]) and the Bipolar Depression Rating Scale (BDRS).[11] Functional capacity was measured using the University of California San Diego Performance Skills Assessment-B (UPSA-B), which includes Financial Skills and Communications Skills subscales.[12] Symptom data were not collected for HC individuals. Chlorpromazine (CPZ) equivalent antipsychotic doses were calculated using published guidelines for conventional[13] and atypical[14] antipsychotics.

Cognitive Domains Analyzed

Participant data from 3 tasks covering 3 different cognitive domains were used in latent profile analyses. These tasks were the Dot Probe Expectancy (DPX) task (used to measure cognitive control), the Relational and Item-Specific Encoding (RISE) task (used to measure episodic memory), and the Jittered Orientation Visual Integration (JOVI) task (a perceptual task used to measure visual integration). These tasks have been psychometrically "optimized" (http://cntracs.ucdavis.edu). Specifically, they are designed to (1) minimize task length; (2) simplify task administration across multiple sites; (3) maximize sensitivity and selectivity in assessing the specific cognitive

mechanisms of interest; and (4) enhance reliability and minimize floor and ceiling effects. Furthermore, optimization of each task is designed to enhance its psychometric properties while preserving high construct validity. Details of these tasks have been described in detail elsewhere[7,15–20] and are provided in brief in supplementary materials. The extracted DPX performance measure was d-prime context (a function of AX hits minus BX false alarms). The extracted RISE performance measure was a combination of d-prime (a function of hits minus false alarms) values for all 3 task trial types (associative recognition, relational encoding recognition, and item-specific encoding recognition). The extracted JOVI performance measure was a combination of accuracies from trials with 7–8, 9–10, 11–12, 13–14, and 15–16 degrees of orientational jitter. More specifically, the RISE and JOVI combined measures were defined by loadings from factors extracted by principle component analysis (SPSS v. 25 [Armonk, NY]). Only components with eigenvalues greater than one were retained, resulting in one component being extracted for the RISE and one component for the JOVI. These components explained 78% and 68% of the variances in RISE and JOVI, respectively.

LPA and CFA

LPA (a special case of cluster analysis, within the family of mixture cluster analysis) was performed in Mplus vs 8[21] using DPX d-prime context, RISE d-prime factor score, and JOVI factor score as features. A CFA was also performed in Mplus to evaluate the fit of a purely dimensional, one-factor solution using these features. Only patient data were used for LPA and CFA. For LPA, a one-profile solution was initially fitted, and the number of classes was systematically increased by one until the fit was no longer significantly improved by further increasing the number of profiles. For all evaluated LPA models, 10 000 random sets of starting values were specified, and the best log likelihood values were replicated. The optimal number of LPA profiles and CFA fit was evaluated using included the Akaike Information Criterion (AIC)[22] and Bayesian Information Criterion (BIC).[23] Lower AIC/BIC values indicated better fit. Comparing AIC between models, a model with difference < 2 (from the model with the lowest AIC) had substantial support, between 4 and 7 considerably less support, and > 10 virtually no support.[24] Comparing BIC between models, a difference < 2 was considered inconsequential ("weak"), 2 to 6 as "positive," 6 to 10 as "strong," and greater than 10 as "very strong".[25] Vuong-Lo-Mendell-Rubin and Lo-Mendell-Rubin adjusted LR tests[26] were also performed to compare LPA solutions. These tests compare the fit of a specified ("X") profile solution to models with one fewer profile ("X" - 1); a significant P value indicates the former solution ("X") should be preferred. Patients were assigned to the latent profile to which they had the

highest probability of membership. The magnitudes of profile differences for each feature were further evaluated by ANOVA F and P values with profile membership as a fixed factor. An additional exploratory ANOVA comparing profiles was also performed after adjusting for diagnosis. It should be noted that significant between-profile differences were expected between profiles as they were constructed to be maximally differentiated.

Clinical Comparisons

Between-diagnosis and between-profile demographic, behavioral, and clinical comparisons as well as analysis of medication effects were conducted by ANOVA or chi-square analysis (for categorical data) in SPSS v. 25. Measures showing significant ($P < .05$) between-group differences were followed up by exploratory post hoc tests (threshold $P < .05$) as well as an a priori linear contrast (see Results) to discern the nature of the effects. Between-profile behavioral and clinical comparisons (ie, main effects of profile) were also performed using Diagnostic and Statistical Manual of Mental Disorders (DSM)-diagnosis (BD/SZ/SZ-A) and/or parental education (years) as additional factors/continuous covariates in univariate ANCOVAs. These additional analyses were performed to determine if clinical differences between profiles were affected by differences in the ratio of BD/SZ/SZ-A patients or educational attainment potential within each profile. Complete parental education data was missing for 38 patients.

Results

Demographics

Demographic and clinical information for participants segregated by DSM-based diagnosis are shown in table 1. Significant group differences were observed on gender ratio and the majority of clinical measures.

DSM-Based Behavioral Comparison

Behavioral data segregated by diagnosis are presented in table 2 and supplementary table 1. HCs performed significantly more poorly than all 3 patient groups (BD, SZ-A, SZ) for all 3 primary behavioral measures of interest ($P < .05$). SZ patients performed significantly worse on the RISE than BD patients ($P < .05$). No other significant between-group differences were observed.

LPA and CFA Results

LPA was performed in patient participants using DPX d-prime context z-score (cognitive control), RISE factor score (episodic memory), and JOVI factor score (visual integration) as features (see Methods; fit measures presented in table 3). The two-profile solution suggested better fit than the one-profile solution for all metrics.

Table 1. Demographic and Clinical Information

	HC	BD	SZ	SZ-A	F or χ^2 (P)
N	73	59	88	76	−
Age	37.2 (11.3)	38.4 (10.8)	35.6 (10.7)	36.6 (10.9)	0.8 (.47)
% Male	54.8	35.6	62.5	53.9	10.5 (.02)
% per Site (1/2/3/4/5)	29/14/16/27/14	8/24/32/7/29	28/17/13/18/24	32/11/24/11/24	34.4 (<.01)
Education level (y)	14.8 (2.3)	14.7 (2.6)	12.8 (2.1)	13.6 (2.5)	12.0 (<.01)
Parental education level (y)	13.9 (2.7)	14.3 (2.5)	13.4 (3.3)	14.2 (2.7)	1.5 (.22)
SBS total	−	1.5 (0.9)	7.7 (1.2)	4.7 (1.3)	497.3 (<.01)
BDRS total	−	5.5 (5.3)	4.3 (4.6)	7.0 (6.5)	5.0 (.01)
Mood lability score		0.5 (0.1)	0.2 (0.1)	0.4 (0.1)	3.8 (.02)
YMRS total		10.0 (7.7)	9.9 (6.2)	13.1 (7.4)	5.1 (<.01)
BPRS total		40.2 (8.8)	43.2 (12.4)	49.7 (14.6)	10.8 (<.01)
CAINS anhedonia		8.4 (5.6)	12.3 (6.9)	14.4 (7.1)	7.8 (<.01)
CAINS blunting		0.8 (1.7)	3.8 (3.0)	3.3 (3.1)	22.0 (<.01)
UPSA-B total	83.9 (11.3)	84.6 (9.0)	75.0 (13.8)	77.8 (13.0)	10.7 (<.01)
Financial skills	43.7 (6.1)	42.9 (5.5)	39.1 (8.1)	40.9 (8.2)	6.2 (<.01)
Communication skills	40.3 (7.4)	41.5 (6.4)	35.8 (8.3)	37.0 (8.0)	8.7 (<.01)
% Taking antipsychotic	−	49.2	76.1	71.1	110.5 (<.01)
Antipsychotic dose (mg CPZ equivalent)		391.6 (522.7)	371.9 (301.0)	577.4 (778.2)	2.03 (.14)
% Taking mood stabilizer		69.5	13.6	28.9	92.5 (<.01)
% Taking antidepressant		59.3	26.1	56.6	74.0 (<.01)
% Taking anxiolytic		20.3	17.0	19.7	16.4 (<.01)

Note: BD, bipolar disorder; BDRS, Bipolar Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; CPZ, chlorpromazine; HC, healthy control; SBS, Schizo-Bipolar Scale; SZ, schizophrenia; SZ-A, schizoaffective disorder; UPSA-B, University of California San Diego Performance-Based Skills Assessment; YMRS, Young Mania Rating Scale. Numbers in parentheses represent the standard error.

Table 2. Primary Behavioral Data Segregated by Diagnosis

	HC	BD	SZ	SZ-A	ANOVA Model F or χ^2 (P)
Cognitive control (Z Score)	0.45 (0.86)	0.04 (0.82)	−0.19 (1.03)	−0.25 (1.08)	8.1 (<.001)
Episodic memory (RISE Factor Score)	0.50 (0.77)	0.09 (0.83)	−0.17 (1.06)	−0.36 (1.06)	11.3 (<.001)
Visual integration (JOVI Factor Score)	0.44 (0.90)	−0.03 (1.02)	−0.12 (0.96)	−0.26 (1.00)	7.2 (<.001)

Note: BD, bipolar disorder; HC, healthy control; SZ, schizophrenia; SZ-A, schizoaffective disorder. Numbers in parentheses represent the standard deviation.

The 3-profile solution suggested better fit than the two-profile solution based on AIC; likelihood ratio tests also suggested better fit for the 3-profile solution. The 4-profile solution also suggested better fit than the 3-profile solution based on AIC; likelihood ratio tests, however, suggested no significant improvement over the 3-profile solution. The 3-profile solution, therefore, was considered the optimal model. For this solution, average latent profile probabilities were 88%, 92%, and 82%.

We then more closely examined the composition of the 3-profile solution. The solution was best described as a "High" ability profile (*n* = 142) with high scores on all 3 domains, a "Moderate" ability profile (*n* = 66) with moderate scores, and a "Low" ability profile (*n* = 15) with low scores (table 4, figure 1). As expected by clustering, profiles significantly differed on d-prime context ($F(2,220) = 268.1$, $P < .001$), RISE factor score ($F(2,220) = 47.1$, $P < .001$), and JOVI factor score ($F(2,220) = 35.1$, $P < .001$). Post-hoc tests further showed that each profile was significantly different from each other for all domains (all *P* values < .001) with the exception of the JOVI, in which the difference between Moderate and Low profiles did not reach significance ($P = .15$). Weighted linear contrasts (testing the significance of the linear pattern High > Moderate > Low), however, were significant for all 3 domains (all *P* values < .001). Exploratory comparisons between patients in the High ability profile and HC subjects showed no differences on d-prime context ($t = 0.05$, $P = .97$) or JOVI ($t = 1.73$, $P = .09$). High ability patients, however, still performed significantly worse than HCs on the RISE (factor

Table 3. Model Fit Statistics for Latent Profile (LPA) and Confirmatory (single) Factor Analysis (CFA)

Number of Profiles	LL	AIC	ΔAIC (vs Previous Unless Specified)	BIC	ΔBIC (vs Previous Unless Specified)	VLMR LR Test P-value (vs Previous)	LMR Adjusted LR Test P-value (vs Previous)
1	−949.1	1910.3	–	1930.7	–	–	–
2	−907.8	1835.6	−74.7	1869.6	−61.1	<.01	<.01
3	*−900.4*	*1828.8*	*−6.8*	*1876.5*	*6.9*	*.03*	*.04*
4	−892.4	1820.9	−7.9	1882.2	5.7	.10	.11
One-factor CFA	−914.5	1847.1	18.3 (vs 3-profile LPA)	1877.8	1.3 (vs 3-profile LPA)	–	–

Note: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; LL, log-likelihood. Optimal LPA result (3 profiles) is italicized. Smaller minus LL, AIC, and BIC values suggest better fit. A significant result using the Vuong-Lo-Mendell-Rubin likelihood ratio (VLMR LR) test (threshold $P < .05$) to compare nested models also suggests better fit.

score $t = 2.85$, $P = .01$). Trial type-specific performance data for each task segregated by latent profile are presented in supplementary table 2.

Because the 3-profile solution suggested a one-dimensional pattern (with patients with Low, Moderate, and High scores clustering together) we next examined the fit of a one-factor (ie, one-dimensional/continuous) solution using CFA (table 3) and compared it to the 3-profile LPA solution. Fit comparisons were inconclusive. Specifically, although AIC suggested poorer fit (vs 3 LPA profiles), the difference in BIC (<2) was inconsequential (see Methods). In combination with results from the between-profile ANOVA, therefore, cluster results were best described as having a one-dimensional structure.

Between-Profile Demographic and Clinical Comparison

Demographic, clinical, and medication data for each latent profile are shown in table 4. No differences were observed in the ratio of BD/SZ/SZ-A patients or Schizo-Bipolar Scale scores between profiles.

ANOVA analyses revealed that profiles significantly differed in YMRS and BPRS total score as well as UPSA-B total score. Trend-level differences were also observed on education and parental education level. The UPSA-B total score was driven by significant differences in Communication subscore. Post hoc tests further demonstrated significant differences between High and Moderate profiles for YMRS score ($P = .005$), High and Moderate ($P = .012$) and High and Low ($P = .037$) profiles for BPRS score, and High and Moderate for UPSA-B Total score ($P = .001$) and Communication subscore ($P = .004$). No differences were observed between profiles on any medication-related measure.

As the observed latent profile pattern was dimensional across domains, we hypothesized that symptom severity would increase as profile varied from High to Low ability. Consistent with our hypothesis, linear contrasts demonstrated the BPRS difference mirrored profile dimensions (table 4, "Linear Contrast" column). Linear contrasts were not significant for any other measure.

Although no difference was observed in the ratio of BD/SZ/SZ-A patients between profiles, only one patient with BD was included in the Low ability profile, and the overall proportion of BD patients decreased as a function of ability. It was conceivable, therefore, that profiles varied clinically due in part to differences in symptom severity between DSM-based diagnostic groups (table 1). To test this possibility, measures that showed significant differences in the first set of tests were used as dependent variables in an ANCOVA analysis with profile and diagnosis as fixed factors. Main effects of profile remained significant after this adjustment for all behavioral and clinical measures (table 4, last column).

An exploratory analysis was also conducted to determine if differences between profiles on each task persisted after accounting for educational attainment potential (ie, parental education years). Using ANCOVA with profile as a fixed factor and parental education years as a continuous covariate, main effects of profile remained highly significant ($P < .001$) for all 3 measures.

Discussion

The present study used LPA across 3 distinct cognitive domains (cognitive control, episodic memory, and visual integration) to identify distinct profiles across psychotic disorders. The optimal solution was composed of 3 profiles: A "High" ability profile that consisted of patients with high performance (mostly indistinct from HC levels) on all 3 tasks, a "Moderate" ability profile that consisted of patients with moderate performance, and a "Low" ability profile that consisted of patients with low performance. As a comparison of these profiles suggested a dimensional structure across all 3 domains, a continuous, single-factor solution using CFA was estimated. BIC values suggested fit was nearly identical for the single-factor solution compared to the 3-profile solution suggesting an underlying one-dimensional structure across all cognitive variables. Examining diagnostic ratios between profiles, no significant differences were observed in the ratio of BD/SZ/SZ-A patients or Schizo-Bipolar Scale scores

Table 4. Primary Behavioral and Clinical Data Segregated by Latent Profile (High, Moderate, and Low Ability, With Healthy Control Averages Included for Visual Comparison)

	HC	High Ability (Patients)	Moderate Ability (Patients)	Low Ability (Patients)	F or χ^2 (P)	Linear Contrast Beta (P)	Dx Adjust F (P)
N	73	142	66	15	–	–	–
Cognitive control (Z Score)	0.45 (0.86)	0.46 (0.55)	−1.00 (0.54)	−2.12 (0.43)	268.1 (<.01)	−1.82 (<.01)	261.0 (<.001)
Episodic memory (RISE Factor Score)	0.50 (0.77)	0.15 (0.88)	−0.41 (0.80)	−2.00 (0.76)	47.1 (<.01)	−1.52 (<.01)	43.5 (<.001)
Visual integration (JOVI Factor Score)	0.44 (0.90)	0.22 (0.87)	−0.71 (0.85)	−1.07 (0.88)	35.1 (<.01)	−0.91 (<.01)	33.9 (<.001)
% BD/SZ/SZ-A	–	30/38/32	23/44/33	7/33/60	7.11 (.13)	–	–
Age	37.2 (11.3)	35.7 (10.4)	38.2 (11.6)	39.1 (10.5)	1.67 (.19)		
% Male	55	54	47	67	2.08 (.35)		
Education level (y)	14.8 (2.3)	13.8 (2.6)	13.0 (1.8)	13.5 (3.4)	2.39 (.09)		
Parental education Level (y)	13.9 (2.7)	14.3 (2.7)	13.2 (3.4)	13.6 (2.3)	2.69 (.07)		
% per Site (1/2/3/4/5)	29/14/16/27/14	26/18/22/11/23	23/12/18/18/29	13/20/33/7/27	6.56 (.59)		
SBS total	–	5.0 (2.9)	5.1 (2.7)	5.7 (1.9)	0.41 (.67)		
BDRS total	–	5.4 (5.9)	6.1 (4.9)	4.3 (5.6)	0.74 (.48)		
YMRS total		10.0 (6.8)	13.0 (7.2)	11.7 (71.8)	4.10 (.02)	1.18 (.38)	4.08 (.02)
BPRS total		42.7 (11.4)	47.5 (14.2)	50.0 (17.2)	4.60 (.01)	5.12 (.04)	3.52 (.03)
CAINS anhedonia		10.9 (6.8)	11.9 (6.7)	12.2 (8.7)	0.62 (.54)	–	–
CAINS blunting		2.8 (3.1)	2.7 (2.9)	4.1 (3.0)	1.40 (.25)		
UPSA-B total	83.9 (11.3)	80.6 (12.1)	74.3 (14.4)	75.9 (10.0)	5.74 (<.01)	−3.37 (.17)	4.87 (.01)
Financial skills	43.7 (6.1)	41.6 (7.6)	38.8 (7.7)	40.3 (7.1)	2.86 (.06)	–	–
Communication skills	40.3 (7.4)	38.9 (7.3)	35.4 (9.4)	35.6 (6.9)	4.90 (.01)	−2.39 (.12)	4.03 (.02)
% Taking antipsychotic	–	65.5	68.2	80.0	1.33 (.51)	–	–
Antipsychotic dose (mg CPZ equivalent)		455.9 (630.6)	439.1 (422.1)	407.4 (431.6)	0.04 (.96)		
% Taking mood stabilizer		34.5	31.8	33.3	0.15 (.93)		
% Taking antidepressant		47.9	37.9	53.3	2.24 (.33)		
% Taking anxiolytic		18.3	22.7	6.7	2.13 (.34)		

Note: BDRS, Bipolar Depression Rating Scale; BPRS, Brief Psychiatric Rating Scale; CPZ, Chlorpromazine; CMH, Cochran-Mantel-Haenszel; GAF, Global Assessment of Function; HC, healthy control; PAS, Premorbid Adjustment Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale of the Assessment of Positive Symptoms; SBS, Schizo-Bipolar Scale. ANCOVA model *F* tests were conducted using only patient data. Linear contrasts and (DSM) diagnosis-adjusted F tests on continuous variables were only conducted if the initial ANOVA *F* value was significant (indicating a significant between-class group difference). "Linear contrast" was High > Moderate > Low or Low > Moderate > High. Numbers in parentheses represent the standard deviation. "Dx Adjust" = main effect of profile in ANCOVA model with diagnosis (bipolar disorder [BD]/schizophrenia [SZ]/schizoaffective disorder [SZ-A]) as an additional covariate.

between profiles, suggesting that having a prevalence of BD or SZ-like symptoms did not determine profile membership (other than the "Low" ability profile which had only one BD patient) and that deficits in the 3 domains examined were not specific to one disorder. Profile differences in performance remained significant after adjusting for parental education. BPRS symptom severity and deficits in everyday communication skills varied inversely with increasing performance independent of diagnosis. Overall, these results suggest that cognitive deficits in psychosis tested across disparate domains may be characterized as a single continuum of ability (ranging from poor to near-normal) that also correlates with symptom severity.

Meta-analyses have demonstrated that cognitive dysfunction in SZ may be a "global" condition, affecting most cognitive domains with varying degrees of severity.[27–29] A similar profile of deficits has also been reported in SZ-A and BD, with less severe deficits in BD and mixed degrees of severity in SZ-A (reviewed by Barch and Sheffield[4]). Consistent with the results of our study, as a whole these findings suggest a domain-overlapping, one-dimensional structure to cognitive dysfunction across these illnesses. What might be the core neuronal process(es) that can underlie such global impairment? It has been argued that one potential mechanism is dysfunction of the dorsolateral prefrontal cortex (DLPFC). Although the 3 tasks examined in the present study recruit distinct neuronal
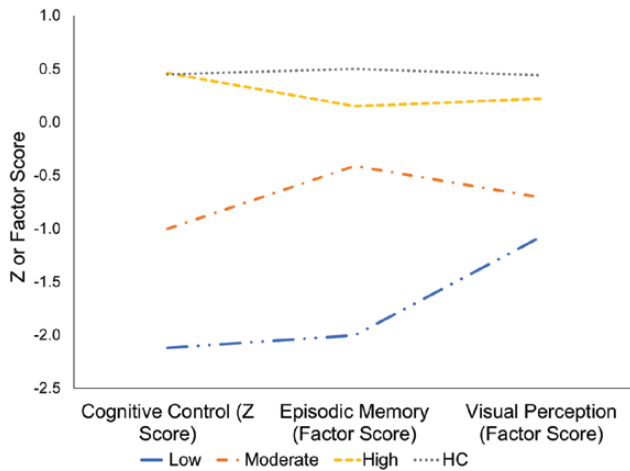
Fig. 1. Latent profile analysis (LPA) results. Three profiles were observed in patients: A "High" ability profile, a "Moderate" ability profile, and a "Low" ability profile. "Cognitive Control" was based on DPX d-prime context value, "Episodic Memory" based on RISE factor score, and Visual Perception based on JOVI factor score (see Methods). Healthy controls (HCs; top, dotted line) were included for comparison but not in the sample LPA.

circuits,[15,30,31] the common region activated by all 3 is the DLPFC, which (along with the superior parietal cortex) makes up the frontoparietal network most associated with cognitive control. As cognitive control is defined as the ability to use goals and plans to orchestrate behavior, on a neuronal level the DLPFC may be equivalent to the "conductor" ensuring the correct groups of orchestral instruments are playing on time and in tune depending on the demands of the task. Illustrating this point, top-down influences have been frequently observed during perceptual tasks in order to facilitate stimulus processing, interpretation, encoding, and recall.[32] It follows that the degree to which the prefrontal cortex and cognitive control is disrupted may be directly related to the overall level of cognitive impairment in psychiatric populations independent of DSM diagnosis. Additional mechanisms may, of course, contribute to dysfunction across domains, eg, abnormalities in "bottom-up" perceptual (eg, visual or auditory) processing.[33] Notably, however, previous work (in an independent sample collected prior to the present dataset) by the CNTRACS consortium using another perceptual task (the contrast-contrast task) suggests that deficits in contrast gain control in SZ may be accounted for by reduced attentional control (ie, attention "lapsing"),[34] an index related to frontoparietal cognitive control.[35] While our cognitive control-based interpretation is therefore, in our view, the most parsimonious given the present and previous findings, additional research using perceptual tasks (with experimental control over attention lapsing) together with the measures used in the present paper could be used to formally test whether another mechanism (such as early visual perception) could reproduce the single factor dimensional pattern of cognitive deficits observed in this study.

The dimensional structure observed here is conceptually consistent with previous findings from an LPA of executive function in SZ and BD,[3] which also reported profiles segregated by performance deficit severity across diagnoses. Critically, the dimensional structure observed here also does not conceptually conflict with the clusters ("biotypes") identified by the Bipolar-Schizophrenia Network for Intermediate Phenotypes (B-SNIP) consortium from a k-means cluster analysis of cognitive control and sensorimotor reactivity in BD, SZ, and SZ-A patients.[36] Although the 3 clusters identified by B-SNIP did not demonstrate parallel deficits in control and reactivity (with one biotype showing the highest reactivity but only moderate loss of cognitive control), performance deficits (vs HCs) for each biotype across the 3 cognitive control measures examined were similar. One may also argue that our results are not directly comparable with the B-SNIP findings as we did not include measures of sensorimotor reactivity. Nonetheless, our results combined with these previous studies suggest that cognitive deficits in these illnesses are best characterized as having a dimensional structure, with a potential common mechanism underlying these deficits across disorders.

Surprisingly, the largest group of patients ("High" performers) was not significantly different from HCs except in episodic memory, suggesting that RISE ability features more prominently than DPX or JOVI task performance in psychotic illnesses. Related to this point, previous work has also found that episodic memory performance is one the most impaired cognitive deficits in SZ.[29] It is also possible that severity in performance deficits is influenced by differences in task sensitivity. As the present sample (particularly BD patients) had relatively high functional capacity (based on UPSA-B scores), it is possible deficits in these domains would have only been apparent using very difficult tasks with high discriminating power (that said, we believe these tasks were sufficiently sensitive for this study given the significant differences in performance between HC and patient groups; furthermore, all tasks utilized by the CNTRACS consortium were designed to optimize their psychometric properties including sensitivity and selectivity). As a more chronically ill, lower functioning sample may show a different distribution, we caution against overinterpreting our results as suggesting the majority of patients with psychotic illnesses are cognitively "normal." Finally, the lack of differences on the DPX and JOVI tasks in the high performing groups does not also imply that cognition in these individuals has not been disrupted by their psychotic illness. Kendler and colleagues have reported that higher cognitive ability individuals with SZ perform worse than would be predicted by their parents' IQ scores.[37] Future studies examining additional tasks in these domains will be necessary in order to determine the generalizability of this finding.

As frequently occurs in studies involving patients with psychosis, the potential confounding effects of medication

on the observed findings cannot be completely disentangled. Although we did not observe any relationship between medication status, type, or dose and the likelihood a patient belonged to a particular profile, the present study was naturalistic and medication effects were therefore not tightly controlled. It thus remains possible that medication history is related to the observed profiles. Related to this point, previous cross-sectional work in an independent sample found that unmedicated patients showed lower DLPFC activation and worse performance during the AX-CPT (the task the DPX is based on) relative to medicated patients.[38] As this study was based on a univariate dimensional approach, however, it does not necessarily contradict the present findings.

Overall, our results suggest that cognitive deficits in psychotic illness can be described as having cross-diagnostic, one-dimensional structure across the domains of cognitive control, episodic memory, and visual perception. Clinically, this result also suggests an effective treatment may be found that can broadly improve cognition across multiple illnesses. Ultimately, however, to prove clinically useful future studies of these profiles should include replication in a larger sample, comparison of longitudinal outcomes, analysis of controlled treatment effects, and links to systems-level dysfunction in neuronal circuits. Latent class/profile analyses may also be performed on young adults and adolescents at high risk for psychotic illness in order to determine if similar profiles exist in these participants, if they persist into illness, and/or are predictive of illness. Finally, we stress that this method may be readily applied to a variety of (or in combination with) other neurocognitive processes (eg, sensorimotor reactivity) to generate profiles of patients which may be evaluated in the same manner and provide greater insight into the cross-diagnostic mechanisms of cognitive dysfunction.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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