

Cognitive Subtyping in Schizophrenia: A Latent Profile Analysis

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Cognitive dysfunction is a core feature of schizophrenia. The subtyping of cognitive performance in schizophrenia may aid the refinement of disease heterogeneity. The literature on cognitive subtyping in schizophrenia, however, is limited by variable methodologies and neuropsychological tasks, lack of validation, and paucity of studies examining longitudinal stability of profiles. It is also unclear if cognitive profiles represent a single linear severity continuum or unique cognitive subtypes. Cognitive performance measured with the Brief Assessment of Cognition in Schizophrenia was analyzed in schizophrenia patients ($n = 767$). Healthy controls ($n = 1012$) were included as reference group. Latent profile analysis was performed in a schizophrenia discovery cohort ($n = 659$) and replicated in an independent cohort ($n = 108$). Longitudinal stability of cognitive profiles was evaluated with latent transition analysis in a 10-week follow-up cohort. Confirmatory factor analysis (CFA) was carried out to investigate if cognitive profiles represent a unidimensional structure. A 4-profile solution was obtained from the discovery cohort and replicated in an independent cohort. It comprised of a “less-impaired” cognitive subtype, 2 subtypes with “intermediate cognitive impairment” differentiated by executive function performance, and a “globally impaired” cognitive subtype. This solution showed relative stability across time. CFA revealed that cognitive profiles are better explained by distinct meaningful profiles than a severity linear continuum. Associations between profiles and negative symptoms were observed. The subtyping of schizophrenia patients based on cognitive performance and its associations with symptomatology may aid phenotype refinement, mapping of specific biological mechanisms, and tailored clinical treatments.

Key words: schizophrenia/cognition/cognitive subtypes/heterogeneity

Introduction

Heterogeneity in schizophrenia remains a key concern for the field. Variability in symptomatology and trajectory of illness have hindered the search to elucidate the underlying biological mechanisms and the development of new treatments. Since the early definition of schizophrenia by Kraepelin¹ and Bleuler,² efforts for phenotype refinement have been made through subtyping individuals into more homogeneous subgroups based on clinical characteristics. These efforts, however, have yet to improve treatment development or clarify the sources of heterogeneity, potentially due to limitations in the temporal stability of symptomatology in schizophrenia.

While cognitive impairment in schizophrenia co-occurs with symptomatology, it continues to be an area of unmet clinical need due to the lack of any medication efficacy for cognitive deficits. Cognitive impairment is a core feature of schizophrenia, is relatively stable across illness course,³ and is of importance due to its robust associations with functional outcomes.⁴ Dysfunction in cognitive domains of verbal memory and fluency, processing speed, working memory, attention, and executive function have been extensively documented in schizophrenia.^{5–7} These heterogeneous patterns of deficits have been observed throughout the disease course in schizophrenia,³ first-episode psychosis,⁸ individuals at risk of psychosis,⁹ and first-degree relatives.¹⁰ Given its trait-like characteristics, cognition has been suggested as an intermediate phenotype candidate that could index liability to schizophrenia rather than the disease itself.¹¹ The delineation of individuals with schizophrenia using cognitive profiles may, therefore, lead to greater clinical precision by refining and isolating impairments associated with specific neural substrates.

The subtyping of individuals with schizophrenia based on cognitive performance has yielded at least 3 distinct cognitive subtypes characterized by less-impaired cognitive performance, intermediate-impaired cognitive subgroup, and a globally impaired subgroup (see review^{12,13}). While these studies have revealed the existence of cognitive subtypes and its associations with symptoms and functional outcomes, several questions remain unresolved. First, the substantial methodological variability and types of neurocognitive assessments used in previous studies may influence the number of observed profiles. Second, the validity and generalizability of the emergent profiles are rarely tested in an independent sample. Third, the cross-sectional nature of these studies limits the interpretability of the derived cognitive profiles in terms of subtype stability, illness trajectory, or outcomes. Fourth, it is unclear if cognitive profiles merely reflect a linear severity continuum, or if they represent unique variations in a subgroup of individuals that map onto different underlying biological mechanisms, trajectory, or prognoses.

The aims of this study, therefore, were (1) to identify homogeneous groups of individuals with schizophrenia based on the latent profile of their cognitive performance; (2) to assess the replicability of the derived cognitive profiles in an independent cohort; (3) to examine the longitudinal stability of these profiles across time using latent transition analysis (LTA); (4) to evaluate if the subtypes map onto a single latent cognitive dimension that differs in severity or if they represent distinct subtypes. To our knowledge, this study represents the largest sample to date that uses latent profile analysis (LPA) and LTA to derive cognitive profiles in schizophrenia and the first study to examine the longitudinal stability of these profiles.

Methods

Participants

Two cohorts of schizophrenia participants were analyzed in this study. The first cohort of participants ($n = 659$) was recruited as part of the Singapore Translational and Clinical Research in Psychosis program. The second cohort of participants was drawn from a 10-week randomized controlled trial on the efficacy of pregnenolone vs placebo in schizophrenia patients ($n = 108$). Details of the first cohort¹⁴ and the second cohort¹⁵ have been reported previously. The first cohort was used as the discovery data set and the second cohort as a replication data set. The key exclusion criteria for both cohorts included the history of neurological injuries, mental retardation, and substance abuse. Diagnosis of schizophrenia was ascertained with the Structured Clinical Interview for DSM-IV-TR Axis I Disorder, patient edition.¹⁶ Healthy controls ($n = 1012$) were also recruited as part of the first cohort¹⁴ and screened for psychopathological history and first-degree family history of psychiatric conditions using the DSM-IV-TR, nonpatient edition.¹⁶ Both studies

were reviewed and approved by the National Healthcare Group's Domain Specific Review Board. Written informed consent was obtained from all participants.

Measures

Neuropsychological assessment was administered using the Brief Assessment of Cognition in Schizophrenia (BACS).¹⁷ The BACS consists of 6 subtests, including verbal memory, digit sequencing, token motor task, semantic fluency, symbol coding, and tower of London. These tasks map onto cognitive domains measuring verbal memory, working memory, motor speed, verbal fluency, speed and attention, and executive function respectively. The BACS has been validated locally and normative data have been established by our group.¹⁸ Cognitive scores were standardized (z -scored) using means and SDs from healthy controls and adjusted for age and sex.^{14,18} The standardized residuals of the cognitive scores were used in subsequent analyses. For the replication cohort,¹⁵ the BACS was administered at 3 timepoints, 4 weeks apart, as part of the 10-week clinical trial. Listwise deletion was applied to missing BACS data. Clinical psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS).¹⁹ Antipsychotic doses were calculated using chlorpromazine (CPZ) equivalents.^{20–23}

Statistical Analysis

Discovery Phase. LPA, an empirically derived clustering method that aims to uncover hidden groups with similar responses based on the observed data,²⁴ was first performed using data from the first cohort ($n = 659$)¹⁴ to determine the number of homogeneous groups based on BACS subtests. The optimal number of profiles was determined by the following model fit indices, with lower values indicative of better fit^{25,26}: Akaike's information criteria (AIC),²⁷ Bayesian information criteria (BIC),²⁸ and sample-size adjusted BIC (ssaBIC).²⁹ Vuong–Lo–Mendell–Rubin (VLMR) and Lo–Mendell–Rubin (LMR) adjusted likelihood ratio tests (LRTs) were used to compare the K and $K-1$ profile models.³⁰ p -values $>.05$ indicate that the $K-1$ model is preferred.³⁰ Entropy was computed to determine the accuracy of profile classification, with higher values indicative of better separation between profiles.³¹ Interpretability and parsimony were also considered in optimal model selection.

Replication Phase. Next, LPA was performed using the second cohort ($n = 108$)¹⁵ to examine if the number of profiles and characteristics determined in the discovery phase could also be observed in an independent sample. Sensitivity analysis was also performed using LPA by combining both cohorts and examining resultant profile changes (if any).

Longitudinal Stability of Profiles. Once the optimal profile model was determined in the discovery and replication

Table 1. Demographics and clinical characteristics of cohorts

	Healthy control (n = 1012)		Total case (n = 767)		Discovery (n = 659)		Replication (n = 108)		Statistics ^a	p
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age	36.12	10.813	38.55	9.565	38.77	9.73	37.21	8.425	32 160.00	.11
Gender (male/female)	529/483	—	425/342	—	351/308	—	74/34	—	8.74	<.01
Total years of education	13.3437	2.58856	11.94	3.04	11.95	3.06	11.89	2.95	34 844.00	.80
Age of onset	—	—	23.75	7.24	23.67	7.38	24.25	6.33	32 482.00	.16
Duration of illness	—	—	14.86	9.64	15.17	9.87	12.95	7.87	31 475.00	.06
CPZ	—	—	539.96	662.70	542.69	690.81	523.53	460.64	30 479.00	.03
PANSS positive	—	—	11.89	5.15	12.23	5.22	9.89	4.19	24 698.50	<.01
PANSS negative	—	—	12.52	5.53	12.83	5.66	10.67	4.29	26 218.00	<.01
PANSS gen	—	—	24.16	7.06	24.83	7.18	20.21	4.69	20 216.50	<.01
PANSS total	—	—	48.43	14.16	49.74	14.27	40.77	10.65	20 641.00	<.01
BACS verbal memory	—	—	-1.12	1.19	-1.21	1.17	-0.58	1.18	-5.21	<.01
BACS digit sequencing	—	—	-0.98	1.19	-1.03	1.19	-0.72	1.18	-2.46	.01
BACS token motor	—	—	-1.56	1.36	-1.62	1.40	-1.23	1.03	-2.72	.01
BACS semantic fluency	—	—	-1.20	1.05	-1.25	1.06	-0.90	0.96	-3.18	.00
BACS symbol coding	—	—	-2.03	1.29	-2.06	1.30	-1.83	1.19	-1.69	.09
BACS tower of London	—	—	-0.96	1.55	-1.02	1.55	-0.58	1.48	-2.79	.01

Note: ^aTest statistics comparing discovery and replication cohort using χ^2 , t test, and Mann-Whitney U test. CPZ, daily chlorpromazine equivalence; PANSS, Positive and Negative Syndrome Scale; BACS, Brief Assessment of Cognition in Schizophrenia.

phase, LTA, a type of longitudinal mixture modeling, was performed using the 10-week replication cohort ($n = 108$) to determine if individuals transition between profiles across time. The LTA consists of 2 components: (1) the measurement model (ie, LPA), which examines the latent profiles at each timepoint; (2) the autoregressive model, which examines the individual-level transition between the profiles across timepoints.³²

To determine if the profiles identified at each timepoint had the same structure across timepoints (ie, if profile 1 in timepoint 1 was the same as profile 1 in timepoint 2), competing models of measurement invariance and measurement noninvariance were performed and compared with the LRT.^{32,33} The measurement invariance model is preferred as it indicates that the measurement model has the same meaning (ie, number and type of classes) across time.³²

Single Latent Dimension vs Distinct Subtypes. A 1-factor confirmatory factor analysis (CFA) was performed and compared to the LPA results to examine if the optimal cognitive profile represents a single dimension of severity continuum or distinct subtypes. The AIC,²⁷ BIC,²⁸ and ssaBIC²⁹ were used to aid CFA and optimal LPA model comparison. A better CFA than LPA fit would indicate that the hidden groups extracted from the LPA merely reflects a 1-dimensional graded pattern of severity.

Comparison of Clinical Variables Between Profiles. Once the optimal model was determined, clinical characteristics were compared between profiles using the combined sample discovery and replication cohort. ANOVA was used to compare between-profile BACS performance. Clinical variables were compared with the Kruskal–Wallis test and post hoc comparisons were carried out using Mann–Whitney U test. Bonferroni correction was applied (0.05/6).

The LPA, LTA, and CFA were performed in Mplus Version 8.³⁴ All other statistical analyses were performed in IBM SPSS version 23.³⁵

Results

Demographics and Clinical Characteristics

Demographics and clinical characteristics of healthy controls ($n = 1012$) and cases ($n = 767$) are shown in [table 1](#). Significant differences in sex and clinical symptomatology were observed between the discovery and replication cohort ([table 1](#)).

Discovery Phase

Latent profile models (1–5 solutions) were performed on the discovery cohort ([table 2](#)). Results indicated that the 2-profile solution provided a superior fit to the 1-profile solution for all fit indices. The 3-profile solution showed lower AIC, BIC, and ssaBIC than the 2-profile solution. While the VLMR and LMR p -values of 4-profile

solution were nonsignificant compared to the 3-profile solution, the 4-profile solution showed lower AIC, BIC, and ssaBIC values and had the highest entropy amongst the models. Only a small decrease in AIC, BIC, and ssaBIC was observed for 5-profile solution. The 5-profile solution showed a lower entropy value and nonsignificant VLMR and LMR p -values. Based on parsimony and interpretability, the 4-profile solution was chosen (profile 1, $n = 284$; profile 2, $n = 33$; profile 3, $n = 284$; profile 4, $n = 58$; [supplementary figures 1 and 2](#)).

Replication Phase

LPA was conducted using baseline cognitive data from the replication cohort ([table 2](#); [supplementary figures 1 and 3](#)). Results indicated that 3-profile solution had the highest entropy and a nonsignificant VLMR and LMR p -value compared to other solutions. The 4-profile solution showed a better fit than the 3-profile solution based on lower AIC, BIC, and ssaBIC. Although fit comparisons appeared to be equivocal between the 3-profile and 4-profile solution, given that there was no evidence to suggest that the 4-profile solution had a poorer fit than the 3-profile solution, and in combination with results from the discovery phase, the 4-profile solution was selected as the optimal solution in the replication cohort (profile 1, $n = 32$; profile 2, $n = 41$; profile 3, $n = 25$; profile 4, $n = 10$).

LPA of the combined discovery and replication cohort showed the highest entropy for 4-profile solution, with low AIC, BIC, and ssaBIC values ([table 2](#)). The 4-profile solution ([figure 1](#)) was described as “less-impaired” subtype (profile 1, $n = 334$) with high scores on all domains, 2 subtypes with “intermediate cognitive impairment” (profile 2, $n = 46$; profile 3, $n = 332$) with moderate scores and a “globally impaired” cognitive subtype (profile 4, $n = 55$) with poor scores on all domains.

Longitudinal stability of profiles

To determine if the 4-profile solution showed the same structure across timepoints, competing tests of measurement invariance and measurement noninvariance were performed. The LRT indicated nonsignificance (likelihood ratio difference = 69.896, $df = 48$, $p > .05$), suggesting measurement invariance ([supplementary table 1](#); [supplementary figure 1](#)).

Longitudinal stability was also examined using LTA. Latent transition probabilities indicated that most individuals remained at their respective profiles from T1 to T2 and T2 to T3 ([table 3](#); [supplementary figure 1](#)) as shown by the high transition probability ($>.8$) for most profiles. To further examine if pregnenolone influenced the transition profile in the second cohort, another LTA with drug (pregnenolone vs placebo) as a covariate was performed. A similar pattern of transition probability was observed in the LTA using this model ([table 3](#)).

Table 2. Fit indices for latent profile analysis for discovery ($n = 659$) and replication cohort ($n = 108$)

Data set	No. of profiles	Log likelihood	AIC	Δ AIC	BIC	Δ BIC	ssaBIC	Entropy	VLMR	VLMR p -value	LMR	LMR p -value
Discovery	1	-6549.94	13 123.89	—	13 177.78	—	13 139.68	—	—	—	—	—
	2	-6165.03	12 368.07	-755.82	12 453.39	-724.38	12 393.07	0.77	-6549.94	.00	753.24	.00
	3	-6083.28	12 218.56	-149.50	12 335.32	-118.07	12 252.77	0.75	-6165.03	.07	159.98	.07
	4	-6036.52	12 139.03	-79.53	12 287.23	-48.10	12 182.45	0.82	-6083.28	.31	91.52	.31
	5	-6000.70	12 081.40	-57.63	12 261.03	-26.19	12 134.03	0.75	-6036.52	.16	70.09	.17
Replication (T1)	1	-1012.42	2048.83	—	2081.02	—	2043.10	—	—	—	—	—
	2	-938.24	1914.47	-134.36	1965.43	-115.59	1905.40	0.82	-1012.42	.00	143.97	.00
	3	-911.01	1874.01	-40.46	1943.75	-21.68	1861.60	0.89	-938.23	.04	52.84	.04
	4	-894.17	1854.35	-19.67	1942.86	-0.89	1838.59	0.83	-911.01	.14	32.67	.15
	5	-889.19	1858.38	4.04	1965.67	22.81	1839.28	0.85	-894.17	.46	9.67	.47
Replication (T2)	1	-999.25	2022.50	—	2054.69	—	2016.77	—	—	—	—	—
	2	-926.67	1891.34	-131.16	1942.30	-112.38	1882.27	0.85	-999.25	.00	140.86	.00
	3	-913.63	1879.26	-12.08	1949.00	6.69	1866.84	0.81	-926.67	.43	25.31	.44
	4	-906.81	1879.62	0.36	1968.13	19.13	1863.86	0.79	-913.63	.32	13.24	.33
	5	-895.96	1871.92	-7.70	1979.20	11.08	1852.82	0.79	-906.81	.70	21.06	.71
Replication (T3)	1	-1012.89	2049.78	—	2081.97	—	2044.05	—	—	—	—	—
	2	-939.21	1916.42	-133.36	1967.38	-114.59	1907.35	0.80	-1012.89	.23	143.00	.23
	3	-907.99	1867.99	-48.43	1937.72	-29.66	1855.57	0.83	-939.21	.39	60.58	.39
	4	-894.44	1854.88	-13.11	1943.39	5.67	1839.12	0.88	-907.99	.21	26.30	.21
	5	-884.58	1849.17	-5.71	1956.45	13.06	1830.07	0.89	-894.44	.24	19.13	.24
Discovery + replication (T1)	1	-7602.19	15 228.39	—	15 284.10	—	15 245.99	—	—	—	—	—
	2	-7141.80	14 321.61	-906.78	14 409.81	-874.29	14 349.48	0.77	-7602.19	.00	901.40	.00
	3	-7046.41	14 144.82	-176.79	14 265.52	-144.29	14 182.96	0.75	-7141.80	.14	186.77	.14
	4	-6980.87	14 027.73	-117.09	14 180.93	-84.59	14 076.14	0.83	-7046.41	.01	128.33	.01
	5	-6932.49	13 944.98	-82.75	14 130.68	-50.25	14 003.66	0.76	-6980.86	.03	94.71	.03
1-factor CFA		-7046.96	14 129.93	—	14 213.49	—	14 156.33	—	—	—	—	—

Note: AIC, Akaike's information criteria; BIC, Bayesian information criteria; ssaBIC, sample-size-adjusted BIC; VLMR, Vuong-Lo-Mendell-Rubin; LMR, Lo-Mendell-Rubin; CFA, confirmatory factor analysis.

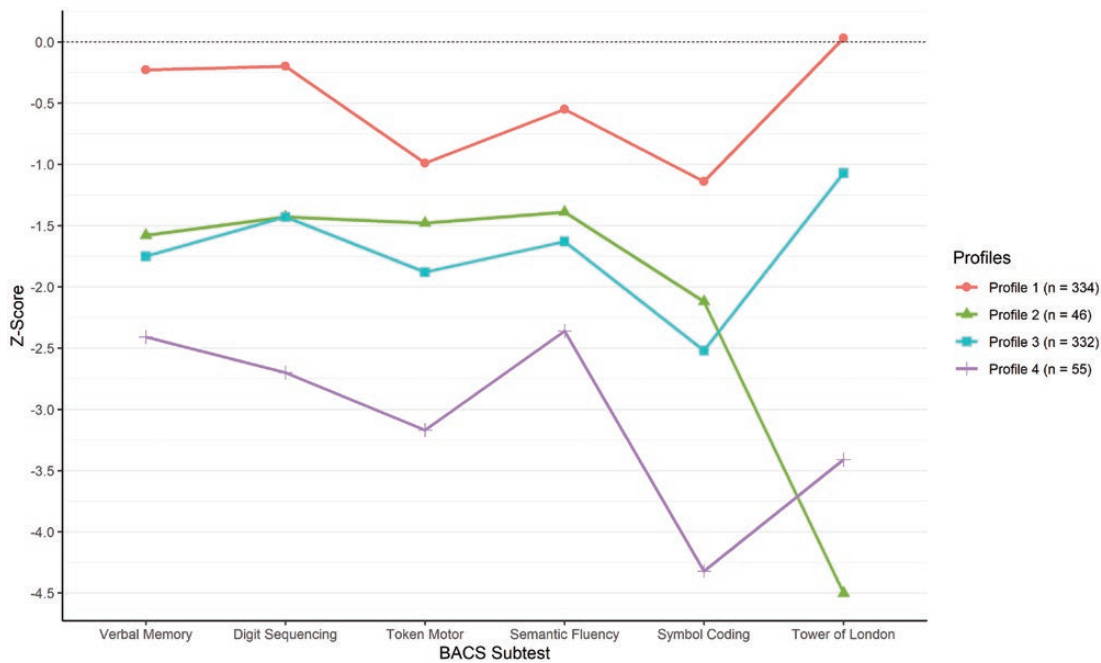


Fig. 1. Latent profile plot of Brief Assessment of Cognition in Schizophrenia (BACS) for the combined discovery and replication cohort ($n = 767$). Bold dotted lines represent the mean z-score for healthy controls.

Single Latent Dimension vs Distinct Subtypes

Next, a CFA was conducted to examine if a 1-factor solution (ie, dimensional structure) or a latent profile structure better fit the data (table 2). Compared to the fit indices for the 4-profile solution, the 1-factor CFA solution showed poorer fit ($\Delta AIC = 102.2$, $\Delta BIC = 32.6$).

Comparison of Clinical Variables Between Profiles

Demographics and clinical characteristics for each profile are presented in table 4. Significant differences were observed between profiles for all clinical and cognitive characteristics. Profile 1 showed the least severe clinical characteristics and best cognitive performance and significantly differed from profile 4, which showed the greatest clinical severity and poorest cognitive performance. In addition, profiles 2 and 3 showed an intermediate pattern, with a number of significant differences from either or both profiles 1 and 4, but only a single difference between profiles 2 and 3, in executive function, for which profile 2 showed worse performance ($p < .01$). Further comparison of profile 1 with healthy controls ($n = 1012$) found no significant difference in executive function between groups ($F(1, 1344) = 0.294$, $p = .59$), while differences in cognitive performance was observed for all other subtests ($p > .05$; figure 1). Across profiles, a trend-level difference was observed for the duration of illness, where profile 4 showed the longest duration, followed by profile 2, profile 3, and profile 1 (table 4).

Discussion

This study employed a data-driven approach (ie, LPA and LTA) to elucidate cognitive latent profiles in schizophrenia and tested the replicability of the findings using the same cognitive battery (ie, BACS). Our results suggest 4 distinct meaningful cognitive profiles in schizophrenia, characterized by a “less-impaired” cognitive subtype, 2 subtypes with “intermediate cognitive impairment” differentiated by executive function performance and a “globally impaired” cognitive subtype. This 4-profile cognitive solution was replicated in a separate cohort and showed stability in profile membership across time. A comparison of this 4-profile solution with a single-factor CFA suggests that distinct homogeneous cognitive subtypes may better explain cognitive heterogeneity in schizophrenia than a unidimensional cognitive structure that differs in severity.

Consistent with the literature on cluster-analytic studies of cognition in schizophrenia, this study provides support for cognitive heterogeneity in schizophrenia delineated by the 3 main groups of cognitive subtypes.¹² The “less-impaired” cognitive subtype (profile 1) is defined by cognitive performance within ~ 0.5 SD of healthy controls across all cognitive subtests except symbol coding task. The “intermediate cognitive impairment” subtype is composed of 2 profiles characterized by moderate cognitive impairment of ~ 1.5 SD below healthy controls across all subtests except for symbol coding. The 2 profiles in this subtype are further differentiated by executive function performance, indexed by tower of London task, in which profile 2 showed poorer performance than

Table 3. Transition probabilities across time

	T1 (rows) to T2 (columns)				T2 (rows) to T3 (columns)					
	Profiles	1	2	3	4	Profiles	1	2	3	4
LTA without covariate	1	1	0	0	0	1	1	0	0	0
	2	0.037	0.963	0	0	2	0	1	0	0
	3	0	0.135	0.865	0	3	0	0	1	0
	4	0	0.199	0.141	0.66	4	0	0	0.249	0.751
LTA with covariate	1	1	0	0	0	1	1	0	0	0
	2	0.062	0.938	0	0	2	0.024	0.976	0	0
	3	0	0.129	0.871	0	3	0	0.018	0.942	0.04
	4	0	0.216	0.168	0.616	4	0	0	0.34	0.66

Note: LTA, latent transition analysis.

Table 4. Clinical characteristics of profiles using the combined discovery and replication cohort (n = 767)

	Profile 1 (n = 334)		Profile 2 (n = 46)		Profile 3 (n = 332)		Profile 4 (n = 55)		F/ χ^2	p	Post hoc Bonferroni P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD			
Age	37.85	8.98	39.46	9.69	39.08	10.00	38.87	10.16	3.99	.26	
Age of onset	24.46	6.94	23.37	8.94	23.44	7.11	21.63	7.84	12.98	<.01	1 > 4
Duration of illness	13.48	9.26	16.13	9.76	15.64	9.90	17.38	9.30	13.32	<.01	1 < 3, 4
CPZ	391.34	493.77	625.56	612.60	645.67	778.07	747.33	684.47	38.42	<.01	1 < 2, 3, 4
PANSS positive	11.69	5.19	12.20	5.21	11.72	4.93	14.00	5.82	9.64	.02	1, 3 < 4
PANSS negative	10.64	4.09	13.85	6.28	13.50	5.88	17.25	6.08	93.22	<.01	1 < 2, 3 < 4
PANSS gen	22.81	6.55	24.00	5.33	24.55	7.05	30.45	8.06	49.64	<.01	1 < 2, 3 < 4
PANSS total	45.07	12.80	50.04	12.61	49.71	14.32	61.04	14.76	57.47	<.01	1 < 2, 3 < 4
Total years of education	13.28	2.66	10.57	2.32	11.14	3.02	9.77	2.46	139.58	<.01	1 > 2, 3 > 4
BACS verbal memory	-0.23	0.92	-1.58	0.94	-1.75	0.85	-2.41	0.76	214.45	<.01	1 > 2, 3 > 4
BACS digit sequencing	-0.20	0.89	-1.43	1.04	-1.43	0.92	-2.70	0.95	174.98	<.01	1 > 2, 3 > 4
BACS token motor	-0.99	1.14	-1.48	1.06	-1.88	1.28	-3.17	1.41	63.80	<.01	1 > 2, 3 > 4
BACS semantic fluency	-0.55	0.91	-1.39	1.03	-1.63	0.76	-2.36	0.94	126.38	<.01	1 > 2, 3 > 4
BACS symbol coding	-1.14	0.89	-2.12	1.07	-2.52	0.93	-4.32	0.82	250.91	<.01	1 > 2, 3 > 4
BACS tower of london	0.03	0.82	-4.50	0.78	-1.07	0.92	-3.41	1.08	528.31	<.01	1 > 3 > 4 > 2

Note: CPZ, daily chlorpromazine equivalence; PANSS, Positive and Negative Syndrome Scale; BACS, Brief Assessment of Cognition in Schizophrenia.

profile 3. The “globally impaired” subtype (profile 4) is characterized by poor cognitive performance of >2 SD below the norm. Notably, a common feature across all subtypes is prominent impairment in the cognitive domain of processing speed indexed by the symbol coding task, supporting these processes as central features of cognitive impairments in schizophrenia.^{3,36}

Currently, it remains elusive if cognitive heterogeneity in schizophrenia represents a continuum of severity or a distinct set of meaningful subtypes. Consistent with previous studies,^{37–39} our results suggest a severity continuum, but one that can be characterized by distinct subtypes. Specifically, the comparison between the derived profile solution and a unidimensional solution suggests that, while a graded pattern of cognitive impairment could be observed across the cognitive subtypes, the separation between the profiles could be further differentiated by executive functioning performance. Converging with previous findings,^{40,41} this study also found that in the “less-impaired” cognitive subtype, only the executive function domain showed no difference in performance with healthy controls. Moreover, unlike previous studies that postulated that the mixed profiles in the intermediate subtype could be viewed as unidimensional due to its considerable overlap in impaired cognitive domains,¹² this study showed that executive function clearly delineated the 2 “intermediate cognitive impairment” subtypes (ie, profiles 2 and 3). Notably, our results also highlighted consistency with previous findings that found similar profiles differentiated by executive function performance as indexed by different cognitive batteries.^{39,41} Dovetailing with recent findings, executive function has been found to be a liability for general psychopathology rather than vulnerability to a specific disorder.^{40,42,43} Together, these findings suggest the need for further evaluation of executive function as an endophenotype to explain cognitive heterogeneity within schizophrenia and its interaction with functional trajectory. At the same time, executive function is not itself unidimensional and is comprised of higher-order cognitive processes (ie, shifting, updating, inhibiting, and working memory maintenance and manipulation) that regulates basic cognitive processes to promote self-directed behavior toward a goal.^{40,44} Hence, future studies examining the specific executive function processes will be necessary to confirm the generalization of these findings.

As expected, significantly better clinical outcomes (as indexed by age of illness onset, duration of illness, CPZ, PANSS symptomatology, and total years of education) were observed in the “less-impaired” cognitive subtype compared to the “globally impaired” subtype. This result is consistent with previous studies showing that, in addition to better clinical outcomes,⁴⁵ cognitively intact individuals with schizophrenia have relatively fewer brain structural abnormalities^{46,47} and lower polygenic risk score for schizophrenia.⁴⁸ While no significant differences

were observed in clinical variables for the “intermediate cognitive impairment” subtypes (ie, profile 2 vs profile 3), trend-level differences in clinical severity could be seen in that profile 1 showed the best outcomes followed by profile 3, profile 2, and then profile 4. In regard to associations between subtypes and negative symptoms,^{45,48,49} it has been postulated that cognition and negative symptoms could share common underlying substrates given the unique associations between both constructs in schizophrenia.⁵⁰ Consistent with this hypothesis, we found a graded worsening of negative symptoms across profiles. In this regard, cognitive subtyping in schizophrenia may be particularly useful to identify individuals, such as profile 2, for targeted cognitive remediation, consequently improving cognition and functional outcomes, such as negative symptoms.⁵¹

Surprisingly, a high proportion of patients were classified as being “less impaired.” This may be attributed to the relatively low negative symptoms severity score observed across cases, suggesting that these patients were relatively well functioning. Nevertheless, it should be noted that patients classified as being “less impaired” should not be interpreted as having intact cognition. The mean BACS scores in the “less-impaired” group were still below the healthy control standardized means for all tasks, except for the tower of London task. Furthermore, the other 3 profiles showed large deficits in cognitive performance of at least more than 1 SD from that of healthy controls BACS *z*-scores.

Results of the LTA showed that profile membership was generally stable across follow-up timepoints. Upon closer examination, subtle differences in stability were apparent for transition from T1 to T2 and T2 to T3, possibly due to differences in practice effects of the BACS from T1 to T2 compared to T2 to T3.

The results of this study should be interpreted with the following caveats. First, given the data-driven approach adopted in this study, the subtypes derived could be driven by the applied neuropsychological assessments. Specifically, the derived profile 2 may in part be driven by the psychometrics of the tower of London task where negative distributional skewness may be observed in patients due to a slight ceiling effect in healthy controls on this task. Nevertheless, the subtypes derived in the discovery cohort were replicated in an independent cohort and were stable across timepoints. In addition, it should be noted that the present study only employed a single battery of 6 subtests (ie, BACS) to index the various cognitive domains. Future research would benefit from examining a more comprehensive set of tests in the same study. Future studies are also needed to extend findings for conceptual replication using other cognitive batteries operationalizing the same underlying cognitive domains.^{45,52} Second, this study did not control for medication effects and educational attainment, which could be related to the derived profiles.¹³ While the trend-level

dosage effect of these variables could be observed across the profiles, disentangling this relationship remains a challenge. In the case of educational attainment, it is unclear if illness chronicity influences educational opportunities or vice versa. Third, while this study is one of the first to examine the longitudinal stability of cognitive profiles, it should be noted that the stability of profiles was examined in a cohort with a 10-week follow-up. Further studies with a greater follow-up duration are required to determine long-term profile stability. Fourth, while the small sample size in the replication cohort could influence the statistical power to detect a clear fit comparison between the 3-profile and 4-profile solution,⁵³ findings of the present study are still important as it is the first study to show that these profiles are stable across time. Nevertheless, future studies with larger replication samples are warranted.

In conclusion, this study showed that cognitive heterogeneity in schizophrenia could be explained by a severity continuum that is separated by distinct subtypes, driven by differences in executive function. Profile membership appeared to be stable across timepoints (although the follow-up period was brief) and was associated with symptomatology. Clinically, these results suggest the need to tailor treatment options based on cognitive impairment. Future conceptual replication of these findings is needed with longer follow-up periods to fully understand the neural and genetic mechanisms underlying these profiles in schizophrenia. In addition, future studies integrating cognitive and neurobiological phenotypes may be useful to unravel heterogeneity in schizophrenia.^{54,55}

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*.

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References

1. Kraepelin E. *Dementia Praecox and Paraphrenia*. Huntington, NY: Krieger; 1919.
2. Bleuler E. *Dementia Praecox or the Group of Schizophrenia*. New York, NY: International Universities Press; 1950.
3. Sheffield JM, Karcher NR, Barch DM. Cognitive deficits in psychotic disorders: a lifespan perspective. *Neuropsychol Rev*. 2018;28(4):509–533.
4. Bowie CR, Harvey PD. Cognitive deficits and functional outcome in schizophrenia. *Neuropsychiatr Dis Treat*. 2006;2(4):531–536.
5. Nuechterlein KH, Barch DM, Gold JM, Goldberg TE, Green MF, Heaton RK. Identification of separable cognitive factors in schizophrenia. *Schizophr Res*. 2004;72(1):29–39.
6. Fioravanti M, Bianchi V, Cinti ME. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. *BMC Psychiatry*. 2012;12:64.
7. Heinrichs RW, Zakzanis KK. Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. *Neuropsychology*. 1998;12(3):426–445.
8. Aas M, Dazzan P, Mondelli V, Melle I, Murray RM, Pariante CM. A systematic review of cognitive function in first-episode psychosis, including a discussion on childhood trauma, stress, and inflammation. *Front Psychiatry*. 2014;4:182.
9. Bora E, Lin A, Wood SJ, Yung AR, McGorry PD, Pantelis C. Cognitive deficits in youth with familial and clinical high risk to psychosis: a systematic review and meta-analysis. *Acta Psychiatr Scand*. 2014;130(1):1–15.
10. Snitz BE, Macdonald AW III, Carter CS. Cognitive deficits in unaffected first-degree relatives of schizophrenia patients: a meta-analytic review of putative endophenotypes. *Schizophr Bull*. 2006;32(1):179–194.
11. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160(4):636–645.
12. Carruthers SP, Van Rheenen TE, Gurvich C, Sumner PJ, Rossell SL. Characterising the structure of cognitive heterogeneity in schizophrenia spectrum disorders. A systematic review and narrative synthesis. *Neurosci Biobehav Rev*. 2019;107:252–278.
13. Green MJ, Girshkin L, Kremerskothen K, Watkeys O, Quidé Y. A systematic review of studies reporting data-driven cognitive subtypes across the psychosis spectrum. *Neuropsychol Rev*. 2019; doi:10.1007/s11065-019-09422-7.
14. Lam M, Collinson SL, Eng GK, et al. Refining the latent structure of neuropsychological performance in schizophrenia. *Psychol Med*. 2014;44(16):3557–3570.
15. Marx CE, Lee J, Subramaniam M, et al. Proof-of-concept randomized controlled trial of pregnenolone in schizophrenia. *Psychopharmacology (Berl)*. 2014;231(17):3647–3662.
16. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition. SCID-I/P*. New York: Biometrics Research, New York State Psychiatric Institute; 2002.
17. Keefe RS, Goldberg TE, Harvey PD, Gold JM, Poe MP, Coughenour L. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and comparison with a standard neurocognitive battery. *Schizophr Res*. 2004;68(2–3):283–297.
18. Eng GK, Lam M, Bong YL, et al. Brief assessment of cognition in schizophrenia: normative data in an English-speaking

- ethnic Chinese sample. *Arch Clin Neuropsychol*. 2013;28(8):845–858.
19. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
 20. Atkins M, Burgess A, Bottomley C, Riccio M. Chlorpromazine equivalents: a consensus of opinion for both clinical and research applications. *Psychiatr Bull*. 1997;21(4):224–226.
 21. Barnes TR, Paton C. Improving prescribing practice in psychiatry: the experience of the Prescribing Observatory for Mental Health (POMH-UK). *Int Rev Psychiatry*. 2011;23(4):328–335.
 22. Davis JM. Dose equivalence of the antipsychotic drugs. *J Psychiatr Res*. 1974;11:65–69.
 23. Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. *Schizophr Bull*. 2014;40(2):314–326.
 24. Oberski D. Mixture models: Latent profile and latent class analysis. In: Robertson J, Kaptein M, eds. *Modern Statistical Methods for HCI*. Cham, Switzerland: Springer International Publishing; 2016:275–287.
 25. Burnham KP, Anderson DR. Multimodel inference: understanding AIC and BIC in model selection. *Sociol Methods Res*. 2004;33(2):261–304.
 26. Raftery AE. Bayesian model selection in social research. *Sociol Methodol*. 1995;25:111–163.
 27. Akaike H. Factor analysis and AIC. *Psychometrika*. 1987;52(3):317–332.
 28. Schwarz G. Estimating the dimension of a model. *Ann Stat*. 1978;6(2):461–464.
 29. Sclove SL. Application of model-selection criteria to some problems in multivariate analysis. *Psychometrika*. 1987;52(3):333–343.
 30. Lo Y, Mendell NR, Rubin DB. Testing the number of components in a normal mixture. *Biometrika*. 2001;88(3):767–778.
 31. Celeux G, Soromenho G. An entropy criterion for assessing the number of clusters in a mixture model. *J Classification*. 1996;13(2):195–212.
 32. Nylund KL. *Latent Transition Analysis: Modeling Extensions and an Application to Peer Victimization* [Doctoral Dissertation]. Los Angeles, CA: University of California; 2007.
 33. Satorra A, Bentler PM. A scaled difference chi-square test statistic for moment structure analysis. *Psychometrika*. 2001;66(4):507–514.
 34. Muthén LK, Muthén BO. *Mplus User's Guide*. 8th ed. Los Angeles, CA: Muthén & Muthén; 1998–2017.
 35. IBM Corp. *IBM SPSS Statistics for Windows, Version 23.0*. Armonk, NY: IBM Corp. 2015.
 36. Dickinson D, Ramsey ME, Gold JM. Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Arch Gen Psychiatry*. 2007;64(5):532–542.
 37. Goldstein G, Allen DN, Seaton BE. A comparison of clustering solutions for cognitive heterogeneity in schizophrenia. *J Int Neuropsychol Soc*. 1998;4(4):353–362.
 38. Seaton BE, Goldstein G, Allen DN. Sources of heterogeneity in schizophrenia: the role of neuropsychological functioning. *Neuropsychol Rev*. 2001;11(1):45–67.
 39. Hill SK, Ragland JD, Gur RC, Gur RE. Neuropsychological profiles delineate distinct profiles of schizophrenia, an interaction between memory and executive function, and uneven distribution of clinical subtypes. *J Clin Exp Neuropsychol*. 2002;24(6):765–780.
 40. Snyder HR, Miyake A, Hankin BL. Advancing understanding of executive function impairments and psychopathology: bridging the gap between clinical and cognitive approaches. *Front Psychol*. 2015;6:328.
 41. Dawes SE, Jeste DV, Palmer BW. Cognitive profiles in persons with chronic schizophrenia. *J Clin Exp Neuropsychol*. 2011;33(8):929–936.
 42. Bloemen AJP, Oldehinkel AJ, Lacleulle OM, Ormel J, Rommelse NNJ, Hartman CA. The association between executive functioning and psychopathology: general or specific? *Psychol Med*. 2018;48(11):1787–1794.
 43. Harden KP, Engelhardt LE, Mann FD, et al. Genetic associations between executive functions and a general factor of psychopathology. *J Am Acad Child Adolesc Psychiatry*. 2020;59(6):749–758.
 44. Miyake A, Friedman NP. The nature and organization of individual differences in executive functions: four general conclusions. *Curr Dir Psychol Sci*. 2012;21(1):8–14.
 45. Lewandowski KE, Baker JT, McCarthy JM, Norris LA, Öngür D. Reproducibility of cognitive profiles in psychosis using cluster analysis. *J Int Neuropsychol Soc*. 2018;24(4):382–390.
 46. Woodward ND, Heckers S. Brain structure in neuropsychologically defined subgroups of schizophrenia and psychotic bipolar disorder. *Schizophr Bull*. 2015;41(6):1349–1359.
 47. Cobia DJ, Csernansky JG, Wang L. Cortical thickness in neuropsychologically near-normal schizophrenia. *Schizophr Res*. 2011;133(1-3):68–76.
 48. Dickinson D, Zaidman SR, Giangrande EJ, Eisenberg DP, Gregory MD, Berman KF. Distinct polygenic score profiles in schizophrenia subgroups with different trajectories of cognitive development. *Am J Psychiatry*. 2020;177(4):298–307.
 49. Lewandowski KE, Sperry SH, Cohen BM, Ongür D. Cognitive variability in psychotic disorders: a cross-diagnostic cluster analysis. *Psychol Med*. 2014;44(15):3239–3248.
 50. Lim J, Lee SA, Lam M, et al. The relationship between negative symptom subdomains and cognition. *Psychol Med*. 2016;46(10):2169–2177.
 51. Sevy S, Lindenmayer JP, Khan A, Ljuri I, Kulsa MKC, Jones O. Differential improvement of negative-symptom subfactors after cognitive remediation in low-functioning individuals with schizophrenia. *Schizophr Res Cogn*. 2020;19:100145.
 52. Stroebe W, Strack F. The alleged crisis and the illusion of exact replication. *Perspect Psychol Sci*. 2014;9(1):59–71.
 53. Wurpts IC, Geiser C. Is adding more indicators to a latent class analysis beneficial or detrimental? Results of a Monte-Carlo study. *Front Psychol*. 2014;5:920.
 54. Clementz BA, Sweeney JA, Hamm JP, et al. Identification of distinct psychosis biotypes using brain-based biomarkers. *Am J Psychiatry*. 2016;173(4):373–384.
 55. Tamminga CA, Pearson G, Keshavan M, Sweeney J, Clementz B, Thaker G. Bipolar and schizophrenia network for intermediate phenotypes: outcomes across the psychosis continuum. *Schizophr Bull*. 2014;40(suppl 2):S131–S137.