IEEE Access
Multidisciplinary | Rapid Review | Open Access Journal

Received October 17, 2020, accepted October 30, 2020, date of publication November 16, 2020,
date of current version December 9, 2020.

Digital Object Identifier 10.1109/ACCESS.2020.3037658

Biomarkers for Prediction of Schizophrenia: Insights From Resting-State EEG Microstates

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This work was supported by in part the Beijing Natural Science Foundation under Grant Z200024, in part by the National Key Research and Development Program of the Ministry of Science and Technology of China under Grant 2016YFF0201002, in part by the University Synergy Innovation Program of Anhui Province under Grant GXXT-2019-044, in part by the National Natural Science Foundation of China under Grant 61301005 and Grant 61572055, in part by the Electrophysiological Biomarkers in Schizophrenia project of Beijing Key Laboratory under Grant Z161100002616017, in part by the Graduate Innovation Foundation for Beihang University under Grant YCSJ-01-2015-11, in part by the Research Plan for Innovation in Clinical Technology by Beijing Hospitals Authority under Grant XMLX201805, and in part by the Thousand Young Talent Plan (to J.C.Z.) between Beihang University and Jiangsu Yuwell Medical Equipment and Supply Company Ltd.

ABSTRACT Schizophrenia is a devastating disease with a prevalence of 1% in populations around the world. Current diagnostic techniques of schizophrenia and high-risk population are based on subjective psychiatric interviews. Early diagnosis and intervention can mitigate progression and improve treatment outcomes. However, the lack of biomarkers that support objective examinations has been a long-term bottleneck in clinical diagnosis and assessment of schizophrenia and its high-risk state. In the present study, resting-state 128-channel electroencephalogram (EEG) data were acquired from 65 participants, including clinically-stable individuals with first-episode schizophrenia (FESZ), individuals at ultra-high-risk (UHR) and high-risk (HR), and healthy controls (HC). Microstate analysis was used to assess the dynamics of functional networks in these participants. Three features were extracted for each class of microstate (A, B, C, D, E, F): duration, occurrence and time coverage. Furthermore, clinical examinations and cognitive tests were performed. Behavioral results showed poorer performances in the participants as the disease progressed. Moreover, microstate features computed from resting-state EEG microstates (especially microstate class D) were capable of distinguishing the four groups of individuals. Combined biomarkers including clinical examinations, cognitive tests and EEG microstate parameters were identified as a potential effective diagnostic tool, achieving the highest classification performance using the random forest model compared with the support vector machine (SVM) and long short term memory (LSTM) networks, with an average classification of 92%, mean sensitivity of 91.8%, and specificity of 90.8% among the four groups, which were much higher than that only using behavioral features. The results demonstrate that microstate-based indicators together with behavioral results may act as biomarkers for early diagnosis and prediction of at-risk individuals of schizophrenia. Furthermore, our findings illustrate the potential use of resting-state EEG in clinical screening, classification and quantitative evaluation of patients with neurodevelopmental disorders.

INDEX TERMS Biomarker, early diagnosis, EEG microstate, schizophrenia.

I. INTRODUCTION

Schizophrenia is a devastating disease with a prevalence of 1% in populations around the world [1]. Cognitive dysfunction, social impairment and behavioral disorganization are three core symptoms of schizophrenia. Individuals are usually affected in their late teens or early twenties with an enormous variety of psychiatric characteristics and comorbid conditions, which include depression, affecting almost 50% of schizophrenic patients; substance abuse in approximately

The associate editor coordinating the review of this manuscript and approving it for publication was Alberto Botter.

47%; posttraumatic stress disorder in approximately 29%; obsessive-compulsive disorder in approximately 23%; and panic disorder in approximately 15% of psychotic individuals [2]. Increasing numbers of studies have postulated that schizophrenia is a neurodevelopmental disorder, although the underlying etiology remains unknown [1], [3], [4]. Emerging evidence points to genetic factors, in combination with environmental factors, as possibly leading to risk of schizophrenia [1], [4]. These findings have generated a broad consensus that schizophrenia requires robust diagnostic, prophylactic and therapeutic strategies.

Schizophrenia is currently diagnosed principally on the basis of behavioral characteristics as defined in psychiatric diagnostic manuals (*e.g. Diagnostic and Statistical Manual of Mental Disorders*, Fifth edition (DSM-V)). These definitions emphasize the co-occurrence of positive symptoms (e.g. confused thoughts and disorganized speech), negative symptoms (e.g. blunting of affect and lack of social interest) and cognitive symptoms (e.g. difficulty concentrating) [5]. These definitions embrace a wide range of heterogeneous circumstances, therefore two patients with schizophrenia may have different symptoms. Kendler [6] highlighted the limitations of current diagnostic criteria that restrict assessments of schizophrenia to subjective diagnostic parameters. Furthermore, early detection of schizophrenia is challenging when using these subjective diagnostic factors, especially in the prodromal stage. One possible reason may be that no conspicuous psychotic symptoms appear during the early stage of schizophrenia. There is a typical delay of two years between the onset of psychiatric symptoms and the diagnosis, and antipsychotic treatment, of schizophrenia [7].

Early diagnosis of schizophrenia is important not only because it provides an opportunity for brain development in young affected individuals, but it also has the potential to yield greater treatment outcomes and early intervention more effectively reduces disability in young schizophrenia patients [8], [9]. Additionally, a great number of studies [10], [11] have found that the transition rate from being ultra-high risk to the first onset of schizophrenia could be significantly reduced if diagnosis and intervention had started earlier.

Elucidating biomarkers of schizophrenia for early identification of the illness is of great importance but remains a serious challenge. Unfortunately, there is currently no reliable biomarker which can be used to identify individuals at risk of schizophrenia. Due to its genetic complexity [12], no clinically meaningful genotype has been described that could detect risk of schizophrenia at present. Electrophysiological and imaging studies have suggested that some indicators (e.g. P50, N100, P300, mismatch negativity) may be useful in the detection of risk of schizophrenia [13]–[15]. However, controversial results have been reported about the reliability, specificity and sensitivity of these indicators [15], [16]. Moreover, structural and functional magnetic resonance imaging is expensive, and that may not be a practical approach for detection of schizophrenia in young individuals. Furthermore, single indicators may not be sufficiently predictive for asymptomatic at-risk populations. Therefore, reliable biomarkers that are more cost-effective are required for prediction of schizophrenia.

Compared to other modalities (e.g., fMRI, MEG), EEG measures have several characteristics that make them ideal for use as biomarkers in the diagnosis of schizophrenia. First, EEG can be recorded in a passive paradigm that does not require attention, behavioral readout or task engagement [17]. As a result, EEG is well suited for use in populations that may have difficulty engaging in behavioral studies, such as those with schizophrenia. Second, because of its high temporal resolution [18], EEG biomarkers can be uniquely used to track the information flow in the brain, and thus can be used to identify the earliest stages of information processing impairment [17]. The characteristics make EEG suitable to detect abnormal brain activities in the prodromal phase of schizophrenia and monitor the severity of schizophrenia progression. Third, because EEG biomarkers can indicate underlying neuronal activity [19], they can be seen as objective induces of cognitive impairment — a prominent feature of schizophrenics [17]. Fourth, EEG biomarkers are optimal for screening because EEG can be obtained using a relatively inexpensive and non-invasive device, which is widely available, convenient and fast [20]. Fifth, EEG provides a more direct measurement of electrical activity during neurotransmission in comparison to other neuroimaging modalities (e.g., fMRI) [21]. Last, resting-state EEG is attractive for clinical research due to its straightforward standardization, simplicity to subjects, sensitivity to brain diseases, and high retest reliability [22]. A recent study has proposed that EEG microstates are a candidate endophenotype for schizophrenia [23]. Biomarkers based on microstates in resting-state electroencephalogram (EEG) in combination with clinical examination and cognitive tests may be promising indicators for prediction of schizophrenia. EEG microstate analysis is a well-established approach for characterization and evaluation of brain network dynamics in fine temporal resolution (usually millisecond) in health and disease [24], [25]. EEG microstates are defined as successive quasi-stable time periods that are characterized by global patterns of scalp potential topographies recorded by multichannel EEG arrays [26]. Resting-state EEG microstates are considered reflective of the momentary local states and interactions of large-scale distributed brain networks [27]. Previous studies [27]–[30] have found that patients with schizophrenia exhibit significant changes in resting-state EEG microstates, indicating that they may be a biomarker for detection of schizophrenia.

In the present study we examined whether microstates in resting-state EEG together with clinical examination and cognitive tests could be used as biomarkers for prediction of schizophrenia. We performed EEG microstate analysis on 5 minute eyes-closed resting state EEG data in four groups of people, including patients with first-episode schizophrenia (FESZ), individuals at ultra-high risk (UHR) of schizophrenia, those at high risk (HR) and healthy

TABLE 1. Demographics of patients with FESZ, inidividuals at UHR and HR, AND HC.

Group	FESZ (n=20)			UHR (n=19)			HR (n=12)			HC (n=14)
Characteristic	Mean (SD)	t values	P values	Mean (SD)	t values	P values	Mean (SD)	t values	P values	Mean (SD)
Age	23.86 (6.56)	-0.36	0.72	23.10 (5.84)	-0.83	0.41	24.64 (6.11)	0.08	0.94	24.50 (3.74)
Education (years)	12.89 (3.16)	-0.48	0.64	13.35 (2.85)	-0.2	0.98	11.14 (3.59)	-1.77	0.09	13.38 (3.32)
Duration of illness (months)	32.54 (30.56)			29.32 (24.54)						

Note. FESZ: first-episode schizophrenia, UHR: ultra-high risk of schizophrenia, HR: high risk of schizophrenia, HC: healthy controls.
SD: Standard Deviation

controls (HC). In addition, statistical analyses were conducted in clinical and cognitive tests data, as well as EEG data. We hypothesize that these behavioral results in combination with electrophysiological results could be usable as biomarkers to discriminate different stages of schizophrenia.

II. MATERIALS AND METHODS

A. PARTICIPANTS

Sixty five participants were recruited to the present study, aged 13 to 40 years, from outpatient clinics at Beijing Anding Hospital and from communities across China (Table 1). An estimation of the required sample size was performed based on similar research previously conducted by Üçok and colleagues [31]. We estimated that the mean difference was -10.93 and standard deviation was 5.45. For $\alpha = 0.05$ and 1-$\beta = 90\%$, it was estimated that the number of samples in each group was 6 for achieving a meaningful difference. Taking into account a drop-out rate of 25%, at least 8 participants were required to be included in each group. In the present study, we recruited 12 participants in the HR group, 14 participants in HC group, 19 participants in the UHR group, and 20 participants in the FESZ group. Therefore, the number of participants in the four groups met the minimum number calculated from the sample size estimation. These participants were divided into four groups: 20 that were clinically stable, first psychotic episode outpatients with a Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV) diagnosis of schizophrenia; 19 UHR individuals assessed by the Structured Interview for Schizophrenia-Risk Syndrome, Criteria of Schizophrenia-risk Syndromes (SIPSCOPS); 12 HR individuals who were unaffected first-degree relatives of schizophrenic patients that fulfilled the DSM-IV diagnostic criteria; and 14 age- and sex-matched HC from the community. Diagnostic eligibility was confirmed from the Structural Clinical Interview for DSM-IV Disorders (SCID) for all participants.

Exclusion criteria for all participants were as follows: having less than 6 years of education, a history of head trauma, presence or history of any psychiatric disorder, presence or history of neurological diseases (e.g. epilepsy), presence or history of substance abuse (e.g. alcohol abuse) as assessed by DSM-IV, significant auditory or visual impairment, pregnancy evaluated by a urine pregnancy test for women or significant intellectual disability (IQ < 70) as measured by the Chinese version of the Wechsler Adult Intelligence Scale (WAIS). Additional exclusion criteria for the HC were as follows: presence of other psychotic disorders, bipolar disorders or recurrent major depressive disorder; a family history of psychotic disorder based on self-reporting; or exhibiting any form of avoidant, paranoid, schizoid, schizotypal or borderline personality disorder. Considering the impact of antipsychotic and psychotropic drugs on EEG microstate results, we therefore only included antipsychotic (or psychotropic)-naïve participants.

All interviewers were trained at the Treatment Unit of Beijing Anding Hospital. All participants were right-handed, native Chinese speakers with normal or corrected to normal vision. Signed and oral informed consent was provided by all participants, or guardians if the participant was less than 18 years old. The study was approved by the Science and Ethical Committee of Beijing Anding Hospital of Capital Medical University.

B. BEHAVIORAL EXAMINATIONS

1) CLINICAL EXAMINATIONS

Clinical characteristics for patients with FESZ were assessed on the Positive and Negative Syndrome Scale (PANSS) and the Calgary Depression Scale for Schizophrenia (CDSS). Except for CDSS, UHR individuals, HR individuals and HC were assessed using the Structured Interview for Prodromal Syndromes (SIPS). PANSS is a rating scale which help researchers and clinicians measure the severity of psychiatric symptoms in patients with schizophrenia. CDSS is a reliable scale for assessing the level of depression in schizophrenia, especially in individuals considered to be at UHR or HR for the condition. SIPS has been developed to assess the positive, negative, disorganization and general symptoms of individuals at UHR and HR, in addition to HC.

2) COGNITIVE TESTS

Neurocognitive ability and social cognition for participants were assessed using the MATRICS Cognitive Consensus Battery (MCCB), developed to evaluate cognitive performance in schizophrenia. MCCB principally assesses seven cognitive functions, including information processing speed, attention/alertness, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. MCCB comprises a set of tests, such as the Trail Making Test (TMT), Symbol Coding Test, Hopkins Verbal Learning Test-Revised (HVLT-R), WMS-III Spatial Span Test, Digit Span Test, Continuous Performance Test (CPT), Neuropsychological Assessment Battery Mazes edition, Brief Visuospatial Memory Test-Revised, Animal Naming Test and the Managing Emotions Test. These tests are widely used for cognitive functioning assessments. For example, TMT is a neuropsychological test of perception, motor functions, visual attention and information processing speed. HVLT-R is an evaluation tool for verbal learning and memory. CPT is a well-known test to measure an individual's sustained and selective attention.

C. EEG MEASUREMENTS AND MICROSTATE ANALYSIS

1) EEG DATA ACQUISITION AND PREPROCESSING

EEG data were recorded using NetStation software and a Net Amps 400 amplifier (Electrical Geodesic Inc., EGI, Eugene, OR). Data were continuously sampled at a rate of 1000 Hz from a 128-electrode HydroCel Geodesic Sensor Net in accordance with the 10-20 system, with Cz as a reference electrode. The 128-channel HydroCel Geodesic Sensor Net covered the entire scalp in sufficient density to ensure that all relevant data were captured. Impedance was maintained below 50 kΩ. Participants were seated in a comfortable, upright position facing a computer monitor in an electrically-shielded room. The amplified and digitized EEG signal was transmitted to a recording computer placed outside the scanner room via fiber optic cables. Participants were instructed to stay awake, keep as calm as possible, to close their eyes and relax for five minutes without falling asleep.

The EEG datasets were imported into the EEGLAB toolbox [32] in Matlab (Mathworks, Natick, MA) for preprocessing. A channel location file was loaded and the datasets then band-pass filtered between 1 and 80 Hz and notch filtered at 50 Hz. A blind source separation algorithm was inserted into the Automatic Artifact Removal plug-in to remove artifacts such as saccades, muscular artifacts and eye blinks. Continuous EEG data were then segmented into 2 second-long epochs. All EEG epochs with an amplitude exceeding $\pm$ 100 μV at any electrode were removed. Bad or noisy channels were identified manually and modified using interpolation algorithms. Bad trials were removed manually. EEG signals were then re-referenced to a common average reference and filtered between 2 and 20 Hz for microstate analysis.

2) EEG MICROSTATE ANALYSIS

After preprocessing, EEG microstate analysis was conducted in each participant using the Microstate plug-in in EEGLAB. The overall analysis pipeline is shown in Figure 1. The microstate analysis consisted of a bottom-up procedure for construction of the microstate classes [30] and a top-down procedure in which the topographical map of each subject in each group was assigned to the corresponding EEG microstate class with greatest spatial correlation.

EEG microstates are defined as global patterns of scalp potential topographies recorded using multichannel EEG electrode arrays which changes dynamically over time in an organized manner [26]. Using modified k-means clustering, these scalp potential topographies were clustered into mean EEG microstate classes. Extensive EEG studies have found that during rest and task execution, EEG microstate maps fall into four standard classes [30], [33], [34]. The four microstate classes demonstrate right-frontal to left-posterior (microstate class A), left-frontal to right-posterior (microstate class B), midline frontal-occipital (microstate class C), and fronto-central maximal (microstate class D) activity and are quasi-stable for approximately 80–120 milliseconds [34]. Moreover, these four microstate classes have been exhibited to be relatively consistent across participants (in both health and disease) and throughout the lifespan [33]. In the present study, Cartool toolbox [35] was used for the calculation of the optimal number of cluster maps based on the cross-validation criterion [25], [36].

The local maxima of the Global Field Power (GFP) were analyzed to improve the signal-to-noise ratio [37] in EEG signals. For identification of the most representative class of stable topographies, EEG data were extracted at the time frames corresponding to GFP peaks and utilized the time point of those peaks in the modified k-means clustering analysis, which was conducted at both an individual and group level. The clustering of eye-closed resting state EEG data was based on Global Map Dissimilarity criteria [38], disregarding map polarity. At the individual level, original maps were randomly and repeatedly selected as seeds using modified k-means clustering, then clustered into the optimal classes determined by the cross-validation criterion. Individual model maps were computed by averaging all maps after permutation of the polarities of the maps to find the minimum variance of the mean. At the group level, group model maps were computed based on individual model maps of all participants, producing one-to-one assignments for minimal overall variance [27]. Group model maps then acted as a template to sort individual model maps of each participant into one of the microstate classes. To assure that the topographies of the selected classes are similar across groups, the spatial correlation analysis was performed [23], [36].

Three parameters were computed for quantification of the microstates for each microstate class in each participant, including duration, occurrence and time coverage. Average duration refers to the mean length of time during which

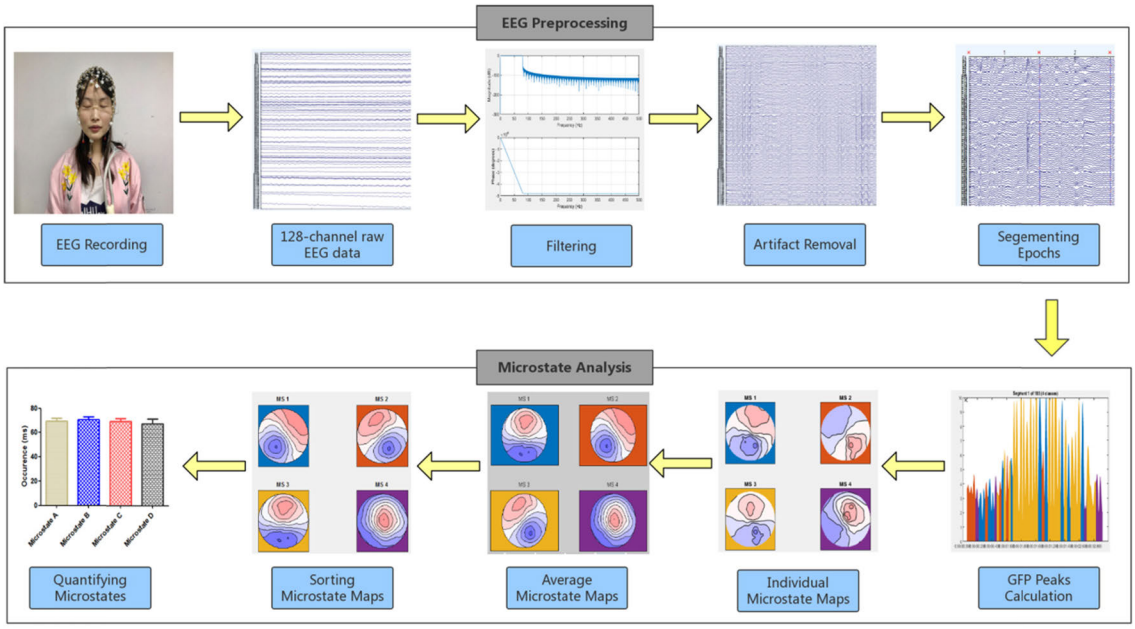

FIGURE 1. Microstate analysis methodology pipeline.

successive GFP maps were assigned to the same microstate class. The average number of occurrences per second was calculated across all epochs of a specific class. Time coverage was the mean percentage of time covered across epochs in a given class.

D. CLASSIFICATION USING MACHINE LEARNING ALGORITHM

To distinguish the four groups (FESZ, UHR, HR and HC), we used three machine learning algorithms, including the support vector machine (SVM) [39] model, random forest, and long short-term memory (LSTM), for classification based on the behavioral features and the combination of behavioral and EEG microstate features (Figure 5). SVM is a well-regarded supervise learning model and widely used in classification task as well as regression problems. We used SVM for classification because it is suitable for the current application scenario. SVM demonstrates many unique advantages in resolving small sample, nonlinear and high dimensional pattern recognition [40]. SVM is suitable for the current study which has small sample size. Other machine learning methods (e.g., neural networks) often requires large sample size otherwise it may cause overfitting problem [41]. Furthermore, SVM can work efficiently with complex, nonlinear and real-world data whereas other algorithms (e.g., linear discriminant analysis) can only be applied on groups that can be separated by a linear combination of feature [42]. SVM is also a powerful method in detecting complex and subtle differences between groups [42], and has been widely used in neuroimaging settings in schizophrenia diagnostic studies [42], [43]. Therefore, we used SVM for classification. Furthermore, we used random forest algorithm [44] for classification in comparison to SVM. Random forest was chosen because it has been successfully applied in schizophrenia classification studies, and has shown the best performance in identifying schizophrenia subgroups compared to SVM and logistic regression [45]. As a robust, relatively simple and easily interpretable classifier, random forest model is discriminative, suitable for small sample size and capable of capturing nonlinear relationships across input features. For feature extraction, behavioral features were from the demographics and cognitive tests. In addition to the behavioral features, resting-state EEG microstate parameters in the four groups constituted combined features. Regarding the classification, 80% of the data formed the training set, and the remaining 20% was the test set. Then cross-validation was performed. LSTM is a special kind of recurrent neural network (RNN) architecture used in the deep learning field, which may be possible to connect previous information to the current task [46]. LTSM has been used for the diagnosis and prediction of diseases (e.g., Alzheimer's disease) [46]. Here we used LSTM to classify the four groups (FESZ, UHR, HR, and HC) with 5-fold cross-validation, learning rate as 0.001 and training times as 100. We calculated the average classification accuracy and compared the accuracy between computation only using behavioral features and using combined features. Furthermore, we also computed sensitivity and specificity.

E. STATISTICAL ANALYSIS

Statistical analysis was conducted on both behavioral (including clinical examinations and cognitive tests) and EEG data. Independent sample t-tests were performed on the behavioral data to measure the differences among the four groups

TABLE 2. Behavioral performance of FESZ patients using PANSS examination.

PANSS	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)
POSITIVE SYMPTOMS		NEGATIVE SYMPTOMS		COGNITIVE OR GENERAL PSYCHOPATHOLOGY		COGNITIVE OR GENERAL PSYCHOPATHOLOGY	
Delusions	4.68 (1.16)	Blunted affect	2.82 (1.52)	Somatic concern	2.43 (1.07)	Unusual thought content	4.68 (0.95)
Conceptual disorganization	3.32 (1.63)	Emotional withdrawal	2.86 (1.51)	Anxiety	1.79 (0.96)	Disorientation	1.07 (0.38)
Hallucinatory behavior	3.18 (2.00)	Poor rapport	2.82 (1.31)	Guilt feelings	1.50 (0.96)	Poor attention	3.54 (1.67)
Excitement	2.07 (1.33)	Passive/ apathetic social withdrawal	3.25 (1.53)	Tension	2.18 (1.19)	Lack of judgement and insight	4.86 (0.93)
Grandiosity	1.32 (0.77)	Difficulty in abstract thinking	2.44 (1.50)	Mannerism and posturing	2.50 (1.62)	Disturbance of volition	3.52 (1.69)
Suspiciousness/ persecution	4.64 (0.95)	Lack of spontaneity and flow of conversation	2.96 (1.50)	Depression	1.79 (1.13)	Poor impulse control	2.18 (1.57)
Hostility	3.54 (1.20)	Stereotyped thinking	2.19 (1.27)	Motor retardation	2.18 (1.42)	Preoccupation	1.75 (1.08)
				Uncooperativeness	2.59 (1.47)	Active social avoidance	3.64 (1.28)
						PASS total score	82.71 (12.44)

(FESZ, UHR, HR and HC) in demographic, PANSS, CDSS, SIP and MCCB tests. All t-tests were 2-sided with $\alpha = 0.05$. For EEG data, independent t-tests were also performed to investigate statistical differences within EEG microstate parameters among the four groups (e.g. duration). Furthermore, differences between microstate classes and groups (FESZ, UHR, HR and HC) were ascertained by performing an ANOVA. In the case of significant interactions between microstate classes and groups, subsequent post-hoc t-tests were performed after univariate ANOVAs to further explore intergroup differences.

III. RESULTS

A. DEMOGRAPHICS

Demographic information of the four groups (FESZ, UHR, HR and HC) is shown in Table 1. Compared to HC, no significant difference was found in the age, gender or years of education in FESZ, UHR or HR individuals. The duration of schizophrenia was 34.54 months in FESZ patients and 29.32 months in UHR individuals.

B. BEHAVIORAL RESULTS

1) CLINICAL CHRACTERISTICS

Tables 2-4 display clinical performance of patients with FESZ, UHR and HR individuals, and HC. On the PANSS examination (Table 2), positive and negative symptoms, cognitive performance or general psychopathology were scored in patients with FESZ. The mean total PANSS score was 82.71 (SD = 12.44). Compared to HC, FESZ patients demonstrated significant differences in 8 items (e.g. depression) by CDSS examination (Table 3). UHR individuals exhibited significant differences in 9 items and HR individuals showed significant differences in 4. CDSS total scores were 1.18 (SD = 1.25), 2.20 (SD = 2.48), 0.79 (SD = 1.31) and 0.13 (SD = 0.50) in FESZ patients, UHR individuals, HR individuals and HC, respectively. The severity measured by CDSS was in the order: UHR > FESZ > HR > HC. Table 4 displays behavioral performance of the three groups (UHR, HR and HC) by SIPS examination. Compared to HC, UHR patients were significantly different ($P \leq 0.001$) in all items concerning positive, negative, disorganization and general symptoms on the SIPS test, whereas HR individuals exhibited significant differences in most items on the SIPS test compared to HC. Severity as tested by performance in the SIPS examination among these participants, in decreasing order were: UHR > HR > HC.

2) COGNITIVE CHRACTERISTICS

Figure 2 displays the results of cognitive tests in the four groups (FESZ, UHR, HR and HC). Compared to HC, FESZ patients had significantly worse performance on almost all cognitive tests, such as information processing speed, working memory and social cognition. Except for working memory and social cognition, there were significant differences in most cognitive tests between the UHR and HC groups. We found significant differences between the HR and HC groups in CPT, information processing speed,

TABLE 3. Behavioral performance of the four groups (FESZ, UHR, HR and HC) BY CDSS examination.

Group	FESZ (n=20)			UHR (n=19)			HR (n=12)			HC (n=14)
	Mean (SD)	t values	P values	Mean (SD)	t values	P values	Mean (SD)	t values	P values	Mean (SD)
CDSS										
Depression	0.26(0.45)	1.61	<0.0001	0.60(0.60)	3.36	<0.0001	0.14(0.36)	0.71	0.48	0.06(0.25)
Hopelessness	0.04(0.19)	0.77	0.45	0.25(0.55)	1.81	<0.0001	0(0)	0	0	0(0)
Self-Deprecation	0.22(0.42)	2.09	<0.0001	0.40(0.68)	2.34	<0.0001	0.21(0.43)	2.02	<0.0001	0(0)
Guilty ideas or reference	0.04(0.19)	0.77	0.45	0.05(0.22)	0.89	0.38	0(0)	0	0	0(0)
Pathological guilt	0.04(0.19)	0.77	0.45	0(0)	0	0	0(0)	0	0	0(0)
Morning depression	0(0)	0	0	0.10(0.45)	0.89	0.38	0(0)	0	0	0(0)
Early awakening	0.15(0.36)	1.63	<0.0001	0.05(0.22)	0.89	0.38	0.07(0.27)	1.07	0.03	0(0)
Suicide	0.04(0.19)	0.77	0.45	0.16(0.37)	1.63	<0.0001	0(0)	0	0	0(0)
Observed depression	0.37(0.49)	2.32	<0.0001	0.60(0.59)	3.36	<0.0001	0.36(0.50)	2.09	<0.0001	0.06(0.25)
CDSS total score	1.18(1.25)	3.22	<0.0001	2.20(2.48)	3.28	<0.0001	0.79(1.31)	1.87	0.002	0.13(0.5)
Current score	55.11(11.09)	-10.61	<0.0001	53.89(13.41)	-9.10	<0.0001	87.57(8.69)	-0.13	0.90	87.94(7.17)
Last year's highest score	70.18(13.33)	-5.54	<0.0001	69.16(19.06)	-4.14	<0.0001	91.79(7.99)	0.86	0.40	89.63(5.65)
Degree	4.61 (0.63)	22.83	<0.0001	2.68(0.75)	8.97	<0.0001	1(0)	0	0	1(0)

attention facilitation and the total scores of cognitive tests. Furthermore, behavioral performance in the MCCB and other tests were ranked in the order: FESZ < HR < UHR < HC. The results of the MCCB and other cognitive tests are shown in Table 6.

C. EEG MICROSTATE PARAMETERS

We found that the optimal number of EEG microstate maps were 6. Figure 3 illustrates the six average microstate classes (classes A, B, C, D, E, F) in the four groups (FESZ, UHR, HR and HC). The six microstate classes explained 90.4%, 91.1%, 85.7% and 90.4% of the global variance across the FESZ, UHR, HR and HC groups, respectively. We also found high spatial correlation coefficients (>90%), which suggested that the microstate classes were similar between groups.

Figure 4 depicts the three microstate parameters (including duration, occurrence and time coverage) in the four groups (FESZ, UHR, HR and HC). The predominant differences among the four groups were in microstate class D. For microstate class D, the duration was significantly lower in the FESZ group than it was in the HC group ($P = 0.01$, Cohen's $d = 0.93$), consistent with findings in previous studies [28]–[30], [47], [48]. UHR and HC groups also exhibited significantly reduced duration in microstate D in comparison with the HC group (UHR: $P = 0.01$, Cohen's $d = 0.96$; HR: $P = 0.04$, Cohen's $d = 0.86$). Compared to the HC group, the FESZ and UHR groups showed significantly decreased occurrence in microstate class D (FESZ: $P = 0.02$, Cohen's $d = 0.85$; UHR: $P = 0.05$, Cohen's $d = 0.73$), but there were no significant difference in occurrence in microstate class D between the HR and HC groups (HR: $P = 0.60$, Cohen's $d = 0.22$). The FESZ, UHR and HR groups exhibited decreased time coverage in microstate class D than the time coverage in the HC group (FESZ: $P = 0.006$, Cohen's $d = 1.04$; UHR: $P = 0.01$, Cohen's $d = 0.96$; HR: $P = 0.15$, Cohen's $d = 0.58$).

One-way ANOVA revealed significant differences in duration in microstate class D [$P = 0.02$, $F(3, 65) = 3.65$], and time coverage in microstate class D [$P = 0.02$, $F(3, 65) = 3.47$] across the four groups (FESZ, UHR, HR and HC). There were no significant differences in occurrence in microstate class D [$P = 0.08$, $F(3, 65) = 2.33$].

D. CLASSIFICATION RESULTS

Table 5 summarizes the classification results of the four groups (FESZ, UHR, HR and HC) using the three classification models (SVM, random forest and LSTM). Parameters (e.g., kernel type, cost function) may have an effect on the classification accuracy of the SVM model. For example,

TABLE 4. Behavioral performance of three groups (UHR, HR AND HC) by SIPS examination.

Group	UHR (n=19)			HR (n=12)			HC (n=14)
	Mean (SD)	t values	P values	Mean (SD)	t values	P values	Mean (SD)
SIPS							
POSITIVE SYMPTOMS							
Unusual Thought Content/Delusional Ideas	2.84(1.71)	6.13	<0.001	0.07(0.27)	-0.36	0.72	0.13(0.5)
Suspiciousness/ Persecutory Ideas	2.32(1.49)	5.73	<0.001	0.50(0.86)	1.62	0.009	0.13(0.34)
Grandiose Ideas	0.37(0.68)	1.69	0.001	0(0)	-0.93	0.06	0.06(0.25)
Perceptual Abnormalities/Hallucinations	2.00(1.97)	4.05	<0.001	0.14(0.54)	1.07	0.03	0(0)
Disorganized Communication	1.89(1.33)	5.69	<0.001	0.14(0.36)	1.58	0.001	0(0)
NEGATIVE SYMPTOMS							
Social Anhedonia	1.84(1.26)	5.84	<0.001	0.36(0.84)	1.70	0.001	0(0)
Avolition	1.58(1.43)	4.42	<0.001	0(0)			0(0)
Expression of Emotion	1.79(1.27)	5.61	<0.001	0.14(0.54)	1.07	0.03	0(0)
Experience of Emotions and Self	1.58(1.31)	4.57	<0.001	0.07(0.27)	0.10	0.93	0.06(0.25)
Ideational Richness	1.21(1.18)	3.81	<0.001	0.36(0.63)	1.72	0.001	0.06(0.25)
Occupational Functioning	2.21(1.44)	5.89	<0.001	0.36(0.84)	1.34	0.01	0.06(0.25)
DISORGANIZATION SYMPTOMS							
Odd Behavior of Appearance	0.68(1.00)	2.72	<0.001	0.07(0.27)	1.07	0.03	0(0)
Bizarre Thinking	1.21(1.27)	3.54	<0.001	0(0)	-0.93	0.36	0.06(0.25)
Trouble with Focus and Attention	1.79(1.18)	6.04	<0.001	0.71(0.83)	3.47	<0.001	0(0)
Impairment in Personal Hygiene	0.89(1.37)	2.61	<0.001	0(0)			0(0)
GENERAL SYMPTOMS							
Sleep Disturbance	0.95(1.31)	2.88	<0.001	0.36(0.75)	1.92	<0.001	0(0)
Dysphoric Mood	2.37(1.64)	5.56	<0.001	0.64(1.01)	2.23	<0.001	0.06(0.25)
Motor Disturbances	0.63(1.21)	2.08	<0.001	0(0)			0(0)
Impaired Tolerance to Normal Stress	1.47(1.71)	3.44	<0.001	0.43(0.76)	2.27	<0.001	0(0)

if the parameter gamma value in kernel function is too large, then it may result in over-fitting. If the gamma value is too small, then it will lead to under-fitting [49]. So we optimized the parameters to improve the SVM classification accuracy. Using the SVM model inserted in LIBSVM [39], we obtained the highest classification accuracy using 5-fold cross-validation of the four groups (FESZ, UHR, HR and HC) of 49% and 66% based on behavioral features and combined features, with $-t = 0$, $-c = 6$, $-g = 1$, $-b = 1$. Where -t represents to kernel type (0 represents linear kernel), -b represents probability estimates, -c represents the cost of the penalty, -g represents gamma in kernel function. On the basis of behavioral features, we attained the classification accuracy of 65%, 53%, 17% and 50% for the FESZ, UHR, HR and HC groups, respectively. On the basis of combined features extracted from both behavioral tests and EEG examinations, we attained the classification accuracy of 85%, 50%, 68% and 50% for the for the FESZ, UHR, HR and HC groups, respectively. Moreover, the mean sensitivity and mean specificity of the four groups were 49.2% and 48.0% only using behavioral features. When using both behavioral features and EEG microstate features, the mean sensitivity and mean specificity were 63.4% and 65.9%. Using the LSTM network, we obtained an average classification accuracy of 53%, sensitivity of 52.9%, specificity of 43.5% based on the behavioral features, and an average classification accuracy of 69%, sensitivity of 68.9%, specificity of 69.4% based on the behavioral and EEG microstates combined features. Using random forest, we obtained the best classification results compared to SVM and LSTM. For the random forest model, the average classification accuracy was 92% using combined features, and 69% using behavioral features. The sensitivity and specificity were 91.8% and 90.8% for the combined features, and 74.3% and 63.8% for the behavioral features.

IV. DISCUSSION

In this study we compared clinical examinations, cognitive tests and resting-state EEG microstates of FESZ patients, UHR individuals, HR individuals and HC. We also applied the SVM, random forest and LSTM for classification of the four groups. To the best of our knowledge, the present

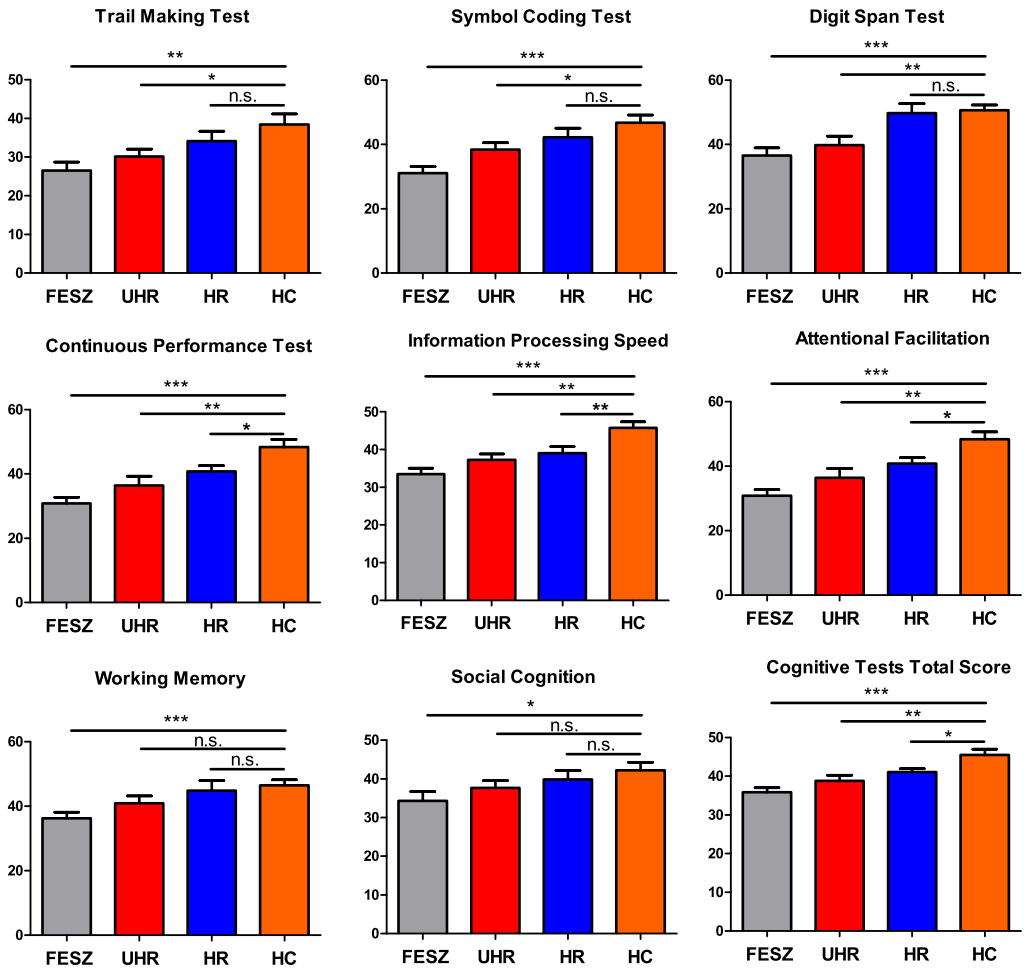

FIGURE 2. Behavioral performance of the four groups (FESZ, UHR, HR and HC) in the MCCB and other cognitive tests. *P < 0.05, **P < 0.01, and n.s. denote not significant. Error bars are the standard error of the mean (s.e.m.).

study is the first to compare four groups of individuals using all three forms of examination. As expected, we found that participants showed decreased performance as the disease progresses. Furthermore, combined features consisting of behavioral indicators and EEG microstates achieved an average classification accuracy of 92% among the four groups using the random forest model, which was higher than accuracy based on the behavioral features. These findings suggest that EEG microstates, in combination with clinical and cognitive assessments, may be biomarkers for the prediction of schizophrenia.

Clinical examinations are predominant tools for diagnosis of schizophrenia at present. We used PANSS to rate the clinical symptoms of the FESZ group. The mean total PANSS score of positive and negative symptoms, in addition to cognitive or general psychopathology, was 82.71 (SD = 12.4), demonstrating that the FESZ group could be considered mildly ill [50]. CDSS was used for evaluation of depression levels in patients with FESZ, UHR and HR individuals and HC. The mean total CDSS scores were ranked in the order: UHR > FESZ > HR > HC. Compared with HC, the other three groups exhibited significant differences in total CDSS scores. In particular, the FESZ and UHR groups had item scores that were significantly raised on the CDSS than the HR group. Depression is a common comorbid condition in schizophrenia, affecting approximately 50% of schizophrenic patients [2]. Our results demonstrated that besides FESZ patients, UHR individuals also had clear depressive symptoms, whereas HR individuals appeared to be less affected by depression than the FESZ and UHR groups. Interestingly, UHR individuals exhibited more severe depressive symptoms then FESZ patients, consistent with a previous study [15]. One possible reason may be that the depression suffered by an individual is a probabilistic event (7% - 75%). Prodromal stages of schizophrenia are usually diagnosed using SIPS. In this study, the severity of schizophrenia was assessed using SIPS in the UHR, HR and HC groups. The SIPS results scored the groups as: UHR > HR > HC. Higher scores represented greater risk for schizophrenia. The results indicate that the SIPS scores became higher as mental condition worsened. Therefore, we can infer from the clinical examinations that clinical symptoms may become increasingly severe

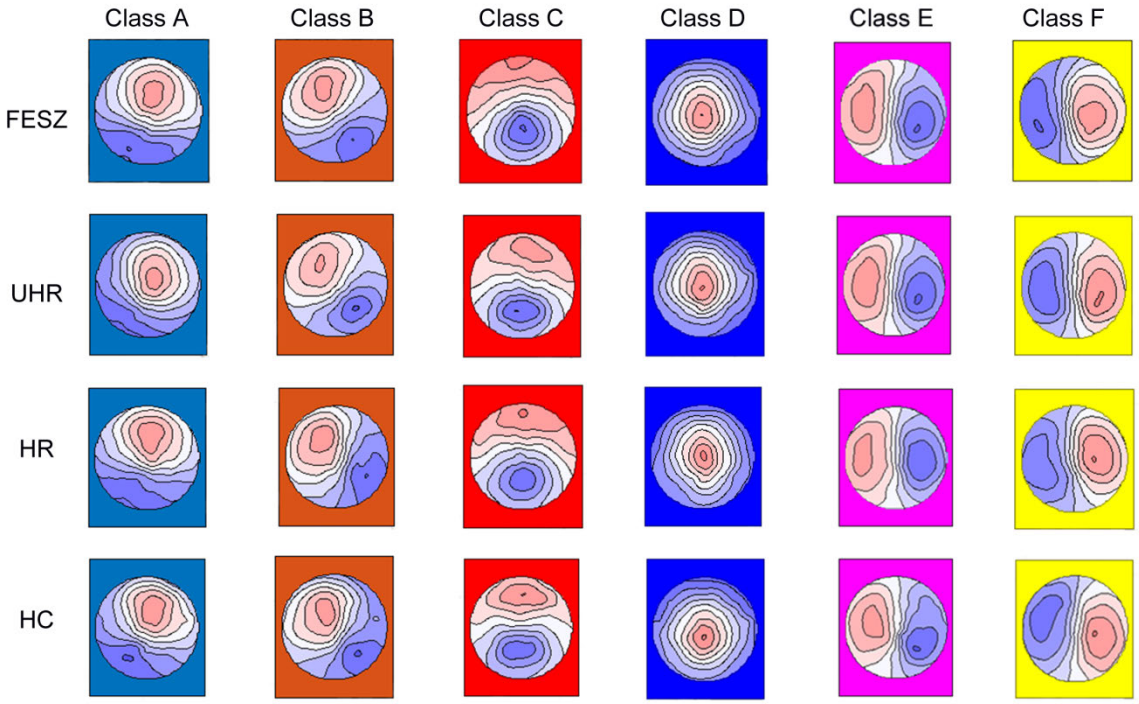

FIGURE 3. Spatial configuration of the six microstate classes (A-F) in the four groups (FESZ, UHR, HR and HC).

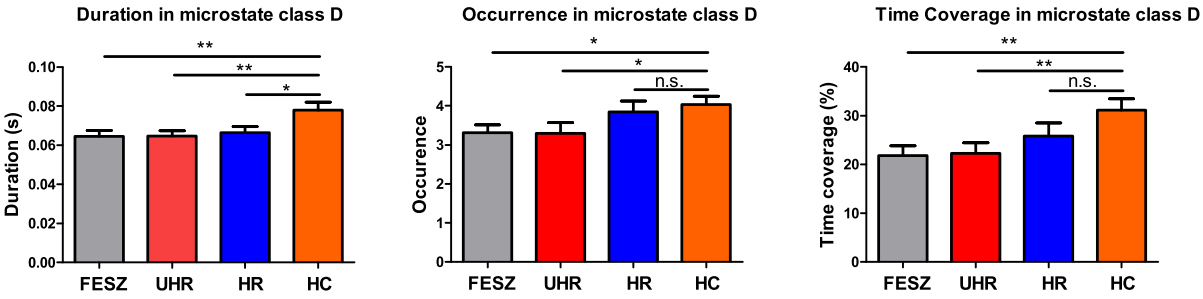

FIGURE 4. Statistical results of microstate parameters of the microstate classes (prdominant class D) in the four groups (FESZ, UHR, HR and HC). *P < 0.05, **P < 0.01, and n.s. denote not significant. Error bars are the standard error of the mean (s.e.m.).

as schizophrenia progresses in schizophrenic patients and individuals at risk.

Cognitive deficits are a core feature of schizophrenia. Individuals at risk also have cognitive deficits [31]. We investigated cognitive functions in the four groups (FESZ, UHR, HR and HC) using the MCCB. We found that in most tests (e.g. trail making test, continuous performance test), the results were scored in the order: FESZ < UHR < HR < HC. FESZ patients exhibited performance in all cognitive tests that was worse than HC. These tests evaluated some functions, including attention, working memory, social functions, perceptual function and motor function [51]. We only included drug naive participants, thus the effects of antipsychotics drugs on cognitive outcomes was excluded. Individuals that were UHR of schizophrenia had significantly poorer performance in several cognitive tests than HC, including the trail making test, symbol coding test, digit span test and some other cognitive tests. However, UHR individuals did not exhibit a significant difference in working memory or social cognition compared to HC. The cognitive results of the HR group were different from HC only in a limited manner. Moreover, total MCCB scores ranked in increasing order were: FESZ < UHR < HR < HC. Lower scores represent worse performance. These results suggest that cognitive deficits gradually increase as the disease progresses, supporting the staging model of psychosis. In addition, the cognitive results indicate that most impairments of cognitive function are apparent from the UHR stage.

In the present study, EEG signals were recorded from 128 EEG electrodes which were placed based on the international 10-20 system using the 128-channel HydroCel Geodesic Sensor Net. The 128-channel HydroCel Geodesic

TABLE 5. Classification results based on SVM, random forest and LSTM algorithms using behavioral features, and combined features to separate the four groups (FESZ, UHR, HR and HC).

Classification algorithms	Features	Average classification accuracy	Sensitivity	Specificity
SVM	Clinical + cognitive induces + EEG microstate parameters (combined features)	66 %	63.4%	65.9%
	Clinical +cognitive Induces (behavioral features)	49%	49.2%	48.0%
Random forest	combined features	92%	91.8%	90.8%
	behavioral features	69%	74.3%	63.8%
LSTM	combined features	69%	68.9%	69.4%
	behavioral features	53%	52.9%	43.5%

Sensor Net covered the entire scalp in sufficient density to ensure that all relevant data were captured. After EEG preprocessing, the 128-channel cleaned EEG data were analysed using the standard EEG microstates analysis pipeline. EEG microstates are defined as global patterns of scalp potential topographies recorded using multichannel EEG electrode arrays which changes dynamically over time in an organized manner [26], [52]. Using modified k-means clustering, these scalp potential topographies were clustered into mean EEG microstate classes. Extensive EEG studies have found that during rest and task execution, EEG microstate maps fall into four standard classes [26], [29], [30]. The four microstate classes demonstrate right-frontal to left-posterior (microstate class A), left-frontal to right-posterior (microstate class B), midline frontal-occipital (microstate class C), and fronto-central maximal (microstate class D) activity and are quasi-stable for approximately 80–120 milliseconds [34]. Moreover, these four microstate classes have been exhibited to be relatively consistent across participants (in both health and disease) and throughout the lifespan [33]. Here, using the cross-validation criterion [25], [36] inserted in the Cartool toolbox, we found that the optimal number of EEG microstate maps was 6 among the four groups, which suggested that 4 microstate classes may be not sufficient to describe the data, and 6 cluster maps optimally explained the data. High spatial correlation coefficients indicate that the microstate classes were similar among groups.

Consistent with previous studies [28]–[30], [47], [48], [53], [54], we found significant differences in EEG microstates in FESZ patients and individuals at risk compared to HC. EEG microstate analysis has been increasingly used for investigation of the spatial and temporal properties of resting-state networks in health and disease [26], [55]. Actually, there are various methods for investigating networks in a resting state during which the brain is considered inherently active in an organized manner in order to be optimally prepared for processing incoming stimuli [56]–[58]. Functional magnetic resonance imaging (fMRI) has been used for interpretation of resting state networks in the correlation between blood oxygen-level-dependent (BOLD) fluctuations in different brain areas [59], whereas EEG measures correlations between fluctuations in amplitude of oscillation activity in different regions of the brain [60]. Compared to fMRI, EEG is a direct measurement of the dynamics and synchronous polarization in spatially-aligned neurons [26]. Furthermore, EEG is much less expensive. Using 128-channel high-density EEG, we ascertained the global topography of momentary activity of the brain with high temporal resolution. The topography remains stable for approximately 80 to 120 milliseconds (ms), so EEG microstates comprise periods of quasi-stability [61], [62]. We applied resting-state EEG microstate techniques in FESZ patients, UHR individuals, HR individuals and HC. Previous studies [29], [37] have demonstrated that four microstate classes (A, B, C and D) are optimal across participants. We found that six microstate classes (A-F) were sufficient to describe the data of schizophrenia and its risk state. We demonstrated the spatial configuration of the six microstate classes (A-F) in the four groups (FESZ, UHR, HR and HC), and found a stable pattern in each microstate class, in addition to consistent topography of the six microstate maps in the four groups. These findings indicate that resting state EEG microstates may be cost-effective indicators of brain activity in patients with schizophrenia, individuals at risk and HC.

Furthermore, we calculated microstate parameters of the six microstate classes (A, B, C, D, E and F) in the four groups (FESZ, UHR, HR and HC), including duration, occurrence and time coverage. Microstate class D exhibited the most predominant differences among groups. Previous studies have suggested that microstate class D is related to the attention network and may result in a progressive attachment of mental states from internal and external information input [26], [63]. Compared to HC, FESZ patients exhibited significant differences in time coverage of class D. Time coverage in UHR individuals were also significantly different in class D. HR Individuals showed no significant differences in time coverage of D. In addition, the other three groups showed significantly lower duration in microstate class D than the HC group (in the order: HC > HR > UHR > FESZ). Many studies [29], [30], [47], [48], [53] have reported reduced duration of class D in patients with schizophrenia, and an improvement in psychotic symptoms through drug administration that prolongs class D [47]. We also found that, compared to the HC group, the HR, UHR and FESZ groups exhibited successively decreased occurrence of microstate class D. Previous studies have found that antipsychotic medication can increase the occurrence of microstate class D

in patients with schizophrenia [47]. Thus, abnormalities in microstates D possibly representing potential biomarkers for diagnosis of neuropsychiatric and neurodegenerative disorders (e.g. schizophrenia).

In addition, we explored the role of behavioral indicators and combined features (including both behavioral indicators and EEG microstate parameters) as diagnostic markers in the classification of the four groups (FESZ, UHR, HR, and HC). Currently, the diagnostic methods of schizophrenia and high-risk population are on the basis of essentially subjective psychiatric interviews [64]. The lack of disease biomarkers that support objective laboratory testing has been a long-term bottleneck in clinical diagnosis and evaluation of schizophrenia. Previous clinical studies have shown that early intervention can reduce disease progression and improve treatment outcomes [65]–[67]. The establishment of biomarkers will contribute to early disease prevention and thus improve prognosis. In this study, three classification models (SVM, random forest, and LSTM) were used to classify the four groups (FESZ, UHR, HR, and HC) based on the behavioral features and combined features. The classification performance (measured by average classification accuracy, sensitivity and specificity) was relatively lower only using behavioral features than using the combined features, which indicate that EEG microstate parameters together with behavioral indicators may be potential objective biomarkers for prediction of schizophrenia. Moreover, classic deep learning algorithms SVM and random forest achieved better performance than the LSTM deep learning algorithm, which may be due to the following reasons. First, our sample size is small which may be not suitable to apply the deep learning approaches. We only had 65 participants including 4 groups (FESZ, UHR, HR and HC), and each participant had 5 minutes resting state EEG data, whereas deep learning approaches usually require large sample size to achieve good results [68]. Second, one of the biggest benefits of deep learning over various machine learning algorithms is its ability to automatically extract features, but deep learning have obstacles, such as the lack of quality training data and poor interpretability [69]. Here, we defined EEG microstates-related features and behavioral features (e.g., cognitive measurements) which had good interpretability. Third, EEG data is one-dimensional data with a low signal-to-noise ratio (SNR), making EEG data different from other types of data (e.g., images, text and speech) for which deep learning has been most successful [68]. Furthermore, all three classifiers predicted the schizophrenia and risk group with relative high accuracy. Additionally, the random forest classifier outperformed the SVM and LSTM classifiers in predicting FESZ, UHR, HR and HC groups. Our results suggest that these groups can be partly attributed to distinct resting-state EEG microstates alterations. Extracting the most predictive features in the random forest classification indicates that random forest is suitable to predict schizophrenia, and different parameters in EEG microstates (especially class D) were informative for the classification of schizophrenia and risk group.

EEG and related measures have been used as putative biomarkers for schizophrenia prediction. Different signal processing methods have been proposed to contribute to better understanding of schizophrenia, including ERPs, EEG power spectrum, EEG oscillations, EEG connectivity, independent component analysis (ICA) and principle component analysis (PCA) [15], [70]–[74]. However, these methods are often used in two-class classification studies (e.g., distinguish schizophrenia patients and healthy controls), and there are a few studies using these methods to monitor the progression of schizophrenia. Most of these methods have achieved classification accuracy, sensitivity and specificity below 0.8 in separating schizophrenia patients from HC [70]–[73]. In the current study, EEG microstates were used for discriminating schizophrenia progression, and we found that microstate class D showed most predominant differences in schizophrenia patients and risk populations. We also obtained higher than 66% of classification accuracy, sensitivity and specificity in the four-class classification (FESZ, UHR, HR and HC). These results indicate that EEG microstates may be promising biomarkers for schizophrenia prediction.

Our findings suggest that the combined features which included MCCB tests, CDSS examinations and EEG microstates, especially the dynamics of microstate class D are candidate biomarkers for schizophrenia and risk groups. Previous studies have found that EEG microstates are highly reproducible [23], and abnormal dynamics of EEG microstates are consistently identified in patients with schizophrenia [23], [26]. However, few studies have applied EEG microstates to schizophrenia risk groups. For biomarkers, it is important that ultra-high risk (UHR) and unaffected relatives/ high risk (HR) individuals also show abnormalities, pointing to the genetic underpinnings of schizophrenia [23]. To our knowledge, this is the first study to reveal that EEG microstate class D was significantly different among patients with FESZ, individuals with UHR and HR, and HC. Our findings suggest that microstates D captures some of the genetic components that are shared by patients with schizophrenic and those at risk. The biomarkers also provide an opportunity for early diagnosis and intervention for the risk population. Because the dynamic of microstates can be changed by transcranial magnetic stimulation (TMS) [75] and neurofeedback [76], the findings open the way for the development of new therapies for schizophrenia.

These combined features are relevant physiologically. Meta-analysis studies have found that abnormalities in EEG microstates have been related to schizophrenia with medium effect sizes [63]. Previous studies support the notion that EEG microstates can provide information of potential clinical value and are thought to be useful for monitoring schizophrenia [63]. A negative correlation was found between the schizophrenia symptoms and EEG microstate D duration [47]. Shortening of microstate D correlated with the

TABLE 6. Behavioral performance of the four groups (FESZ, UHR, HR and HC) in THE MCCB tests.

Group	FESZ (n=20)			UHR (n=19)			HR (n=12)			HC (n=14)
	Mean (SD)	t values	P values	Mean (SD)	t values	P values	Mean (SD)	t values	P values	Mean (SD)
Cognitive Tests										
IQ	100.47 (11.48)	-3.75	0.001	107.75 (11.68)	-1.69	0.10	105.41 (13.81)	-1.90	0.07	114.68 (12.50)
Hopkins Verbal Learning Test-Revised	40.61 (8.86)	-2.17	0.036	42.50 (9.52)	-1.31	0.20	42.29 (5.21)	-1.71	0.10	46.25 (7.17)
WMS-III Spatial Span Test	35.54 (10.12)	-2.07	0.045	41.60 (12.22)	-0.08	0.94	40.43 (14.91)	-0.33	0.75	41.88 (9.12)
Neuropsychological Assessment Battery Mazes edition	34.50 (10.92)	-2.96	0.005	37.65 (9.95)	-2.01	0.05	37.43 (9.48)	-1.90	0.07	44.88 (11.65)
Brief Visuospatial Memory Test-Revised	38.68 (13.36)	-1.61	0.046	38.95 (11.79)	-1.60	0.12	45.00 (11.43)	0.05	0.96	44.81 (9.57)
Animal Naming Test	42.50 (10.58)	-3.06	0.004	42.75 (10.05)	-2.93	0.006	41.07 (6.02)	-4.02	0.0001	51.94 (8.39)
Managing Emotions Test	34.32 (12.77)	-2.19	0.001	37.67 (8.24)	-1.64	0.11	39.86 (8.76)	-0.78	0.44	42.27 (7.78)
Visual Learning	38.68 (13.36)	-1.61	0.046	38.95 (11.79)	-1.60	0.12	45.00 (11.43)	0.05	0.96	44.81 (9.57)
Reasoning and Problem Solving	34.50 (10.92)	-2.96	0.005	37.65 (9.95)	-2.01	0.05	37.43 (9.48)	-1.90	0.07	44.88 (11.65)

hallucinations in schizophrenic patients with auditory verbal hallucinations [77]. Regarding the relationship between cognitive features and EEG microstate features, microstate D is due to flexible changes in attention, and related to the frontoparietal attention network [37]. Moreover, EEG microstates can be influenced by cognitive training. For example, the percentage of time spent producing microstate D has been increased after neurofeedback intervention [76]. Therefore, the cognitive, clinical and microstate features are relevant physiologically.

It appears quite natural that people at a more advanced stage of schizophrenia showed more remarkable cognitive impairments and poorer clinical performance. As the disease progresses, the cognitive deficits and clinical symptoms gradually increase. The cause of schizophrenia remains unknown [1]. According to a neurodevelopmental model of schizophrenia [1], the developmental trajectory of schizophrenia may include excessive pruning of excitatory pathways and reduced elaboration of inhibitory pathways, resulting in altered excitatory–inhibitory balance in the prefrontal cortex. Reduced myelination would alter connectivity [1]. This model divides schizophrenia into four stages, including HR, UHR, FESZ and chronic schizophrenia, with more sever clinical symptoms and cognitive deficits as the disease progresses [1]. Furthermore, EEG microstates (especially class D) change as the disease progresses, which may be because the abnormal microstate dynamics in schizophrenia are considered as an imbalance between processes that load on saliency, which are increased, and processes that integrate contextual information (microstate class D), which are reduced [23]. Thus these features change due to the change in the condition.

V. CONCLUSION

Schizophrenia has been considered a neurodevelopmental disorder, the neurodevelopmental model [1] having divided the trajectory of schizophrenia into four different stages, comprising HR, UHR, FESZ and chronic disability stages. In the present study, we recruited four groups of individuals at different stages of schizophrenia. The biomarkers used for the prediction of schizophrenia are combined biomarkers including behavioral examinations and EEG microstates parameters. Specifically, the combined biomarkers consist of resting-state EEG microstates (including duration, occurrence and time coverage), cognitive measures (including MCCB tests) and clinical examinations (including CDSS tests). The average classification accuracy, mean sensitivity and mean specificity of the four groups were higher on the computation of combined features extracted from behavioral indicators and EEG microstates than only using behavioral features, especially when using the random forest model. We also found six optimal cluster maps across the groups. The results may indicate that certain abnormalities in behavioral and EEG microstates (especially in microstate class D) may be associated with the progression of schizophrenia. These abnormalities may become biomarkers for prediction of schizophrenia, which raises the possibility of postponing or even preventing the onset of schizophrenia, decreasing the

severity of the disease and ameliorating the circumstances of the individual, their family and social consequences.

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APPENDIX A

See Table 6.

APPENDIX B

See Fig. 5.

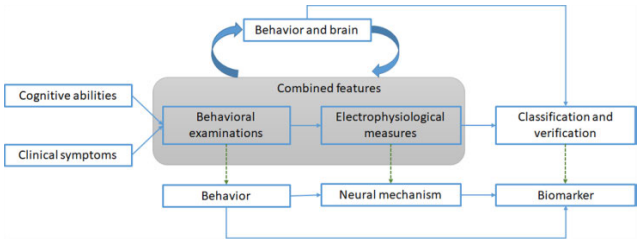

FIGURE 5. A behavior-brain model of schizophrenia diagnosi. To explore biomarkers of schizophrenia, we computed and compared the average classification accuracy of the four groups (FESZ, UHR, HR, HC) based on behavioral features and combined features extracted from both behavioral measures and EEG microstates. The biomarkers which were used for predicting schizophrenia included behavioral examinations (e.g., MCCB, CDSS) and EEG microstates (e.g., duration, occurrence and time coverage).

ACKNOWLEDGMENT

The authors would like to thank for Zhen Mao, Yanbin Xiong, and Xiaohui Zhao for valuable work with the data collection.

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