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Original article

Differential profiles of executive function dimensions in first-episode and chronic schizophrenia: Identifying markers of illness stage

Xiaolong Yang [a,b,1], Tongyi Zhang [a,1], Xulong Ren [c], Yongjie Wang [b], Hongbo Lv [b], Meifang Su [a,d], Xiaoning Huo [b,*], Xin Zhao [a,*]

[a] School of Psychology, Northwest Normal University, Lanzhou, China
[b] The Third People's Hospital of Lanzhou, Lanzhou, China
[c] Lanzhou Vocational Technical College, Lanzhou, China
[d] The High School Affiliated to Lanzhou Jiaotong University, Lanzhou, China

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ABSTRACT

Background and objectives: Executive function (EF) impairment represents a core feature of schizophrenia, yet how specific EF dimensions differ across illness stages remains poorly understood. This study aimed to characterize the differential profiles of three EF dimensions between first-episode schizophrenia (FES) and chronic schizophrenia (ChSz) patients, and to identify which dimensions most strongly differentiate between these illness stages.

Methods: A total of 182 schizophrenia patients (85 FES, illness duration $\leq$ 2 years; 97 ChSz, illness duration $\geq$ 5 years) completed five behavioral paradigms assessing inhibitory control, working memory, and cognitive flexibility. Mixed-model ANCOVA examined differential EF impairment patterns between groups. Random forest classifiers with nested cross-validation and Shapley Additive Explanations (SHAP) were employed to determine the relative multivariate importance of EF dimensions in distinguishing between illness stages.

Results: Mixed-model ANCOVA revealed a significant group-by-dimension interaction. FES patients exhibited milder deficits in inhibitory control and working memory updating compared to ChSz patients (all $p_{fdr} < 0.05$), with the largest effect size for interference inhibition ($\eta^2 = 0.140$). Correlation analyses linked EF impairments to illness duration, symptom severity, and antipsychotic dosage. SHAP analysis identified interference inhibition and working memory updating as the dimensions most strongly associated with illness stage.

Conclusions: This study revealed stage-specific EF impairment profiles in schizophrenia, with inhibitory control and working memory updating showing the greatest differences between FES and ChSz patients. These dimensions may serve as sensitive markers for differentiating illness stages and represent potential targets for stage-specific cognitive interventions.

Introduction

Schizophrenia is a severe psychiatric disorder that significantly affects an individual's functioning and quality of life. The illness typically progresses through distinct phases, including high genetic risk, ultra-high risk for psychosis (UHR), first-episode schizophrenia (FES), and chronic schizophrenia (ChSz) .[1] These stages are characterized by abnormalities associated with genetic, prenatal, and environmental factors.[2] These abnormalities differ across phases and become more pronounced during certain stages.[3] FES, the initial clinical manifestation, stems from neurodevelopmental abnormalities,[4] whereas ChSz reflects the cumulative effects of disease chronicity, prolonged treatment exposure, and neural deterioration.[5]

Patients with schizophrenia exhibit positive symptoms (hallucinations and delusions), negative symptoms (atypical emotional and social functioning), and cognitive deficits.[6] Cognitive impairment, which involves the deterioration of mental abilities related to memory, attention, and executive function (EF), represents a core feature of schizophrenia. Unlike the secondary cognitive issues observed in affective psychotic disorders or substance-induced psychosis, cognitive deficits in

* Corresponding authors.
E-mail addresses: lzsyhxn@163.com (X. Huo), psyzhaoxin@nwnu.edu.cn (X. Zhao).
[1] These authors contributed equally to this work.

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schizophrenia emerge during the prodromal stage and persist throughout the illness.[7] However, the degree of cognitive dysfunction among schizophrenia patients is not uniform, ranging from nearly intact cognition to severe impairment.[8] Notably, recent meta-analytic evidence indicates that such neurocognitive variability is already evident prior to the formal onset of psychosis and persists across the psychosis spectrum.[9–11] This variability underscores the importance of examining how specific cognitive dimensions differ across illness stages, rather than assuming uniform deterioration.[12]

EF refers to a set of higher-order cognitive processes that enable individuals to regulate their thoughts, actions, and emotions in the service of goal-directed behavior.[13] Deficits in this domain can hinder goal-directed activity and contribute to aggression, violence,[14] and poor medication adherence in schizophrenia patients,[15] leading to worse clinical outcomes.[16] EF is a multidimensional construct comprising several facets, each of which may be differentially associated with specific clinical symptoms.[17] Various EF impairments are linked to schizophrenia, including difficulties in inhibiting prepotent responses, reduced cognitive flexibility, and disturbances in working memory updating. These impairments align with Miyake et al.'s three-factor model,[18] which characterizes (i) inhibition, (ii) shifting, and (iii) updating as separable yet interrelated components. This framework robustly captures individual variation across diverse age groups and clinical populations.[19,20] Given their distinct neurobiological substrates, it is essential to assess these dimensions separately when examining their associations with illness stages.

EF deficits are well-documented across all phases of schizophrenia. Nevertheless, the specific EF profiles associated with each illness stage remain poorly understood. Previous research indicates that EF is already impaired in the early stages of schizophrenia and may differ in severity between early and chronic stages.[21] Studies have reported that FES patients show mild deficits in inhibitory control, while ChSz patients exhibit more severe impairments.[22,23] However, given that EF is a multidimensional construct comprising several facets, whether different EF dimensions are consistently more impaired in ChSz compared with FES remains unclear. Moreover, which EF dimensions most strongly differentiate between FES and ChSz remains unexplored. Thus, addressing these knowledge gaps is crucial for understanding cognitive deficits in schizophrenia and identifying stage-specific treatment targets.

Elucidating the stage-related differences in executive dysfunction may reveal phase-specific mechanisms underlying cognitive deficits in schizophrenia and identify targeted interventional opportunities.[24] Such insights are particularly relevant given that cognitive remediation therapies may yield greater benefits when tailored to the specific EF deficits characteristic of each illness stage.[25] In this study, we aimed to systematically assess the three EF dimensions (inhibitory control, working memory, and cognitive flexibility) in FES and ChSz patients using five behavioral paradigms. We sought to determine the differential patterns of these EF dimensions between FES and ChSz patients and to identify which dimensions most strongly differentiate between these illness stages using machine learning with rigorous nested cross-validation (CV) and Shapley Additive Explanations (SHAP) analysis.

Methods

Data collection

Participant recruitment

The study was conducted from March to August 2023, including 182 individuals diagnosed with schizophrenia (85 FES patients and 97 ChSz patients; Table 1). FES and ChSz patients were defined according to the patient edition of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV). Illness duration was ≤2 years for FES patients and ≥5 years for ChSz patients (Fig. 1A) .[26] Patients with illness duration between two and five years were excluded to ensure clear differentiation between early and chronic illness stages and to minimize potential overlap between groups.[26] Symptom severity was evaluated using the Positive and Negative Syndrome Scale (PANSS) .[27] Detailed clinical information, such as illness duration and antipsychotic drugs, was obtained from patients' electronic medical records.

Table 1
Participants' demographics and clinical characteristics.

Variable	FES patients (*N* = 85)	ChSz patients (*N* = 97)	*t*/χ2	Corrected *P*-value
Age (years)	36.11 ± 11.73	39.30 ± 15.07	−1.605	0.110
Gender				
Male	44 (51.76 %)	49 (50.52 %)	…	0.984
Female	41 (48.24 %)	48 (49.48 %)		
Education level	11.19 ± 4.11	10.66 ± 3.72	0.915	0.362
BMI (kg/m^2)	23.41 ± 3.35	24.55 ± 5.62	−1.687	0.094
PANSS Scale				
PANSS Positive	22.92 ± 5.65	20.68 ± 4.76	2.866	**0.005****
PANSS Negative	18.38 ± 6.31	24.37 ± 7.00	−6.076	**< 0.001*****
PANSS General Psychopathology	38.29 ± 7.56	41.08 ± 6.21	−2.695	**0.008****
PANSS Total	79.59 ± 14.54	86.13 ± 11.44	−3.343	**0.001****
Course of illness (years)	0.84 ± 0.54	9.03 ± 3.61	−22.054	**< 0.001*****
OZP equivalent dosage (mg/day)	9.14 ± 3.02	14.35 ± 5.26	−8.325	**< 0.001*****

Note. Bold values indicate statistical significance. Asterisks denote significance levels: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. The corrected *P*-value refers to the significance level after FDR BH correction.
Abbreviations: FES patients, patients with first-episode schizophrenia; ChSz patients, patients with chronic schizophrenia. PANSS, Positive and Negative Syndrome Scale; OZP, olanzapine equivalent dosage.

Both FES and ChSz patients were recruited from inpatients at the Third People's Hospital of Lanzhou. Two resident psychiatrists diagnosed the patients using the ICD-10 diagnostic criteria for schizophrenia (F20.900), which were further confirmed using the SCID-IV. All patients were stable and received consistent treatment without expected medication changes during the study. Inclusion criteria were aged 18–65 years and the ability to communicate effectively, complete experimental tasks, and voluntarily sign the informed consent form. Individuals with severe physical diseases, visual abnormalities, or adverse drug reactions were excluded (Supplementary Table S1).

Assessments

This study was based on the influential model subdividing EF into three core dimensions: inhibitory control, working memory (updating and maintenance), and cognitive flexibility.[13] Working memory updating is the continuous replacement of old information with new information in working memory, according to current task requirements. Working memory maintenance is the ability to maintain and process information over time, often directly linked to short-term memory capacity.[28] Inhibitory control involves the ability to suppress dominant responses and adapt to a changing environment, minimizing the impact of irrelevant information on ongoing information processing. Accordingly, inhibition is also divided into two dimensions: interference inhibition (also termed interference control) and response inhibition (behavioral inhibition) .[29] Cognitive flexibility is considered a single dimension, representing the ability to flexibly switch between different tasks and thought modes.[30]

Based on established task complexity considerations, we selected five

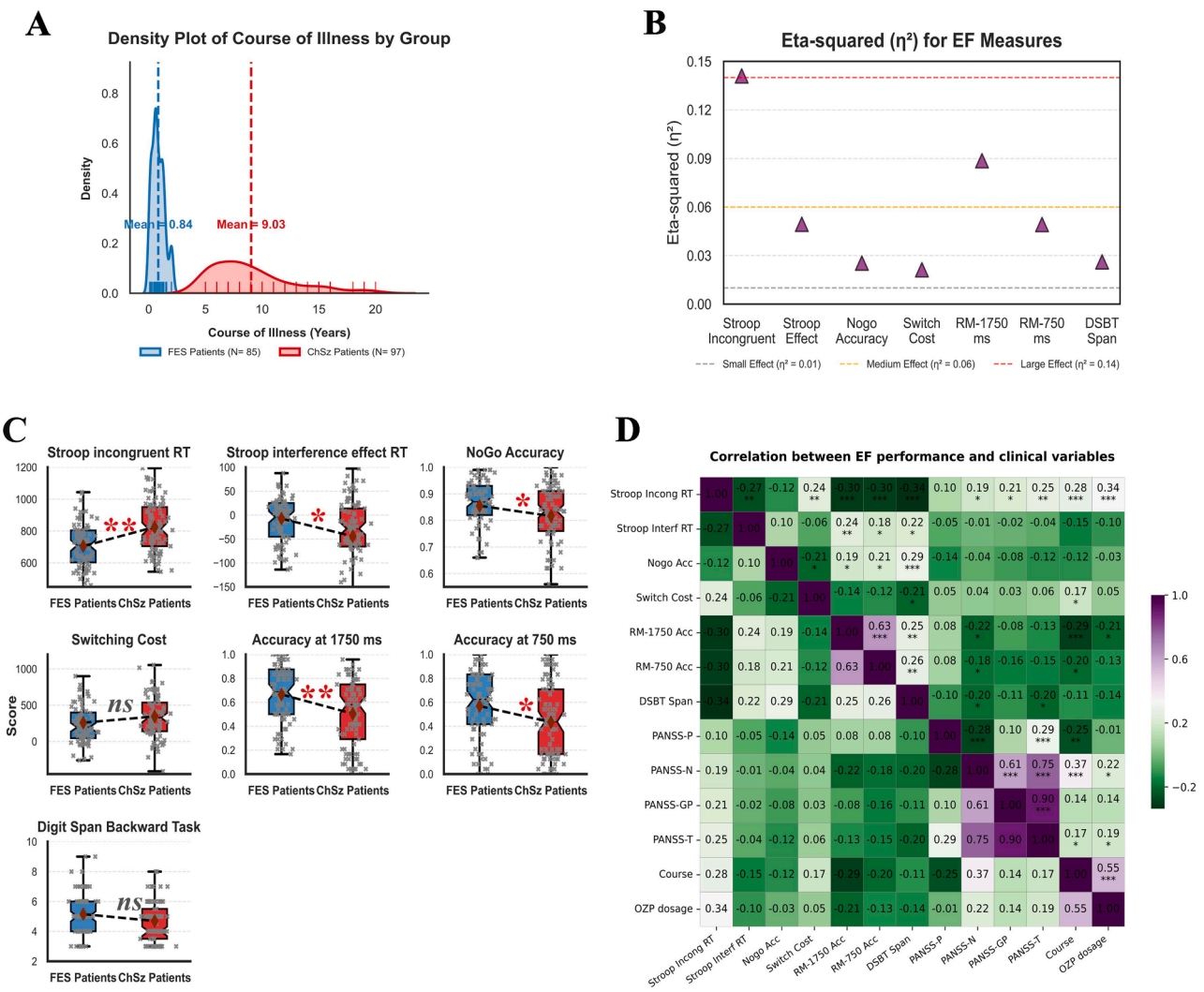

Fig. 1. Clinical and executive function performance in FES and ChSz patients. ***Note.*** A) Distribution of illness duration (years) among FES and ChSz patients. B) Effect sizes (η^2) of group differences in EF measures based on Gignac and Szodorai (2016): small ($\eta^2 \leq 0.01$), medium ($0.01 < \eta^2 \leq 0.06$), and large ($0.06 < \eta^2 \leq 0.14$). C) Comparison of EF performance between FES and ChSz patients, adjusted for sociodemographic variables (age, gender, and education level) with corrections for multiple comparisons (FDR-adjusted). D) Correlations between EF performance metrics, PANSS scores, illness duration, and olanzapine equivalent dosage in schizophrenia patients, applying FDR correction. Asterisks indicate statistical significance: $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$; ns, not significant. **Abbreviations:** ACC, accuracy; RT, reaction time; PANSS-P, Positive Subscale of the PANSS; PANSS-N, Negative Subscale of the PANSS; PANSS-GP, General Psychopathology Subscale of the PANSS; PANSS-T, Total Score of the PANSS; FES patients, patients with first-episode schizophrenia; ChSz patients, patients with chronic schizophrenia; OZP, olanzapine equivalent dosage.

behavioral tasks to measure these EF dimensions[31]: (1) a *number running memory* task to examine working memory updating; (2) a *digit span backward* task to measure working memory maintenance (span); (3) a *Stroop* task to measure interference inhibition; (4) a *Go/No-Go* task to measure response inhibition; and (5) a *number switching* task to measure shifting (see Supplementary Methods for details). All behavioral tasks were performed using *E*-Prime 3.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). *Inhibitory control:* The two measurements for assessing interference inhibition included the reaction times for the incongruent stimuli and the reaction time difference between congruent and incongruent condition trials (i.e., the interference effect) in the Stroop task. One measurement for assessing response inhibition included the accuracy of the No-Go stimuli in the *Go/No-Go* task. *Working memory:* Two measurements for assessing working memory updating included the proportion of digits correctly recalled and placed in the correct sequence at two different presentation speeds (1750 ms and 750 ms per digit) in the running memory task. One measurement for assessing numeric working memory maintenance capacity included the length of the last correctly repeated sequence until concluding the test (i.e., the total number of successful trials) in the digit span backward task. *Cognitive flexibility:* One measurement, including the reaction time difference between switch and non-switch trials (switch cost), was used to assess cognitive flexibility in the number-letter switching task.

Data analysis

EF behavioral task and clinical scale analyses

We performed a mixed-model analysis of covariance (ANCOVA) with group (FES vs. ChSz patients) as a between-subjects factor and all EF measurements as within-subjects factors while controlling for sociodemographic variables and olanzapine equivalent dose (mg/day) to examine whether schizophrenia differentially affects EF performance.[32] Then, multiple one-way ANCOVAs were performed to examine group differences in each EF measure, controlling for sociodemographic variables and olanzapine equivalent dose. A Benjamini-Hochberg false discovery rate correction was applied to adjust for multiple comparisons.[33]

Eta squared (η^2) effect sizes were calculated to describe the magnitude of effect sizes, with values interpreted as small ($\eta^2 \leq 0.01$), medium ($0.01 < \eta^2 \leq 0.06$), or large ($0.06 < \eta^2 \leq 0.14$) .[34] Chi-squared tests were used to compare categorical variables between these groups. Finally, we used Pearson correlation analyses to examine the relationships between clinical symptoms and EF.

Machine learning modeling procedure

(1) Features and models

Participants were categorized into FES and ChSz groups. Seven EF assessments, subsuming the three EF dimensions measured by five behavioral paradigms, were used for classification (Table 2). Random forest (RF) was employed for classification tasks.

(2) Machine learning procedure

Machine learning and CV were implemented using Python (version 3.10.11) and the scikit-learn package (version 1.3.0) .[35] The original data were preprocessed to accommodate missing values, outliers, and class imbalance issues.[36,37] Thereafter, the preprocessed data were randomly split into a discovery dataset with 80 % of FES and ChSz groups (training set) and a lock-box test dataset with the remaining 20 % of these samples (test set) to determine out-of-sample classification performance (Fig. 1) .[38–40] The random split was stratified for the diagnostic label (FES vs. ChSz), ensuring a balanced representation of labels in each dataset.[40,41] Using the discovery dataset, we performed a nested CV loop (double CV), differentiating two CV roles to avoid circularity introduced by overfitting when the same sample subset is used for both hyperparameter tuning and model validation. Specifically, the inner CV ($k = 3$), encompassing 80 % of the discovery sample, operates all data-dependent decisions while determining optimal hyperparameters within a nested CV loop. The outer CV ($k = 3$) is subsequently utilized for parameter assessment and model selection.[42] Hyperparameter optimization was performed exclusively within the discovery set, ensuring that the test set was never used during model development and served solely for final out-of-sample performance evaluation.

We employed Optuna (version 3.5.0) ,[43] optimizing candidate hyperparameters by maximizing the area under the receiver operating characteristic curve (AUC) within the inner loop validation sets, for optimal hyperparameter selection. The AUC metric represents the degree of separability, reflecting the ability to distinguish between FES and ChSz patients. Hyperparameters achieving the highest average performance in the 3 × 3 nested CV were selected. These hyperparameters were used to train a model on the entire discovery sample and tested on an independent test set.[44–46] Furthermore, sensitivity, specificity, and balanced accuracy performance were assessed. Machine learning was iterated 100 times to mitigate potential bias from random data splits. Furthermore, we plotted the relationship between each symptom dimension score and performance metrics within the patient group across 100 splits to verify the stability of classification performance across different PANSS symptom scores and illness duration distributions in the test set.

(3) Feature importance analysis

We assigned an importance score (i.e., Shapley value) to each feature to evaluate the contributions of EF features to the classification models[47,48] through the SHAP library (version 0.39.0) model-agnostic SHAP *KernelExplainer* approach, which is generally used to estimate Shapley values for prediction models.[48] SHAP KernelExplainer employs a Monte Carlo approach to randomly sample feature combinations based on input predictors. Initially, it estimates the importance of these combinations with varying features in model predictions. Subsequently, individual Shapley values are calculated to denote the contribution of each feature to the target prediction based on a weighted linear regression model.[48]

Table 2
Comparison of EF dimensions between FES and ChSz patients, controlling for demographic variables and OZP equivalents.

Variable	FES patients ($N = 85$)	ChSz patients ($N = 97$)	*F* value	Corrected *P*-value	η^2
EF dimension 1: Inhibition Control					
RT in Stroop incongruent (ms)	705.13 ± 141.00	825.01 ± 154.64	9.505	**0.006****	0.14
Stroop interference effect (ms)	−7.42 ± 68.52	−44.27 ± 90.75	3.254	**0.012***	0.05
Acc in No-go trials	0.85 ± 0.10	0.82 ± 0.13	1.354	**0.023***	0.03
EF dimension 2: Working Memory					
Acc in RM 1750 ms	0.67 ± 0.24	0.50 ± 0.27	5.524	**0.009****	0.09
Acc in RM 750 ms	0.57 ± 0.28	0.43 ± 0.31	4.599	**0.011***	0.05
Span in DSBT	5.15 ± 1.37	4.69 ± 1.46	3.183	0.251	0.03
EF dimension 3: Cognitive Flexibility					
Switch cost (ms)	258.26 ± 296.54	344.43 ± 290.45	1.867	0.078	0.02

Note. Corrected P-values account for multiple comparisons. Asterisks indicate significance levels: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.
Abbreviations: RT, reaction time; RM, running memory; DSBT, Digit Span Backward Test.

Results

Differential effects of EF dimensions in FES and ChSz patients

We administered five behavioral paradigms to assess three EF dimensions: inhibitory control, working memory maintenance and updating, and cognitive flexibility.[31] A mixed-model ANCOVA, controlling for age, sex, educational level, and olanzapine equivalent dose, revealed a significant two-way interaction between the groups (FES vs. ChSz patients) and EF measurements ($p < 0.05$), indicating differential impairment patterns. Given the significant interaction, this was followed by one-way ANCOVAs to examine group differences in each EF measure. Results revealed significant differences between FES and ChSz patients in inhibitory control and working memory updating (all $p_{fdr} < 0.05$) but not in cognitive flexibility or working memory maintenance (all $p_{fdr} > 0.05$) (Table 2, Fig. 1C). The largest effect size was observed for reaction times to incongruent stimuli (interference inhibition) in the Stroop task ($\eta^2 = 0.140$), followed by a medium effect size for accuracy at 1750 ms (working memory updating) in the number running memory task ($\eta^2 = 0.090$) (Fig. 1B). Notably, these findings remained broadly consistent when PANSS total score was included as an additional covariate (Table S2), indicating that the observed group differences in EF were largely not attributable to differences in symptom severity.

Association of psychopathology dimensions with specific EF measurements

We investigated the potential associations between the multifaceted EF measurements, clinical symptoms (PANSS scores), illness duration, and antipsychotic medication dosage (olanzapine equivalent) using Pearson correlation analysis (Fig. 1D). Stroop incongruent reaction time showed a significant positive correlation with PANSS total score ($r = 0.254$, $p_{fdr} < 0.01$), illness duration ($r = 0.278$, $p_{fdr} < 0.001$), and olanzapine equivalent dose ($r = 0.344$, $p_{fdr} < 0.001$). Working memory updating, assessed by accuracy in the running memory task at 1750 ms

and 750 ms delays, demonstrated a significant negative correlation with illness duration ($r = -0.295$ and -0.199, respectively; both $p_{fdr} < 0.05$) and olanzapine equivalent dose ($r = -0.208$, $p_{fdr} < 0.05$ for 1750 ms). PANSS negative symptom scores were significantly negatively correlated with working memory updating ($r = -0.216$ and -0.180 for 1750 ms and 750 ms, respectively; both $p_{fdr} < 0.05$) and working memory maintenance, as measured by digit span backward ($r = -0.195$, $p_{fdr} < 0.05$). Cognitive flexibility showed a significant positive correlation with illness duration ($r = 0.170$, $p_{fdr} < 0.05$), as measured by switch cost (ms).

EF dimensions associated with illness stage identified by machine learning

Multivariate classification models were employed to identify which EF dimensions most strongly differentiate between FES and ChSz illness stages. We constructed classification models using RF. The original data were repeatedly split into discovery and test sets, with each discovery set nested for hyperparameter tuning and model validation using a CV design. The resulting best model from each repeat was applied to the corresponding test set to obtain out-of-sample performance and repeated for 100 tests, yielding 100 test sets (Fig. 2C). This approach can effectively gauge generalization while accommodating practical constraints in clinical data acquisition.[40,41]

Classification performance of machine learning models

We used two feature sets for our classification experiments: (1) EF assessments, reflecting three EF dimensions measured by five behavioral paradigms; and (2) the same EF assessments, regressing out sociodemographic variables (age, sex, and educational level) and olanzapine equivalent dose. Performance metrics were assessed on the 100 test sets. We aimed to identify EF dimensions associated with illness stage regardless of sociodemographics and medication dose for the feature set relying solely on EF assessments. The RF model achieved the highest out-of-sample classification performance (AUC = 0.74; BAC = 0.69) (Fig. 2A; Supplementary Table S3). When using the feature set controlling for sociodemographic variables and olanzapine equivalent dose, the model still achieved an AUC of 0.68 (Fig. 3A; Supplementary Table S3). It is important to note that the classification performance reported here is intended to demonstrate the discriminative utility of EF dimensions for identifying stage-related differences, rather than to imply clinical-level diagnostic accuracy or direct clinical application.

Feature importance in classifiers

We performed the SHAP analysis of the best-performing classifiers trained on the EF dimension assessments to determine the directional contribution of each EF dimension to the classification. Absolute Shapley values derived from the best-performing classifier (highest AUC)

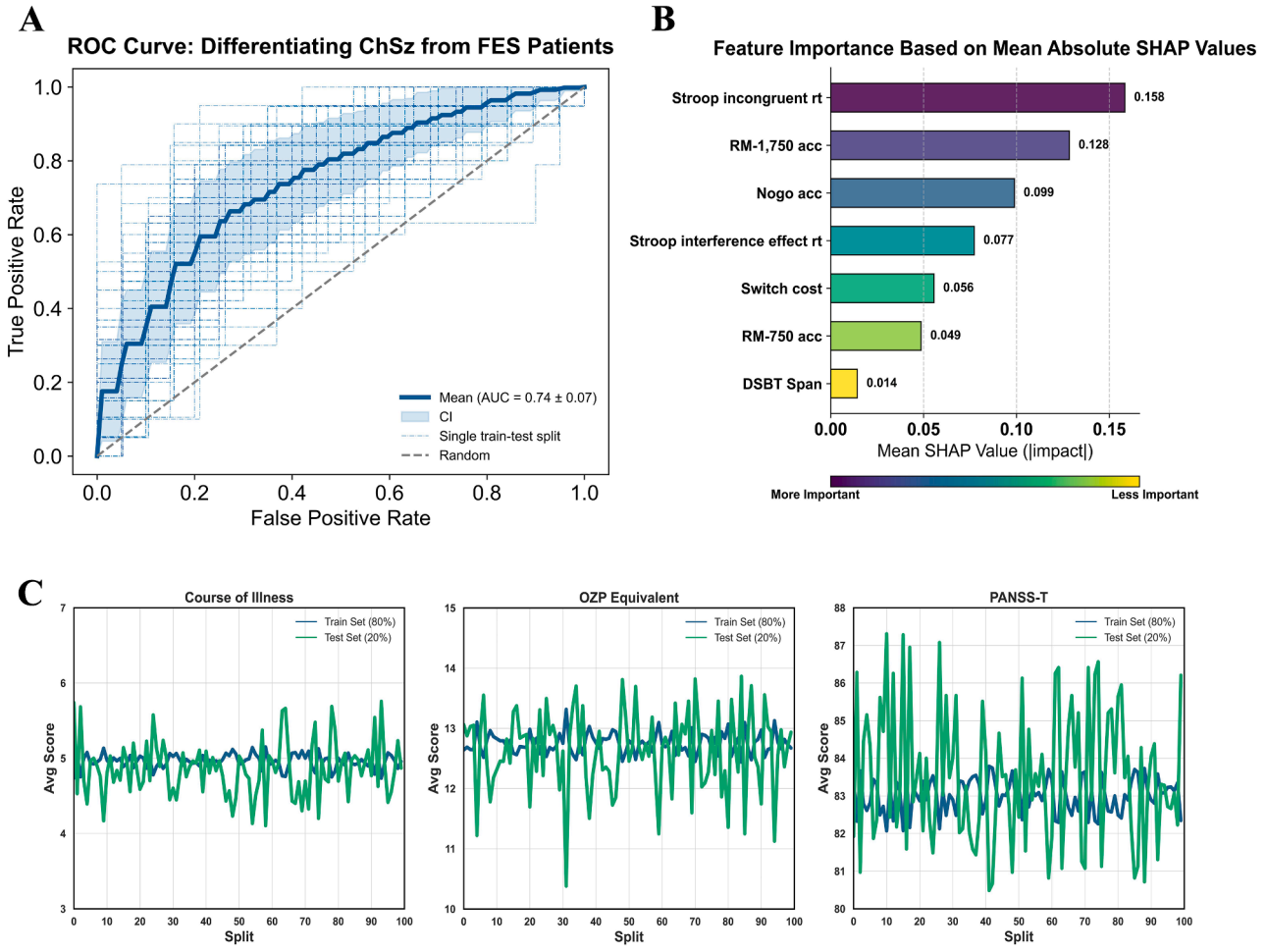

Fig. 2. Machine learning classifier performance and feature importance. ***Note.*** A) Receiver operating characteristic (ROC) curve for the machine learning classifier evaluating its ability to distinguish ChSz from FES patients using EF-related features on the test set. B) Feature importance plot showing EF features ranked on the X-axis by their absolute average Shapley values, reflecting their sensitivity to illness stage. C) The machine learning (train-test) was repeated 100 times to avoid potential bias from random splitting. SHAP values reflect relative feature importance within the model and should not be interpreted as evidence of causal effects. **Abbreviations:** ACC, accuracy; RT, reaction time; DSBT, Digit Span Backward Task; RM, running memory; FES patients, patients with first-episode schizophrenia; ChSz patients, patients with chronic schizophrenia.

identified in the 100 test sets were used to rank each EF dimension score according to their association with illness stage. Interference inhibition and working memory updating emerged as the dimensions most strongly associated with illness stage (Fig. 2B). These results were replicated in additional models controlling for sociodemographic variables and olanzapine equivalent dose (Fig. 3B, 3C).

Discussion

The present study integrates multidimensional EF assessment with interpretable machine learning methods to investigate the multivariate relationships among EF dimensions and identify which dimensions most strongly differentiate between FES and ChSz illness stages. We systematically assessed multiple EF dimensions across FES and ChSz patients, revealing differential impairment patterns between the two groups, rather than global deficits. These profiles demonstrated considerable discriminative utility in distinguishing illness stages through machine learning with stringent nested CV (AUC = 0.74). Importantly, our SHAP approach parsed the relative importance of EF dimensions, identifying interference inhibition and working memory updating as the dimensions most strongly associated with illness stage. Our findings provide novel insights into the stage-related differences in cognitive impairments in schizophrenia and underscore the relevance of EF dimensions as potential targets for stage-specific interventions.

Differential effects of EF dimensions in FES and ChSz patients

Our study demonstrated differential impairments in EF dimensions among ChSz patients compared to FES patients, rather than global deficits. After controlling for sociodemographic factors and antipsychotic medication dosage, inhibitory control (including interference inhibition and response inhibition) and working memory updating were the primary dimensions differentiating the two patient groups, with FES patients performing better than ChSz patients. The effect sizes were larger for interference inhibition and working memory updating compared to response inhibition. Our findings are consistent with previous research reporting that FES patients exhibited significantly faster response times than ChSz patients on the Stroop task, indicating better inhibitory control.[49] Additionally, Liu et al. (2010) suggested that deficient inhibition of return is present in ChSz but not FES patients.[22] Hutton et al. (2002) also found that ChSz patients were more impaired than FES patients in inhibitory control and additionally demonstrated impulsive responding.[50] Although working memory performance declines slightly with age and illness duration,[51] effect sizes for accuracy variables showed larger deficits in ChSz patients compared to FES patients on the N-back working memory updating task.[52] Furthermore, we found positive correlations between interference inhibition and symptom severity, illness duration, and antipsychotic medication dosage. In contrast, working memory updating was negatively correlated with illness

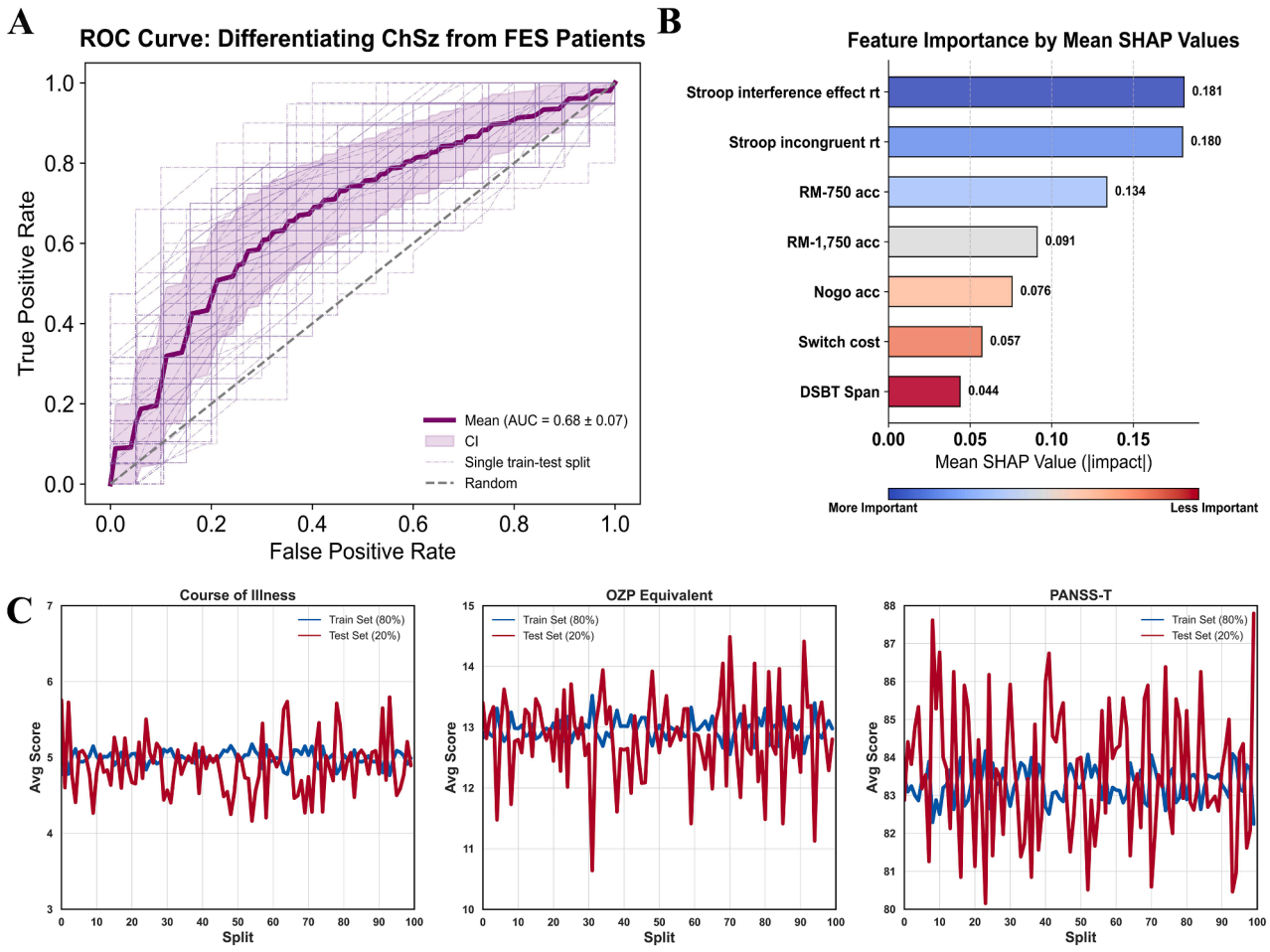

Fig. 3. Machine learning classifier performance and feature importance (based on EF features, regressing out sociodemographic variables and OZP equivalent dose). ***Note.*** A) Receiver operating characteristic (ROC) curve for the machine learning classifier evaluating its ability to distinguish ChSz from FES patients using EF-related features on the test set. B) Feature importance plot showing EF features ranked on the X-axis by their absolute average Shapley values, reflecting their sensitivity to illness stage. C) The machine learning (train-test) was repeated 100 times to avoid potential bias from random splitting. SHAP values reflect relative feature importance within the model and should not be interpreted as evidence of causal effects. **Abbreviations:** ACC, accuracy; RT, reaction time; DSBT, Digit Span Backward Task; RM, running memory; FES patients, patients with first-episode schizophrenia; ChSz patients, patients with chronic schizophrenia.

duration and medication dosage, suggesting that this cognitive domain may be more impaired in later illness stages. Prior research has shown that executive dysfunction is specifically associated with diminished motivation in first-episode psychosis,[53] and that working memory deficits constitute a risk factor for developing severe apathy in schizophrenia.[54] Apathy, characterized by diminished motivation and goal-directed behavior, may partly stem from impaired ability to update and maintain goal-relevant information in working memory. Thus, the greater impairment in working memory updating capacity observed in chronic patients may contribute to the worsening of motivational deficits commonly reported in this population.

Interestingly, we found no significant differences in cognitive flexibility and working memory maintenance between FES and ChSz patients. Thus, cognitive flexibility, a core impaired cognitive domain in schizophrenia,[55] remains relatively stable across illness stages. Similarly, Leonard et al. (2013) found that illness duration was no longer correlated with working memory maintenance in schizophrenia patients while controlling for the influence of age.[51] Notably, cognitive flexibility was not significantly correlated with any clinical variables in our study, which is consistent with research suggesting that cognitive flexibility is more closely linked to neural dysfunction than clinical symptom severity.[56,57]

The observed differences in EF dimensions between FES and ChSz patients may be attributed to several factors. First, longer illness duration is linked to impaired prefrontal cortex activation during executive tasks[58] and reduced prefrontal cortical gray matter volumes.[59,60] These neurobiological changes likely contribute to the poorer performance on specific EF dimensions in ChSz patients compared to FES patients. Second, the long-term effects of antipsychotics may partially account for the decline in EF performance in ChSz patients. Antipsychotic use is associated with cognitive side effects, including EF impairments.[61] ChSz patients, having been exposed to longer antipsychotic treatment than FES patients may be more affected by these cognitive side effects,[62] potentially contributing to the observed deficits in specific EF dimensions.[63] However, it is important to note that due to the cross-sectional nature of our study, we cannot definitively attribute the observed differences to illness progression per se, as age, illness duration, and cumulative antipsychotic exposure are inherently confounded in comparisons between FES and ChSz patients.

EF dimensions as markers of illness stage

Previous machine learning studies have applied various neurobiological and neurocognitive measures to classify schizophrenia patients. For example, functional connectivity in the salience network distinguished FES patients from healthy controls with an accuracy of 73.0 %,[64] and support vector machines based on duration mismatch negativity in the delta frequency band achieved accuracies of 65 %–70 % for the same comparison.[65] More recently, Wang et al. (2025) demonstrated that baseline cognitive performance could predict antipsychotic response in drug-naïve FES patients with 68.8 % accuracy.[66] However, fewer studies have focused on differentiating between FES and ChSz patients. Our machine learning classifiers achieved an AUC of 0.74 in distinguishing ChSz from FES patients by carefully assessing three EF dimensions via five behavioral tasks. After controlling for sociodemographic variables and olanzapine equivalent dose, the RF model still achieved an AUC of 0.68. These findings suggest that EF dimensions can serve as informative markers for differentiating illness stages in schizophrenia.

Furthermore, we identified through the SHAP approach that among the EF dimensions, interference inhibition and working memory updating emerged as the most important features in the machine learning models. Rather than positioning machine learning as a superior predictive method, we employed it as a multivariate, interpretable complement to conventional univariate analyses. This multivariate approach underscores the sensitivity of these EF dimensions to illness stage, aligning with our univariate findings of differential impairments between ChSz and FES patients. The convergence between traditional statistical analyses and machine learning findings strengthens confidence in the robustness of our results. Therefore, the assessment of specific EF dimensions, particularly interference inhibition and working memory updating, may help characterize illness stage in schizophrenia. The ability to suppress interfering stimuli or responses appears to be a key factor that differs between early and chronic stages of schizophrenia spectrum disorders. This finding aligns with previous research emphasizing the significance of inhibitory control deficits in schizophrenia.[67] Impairments in interference inhibition may be more pronounced in later illness stages, making this dimension particularly sensitive to illness stage differences. Similarly, the importance of working memory updating in the machine learning models supports the notion that working memory updating impairments are a core feature of schizophrenia spectrum disorders.[68,69] The machine learning models captured the differential impairment in working memory updating between FES and ChSz patients; thus, this dimension may be particularly sensitive to illness stage differences. Working memory updating deficits may be more severe in chronic patients, serving as a potential marker for differentiating illness stages.

Limitations and considerations

This study has several limitations. First, the cross-sectional design limits our ability to draw causal inferences about the relationship between illness duration and EF performance in schizophrenia. The observed differences between FES and ChSz patients cannot be definitively attributed to illness progression, as potential confounding effects of age, illness duration, and long-term antipsychotic exposure cannot be fully disentangled in a cross-sectional comparison. Longitudinal studies tracking the progression of cognitive deficits are necessary to establish a clearer understanding of the temporal dynamics and potential causal mechanisms underlying these associations. Second, applied machine learning relies on multiple datasets from independent medical centers for extensive validation. However, such concerns are moderated by our use of multiple random splits to set aside a test lock box in each repeat while performing nested CVs on the remaining sample, as established previously.[40,41] This strategy effectively gauges the out-of-sample generalization performance while balancing practical clinical data collection issues.[70] Nevertheless, future multisite and population-level EF studies may help expand the generalizability of our findings.[71] Third, the potential impact of different pharmacological agents on EF performance cannot be entirely ruled out, although we converted antipsychotic medication doses to olanzapine equivalents and controlled for medication effects in our analyses (Supplementary Figure S2) .[72,73] However, it should be noted that dose equivalence conversions do not fully capture qualitative pharmacological differences between antipsychotic agents, such as variations in receptor binding profiles (e.g., dopaminergic, muscarinic, and histaminergic affinity), which may differentially affect cognitive performance.[74,75] Additionally, although we controlled for current antipsychotic dosage (olanzapine equivalent), we were unable to account for cumulative lifetime antipsychotic exposure, which may differ between FES and ChSz patients and could contribute to the observed EF differences. Future studies should recruit medication-naïve patients or those receiving a more homogeneous treatment regimen to minimize confounding effects and facilitate more precise interpretations of the observed cognitive deficits.

Conclusion

This study identified distinct patterns of EF impairments that differentiate between FES and ChSz patients, with inhibitory control and working memory updating emerging as the dimensions most strongly associated with illness stage. These stage-related differences in executive functioning may be relevant for clinical characterization and patient

stratification. These findings provide a foundation for further research into the cognitive heterogeneity of schizophrenia and support the development of stage-specific interventions. By integrating multidimensional EF assessments with interpretable machine learning methods as a multivariate complement to conventional analyses, this study contributes to a better understanding of how EF profiles differ across illness stages and highlights potential targets for tailored cognitive interventions.

Publication ethics

This study was approved by the Ethics Committee at the Third People's Hospital of Lanzhou and Northwest Normal University (approval number: #2024120103). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after receiving comprehensive information regarding the study aims, procedures, potential risks, and benefits.

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Data availability

The raw data of our used sample are protected and are not publicly available due to data privacy. These data can be accessed upon reasonable request by the corresponding author (Xin Zhao). Derived data supporting the findings of this study are available from the corresponding authors (Xin Zhao) upon request.

Code availability statement

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

Authorship contribution

Xiaolong Yang: Conceptualization, Funding acquisition, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Tongyi Zhang: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. Xulong Ren: Data curation, Investigation. Yongjie Wang: Data curation, Investigation. Hongbo Lv: Data curation, Investigation. Meifang Su: Formal analysis, Methodology. Xiaoning Huo: Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing. Xin Zhao: Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejpsy.2026.100351.

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