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Subgroups of cognitive impairments in schizophrenia characterized by executive function and their morphological features: a latent profile analysis study

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Abstract

Background The heterogeneity of cognitive impairments in schizophrenia has been widely observed. However, reliable cognitive boundaries to differentiate the subgroups remain elusive. The key challenge for cognitive subtyping is applying an integrated and standardized cognitive assessment and understanding the subgroup-specific neurobiological mechanisms. The present study endeavors to explore cognitive subgroups and identify their morphological features.

Methods A total of 920 schizophrenia patients and 169 healthy controls were recruited. MATRICS Consensus Cognitive Battery was applied to assess cognitive performance and recognize cognitive subgroups through latent profile and latent transition analysis. Cortical thickness and gray matter volume were employed for the morphological features across subgroups.

Results Four reproducible cognitive subgroups were identified, including multidomain-intact, executive-preserved, executive-deteriorated, and multidomain-deteriorated subgroup. After 12 weeks of follow-up, the cognitive characteristics of three out of the four subgroups kept stability, except for multidomain-deteriorated subgroup in which 48.8% of patients with improved cognition transited into the executive-deteriorated subgroup. Across subgroups, significant gradient features of brain structure were exhibited in fronto-temporal regions, hippocampus, and insula. Compared to healthy controls, multidomain-intact subgroup showed the most intact cognition and morphology, and multidomain-deteriorated subgroup with youngest age showed morphological decline in extensive regions. The remaining two subgroups showed intermediate cognitive performance, but could be distinguished by executive function and morphological differences in posterior cingulate cortex.

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Conclusions Our study provides novel insights into the heterogeneity of cognitive impairments in schizophrenia and the morphological features from cross-sectional and longitudinal levels, which could advance our understanding of complex cognition-morphology relationships and guide personalized interventions.

Keywords Schizophrenia, Heterogeneity, Cognitive subgroup, Latent profile analysis, Cortical thickness, Gray matter volume

Background

Cognitive impairment, as one of the core characteristics in schizophrenia, has been established as significantly influencing patient's functional outcomes [1, 2]. Patients with cognitive impairments experience greater interference with real-world functioning, more symptom burdens, and worse quality of life. These impairments manifest in many neurocognitive domains such as processing speed, working memory, attention, verbal memory, fluency, and executive function [3, 4], with variability in the patterns of impairments across schizophrenia patients. Previous studies have identified distinct cognitive subgroups in schizophrenia patients. These subgroups differ in their level of overall impairments, ranging from mild to severe in two to four subgroups [5–7], or had prominent impairments in several domains of cognition, such as diminished verbal fluency, diminished verbal memory and motor control, diminished face memory and slowed processing, and diminished intellectual function [8]. Despite these advances, a unified conclusion regarding cognitive impairments in schizophrenia has not yet been reached, which is possibly due to unintegrated cognitive domains, varying assessment tools, and lack of biological mechanism verification.

The abnormalities in brain morphology have been widely observed in schizophrenia and closely relate to cognitive impairments [9]. Patients with schizophrenia display extensive cortical thinning and gray matter loss in the frontal and temporal regions compared to healthy controls [10, 11]. These morphological alternations correlate with declines in executive function, working memory, verbal memory, language learning, and processing [12, 13]. Additionally, volume reductions in the temporolimbic structures may affect overall cognitive function [14]. However, the heterogeneity of cognitive impairments still prevents consistent results. For instance, Woodward and Heckers [15] found that cognitively preserved patients with schizophrenia did not exhibit any localized changes in gray matter compared to healthy control; however, cognitively impaired patients exhibited widespread reductions in gray matter and white matter. Furthermore, cortical thinning appears to follow a similar trend, being more pronounced in severely impaired cognition as compared to preserved cognition [16]. Taken together, these studies indicate that cortical volume or thickness may not be uniformly decreased across all individuals with schizophrenia; rather, they may differ with the severity of cognitive impairments. Therefore, it is critical to delineate the heterogeneous patterns of cognitive impairments and identify the brain characteristics of each profile.

To analyze the heterogeneity of cognitive impairments, data-driven methods are generally used, such as *k*-means clustering, Gaussian Mixture Model, and the latent profile analysis (LPA). Among them, LPA, as an individual-centered and model-based clustering approach [17], has unique advantages. Compared to traditional clustering methods, LPA has fewer prerequisites for application, more reasonable clustering criteria and result testing, and less arbitrariness [17–19]. This method can limit model parameters based on theory or practice, which makes the classification more objective and realistic. The flexibility of LPA makes it adaptable to the heterogeneous study of complex psychiatric and psychological phenomena [20]. For example, this approach has been shown to be useful in identifying cognitive phenotype in schizophrenia [21], Alzheimer [22], and epilepsy [23], as well as in examining cognitive decline in traumatic brain injury [24]. By using LPA, a recent study revealed some cognitive profiles in schizophrenia patients based on partial domains of cognition [7], and also left the question of whether they represent unique biological variations in a subset of individuals. Besides, we also plan to apply the latent transition analysis for the longitudinal data at different time points to test the longitudinal stability of cognitive profiles.

Thus, to advance our understanding of the cognitive heterogeneity and its relationship with morphology, this study intends to identify subgroups of schizophrenia patients with distinct cognitive impairment profiles using LPA based on comprehensive cognitive subtests, and examine their clinical features and morphological structure via magnetic resonance imaging (MRI). The MATRICS Consensus Cognitive Battery, recognized as the gold standard for cognitive assessment in schizophrenia, is utilized to ensure the integrated and standard assessment for cognitive performance. To foreshadow the result, we (1) confirm the existence of "intact" and "severely impaired" cognitive subgroups, (2) identify specific patterns of structural variations in different cognitive

impairment subgroups, and (3) we also hypothesized that symptom severity would increase as profile varied from intact to severe subgroup.

Methods

Participants

The subjects consisted of 920 patients with schizophrenia and 169 healthy controls (HC). All patients were divided into three cohorts: Discovery Set ($n=661$), LPA-Replication Set ($n=169$), and Neuroimaging-Validation Set ($n=90$). The Discovery Set was derived from large multicenter cross-sectional data, and LPA-Replication Set was selected from two 24-week clinical trials in which patients completed 12- and 24-week follow-up. Table 1 provides an overview of three cohorts and the detailed source of the sample is described in Additional file 1: S1. Participants [25, 26].

The inclusion criteria for patients in Discovery Set and LPA-Replication Set were as follows: (1) subjects aged 16–60 years, (2) met schizophrenic criteria of the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) [27] or International Classification of Diseases-tenth edition (ICD-10) [28]. And the key exclusion criteria included (1) a history of clinically unstable systemic medical disorder; (2) a DSM-5/ICD-10 diagnosis of substance use disorder, intellectual disability, autism spectrum disorder, and dementia; (3) failure to complete cognitive assessments at enrollment. The Neuroimaging-Validation Set is a sample of patients with first-episode schizophrenia who met DSM-5 or ICD-10 criteria for schizophrenia and was independently recruited from the First Affiliated Hospital of Zhengzhou University. Inclusionary criteria for Neuroimaging-Validation Set included an age range of 16–45 years, duration of the disease less than 2 years, and a total PANSS score greater than 60. Exclusion criteria were consistent with those of the two datasets described above. In addition to our patient population, 169 HC (124 LPA-HC, 45 Neuroimaging-HC) were recruited from the communities, streets, and schools in Changsha, Nanjing and Zhengzhou cities. Moreover, HC with first-degree relatives with any mental illness were also excluded.

Cognitive and clinical assessment

For all participants, the cognitive performance was assessed via Chinese version of MATRICS Consensus Cognitive Battery (MCCB) [29, 30]. The operators at each center underwent rigorous training and the quality of MCCB assessment was checked by our team during data collection. The MCCB battery requires approximately 90 min to administer. It consists of seven cognitive domains derived from nine subtests: processing speed [Trail Making Test: part A (TMT), Brief Assessment of Cognition in Schizophrenia: symbol coding (BACS SC), and category fluency: animal (Animal fluency)], attention/vigilance (Continuous Performance Test, CPT), working memory (digital sequence and Wechsler Memory Scale Spatial Span, WMS III), verbal learning and memory (Hopkins Verbal Learning Test-Revised, HVLT-R), visual learning and memory (Brief Visuospatial Memory Test-Revised, BVMT-R), reasoning and problem solving (Neuropsychological Assessment Battery, NAB), and social cognition (Mayer–Salovey–Caruso Emotional Intelligence Test, MSCEIT). The raw scores of the 9 cognitive subtests were converted to T scores according to Chinese norms (corrected for age, gender, and education), and the T scores were utilized as the primary measurement.

All patients completed MCCB assessments during enrollment, and as part of the 24-week clinical trial, patients in the LPA-Replication Set conducted MCCB assessments at three time points (baseline, 12w, 24w). The Positive and Negative Syndrome Scale (PANSS) was conceived as an effective instrument to evaluate clinical psychopathology [31]. In the combined sample of Discovery Set and LPA-Replication Set, 669 individuals received a single antipsychotic (290 risperidone, 215 olanzapine, 72 amisulpride, 42 aripiprazole, 29 paliperidone, 9 ziprasidone, 3 quetiapine, 2 blonanserin, 1 lurasidosne, 1 perospirone, and 5 clozapine); 50 individuals received 2 or more antipsychotics (19 with clozapine and only 1 with first-generation antipsychotics: perphenazine); 86 individuals were drug-naive; 25 individuals had missing medication records. And because of their condition, 14 individuals were on mood stabilizers (9 valproate and 5 lithium) and 4 were on benzodiazepines. Daily doses of antipsychotics were recorded and converted to chlorpromazine equivalents (CPZeq) [32].

MRI data acquisition and preprocessing

A subsample of 274 patients from the combined Discovery Set and LPA-Replication Set, and 73 healthy subjects from LPA-HC underwent brain MRI examinations with 3D T1-weighted sequences at two sites at baseline (site 1: the Second Xiangya Hospital, 183 patients and 37 HC; site 2: the Nanjing Brain Hospital, 91 patients and 36 HC). And additional 90 patients from Neuroimaging-Validation Set and matched 45 HC from Neuroimaging-HC also underwent MRI examinations in the First Affiliated Hospital of Zhengzhou University (site 3).

Image processing was conducted using the Freesurfer package (version6.0, http://surfer.nmr.mgh.harvard.edu), comprising cortical thickness maps, mean volume estimates for intracranial volume (ICV), and total brain volumes (TBV); image processing was also conducted using the CAT12 package (CAT12, r1653, http://dbm.neuro.uni-jena.de/cat/index.html) to obtain gray matter volume

Table 1 Demographics and clinical measures by three cohorts

	Schizophrenia patients				HC			Differences between three cohorts			Differences between patients and HC	
	Discovery set	LPA-Replication Set	Neuroimaging-Validation Set	Total sample of patients	LPA-HC	Neuroimaging-HC	Total sample	Statistics	*p*-values	Post hoc	Statistics	*p*-values
Number	661	169	90	920	124	45	169	-	-	-	-	-
Age, y	25.38 ± 8.48	23.27 ± 6.16	22.66 ± 6.16	24.73 ± 7.96	24.01 ± 7.25	22.49 ± 1.5	23.60 ± 6.29	8.22	**< 0.001**	**D > R,NV**	2.04	0.42
Age of onset, y	23.24 ± 7.97	21.77 ± 6.05	22.3 ± 6.08	22.88 ± 7.50	NA	NA	NA	2.91	0.06	-	NA	NA
Female sex (%)	61.12	66.27	48.90	60.87	64.52	51.50	60.90	7.51	0.02	R > NV	0.001	0.985
Education, y	12.16 ± 2.91	11.66 ± 2.82	10.57 ± 2.31	11.91 ± 2.88	13.82 ± 3.08	10.78 ± 2.09	13.01 ± 3.15	13.27	< 0.001	D,R > NV	−4.23	< 0.001
BMI, kg/m^2	21.78 ± 3.88	22.73 ± 4.06	-	22.02 ± 3.95	21.59 ± 3.28	-	21.59 ± 3.28	−2.73	**0.006**	**D < R**	0.88	0.39
Duration[a], m	12.00 (31.00)	13.00 (24.00)	2.00 ± 5.00	12.00 (26.00)	NA	NA	NA	89.02	< 0.001	D,R > NV	NA	NA
CPZeq, mg	318.42 ± 207.53	330.5 ± 145.36	-	321.20 ± 194.83	NA	NA	NA	0.50	0.48	-	NA	NA
PANSS Positive	21.18 ± 6.93	15.09 ± 6.6	23.06 ± 4.87	20.25 ± 7.15	NA	NA	NA	64.31	**< 0.001**	**R < D** < NV	NA	NA
PANSS Negative	20.64 ± 7.69	19.44 ± 7.74	24.91 ± 5.65	20.84 ± 7.65	NA	NA	NA	16.31	< 0.001	D,R < NV	NA	NA
PANSS General	40.28 ± 9.88	36.78 ± 12.8	45.96 ± 6.67	40.19 ± 10.48	NA	NA	NA	23.72	**< 0.001**	**R < D** < NV	NA	NA
PANSS Total scores	82.31 ± 19.1	71.32 ± 24.38	94.14 ± 13.18	81.45 ± 20.56	NA	NA	NA	41.62	**< 0.001**	**R < D** < NV	NA	NA
MCCB domain												
Speed of processing	36.19 ± 9.41	36.35 ± 8.59	26.49 ± 11.16	35.26 ± 9.88	47.94 ± 6.94	46.13 ± 7.22	47.46 ± 7.04	43.04	< 0.001	D,R > NV	−19.26	< 0.001
Attention/vigilance	41.31 ± 12.49	41.96 ± 11.62	29.53 ± 12.00	40.09 ± 12.82	53.36 ± 10.61	51.04 ± 8.24	52.68 ± 10.01	37.91	< 0.001	D,R > NV	−13.57	< 0.001
Working memory	41.93 ± 12.44	42.73 ± 12.21	38.12 ± 10.60	41.69 ± 12.27	46.39 ± 11.04	46.71 ± 10.03	46.49 ± 10.72	4.56	0.01	D,R > NV	−5.00	< 0.001
Verbal learning	37.84 ± 12.82	36.76 ± 10.45	35.83 ± 10.26	37.45 ± 12.19	45.18 ± 9.92	44.47 ± 7.13	44.99 ± 9.25	1.41	0.25	-	−9.23	< 0.001
Visual learning	39.97 ± 13.38	41.34 ± 12.20	37.69 ± 15.14	40.00 ± 13.37	52.32 ± 11.67	47.00 ± 10.06	50.91 ± 11.48	2.18	0.11	-	−11.05	< 0.001
Reasoning/problem solving	42.69 ± 13.57	40.39 ± 12.21	33.24 ± 9.26	41.32 ± 13.25	51.04 ± 10.17	36.60 ± 8.26	47.20 ± 11.60	21.52	< 0.001	D,R > NV	−5.90	< 0.001
Social cognition	40.03 ± 12.22	38.81 ± 11.05	32.63 ± 10.53	38.82 ± 11.99	48.73 ± 9.41	40.42 ± 9.10	45.88 ± 10.08	14.90	< 0.001	D,R > NV	−7.14	< 0.001

CPZeq daily chlorpromazine equivalents; *PANSS* Positive and Negative Syndrome Scale; *MCCB* the MATRICS Consensus Cognitive Battery, *HC* healthy control, *D* Discovery Set, *R* LPA-Replication Set, *NV* Neuroimaging-Validation Set

[a] The duration of illness was expressed as the median and interquartile range

(GMV). Before statistical analysis, the preprocessed maps were uniformly processed through Combat to eliminate site effects. Details of image acquisition, data preprocessing, and Combat Harmonization are given in Additional file 1: S2. MRI Acquisition Protocol and S3. MRI data preprocessing [33–40].

Latent profile analysis and latent transition analysis for cognition

LPA was first performed on the scores of nine subtests of MCCB in the Discovery Set to identify potentially homogeneous groups of schizophrenic patients, and then in the LPA-Replication Set to determine whether the number and characteristics of profiles identified in the Discovery Set could also be observed. In each dataset, models of one to five latent profile(s) were modeled separately. The optimal model was selected based on the fit indices, as well as interpretability and parsimony. The model fitting indices included Akaike's Information Criteria (AIC) [41], Bayesian Information Criteria (BIC) [42], sample-size adjusted BIC (aBIC), entropy [43], Bootstrap Likelihood Ratio Test (BLRT) [44], and Lo-Mendel-Rubin adjusted likelihood ratio test (LMR) [45]. Lower AIC, BIC, and aBIC values indicate a better model fit. Significant BLRT and LMR indicate that k class solution superior to k-1 class solution. Since BIC, aBIC, and BLRT are considered to be robust fitting indicators [46], they are considered preferentially in the selection of the optimal model. The entropy (ranges from 0 to 1) is used to evaluate the classification accuracy of the model, with higher entropy representing higher classification accuracy. Since entropy is susceptible to sample size, values above or close to 0.8 are acceptable [47].

Then, latent transition analysis (LTA) was performed using longitudinal data from the LPA-Replication Set to characterize the dynamic transitions of the samples between classes over time. LTA estimated the transition probability from one latent class at time 1 to other latent classes at time $t+1$. The LPA and LTA were performed in Mplus (version 8.3) [48]. Once the optimal model was determined, the combined sample of Discovery Set and LPA-Replication Set was used for classification and subsequent analysis.

Statistical analysis

Group differences of basic demographics and clinical variables were examined with *t*-tests, analysis of variance (ANOVA), and chi-square tests, followed by Bonferroni post hoc comparisons. For data that did not fit normal distribution, nonparametric test was applied. If there is a profile shift in the longitudinal data, the effect of group on the PANSS scores were analyzed with a repeated-measures ANOVA, with between factor group (patients shifted to other profile vs stabilized in the original profile) and within factors PANSS scores and time (baseline and 12 weeks follow-up). All the above operations were performed in SPSS Statistics 25.0.

After controlling for age, gender, education, and ICV (only for GMV comparisons), statistical maps for group effects on cortical thickness at each vertex and GMV at each voxel were generated using analysis of ANOVA in SPAMRI (v1.2) [38] and SPM12 (v7219, http://www.fil.ion.ucl.ac.uk/spm), respectively (see in Additional file 1: S3. MRI data preprocessing). The surviving clusters from ANOVA were selected as regions of interest (ROIs) and then mean thickness or GMV values of ROIs were extracted for post hoc analysis. Meanwhile, ICV, absolute TBV, and TBV adjusted for ICV were examined using ANOVA with age, gender, education, and type of MRI scanner entered as covariates. Multiple comparisons were corrected using Bonferroni method.

On the other hand, we validated the replicability of MRI features related to cognitive subgroups in the independent Neuroimaging-Validation Set. First, the latent profile model was trained on seven MCCB domain scores in the combined Discovery Set and LPA-Replication Set and then predicted the cognitive profile in the Neuroimaging-Validation Set. Next, the ROI values of subgroups were extracted from Neuroimaging-Validation Set, and the same post hoc analyses and Bonferroni correction for multiple comparisons were conducted.

Results

Demographics and clinical characteristics

Demographics and clinical characteristics of cases ($n=920$) and HC ($n=169$) are shown in Table 1 and Additional file 1:Table S1. While there were modest differences in demographics and clinical symptoms between the Discovery and the LPA-replication Set, no significant differences were observed in cognitive performance.

Cognitive subtyping by LPA based on MCCB

Discovery phase

Based on Discovery Set, LPA was conducted and Table 2 depicts the fit statistics from the series of latent profile models with one to five profiles. The values of AIC, BIC, and aBIC decreased as the number of extracted profiles increased, while the p values of BLRT were consistently significant ($p<0.001$), indicating that a greater number of profiles fit the data increasingly better. But the decrements of AIC and aBIC slowed for model 3–5, so the fitting and profile interpretation of models 3–5 should be carefully considered. While the 4-profile model showed slightly higher BIC than 3-profile model, the 4-profile model showed lower AIC and aBIC. Although 5-profile model showed the lowest AIC and aBIC among the

Table 2 Fit indices for latent profile analysis for Discovery Set ($n=661$) and LPA-Replication Set ($n=169$)

	Profile	AIC	BIC	aBIC	Entropy	LMR	LMR *p* value	BLRT	BLRT *p* value	Profile proportions
Discovery	1	44,000.794	44,081.682	44,024.531						
	2	43,174.626	43,300.452	43,211.551	0.791	833.335	< 0.001	−21,982.397	< 0.001	0.31/0.69
	3	42,967.633	**43,138.396**	43,017.745	0.747	223.551	< 0.001	−21,559.313	< 0.001	0.15/0.29/0.56
	4	42,932.819	43,148.519	42,996.117	0.645	53.983	0.48	−21,445.817	< 0.001	0.16/0.30/0.28/0.26
	5	**42,888.194**	43,148.831	**42,964.680**	0.660	63.645	0.12	−21,418.409	< 0.001	0.21/0.06/0.33/0.22/0.18
LPA-Replication (T1)	1	11,678.640	11,734.979	11,677.985						
	2	11,476.226	11,563.863	11,475.207	0.853	218.162	< 0.001	−5821.320	< 0.001	0.25/0.75
	3	11,434.379	**11,553.315**	11,432.996	0.766	60.665	0.07	−5710.113	< 0.001	0.19/0.54/0.27
	4	11,419.953	11,570.188	11,418.206	0.798	33.768	0.50	−5679.189	< 0.001	0.52/0.20/0.13/0.15
	5	**11,415.366**	11,596.901	**11,413.256**	0.808	24.116	0.59	−5661.976	0.29	0.06/0.15/0.12/0.50/0.16
LPA-Replication (T2)	1	11,666.054	11,722.392	11,665.399						
	2	11,494.283	11,581.920	11,493.264	0.707	188.104	0.13	−5815.027	< 0.001	0.47/0.53
	3	11,436.208	**11,555.144**	11,434.825	0.832	76.582	0.03	−5719.141	< 0.001	0.09/0.61/0.30
	4	11,426.091	11,576.326	11,424.344	0.808	29.542	0.51	−5680.104	0.04	0.11/0.11/0.52/0.26
	5	**11,420.235**	11,601.770	**11,418.125**	0.830	25.361	0.46	−5665.045	0.24	0.03/0.13/0.51/0.10/0.23
LPA-Replication (T3)	1	11,737.553	11,793.892	11,736.898						
	2	11,515.588	11,603.225	11,514.569	0.762	237.339	0.14	−5850.777	< 0.001	0.43/0.57
	3	11,423.722	**11,542.658**	11,422.339	0.851	109.727	< 0.001	−5729.794	< 0.001	0.07/0.57/0.36
	4	11,416.320	11,566.555	11,414.573	0.796	26.878	0.72	−5673.861	0.07	0.07/0.50/0.20/0.23
	5	**11,399.125**	11,580.659	**11,397.014**	0.793	36.484	0.11	−5660.160	< 0.001	0.06/0.29/0.22/0.30/0.13
Discovery + LPA-Replication (T1)	1	55,688.616	55,773.602	55,716.440						
	2	54,660.445	54,792.645	54,703.727	0.795	1032.806	< 0.001	−27,826.308	< 0.001	0.28/0.72
	3	54,410.132	54,589.546	54,468.871	0.740	266.351	< 0.001	−27,302.222	< 0.001	0.15/0.59/0.26
	4	54,358.213	54,584.841	54,432.410	0.639	70.864	0.27	−27,167.066	< 0.001	0.17/0.28/0.32/0.23
	5	**54,304.098**	**54,577.941**	**54,393.754**	0.669	73.028	0.04	−27,131.106	< 0.001	0.04/0.21/0.19/0.20/0.36

AIC Akaike's information criteria, *BIC* Bayesian information criteria, *aBIC* sample-size adjusted BIC, *LMR* Lo-Mendel-Rubin adjusted likelihood ratio test, *BLRT* Bootstrap Likelihood Ratio Test

models, it resulted in one group with too few participants (6% of cases), which typically represents spurious classification and is not meaningful [49, 50]. Thus, a 4-profile model fits the data best.

Replication phase

Fit statistics of replication phase are provided in Table 2. Results indicated that 4-profile model had a lower AIC and aBIC, a significant BLRT p-value compared to 3-profile model, and also a favorable entropy value. The BLRT p-value indicated that 5-profile model did not fit as well as a 4-profile model. Additionally, model 5 contained one profile of less than 10% of the sample. Based on these criteria, a 4-profile model was considered optimal.

Cognitive patterns of subgroups

LPA of the combined Discovery Set and LPA-Replication Set showed appropriate AIC, BIC, aBIC, and BLRT p-value for 4-profile model (Table 2). The cognitive characteristics of four subgroups are depicted in Fig. 1 and Additional file 1: Table S2. Profile 4 showed only slightly decreased performance in Symbol Coding ($p=0.004$) and Continuous Performance Test ($p=0.01$) (2/9 subtests) compared to HC, named multidomain-intact subgroup. Profile 3 showed moderately decreased performance in most subtests ($p<0.001$) except Wechsler Memory Scale Spatial Span (WMS) and Neuropsychological Assessment Battery (NAB) compared to HC, named executive-preserved subgroup. Profile 2 showed moderately decreased performance in nine subtests, especially in WMS ($p=1.39\times10^{-18}$) and NAB ($p=3.04\times10^{-53}$) compared to HC, named executive-deteriorated subgroup. Profile 1 showed more severe impairment in eight subtests ($p<0.001$) (except NAB) than profile 2, named multidomain-deteriorated subgroup. This 4-profile solution consisted of 23% profile 4 ($n=194$), 32% profile 3 ($n=265$), 28% profile 2 ($n=231$), and 17% profile 1 ($n=140$). In addition, cognitive scores of subgroups were standardized to Z-scores using HC's MCCB scores as a criterion (Additional file 1: Figure S1).

Clinical features of cognitive subgroups

Significant differences for demographic and clinical characteristics among cognitive profiles are summarized in Fig. 2 and Additional file 1: Table S2. In particular, multidomain-deteriorated and executive-preserved subgroup had similar age and age of onset, both of which were younger than multidomain-intact and executive-deteriorated subgroup. Multidomain-deteriorated subgroup received less years of education than executive-deteriorated subgroup. In addition, executive-deteriorated subgroup had the highest proportion of females (83%) compared to other subgroups, while executive-preserved subgroup had the lowest proportion of females (42.3%).

There was no significant difference in positive symptoms among the four groups; however, the negative symptoms, general pathology scores, and total PANSS scores were most severe in multidomain-deteriorated subgroup (all $p<0.001$), least severe in multidomain-intact subgroup (all $p<0.05$), and intermediate in the two moderate subgroups. There was no significant difference in the duration of disease among groups. And on medication, only executive-preserved subgroup was observed to have a higher daily dose than multidomain-intact subgroup.

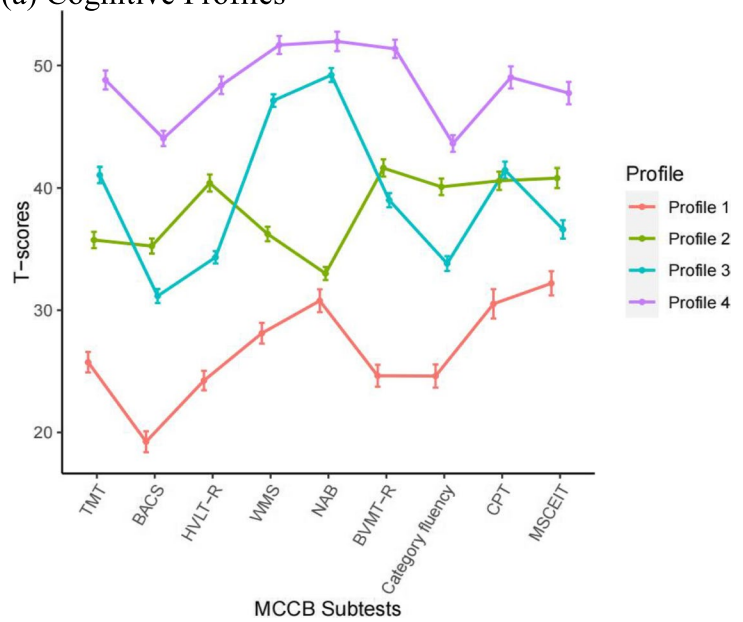
Longitudinal stability of cognitive profiles and symptomatology reductions

Given the best fit of the 4-profile solution, a latent transition analysis of 4 profiles was performed. Table 3 depicts latent transition probabilities for each profile from T1 to T2 and T2 to T3. Most profiles exhibit high transition probabilities to themselves (>0.8), suggesting that most individuals remain at their respective profiles over time. However, 48.8% of profile 1 ($n=18$) shifted to profile 2 from T1 to T2 in the longitudinal cohort, and the rest ($n=19$) remained in profile 1. At baseline, cognitively stable patients in profile 1 performed significantly worse on the WMS compared to cognitively improved patients (24.63 ± 7.81 vs 33.00 ± 9.32, $p=0.005$), whereas there was neither a significant difference in the other eight subtests, nor in symptoms (Additional file 1: Table S3). Longitudinally, the repeated measures ANOVA indicated a significant main effect of time of PANSS score (all $p<0.001$), neither a main effect of group nor a group*time interaction were found. This result suggests that both groups showed symptomatic reductions from baseline to 12 weeks, but there was no difference in the degree of improvement between the two groups (Additional file 1: Table S4).

Differences in cortical thickness among subgroups

Significant differences were found in cortical thickness among the groups (Fig. 3, Additional file 1: Table S6 and Table S8), whereas this effect was not apparent in the multidomain-intact subgroup, which showed only decreased cortical thickness in right precentral gyrus (preCG). Executive-preserved subgroup exhibited significantly reduced cortical thickness in left supramarginal gyrus, left superior frontal gyrus (SFG), right preCG, right pars opercularis (POp), and right lateral orbital frontal cortex compared to the HC. The executive-deteriorated subgroup demonstrated similar but more extensive cortical thinning, with additional reductions in the left middle temporal gyrus. Furthermore, the

(a) Cognitive Profiles



(b) Cognitive Differences Among Groups

MCCB subtestsc	Profile 1 multidomain -deteriorated	Profile 2 executive-deteriorated	Profile 3 executive-deteriorated	Profile 4 multidomain-intact	post hoc
TMT	↓↓↓	↓↓	↓	none	1<2<3<4
BACS	↓↓↓	↓↓	↓↓↓	↓	1<2;1<3<4; 2>3
HVLT-R	↓↓↓	↓	↓↓	↑	1<2;1<3<4; 2>3
WMS	↓↓↓	↓	none	↑	1<2<3
NAB	↓↓↓	↓↓↓	none	none	1,2<3<4
BVMT-R	↓↓↓	↓	↓↓	none	1<2,3<4
Category fluency	↓↓↓	↓	↓↓	none	1<2;1<3<4; 2>3
CPT	↓↓↓	↓	↓	↓	1<2,3<4
MSCEIT	↓↓	↓	↓	none	1<3<2<4

Fig. 1 Cognitive profiles by latent profile analysis (**A**) and their differences among groups (**B**). The figure represents the cognitive performance of each profile from the combined Discovery and LPA-Replication Set: points indicate mean T-scores obtained at each subtest and error bars reflect the 95% confidence interval. "↓" means that the cognitive test is significantly worse than HC, and "↑" is the opposite. p<0.05↓, p<10^-20↓↓, p<10^-40↓↓↓, "none" means that the cognitive test is not significant compared to HC. Post hoc was corrected by Bonferroni method. TMT = Trail Making Test Part A, BACS = Brief Assessment of Cognition in Schizophrenia: Symbol coding, HVLT-R = Hopkins Verbal Learning Test-Revised, WMS = Digital Sequence and Wechsler Memory Scale Spatial span, NAB = Neuropsychological Assessment Battery, BVMT-R = Brief Visuospatial Memory Test-Revised, CPT = the Continuous Performance Test, MSCEIT= Mayer-Salovey-Caruso Emotional Intelligence Test

multidomain-deteriorated subgroup showed significantly reduced cortical thickness in the left supramarginal gyrus, left SFG, left middle temporal gyrus, right preCG, and right POp compared to HC.

Additionally, Jonckheere-Terpstra test showed that there was a statistically significant trend of less loss of cortical thickness with higher levels of cognitive performance (from profile 1 to profile 4 and to HC) in left supramarginal gyrus ($z = 5.19$, $p < 0.001$), left SFG ($z = 4.51$, $p < 0.001$), left middle temporal gyrus ($z = 3.31$, $p = 0.001$), right preCG ($z = 4.44$, $p < 0.001$), right POp ($z = 4.11$, $p < 0.001$), and right lateral orbital frontal cortex ($z = 3.30$, $p = 0.001$).

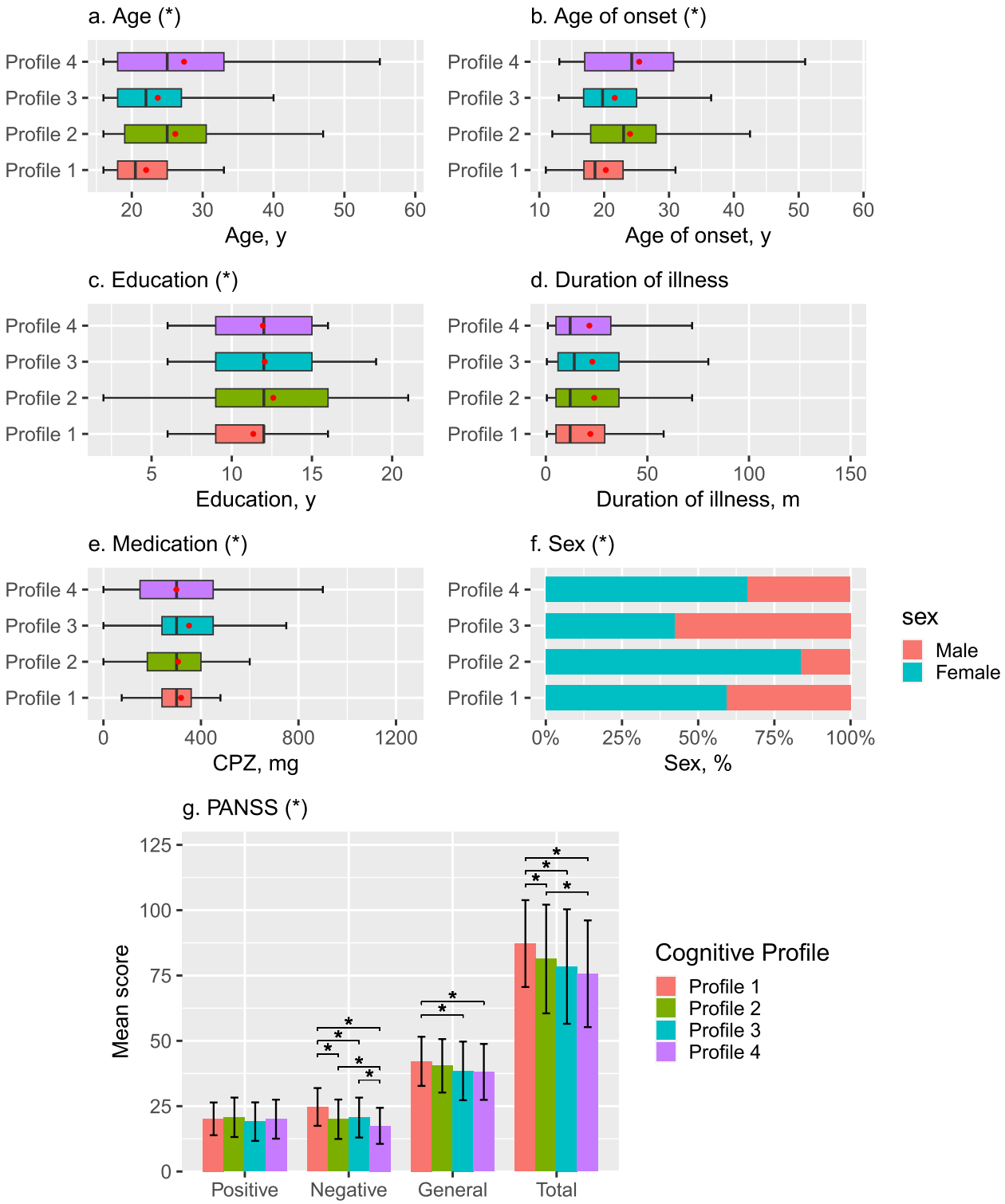


Fig. 2 Clinical and demographic features across cognitive subgroups. (*) implies significant differences between the four subgroups. Profile 1 = multidomain-deteriorated subgroup, Profile 2 = executive-deteriorated subgroup, Profile 3 = executive-preserved subgroup, Profile 4 = multidomain-intact subgroup, PANSS = Positive and Negative Syndrome Scale

Table 3 Transition probabilities across time by using latent transition analysis

T1 (rows) to T2 (columns)					T2 (rows) to T3 (columns)				
Profiles	1	2	3	4	Profiles	1	2	3	4
1	0.512	0.488	0	0	1	0.893	0.107	0	0
2	0	0.812	0	0.188	2	0	1	0	0
3	0	0	0.891	0.109	3	0	0	1	0
4	0	0	0	1	4	0	0	0	1

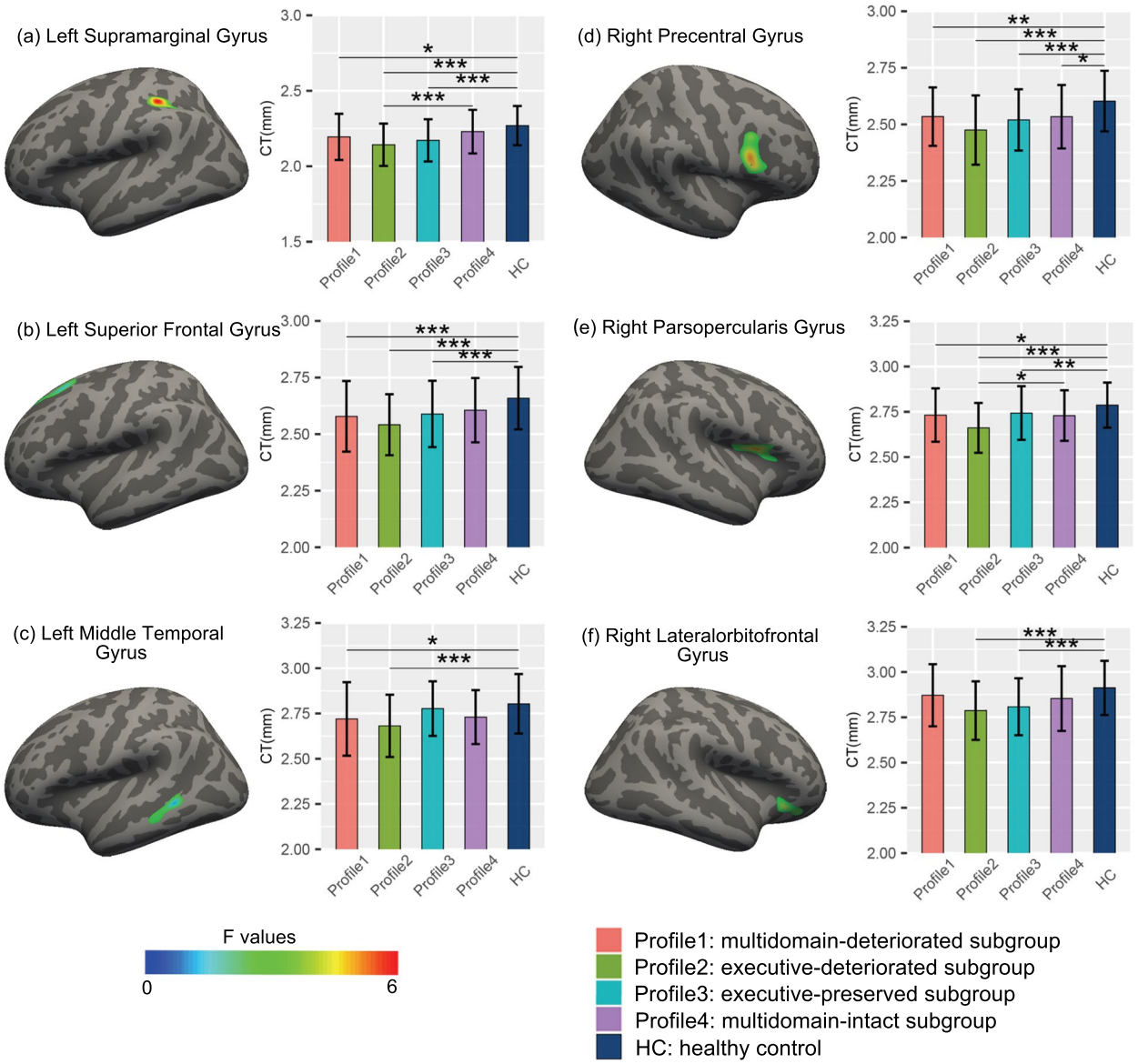


Fig. 3 Cortical thickness differences across cognitive subgroups. a-f Brain maps show cortical regions with thickness differences among profiles (p<0.05, corrected by Random Field Theory), and bar charts show the post-hoc ROI analysis (p<0.05, corrected by Bonferroni)

Differences in GMV among subgroups

The pattern of GMV loss mirrored that of cortical thinning across the subgroups, i.e., executive-deteriorated subgroup displayed the most extensive and pronounced abnormalities compared to HC (Fig. 4, Additional file 1: Table S7-8). The multidomain-intact subgroup did not differ significantly from the HC in any regional brain volume. Compared to HC and multidomain-intact subgroup, executive-preserved subgroup had reduced GMV in left hippocampus and left insula; executive-deteriorated subgroup had reduced GMV in right superior temporal gyrus, left hippocampus, right medial prefrontal cortex (mPFC), left insula, left posterior cingulate cortex/precuneus (PCC/PCu), left supplementary motor area (SMA), and left inferior parietal gyrus, and multidomain-deteriorated subgroup had reduced GMV in right superior temporal gyrus, left hippocampus, right mPFC, and left insula. Notably, between the two groups with

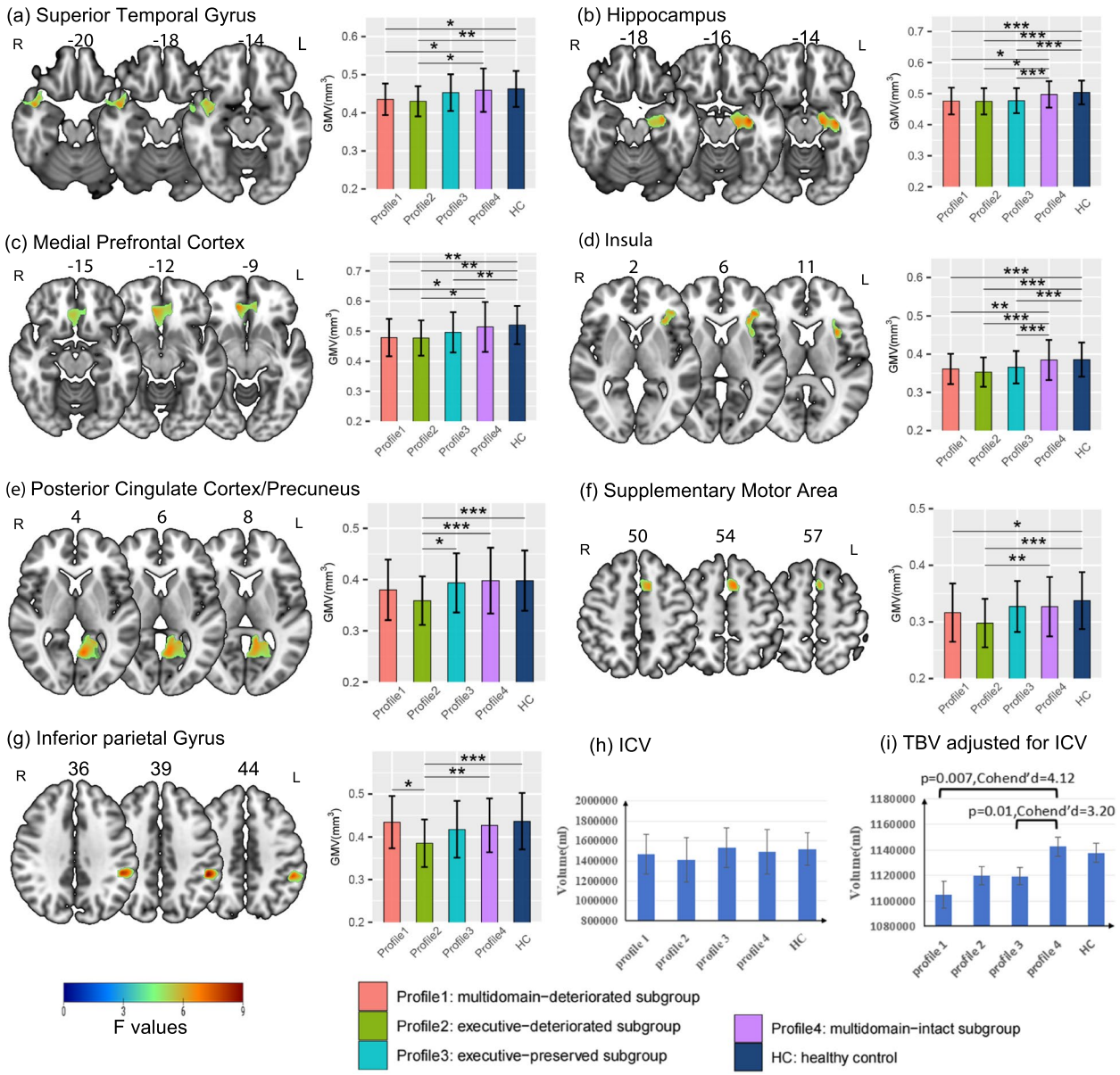


Fig. 4 GMV differences across cognitive subgroups. **a**-**g** Brain maps show gray matter regions with GMV differences among profiles ($p<0.05$, corrected by cluster-based Family Wise Error), and bar charts show the post-hoc ROI analysis (p<0.05, corrected by Bonferroni).*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. GMV = gray matter volume, L = left, R = right. h and i: Mean differences in global brain measures that survived Bonferroni correction. ICV = intracranial volume, TBV = total brain volume

moderate cognitive deficits, executive-deteriorated subgroup had lower GMV in PCC/PCu compared to executive-preserved subgroup.

Additionally, Jonckheere-Terpstra test showed that there was a statistically significant trend of less loss of GMV with higher levels of cognitive performance (from profile 1 to profile 4 and to HC) in right superior temporal gyrus ($z=4.40$, $p<0.001$), left hippocampus ($z=4.88$, $p<0.001$), right mPFC ($z=4.39$, $p<0.001$), left insula ($z=4.91$, $p<0.001$), left PCC/PCu ($z=3.85$, $p<0.001$), left SMA ($z=4.86$, $p<0.001$), and left inferior parietal ($z=3.07$, $p=0.002$).

Differences in WMV among subgroups

As showed in Additional file 1: Table S7 and Figure S3, the multidomain-deteriorated and executive-preserved subgroup exhibited a significantly decreased WMV of left hippocampus compared to the multidomain-intact subgroup, whereas the multidomain-intact subgroup showed significantly increased WMV of left hippocampus compared to HC.

Global brain estimates

Figure 2 and Additional file 1: Figure S2 present comparisons of ICV, absolute TBV, and TBV adjusted for ICV. There was no significant group difference in ICV in any group. And adjusting for ICV, TBV was significantly reduced in multidomain-deteriorated subgroup ($p=0.007$, Cohen's $d=4.12$) and executive-preserved subgroup ($p=0.01$, Cohen's $d=3.20$) compared to multidomain-intact subgroup.

Validation of morphological features

The LPA model divided the Neuroimaging-Validation Set into 23.33% profile 1, 25.56% profile 2, 24.44% profile 3, and 26.67% profile 4. Clinical data and profile results are included in Additional file 1: Table S10-11 and Figure S4. As shown in Additional file 1: Figure S5 −6, MRI features show high similarity in trends among groups. Particularly, Jonckheere-Terpstra test showed a significantly similar trend for loss of cortical thickness in left supramarginal gyrus ($z=3.546$, $p<0.001$), left SFG ($z=4.477$, $p<0.001$), right POp ($z=2.40$, $p=0.016$), and loss of GMV in left hippocampus ($z=2.784$, $p=0.005$).

Discussion

To the best of our knowledge, this is the first study using a data-driven LPA and LTA approach to uncover cognitive subgroups, their longitudinal stability and structural features in schizophrenia. In this study, we identified four heterogeneous subgroups of cognitive impairments and their structural brain characteristics (cortical thickness and GMV) through the data-driven LPA and LTA based on cognitive data (MCCB) in a large cohort of schizophrenia patients. These four profiles were well-validated in an independent cohort and showed consistency in the structure of profile over time. The current study has 3 main findings: (1) Four distinct cognitive profiles were identified in schizophrenia: a multidomain-intact subgroup, two moderately impaired groups driven by executive function (executive-preserved and executive-deteriorated), and a multidomain-deteriorated subgroup; (2) Cognitive subgroups exhibited significant gradient features in fronto-temporal regions, hippocampus, and insula; and (3) Multidomain-intact subgroup exhibited better clinical outcomes compared to multidomain-deteriorated subgroup.

Cognitive subgroups in schizophrenia

Our finding confirmed the heterogeneity of cognition based on full subtests of MCCB in schizophrenia, which is partially consistent with current reports. However, the optimal solution is not unified, and currently, there are 3-profile and 4-profile solutions [6, 21, 51]. In our 4-profile solution, the multidomain-deteriorated (profile 1) and multidomain-intact subgroups (profile 4) were overlapped with "High" and "Low" ability profile in 3-profile solution [21]. But we further subdivided the "Moderate" ability profile into two subsets (profiles 2 and 3), which were mainly distinguished by executive function performance. Specifically, multidomain-intact subgroup (profile 4) closely approximates HC across all cognitive subtests except for BACS and CPT within ~0.5 SD. Executive-preserved (profile 3) and executive-deteriorated subgroups (profile 2) are characterized by moderate cognitive impairments of 0.5 ~ 1.5 SD below HC, except that WMS and NAB in profile 3 are equivalent to those of HC, and NAB in profile 2 exceeds 1.5 SD. Multidomain-deteriorated subgroup (profile 1) is defined by cognitive performance of > 1.5 SD below the norm. Notably, the common features among our four profiles are the significant impairments in processing speed indexed by BACS and attention/vigilance indexed by CPT subtests, supporting these domains as sensitive features of cognitive impairments in schizophrenia [4].

Moreover, our results also highlight consistency with previous findings that executive function clearly delineated the two intermediate cognitive impairment subtypes [7, 52]. Executive functioning deficits are often regarded as one of the main neuropsychological deficits in schizophrenia [53]. Frequently, the Wisconsin Card Sorting Test and the Stroop Task were reported deficits in schizophrenia [54], which suggest that the cause of executive functioning deficits was the abnormality in several cognitive processes like speed of processing and attention/vigilance [55]. And executive function robustly indexes

genetic risk for general psychopathology [56]. Besides, there were heterogeneity in executive function impairment in schizophrenia, with varying types and degrees [57, 58]. This may be partly due to differences in evaluation methods, but more importantly, it reflects the diversity of damage. Further evaluation of executive function as an endophenotype is needed in the future to explain cognitive heterogeneity in schizophrenia. Together, these findings suggest that from the perspective of overall cognitive impairment, schizophrenia exhibits common cognitive impairments in symbol encoding and attention retention, but heterogeneous impairments in most other cognitive domains, especially in executive function.

In addition, we observed that the separation between executive-deteriorated subgroup (profile 2) and executive-preserved subgroup (profile 3), relied on language-related functions (indexed by HVLT-R and Category Fluency) and executive functions (indexed by WMS and NAB). Executive-deteriorated subgroup exhibited relatively better language-related functions but relatively poorer executive functions, while executive-preserved subgroup retained intact executive functions but surprisingly showed poorer language functions compared to executive-deteriorated subgroup. Language functions involve executive components, such as retrieval capabilities, initiation, inhibition, and self-monitoring [59]. However, previous studies investigating the involvement of executive functions in verbal fluency tasks also reported ambiguous results. For instance, some studies failed to identify a clear relationship between semantic task performance and executive functions in one or more executive subdomains [60, 61]. In contrast, other studies have reported that better working memory, inhibition, and cognitive flexibility performance may lead to higher total scores of produced words [62, 63]. Additionally, one study found that the relationship between memory performance and language fluency is specific to females [64]. Notably, in this study, the proportion of females in executive-deteriorated subgroup was significantly higher than that in executive-preserved subgroup. Therefore, we speculate that the contribution of executive functions to language functions may vary across different subgroups, but this requires further clarification through advanced language and executive tasks.

Longitudinally, more than 80% of individuals in executive-deteriorated, executive-preserved, and multidomain-intact subgroups (profiles 2, 3, 4) maintained consistency at three time points. Interestingly, almost half of multidomain-deteriorated subgroup (profile 1) turned into executive-deteriorated subgroup (profile 2) after 12 or 24 weeks. WMS showed significant differences between the transition group and the non-transition group in profile 1 (Table S3), which suggests the potential ability of WMS to screen and identify these patients and re-emphasizes the core position of executive function within cognition. Besides, when there are differences in the improvement of WMS, there is no difference in symptom changes between subgroups. This suggests that cognition is independent of symptoms and can provide unique characteristic information in schizophrenia. However, as part of two longitudinal clinical trials, we interpreted our results with caution because the follow-up time point could be confounded by medication effect or follow-up bias.

Morphological features of cognitive subgroups

From profile 1 to 4, we observed cognitive impairment ranging from severe to mild, but the morphological deficits to the brain were not entirely consistent. The severity of cognitive impairment associated with morphological deficits displays variance across profiles 2 to 4, but the deficits of profile 1 were not the most severe. Similar trends, although not all significant, were observed in the Neuroimaging-Validation Set. The reason for this finding may be the insufficient sample size of the subtype in the Neuroimaging-Validation Set.

The multidomain-intact cognitive subgroup (profile 4) exhibited relatively intact morphology compared to HC, with only preCG thinning. Consistent with our findings, previous studies have reported reduced preCG morphology in patients with preserved or mildly impaired cognition, but differed in that they also observed structural deficits in several other regions at the same time [13, 65]. The inconsistencies in results may relate to differences in the mean age of the preserved samples across studies; our sample is generally young. And earlier studies have solely utilized IQ or verbal memory functions to classify their subgroups, which may also have led to inconsistent outcomes [13, 65]. The literature has emphasized the significance of motor dysfunction in the core pathophysiological pathways of schizophrenia, suggesting that it underlies higher-level cognitive function [66, 67]. Consequently, it is not surprising that morphological deficits in the preCG were observed in the multidomain-intact subgroup. We speculate that the preCG may serve as the neural correlate of subtle cognitive impairments.

The executive-preserved subgroup (profile 3) and the executive-deteriorated subgroup (profile 2) each exhibited unique patterns of morphological decline. When compared to the most intact subgroup, the executive-preserved subgroup (profile 3) exhibited primarily gray matter loss in the hippocampus and insula, along with cognitive domain declines except for executive function. In contrast, the executive-deteriorated subgroup (profile 2) displayed additional deficits in the PCC/PCu, which has been widely observed to be closely linked to working memory [68–70], compared to the executive-preserved

subgroup (profile 3). Some studies on schizophrenia have demonstrated gray matter loss in the PCC [68, 71, 72], while other groups have found no significant differences between schizophrenia patients and controls [73, 74]. Additionally, Zhou et al. [75] identified distinct altered patterns of the default mode network (i.e., PCC/PCu) in both deficit schizophrenia and non-deficit schizophrenia patients, which were associated with poor cognitive function. These findings, coupled with the distinct deficit patterns of the PCC/PCu observed in our results, suggest that there are naturally different homogeneous groups within schizophrenia with distinct psychopathological underpinnings. Moreover, the PCC/PCu is a major hub of default mode network engaged in the monitoring of internal processes, episodic, working, and visuospatial memory [76]. Given the crucial role of the PCC in working memory, the volumetric loss observed in this study may serve as a neurobiological mechanism underlying executive dysfunction in schizophrenia.

Counterintuitively, the structural abnormalities in the multidomain-deteriorated subgroup are not the most prominent, but rather closer to the executive-preserved subgroup. The mean age of our overall sample is small, and in particular profile 1 as well as profile 3 is somewhat younger than the other two groups. Given that age was significantly associated with brain structural deficits in the current study (data not shown), this may partially explain the present finding. Instead, we found evidence of the largest reduction in TBV (adjusted for ICV) in the multidomain-deteriorated subgroup compared to the multidomain-intact subgroup, with no statistically significant difference in ICV between the groups. TBV loss in the cortex of normal ICV has been regarded as a marker of neurodegeneration and atrophy [15]. Recent work shows that cognitive subgroups appeared to be susceptible to some brain atrophy [15, 65], and accelerated aging occurs very early in schizophrenia [77]. Maturational and/or adult neurodegenerative processes may be more significant contributors to the neural tissue underpinnings of multidomain-deteriorated subgroup. Another interesting observation is the cognitive recoverability observed in the multidomain-deteriorated subgroup. According to our 12-week follow-up, 48.8% of this subgroup demonstrated some degree of cognitive function recovery, whereas the cognitive performance of the other three subgroups remained relatively stable. This suggests that the impairments in the multidomain-deteriorated subgroup may be classified as either transient or persistent. Moreover, the transient type may exhibit less structural deficits. However, we did not have a sufficient number of subjects in this subgroup to validate this hypothesis. We aim to further investigate this aspect in future studies.

Clinical relationship features of cognitive subgroups

Consistent with our hypothesis, we observed that the negative symptom severity increased as profile varied from multidomain-intact to multidomain-deteriorated subgroup. Substantial evidence suggests that negative symptoms are associated with poor cognitive resources, executive function, and social cognition [78, 79]. Our findings further support the concept that negative symptoms may overlap with cognitive impairments in schizophrenia, or may share similar neurobiological substrates [80].

Limitation

Our study has several strengths including the comprehensive and standardized cognitive assessment with complete dimensions, the neuroanatomical features of cognitive subgroups, and their longitudinal transition. However, several limitations are also required to be considered. First, to obtain a universal cognitive subtype and enhance their generalizability, this study included as many schizophrenia samples as possible throughout the entire course of the disease. Therefore, it inevitably leads to the heterogeneities of participants, such as multi-center design, larger age span, differences in disease duration, and medication use. Although we have made some adjustments to these factors, we still need to pay attention to their impact when understanding the results. For the scanner variations, we endeavored to minimize site effects using Combat Harmonization, but it may lead to potential undetected subtle differences between subgroups. To minimize the effect of age, the cognitive scores are converted to T scores based on the standard norm, which is the deviation value from the score of the same age. Thus, age should not affect the differentiation of cognitive subtypes, the age differences between subtypes may be due to an uneven age distribution caused by differences in sample size between the subtypes, as well as different pathological mechanisms between subtypes. For the span of disease duration, we did not find the difference in duration between subtypes, suggesting that cognitive subtyping is unlikely to be confounded by disease duration. As for medication, cumulative medication usage in schizophrenia patients made it challenging to disentangle antipsychotic-induced changes from the inherent disease processes. We examined the impact of medication exposure on class classification using the three-step analysis, suggesting that the effect of medication exposure on classification is actually small (Additional file 1: S4. Multinomial Logistic Regression Analysis [81]; S6.Results of Multinomial Logistic Regression; Table S5). Moreover, after controlling for medication exposure (Additional file 1: Table S9), the morphological differences between cognitive subgroups

are unaltered and a correlation between CPZeq and any ROI was absent, which suggests that these factors do not affect our findings. Finally, the cognitive data in the Neuroimaging-Validation Set are domain scores rather than subtest scores, which might impact the classification models. Additionally, a larger sample size of repeated experiments will help further validate our results.

Conclusions

In summary, the profile solution confirms the existence of cognitive decline in schizophrenia, characterized by varying severity levels of cognitive performance. Moreover, the severity continuum can be subclassified based on executive function. Distinct cognitive phenotypes are associated with the extent of brain morphological abnormalities, which may facilitate a more comprehensive biological understanding of cognitive functioning. This study provides a framework for defining cognitive subgroups in schizophrenia, refined through LPA and further enhanced by neuroimaging data.

Abbreviations

LPA	Latent Profile Analysis
MRI	Magnetic resonance imaging
HC	Healthy controls
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
ICD-10	International Classification of Diseases-tenth edition
MCCB	MATRICS Consensus Cognitive Battery
TMT	Trail Making Test: part A
BACS	Brief Assessment of Cognition in Schizophrenia: symbol coding
CPT	Continuous Performance Test
HVLT-R	Hopkins Verbal Learning Test-Revised
BVMT-R	Brief Visuospatial Memory Test-Revised
WMS	Digital sequence and Wechsler Memory Scale Spatial Span
NAB	Neuropsychological Assessment Battery
MSCEIT	Mayer–Salovey–Caruso Emotional Intelligence Test
PANSS	Positive and Negative Syndrome Scale
CPZeq	Chlorpromazine equivalents
ICV	Intracranial volume
TBV	Total brain volumes
GMV	Gray matter volume
AIC	Akaike's Information Criteria
BIC	Bayesian Information Criteria
aBIC	sample-size adjusted BIC
BLRT	Bootstrap Likelihood Ratio Test
LMR	Lo-Mendel-Rubin adjusted likelihood ratio test
LTA	Latent transition analysis
ROIs	Regions of interest
preCG	Precentral gyrus
SFG	Superior frontal gyrus
POp	Pars opercularis
mPFC	Medial prefrontal cortex
PCC/PCu	Posterior cingulate cortex/precuneus
SMA	Supplementary motor area

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03835-9.

Additional file 1: S1. Participants; S2. MRI Acquisition Protocol; S3. MRI Data Preprocessing; S4. Multinomial logistic regression analysis; S5. Demographics and Clinical characteristics (Table S1-4, Figure S1); S6. Results of Multinomial logistic regression (Table S5); S7. Morphological Characteristics Among Subgroups (Table S6-9, Figure S2-3); S8. Neuroimaging Validation (Table S10-11, Figure S4-6). Table S1. Demographics and clinical measures by Discovery Set and LPA-Replication Set. Table S2. Clinical characteristics of profiles using the combined Discovery and LPA-Replication Set (n = 830) and healthy control (n=124). Table S3. Cognitive characteristics of transition and non-transition group in profile 1 at baseline. Table S4. Symptomatology and MCCB scores of transition and non-transition group in profile 1 at baseline and 12w-follow up. Figure S1. Z-scores for cognitive performance in 4 subgroups. Table S5. Classification covariates analysis on medication exposure. Table S6. Brain regions with significant differences in cortical thickness. Table S7. Brain regions with significant differences in gray/white matter volume. Table S8. Cognitive subgroup cortical thickness and GMV comparisons. Table S9. Cognitive subgroup cortical thickness and GMV comparisons after controlling for medication exposure. Figure S2. Mean differences in global brain measures that survived Bonferroni correction across cognitive subgroups and healthy controls. Figure S3. WMV differences across cognitive subgroups. Table S10. Demographics and clinical characteristics of Neuroimaging-Validation Set. Table S11. Clinical characteristics of cognitive profiles predicted using latent profile model in the Neuroimaging-Validation Set (n=90). Figure S4. Predictive outcomes of cognitive profiles in the Neuroimaging-Validation Set by the latent profile model. Figure S5. Cortical thickness differences across cognitive subgroups in the Neuroimaging-Validation Set. Figure S6. GMV differences across groups in cognitive subgroup in the Neuroimaging-Validation Set.

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Authors' contributions

YY.H. processed the data of the participants, ran the statistical analysis and edited the manuscript. WY.W. formulated the research questions, contributed to the design of the study, and executed the data processing. Authors GR.H., TN.S., L.L., Y.Y., XY.W., YJ. L., JM.X, XJ.P., CH.S., JD.C., DY.K., Y.W., and SZ.G. collected the data of participants. J.H. supervised data analysis. XJ.X. and XQ.S. supervised the implementation of the project in Nanjing and Zhengzhou, respectively. JP.Z. supervised the design of the study. YZ.P. supervised the design of the study and contributed to an early version of the manuscript. RR.W. formulated the research questions, supervised the design of the study and edited the final manuscript. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All procedures involving patients were approved by the local ethical committees (the Second Xiangya Hospital of Central South University, the approval number 2017027 and 2016027) and written informed consent was obtained from all participants or their legal guardians (for participants < 18 years).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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