Heterogeneous executive functions in schizophrenia delineate patient subtypes with different symptom profiles, inflammatory levels, and treatment responses: a cross-time clustering and validation study

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Abstract

Introduction: Executive function (EF) is a heterogeneous neuropsychological construct, and impairments in EF dimensions represent a core aspect of psychopathology in schizophrenia that vary across individual patients. Currently, how this inter-individual variability characterizes schizophrenia subgroups, along with their distinctions in clinical characteristics and prognostic outcomes, remains unclear.

Methods: Three EF dimensions (inhibitory control, working memory, cognitive flexibility) were assessed in the main sample (*N*=329), its follow-up subset, and an independently "recurring local validation" patient sample (*N*=114). Fuzzy clustering was applied to baseline EF assessments to discover and validate the core subtypes after excluding cluster-ambiguous cases in the main and independent samples, respectively. Subtype-based classification trained on the main sample was then tested in the independent sample. Importantly, the stability of these subtypes and their remission statuses, along with associated longitudinal changes in clinical and biological factors, were evaluated, and baseline subtype memberships were also used to predict outcomes.

Results: Two longitudinal stable, independently validated core EF subtypes were identified, with significantly variable baseline positive, affective, and cognitive symptoms; working memory updating functioning; and peripheral inflammatory and metabolic levels. This two-subtype differentiation allowed an accurate classification of novel patients' subtype memberships and patients' remission statuses not due to overall severity at intake. Remitted patients experienced significantly greater reductions in negative and cognitive symptoms, improved working memory maintenance, lower peripheral inflammatory levels, and more-superior metabolic functions over time.

***Conclusions*:** EF subtyping successfully captured the symptomatic, biochemical, and prognostic variations in individuals with schizophrenia, which could help to stratify patients with this disorder for targeted treatments.

Keywords: Executive dysfunction, machine learning clustering, prognostic prediction, peripheral immune-metabolic, schizophrenia, subtyping

Introduction

Cognitive impairment is prevalent in patients with schizophrenia and is a core aspect of psychopathology[1]. This deficit emerges in the prodromal phase and persists throughout the illness but is difficult to treat using current anti-psychotics[2]. Symptoms behaviorally measurable by clinical scales, such as the Positive and Negative Symptom Scale (PANSS), are thought to arise from the impairments in functions related to memory, attention, and executive tasks[3,4]. Executive functioning (EF) represents a series of higher-order cognitive processes, which involves impulse control and behavior orchestration[5]. Deficits in EF thus could hinder goal-directed activity and contribute to aggression, violence, and poor compliance with medication, leading to worse clinical outcomes[6]. While EFs are reported to be consistently affected in patients with schizophrenia, these effects have high inter-individual variability (ranging from mildly to severely impaired)[7]. This heterogeneity may allow for differentiating patient subgroups by EF severity to moreover capture different clinical outcomes of schizophrenia. However, to date, a prediction of patient prognostic status in this disorder from baseline data remains challenging.

Multiple attempts have been made to investigate cognitive subtypes in schizophrenia using clustering analysis; these attempts used features from comprehensive neuropsychological assessment batteries, such as the MATRICS Consensus Cognitive Battery and the Brief Assessment of Cognition in Schizophrenia[8]. Besides the commonly identified near-normal (or intact expect EF) and globally (or multidomain) impaired cognitive subgroups, there are intermediate-decline subgroups differentiated by the expression patterns on EF dysfunction[9]. These cognitive subgroups are shown to remain stable over time, except for the multidomain-deteriorated subgroup, with nearly half of affected patients transitioning into the executive-deteriorated subgroup[10]. Furthermore, the deficits of EF in schizophrenia involve multiple aspects, including heightened challenges in inhibiting automatic responses and switching to new responses, diminished cognitive flexibility, and

disruptions in maintaining and updating goal-related or rule-based information in working memory. Importantly, EF deficits have a close link with the multidimensional symptoms in schizophrenia; specifically, patients with the positive and deficit/disorganized symptom subtypes present differentiated cognitive profiles as delineated by executive/attentional functions. Also, EF deficits may contribute to the varying degrees of individual positive, negative, and disorganized symptoms, reflecting their heterogeneous role in psychopathology. Although some dimensions of EF can be more severely affected than others in patients with schizophrenia[11], their characterized EF subtypes remain unclear, with added concerns related to distinctions in symptomatology, longitudinal stability, and the implications for prognostic outcome and remission status.

In the field of psychiatry, prognostic prediction is crucial for early assessment and intervention but remains a significant challenge given prior investigations of entire patient groups employing baseline data mostly have approached chance-level accuracy[12,13]. In turn, subtype-based prediction may be more promising in facilitating timely treatment allocation of patients through stratified medicine[14]. Importantly, cognitive subgroups correlate with clinical outcomes along a spectrum—patients with the greatest deterioration display the highest severity and longest illness duration, whereas those least affected have milder outcomes and shorter duration. Furthermore, EF alone has been frequently suggested to relate to a greater frequency of sustainable remission in patients with schizophrenia[15]. This relationship is also evident for EF dimensional assessments given that performance in EF dimensions differs between remitted and non-remitted patient groups, with previous studies highlighting working memory and inhibitory function as markers for long-term remission status[16,17]. As a consequence, identifying EF subtypes based on baseline multi-dimensional assessments may hold promise for accurately predicting the prognostic status of patients with schizophrenia. Also, it is unclear how patients of subtypes stratified by varying degrees of deficit in EF dimensions experience a change in EFs and symptoms

as well as other biological factors over time to drive a specific remission outcome. In this context, blood immune and metabolic indicators can be highlighted as relevant. Individuals with schizophrenia often show an altered inflammatory state[18] and lipid metabolism[19]. These may underlie the pathological processes of this disorder[20] and contribute to symptom manifestations[21]. Interestingly, lipid metabolites and inflammatory markers like C-reactive protein may precede psychosis onset, fluctuate with illness phases[22], and correlate with clinical outcomes such as changes in PANSS negative subscale scores[23]. Furthermore, there are subgroups in schizophrenia with varying levels of inflammation, and such distinction is linked to cognitive impairments, including in working memory and response inhibition[24]. Moreover, anti-psychotics influence peripheral inflammation[23,25] and metabolic functions, including lipid metabolism[26], and such effects differ among patients with varying responses to these medications[14,27]. Consequently, differences in blood markers have been observed between responders and non-responders[28].

In this study, we used five well-established behavioral paradigms to systematically assess three dimensions of EF in healthy participants and patients. Baseline assessments of these EF dimensions were used to identify core subtypes in schizophrenia from the main sample (N=160) using two fuzzy clustering methods. These subtypes were validated for their replicability and classifiability in an independent "recurring local validation" sample (N=114) recruited at a different time (Fig. 1). Afterward, the longitudinal stability of the subtypes and their relationship with remission status were evaluated in a re-assessed subset (N=86) of the original main sample. A linear mixed model was employed to analyze remission outcomes in relation to changes in EF, symptoms, and peripheral blood assays (including immune and metabolic markers) from baseline to follow-up. Finally, baseline-determined individual subtype memberships were used to predict remission outcomes, indicating potential clinical applications.

Methods

Sample information

We retrieved 160 participants from our prior hospital-based study enrolling 195 individuals with schizophrenia (from March to July 2023) as the main sample. Patients in this sample were aged 18–65 years with complete EF assessments on five task paradigms and peripheral blood assays. A diagnosis of schizophrenia was reached by two resident psychiatrists using the International Classification of Diseases, Tenth Revision, diagnostic criteria for schizophrenia and were screened using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* IV axis I disorders. These patients were clinically stable, with a change in total PANSS score of <20% on a particular type of anti-psychotics at a maintenance dosage within the last 6 weeks. At baseline, 169 healthy individuals matched for age sex, education level, and socioeconomic status (healthy control [HC] group) who did not have a history of mental illness or brain injury were recruited and assessed (Table 1). To test for the replicability and generalizability of identified EF subtypes, a local validation sample of schizophrenia with identical inclusion and exclusion criteria was collected independently 1 year after main sample collection (N = 114). Participants in the validation sample did not overlap with those in the main sample and completed the same assessments. This study was approved by the Ethics Committee at the Third People's Hospital of Lanzhou City and Northwest Normal University (Lanzhou, China; no. NWNU202404). Written informed consent from all participants was obtained.

In the main sample, 86 patients were followed after a 4–6-week interval, which allowed us to evaluate their prognostic statuses. Remission versus non-re mission prognostic status was determined using the RSWG criteria[29], i.e., using scores of ≤3 points on PANSS items (P1, P2, P3, N1, N4, N6, G5, G9). Fift y-eight participants at follow-up were identified as being in remission; the othe r 28 participants were not in remission. Considering a lack of consensus, we u sed an alternative definition of remission defined by reductions in the total PA

NSS score from baseline to follow-up, as follows: 1) a 25% reduction (68 remitted vs. 18 non-remitted); 2) a 35% reduction (48 remitted vs. 38 non-remitted); and 3) a 50% reduction (16 remitted vs. 70 non-remitted)[30]. Symptom severity in each patient with schizophrenia was evaluated using the PANSS[31]. Scores for four symptom dimensions (i.e., positive, negative, affective, and cognitive factors) were derived for each patient using the Dimensions and Clustering Tool for Schizophrenia Symptomatology (DCTS; http://webtools.inm7.de/sczDCTS/)[32]. Higher scores denote more severe symptoms within each dimension.

EF assessments

Seven metrics from five behavioral tasks[33] were employed to assess three EF dimensions, as previously proposed: cognitive flexibility, inhibition, and working memory (Supplemental Table S1). The inhibition dimension included response inhibition and interference inhibition, while the working memory dimension consisted of maintenance and updating[34]. Interference inhibition was measured using the Stroop Color–Word Task (*Reaction Time for Incongruent Stimuli and Stroop Interference Effect*), response inhibition was measured using the Go/No-Go Task (*Accuracy in No-Go Trials*), cognitive flexibility was measured using the Number-switching Task (*Switching Cost*), working memory updating was measured using the Running Memory Task (*Accuracy at 1750 and 750 ms, respectively*), and working memory maintenance was measured using the Digit Span Backward Task[35] (see Table 2 and details in Supplemental Methods).

Peripheral immune and metabolic marker assays

Eight immunoinflammatory indices were assessed. Elevated levels (values) of neutrophils, monocytes, NLR, PLR, MLR, and the systemic immuno-inflammation index may suggest a more severe inflammatory response[36,37]. In contrast, higher lymphocyte and platelet counts within the normal range potentially indicate a milder inflammatory state and better immune function[38].

We also assessed seven metabolic indices, where elevated levels (values) of triglycerides, total cholesterol, low-density lipoprotein cholesterol, lactate dehydrogenase, creatine kinase, and the ratio of aspartate aminotransferase to alanine aminotransferase ratio have been associated with poorer metabolic function, while higher HDL-C levels are associated with more favorable metabolic health[39].

Identification and replication of subtypes using baseline EF assessments

EF scores in the patient group were normalized by the mean and standard deviation values of those assessed in the healthy group and adjusted for age, gender, and education level, using the regression weights evaluated within the healthy population. Then, residuals of EF assessments were used for clustering patients into cognitive subtypes. We applied a FCM clustering technique, which provided cluster membership likelihoods for all patients (details in Supplement)[32]. The optimal cluster number was determined based on the fuzzy silhouette index, the Xie and Beni index, and Kwon's index[40,41] (Supplemental Table S2). As the clustering quality for each number of clusters would be affected by the fuzzifier m (i.e., the exponent for the fuzzy partition matrix [U]; $1 < m < \infty$) parameter, which controls the amount of fuzzy overlap between clusters, we tuned this parameter to determine the optimal value of m from 1.5 to 2.5 with a step length of 0.25 and that of cluster number from 2 to 7[42], based on their achievable clustering quality according to the three evaluation indices. Variability was assessed by the change of values of the three evaluation indices with m values for a particular cluster number; a smaller change refers to better stability, irrespective of the degree of overlaps between clusters. Stability was tested by bootstrap resampling (details in Supplement)[43].

Given the heterogeneous nature of schizophrenia and the observation of multiple patients with ambiguous memberships, a cutoff over the membership likelihoods was adopted to remove cluster-ambiguous patients. For this, additional evidence from GMM was considered (details in Supplement). Specifically, patients were clustered

again using GMM, and the optimal cluster number was determined by the Bayesian information criterion. After assigning patients to the clusters, we took the intersection of the c-means and GMM results. Since patients within the intersection set should have a higher membership degree than those outside, we followed the heuristic idea in our previous work[32] to define a cutoff that effectively discriminates "inside" and "outside" patients while considering the sample size retained for subsequent analyses. Specifically, the c-means membership values of "inside" patients belonging to each cluster were compared with the remaining individuals; a cutoff value thus would facilitate the identification of cluster cores as the "core subtypes" of schizophrenia.

The same clustering approach (i.e., both c-means and GMM) was repeated on the independent "recurring local validation" sample containing 114 patients with schizophrenia.

Characterization of the yielded subtypes

To characterize the "core" EF subtypes following an exclusion of ambiguous cases, one-way analysis of covariance was employed to investigate differences in EF assessments, symptoms, and peripheral blood assays while controlling the effects of sociodemographic variables, including age, gender, and years of education (Fig. 1). Comparisons regarding EF involved both the subtypes and the HC group, while symptoms and blood assays were available for patients. Resulting p values were corrected for multiple comparisons using the false discovery rate method[44].

Subtype-based classification

Furthermore, we tested for whether patients can be accurately classified per subtype using EF assessments (Fig. 1). Essentially, we trained classifiers (random forest) with nested cross-validation (repeated 100 times) on the baseline EF data to discriminate the cluster label of each patient. The optimal model derived from the cross-validation runs, without any further tuning, was applied on the EF data assessed in the independent validation sample once; the predicted labels were then compared with those obtained when re-clustering the validation sample. Performance of the classifier

was assessed using AUC, balanced accuracy, sensitivity, and specificity. In the classifier setting, Subtype II was defined as the positive category, while Subtype I was defined as the negative category. Therefore, "sensitivity" denotes the model's capacity for detecting true positives (Subtype II cases), while "specificity" reflects the ability to accurately identify Subtype I cases. We moreover trained the classifier by additionally including the healthy subject group within the baseline sample (i.e., multi-class classification) and tested it on an independent sample of patients. This approach aimed to determine which subtype was more likely to be misclassified as healthy and which was more distinct from the healthy population in terms of EF assessments.

Longitudinal stability of EF subtypes

The EF characteristics of the follow-up sample (N = 86, with a follow-up period of 4–6 weeks) were firstly mapped onto the cluster centers from the baseline sample (Fig. 1). Specifically, EF re-assessments at follow-up were z-score–standardized by those assessed in healthy subjects at baseline, and the covariates of age, gender and educational level were adjusted using the regression weights estimated on the baseline EF data. Based on the ensuing residuals, the squared Euclidean distance of each patient to the cluster center derived from baseline EF assessments was calculated. Based on the distance metric, membership values were derived for each participant. The fuzziness coefficient was maintained at the same level as in the baseline (m = 2.5). The ensuing membership values were used to assign each participant to a specific cluster, if this cluster, compared to others, had a higher membership value tied to this participant. Patients with a value below the cutoff of 0.6 were filtered out, resulting in two core subtypes in the follow-up data. Subtype labels were compared between baseline and follow-up for the same patients to assess their subtype-membership's longitudinal stability. Patients assigned to the same clusters in both initial and follow-up stages were regarded as longitudinally stable.

The relationship of subtypes with remission outcomes

We used binary logistic regression analysis to investigate whether the two EF subtypes differed in remission outcomes (Fig. 1). In a logistic regression model, remission status (remission vs. non-remissions) served as the dependent variable, with EF subtype acting as the predictor of interest. Effects of sociodemographic variables (age, gender, and educational level) and medication (OZP-equivalent dosage) were adjusted in the logistic model[45]. Remission outcomes of patients were assessed according to the RSWG criteria[29]. Additional analyses were performed using alternative definitions of a remission based on a reduction in total PANSS score.

Remission statuses classification based on baseline cluster memberships of patients

Baseline c-means membership values were used as input features to train a machine learning classifier (see Supplementary Methods) aimed at determining patients' remission status (remission versus non-remission, based on the RSWG criteria)[30]. This approach allowed us to evaluate whether the model tended to classify patients with high Subtype I or Subtype II membership as remission or non-remission. The trained classifier was moreover applied to the patients who were lost to follow-up, which helped test if the discriminated remission conditions were in a ratio similar that which was observed in reassessed patients.

Change in characteristics over time associated with each subtype toward different prognostic statuses

We moreover explored whether patients belonging to different subtypes present varied changes in EFs, symptoms, and blood immune and metabolic indices from baseline to follow-up. This analysis was conducted using multiple linear mixed-effects models[46], incorporating subtype and time point (baseline versus follow-up) as fixed effects. The dependent variables included 1) scores in four dimensions of psychopathology, 2) EF assessments, and 3) peripheral blood immune and metabolic markers. Sociodemographic variables of age, gender, and years of education were

included as covariates, and their effects were adjusted in the model. An interaction effect between time and subtype suggests that the relationship between the dependent variable and one subtype differs from that with the other over time. The resulting statistics were adjusted for multiple comparisons using the false discovery rate method. In addition, when a significant interaction effect occurred regarding peripheral blood markers, we assessed whether their changes would mediate an association between EF subtypes identified at baseline and the symptom-load and EF performance when reassessed through ordinary least squares path analysis of regression[47]. A percentile bootstrapping approach was employed to derive the CI of the indirect effect of possible mediators on subtype of EF/symptom associations. This included repeatedly resampling the original data for 10,000 times and performing the same regression analysis on the resampled data; if the 95% CI of the generated statistics did not across zero, it indicated an indirect effect for a tested mediator.

Complementary analyses

Several analyses were supplemented: 1) While the use of fuzzy clustering approach better aligns with the heterogeneous psychopathology in schizophrenia, we applied, using *k*-means clustering a hard-clustering method to derive binary subgroups, for a more direct comparison. 2) While we adopted a membership value of 0.6 to filter out patients with an ambiguous assignment in our main analyses, we repeated the study with different cutoffs (0.55, 0.65, 0.70) to determine core patient subtypes and compared their EF, clinical symptoms, inflammatory levels, and treatment responses. 3) Given the significant differences in baseline overall symptom severity between the two EF-defined subtypes, we carried out additional analyses to determine whether the differing prognostic outcomes were simply a reflection of baseline symptom severity levels of individual patients. To investigate this, we analyzed the correlation between baseline total PANSS scores and EF assessments. Next, we adjusted for baseline total PANSS scores in our logistic regression analysis to determine if the remission outcomes for each subtype stayed consistent when overall symptom severity wasn't adjusted for,

as in our original analysis. We also assessed diagnostic and prognostic classification based on subtypes derived from EF residuals, additionally adjusting the total PANSS score.

Results

Two replicable core EF subtypes were identified

Fuzzy c-means (FCM) clustering performed on the adjusted and normalized EF assessments revealed an optimal two-cluster solution (Fig. 2A, 2B and Supplemental Figure S1A), which was replicated by using a Gaussian mixture model (GMM), which demonstrated likewise an optimal two-cluster solution in the same data (Fig. 2C). The c-means membership values of patients within the intersection set for each cluster were significantly greater than those outside the cluster and the intersection set defined by c-means and GMM (p <.01, Wilcoxon rank-sum test) (Fig. 2D, 2E and Supplemental Table S3). In this context, a heuristic cutoff at 0.6 was chosen, which effectively discriminated patients inside the intersection set for each cluster from those outside to choose the cluster cores. As a result, two "core" subtypes for schizophrenia of 58 and 75 patients, respectively, were defined after filtering out 27 ambiguous cases (15 and 12 in each original cluster) (Fig. 2D and Supplemental Table S4). This dichotomous differentiation was replicated in the independent sample, which likewise supported a cutoff value of 0.6 that effectively discriminated patients within the c-means GMM intersection set for each cluster and those outside (Fig. 3A, 3B and Supplemental Figure S1B). Using 0.6 as the cutoff value, the proportion of ambiguous cases approached closest between the results derived from the baseline (9%) and the independent local validation (6%) samples, while ambiguous cases grew prominently, especially in the validation sample, when more conservative cutoffs were applied (25% using 0.65, 43% using 0.7) (Fig. 3C). Of note, among the 74 patients lost to follow-up, a similar distribution of cluster memberships was observed (p > 0.35) (Supplemental Figure S2A). The ratio of patients in each subtype (48.6% Subtype I, 41.9% Subtype II) and that in the ambiguous class (9.4%) did not differ significantly from those of patients

who were reassessed (36% Subtype I, 54.6% Subtype II; $\chi^2 = 2.84$, $p = 0.242$). This indicates that our reassessed patients effectively represented the EF heterogeneity of those lost to follow-up.

Subtypes were characterized by varying profiles in EF, symptomatology, and immunometabolics

(1) EF

Except for one variable (Stroop interference effect), which assessed the interference inhibition dimension ($p_{fdr} = 0.86$, $d = 0.064$), the cognitive flexibility (switching cost, $p_{fdr} = 0.021$, $d = -0.396$), response inhibition (accuracy in *No-Go trials*, $p_{fdr} = 0.049$, $d = 0.358$), interference inhibition (variable reaction times [RTs] for incongruent stimuli, $p_{fdr} < 0.001$, $d = -0.569$), working memory updating (*variable accuracy in 1750 ms*: $p_{fdr} = 0.004$, $d = 0.481$; *variable accuracy in 750 ms*: $p_{fdr} < 0.001$, $d = 0.556$), and maintenance ($p_{fdr} < 0.024$, $d = 0.445$) were significantly different between Subtype II and healthy subjects (Fig. 4A and Supplemental Table S5). Compared to healthy subjects, Subtype I patients showed greater restrictions in certain EF deficits, i.e., only response inhibition ($p_{fdr} = 0.049$, $d = -0.011$) and cognitive flexibility ($p_{fdr} = 0.021$, $d = -0.415$). Meanwhile, Subtypes I and II differed significantly in working memory updating (*variable accuracy in 750 ms*: $p_{fdr} = 0.036$, $d = 0.386$).

(2) Clinical scales

Subtype II patients showed greater severity in their multidimensional symptom profiles, with significantly greater scores on three dimensions of PANSS assessments (positive symptoms: $p_{fdr} = 0.002$, affective symptoms: $p_{fdr} = 0.020$, and cognitive symptoms: $p_{fdr} = 0.026$), total PANSS score ($p_{fdr} = 0.011$), total Hamilton Depression Rating Scale (HAMD) score ($p_{fdr} = 0.024$), HAMD cognitive impairment factor ($p_{fdr} = 0.011$), and HAMD retardation factor ($p_{fdr} = 0.040$) as well as the total Hamilton Anxiety Rating Scale (HAMA) score ($p_{fdr} = 0.020$) and HAMA psychic anxiety factor ($p_{fdr} = 0.020$), along with a non-significantly higher baseline anti-psychotic (olanzapine

[OZP])-equivalent dosage (p = 0.09), compared to Subtype I patients (Fig. 4B and Supplemental Table S6).

(3) Peripheral blood assessments

Regarding peripheral blood immune indices, Subtype II patients exhibited a significantly higher neutrophil percentage (p_{fdr} = 0.015), C-reactive protein levels (p_{fdr} = 0.022), neutrophil-to-lymphocyte ratio (NLR) (p_{fdr} = 0.017), platelet-to-lymphocyte ratio (PLR) (p_{fdr} = 0.008), monocyte-to-lymphocyte ratio (MLR) (p_{fdr} = 0.041), and the systemic immuno-inflammation index (p_{fdr} = 0.008) compared to Subtype I patients (Fig. 4C and Supplemental Table S6). In contrast, the lymphocyte percentage (p_{fdr} = 0.009) was significantly lower in Subtype II patients. For peripheral metabolic indices, a significant between-subtype difference was only revealed in the high-density lipoprotein cholesterol (HDL-C) levels, which were lower in Subtype II patients (p_{fdr} = 0.028).

Subtypes can be accurately classified, with more patients in the (milder) Subtype I seeming healthy

Training a classifier within the baseline sample and applied it to the EF assessments of individuals in the validation sample yielded a high discriminative power of the two subtypes (area under the receiver operating characteristic curve [AUC] = 0.79, BAC = 0.72, sensitivity = 0.79, specificity = 0.64) (Fig. 3D and Supplemental Table S7). Repeating the classification analyses on subtypes derived by alternative cutoff values in each patient's membership degree yielded inferior performance (Supplemental Table S7). Including HC when training the classifier misclassified more Subtype I patients (19/74) in the validation sample as healthy than those in Subtype II (5/40) (Fig. 3D).

Subtypes were longitudinally stable

Among the 86 patients with repeated EF assessments, 78 patients were identified as exhibiting the core subtypes, while eight demonstrated an ambiguous cluster

membership (highest membership degree < 0.6). The longitudinal stability analysis showed that more than 90% of the reassessed patients retained their subtype, with three patients each from subtypes I and II shifted to the ambiguous cluster at follow-up (Fig. 5A). One ambiguous case at baseline was assigned to Subtype I at follow-up, while three were assigned to Subtype II. Longitudinal stability decreased when more stringent cutoffs were used over the membership values, i.e., 80% for 0.65 and 74% for 0.7 (Supplemental Figure S3).

Patients of different subtypes differed in remission outcomes that can be moreover predicted from baseline EF performance

The regression analysis, adjusting for baseline OZP dosage, revealed that EF subtype was a significant predictor of remission status when using RSWG criteria (p = 0.013) (Fig. 5C). Specifically, patients with EF Subtype II were significantly less likely to achieve remission compared to those with Subtype I (odds ratio = 0.203, 95% confidence interval [CI] [0.058, 0.714]). The robustness of these results was confirmed through sensitivity analyses using alternative remission criteria based on different total PANSS score reduction thresholds (35% and 50%) (see Supplemental Figure S4).

The classifier achieved an AUC value of 0.78 in the follow-up subset sample, which indicated that the model was more inclined to classify individuals with higher baseline EF Subtype I membership as in remission and those with higher baseline EF Subtype II membership as in non-remission (Fig. 5C and Supplemental Figure S5). The classification performance was comparable when using a PANSS 50% (AUC = 0.76) reduction criterion but was lower when PANSS 25% (AUC = 0.66) or 35% (AUC = 0.65) thresholds were applied (Fig. 5C and Supplemental Table S7). Among the cases accurately classified by the model, patients assigned to the remission group had significantly higher baseline EF Subtype I membership values (mean: 0.80) than those classified as non-remission cases (mean: 0.19) (p < 0.001) (Fig. 5C). In addition, applying the classifier on the baseline memberships of unfollowed patients resulted in the proportion of remitted and non-remitted conditions being similar to the observed

conditions in followed patients (χ^2 = 0.023, p = 0.879 for Subtype I, χ^2 = 0.078, p = 0.780 for Subtype II) (Supplementary Figure S2B).

Subtype I had a better characteristic change over time toward remission

(1) Symptomatology

Both subtypes showed a significant reduction in PANSS negative, positive, affective, and cognitive symptom scores following treatment ($p_{fdr} < 0.001$) (Fig. 5B and Supplemental Table S8). Significant interactions between subtype and time were observed for the negative (p_{fdr} = 0.025) and cognitive symptom dimensions (p_{fdr} = 0.036). Post-hoc analyses revealed that the reduction in negative symptoms over time was significantly more pronounced in Subtype I than in Subtype II. Specifically, although the two subtypes did not significantly differ in negative symptom dimensional scores at baseline (p_{fdr} = 0.139), Subtype I showed significantly lower scores than Subtype II at follow-up ($p_{fdr} < 0.001$). Likewise, no significant difference was detected between subtypes at baseline for cognitive symptoms (Subtype I < Subtype II; p = 0.193), but such contrast became more significant during follow-up ($p_{fdr} < 0.001$).

(2) Executive functioning

The results showed a significant subtype-by-time interaction (p_{fdr} = 0.003) for working memory maintenance (Fig. 5B and Supplemental Table S8). Post-hoc analyses indicated that, although the two subtypes did not differ significantly in working memory maintenance capacity at baseline (p_{fdr} = 0.246), Subtype I had significantly higher scores than Subtype II at follow-up ($p_{fdr} < 0.001$) and its baseline assessment (p_{fd} = 0.037). However, no significant improvement was noted for Subtype II patients during follow-up (p_{fdr} = 0.749).

(3) Peripheral blood indices

We found significant subtype-by-time interactions for the peripheral immune markers lymphocyte count and platelet count, along with the metabolic marker lactate dehydrogenase (all $p_{fdr} < 0.05$). Post-hoc multiple comparisons showed no significant

differences between the two subtypes in these markers at baseline ($p_{fdr} > 0.05$) (Fig. 5B and Supplemental Table S8). However, at follow-up, Subtype II had significantly higher platelet counts ($p_{fdr} < 0.001$) than Subtype I and its baseline assessment. Similarly, lactate dehydrogenase levels were significantly higher in Subtype II compared to Subtype I at follow-up ($p_{fdr} < 0.001$). While there was a non-significant increase in lactate dehydrogenase for Subtype II over time, a reversed pattern was seen in Subtype I, where the lactate dehydrogenase level at follow-up was significantly decreased from that at baseline ($p_{fdr} = 0.003$). The lymphocyte count for patients in Subtype I was also significantly decreased in re-assessment ($p_{fdr} = 0.018$), but, for those in Subtype II, no observation of such a significant reduction was made. Furthermore, we found the change in lactate dehydrogenase levels to significantly mediate the association between EF subtype and the negative symptoms assessed at follow-up (indirect effect: −0.147, 95 % CI [−0.331, −0.011], $p = 0.033$) (Fig. 5C).

Collective features of EF subtypes

Overall, patients with Subtype II showed poorer initial conditions and outcomes relative to those with Subtype I. At baseline, patients with Subtype II showed weaker performance in interference inhibition, working memory updating, and maintenance relatively to healthy individuals (Fig. 6A). These patients similarly demonstrated more severe positive and cognitive symptoms, retardation, and anxiety affective symptoms and higher levels of multiple peripheral immune-inflammatory markers (neutrophils, C-reactive protein, NLR, PLR, MLR), and a metabolic index (high-density lipoprotein cholesterol) relative to Subtype I patients (Fig. 6B). Accordingly, patients within Subtype I have a better prognosis; they are significantly more likely to achieve remission, and individuals with higher baseline Subtype I memberships are often classified as in remission (Fig. 6C). Subtype I patients experience significantly larger reductions in negative and cognitive symptoms, improved working memory maintenance, more stable peripheral immune-inflammatory levels, and superior

metabolic functions (lower lactate dehydrogenase levels) over time than those in Subtype II (Fig. 6C).

Supporting findings

1. In *k*-means clustering, the validity indices and stability analysis both pointed to an optimal solution at cluster number 2 (Supplemental Figure S6), which was likewise obtained using fuzzy clustering. Patients in the two clusters yielding from *k*-means were overlapped with the c-means–derived Subtypes I and II (58 and 75 patients, respectively). However, as follows: 1) The performance of subtype-based classification was markedly reduced (AUC = 0.61) (Supplemental Table S9). 2) The *k*-means method does not provide cluster membership information, and hence it cannot identify cluster-ambiguous samples at baseline. This approach also demonstrated lower longitudinal stability (76/86 [88.37%] patients stable) compared to ambiguous cases filtered out (72/78 [92.31%]) (Supplemental Table S9). 3) *K*-means clusters were significantly associated with patients' remission outcomes using two different definition criteria (RSWG: $p = 0.011$; 50% reduction in total PANSS score: $p = 0.029$), albeit less so than in our main results, where this association was significant in three definition criteria (Supplemental Figure S6, Table S9). 4) *K*-means subtypes failed to capture a significant difference in working memory maintenance capacity between baseline and follow-up assessments (all $p_{fdr} > 0.05$), while the FCM derived Subtype I but not Subtype II ($p_{fdr} = 0.0373$), which improved specificity (Supplemental Table S9).

2. The patients of core subtypes using different membership thresholds (0.55, 0.65, 0.70) replicated the between-subtype differentiations in baseline clinical symptoms, inflammatory markers, and EFs (except for an absent difference in response inhibition with cutoff 0.65) (Supplemental Table S9), as well as remission outcomes (Supplemental Figure S7). For prognostic classification of remission statuses, the main analysis using a membership of <0.60 as the threshold achieved an AUC of 0.78, which was decreased to 0.71 (0.55 and 0.65 membership cutoffs) and 0.65 (0.7 cutoff) (Supplemental Table S9). A similar declining pattern was observed for subtype-based

515 classification with an alternative membership cutoff value (0.7 as the worst: 0.61)
516 (Supplemental Table S9).

517 3. Only one EF variable, which measures interference inhibition, showed a
518 significant correlation with the total PANSS score (r = 0.3, p_{fdr} = 0.033). Adjusting
519 baseline total PANSS score did not alter the significant finding when this score was not
520 controlled in the logistic regression model (all ps < 0.033; Supplemental Figure S8).
521 Repeating our clustering approach on EF assessments with additional adjustment for
522 baseline total PANSS score likewise revealed an optimal solution of two clusters
523 (Supplemental Figure S9A), along with an indication of a 0.6 cutoff over the
524 membership values to derive core subtypes (Supplemental Figure S9B). Between-
525 subtype differentiations were also replicated, except for some measurements in EF and
526 blood immune assays, which were significantly (or moderately) correlated with
527 individual baseline total PANSS scores (e.g., RT in incongruent stimuli, NLR, and
528 PLR). The emerged EF subtypes showed comparable performance in subtype-based
529 classification (AUC = 0.78) (Supplemental Figure S9C) but poorer performance in
530 prognostic classification (AUC = 0.70) when compared to our main results
531 (Supplemental Figure S9D).

532 # Discussion

533 In this study, we used two fuzzy clustering methods to derive core subtypes for
534 schizophrenia based on EF dimensions assessed using five well-established behavioral
535 paradigms. The findings' replicability was confirmed with an independent "recurring
536 local validation" sample. Our results pointed to a two-subtype differentiation, wherein
537 patients were characterized by 1) specific EF deficits in response inhibition and
538 cognitive flexibility (Subtype I) and 2) general EF deficits in all assessed dimensions
539 compared to healthy participants (Subtype II). These two subtypes moreover differed
540 in working memory updating function, along with multiple symptoms and
541 inflammatory and metabolic indices. Using individual EF features from the main
542 sample moreover allowed an accurate classification of patient subtype memberships in

the independent sample. Most patients (92.31%) in the core subtypes kept their subtype-memberships over a 4–6-week follow-up period. Importantly, the subtypes showed varying responses to treatment, with Subtype I more likely to achieve remission, and this difference was not attributed to a difference in overall severity at baseline. Using baseline subtype memberships, remission statuses can be classified with a high discriminative power. Finally, we observed remitted patients to experience significantly larger reductions in negative and cognitive symptoms, improved working memory maintenance, more stable peripheral inflammatory levels, and superior metabolic functions over time.

The importance of cognitive impairments in schizophrenia and their heterogeneity in severity across individual patients have promoted attempts to derive subgroups based on neuropsychological assessments. These attempts have used comprehensive cognitive batteries covering multiple domains that are thought to be affected in patients with schizophrenia. Using cluster analysis and latent profile analysis, previous studies have yielded inconsistent numbers (2–4) of cognitive subgroups according to the varying assessment tools adopted and patient cohorts recruited. These cognitive subgroups generally include a virtually intact and a globally impaired cohort, respectively, with also an intermediate (or selective) impairment cluster usually produced[10,48,49]. Interestingly, such an intermediate subgroup has been further divided by a differential performance in EFs[10,48,50], pointing to a critical role of EF in dissecting the cognitive heterogeneity in schizophrenia. However, previous studies have treated EF as a unidimensional construct when leveraging a broad range of cognitive assessments that overlooked the multi-dimensional aspects of EF. Here, we tapped into the neuropsychological processes underlying three EF dimensions with seven variables derived from five behavioral paradigms and used a fuzzy-clustering approach to depict the heterogeneous EF profile in schizophrenia. This yielded two core subtypes for patients with schizophrenia after filtering out cluster-ambiguous cases. Subtype I exhibited deficits in response inhibition and cognitive flexibility, comparable with

Subtype II, while Subtype II demonstrated more severe deficits in working memory updating function apart from additional deficits in interference inhibition compared to healthy participants. In particular, existing literature consistently highlights that inhibition function, cognitive flexibility, and working memory exhibit significant inter-individual heterogeneity, with patient performance ranging from preserved to severely impaired[10,52,53]. In our recruited schizophrenia cohort, these cognitive functions showed compromised performance regardless of subtyping. However, the varying severity of impairment in inhibition distinguished two subgroups that further showed significant differences in working memory updating function. Variations in EF subdomains have been shown to have genetic[9] and neurobiological underpinnings[54], contributing to different psychopathological processes[55]. Indeed, patients with a severe deficit in working memory are found to have high positive symptoms and low cognitive functioning[56]. Our EF subtypes differed in baseline positive and cognitive symptoms, along with affective problems. Also, there are prior observations that negative and disorganized symptoms are associated with distinctive working memory deficits in patients with schizophrenia[56]. Our longitudinal analyses extended to a dynamic association between working memory maintenance (relative to updating, as more evidently differed between subtypes in baseline) performance improvement and the reduction of negative and cognitive symptoms in one of the subtypes (with a tendency toward remission) over time. Previous research exists linking better executive functioning to a more likely remission outcome in schizophrenia[57,58]. In particular, specific executive processes, such as interference inhibition and working memory, have been strongly associated with symptom remission[15,17,59]. Delving into the mechanisms underlying such relationships pointed to multiple processes that may contribute to the emergence and aggregation of several behavioral symptoms. For example, impaired working memory could undermine patients' capacity to maintain and manipulate mental representations, affecting abstract thoughts and reasoning as well as the processing of emotional cues, thus increasing the risk of developing negative symptoms (e.g., apathy

and diminished expressive behavior)[60,61] while aggravating cognitive and affective symptoms[56,62].

Moreover, Subtype II patients with worse EF performance, greater symptom severity, and a reduced likelihood of being classified as healthy (hence, being more distinctly different from healthy subjects' condition) with a poor prognostic outcome further exhibited significantly elevated baseline inflammatory levels (e.g., higher NLR and C-reactive protein levels) and reduced metabolic function (e.g., lower high-density lipoprotein levels) than those patients with Subtype I. Elevated inflammatory levels have been associated with impairments in specific cognitive functions, such as inhibitory function[24,63,64] and working memory[65]. Moreover, patient subgroups of schizophrenia with varying levels of inflammation were also found to be distinctive in working memory. This relationship is likely mediated by inflammation's effects on the function central executive network in the brain. This effect from peripheral inflammation can occur through multiple pathways, as detailed in previous studies on brain immune cross-talk[63]. Neuroinflammation is also common in schizophrenia, which may exert a more direct impact on functional brain dysconnectivity, thus reducing cognitive functions[66]. Furthermore, anti-psychotics can worsen lipid metabolism while lowering high-density lipoprotein, which has been related to treatment responses, e.g., symptom reduction and daily function recovery.

Importantly, patients in Subtype I, having higher rates of remission, experienced lower lymphocyte and platelet counts than those in Subtype II, which means that individuals in Subtype II had higher levels of immune abnormalities. Previous evidence suggests that elevated lymphocyte counts are a marker of immune abnormalities in schizophrenia[67], where patients having relatively normal lymphocyte counts at the start of treatment showed better responses to anti-psychotic treatment[68]. Also, higher lymphocyte counts, along with a better NLR, are related to overall symptom severity as well as negative and depressive symptoms. Greater changes in PANSS negative subscalescores have been linked to lower baseline platelet counts[23]. Our results suggest

627 that a lower baseline NLR level and reductions in lymphocyte and platelet counts over
628 time relate with more alleviated negative and cognitive symptoms in patients of
629 Subtype I. Furthermore, a decrease in metabolic index parameters, specifically the
630 lactate dehydrogenase level, is found to significantly mediate the association between
631 EF subtypes and their negative symptoms at follow-up, with the decrease being more
632 evident in the milder Subtype I population within schizophrenia. In contrast, an increase
633 in lactate dehydrogenase has been shown to indicate adverse outcomes, such as
634 prominent extra-pyramidal symptoms and the occurrence of violence[69,70].

635 Methodologically, our use of a fuzzy clustering approach to identify cluster-
636 ambiguous patients along continuous EF dimensions matches with a heterogeneous
637 construct of schizophrenia psychopathology and resonates well with the notion that
638 some patients with schizophrenia may not have a clear subtype attribution but lie
639 between more differentiated subtypes or deviate from them given a possibly high
640 continuum in this disorder[71]. In contrast, previous subtyping investigations relied on
641 hard clustering methods (e.g., *k*-means clustering), which assume that each patient has
642 a cluster attribute and the constituted subtypes represent separate, non-overlapping
643 groups[48,49]. While clustering provides common patterns, binary-divisions would
644 contradict with the continuous individual expression along EF dimensions given that
645 EF impairments in patients with schizophrenia represent a spectrum[51]. The
646 heterogeneity is reflected in a varying degree of such impairments across dimensions.
647 Therefore, a soft-clustering approach that allows each individual to belong to multiple
648 clusters with varying memberships better aligns with the differential individual
649 expression level in each EF dimension. Indeed, our application of *k*-means clustering
650 for a direct comparison showed worse subdivisions for schizophrenia, which were more
651 difficult to classify from baseline EF assessments, with poorer longitudinal stability and
652 less robustness to predict outcomes using different ways of defining remission and a
653 lower specificity in capturing a differential change of performance in EF over time. The
654 superiorities of using fuzzy clustering we showed here resonate well with previous

practices in schizophrenia[32] and beyond[72,73], i.e., that this approach derived clusters with enhanced biological interpretability and clinical usefulness to enable a more accurate representation of individuals' disease trajectories where subjects can have mixed characteristics[74]. Furthermore, the membership values yielded from baseline data using fuzzy clustering allowed a discrimination of remission statuses when re-assessed. Interestingly, our subtype-based diagnostic classification, which treated Subtype II as the positive class and Subtype I as the negative class, yielded greater sensitivity (0.79) for detecting positive cases with a poorer remission outcome (Fig. 3D and Table S7). This indicated that our machine learning classifier is particularly adept at detecting patients who are more severe at baseline and are more likely not to be remitted as it is able to classify them as negatives. Clinicians may leverage this model to identify patients who are more likely to experience poor treatment response at earlier stages using the current model.

Several limitations can be mentioned. First, although creating a subtyping framework that is generalizable across various clinical sites and diverse patient populations would be ideal and remarkable, we here adopted a "recurring local validation" method, which involved an independent sample collected at different points within the same medical center. Importantly, this approach has gained increased appreciation in recent years due to repeated practical challenges in developing generic models applicable in clinical psychiatry. Notably, it is suggested to be a means to improve the utility and feasibility of developing machine learning tools that support local medical services. Our strategy of "recurring local validation" hence aligns with emerging artificial intelligence–driven healthcare paradigms, which aim to prevent performance variations and (most likely) degradation across different populations and facilities[75]. Nevertheless, future studies might consider incorporating additional sites in their analyses. Methods such as federated learning can help fine-tune and optimize machine learning models to enhance their performance and generalizability without the need to share individual raw data, thus addressing potential ethical concerns and data

683 privacy constraints across clinical centers. Second, we used detailed EF assessments
684 for subtyping schizophrenia, in contrast with previous studies that evaluated EF as a
685 single construct. Future research could incorporate behavioral assessments from other
686 cognitive domains to explore whether additional subtypes might emerge, allowing for
687 finer differentiation within the heterogeneous patient population. Third, the present
688 work examined several inflammatory and metabolic indices to explore their relations
689 with EF subtypes and corresponding prognostic statuses, but future research is
690 encouraged to evaluate additional factors like glucose and amino acid metabolism (e.g.,
691 glutamate) and pro-inflammatory cytokines (e.g., interleukin-6, interleukin-1β, and
692 tumor necrosis factor–α), which have been associated with schizophrenia's
693 pathophysiological underpinnings, treatment responses, and psychopathological
694 processes[65]. Therefore, these evaluations will help delineate a more comprehensive
695 immunometabolic profile to better characterize cognitive-based schizophrenia subtypes.
696 Finally, although our attrition rate aligns with previous reports[76,77], it raises questions
697 about potential selection bias. However, our complementary analyses demonstrated that
698 the followed patients represented a more general patient cohort with respect to baseline
699 characteristics and the distribution of subtype-memberships, including those were lost
700 to follow-up. Moreover, the prognostic classifier, which was trained on reassessed
701 patients, showed similar proportions of discriminated remitted versus non-remitted
702 conditions in participants not followed up with compared to those observed in the
703 reassessed patients (Supplemental Figure S2A, 2B). Nevertheless, future studies should
704 focus more on managing attrition rates, even though increasing patient adherence to
705 longitudinal study designs remains challenging.

706 In conclusion, multi-dimensional EF assessments differentiated two longitudinally
707 stable subtypes for schizophrenia. These subtypes captured differences in baseline
708 symptomatic and peripheral immunometabolic features, as well as (importantly)
709 prognostic implications, with one subtype demonstrating more prominent symptom
710 reduction, EF performance improvement, and metabolic function recovery over time.

Baseline EF assessments moreover facilitated out-of-sample subtype classification, where the individual membership degrees from our fuzzy clustering approach successfully differentiated patients' remission statuses. Together, these results will assist in stratifying the schizophrenia population for targeted treatments and offer insights into identifying patients more likely to have poor prognoses, allowing for the application of effective interventions at an earlier stage.

Statement of ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. All procedures involving human subjects/patients were approved by the Ethics Committees at the Third People's Hospital of Lanzhou City and Northwest Normal University (Lanzhou, China; ethics approval no. NWNU202404). All participants provided written informed consent after receiving comprehensive information about the study aims, procedures, potential risks, and benefits.

Declaration of interest

None.

Author contributions

T.Y.Z., J.C. and X.Z. conceived and designed the study. T.Y.Z. and X.N.H. acquired and curated the clinical, neuropsychological, and inflammatory data. T.Y.Z. performed the clustering and longitudinal validation analyses. J.C. and X.Z. supervised the methodological development and statistical interpretation. T.Y.Z., J.C. and X.Z. drafted the manuscript. All authors critically revised the manuscript for important intellectual content and approved the final version to be published.

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Data availability statement

Information for the main sample used in the present study has been included in the Supplementary Materials. The raw data of the sample used in this study are protected and not publicly available due to data privacy. These data can be accessed upon reasonable request made to the corresponding author (X. Z.). Derived data supporting

the findings of this study are available from the corresponding authors (X. Z. or J. C.) upon request.

Code availability statement

Scripts to run the main analyses have been made publicly available and can be accessed at https://github.com/Code_Heterogeneous_EFs_in_SCZ.

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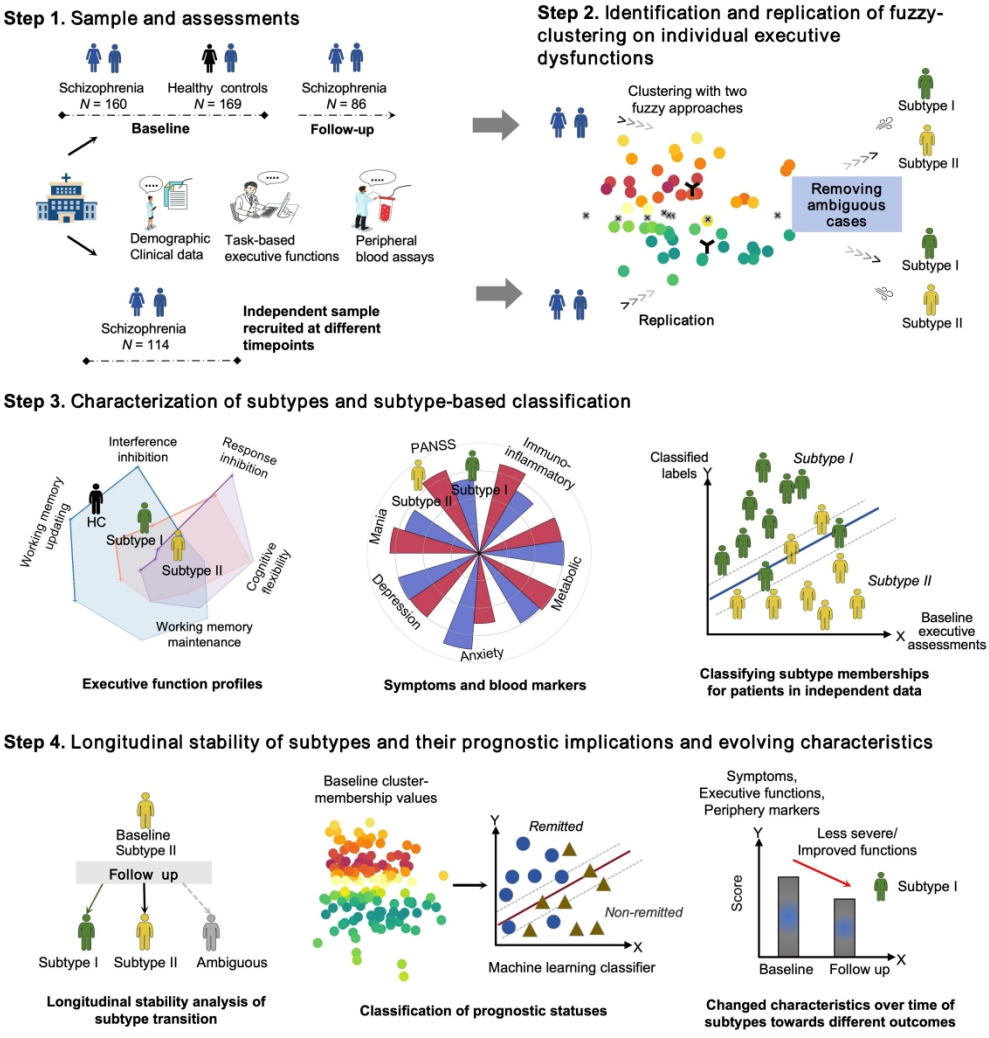

Figure 1. Study overview.

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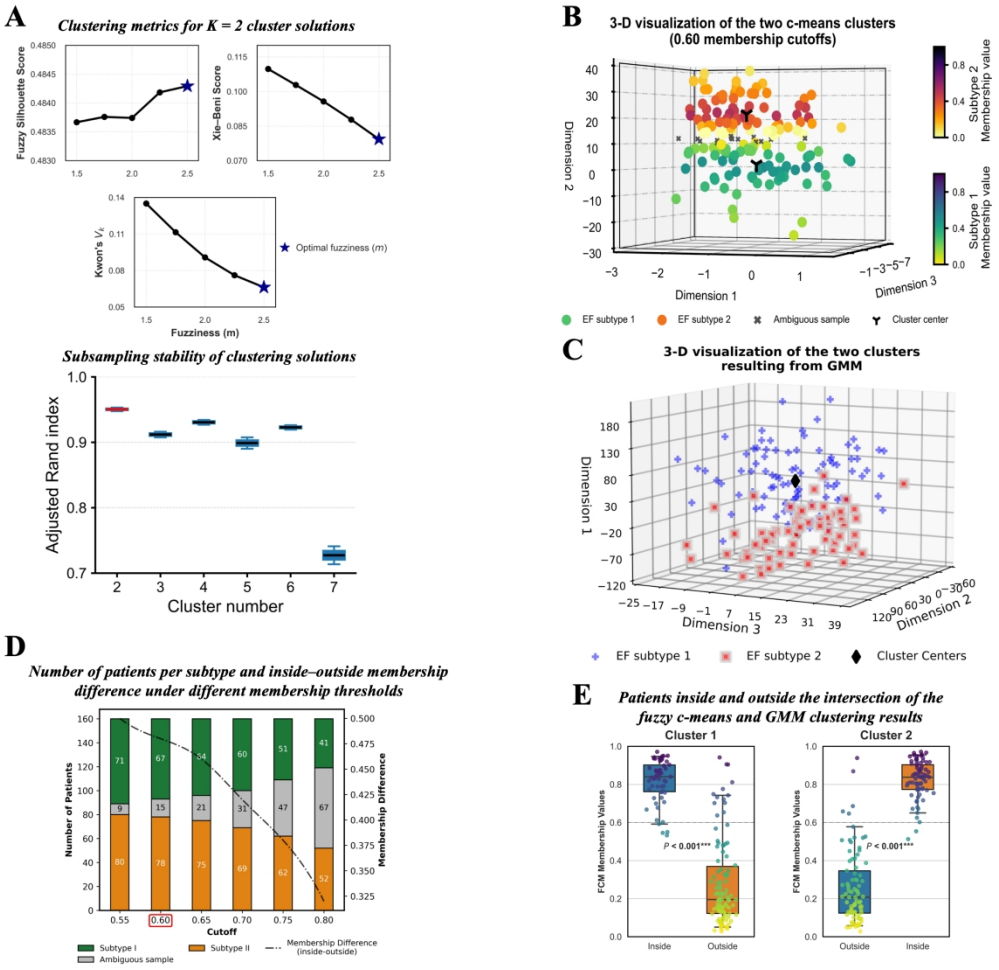

Figure 2. FCM clustering on baseline EF data.

Note: A) FCM clustering results for EF features in the baseline sample. This included clustering quality indices and subsampling (85%) stability assessment repeated for 1,000 times, with higher adjusted Rand index values indicating greater stability. B) The sample distribution results of schizophrenia patients (N =160) in the FCM clustering model (k = 2, m = 2.5). Clustering was based on seven EF indicators. To facilitate visualization, principal component analysis was used to reduce the dimensionality of these indicators, and we took the loading values on the first three components following the principal component analysis. The FCM membership values of each sample are color-mapped in the scatterplot. The black "x" markers between the two subtypes represent ambiguous samples (N = 15). C) The optimal clustering result of the GMM for EF input values. The blue "+" in the plot represents the sample distribution of EF Subtype I, while the red "+" represents the sample distribution of EF Subtype II. D) The number of patients in Subtype I, Subtype II, and ambiguous class under different membership thresholds. The curve represents the membership difference values (inside − outside). E) The distribution of inside and outside sample FCM membership values for clusters 1 and 2. The inside degree is the c-means membership values of patients assigned to the same cluster by GMM and FCM, while other patients are outside.
*p < 0.05, **p < 0.01, ***p < 0.001.

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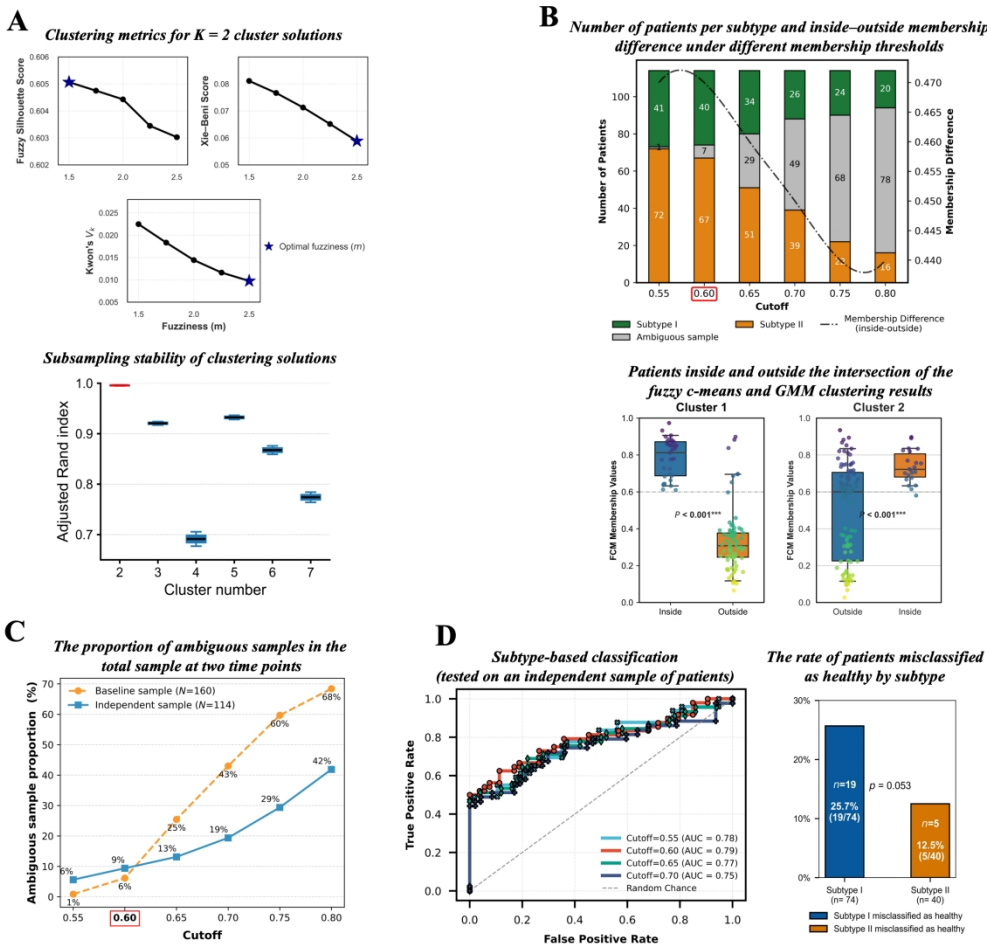

Figure 3. Recurring local validation.

Note: A) shows the results of re-clustering EF features in the validation sample (N = 114) using FCM, with the clustering procedure consistent with the baseline sample. This includes clustering quality indices and subsampling (85%) stability assessment repeated for 1,000 times, with higher adjusted Rand index values indicating higher stability. B) The upper plot displays the quantity distribution of "inside" and "outside" samples under different membership thresholds, with the curve representing membership difference values (inside − outside). The lower plot shows the distribution of inside and outside sample FCM membership values for clusters 1 and 2. The inside degree is the c-means membership values of patients assigned to the same cluster by GMM and FCM, while other patients are outside. C) shows the change in the proportion of ambiguous samples in the total sample as the membership cutoff varies at two time points (baseline vs. validation sample recruited at a separate time). D) Classifiers were trained based on baseline EF assessments and used for predicting the subtype labels in the validation sample. The true subtype labels of the validation sample were obtained by independently re-clustering using the same parameter procedure as the baseline sample. Classifiers were also trained on the pooled categories (subtype 1, subtype 2, HC). In the validation sample, patients in Subtype I were more frequently misclassified as healthy than those in Subtype 2.

*p < 0.05, **p < 0.01, ***p < 0.001.

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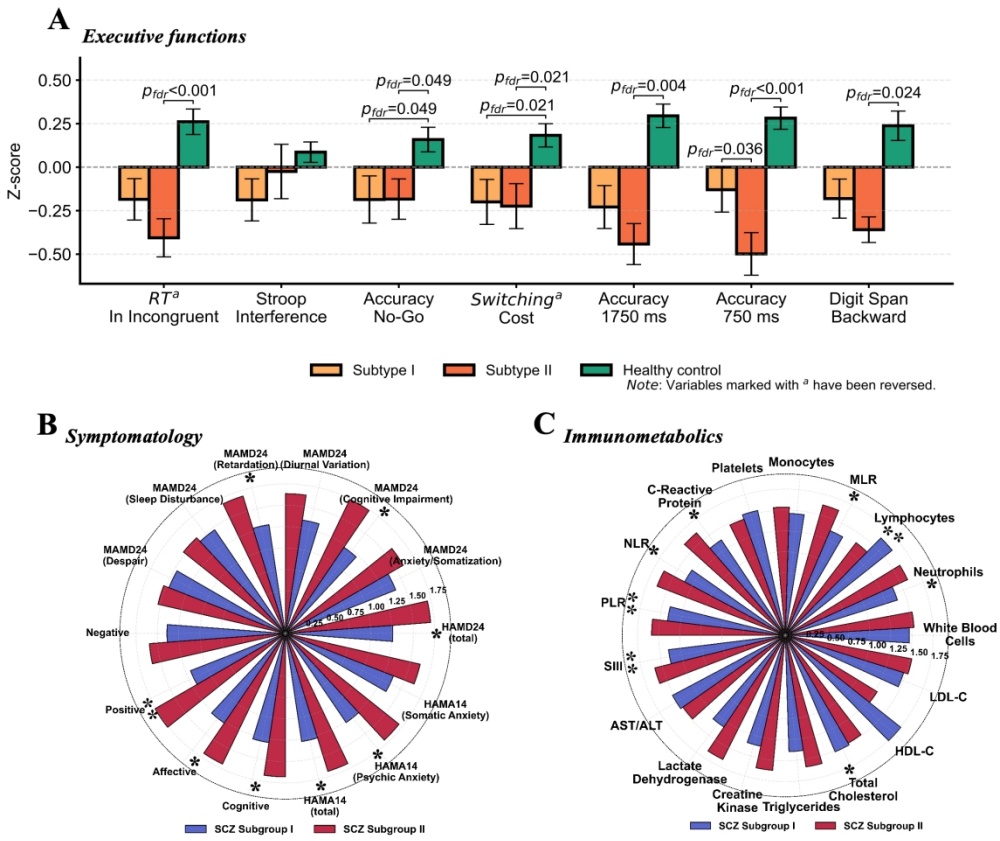

Figure 4. Comparison of EF assessments, clinical symptoms, and peripheral blood markers between subtypes.

Note: One-way analysis of covariance was performed to test potential differences between the subtypes in A) EF assessments, B) clinical symptoms, and C) peripheral blood markers (inflammation and metabolic), controlling for socio-demographic variables (age, gender, and years of education). All results were corrected for multiple comparisons using the false discovery rate method.Abbreviation: SCZ, schizophrenia.*p < 0.05, **p < 0.01, ***p < 0.001.

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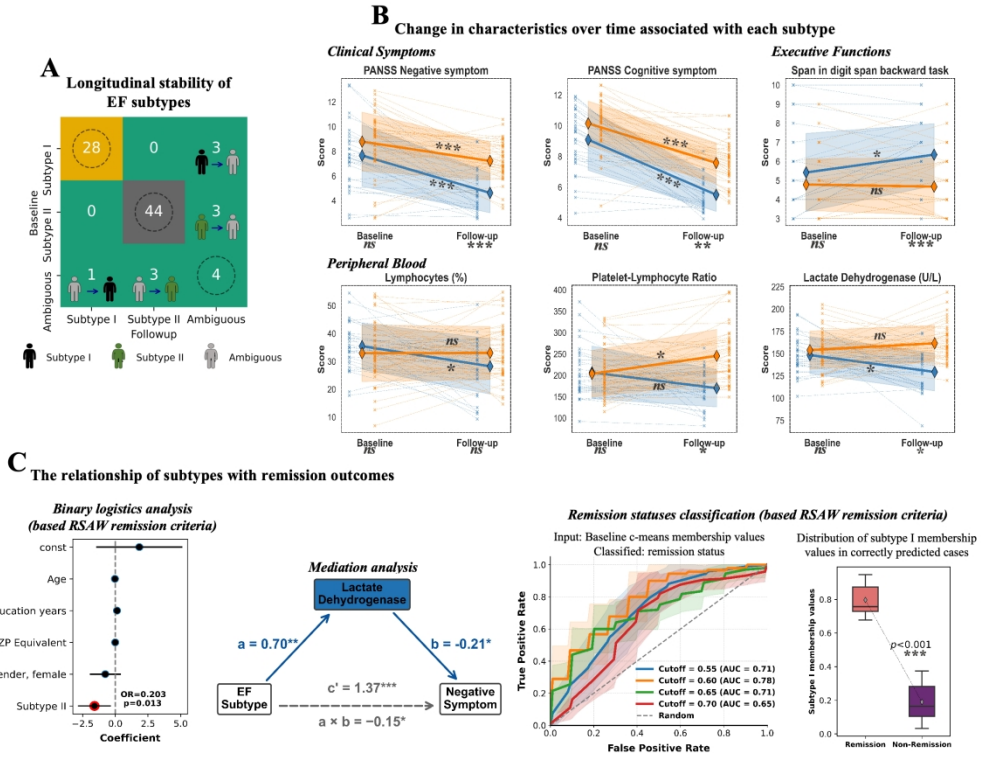

Figure 5. Longitudinal stability and change of characteristics over time associated with each subtype toward different prognostic statuses.

Note: A) shows the longitudinal stability results of EF subtypes under different FCM membership cutoff conditions. The EF subtype labels of the follow-up sample were calculated by mapping the EF features at the follow-up stage to the cluster centers of the optimal model from the baseline sample. The consistency between the subtype labels of the follow-up sample and the baseline sample was evaluated through consistency calculations. Black circles indicate stable individuals (i.e., subtype labels remained consistent between baseline and follow-up stages). B) presents the analysis of changes in characteristics over time, showing the difference test results between the two EF subtypes in (1) clinical scales, (2) EFs, and (3) peripheral blood. Each line represents a patient. Blue line represents Subtype I; orange line represents Subtype II. The significance markers on the x-axis indicate differences between baseline and follow-up groups (controlling for sociodemographic variables, including age, gender, and years of education). The significance markers on the lines indicate within-group differences between Subtypes I and II (controlling for sociodemographic variables). All analyses were adjusted for demographic variables (age, gender, and educational level). C) Binary logistic regression analysis examined whether one EF subtype was more likely to achieve remission after treatment. Significance was determined based on odds ratios. Mediation analysis was performed with path a representing the effect of EF subtypes on the change of lactate dehydrogenase over time. Path b tested the influence of this mediator on negative symptoms assessed at follow-up. c'denotes the direct effect, while a × b represents the indirect (mediation) effect. Baseline EF FCM membership values were used to classify the patients' remission outcomes (remission vs. non-remission, according to RSWG criteria). The box plot on the right panel shows the Subtype I membership values for all corrected classified patients per their remission or non-remission condition.

ns: not significant difference. *p < 0.05, **p < 0.01, ***p < 0.001.

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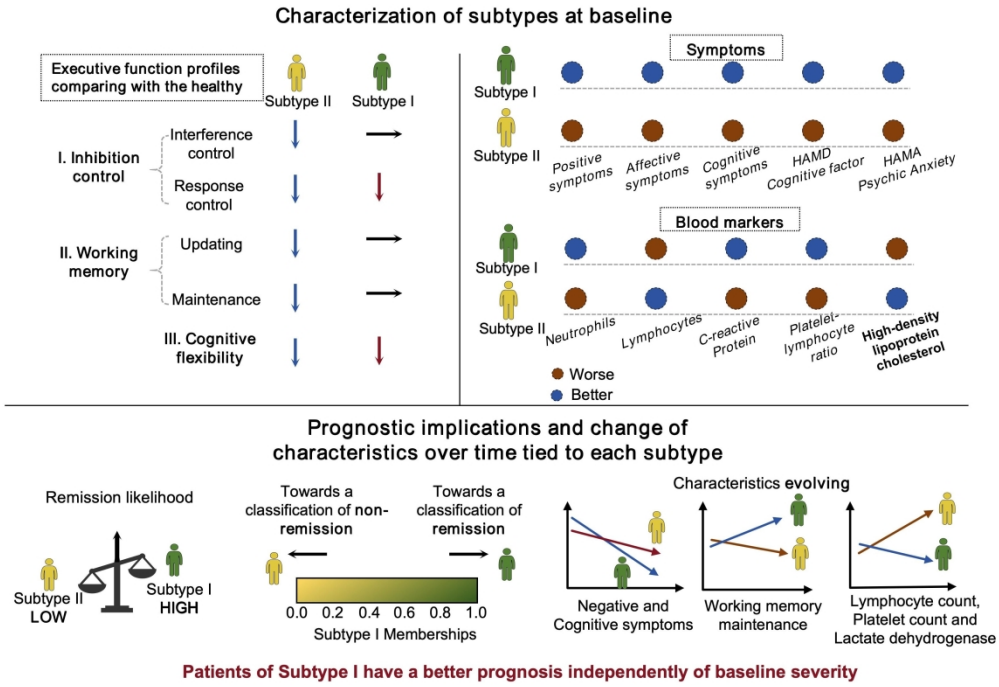

Figure 6. A summary of subtype characterizations.

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Table 1. Demographic, clinical, and EF characteristics of participants

	Baseline sample		Independent sample		
(M ± SD) / *n* (%)	Schizophrenia (*N*= 160)	Healthy controls (*N*= 169)	Schizophrenia (*N*= 114)	*statistic value*	p_{fdr}
Demographic variables					
Age	35.21 ± 9.53	37.69 ± 13.71	36.46 ± 9.65	−1.9133[a] 0.890[b] −1.057[c]	0.227[a] 0.746[b] 0.583[c]
Sex					
Male	97 (60.62%)	88 (52.07%)	75 (65.79%)	2.108[a] 4.699[b] 0.555[c]	0.234[a] 0.048[b] 0.730[c]
Female	63 (39.38%)	81 (47.93%)	39 (34.21%)		
Ethnicity, Han	142 (88.75%)	152 (89.94%)	93 (81.58%)	0.029[a] 3.407[b] 2.248[c]	0.987[a] 0.087[b] 0.682[c]
Education, years	10.88 ± 4.51	10.90 ± 3.94	10.71 ± 4.27	−0.032[a] 0.370[b] 0.319[c]	0.974[a] 0.746[b] 0.750[c]
BMI	23.63 ± 3.78	23.95 ± 4.32	24.58 ± 4.30	−0.713[a] −1.215[b] −1.900[c]	0.635[a] 0.746[b] 0.235[c]
Residence, urban	92 (57.50%)	98 (57.99%)	62 (54.39%)	<0.001[a] 0.228[b] 0.151[c]	1.000[a] 0.633[b] 0.797[c]
SES	23.16 ± 7.61	23.88 ± 5.80	23.61 ± 7.73	−0.961[a] 0.325[b] −0.470[c]	0.635[a] 0.746[b] 0.750[c]
Employed, yes	40 (25.00%)	111 (65.68%)	38 (33.33%)	53.148[a] 27.290[b] 1.879[c]	<0.001[a] <0.001[b] 0.682[c]
Only child, yes	53 (33.12%)	24 (14.20%)	32 (28.07%)	15.380[a] 7.399[b] 0.576[c]	<0.001[a] 0.017[b] 0.730[c]
Marital status					
Unmarried	96 (60.00%)	54 (31.95%)	65 (57.02%)	56.243[a] 37.524[b] 0.758[c]	<0.001[a] <0.001[b] 0.860[c]
Married	38 (23.75%)	108 (63.91%)	32 (28.07%)		
Divorced	25 (15.62%)	7 (4.14%)	16 (14.04%)		

Widowed	1 (0.62%)	0 (0.00%)	1 (0.88%)		
Smoking history					
Never	93 (58.13%)	122 (72.19%)	64 (56.14%)	7.183[a]	0.055[a]
1–3 years	16 (10.00%)	11 (6.51%)	8 (7.02%)	8.659[b]	0.026[b]
>3 years	51 (31.87%)	36 (21.30%)	42 (36.84%)	1.206[c]	0.730[c]
Alcohol consumption history					
Never	107 (66.88%)	99 (58.58%)	70 (61.40%)	3.089[a]	0.285[a]
Occasionally	46 (28.75%)	64 (37.87%)	34 (29.82%)	4.646[b]	0.112[b]
Regularly	7 (4.38%)	6 (3.55%)	10 (8.77%)	2.409[c]	0.730[c]
Executive functions					
Interference inhibition (*Stroop task*)					
Reaction times in incongruent stimuli	757.24 ± 152.37	663.61 ± 149.02	736.82 ± 158.59	5.63[a] −3.90[b] 1.07[c]	<0.001[a] <0.001[b] 0.401[c]
Stroop interference effect	−20.33 ± 74.22	−7.04 ± 44.23	−26.41 ± 90.34	−1.96[a] 2.12[b] 0.59[c]	0.051[a] 0.035[b] 0.648[c]
Response inhibition (*Go/No−Go* task)					
Accuracy in No−Go trials	0.84 ± 0.12	0.88 ± 0.11	0.82 ± 0.13	−2.90[a] 4.08[b] 1.44[c]	0.005[a] <0.001[b] 0.265[c]
Working memory Updating (*Running memory* task)					
Accuracy in 1,750 ms	0.58 ± 0.26	0.74 ± 0.21	0.52 ± 0.32	−6.01[a] 6.47[b] 1.76[c]	<0.001[a] <0.001[b] 0.192[c]
Accuracy in 750 ms	0.50 ± 0.29	0.66 ± 0.22	0.44 ± 0.32	−5.66[a] 6.60[b] 1.74[c]	<0.001[a] <0.001[b] 0.192[c]
Working memory Maintenance (*Digit span backward* task)					
Span in digit span backward task	5.08 ± 1.52	6.06 ± 2.11	4.64 ± 1.58	−4.83[a] 6.45[b] 2.31[c]	<0.001[a] <0.001[b] 0.152[c]
Cognitive flexibility (*Number switching* task)					
Switching cost	305.19 ± 295.26	198.95 ± 238.37	314.20 ± 303.06	3.58[a] −3.41[b] −0.25[c]	0.001[a] 0.001[b] 0.807[c]
Electronic medication records					
First episode, yes	6 (3.75%)	N/A	10 (8.85%)	2.21[c]	0.150[c]
Family History of Psychiatric Disorders, yes	12 (10.62%)	N/A	28 (17.50%)	2.07[c]	0.150[c]
Frequency of episodes	6.18 ± 4.30	N/A	5.00 ± 3.34	2.55[c]	0.045[c]

Age at onset	27.25 ± 8.42	N/A	25.94 ± 8.51	1.26[c]	0.209[c]
Duration of disorder	9.78 ± 7.02	N/A	11.40 ± 7.85	−1.76[c]	0.160[c]
Dose equivalent to olanzapine (mg/day)	14.79 ± 6.48	N/A	13.68 ± 5.66	1.51[c]	0.177[c]
PANSS Scale					
PANSS Positive Symptom	21.66 ± 4.53	N/A	20.58 ± 8.06	1.30[c]	0.268[c]
PANSS Negative Symptom	21.19 ± 6.83	N/A	23.19 ± 9.50	−1.92[c]	0.156[c]
PANSS General Psychopathology	39.73 ± 7.09	N/A	37.89 ± 13.23	1.35[c]	0.267[c]
PANSS Total scores	82.58 ± 14.46	N/A	81.66 ± 27.78	0.32[c]	0.799[c]

Note: Superscript letters denote between-group comparisons—[a] Main-sample schizophrenia vs. Main-sample healthy control; [b] Main-sample healthy control vs. Independent-sample schizophrenia; [c] Main-sample schizophrenia vs. Independent-sample schizophrenia.

Abbreviations: N/A, not applicable; PANSS, Positive and Negative Syndrome Scale; SES, socioeconomic status; BMI, body mass index.