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Altered attentive bias towards interpersonal communication information across phases of schizophrenia: an eye-tracking study

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ABSTRACT

Background Eye movement abnormality in schizophrenia has been studied for several decades. However, patient differences in eye movements across phases of schizophrenia from eye-tracking studies have not been well documented.

Aims This pilot study used eye-tracking technology to investigate attentive bias towards interpersonal communication information across different clinical phases of schizophrenia.

Methods This study included 78 persons at clinical high risk (CHR) for schizophrenia, 68 first-episode (FEZ) patients, and 39 chronically ill patients from the Shanghai At Risk for Psychosis Extending Project (SHARP Extending cohort) as well as 74 healthy controls (HCs). The experiment was an unguided-viewing task composed of 24 trials showing three types of pictures which varied in the degree of interpersonal communication. Type 1 was a scenery picture without people, type 2 was a picture with four people not communicating, and type 3 was a picture with four people communicating. We used two measures: (1) initial fixation duration and (2) total fixation duration.

Results A ratio for both measures was calculated between measures for pictures with more or less interpersonal communication. The ratio of initial fixation duration for pictures with people communicating versus pictures with people not communicating was lowest in chronically ill patients (0.13 (0.34))compared with HCs (0.31 (0.36)), FEZ patients (0.31 (0.46)), and CHR patients (0.36 (0.42)). The difference in the ratios of initial fixation duration for type 2 and type 3 pictures was also significant for female participants (HCs vs chronically ill patients, t=2.706, p=0.009; CHR patients vs chronically ill patients, t=4.079, p<0.001). In addition, the ratio of initial fixation duration on pictures with people not communicating versus pictures without people negatively correlated with participants' high-risk symptoms (r=−0.35, p=0.002) among the CHR group and also correlated with the negative symptom subscore on the Positive and Negative Syndrome Scale (PANSS) among chronically ill patients (r=−0.33, p=0.037). The ratio of initial fixation duration between type 1 and type 3 pictures was associated with PANSS negative symptoms only in female patients with schizophrenia (r=−0.46, p=0.004).

Conclusions These findings suggest an altered attentive bias towards pictures with a high degree of interpersonal communication information across different clinical phases in schizophrenia. The ratio of initial attentive orienting was associated with negative symptoms in female patients.

Key messages

What is already known on this topic

- Eye movement detection is a prospective biological marker candidate that can distinguish different eye movement patterns in various experimental paradigms.
- However, few eye-tracking studies have examined social cues at different phases of schizophrenia.

What this study adds?

- The present study included patients at different phases of schizophrenia (78 clinical high-risk, 68 first-episode, and 39 chronically ill).
- The experiment was an unguided-viewing task composed of 24 trials showing three types of pictures varying in the degree of interpersonal communication.
- Our main findings are that the ratio of initial fixation duration towards pictures showing intense communication compared with pictures of people not communicating was significantly different between the participating groups.
- Post hoc analysis revealed a significant difference female between participants.

How this study might affect research, practice or policy

- These findings suggest altered attentive bias towards pictures of intense interpersonal communication across different clinical phases of schizophrenia.
- The ratio of initial attentive orienting was associated with negative symptoms in female patients but not in male patients, suggesting that negative symptoms have a greater impact on social cognitive deficits in female patients with schizophrenia.

INTRODUCTION

Schizophrenia is a progressive mental disorder, particularly for patients who lack social contact that exacerbates social cognition

dysfunction. Green *et al* proposed that people with schizophrenia have impairments in some social processes (face perception, voice perception, mentalising, and emotion regulation), but not all of them.[1] General consensus agrees that social cognitive deficits may occur prior to the onset of psychotic symptoms and, thus, are vital to the prognosis of the illness.[2–4] However, less is known about whether the social cognitive impairments induce psychotic symptoms at a subclinical stage. The relationship between social cognitive decline and psychotic onset, especially in the early phase, has yet to be clarified.

Eye movement detection is a prospective biological marker candidate because (1) eye-tracking technology can distinguish different eye movement patterns using various experimental paradigms; (2) the diversity of measurements enables comprehensive observation and recording of participants' eye movements; (3) this technology is non-invasive and can be applied to patients even at the onset of symptoms. Benson *et al*[5] first combined three different eye movement tasks (smooth pursuit, fixation stability and free-viewing tasks) and demonstrated a very high accuracy (98.3%) in discriminating individuals with schizophrenia from controls. Recently, eye-tracking studies in schizophrenia have used some new experimental paradigms with social cues to determine disease-specific eye movement features that can serve as indicators for monitoring social cognitive deficits during the course of illness. For instance, the studies with an experimental stimulus of faces expressing emotion consistently found that patients with schizophrenia allocated less attention to these faces with the performance of longer fixation time, slower eye movement speed, reduced instances of fixation and decreased scanpath length.[6–8] Navalón *et al*[9] examined attentional biases to emotional scenes in schizophrenia and also found that patients showed increased attention to threatening scenes and paid less attention to happy scenes. They suggested that patients might allocate more attention towards negative emotional stimuli, reflecting the common manifestation of low self-esteem and defensive mentality with high alertness in schizophrenia. Another eye-tracking study using social cues by Nikolaides *et al* found that patients exhibited a shorter scanpath length, fewer fixations, and a shorter mean distance between fixations, especially when their fixations were on faces but not on the socially informative bodies or background, suggesting a cue-specific abnormality.[10]

To our knowledge, few eye movement studies of clinical high-risk populations exist. Hillmann *et al* showed that individuals with subclinical paranoia had a significantly shorter scanpath and a decrease of scanpath length under stress when looking at neutral faces compared with individuals without paranoia;[11] this is similar to the eye movement features found in patients with recent onset of psychosis.[6–8] Another recent study of patients at clinical high-risk for psychosis tracked eye movement to gesture perception and reported that those at clinical high-risk gazed at abstract gestures fewer times and spent less time fixating than controls.[12] The results indicated that eye movement patterns of persons at clinical high risk for psychosis has the same pattern as patients with schizophrenia. However, room for improvement in current eye movement studies of schizophrenia remains. First, although social cognitive impairments have been associated with psychotic symptoms,[3] the stimuli of eye-tracking studies could be modified to more clearly reveal the disease-specific eye movement patterns associated with social cognitive impairments. Second, the eye-movement findings of clinically high-risk groups should be confirmed by larger sample sizes. Finally, the variations of eye movement patterns towards social cues across different phases of the disease warrant further investigation.

The present study aimed to examine attentional processes towards information of interpersonal communication at different phases of schizophrenia: clinical high-risk (CHR) patients, first-episode (FEZ) patients, and chronically ill patients, as well as healthy controls (HCs). We designed an unguided-viewing task with pictures containing some information about interpersonal communication. We hypothesised the following: (1) CHR, FEZ, and chronically ill patients would show differences in early and overall attentional bias towards pictures of intense interpersonal communication information compared with healthy controls; and (2) the extent of early and overall attentional bias across clinical phases would correlate with psychiatric symptoms and cognitive function.

METHODS

Participants

The sample size was estimated according to previous literature and statistical methods with a confidence level of 80% and statistical significance of p=0.05 level. The calculation formula was as follows: $n=2\sigma^2(t_{\alpha/2}+t_{\beta})^2/(\mu_1-\mu_2)^2$ (σ is the sample SD, μ_1, μ_2 is the mean of two samples, α is the test level, 1-β is the test efficiency). Considering the dropout rate (approximately 10%) and issues with data quality, we planned to enrol 65 subjects for each group. This study involved a total of 288 subjects, including 83 CHR patients, 77 FEZ patients, 49 chronically ill patients, and 79 HCs that were matched based on age and years of education. Subjects were recruited at the Shanghai Mental Health Center (SMHC) between 2017 and 2019. HCs were recruited by advertisement in the community. Inclusion criteria were as follows: (1) age of 18–45 years; (2) capacity to provide informed consent; and (3) completion of at least 6years of primary education. Exclusion criteria were as follows: (1) severe somatic diseases, such as pneumonia, cancer, or heart failure; (2) mental retardation; or (3) dementia. CHR patients was defined and assessed according to the Structured Interview for Prodromal Symptoms (SIPS) and the Scale of Prodromal Syndromes (SOPS, henceforth known as SIPS/SOPS).[13 14] The FEZ patients and chronically ill patients were diagnosed with schizophrenia or schizophreniform psychosis by trained clinical psychiatrists using the Structural Clinical Interview

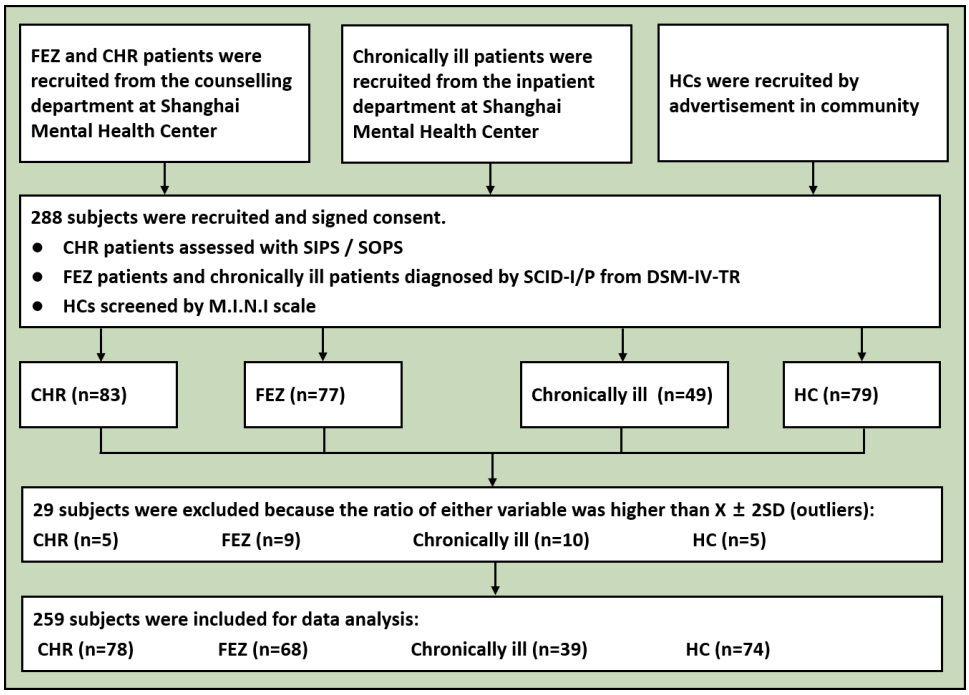

Figure 1 The flowchart for the participant recruitment. CHR, clinical high-risk; DSM-IV-IR, Diagnostic and Statistical Manual of Mental disorders-Fourth Edition, Text Revision; FEZ, first-episode; HCs, healthy controls; M.I.N.I.,Mini-International Neuropsychiatric Interview; SCID-I/P, Structural Clinical Interview for DSM-IV-TR, Patient's version; SD, standard deviation; SIPS, Structured Interview for Prodromal Symptoms; SOPS, Scale of Prodromal Syndromes.

for Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition, Text Revision (DSM-IV-TR), Patient's version (SCID-I/P). Twenty-nine subjects were excluded because the ratios of either variable were higher than X±2SD, indicating that these data were outliers. The procedure of participant recruitment is shown in figure 1. The symptom severity of the FEZ group and chronically ill group were assessed using the Positive and Negative Syndrome Scale (PANSS).[15] Four groups, excluding the chronically ill group, were assessed for cognitive function by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB).[16–20] Most CHR patients and first-episode patients were drug-naïve. The ethics committee of SMHC approved the study protocol. A written, informed consent of all subjects was obtained after receiving a complete description of the study.

Stimuli and apparatus

The stimulus material was made up of 24 coloured pictures within eight groups developed by the authors. Each group had three types of pictures against the same background. Type 1: scenery pictures without people; Type 2: pictures with four people not communicating; Type 3: pictures with four people communicating. The characteristics of the stimuli and the parameters of eye tracking apparatus have been described previously.[21] The experiment paradigm is presented in figure 2.

Procedure

Before the experiment, several clinical assessments such as SIPS and PANSS were completed by one psychiatrist who had completed formal psychiatric assessment scale training. All participants completed a standardised nine-point calibration procedure from the dominant eye to ensure good data quality before the formal experiment began. In each trial, a fixation cross was first presented at the centre of the screen for 1000 ms; then, a picture pair was presented for 4000 ms. The instruction was to ask participants to look at the presented pictures as if they were watching television and then focus on the fixation cross between trials.

Measures

The picture pair was defined as two independent areas of interest (AOI). Two measurements of eye movement data were extracted for testing our hypotheses: (1) the duration of the initial fixation after the picture pair started being presented, and (2) the total gaze duration (from the picture's emergence to its disappearance) on each AOI. Initial fixation refers to the first fixation falling into AOI. The duration of the initial fixation is determined by the subjects' fixation shift (saccade to the next fixation is the end of duration of the previous fixation). The first variable was targeted to reflect the processing of initial attentional orienting, while the second variable was for processing the overall attentional engagement. To facilitate the interpretation of our results, we calculated ratios for each variable using the measure difference between two AOIs, divided by the measure of the AOI with less interpersonal information. The formula was presented in our previous publication[21] and also in footnotes of table 1. When the ratio was positive, the results showed that attentional bias (initial and total) was

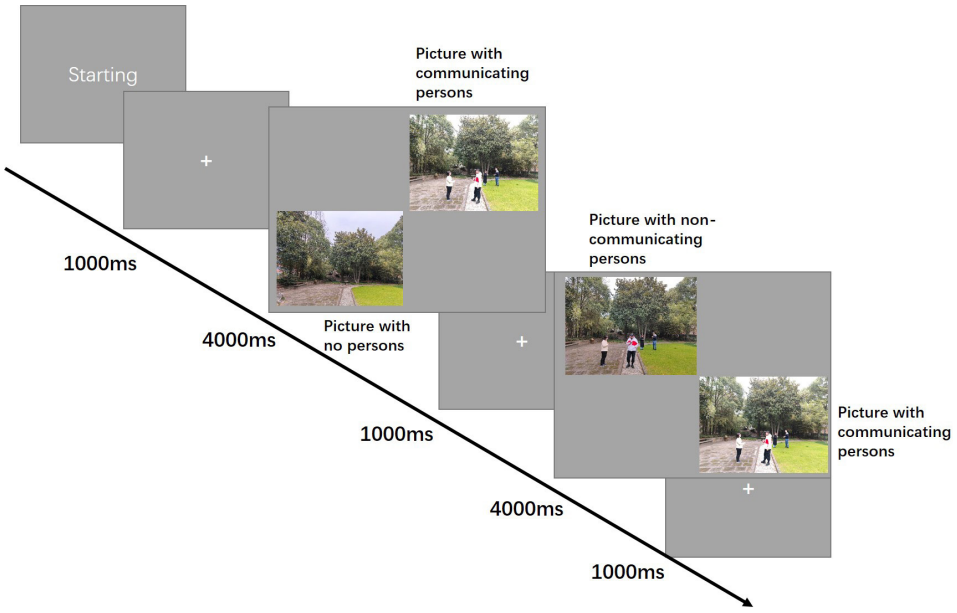

Figure 2 The graph depicts the experimental procedure that is fixed for each time with the sequence of cross fixation (1000 ms) and pictures (4000 ms). Two of the three types of pictures were presented in pairs on 24 trials linked between cross fixation.

more towards pictures with more intensive interpersonal information.

Statistical analysis

We analysed all data using SPSS (V17.0). We used univariate analyses (ANOVAs) to assess age and educational level difference between groups and χ^2 analyses to assess gender difference. We employed univariate analyses of covariance (ANCOVAs) to examine significant differences of variables between patient and control groups, including age and educational level as covariates. As PANSS or SIPS scores data were skewed, we performed Spearman correlation analyses to test correlations between analysed eye movement variables and clinical assessments. For the case-control comparison, the level of significance was set to $p<0.05$.

RESULTS

Demographics and clinical characteristics

Demographics and clinical characteristics are presented in table 2. There was no significant difference in age or educational levels between the HC group, the CHR group, the FEZ group, and the chronically ill patient group, but a gender difference was found between the four groups (χ^2=8.744, p=0.033). The PANSS total score was not significantly different between the FEZ patients and chronically ill patients (t=1.507, p=0.135), but the PANSS general psychopathology subscore was different between the FEZ patients and chronically ill patients (t=3.171, p=0.002). No difference was found for PANSS positive and negative subscores (t=−0.115, p=0.909 and t=−1.477, p=0.143, respectively). The

Table 1 ANCOVA results of gaze measures with age and education as covariates, mean (SD)

Variables	HC (n=74)	CHR (n=78)	FEZ (n=68)	Chronic (n=39)	F	P value
Initial fixation duration (ratios)						
Mode I	0.17 (0.49)	0.21 (0.47)	0.21 (0.55)	0.18 (0.42)	0.121	0.948
Mode II	0.21 (0.50)	0.17 (0.39)	0.29 (0.61)	0.16 (0.33)	0.845	0.470
Mode III	0.31 (0.36)	0.36 (0.42)	0.31 (0.46)	0.13 (0.34)	3.269	0.022*
Total gaze duration (ratios)						
Mode I	1.34 (1.14)	1.69 (1.55)	1.69 (1.55)	1.48 (1.45)	0.962	0.411
Mode II	1.65 (1.19)	1.53 (1.23)	1.39 (1.30)	1.65 (1.62)	0.532	0.661
Mode III	0.15 (0.32)	0.25 (0.55)	0.18 (0.35)	0.35 (0.59)	2.097	0.101

Mode I: (Duration *Picture 2*–Duration *Picture 1*)/Duration *Picture 1*.
Mode II: (Duration *Picture 3*–Duration*Picture 1*)/Duration *Picture 1*.
Mode III: (Duration *Picture 3*–Duration*Picture 2*)/Duration *Picture 2*.
*p<0.05.
ANCOVA, analysis of covariance; CHR, clinical high-risk; Chronic, chronically ill patient group; FEZ, first-episode; HC, healthy control; SD, Standard Deviation.

Table 2 Demographic and clinical characteristics, mean(SD)

Variables	HC (n=74)	CHR (n=78)	FEZ (n=68)	Chronic (n=39)	F/t/χ^2	P value
Age (years)	23.09 (3.46)	23.76 (4.46)	24.53 (4.59)	25.10 (3.67)	2.586	0.054
Gender (M/F), n	33/41	40/38	46/22	24/15	8.744	0.033*
Education (years)	13.27 (2.34)	13.26 (2.83)	13.04 (2.92)	13.38 (3.17)	0.149	0.930
Duration of illness (months)	–	–	–	49.79 (36.48)	–	–
PANSS total score	–	–	79.44 (14.80)	74.23 (20.79)	1.507	0.135
PANSS positive symptom	–	–	19.31 (5.94)	19.46 (7.58)	–0.115	0.909
PANSS negative symptom	–	–	16.68 (7.81)	19.15 (8.80)	–1.477	0.143
PANSS general psychopathology	–	–	40.94 (7.09)	35.62 (9.75)	3.171	0.002**
SIPS/SOPS	–	36.19 (10.04)	–	–	–	–
MCCB total score (T score)	54.26 (6.14)	47.48 (7.77)	43.02 (8.54)	–	32.479	<0.001**
MCCB social cognition (T score)	36.57 (6.57)	35.71 (7.96)	31.98 (7.29)	–	6.305	0.002**

Sample size (PANSS): FEZ=62, Chronic=39; (MCCB): HC=61, CHR=69, FEZ=52; (MCCB social cognition): HC=61, CHR=70, FEZ=54.
*p<0.05, **p<0.01.
CHR, clinical high-risk; Chronic, chronically ill patient group; F, female; FEZ, first-episode; HC, healthy control; M, male; MCCB, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery; PANSS, Positive and Negative Syndrome Scale; SD, Standard Deviation; SIPS/SOPS, Structured Interview for Prodromal Symptoms and the Scale of Prodromal Syndromes.

MCCB total score and social cognition score were found to be different between HCs, CHR patients, and FEZ patients (F=32.479, p<0.001 and F=6.305, p=0.002, respectively). The SIPS score was only available for CHR patients. For the chronically ill group, 57.1% of patients were in monotherapy treatment with only one antipsychotic; the remaining patients were taking several kinds of antipsychotics.

Initial attentive orienting

The ANCOVA results revealed that the ratios of initial fixation duration were significantly different between the four groups (F=3.269, p=0.022) for type 2 and type 3 pictures (see figure 3, table 1). This was the only significant finding for this variable. When presenting type 2 and type 3 pictures simultaneously, we found that the ratio of initial fixation duration decreased in the chronically ill group compared with the HC group (t=2.648, p=0.009), the CHR group (t=2.990, p=0.003), and the FEZ group (t=2.206, p=0.030) (see online supplemental table 1). We also found the measure was not impacted by age or education, but it tended to be largest in the CHR patients and smallest in the chronically ill patients. In addition, the ratio of all four groups was all positive, indicating that the initial fixation duration for the picture with people communicating was always longer than for the picture with people not communicating.

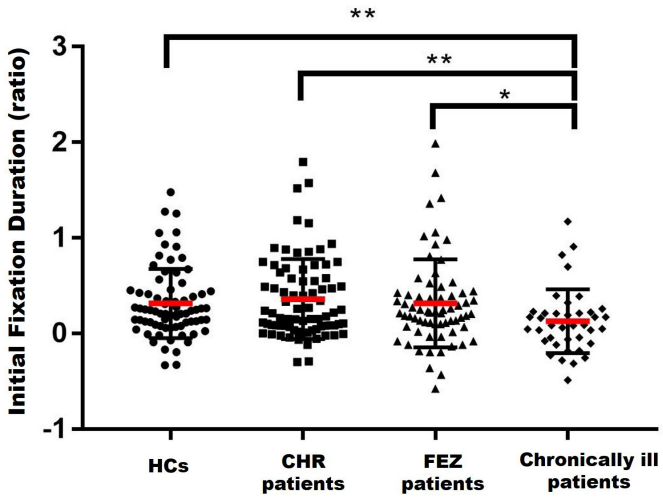

Figure 3 Chronically ill patients showed a smaller ratio of initial fixation duration compared with FEZ patients (p=0.030), CHR patients (p=0.003) and HCs (p=0.009), as indicated by the result of post hoc analysis. This means that chronically ill patients invested less attentive processing resources on pictures with people communicating, while HCs, by contrast, invested more. CHR, clinical high-risk; FEZ, first-episode; HCs, healthy controls.

Post hoc analysis of gender difference in the ratios of initial fixation duration for type 2 and type 3 pictures revealed significant differences only for females in the comparisons between the HC group and chronically ill patient group (t=2.706, p=0.009) or between the CHR group and chronically ill patient group (t=4.079, p<0.001). The detailed statistical results are presented in online supplemental tables 2 and 3.

Overall attentive engagement

The ANCOVA results yielded no significant difference between the four groups for the ratio of total gaze duration. However, we found that the ratio of total gaze duration between type 2 and type 3 pictures tended to be longest for chronically ill patients and shorter for HCs in comparison to CHR and FEZ groups.

Correlation between gaze data and clinical assessments

Spearman's correlation showed that the ratio of initial fixation duration between type 1 and type 2 pictures was negatively correlated with the SIPS score in the CHR group (r=−0.35, p=0.002) (see figure 4) and was also negatively correlated with the PANSS total score in the combined

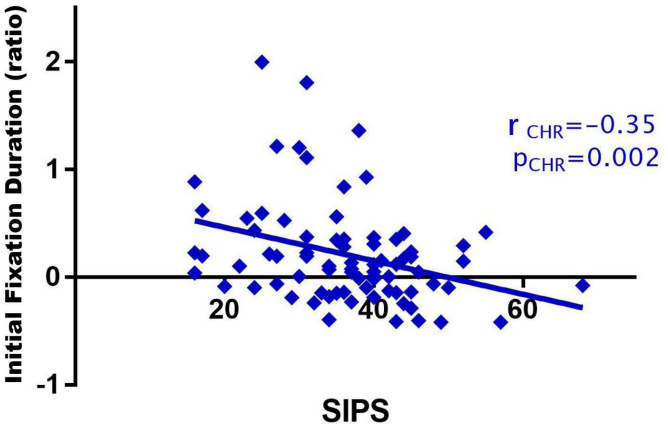

Figure 4 Spearman's correlation yielded negative correlation between SIPS and the ratio of initial fixation duration between type 1 and type 2 pictures in CHR patients (r=−0.35, p=0.002). CHR, clinical high-risk; SIPS, Structured Interview for Prodromal Symptoms.

sample of both FEZ and chronically ill patients (r=−0.19, p=0.048). The ratio of initial fixation duration between type 1 and type 3 pictures was associated with PANSS negative symptoms in the combined schizophrenia groups (r=−0.21, p=0.031) and the chronically ill patients (r=−0.33, p=0.037) but not in the FEZ patients (r=−0.14, p=0.266) (see figure 5).

The gender difference was also demonstrated in correlation analysis. The ratio of initial fixation duration between type 1 and type 3 pictures was associated with PANSS negative symptoms in female patients with schizophrenia (r=−0.46, p=0.004). No significant correlation was found between the ratio of total gaze duration and clinical symptoms.

Correlation between gaze data and other assessments

Spearman's correlation revealed that the ratio of initial fixation duration between type 1 and type 3 pictures was positively correlated with the MCCB social cognition subscore in the FEZ group (r=0.28, p=0.040). The ratio of total gaze duration between type 2 and type 3 pictures was positively correlated with the MCCB social cognition subscore in the HC group (r=0.38, p=0.003). Age was found to be positively correlated with the ratio of initial fixation duration between type 1 and type 2 pictures in the FEZ group (r=0.32, p=0.008).

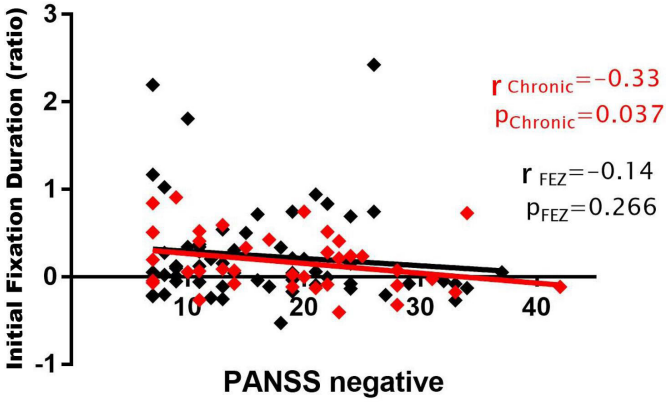

Figure 5 Spearman's correlation revealed negative correlation between PANSS negative symptoms and the ratio of initial fixation duration between type 1 and type 3 pictures in chronically ill patients (r=−0.33, p=0.037) but not in FEZ patients (r=−0.14, p=0.266). FEZ, first-episode; PANSS, Positive and Negative Syndrome Scale.

DISCUSSION

Main findings

Our study aimed to investigate attentive processing towards pictures with interpersonal visual stimuli across clinical phases of schizophrenia by using eye-tracking technology. Our original design was based on the hypothesis that patients might manifest a pattern of symptom-specific eye-tracking features across different phases of disease development. As psychotic symptoms are thought to be closely associated with social connections and eye tracking is a sensitive tool for detecting attentive processing of humans, these advantages support our design. This study was a modest sample-size pilot investigation. Based on our hypotheses, we chose initial attentive orienting and overall attentive engagement as two primary measures. Therefore, we focused on the results of initial fixation duration and total gaze duration.

Our main findings were that (1) the ratio of initial fixation duration of pictures with intense interpersonal communication (type 3) as compared with pictures of people not communicating (type 2) was significantly different between the participating groups. Post-hoc analysis revealed that significant difference was found in females, but not in males. (2) The ratio of total gaze duration was not found to be different between groups. (3) Clinical assessments by SIPS and PANSS were found to be negatively correlated with initial fixation duration. The significant correlation was also found in female patients, but not in male patients. (4) The MCCB social cognition subscore was found to be positively correlated with the ratio of initial fixation duration between type 1 and type 3 pictures in the FEZ group and positively correlated with the ratio of total gaze duration between type 2 and type 3 pictures in the HC group.

Implications

Our findings indicated that initial fixation duration on pictures with people communicating was shortest in chronically ill patients and longest in CHR patients. This indicates that initial attentive orienting is a disease-phase-specific eye movement measure. Additionally, clinical assessments, for example, SIPS and PANSS for assessing psychotic symptoms, negatively correlated with early attentive direction. This implies that symptom severity influenced initial attentive processing and might be a main modulator for the aberrant eye movement. We had assumed that there should be significant differences in total gaze duration between the four groups. However, the only significant results of this evaluation showed the ratio of total gaze duration between type 2 and type 3 pictures to be positively correlated with the MCCB social cognition subscore in the HC group. Because eye movement represents a neurobiological performance integrating top-down modulation and bottom-up feedback,[22] it is thought to be an indicator of cognitive function.

We also found that the MCCB social cognition subscore was positively correlated with the ratio of initial fixation duration between type 1 and type 3 pictures in the FEZ group. This suggests that FEZ patients with better social cognitive functioning also focus more attention at the initial attentional orienting phase to pictures with people communicating.

Our preliminary study demonstrates that eye movement recording can be applied to investigate the processing of interpersonal visual stimuli, and thus, might be a disease-specific approach to identify external characteristics of patients at different phases of illness. Moreover, the findings of the present study are reliable because we found the initial processing was consistently supported by clinical impressions. Patients with schizophrenia manifest impairment in social processing in reflective aspects of face perception, voice perception, mentalising, and emotion regulation.[1] Previous evidence has shown that the eye movements of patients with schizophrenia are aberrant compared with HCs,[23–25] but these findings were not demonstrated to be phase-specific. The strength of our study was that we found significant differences across phases of schizophrenia based on a moderate sample size. Green and colleagues assessed three different aspects of social cognition, including emotion processing, theory of mind, and social relationship perception. They found that the impairments in these three domains were stable throughout schizophrenic illness.[26] The current study refined the grouping by collecting four groups to observe the differences across clinical phases and used eye-tracking to detect the attentive processing toward interpersonal visual stimuli. A pattern of 'less attentive orienting toward more intensive interpersonal information' among patients with schizophrenia was found in this study. This pattern was manifested not only in chronically ill patients but possibly existed in CHR patients as well. FEZ from our sample showed that they had very close early attentive processing similar to HCs. However, we also found that the PANSS score was negatively correlated with initial fixation duration in chronically ill patients, but not in FEZ patients. There might be an explanation that the functional impairment in FEZ patients was not solely determined by psychotic symptoms but might be the integrated consequence of clinical symptoms and individual factors. Interpersonal communication is an interaction related to personal experience and cultural influence. Eye-tracking allows for linking actual interpersonal scenes and experimental observation, and eye movement is a very sensitve measure that can be easily detected.

Furthermore, gender was identified as an impact factor of eye movement measures. Our previous study also found that PANSS negative symptoms were correlated with initial fixation duration in female chronically ill patients.[21] The current study with an enlarged sample size also demonstrated this finding. A specific study design is needed to explore possible reasons for the gender differences of social cognition in patients with schizophrenia.

Limitations

Several limitations need to be acknowledged. First, a follow-up study is required to better prove the eye-movement pattern from the current study as a state or trait feature. This recruited sample came from the Shanghai-At-Risk-For-Psychosis (SHARP) Extending cohort. Future follow-up data from this project are expected to validate the findings reported here. Second, some subjects in the chronically ill patient, FEZ, and CHR groups were taking antipsychotics. The impact of medication on eye movement is seen as controversial, but reports have suggested that the impact is limited.[27] Moreover, we could not analyse the correlation between cognitive function and eye gaze measurements in the chronically ill patients because the cognitive test assessment was not feasible for this group. Last but not least, we may have introduced a selection reporting bias by excluding the data of 29 subjects from the analyses for statistical reasons (sample distribution and outlier characteristics).

Conclusion

In conclusion, the results suggest altered attentive bias towards pictures of intense interpersonal communication information cross different clinical phases of schizophrenia. The ratio of initial attentive orienting was found to be associated with negative symptoms, indicating that the pattern of less attentive orienting toward intensive interpersonal information may be associated with psychotic symptoms. The group differences and significant correlation between eye movement measures and psychotic symptoms were more robust in females than in males.

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Contributors All the authors have given final approval of the version to be published. Their specific contributions are listed as follows: YZ collected and analysed eye-movement data, and drafted the paper. TZ supervised data analysis and revised the paper. LX recruited HC and patients and revised the paper. QG supervised data analysis and revised the paper. XH supervised data analysis and revised the paper. PE contributed to the design of the project and revised the paper. JW contributed to the design of the project and revised the paper. CL contributed to the design of the project, revised the paper and was responsible for the overall content as the guarantor.

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Competing interests None declared.

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Supplementary Table1. Post-hoc analysis of initial fixation duration of Mode III in whole sample

	t	p
HC vs CHR	-0.709	0.479
HC vs FEZ	-0.005	0.996
HC vs Chronic	2.648	0.009*
CHR vs FEZ	0.616	0.539
CHR vs Chronic	2.990	0.003*
FEZ vs Chronic	2.206	0.030*

HC = healthy controls, CHR = clinical high risk, FEZ = first episode schizophrenia, Chronic = chronic inpatient group

*p<0.05

Supplementary Table2. Post-hoc analysis of gender difference in initial fixation duration of Mode III, mean(SD)

	HC(n=41)	CHR(n=38)	FEZ(n=22)	Chronic(n=15)	F	p
female	0.28(0.379)	0.41(0.508)	0.24(0.459)	-0.01(0.232)	2.999	0.034*
	HC(n=33)	CHR(n=40)	FEZ(n=46)	Chronic(n=24)	F	p
male	0.36(0.341)	0.32(0.310)	0.35(0.460)	0.21(0.365)	0.845	0.472

HC = healthy controls, CHR = clinical high risk, FEZ = first episode schizophrenia, Chronic = chronic inpatient group

*p<0.05

Supplementary Table3. Post-hoc analysis of initial fixation duration of Mode III in female

	t	p
HC vs CHR	-1.302	0.197
HC vs FEZ	0.357	0.722
HC vs Chronic	2.706	0.009*
CHR vs FEZ	1.298	0.199
CHR vs Chronic	4.079	<0.0001**
FEZ vs Chronic	1.903	0.065

HC = healthy controls, CHR = clinical high risk, FEZ = first episode schizophrenia, Chronic = chronic inpatient group

*p<0.05, **p<0.001