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Eye Movement Abnormalities Can Distinguish First-Episode Schizophrenia, Chronic Schizophrenia, and Prodromal Patients From Healthy Controls

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***Background*: This study attempts to replicate in a Chinese population an earlier UK report that eye movement abnormalities can accurately distinguish schizophrenia (SCZ) cases from healthy controls (HCs). It also seeks to determine whether first-episode SCZ differ from chronic SCZ and whether these eye movement abnormalities are enriched in psychosis risk syndrome (PRS).*Methods*: The training set included 104 Chinese HC and 60 Chinese patients with SCZ, and the testing set included 20 SCZ patients and 20 HC from a UK cohort. An additional 16 individuals with PRS were also enrolled. Eye movements of all participants were recorded during free-viewing, smooth pursuit, and fixation stability tasks. Group differences in 55 performance measures were compared and a gradient-boosted decision tree model was built for predictive analyses.*Results*: Extensive eye-movement abnormalities were observed in patients with SCZ on almost all eye-movement tests. On almost all individual variables, first-episode patients showed no statistically significant differences compared with chronic patients. The classification model was able to discriminate patients from controls with an area under the curve of 0.87; the model also classified 88% of PRS individuals as SCZ-like.*Conclusions*: Our findings replicate and extend the UK results. The overall accuracy of the Chinese study is virtually identical to the UK findings. We conclude that eye-movement abnormalities appear early in the natural history of the disorder and can be considered as potential trait markers for SCZ diathesis.**

Key words: schizophrenia/eye movement abnormalities/classification/predictive model/psychosis risk syndrome

Introduction

Schizophrenia (SCZ) is a common complex neuropsychiatric disorder with both genetic and environmental factors contributing to overall risk.[1] Although multiple biological abnormalities are routinely found at the group level when SCZ subjects are compared with control groups, no abnormalities have been reported to date that have either the sensitivity of specificity to be of value in helping with diagnosis or informing the choice of treatment in routine clinical psychiatric practice.[1,2]

A variety of eye-movement abnormalities under different conditions have been described in patients with SCZ, including free-viewing, smooth pursuit, and saccadic eye movements.[3–5] Previous studies demonstrated restricted eye searching area in SCZ when cases viewed faces,[6,7] social scenes,[8] and nature scenes.[9,10] Different eye movement patterns were also found in patients with SCZ when viewing context-free images and context-embedded images compared with healthy individuals.[11] Also, some disruption of smooth pursuit has been consistently reported in patients with SCZ, such as decreased closed-loop gain, disrupted open-loop eye acceleration, and significant increased smooth pursuit errors.[12–15] In addition, studies have found that people with SCZ had increased latencies and decreased accuracies of correct anti-saccade responses and made more anti-saccade errors than matched comparison subjects under both anti-saccade task and memory-guided saccade task.[3,16–18] Similar patterns of eye-tracking dysfunction were also observed in siblings and in individuals with ultra-high-risk psychosis.[17,19–21] Most previous studies focused on only a single-eye movement

task with only a few using multi-task models to predict the diagnostic status of healthy individuals vs cases. It therefore, remains unclear whether how sensitive these abnormalities are at distinguishing cases from healthy individuals.

In our previous study, we conducted a series of multi-tasking eye-tracking tests combining free-viewing, smooth pursuit, and fixation stability in patients with SCZ and healthy participants. We found that, by using a gradient-boosted decision tree algorithm, combined eye movement tests can discriminate new patients with SCZ from controls with predictive accuracy of around 80%.[9] In a subsequent study with an expanded sample but based on the same eye-movement tasks, a high-dimensional classifier distinguished patients with SCZ from healthy individuals at 89% area under the curve (AUC).[22] Both 2 studies were conducted in Western populations. Morita et al[23] conducted a study in Japan using similar multi-task protocols and they obtained an accuracy of 82% to distinguish patients with SCZ from controls. However, they used different computational models, measurement variables, and stimulus materials. Given the exceptional discriminant accuracy of these reports using combined eye-tracking tests, we decided it was important to know whether our findings could be replicated in a different ethnic population of cases and controls.

Although psychosis risk syndrome (PRS) has long been identified, the clinical treatment of SCZ traditionally begins at the first episode of acute psychosis.[24] Little attention until recently has been paid to the period preceding the first episode. One meta-analysis reports that only 36% of people with PRS will develop a psychosis disorder 3 years after recognition.[25] This poor specificity and differing outcomes of PRS make it difficult to know how to manage these at-risk individuals.[26] Unsurprisingly, few eye-tracking studies have examined PRS persons with mixed results.[27,28] It is still unclear whether eye movement abnormalities are present and in what proportion of individuals and whether they can predict clinical outcomes.

Here, we conducted a verification study in the Chinese population to test whether or not eye movement performance in a series of eye-tracking tests can distinguish patients with SCZ from healthy individuals with high accuracy. We used exactly the same modeling algorithm as in our previous study.[22] In the present study, we compared eye-movement features extracted from different tasks between patients with SCZ and healthy controls (HCs), and between PRS and healthy individuals. Eye-movement measures were also compared between the first episode and chronic patients with SCZ. Finally, the class probability of eye-tracking data from PRS individuals was estimated using the model trained on patients with SCZ and HC.

Methods and Materials

Participants

Sixty Chinese patients with SCZ were recruited and tested at the Second Xiangya Hospital of Central South University. Diagnosis was determined by a structured clinical interview for DSM-IV.[29] A total of 16 participants with PRS were also recruited from outpatient clinics at the hospital. The Structured Interview for Prodromal Syndromes was applied to confirm the presence of PRS.[30] None of the PRS individuals were on medication before or during the testing period. Most of the SCZ cases (85%) were inpatients present at the time of the study. Detailed medical and psychiatric histories were obtained for all patients and the Chinese version of Positive and Negative Syndrome Scale (PANSS) was also administered.[31] Thirty-four (57%) of the 60 cases were first-episode patients with SCZ. Of all the patients, 3 (5%) were drug-naïve at the time of testing, 4 (7%) were receiving typical antipsychotics only, 45 (75%) atypical antipsychotics only, and 4 (7%) a combination of the 2. A few patients were also receiving additional medications eg, antidepressants (11, 18%), mood stabilizers (3, 5%), benzodiazepines (8, 13%), anticholinergic agents (7, 12%), and β-blockers (4, 7%). Patients and PRS participants who had a neurological illness, diabetes, history of head injury, or poor/incomplete eye-movement data were excluded.

Matched with age and sex to patients, the control group (n = 104) was recruited by word of mouth from the Second Xiangya Hospital staff and students and from students in Changsha University of Science and Technology. None had a psychiatric history or a first-degree family history of psychosis. HC were also excluded if they had epilepsy or other neurological disease(s), diabetes, a history of substance dependence or abuse within 6 months, or a history of head injury with loss of consciousness for more than 5 min. Normal or corrected-to-normal vision was required for all patients and controls. All these Chinese patients with SCZ and HC were used as the training dataset.

The testing dataset comprised 20 patients with SCZ and 20 healthy participants who were enrolled in the United Kingdom. A diagnostic interview using the Structured Clinical Interview for DSM or the Mini International Neuropsychiatric Interview was administered to all cases and controls.[29,32] The same inclusion and exclusion criteria were applied. Neurocognitive tests, such as the Trail Making Test and the Digit Symbol Coding Test, were administered to all patients and HC in both the training and the testing datasets. Results will be reported elsewhere.

Ethical approval of this study was granted by the Ethics Committee in the Second Xiangya Hospital of Central South University. The study was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Eye Movement Recordings

Apparatus. Eye movements were tracked monocularly with EyeLink 1000 eye tracker (SR Research, Ontario, Canada) at a sampling rate of 1000 Hz. Participants saw stimuli using both eyes, but only the dominant eye was recorded. Dominant eye was determined using the hole-in-the-card test. Stimuli, which subtended 41.6 h × 24.1 v degrees of visual angle, were displayed on a 24-inch (61 cm) monitor with a refresh rate of 144 Hz. Participants viewed stimuli at a distance of 70 cm. A 3 × 3 fixation matrix was used for calibrations at the beginning of each task. Automatic drift correction was applied to all tasks. We used a chin-forehead-rest to minimize head movements.

Stimuli and Procedures. The same stimuli, as in our previous studies were used.[9,22] They included the following 3 tasks: (1) free-viewing, (2) smooth pursuit, and (3) fixation stability. Forty-two images were chosen from the original stimuli for the free-viewing task and five were replaced with newer images with more Chinese characteristics. Short breaks were taken during the experiment whenever necessary. Each image was shown for 8 seconds. Those 42 images included expressive, neutral, unturned and cartoonish faces; natural landscapes; man-made environments; animals; and computer-generated images. In the smooth pursuit task, participants were instructed to track a 0.5° circular target on the screen. The target moved horizontally on the horizontal meridian of the screen at 0.4 Hz (HS4) or in Lissajous patterns at a frequency of 0.2 or 0.4 Hz (LS2 and LS4). Each trial lasted 20 seconds. In the fixation stability task, a 0.5° circular target was presented at the center of the screen for 5 seconds. An identical distracter target was then shown to the left or right (1.43° or 2.86°) of the central target. Participants were required to maintain a steady gaze only on the central target in all circumstances. Each trial was performed twice.

Feature Extraction. Eye-tracking data were extracted by the same method as our previous study. The common eye movement parameters were computed, including the number and duration of eye fixations, total scanning length, number and duration of saccades, saccade amplitude, saccade peak, and average velocity. An indicator of fixation dispersal was calculated as a specific measure to identify participants' (restricted or extended) viewing patterns in the free-viewing task.[33] The fixation stability task gave global measures for both single and distracter conditions. A total of 55 eye-movement measures were extracted and calculated in this study, see Supplementary table S1 for details together with our previous publications.[9,22]

Statistical Analysis

Basic statistics and predictive analysis were performed in R (http://www.r-project.org). Pearson's chi-squared test and analysis of variance (ANOVA) were used for the comparison of demographic characteristics and eye movement variables between the 2 groups. If the data did not conform to a normal distribution, rank-based nonparametric tests were conducted. Effect sizes for ANOVA's were calculated. We reported only Hedges's g in this study.[34] To assess the effects of demographic and clinical variables on eye movement measures, such as age, education, and psychotropic medications, a correlation analysis was performed in the SCZ group.

A gradient-boosted decision trees (GBDT) model was built for modeling eye-tracking data and performing discriminant analyses. The decision trees are usually weak learners. In gradient boosting, weak learners work sequentially. Each model tries to improve on the error from the previous model. GBDT is one of the best machine learning algorithms for fitting real distributions due to the combination of gradient boosting and decision trees. The training dataset and testing dataset were completely separate and came from 2 populations. A total of 164 Chinese participants' data were used as the training set. Data from 40 randomly selected participants from the UK cohort were used as the test set. The only target variable was "diagnosis" (SCZ and HC). We used the XGBoost package in R language to build our classifier. A modified version of 5-fold cross-validation was performed, and XGBoost hyperparameter was determined and carefully adjusted to improve the effectiveness of the model and avoid overfitting.[35] All 55 eye-tracking measures obtained from 3 tasks, including free viewing, smooth pursuit, and fixation stability, were used as predictors. Predictive performance was assessed using AUC, sensitivity, specificity, and balanced accuracy on the test dataset.

Results

Demographic and Clinical Characteristics

Demographic variables of all participants in training and testing datasets are summarized in table 1. There was no significant difference in age, sex, and nicotine or alcohol exposure between the SCZ patient and HC groups in the training dataset. Patients spent 4–7 fewer years in education than controls ($P < .001$). Both depression and anxiety subscale scores in Hospital Anxiety and Depression Scale (HADS) were significantly higher in patients than in controls ($P < .001$).

Eye Movements

Free-viewing. Only the differences in eye-tracking results between patients and controls in the training set are described here. They are summarized in supplementary table S2. The results of the testing set are summarized in supplementary table S3. The results of the other 2 tasks are expressed in the same way. In free-viewing task, patients with schizophrenia viewed

Table 1. Demographic and Clinical Characteristics of Patients With Schizophrenia and Healthy Controls

	Training data (Train, N = 164)				Testing data (Test, N = 40)			
	SCZ[a]	CON[a]			SCZ[a]	CON[a]		
	Mean (SD)	Mean (SD)	χ^2 or F[b]	P value	Mean (SD)	Mean (SD)	χ^2 or F[b]	P value
N	60	104			20	20		
Age, years	24.7 (7.8)	25.0 (5.1)	1.58	.210	40.2 (10.7)	38.7 (14.8)	0.73	.398
Sex, F:M	30:30	58:46	0.30[c]	.582	14:6	15:5	0.14 [c]	.71
Education, median, years	8–11	15+	78.55	<.001	12–15	15+	13.37	<.001
HADS_anxiety	10.5 (4.9)	4.0 (2.8)	97.27	<.001	8.5 (5.3)			
HADS_depression	11.2 (3.6)	3.2 (2.3)	233.86	<.001	6.8 (4.9)			
PANSS total score	72.8 (18.1)				56.4 (19.3)			
Illness age-of-onset, years	21.0 (5.1)				25.6 (8.8)			
Illness duration, years	3.7 (5.6)				18.5 (9.5)			
CPZe, mg/day	360.5 (303.0)							
Nicotine, Y:N	16:44	22:82	0.38[c]	.539				
Nicotine intake per day	2.5 (7.0)	1.4 (5.3)	0.22	.644				
Nicotine recent, hours	0.5 (1.1)	0.5 (1.1)	0.002	.964				
Caffeine, Y:N	9:51	25:79	1.38[c]	.240				
Caffeine intake, cups/day	0.3 (0.7)	0.4 (1.1)	1.70	.194				
Caffeine recent, hours	0.5 (1.1)	0.7 (1.3)	1.45	.230				

Note: CPZe, neuroleptic chlorpromazine-equivalent dosage; HADS, Hospital Anxiety and Depression Scale; PANSS, Positive and Negative Syndrome Scale.
[a]Education was bracketed into 4 categories: <8 years, 8–11 years, 12–15 years, 15+ years. Median coded range is shown. Nicotine recent intake and caffeine recent consumption were coded as follows: 0 = NA, 1 = less than 1 h, 2 = 1–2 h, 3 = 2+ h.
[b]F value based on univariate analysis of variance using ranked data if non-normally distributed.
[c]Pearson χ^2 test.

pictures in a way different from HC. Between-group univariate analysis revealed that patients' gaze dispersion was significantly smaller than controls ($P = 10^{-11}$, $g = 1.16$). Their eyes stayed in certain areas of images for a longer period of time ($P < .01$, $g = 0.46$). This was mainly manifested in a significant reduction in the number of fixations ($P = 10^{-4.7}$, $g = 0.74$) and saccadic ($P = 10^{-4.7}$, $g = 0.72$) eye movements as revealed in the group comparisons. Patients displayed smaller ($P = 10^{-5.7}$, $g = 0.80$) and slower ($P = 10^{-8.1}$, $g = 0.98$) saccades during picture viewing. Their scan path length was also significantly shorter compared with controls ($P = 10^{-10.7}$, $g = 1.17$) (supplementary table S2).

There was a statistically significant but weak correlation between age of onset and saccade duration in SCZ group (rho = −0.26, $P = .04$). No correlation was found between other eye-movement measures and clinical characteristics for this task (supplementary figure S1).

Smooth Pursuit. In all three pursuit tracking tasks (HS4, LS2, and LS4), patients with SCZ in training dataset exhibited significantly longer ($10^{-6.5} \le P \le .001$, $0.48 \le g \le 0.84$), larger ($10^{-4.7} \le P \le 0.01$, $0.33 \le g \le 0.68$), and rapid ($10^{-5.1} \le P \le .001$, $0.34 \le g \le 0.78$) corrective saccades compared with controls. For LS2 task, both horizontal and vertical eye-tracking gain in cases were farther from 1 than those in controls (Gain-x, $P = .03$, $g = 0.26$; Gain-y, $P = .048$, $g = 0.29$). Relative to healthy individuals, patients made fewer mild tracking adjustments (fixation frequency, $P = .046$, $g = 0.43$; saccade frequency, $P = .03$, $g = 0.44$) during the fast Lissajous test (LS4), but got inferior accuracy (SNR-x, $P = .01$, $g = 0.43$; SNR-y, $P = .01$, $g = 0.56$) and more positional errors (RMSE-y, $P = .01$, $g = 0.43$) (supplementary table S2).

Significant correlation was found between illness duration and horizontal smooth pursuit log signal to noise ratio in LS2 task (rho = −0.29, $P = .03$). Antipsychotic medication use in patients with SCZ was correlated with vertical global gain (eye/target temporal frequency) in LS2 task (rho = −0.33, $P = .02$). Anxiety symptom scores were significantly correlated with saccade average velocity in LS2 task (rho = 0.29, $P = .02$). For LS4 task, there were significant correlations between age of onset and number of fixations (rho = 0.27, $P = 0.04$), fixation duration (rho = −0.26, $P = .047$), and number of saccades (rho = 0.26, $P = .046$). No other clinical characteristics were found to correlate with patient performance in this task (supplementary figure S2).

Fixation Stability. All of the eye-tracking measures used in the fixation stability task were significantly different between the 2 groups. Patients' gaze stability was remarkably worse than HC. This was reflected in both a single target and single plus distracter targets

conditions. When a single target was present, patients with SCZ made more saccades ($P = .01$, $g = 0.39$), and the number of fixations was clearly increased ($P = .016$, $g = 0.35$). The patients had difficulties in focusing their eye on the target (scan path length, $P < .01$, $g = 0.23$). In distracter conditions, more ($P < .01$, $g = 0.72$) and larger ($P < .001$, $g = 0.72$) saccades were made by patients, as well as increased fixations numbers ($P < .001$, $g = 0.71$) and decreased fixation durations ($P = .001$, $g = 0.39$). Scan path length was also much larger ($P = 10^{-5.0}$, $g = 0.90$) in cases compared with controls (supplementary table S2).

The severity of psychotic symptoms (as assessed by the PANSS total score) in SCZ patients was found to correlate with all indicators in distracter conditions of the task, including number of fixations (rho = 0.38, $P < .01$), fixation duration (rho = −0.34, $P = .01$), number of saccades (rho = 0.37, $P < .01$), saccade amplitude (rho = 0.33, $P = .01$), and scan path length (rho = 0.38, $P < .01$). No other clinical indicators were found to correlate with patient performance in this task (supplementary figure S3).

First Episode vs Chronic Schizophrenia

The clinical characteristics and eye-tracking variables of first episode schizophrenia (FESZ) and chronic schizophrenia (CSZ) are provided in supplementary table S4. Patients with FESZ were significantly younger than chronic ones ($P < .001$). Illness duration was shorter ($P < .001$) in FESZ patients than CSZ cases. No statistically significant differences in other demographic and clinical characteristics such as sex, nicotine or alcohol exposure, symptom severity, age of onset, amount of medication were observed between the 2 groups.

There were no significant differences detected in all eye-tracking measures extracted from both free-viewing and fixation stability tasks between the FESZ group and CSZ group. As indicated by their differences of SNR ($-x/y$), FESZ patients had more accurate tracking compared with CSZ cases in this smooth pursuit task. No other eye movement indicators in smooth pursuit tests were found to be statistically significantly different between the 2 groups (supplementary table S5).

PRS Results

Eye movement data were recorded on 16 individuals with PRS. The clinical characteristics are summarized in supplementary table S6. The abnormal performance in the eye movement tasks presented by individuals with PRS are summarized in supplementary table S7. Compared with HC, PRS individuals showed abnormal indicators in almost all eye-movement tasks, except for the smooth pursuit HS4 task.

Predictive Performance of the GBDT Model

Detailed confusion matrices and additional performance measures for the classifier can be found in table 2. By using combined eye-tracking measures from all tasks, GBDT model distinguished patients with SCZ from controls with an AUC of 0.87 (75% sensitivity and 90% specificity) (figure 1). The importance ranking of all variables for the model is summarized in figure 2. The top 2 most important variables contributing to the

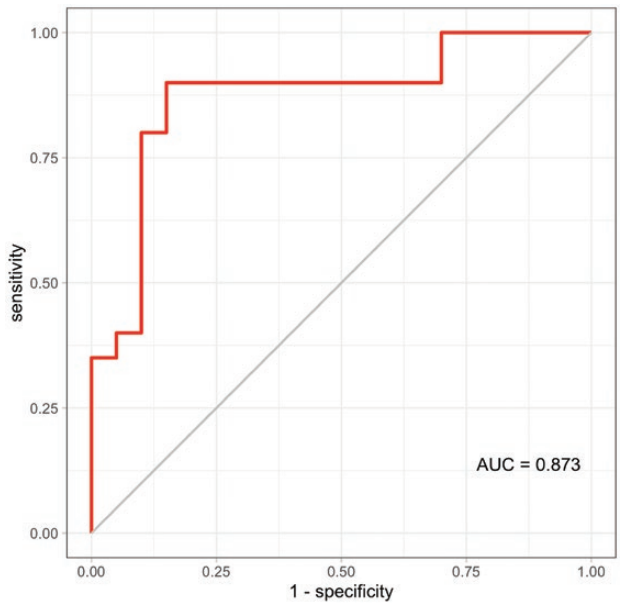

Fig. 1. ROC curve of the GBDT model distinguishes schizophrenia patients from controls. ROC, receiver operating characteristic; GBDT, gradient-boosting decision tree; AUC, area under the curve.

Table 2. Confusion Matrix and Performance Matrix of the Classification Model

	Reference									
Prediction	SCZ	CON	Sensitivity	Specificity	PPV	NPV	F1 score	Accuracy	Balanced Accuracy	AUC
SCZ	15	2	0.75	0.90	0.88	0.78	0.81	0.83	0.83	0.87
CON	5	18								

Note: SCZ, Schizophrenia; CON, Healthy Control; PPV, Positive Predictive Value; NPV, Negative Predictive Value; AUC, Area Under the Curve.

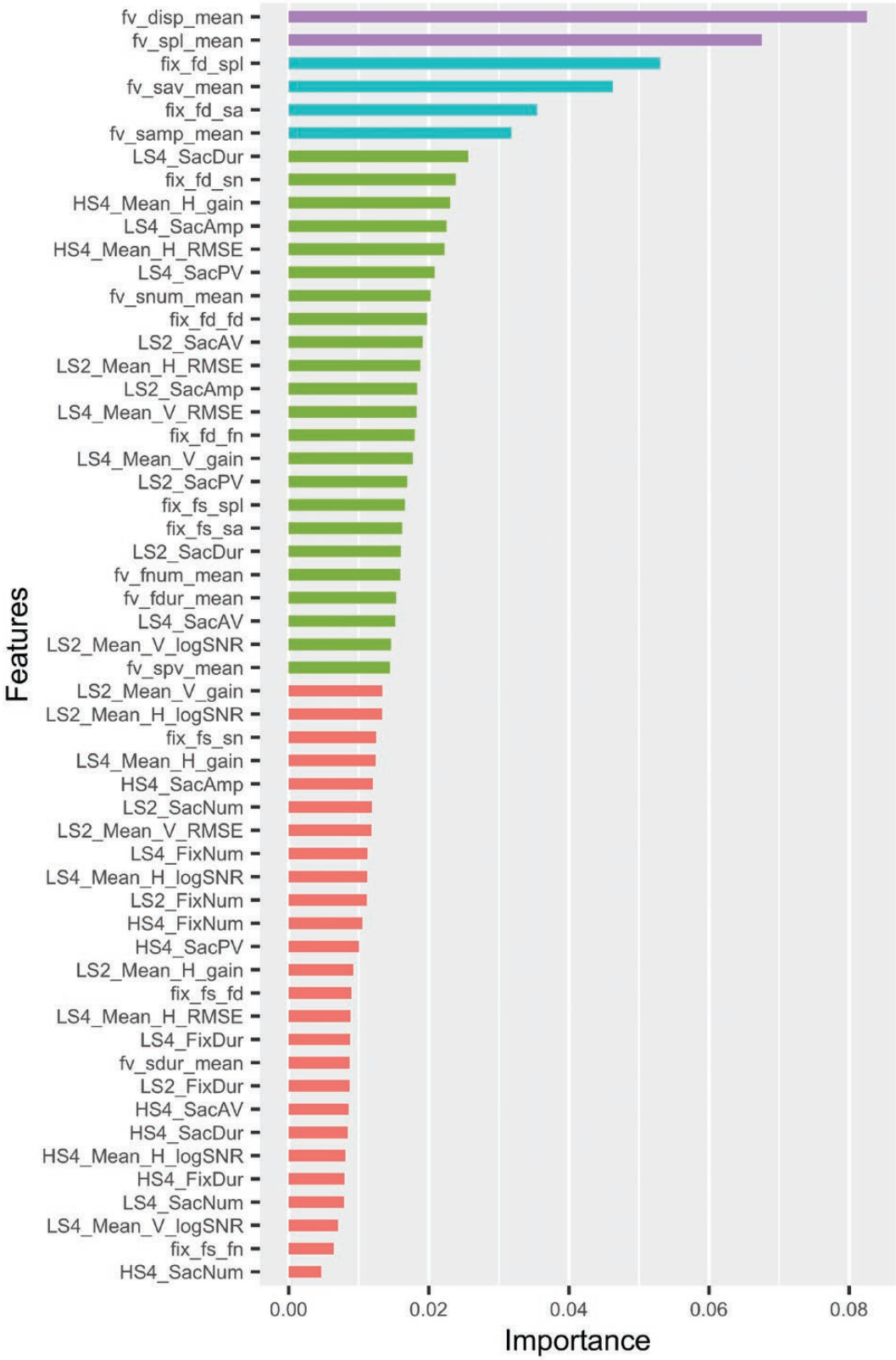

Fig. 2. Ranking of the importance of the eye-movement features on which the GBDT model distinguishes patients with schizophrenia from healthy controls (HC). The *X*-axis marks the gain values that represent the importance of the features in the discriminant model. The bar colors corresponding to different clusters that have similar gain values. Detailed information on the eye-movement features in the figure can be found in supplementary table S1. GBDT, gradient-boosting decision tree.

model were fixation dispersion and scan path length in the free-viewing task. Although there is no direct connection between the GBDT model and general linear model, we found that all of the 6 most important discriminators were also highly significant measures in the univariate analysis between patients and controls (figure 3). When eye-tracking data from 16 individuals with PRS were interrogated by the SCZ-control trained GBDT model, 88% were classified as SCZ (n = 14), the rest 12% were predicted to be controlled (n = 2) (table 3).

Discussion

The present study follows on from work by Benson et al and St. Clair et al and investigates in a new Chinese population the discriminatory power of multiple eye-tracking tasks to distinguish patients with SCZ from healthy participants.[9,22] These tasks included free-viewing, smooth pursuit, and fixation stability test. We also compared eye movement features of first-episode SCZ vs chronic cases. The results show that no significant differences in visual behavior between the first-episode and chronic patients with SCZ on any of the tests, except one measure in the smooth pursuit task. Based on combined eye-tracking measures, a discriminant BGDT model can obtain an AUC of 0.87 between patients with SCZ and controls. Using individual-specific characteristics derived from eye movement tasks, 88% of PRS individuals was classified as abnormal and 12% are misclassified as normal. In the present study, although relatively few analytic measures were used (55 vs 98), we have successfully replicated in a Chinese population our previous findings in a Caucasian population.[22]

Consistent with our previous study, we find that the free-viewing task and fixation stability tests are the most powerful discriminators of patients from controls. Free-viewing scan paths represent visual searching behavior without any specific goal. We calculated the eye-tracking pattern and all general indicators to comprehensively evaluate the eye movement characteristics of the participants when collecting visual information. Our results indicate that patients with SCZ show an abnormal restricted scanning style characterized by less fixation frequency, shortened scan path length, and reduced fixation dispersion. The fixation stability task was designed to represent saccadic inhibition in anti-saccade tests. In the present

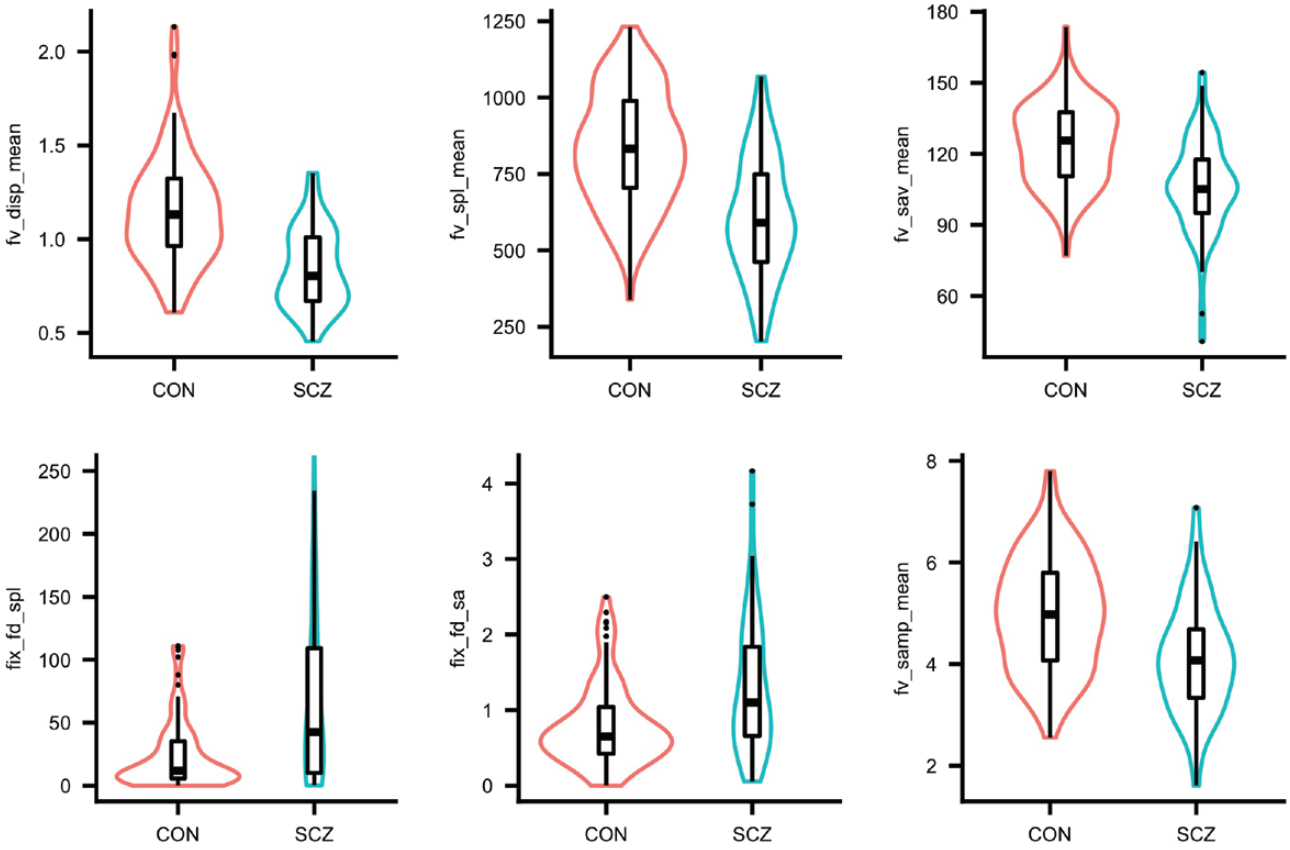

Fig. 3. Data distribution of selected eye-movement measures in schizophrenia and healthy controls (HC). Between-group comparisons of these 6 measures revealed significant differences between schizophrenia group and the healthy group. These eye-movement measures were considered by the classifier to be the top 6 most important measures for differentiating patients from healthy individuals. Detailed information on the eye-movement features in the figure can be found in supplementary table S1. CON, healthy controls; SCZ, patients with schizophrenia.

Table 3. The Prediction Probability of 16 PRS Individuals Assessed by Patient-Control Trained Model

ID	Original group	Discriminant Probability_CON (%)	Discriminant Probability_SCZ (%)	Discriminated group
1	PRS	33.80	66.20	SCZ
2	PRS	3.41	96.59	SCZ
3	PRS	2.82	97.18	SCZ
4	PRS	30.69	69.31	SCZ
5	PRS	1.49	98.51	SCZ
6	PRS	34.38	65.62	SCZ
7	PRS	5.2	94.71	SCZ
8	PRS	96.78%	3.22	CON
9	PRS	35.07	64.93	SCZ
10	PRS	1.39	98.61	SCZ
11	PRS	5.05	94.95	SCZ
12	PRS	21.43	78.57	SCZ
13	PRS	17.13	82.87	SCZ
14	PRS	65.74	34.26	CON
15	PRS	8.97	91.03	SCZ
16	PRS	10.90	89.10	SCZ

Note: PRS, psychosis risk syndrome; SCZ, schizophrenia; CON, healthy control.

study, sustained attention abnormalities were detected in patients under both single and distracter target conditions through eye tracking. Our observations are consistent with those in a previously reported study demonstrating the difficulty for patients with SCZ to maintain steady fixation.[4,36] The fixation stability test may help to expose patients' deficits in implementing inhibitory control and interpret abnormal patterns in saccade, free-viewing, and smooth pursuit tasks. Its high discriminatory power for distinguishing patients from controls has been proved in the present study.

Patients with SCZ showed different eye-movement patterns in free-viewing tasks than HC, indicating that patients have abnormal visual processing patterns in the real world. This may be related to frontal lobe dysfunction since they performed exploratory eye-tracking movements similarly to individuals with frontal lobe lesions.[37] Moreover, a previous study found that patients' visual exploration patterns during free-viewing correlated with their neuropsychological performance.[38] In the present study, individuals with SCZ demonstrated difficulty in inhibiting unnecessary eye movements during fixation stability tasks. The dorsolateral prefrontal cortex (DLPFC) performs the role of regulating executive functions that control the presence of non-essential impulses. An extensive literature has demonstrated the existence of DLPFC dysfunction in patients with SCZ.[39] This may be one of the brain functional mechanisms underlying the poor gaze stability in patients. What is more, brain regions involved in the control of fixation and saccades include the frontal cortex, the thalamus, and the basal ganglia.[40,41] Dysfunction of the prefrontal-thalamic circuit in patients with SCZ, as well as abnormalities in the prefrontal-basal ganglia circuit, have also been demonstrated in previous studies.[42,43] Abnormalities in the structural or functional connectivity of the prefrontal-thalamic-basal ganglia circuit may also directly contribute to the abnormal performance of patients in free-viewing and fixation stability tasks.

In the smooth pursuit task, both horizontal and vertical eye movements for different frequencies were evaluated in the present study. Patients with SCZ had worse performance (ie, less accurate tracking) than HC on almost all tests. Three measures from this task ranked in the top 10 important discriminator of patients from controls, including horizontal global gain in HS4 test, saccade duration and saccade amplitude in LS4 test. Our results are consistent with previous studies, in which smooth pursuit abnormalities are frequently reported in patients with SCZ and their relatives.[12,13,15,44] Pursuit deficits include problems predicting target motion, problems perceiving visual motion information, or problems making sensorimotor transformations.[45,46] It has been suggested that interconnectivity abnormalities in specific brain regions such as middle temporal gyrus, dorsomedial prefrontal cortex, and dorsolateral prefrontal cortex may play a role in smooth pursuit dysfunction in SCZ.[47]

When do eye movement abnormalities first present in individuals with SCZ? In the present study, we found almost no significant differences in eye-tracking performance between first-episode patients with SCZ and chronic cases, see supplementary table S5. Most of the first-episode patients were from acute hospital wards, and a few of them were behaviorally disorganized. All of the first-episode patients had been medicated for less than one month. Three of them were drug-naïve at the testing time. This indicates that eye movement abnormalities may be occurring in the early stages of SCZ. Eighty-eight percent of individuals with PRS were classified as "SCZ" using the training model built with patients with SCZ and HC in the present study. These results are very promising, given that nearly 30% of people at clinical

high risk of psychosis will develop a psychotic disorder 3 years after identification.[25] When summarized our findings suggest that eye movement abnormalities are not a state-dependent phenomenon, and may have clinical utility for identification of at-risk individuals and for early diagnosis of SCZ. We are currently follow-up these PRS individuals to confirm the predictive and diagnostic power of eye-tracking tests.

Strengths

Previous literature has shown that machine learning can be used to identify individuals with mental illnesses based on brain data, with an acceptable score when the accuracy is 75%.[48] In this study, the eye movement data were used to build a discriminative model from the training set, and the model was able to distinguish well (accuracy of 83%) between patients and healthy individuals in a completely independent testing set. Our results independently confirm and revalidate in a separate ethnic population our earlier findings.[22] This suggests 2 important points. First, the phenotype of eye-movement performance does reflect the core features of SCZ.[4,46] Second, the classifier we built is well fitted to do this type of classification. We applied a modified version of 5-fold cross-validation approach to fine-tune the hyperparameters, which made the classifier more effective. In addition, the fact that 57% of the patient group in this study were first-episode patients, as well as the fact that 16 individuals with PRS were also tested, is one of the strengths that distinguishes this study from previous studies. This suggests that duration of the disorder plays a limited role in influencing the discriminatory findings.

Limitations

Firstly, we used a relatively small number of patients as the training set of the model. A larger sample of training set covering patients with different stages of SCZ might have further improved the discriminative accuracy of the model. Secondly, although we were able to eliminate most potential confounders including age, the effect of neuroleptic medication remains problematic as it does where psychiatric patients are compared to unmedicated control subjects. However, the only differences we found modestly significant correlations between neuroleptic medication and components of smooth pursuit. Also, three unmedicated patients with SCZ showed similar abnormalities to medicated patients as did the subjects with PRS who were all unmedicated. Thirdly, the small sample size in the PRS group increases the risk of our findings being false positives due to sampling error and/or reduced test power. Crucially we were unable to report follow-up data for individuals with PRS. Given the large heterogeneity of PRS, the ability to conclusively identify SCZ at an earlier stage by using the eye-movement task still requires a larger sample of follow-up studies. Importantly, however, a recent 3-year follow-up study has reported that it is possible to distinguish psychosis converters from non-converters in the PRS population with an area under ROC curve of 0.80 based on selected measures from the fixation stability task and the free-viewing task.[28] Finally, what features of eye-tracking abnormalities are different in patients with SCZ compared with other psychiatric disorders is not clear from this study. In the future, large international multicenter studies on different ethnic populations will be necessary to test their efficacy in identifying psychiatric disorders.

Conclusions

Our modeling results from multiple eye-tracking tasks demonstrate extensive abnormalities that distinguish individuals with SCZ from controls with a high degree of predictive accuracy. We have also observed that eye movement abnormalities, which do not appear to be a state-dependent phenomenon or due to the effects of psychotropic medication, are present early in the natural history of the disorder and can be considered potential trait markers for SCZ.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin Open* online.

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Conflict of Interest

All authors report no biomedical financial interests or potential conflicts of interest.

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