Title: Self-referential gaze perception of patients with schizophrenia and its relationship with symptomatology and cognitive functions

Running title: Self-referential gaze perception in schizophrenia

Authors:

Sherry Kit Wa Chan[1,2] *, Tianyin Liu[3], Audrey On Yui Wong[1], Gloria Hoi Yan Wong[3], Janet Hsiao[2,4], Christy Lai Ming Hui[1], Wing Chung Chang[1,2], Edwin Ho Ming Lee[1], Eric Yu Hai Chen[1,2]

[1]Department of Psychiatry, The University of Hong Kong,

[2]The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong

[3]Department of Social Work and Social Administration, The University of Hong Kong

[4]Department of Psychology, HKU

***Address for correspondence: Sherry Kit Wa Chan**

Room 219, New Clinical Building, Department of Psychiatry, The University of Hong Kong, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong.

E-mail address: kwsherry@hku.hk.

Tel: (852) 2255 4488

Fax: (852) 2255 1345

Word count of abstract: 249
Word count of text body: 3970

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Abstract

Self-referential gaze perception (SRGP)—the perception that others' gaze is towards oneself—is a core experience in patients with schizophrenia, and may be related to common delusional themes such as delusions of reference. Studies exploring SRGP bias in schizophrenia are limited and results have been inconsistent, particularly regarding its relationship with symptomatology and cognition. Seventy-five patients with schizophrenia-spectrum disorders (25 with high level of reference delusion, 25 with low reference delusion and 25 in clinical remission) and 25 matched healthy controls were compared in a gaze perception task to judge whether averted gaze with varied ambiguity was directed at them. All subjects were assessed with delusion and reference ideations and cognition functions. Psychotic symptoms were assessed in patients. Gaze perception analysis adopted both behavioural and psychophysical approaches. Group differences and predictors of SRGP in ambiguous and unambiguous conditions were investigated. Both groups of symptomatic patients displayed higher ambiguous SRGP rate, and the group with high reference delusions showed more unambiguous SRGP bias. Cognitive functions were negatively associated with SRGP rate while positive and negative symptoms were positively associated. Cognitive function was the only significant predictor for ambiguous-SRGP rate. Patients with psychotic symptoms have hypermentalization of gaze perception as towards oneself, whereas patients with delusions of reference have more profound bias in gaze perception. General cognition is implicated in SRGP rate. Future studies could investigate interventions with targeted psychopathological profiles by improving non-social cognitive functions to test the hypothesis that cognitive functioning is related to SRGP bias and delusional beliefs.

Keywords: self-reference, eye-gaze perception, mentalization, schizophrenia

1. Introduction

Schizophrenia affects up to 1% of the population and is a leading cause of disability worldwide (Collins et al., 2011). Deficit of social cognition has been suggested as one of the features of schizophrenia (Green et al., 2015, 2019) and consistently shown to be related to functional disabilities of patients more than neurocognitive functions (Fett et al., 2011; Halverson et al., 2019). One of the key domains of social cognition is mentalizing, which is the ability to infer intentions, emotions and beliefs of others (Green et al., 2019). Eye contact is an essential element in social interaction (Emery, 2000). Perception of gaze direction, in specific, indicates other's attention and intention (Itier and Batty, 2009). Misinterpretation of mundane and irrelevant information as self-relevant is commonly seen in patients with schizophrenia in the form of delusion or ideations of social nature, such as ideas of reference and persecutory delusions. It has been suggested that delusion of reference can be categorized into two types, reference delusion of communication and reference delusion of observation (Startup et al 2009). Though delusion or idea of reference can occur in isolation in other psychiatric conditions such as depression, the reference delusion of observation is more likely to be linked with delusion of persecution and impairment of theory of mind such as intentional judgement (Frith 1992; Startup et al., 2009). In a descriptive psychopathology study involving 137 patients with schizophrenia-spectrum disorders, for example, one of the core experiences reported in idea of reference is being looked at by others (Wong et al., 2012).

Self-referential gaze perception (SRGP) is theoretically related to the deficit in social cognition and delusions of social nature in schizophrenia. Studies of judgement of gaze direction and SRGP in patients with schizophrenia, however, are limited. To date, only six studies examined the SRGP bias in patients with schizophrenia (Table 1), with inconsistent

results. Rosse and colleagues (1994) first reported that patients with schizophrenia were more likely to judge averted gaze as directed to themselves compared to healthy controls. Since then, two more studies (Hooker and Park, 2005; Tso et al., 2012) reported similar findings. Patients were also found to have a higher tendency to judge averted gaze as directed to oneself particularly in ambiguous gaze directions (Rosse et al., 1994; Hooker and Park, 2005; Tso et al., 2012). Nonetheless, three other studies (Franck et al., 1998, 2002; Kohler et al., 2008) reported no difference in SRGP bias between groups. In two earlier studies (Franck et al., 1998, 2002), the basic perceptual function of determining gaze direction (left or right) was found to be preserved in patients with schizophrenia. Another study further suggested that early unconscious processing of eye gaze was intact in patients with schizophrenia (Seymour et al., 2016). These results imply that any misinterpretation of gaze direction is likely to be due to biases at a later stage of gaze processing when attributing mental states to others based on gaze perception, which may be related to ideations and delusions of a social nature.

Symptomatology of patients, in particular the presence of delusions such as reference delusions, may be related to the attributing bias in gaze intention, and thus associated with an increase in SRGP. However, of the previous six studies, only two reported significant relationships between symptoms and SRGP. None of the studies specifically investigated delusion of reference, despite their direct relevance and high prevalence in patients (up to 70%) (International Pilot Study of Schizophrenia and World Health Organization, 1973). One study (Rosse et al., 1994) only compared between patients with and without paranoia and found a significant group difference in SRGP bias. Another study (Tso et al., 2012) suggested that negative symptoms were associated with higher self-referential bias of gaze perception but not positive psychotic symptoms. Therefore, the relationship between symptoms and self-referential gaze perception is still unclear. General cognitive functions such as attention are

related to social cognition (Green et al., 2019). However, only one study explored the relationship of general cognitive functions and gaze perception in patients with schizophrenia without examining the inter-relationship between gaze perception, symptom severity and cognitive functions (Tso et al., 2012).

One possible reason for the inconsistent results mentioned above is methodological issues. First, sample size of studies was relatively small, ranging from 25 to 64, which may not be sufficiently powered for certain analyses. Second, the role of psychopathology, particularly delusion of reference, and that of cognitive functions was insufficiently explored. This could partly be related to a previous lack of detailed assessment for theoretically related symptoms. Earlier studies have noted the difficulties in defining and objectively measuring ideas of reference, for example (Kendler et al., 1989). In recent years, increased use of more detailed delusions and ideation assessment tools, such as the Peters Delusion Inventory (PDI) (Peters et al., 1999) and the Ideas of Reference Interview Scale (IRIS) (Wong et al., 2012) allowed more detail psychopathological studies (Wong, 2020, Tonna et al., 2018). Third, previous studies used experimental designs that varied in both stimuli and analysis methods. The number of gaze directions used in these studies ranging from 5 to 13 with only one study incorporated 13 gaze directions in the experimental design (Franck et al., 2002). Fewer gaze directions may restrict the sensitivity and comprehensiveness of the eye gaze perception assessment. Furthermore, most studies used accuracy of gaze direction judgement as the main outcome and only two studies used a psychophysical approach for analysis (Hooker and Park, 2005; Tso et al., 2012).

To address these methodological limitations, the current study aimed primarily to examine the SRGP of patients with schizophrenia in comparison with healthy controls in a larger sample

using detailed psychopathological assessment and a relatively large range of gaze directions as experimental stimuli, and adopting both the psychophysical approach and behavioural accuracy for analyses of behavioural outcomes. We hypothesized that patients with high levels of reference delusion would have more SRGP bias compared with patients with low levels of reference delusion, clinically remitted patients and healthy controls. The secondary aim of the study is to determine the relationship between psychopathology and cognitive functions and the SRGP bias. We hypothesized that both positive and negative symptoms and cognitive functions would be related to SRGP bias. Results of this study will help to delineate the pattern of SRGP in patients with schizophrenia and provide further understanding about the nature of mentalization impairment in patients with schizophrenia.

2. Methods

2.1. Study setting and sampling

Four groups of participants were recruited, with 25 in each group, totalling 100. Three groups of patients with diagnosis of schizophrenia-spectrum disorders based on DSM-IV diagnostic criteria were recruited from an early intervention service and adult psychiatric outpatient clinics of public healthcare units in Hong Kong (Tang et al., 2010). Patients with reference delusion scoring 3 or above on the 'ideas and delusions of reference' item of Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen, 1984) were grouped in a high reference group (HRef). Patients with positive psychotic symptoms (scoring 3 or above on any of the four SAPS total subscale) but scoring less than 3 in the 'ideas and delusions of reference item on SAPS item were grouped into a low reference group (LRef). Patients who were in clinical remission with a total score of SAPS equal to or less than 2 were included in the clinical remission group (Rem). Patients with known history of organic brain disorder, comorbid substance abuse and intellectual disability were excluded. Healthy controls (HC) with no

personal or family history of mental illness were recruited from the community. All four groups of participants were matched in gender, age and years of education. The sample size was calculated based on the most recent study (Tso et al., 2012). All participants were assessed for normal or corrected-to-normal visual acuity using the Snellen chart. Face-to-face interview was conducted after obtaining written informed consent. This study was approved by the Institutional Review Board of the University of Hong Kong and Hong Kong West Cluster of Hospital Authority (IRB ref no.: UW11-101).

2.2. Assessments

Patient groups were assessed with SAPS and Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989). Duration of illness was documented and defined as the time interval between onset of first psychotic symptoms and the assessment. Antipsychotic medication prescribed to each patient at the time of assessment was obtained and the defined daily dose (DDD) was calculated (Leucht et al., 2016). To provide more detailed psychopathology information on delusions, PDI (Peters et al., 1999) and IRIS (Wong et al., 2012) were used to measure delusional ideation and idea of reference respectively for all participants. Cognitive functions were assessed for all participants with digit span forward, digit span backward and digit symbol substitution test of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) to measure attention and processing speed.

2.3. Experimental task

A gaze perception task was developed and programmed using E-prime Professional 2.0 based on previous studies (Rosse et al., 1994; Franck et al., 2002; Hooker and Park, 2005). The stimuli of task are photographs of six Chinese models (3 men and 3 women) taken facing straight to camera with 13 different gaze directions (0°, 5°, 10°, 15°, 20°, 25° and 30° to the left and right, respectively) each. The production of photographic stimuli followed the standard

procedures used in the previous studies (Rosse et al., 1994; Franck et al., 1998; Hooker and Park, 2005). The use of photographs of Chinese models allows for ecological assessment of the response of the participants. The task has six blocks and each block contains 30 trials of randomly selected stimuli from one model with a pre-determined distribution of gaze directions. Participants were instructed to respond yes or no to the question: 'Do you feel as if the person in the picture is looking at you? (self-referential gaze)'. In each trial, the stimulus was presented for 200ms, followed by a fixation cross for 1800ms, and then an interval of blank page for 500ms until the next stimulus showed up (Figure 1). Stimuli presentation time was set at 200ms because previous study suggested that conscious perception arises around 200ms (Koivisto and Grassini, 2016). Participants were allowed to respond during the 2500ms of each trial. Response time and accuracy of participants were recorded automatically by the E-prime program. If no response was made within the 2500ms for one trial, it would be recorded as missing. All participants were given a short practice run to familiarize themselves with the procedure of the task before proceeding to the experiment.

2.4. Data analysis

The current study adopted two approaches to analyse the gaze perception data. In the first approach, accuracy of each trial recorded by E-prime was used for analysis. Averted gaze directions of 10° and 15° were considered as ambiguous; that of 20°, 25° and 30° were considered as unambiguous. Rate of SRGP (response of 'looking at me') was calculated for each gaze direction. The average rate of SRGP among trials of gaze directions of 10° and 15° was denoted as ambiguous-SRGP rate and that of 20°, 25° and 30° was denoted as unambiguous-SRGP rate. The second approach adopted a psychophysical analysis method from previous literature (Hooker and Park, 2005; Tso et al., 2012). This approach assumes that responses of self-referential gaze perception lie along the continuum of eye-contact signal

strength, resembling a logistic function. Eye-contact signal strength was determined by the angle of the eyes, which ranged from 0 (the most averted gaze in this study) to 1 (direct gaze) with six even gradual increments (apart from center), i.e., ⅙ unit of signal strength change. To elaborate, in our study design, center (0°), 5°, 10°, 15°, 20°, 25° and 30° gazes were coded as having eye-contact signal strength of 1, 0.83, 0.67, 0.5, 0.33, 0.17 and 0 respectively. The percentage of 'yes' response against eye-contact signal strength of each participants were fitted to a logistic regression model: $P=1/(1+c \cdot bx)$ (Tso et al., 2012). In which, P is the percentage of 'yes' response, that is the feeling of being looked at, x is eye-contact signal strength, and c and b are constant parameters provided by the R aod package (Lesnoff and Lancelot, 2012). Only participants whose response fitted the logistic regression curve were included in further analysis. A total of 95 (95%) participants were included (4 HRef patients, and 1 healthy control were excluded). As the cone of direct gaze of normal population has been suggested as 8-9° (Jenkins and Langton, 2003; Gamer and Hecht, 2007; Balsdon and Clifford, 2018), 5° was also considered as direct gaze stimuli in the current study, together with the center gaze direction. Therefore, 40% of the stimuli (center + 5°) was considered as direct-looking (out of the 30 trials, four center trials and four 5° trails to the left and four to the right) and thus the eye-contact signal strength at 40% response cutoff (P0.4) was considered as the base rate of 'yes' response in the current study. Signal strength at P0.4 was obtained from each included participant for further analysis.

Differences in demographics, clinical measures and cognitive functions amongst groups were explored using ANOVA and Kruskal-Wallis tests depending on the nature of the variables. Raw scores of cognitive function measurements were transformed into standardized z-scores. The z-scores of each individual were then averaged to generate the composite score of cognitive function. Because of the non-parametric nature of the variables, generalized linear

models were used to analyse the group differences in unambiguous-SRGP, ambiguous-SRGP and P0.4 controlled for age, gender and years of education. Post-hoc analysis was conducted to explore the specific difference between different two groups using the least significant difference (LSD) test. Ambiguous-SRGP was further transformed using box-cox transformation (Box and Cox, 1964) for linear regression analysis because of its non-parametric nature of variable distribution and univariate ANOVA was also conducted to assess the group differences. Because of the three patient groups were allocated based on the level of psychotic symptoms, Jonckheere-Terpstra test (Ali et al., 2015) for rank-ordered group was used compare the three-group difference on SRGP and P0.4 as supplementary analysis. The Spearman correlation test was used to examine the relationships between the gaze perception measures and demographic, clinical and cognitive variables because of the non-parametric nature of the variables. The Benjamini-Hochberg procedure was employed to correct for multiple comparisons with the false discovery rate set at 0.1 (Benjamini and Hochberg, 1995). Linear regression was conducted on ambiguous-SRGP with significant clinical and cognitive measures as independent variables. Data analysis was conducted with SPSS 25 and R 3.5.0 (Team, 2018)'s aod package (Lesnoff and Lancelot, 2012).

3. Results

There were no significant differences in age, gender, years of education and duration of illness between the groups but significant difference of DDD was found between the three patient groups (Table 2).

3.1. Group differences in SRGP

Figure 2 shows the group comparisons in SRGP. Significant group differences were identified for ambiguous-SRGP (10° and 15°) (Wald $\chi 2 = 19.199$, $p < 0.001$) and unambiguous-

SRGP (20°, 25° and 30°) rates (Wald $\chi 2 = 15.546$, $p < 0.001$) (Supplementary Table 1). The ambiguous-SRGP pairwise comparisons showed significant difference between HRef group and Rem group, HRef and HC group, LRef group and Rem Group, and LRef group and HC group (Supplementary Table 1). But no difference was found between HRef and LRef groups and Rem and HC groups. For unambiguous-SRGP, pairwise comparisons only found significant difference between HRef group and all other groups (Figure 2a, Supplementary result table 1). There was no significant overall group difference in P0.4 eye contact signal strength (Wald $\chi 2 = 6.652$, $p = 0.084$) (Supplementary Table 2). However, pairwise comparisons found significant differences between HRef and HC groups (Figure 2b, Supplementary Table 2). The results of univariate ANOVA analysis of the transformed ambiguous-SRGP was the same as that of the generalized linear model analysis (Supplementary Table 3). Similar results were found using Jonckheere-Terpstra test for the three patient group comparison (Supplementary Table 4).

3.2. Relationship between demographic, clinical and cognitive function and SRGP

Cognitive function composite score, SAPS and SANS total scores were found to be significantly associated with P0.4 signal strength, ambiguous-SRGP and unambiguous-SRGP rates. PDI score was associated with ambiguous-SRGP rate. IRIS total score and DDD of antipsychotics were associated with unambiguous-SRGP rate. Table 3 shows the details of the results. The overall linear regression model with transformed ambiguous-SRGP rate as dependent variable, and cognitive function composite score, SAPS and SANS total scores as independent variables was significant ($F=4.226$, $p=0.008$). Only cognitive function composite score was significant in the model ($B=-0.253$, $p=0.044$) and SAPS total score showed a trend significance ($B=0.21$, $p=0.065$).

4. Discussion

4.1 Summary of results

This study explored the SRGP in patients with schizophrenia with different levels of psychotic symptoms—high reference delusion, low reference delusion and symptomatic remission groups—and in healthy controls. Two approaches for analysing gaze perception measurements were adopted. One is using self-referential gaze perception rate (percentage of endorsing 'looking at me'). Responses were further categorised into those responding to ambiguous stimuli (averted gaze 10° and 15°) and unambiguous stimuli (averted gaze 20°, 25° and 30°), constituting the ambiguous-SRGP rate and the unambiguous-SRGP rate respectively. Both groups of symptomatic patients displayed higher ambiguous SRGP rate, and the group with high reference delusions showed more unambiguous SRGP bias. Psychophysical analysis was used as the second approach. Only high reference delusion group was found to have significantly lower eye-contact signal strength at P0.4 threshold compared with healthy control group. Cognitive functions, positive and negative symptoms were associated with SRGP rate and eye-contact signal strength at P0.4. Cognitive function was the only significant predictor for ambiguous-SRGP rate.

4.2 Comparison of SRGP between subjects

Our findings that patients with schizophrenia had more SRGP than healthy controls were similar to some of the previous studies (Rosse et al., 1994; Hooker and Park, 2005). Judging averted gaze as directing to self is a form of hypermentalization. Our results echoed with previous imaging studies that patients with schizophrenia have a hyper-mentalizing tendency (Ciaramidaro et al., 2015; Green et al., 2015; Bliksted et al., 2019). Future study on the relationship of SRGP and theory of mind may enhance the psychometric value of this behavioural experiment. We further examined the SRGP of patients with different levels of

psychotic symptoms, specifically focusing on reference delusion. Humans have a prior expectation that other people's gaze is directed towards themselves and such expectation plays a dominant role when there is high uncertainty (Mareschal et al., 2013). Therefore, stimuli were further divided into ambiguous and unambiguous. Patients with psychotic symptoms (regardless of levels of reference delusions) reported similar SRGP rate in response to ambiguous stimuli, which was significantly more than that observed in both remitted patients and healthy controls. When judging unambiguous gaze directions, however, patients with reference delusions were found to have significantly more SRGP bias than any other groups. Furthermore, SAPS total score was significantly associated with all gaze perception measurements. PDI, a measure of delusions, was also found to have significant positive association with the ambiguous-SRGP rate. These suggested that having psychotic symptoms, particularly delusion, may have changed the prior expectation, leading to stronger self-referential judgement towards ambiguous gaze directions. Patients with high levels of reference delusion are likely to have stronger self-referential bias even with relatively high certainty and more irrelevant stimuli. IRIS, a measure of reference ideas and delusions, was also found to be associated with the unambiguous-SRGP rate. These results corroborated previous imaging findings of a linkage between hyper-mentalizing, over-attributing intentions to others, and paranoid symptoms (Ciaramidaro et al., 2015). Perceptual experience is likely a result of the interaction between prior expectation and level of ambiguity of the information received. Presence of delusions changes the prior expectation of an individual and leads to perceptual mis-judgement, which may then feed back to the existing delusional beliefs of patients and contribute to the persistence of psychotic symptoms (Corlett et al., 2009; Fletcher and Frith, 2009).

4.3 Relationship between SRGP, symptomatology and cognitive functions

In agreement with the only previous study that explored the link between general cognitive functions and SRGP (Tso et al., 2012), the current study also found a positive relationship between general cognition and SRGP, more specifically the attention and processing speed. Results of the current study further suggested that the model of attention and processing speed together with positive and negative symptoms in relationship with the SRGP of ambiguous stimuli was significant. Within the model, only the composite score of attention and processing speed was significant while positive symptoms showed a trend significance. The lack of significance for SANS in the model could be explained by its potential correlation with cognitive functions. These suggested that cognitive function such as attention and processing speed play a significant role in social cognition, particularly in mentalization, as pointed out by a previous review (Green et al., 2019). Accordingly, improving the general cognitive functions such as attention in symptomatic patients with schizophrenia may help to reduce self-referential gaze perception and hence weaken the reconsolidation of delusional belief.

4.4 Different eye gaze perception measurements

This is the first study to examine gaze perception using both a behavioural and a psychophysical approach and results suggested that both approaches yielded similar findings. Only two previous studies used psychophysical approach to explore gaze perception. One used response at a base rate of 30% threshold (Hooker and Park, 2005) and the other calculated responses over an eye-contact signal strength continuum (Tso et al., 2012). The current study used a psychophysical approach with 40% as base rate (P0.4) in reference to the experimental design, and found that the high reference delusion patients had significantly lower eye-contact signal strength than the healthy controls at the P0.4 threshold. Cognitive functions, SAPS and SANS scores were significantly associated with P0.4 signal strength. The psychophysical approach assumes that SRGP responses follow a logistic function; however, a previous study

showed that response in some conditions did not fit the logistic function (Tso et al., 2012). Although the responses of 95% of subjects in the current study fit well to a logistic function, some subjects had to be excluded from further analysis. This highlighted the limitations of psychophysical approach in analysing self-referential gaze perception responses.

4.5 Limitations

The current study has the biggest sample compared to previous studies, nonetheless the power of the study may still be limited for some of the statistical explorations. Though no significant differences were found amongst patient groups, the different chronicity of patients may contribute to the variations in the outcomes. Affective symptoms may have also influenced the perceptual judgement, yet it was not explored in the current study or any other previous studies. The cross-sectional design of the current study could not explore the stability of SRGP. Only attention and working memory were assessed as general cognitive functions. It is therefore unclear if other cognitive functions may be related.

4.6 Conclusion

Current study explored SRGP in patients with schizophrenia with varied levels of psychotic symptoms. Results suggested that patients with psychotic symptoms had hypermentalization of gaze direction as towards oneself and it was positively related to psychotic symptoms and negatively associated with cognitive functions. Therefore, SRGP is likely to be a state phenomenon. However, further longitudinal study would be needed to confirm the state effect. The misperception of self-referential gaze may reinforce the existing delusional belief of patients and contribute to the persistence of psychotic symptoms. Improving general cognitive functions in symptomatic patients with schizophrenia may help to reduce SRGP and hence reduce the reconsolidation of the delusional belief. Future studies could investigate

interventions with targeted psychopathological profiles using strategies to improve general cognitive functions to test the hypothesis that cognitive functioning is related to SRGP bias and delusional beliefs. Exploration of the stability of SRGP using longitudinal samples of first episode patients as well as the impacts of other symptom dimensions should also be conducted to allow for comprehensive understanding of SRGP bias.

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