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Classification of schizophrenia spectrum disorder using machine learning and functional connectivity: reconsidering the clinical application

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Abstract

Background Early identification of Schizophrenia Spectrum Disorder (SSD) is crucial for effective intervention and prognosis improvement. Previous neuroimaging-based classifications have primarily focused on chronic, medicated SSD cohorts. However, the question remains whether brain metrics identified in these populations can serve as trait biomarkers for early-stage SSD. This study investigates whether functional connectivity features identified in chronic, medicated SSD patients could be generalized to early-stage SSD.

Methods Data were collected from 502 SSD patients and 575 healthy controls (HCs) across four medical institutions. Resting-state functional connectivity (FC) features were used to train a Support Vector Machine (SVM) classifier on individuals with medicated chronic SSD and HCs from three sites. The remaining site, comprising both chronic medicated and first-episode unmedicated SSD patients, was used for independent validation. A univariable analysis examined the association between medication dosage or illness duration and FC.

Results The classifier achieved 69% accuracy ($p=0.002$), 63% sensitivity, 75% specificity, 0.75 area under the receiver operating characteristic curve, 69% F1-score, 72% positive predictive rate, and 67% negative predictive rate, when tested on an independent dataset. Subgroup analysis showed 71% sensitivity ($p=0.04$) for chronic medicated SSD, but poor generalization to first-episode unmedicated SSD (sensitivity = 48%, $p=0.44$). Univariable analysis revealed a significant association between FC and medication usage, but not disease duration.

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Conclusions Classifiers developed on chronic medicated SSD may predominantly capture state features of chronicity and medication, overshadowing potential SSD traits. This partially explains the current classifiers' non-generalizability across SSD patients with different clinical states, underscoring the need for models that can enhance the early detection of schizophrenia neural pathology.

Keywords Schizophrenia spectrum disorder, Schizophrenia, Machine learning, Functional connectivity, Classification

Introduction

Evidences from studies and clinical experiences has demonstrated that signs and symptoms of psychiatric disorders do not map well to their neurobiological abnormalities [1, 2]. This was largely due to the heterogeneities within psychiatric disorders, as the variability within disorders exceeds the variability between disorders, making it problematic to treat them as a single entity when investigating their neurobiological substrates. Schizophrenia spectrum disorders (SSD) are a range of disorders with the same symptoms as schizophrenia. Currently, the diagnosis, subtyping, prognosis, and treatment selection for SSD rely primarily on signs and symptoms, as there are no biomarkers to assist in clinical decision-making. It is urgent to build and validate an objective biomarker for the early diagnosis of SSD.

In recent years, there has been growing interest in utilizing neuroimaging combined with machine learning for diagnosing SSD [3–13]. Previous studies using support vector machine (SVM) and other machine learning methods found that unimodal or multimodal MR imaging could achieve 72-80% accuracy to differentiate those with SSD from healthy controls (HCs) [14–18]. For example, a recent study reported promising results that function and connectivity of the striatum may be a potential trait marker for schizophrenia using a functional MR imaging dataset from seven independent centers [19]. A "trait biomarker" refers to the brain signs that are not state dependent. On the other hand, another previous study [20] found that structural neuroimaging had not diagnosed first-episode psychosis using 5 independent datasets.

Most studies target chronic, medicated patients. Can these models also apply to early-stage cases, or only to chronic, medicated SSD? Identifying a trait biomarker for early-stage psychiatric patients is vital for timely diagnosis and intervention, especially when the optimal treatment plan remains uncertain. Early identification of the disease could enable timely interventions that may prevent future deterioration [21, 22].

To the best of our knowledge, there is limited research directly addressing this specific question: whether FC features identified in chronic, medicated SSD represent true trait biomarkers that can be generalized to early-stage patients rather than state-dependent characteristics. We chose to focus on FC because it has been widely recognized in many studies as a robust and reliable biomarker for SSD [23]. Among several machine learning methods, the SVM is widely used, well established, and comparable across many studies in classifying schizophrenia patients [9, 14, 24, 25]. To maintain consistency with previous schizophrenia classification studies and facilitate direct comparison, we utilized SVM, which has been widely used for discriminating psychopathological subtypes of schizophrenia based on brain functional connectivity (FC) patterns [26].

In the present study, the participants included both chronic medicated and first-episode unmedicated patients. This diverse sample allows us to assess the model performance across patient groups, offering insights into the generalizability of machine learning for schizophrenia classification. Here, we included 4 centers, and trained SVM model using data from 3 centers and tested the model in another center. We aimed to investigate whether FC features identified in chronic, medicated SSD could be generalized to early-stage SSD patients, testing if these features represent true trait biomarkers of the disorder rather than state-dependent characteristics. To capture FC abnormalities, we computed connectivity between all pairs of regions across the entire brain. This whole-brain approach was chosen because SSD-related dysfunction affects multiple brain areas, allowing us to identify potential connectivity biomarkers.

Materials and methods

Participants

We recruited participants from four distinct datasets, which altogether comprised a total of 1077 individuals, including 502 patients diagnosed with Schizophrenia Spectrum Disorders (SSD) and 575 Healthy Controls (HCs). Dataset CMU (the First Affiliated Hospital of China Medical University) is unique as it was used for independent testing of the model and includes 275 SSD patients and 275 HCs from a certain center. The SSD patients in dataset CMU consist of 92 chronic medicated SSD, 74 first-episode medicated SSD, and 44 first-episode unmedicated SSD. Dataset PKU (Peking University Sixth Hospital), COBRE (Center for Biomedical Research Excellence) and UCLA (University of California, Los Angeles) were used for training the SVM classifier and include a total of 227 chronic and medicated SSD patients and 300 HCs from different centers. The first-episode SSD was defined as patients who were experiencing their first psychotic episode with illness duration less than 12 months. All participants provided written

informed consent in accordance with the procedures approved by the ethics committees or institutional review boards of the China Medical University, the Sixth Hospital of Peking University, the University of New Mexico, and the University of California Los Angeles Institutional Review Board. Clinical trial number: not applicable. The demographic and clinical characteristics of the participants are presented in Table 1. For further details regarding the four datasets, please refer to the Supplementary Materials.

Age, sex and head motion between those with SSD and the HCs in the training datasets (PKU, COBRE, and UCLA) and test dataset (CMU) are shown in Supplementary Materials Figure S2.

Image acquisition and fMRI data processing

All participants underwent scanning for 5–8 min using 3.0 Tesla MRI equipment. Previous studies demonstrated that the FC parameters derived from RS stabilized with acquisition times as brief as 5 min which is sufficient for reliable estimates of correlation strengths [27]. The gain of additional scanning time in the increase of reliability and the decrease of spurious correlations between networks approaches asymptotic levels within 5–6 min [27]. Similarly, ~5½ min acquisition duration has been found to be adequate for a stable spatial estimation of brain networks in pediatric populations [28]. The detailed imaging acquisition protocols for the four datasets are provided in the Supplementary Materials.

All images were preprocessed using SPM12 (www.fil.ion.ucl.ac.uk/spm/) and Data Processing & Analysis of Brain Imaging (DPABI) [29]. The volumes from the first 10 time points were discarded to allow the signal to reach equilibrium. Slice-timing correction and realignment were applied to the remaining volumes. Functional images were spatially normalized to the Montreal Neurologic Institute (MNI) space and resampled to $3 \times 3 \times 3 mm^3$. Spatial smoothing (Gaussian kernel with a 4-mm full width at half-maximum) was not applied to avoid introducing artificial local spatial correlations between voxels [30]. Additionally, since the data were analyzed by parcels, smoothing could lead to signal overlap between different parcels. Linear trends were removed from the time courses. Temporal bandpass filtering (0.01–0.1 Hz) was performed. Finally, confounding covariates, including the Friston-24 head motion parameters and white matter, cerebrospinal fluid, and global signals, were regressed out [31]. The above steps were consistent with previous studies [19, 32–34]. As participants with a high head motion can introduce biases to FC calculation and hence the subsequent machine learning modeling, we excluded subjects with head motion (FD) greater than 0.3 according to previous studies (the remaining subjects in dataset CMU = 536 [total SSD = 268, chronic medicated SSD = 88, first-episode medicated SSD = 73, first-episode unmedicated SSD = 43, HC = 268], dataset PKU = 199 [SSD = 99, HC = 100]], dataset COBRE = 77 [SSD = 27, HC = 50], dataset UCLA = 143 [SSD = 34, HC = 109]).

Table 1 Demographics and clinical features of participants

Site	Group	*N*	Age (y)	Male/Female	BPRS	Positive	Negative	General	Illness Duration (months)
Dataset CMU	Patient	275	25.0 ± 9.8	109/166	31.8 ± 12.4	N/A	N/A	N/A	32.9 ± 50.9 (*n* = 244)
	Control	275	25.3 ± 6.5	113/162	18.6 ± 1.9	N/A	N/A	N/A	N/A
	Patient (first-episode unmedicated)	44	24.0 ± 9.8	26/18	41.2 ± 12.3	N/A	N/A	N/A	3.8 ± 4.1
	Control (age- and sex-matched)	44	24.4 ± 7.4	28/16	18.6 ± 1.3	N/A	N/A	N/A	N/A
Dataset PKU	Patient	106	27.1 ± 6.7	43/63	N/A	25.8 ± 5.4	21.5 ± 6.9	37.7 ± 6.2	53.0 ± 52.9
	Control	100	25.8 ± 5.4	47/53	N/A	N/A	N/A	N/A	N/A
Dataset COBRE	Patient	71	38.1 ± 14.0	57/14	N/A	N/A	N/A	N/A	192.5 ± 149.9 (*n* = 70)
	Control	74	35.8 ± 11.6	51/23	N/A	N/A	N/A	N/A	N/A
Dataset UCLA	Patient	50	36.5 ± 8.9	38/12	N/A	N/A	N/A	N/A	N/A
	Control	126	31.1 ± 8.7	59/67	N/A	N/A	N/A	N/A	N/A

The Brainnetome Atlas [35] was chosen because it is based on connectional architecture, aligning perfectly with our focus on functional connectivity features. The average time series of 246 nodes within the atlas were extracted for each individual by averaging the whole time series throughout all voxels in each node. FC between each pair of nodes was calculated using Pearson's correlation analysis, producing $(246 \times 245)/2 = 30{,}135$ unique FCs for each subject. Fisher r-to-z transformation was performed for all FCs. We inspected the average FC patterns of the four centers and their correlations, ensuring that the data variance was acceptable (Figure S1). Figure 1 presents an overall flowchart of the study.

Classification to discriminate diagnostic groups and clinical subgroups

We pooled dataset PKU, dataset COBRE and dataset UCLA as the training data and used dataset CMU as the test data. The Fisher z-transformed FC measures were normalized by using the group mean and standard deviation from the training dataset for both the training and test datasets. All analyses codes are available here: https://github.com/lichao312214129/SSD_classification. The machine learning analyses were implemented by Scikit-learn package [36] using Python language.

To mitigate the poor sample-to-feature ratio, principal component analysis (PCA) was used to reduce the dimensionality in feature space. The top principal components with the highest eigenvalues that cumulatively explained 95% of the variance were selected (70%, 80% and 99% explained variance were also tried; please see Supplementary Materials Figure S3). Then, PCA scores on the selected principal components were fed into a linear SVM classifier (regularization parameter $C = 1$; logistic regression classifier was also tried, please see Supplementary Materials Figure S3) for training a classification model. Of note, we used svm. SVC with the set class_weight parameter to 'balanced', which automatically adjusts weights inversely proportional to class frequencies in the input data. This approach ensured that the class with fewer samples gets a higher weight, helping to address any class imbalance in our dataset. We used the trained model to classify the subjects in the test dataset and evaluated the classification performance of the model. Furthermore, we investigated the classification performances of the trained model in individuals with chronic medicated SSD, first-episode medicated SSD and first-episode unmedicated SSD separately in dataset CMU.

Complementary machine learning setups

In order to facilitate comparison with previous studies, we also using three other machine learning strategies which were commonly used in previous studies. The three other machine learning strategies were 5-fold cross-validation that pooled all datasets, leave-one-site-out cross-validation, and 5-fold cross-validation that recruited only first-episode unmedicated SSD (within dataset CMU).

For each fold of the 5-fold cross-validation, we followed the same preprocessing and analysis steps as described above, including z-normalization, PCA for dimensionality reduction, and classification using a linear SVM with the same parameters. We used the trained model to classify the unseen test data (1/5) and evaluated the classification performance of the model. After a 5-fold training and testing loop, every participant had a predicted label and a real label. According to these labels, we further evaluated the classification performance of each subgroup for datasets CMU and PKU, e.g., unmedicated SSD or unmedicated schizophreniform subgroups.

For each fold of the leave-one-site-out cross-validation, one dataset was used as the test data while the other three served as training data. The machine learning processes, including z-normalization, PCA for dimensionality reduction, and classification using a linear SVM ($C = 1$), were consistent with the approach used when pooling all datasets. We used the trained model to classify the unseen dataset (1/4) and evaluated the classification performance of the model. After a 4 leave-one-site-out cross-validation loop, every participant had a predicted label and a real label. According to these labels, we further evaluated the classification performance of each dataset.

For each fold of the 5-fold cross-validation that included only the first-episode unmedicated SSD in dataset CMU, the machine learning processes were the same as that when pooling all datasets together. This subsample included 44 first-episode unmedicated SSDs and 44 age- and sex-matched HCs (Table 1).

Next, we used a linear regression model to regress out the effect of site, age, sex and head motion for all subjects. Specifically, effects of site, age, sex, and head motion were adjusted by using a linear regression model fitted on the whole dataset prior to cross-validation procedure.

Furthermore, regressing out the effect of site, age, sex and head motion for all subjects together may introduce risk data leakage between the training dataset (datasets PKU, COBRE, and UCLA) and the test dataset (dataset CMU). Therefore, we additionally estimated the effect of age, sex and head motion in an analysis limited to the training dataset and then applied the estimated parameters (beta values) to all subjects. The results were shown in Figure S4.

Statistical analysis

Permutation testing has been used to statistically analyze the model's classification performance [37]. Specifically,

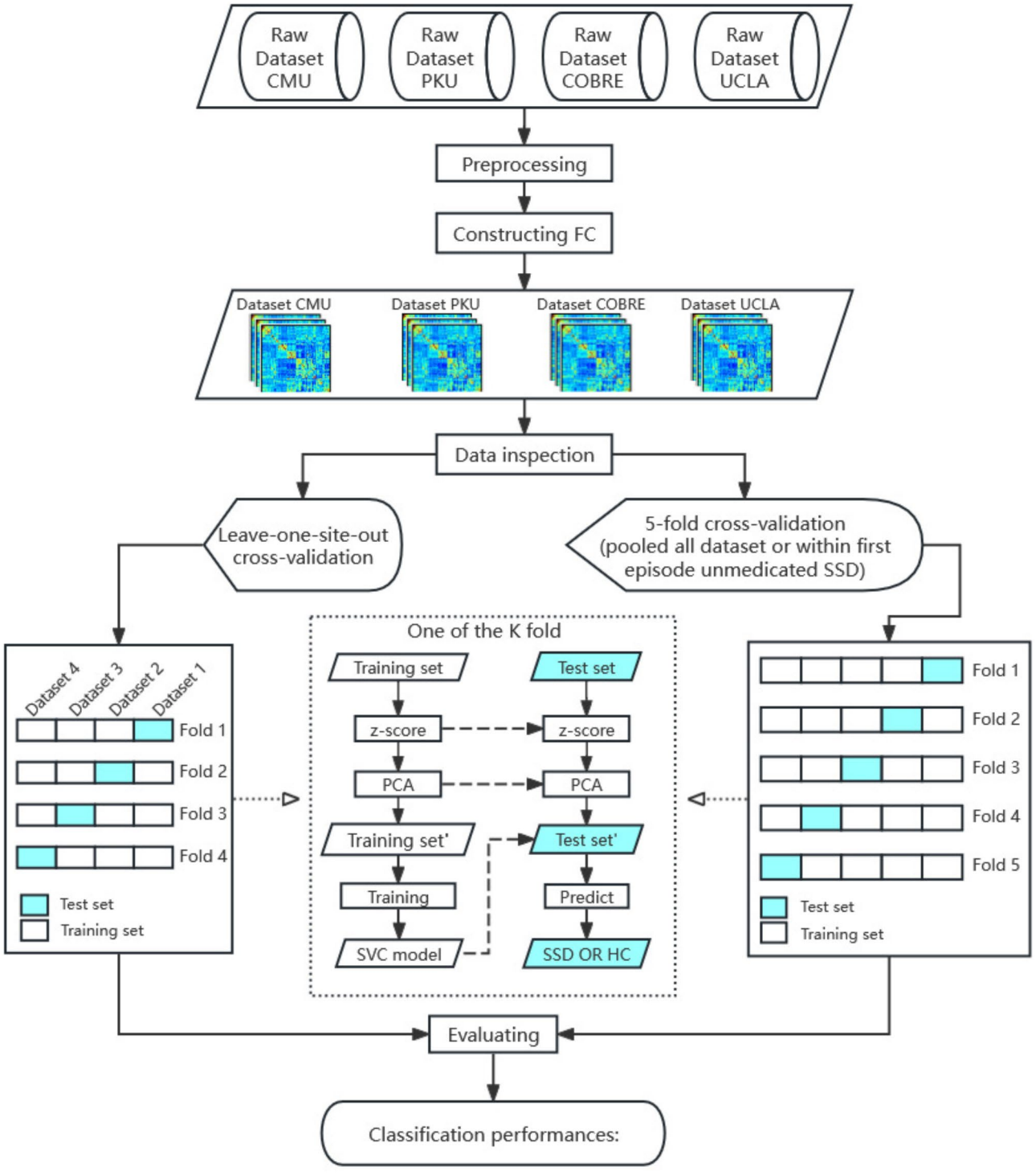

Fig. 1 Flowchart of the study. SSD = schizophrenia spectrum disorder; HC = healthy control; PCA = principal component analysis; SVM = support vector machine

we conducted 500 permutations of the training set labels while keeping the test set labels unchanged. For each permutation, we followed the same cross-validation procedure used in our original analysis to ensure consistency. This approach allows us to generate a null distribution of classification accuracies under the assumption of no true relationship between features and labels. The p-value was calculated as the proportion of permutation accuracies that were greater than or equal to our observed accuracy, plus one, divided by the total number of permutations

plus one (p = (k + 1)/(500 + 1)), where k is the number of permutations with accuracy ≥ observed accuracy). This method effectively accounts for the non-independence of predictions in cross-validation schemes and provides a more accurate estimate of significance. These results were provided in Figure S9 and S10. The statistical significance level $p < 0.05$ was considered statistically significant.

Since there were very few of those with chronic unmedicated SSD in this study (9 individuals), the following strategies were used to investigate the effect of illness duration or medication history on FC. We tested the effect of medication on FC by comparing first-episode medicated SSD with first-episode unmedicated SSD to reduce confounding by illness duration using network-based statistic (NBS) approach [38]. In addition, we tested the effect of illness duration by comparing chronic medicated SSD with first-episode medicated SSD to reduce confounding by medication.

We took age, sex, education level, framewise displacement (FD) and illness duration as covariates to detect the effect of medication, while we took age, sex, education level and FD as covariates to detect the effect of illness duration. The NBS is a nonparametric statistical method to address the multiple comparisons problem on a graph and control the familywise error rate (FWER). We set the primary cluster-forming threshold to 3 (t statistics) and the corrected significance to 0.05 (two-tailed test) with 1000 times permutation tests. Demographic and clinical information for the individuals with chronic SSD, first-episode medicated SSD and first-episode unmedicated SSD are shown in Figure S5 (Supplementary Materials).

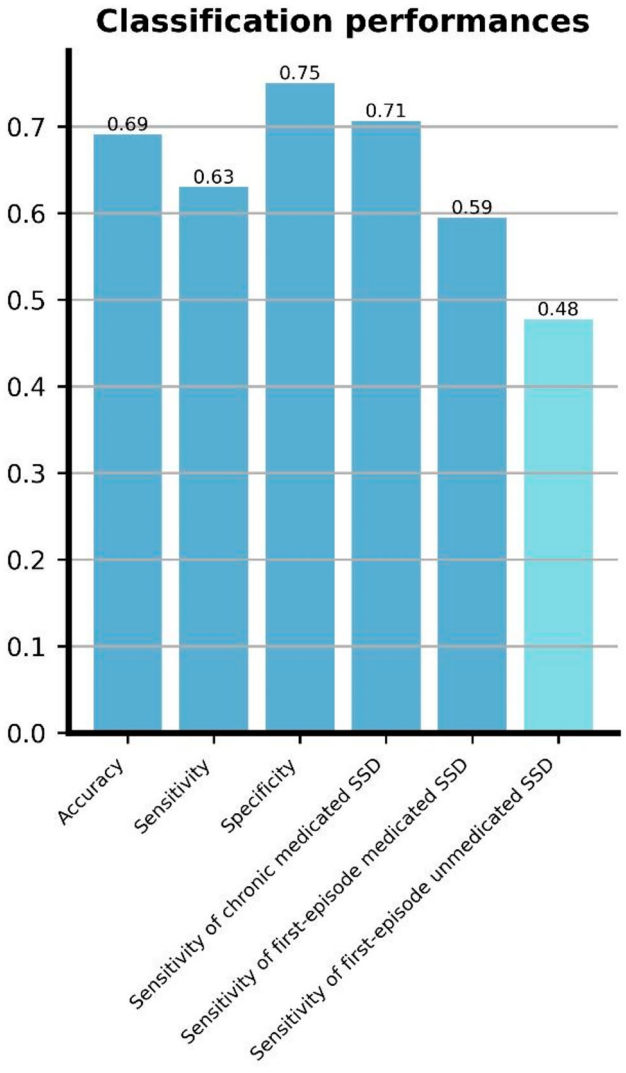

Fig. 2 Chronic SSD model testing on dataset CMU. SSD = schizophrenia spectrum disorder

Results

Classification performances

The classification model trained using data from individuals with chronic SSD from three sites (datasets PKU, COBRE, and UCLA) classified those with SSD from the HCs in another site (dataset CMU) with 69% accuracy ($p = 0.002$), 63% sensitivity and 75% specificity (Fig. 2). Subgroup analysis indicated that this model identified chronic medicated SSD in dataset CMU with 71% sensitivity (92 individuals with chronic medicated SSD; $p = 0.04$) but did not generalize to those with first-episode SSD, including first-episode unmedicated SSD ($n = 44$; sensitivity = 48%, $p = 0.44$) and first-episode medicated SSD ($n = 74$; sensitivity = 59%, $p = 0.14$).

In the main results, we used 12 months as the threshold to define first-episode versus chronic SSD. In Fig. 3, we present the classification performance of the model trained using chronic schizophrenia spectrum disorder (SSD) from datasets PKU, COBRE, and UCLA to identify chronic medicated, first-episode medicated, and first-episode unmedicated SSD in dataset CMU, using different thresholds to define first-episode and chronic SSD. When a 24-month threshold was used to define first-episode and chronic SSD, the model exhibited a sensitivity of 72% in identifying chronic medicated SSD individuals in dataset CMU, with a sample size (N) of 81 and a p-value of 0.03; it showed a sensitivity of 62% for first-episode medicated SSD individuals, with a sample size of 81 and a p-value of 0.09; and a sensitivity of 49% for first-episode unmedicated SSD individuals, with a sample size of 47 and a p-value of 0.46. When the threshold was increased to 36 months, the model's sensitivity in identifying chronic medicated SSD individuals in dataset CMU rose to 74%, with a sample size of 65 and a p-value of 0.02; the sensitivity for first-episode medicated SSD individuals was 61%, with a sample size of 88 and a p-value of 0.10; and the sensitivity for first-episode unmedicated SSD individuals remained at 49%, with a sample size of

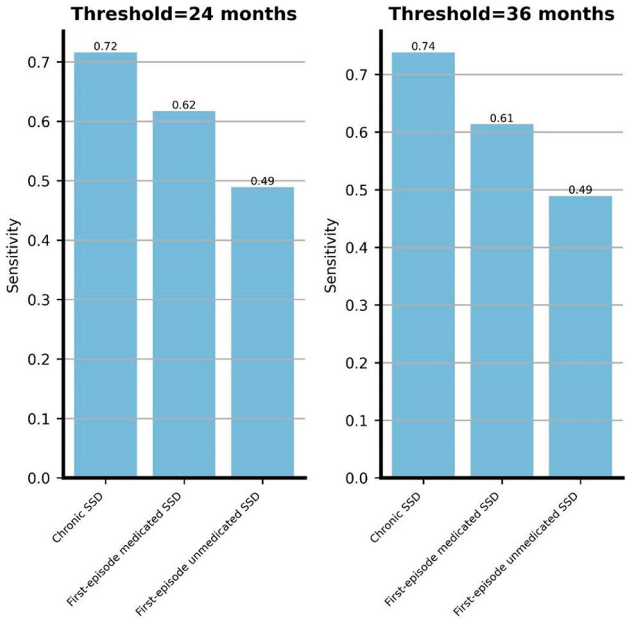

Fig. 3 Chronic SSD model testing on dataset CMU across thresholds. SSD = schizophrenia spectrum disorder

47 and a p-value of 0.43. These results indicate that the model can reliably distinguish between SSD patients and HCs based on varying time thresholds and medication status, with high statistical significance in some cases.

Additional analyses revealed that the classification model trained on chronic SSD from datasets PKU, COBRE, and UCLA did not generalize to unmedicated SSD, including unmedicated schizophreniform and schizophrenia (SZ) (Supplementary Materials Figure S6).

For the 5-fold cross-validation that pooled all datasets, the classification model achieved 77% (± 1.7%, $p = 0.002$) accuracy, 74% (± 2.0%) sensitivity and 0.79 (± 2.9%) specificity. For the leave-one-site-out cross-validation, the classification model achieved 72% (± 2.5%, $p = 0.002$) accuracy, 72% (± 7.6%) sensitivity and 0.74 (± 4.4%) specificity. For the 5-fold cross-validation of first-episode unmedicated SSD, the classification model achieved 71% (± 7.7%, $p = 0.02$) accuracy, 71% (± 9.8%) sensitivity and 0.73 (± 18%) specificity. The above performances are shown in Table 2.

Classification weights of FCs features

To enhance transparency in our classification models, we have visualized the feature weights of the FCs (Figure S8). Specifically, we displayed the feature weights (scaled to 0–1) of the linear SVM model fitted on Dataset PKU, COBRE, and UCLA (chronic SSD) and the feature weights (scaled to 0–1) of the linear SVM model fitted on first-episode unmedicated SSD patients. To illustrate the differences between the model trained on chronic patients and the model trained on early-stage patients, we presented the absolute difference between their feature weights (shown in the third panel of Figure S8).

Effect of illness duration or medication history on FC

We found that individuals with first-episode medicated SSD had different FCs than those with first-episode unmedicated SSD in a number of networks, e.g., the basal ganglia/striatum and the visual and frontoparietal control networks (Fig. 4). However, individuals with chronic medicated SSD had FC that was not significantly different from those with first-episode medicated SSD.

Correction of site and covariates

After adjusting for site, age, sex, and head motion effects, the classification model demonstrated significantly better performance than a random model. However, it was unable to accurately classify first-episode unmedicated SSD (as shown in Figure S4). Furthermore, a correction for site and covariates was applied in the 5-fold cross-validation process that pooled all datasets and that including those containing only first-episode unmedicated SSD (Supplementary materials, Figure S7).

Discussion

In this study, we used FC as a neuroimaging marker and linear SVM for classification to investigate if a model trained on chronic SSD patients could identify trait biomarkers generalizable to early-stage SSD individuals, utilizing a large multicenter sample. We found that while the classification model trained on chronic medicated SSD from datasets PKU, COBRE, and UCLA, identified individuals with chronic medicated SSD in dataset CMU, it did not generalize to first-episode unmediated SSD. Univariable analysis indicated that medication

Table 2 Model performance across different Cross-validation methods for SSD classification

Validation Method	Sample Size	Accuracy	Sensitivity	Specificity	AUC	F1-score	PPV	NPV	*P*-value
5-fold (All datasets)	1077	77% (± 1.7%)	74% (± 2.0%)	79% (± 2.9%)	0.85 (± 0.02)	77% (± 2%)	75% (± 2%)	78% (± 2%)	0.002
Leave-one-site-out	1077	72% (± 2.5%)	72% (± 7.6%)	74% (± 4.4%)	0.80 (± 0.03)	71% (± 2%)	66% (± 11%)	76% (± 7%)	0.002
5-fold (the first-episode unmedicated SSD vs. HCs)	88	71% (± 7.7%)	71% (± 9.8%)	73% (± 18%)	0.72 (± 0.16)	69% (± 12%)	71% (± 16%)	72% (± 14%)	0.02

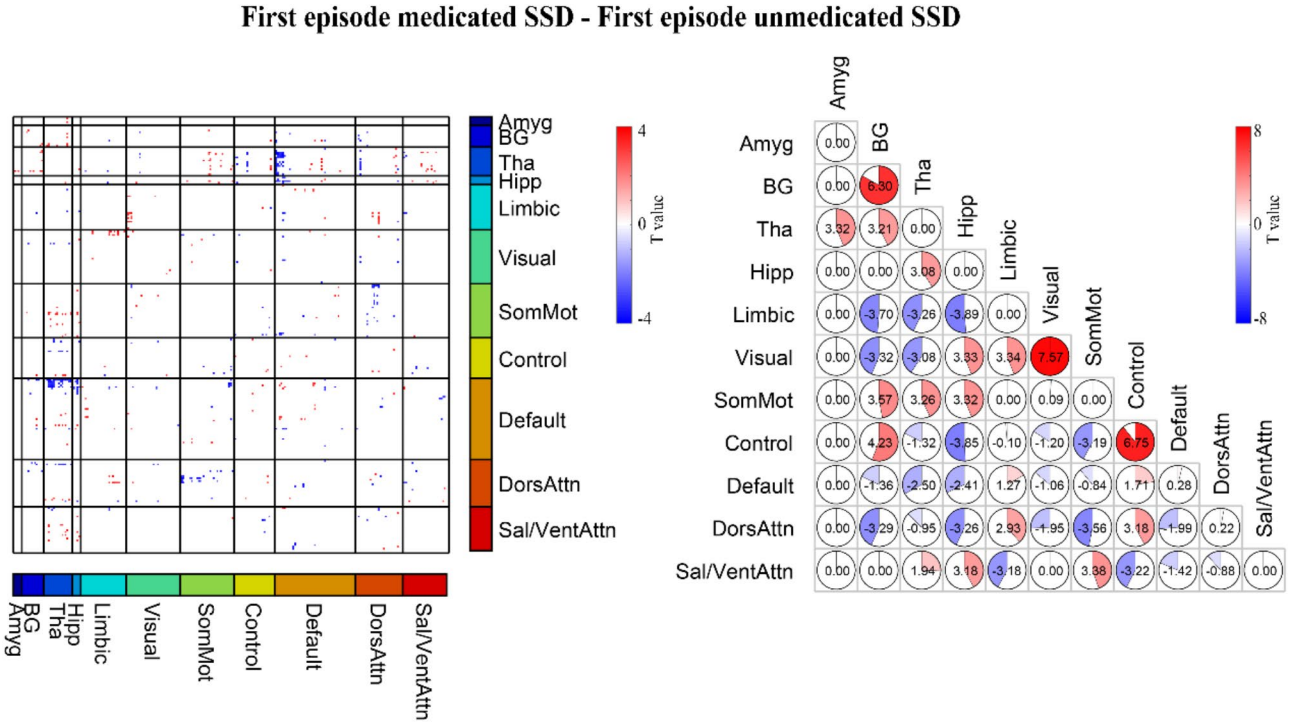

Fig. 4 FC differences between medicated and unmedicated first-episode SSD. (**A**) Differences are displayed as t-statistic values for each connectivity. (**B**) Differences are displayed as average t-statistic values within and between networks. Amyg = amygdala; BG = basal ganglia; Tha = thalamus; Hipp = hippocampus; SomMot = somatomotor; Control = frontoparietal control; Default = default mode; DorsAttn = dorsal attention; Sal/VentAttn = salience/ventral attention; SSD = schizophrenia spectrum disorder

usage significantly affected FC, whereas illness duration did not. Collectively, these findings suggest that the classification model trained using chronic medicated SSD may mainly identify the state of chronic medication usage rather than the trait biomarker of SSD. Given these findings, it may be beneficial to carefully reevaluate the clinical applicability of current machine learning studies involving chronic medicated SSD patients. Additionally, further consideration of how medication usage affects FC could provide valuable insights for future research.

The classification models trained on chronic SSD from datasets PKU, COBRE, and UCLA identified patients with chronic SSD in dataset CMU. These findings were consistent with previous studies that found that neuroimaging combined with machine learning can classify individuals with chronic medicated SSD [14, 16, 18, 25, 39–42]. Additionally, FC combined with SVM effectively identified SSD individuals across the whole sample using three strategies: 5-fold cross-validation on all data, leave-one-site-out cross-validation, and five-fold cross-validation limited to first-episode unmedicated SSD patients. These findings are also in line with previous studies that found that neuroimaging combined with machine learning can identify those with first-episode SSD [43] or first-episode unmedicated SSD [15, 33, 44].

The classification model trained on chronic SSD from datasets PKU, COBRE, and UCLA did not generalize to the first-episode SSD in dataset CMU. Early and accurate identification of SSD could enable timely interventions, potentially preventing future deterioration [21, 22, 45]. If the classification model identified the trait biomarker of SSD, then we may expect it to diagnose SSD at the early stage. Unfortunately, our study found that the classification model trained using chronic SSD could not be generalized to first-episode SSD, especially first-episode unmedicated SSD. This finding supports and extends the idea of a previous study [20] that we should reconsider current evidence for the diagnostic value of machine learning and neuroimaging more cautiously. Beyond first-episode SSD, the classification model failed to generalized to unmedicated SZ, which typically have a longer illness duration (Supplementary Materials Figure S6; note that there was an overlap between unmedicated SZ and first-episode SSD). This finding further suggested that the failure of generalization cannot be solely attributed to the short illness duration of first-episode SSD in dataset CMU.

The relatively poor classification performance (sensitivity = 48%) may be attributed to several key factors inherent to the early stage of the illness. The first-episode patients typically show more heterogeneous clinical

presentations and neurobiological patterns compared to chronic patients, making their brain connectivity patterns more variable and harder to classify. Furthermore, the neurobiological changes in early-stage SSD represent a more dynamic and subtle phase of the illness, whereas chronic stages are characterized by more stable and pronounced alterations due to disease progression and medication effects. These fundamental differences between early and chronic stages of SSD reflect the natural course of the disease, where early stages exhibit greater variability and subtlety in neural changes, while chronic stages show more established and consistent patterns of brain alterations.

We found that medication usage had a significant effect on FC, but disease duration had no significant effect on FC. This finding was an extension of and complement to a previous study [46]. The previous study compared ultrahigh-risk subjects, first-episode SSD patients, chronic SSD patients and HCs, revealing distinct patterns of functional dysconnectivity between first-episode and chronic SSD individuals. As an extension, our study suggests that the distinct patterns of dysconnectivity between first-episode and chronic SSD may be related to medication usage rather than illness duration. A recent study found that illness duration had no effect on any cognitive domain when completely controlling for medication by using never-medicated individuals on the SSD [47]. This finding partially supports the current finding. In addition, although we did not detect a significant effect of illness duration on FC, the classification model trained using chronic SSD could not be generalized to first-episode medicated SSD, which may suggest an interaction effect of medication usage and illness duration on FC.

Limitation

First, we used only FC as a feature to diagnose SSD, which may be a main concern. However, our machine learning pipeline using FC achieved good performance in identifying chronic SSD as well as good performance using other strategies to identify first-episode unmedicated SSD compared to previous studies (Supplementary Materials Fig. 4). These findings suggest that the failed generalization to first-episode SSD was not due to the selection of features or machine learning methods. In addition, considering that a large number of published studies used functional metrics to classify individuals with chronic SSD, it is necessary to test the actual clinical application value. Second, the ideal statistical method to test the effect of medication usage or/and illness duration on FC is the two-factor analysis of variance. However, since there were very few patients with chronic unmedicated SSD, we were unable to use this method in the two-factor analysis of variance. Third, different (unharmonized) scanners and acquisitions parameters may have affected the results. Fourth, the lack of medication and substance use information across our datasets, which constraints the comparison with other studies and the control for potential confounding effects. Fifth, our study relied solely on functional connectivity metrics for classification. While functional connectivity is a well-established neuroimaging marker in SSD research, incorporating multiple brain metrics (such as structural connectivity, grey matter volume, or task-based activation patterns) could potentially provide complementary information and improve the classification performance. Future studies should consider integrating multiple neuroimaging modalities to develop more comprehensive and robust biomarkers for early-stage SSD.

Conclusion

In conclusion, we found that the classification model trained using chronic medicated SSD successfully identified chronic medicated SSD, but it did not generalize to first-episode SSD, especially unmedicated SSD. Univariable analysis showed that medication usage had a significant effect on FC, but disease duration had no significant effect on FC. These findings suggest that the classification model trained using chronic medicated SSD may mainly identify the state of chronic medication usage rather than the trait biomarker of SSD. We should reconsider the current machine learning studies in chronic medicated SSD more cautiously in terms of the clinical application.

Abbreviations

MR	Magnetic Resonance
ROI	Region of Interest
FC	Functional Connectivity
SVM	Support Vector Machine
SSD	Schizophrenia Spectrum Disorder
HC	Healthy Control
PCA	Principal Component Analysis
Amyg	Amygdala
BG	Basal Ganglia
Tha	Thalamus, Hipp: Hippocampus
SomMot	Somatomotor
DorsAttn	Dorsal Attention
Sal/VentAttn	Salience/Ventral Attention

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Author contributions

CL, JC, and MD contributed equally to this work in conception, design, data analysis, data interpretation, and manuscript drafting. HY contributed to the study design, data collection, data interpretation, and critical revision of the manuscript. YT, JQ, and FW, as corresponding authors, were responsible for the overall direction and planning of the research, supervised the project, and made substantial contributions to the study design, data collection, data interpretation, and critical revision of the manuscript. FC, NM, SW, and XL contributed to data analysis. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Data availability

This study includes data from four datasets. Two datasets are publicly available: dataset 3 from the Center for Biomedical Research Excellence (available at fcon_1000.projects.nitrc.org/indi/retro/cobre.html) and dataset 4 from the University of California, Los Angeles (available at OpenfMRI database, accession number ds000030). The datasets from The First Affiliated Hospital of China Medical University (dataset 1) and Peking University Sixth Hospital (dataset 2) contain clinical information and are not publicly available due to privacy concerns, but are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki. All participants provided written informed consent in accordance with the procedures approved by the ethics committees or institutional review boards of the China Medical University, the Sixth Hospital of Peking University, the University of New Mexico, and the University of California Los Angeles Institutional Review Board.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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