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ORIGINAL ARTICLE

Can interpersonal hypersensitivity under subconscious condition explain paranoid symptom in schizophrenia?

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Abstract

Introduction: Interpersonal hypersensitivity is often observed in schizophrenia and has been associated with psychopathological deficits in schizophrenia. Here, we investigated dysfunctions of interpersonal information processing in schizophrenia at both conscious and subconscious levels.

Methods: The experiment included 143 schizophrenia patients and 59 healthy controls. A continuous flashing suppression approach based on binocular rivalry was employed, which included two modes: invisible (subconscious) and visible (conscious). The accuracy and reaction time of a Gabor patch direction–detection task were assessed under three types of stimuli in both modes: images with no person (type 1), images with two to three noncommunicating persons (type 2), and images with more than three communicating individuals (type 3).

Results: In the visible mode, the accuracy of the Gabor patch direction–detection task in the case group was significantly lower than in the control group for the third type of stimuli ($P = 0.015$). In the invisible mode, however, the accuracy was higher in the case group than in the control group ($P = 0.037$). The response time difference of the Gabor patch direction–detection task for the third type of images in the invisible mode was negatively correlated with the duration of the illness ($P = 0.008$).

Discussion: These findings suggest that schizophrenia patients exhibit attentional bias to interpersonal interaction behaviors at both conscious and subliminal levels but toward opposite directions. Our findings shed light on the subconscious deficits under the paranoid symptom in schizophrenia.

Introduction

Interpersonal interactions play significant roles in the onset, maintenance, and remission of psychiatric disorders including autism, social phobia, personality disorders, and schizophrenia (King-Casas and Chiu, 2012). Difficulties in interpersonal understanding and impairments of interpersonal skills in social interactions are common in clinical observations of patients with schizophrenia. However, much less is known about the relationship between interpersonal processing patterns and clinical symptoms such as persecutory delusions, delusions of reference, and auditory hallucinations. Most studies have explored the social cognitive bias in schizophrenia from the domains of emotional processing, social perception, attributional style, and theory of mind (Green and Horan, 2010). In the theory proposed by Freeman

et al. (2007), reasoning bias plays an important role in suspicious thoughts and persecutory delusions. Social interactions are also involved in the reasoning process; for example, people need to make rapid and accurate judgments about others in a conversation. In schizophrenia, social cognitive improvement is usually based on the decline or disappearance of symptoms, indicating that social cognitive functioning (including interpersonal ability) is associated with clinical symptoms.

Interpersonal sensitivity is most likely to be related to successful interpersonal interaction (Liu, 2013). Interpersonal sensitivity can be defined as the correct identification and comprehension of another's behaviors, feelings, and motives (Rothenberg, 1970). Schizophrenia patients, particularly those with delusions of reference or persecutory delusions, have aberrant interpersonal sensitivity to their surroundings. We conducted a pilot study to ask schizophrenia patients with delusions and non-psychotic patients to rate 30 images depicting different levels of interpersonal interactions in three domains: happiness depicted in the image, impact on the participant, and relevance to the participant. We found that the schizophrenia patients gave much higher scores to the images with more than three people communicating in the domain of relevance to the participants compared with nonpsychotic patients. It remains unclear whether this high interpersonal sensitivity derives from the conscious level, the subconscious level, or from both.

Binocular rivalry refers to the unstable perceptual experience arising when an observer views a different image with each eye: Each image reaches awareness in turn as the other becomes temporarily invisible (Blake and Logothetis, 2002; Brascamp and Blake, 2012). Through changing the salience of the images, the target image could be persistently invisible because of strong interocular suppression. Compared to backward masking – another commonly applied technique in the study of unconscious processing – the continuous flashing suppression (CFS) paradigm can render the information invisible (unconscious) throughout a relatively long period (Tsuchiya *et al*., 2006). Jiang and his colleagues investigated the effect of invisible images on the distribution of spatial attention by use of the binocular rivalry paradigm and found that an 800-ms presentation of the unconscious images could result in attentional bias (Jiang *et al*., 2006). This paradigm has been widely used in subconscious studies of sexual orientation (Jiang *et al*., 2006), nicotine addiction (Yan *et al*., 2009), depression (Yang *et al*., 2011), anxiety disorders (Tan *et al*., 2011), and autism spectrum disorder (Akechi *et al*., 2014). Most studies using the CFS paradigm have explored the subconscious processing of affective stimuli to assess social cognition and social performance (Jiang *et al*., 2009; Tan *et al*., 2011; Yang *et al*., 2011; Anderson *et al*., 2012; Stein and Sterzer, 2012; Vizueta *et al*., 2012; Willenbockel *et al*., 2012; Gray *et al*., 2013; Troiani and Schultz, 2013; Akechi *et al*., 2014; Kring *et al*., 2014; Doi and Shinohara, 2015). The present study utilized neutral stimuli to detect the attentional bias toward interpersonal information at the conscious and subconscious levels in schizophrenia. We have also used this design to assess the social cognition impairment in children with schizophrenia (Wang *et al*., 2013).

Given the above knowledge, we hypothesized: (i) patients with schizophrenia would show impaired processing patterns of interpersonal information either at conscious or subconscious levels or at both compared with controls; (ii) within the schizophrenia group, the deficits in different level processing of interpersonal information would be associated with clinical symptoms. In the current study, we used a CFS approach based on binocular rivalry to examine these hypotheses. Specifically, we examined the conscious and subconscious processing dysfunctions of interpersonal information in patients with schizophrenia. This investigation of deficits on both conscious and subconscious levels may improve understanding of the relationship between clinical symptoms and interpersonal impairments in schizophrenia.

Methods

Participants

The experiment was performed in accordance with the protocol of this study and approved by the local institutional ethics board (Institutional Review Board of Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine). All participants provided written informed consent after receiving a clear description of the experiment.

All participants were Chinese and right handed, had normal or corrected-to-normal vision, and were matched for age and gender. A total of 143 patients were enrolled from the inpatient services of the Shanghai Mental Health Center, Shanghai, China, who met the following inclusion criteria: age between 18 and 50; a diagnosis of schizophrenia based on the Structured Clinical Interview for Diagnostic and Statistical Manual Patient Edition for DSM-IV (First *et al*., 1997, 1999); delusions as the primary symptom; general intelligence (IQ) more than 70. The control

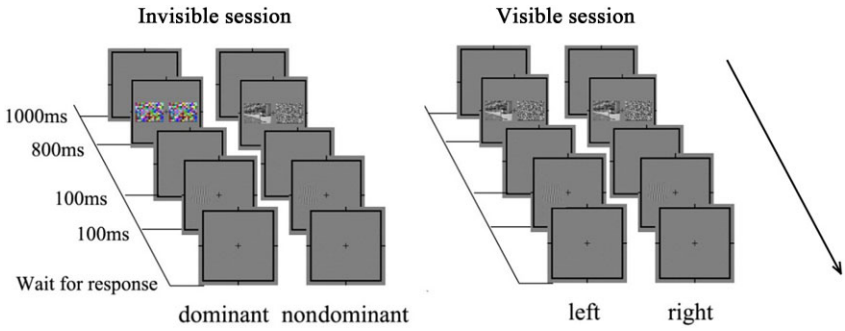

Figure 1. In the invisible session, the dominant eye was presented with two colored mosaic patches, and the nondominant eye was simultaneously presented with a monochromemosaic patch and a monochrome version of one of the 30 target images (800 ms). After a 100-ms interval, a Gabor patch was presented to both eyes for 100 ms. The task of the participant was to determine the direction of the skew (left or right) and to press the right or left side of the mouse accordingly. The only difference in the visible session was: both eyes were presented with paired images of a monochrome mosaic patch and a monochrome version of one of the 30 images, which alternated between the right and left sides of the visual field.

group consisted of 59 college students and staff at Shanghai Jiao Tong University School of Medicine, Shanghai, China. Inclusion criteria for the control group were: age between 18 and 50; no Axis I or Axis II diagnosis according to the Structured Clinical Interview for DSM-IV; and no history of Axis I disorders in their first-degree relatives. Participants with a history of neurological or severe somatic illness, head trauma, alcohol dependence, or substance abuse were excluded. The IQ score was evaluated by an independent assessor using the Wechsler Adult Intelligence Scale-Chinese Revision (Gong, 1982). The severity of schizophrenia at the time of the experiment was assessed by one clinician using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*., 1987). We also assessed the delusions of reference on a similar 7-point Likert scale (1 = not at all; 7 = extremely severe) with reference to the rating standard of "delusion" item in PANSS. Depression and anxiety symptoms were also measured with the Beck Depression Inventory (BDI) (Beck *et al*., 1961) and Self-Rating Anxiety Scale (SAS) (Zung, 1971).

Stimuli and procedure

A total of 30 images depicting different levels of interpersonal interactions were selected from a series of candidate images, which were photographed by the authors. The images fell into three categories (10 images for each): images with no person (type 1), images with two to three noncommunicating people (type 2), and images with more than three communicating people (type 3). We used Photoshop 7.0 software (Adobe Systems Inc., San Jose, CA, USA) to alter the color, brightness, and size of these images to generate monochrome images 150 mm × 112 mm. These images were the same as those used in the pilot study, in which we asked patients to rate the images in three domains. The procedure of stimuli in two sessions is shown in Figure 1. The detailed description of the experiment procedure is given in the Supporting Information.

Before the experiment, the participants practiced 50 trials for the invisible session to gain familiarity with the experimental sequence. During the experiment, they were instructed to press a different button to reject the trial if they were aware of the intact images presented to the nondominant eye. Data for participants who rejected more than three trials in the invisible session were excluded from further data analyses.

After the tests, the participants were instructed to rate each of the 30 images on three dimensions – happiness depicted in the image, impact on the participant, and relevance to the participant – on three, 9-point Likert scales, where "1" meant extremely unhappy, no impact, or completely irrelevant, and "9" meant extremely happy, huge impact, or highly relevant.

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS; SPSS Inc., Chicago, IL, USA) version 16.0 for Windows. Chi-square analyses were conducted to assess the gender, age, and educational level differences between the two groups. Univariate analyses of covariance (ANCOVAs) were employed to examine significant differences of ratioAcc_{img} and diffRT_{img} between patient and control groups for both the invisible and visible sessions, including age, IQ score, BDI score, and SAS score as covariates. For the case–control comparison,

the level of significance was set to $P < 0.05$ (two-tailed). Correlation analyses were performed to test for correlations between attentional effect measures and clinical measures/image ratings. With respect to multiple testing in the context of six attentional effect measures, we adjusted the significance requirement from alpha = 0.05 to alpha = 0.008 (dividing 0.05 by 6).

Results

Demographic and clinical data

A total of 143 schizophrenia patients and 59 healthy controls completed both the invisible and visible mode tests. The data of 55 schizophrenic patients and 38 healthy controls in the invisible session and 40 schizophrenic patients and 34 healthy controls in the visible session were valid and included into the final analysis. The mean (SD) ages in the patient and control groups were 30.80 (8.744) years and 28.24 (7.149) years, respectively; there were 29 males and 26 females in the patient group and 18 males and 20 females in the control group. There were no statistically significant differences in age and gender distribution between the two groups (t =–1.494, $P = 0.139$; Fisher's exact test $P = 0.676$). Education level was ranked from 1 to 6 (1 = illiteracy, 2 = primary school, 3 = junior high school, 4 = senior middle school, 5 = college, 6 = graduate). Patients had less education than members of the control group (Mann–Whitney $U = 526.5$, $P < 0.001$). The mean (SD) IQ scores were 89.95 (10.084) for the patient group and 111.16 (8.491) for the control group ($t = 10.618$, $P < 0.001$). The mean (SD) PANSS and delusions of reference scores of the patients were 61.76 (21.374) and 3.02 (1.65). The mean (SD) BDI and SAS scores of the patients were 4.86 (8.990) and 25.12 (7.124), respectively, which were significantly different from the control group (t =–3.279, $P = 0.002$; t=–1.944, $P = 0.057$). The mean duration of illness was 96.04 (83.313) months. All patients were treated with antipsychotic medications.

Visible session

An ANCOVA with age, IQ score, BDI score, and SAS score as covariates was performed to assess the group difference of $ratioAcc_{img}$ and $diffRT_{img}$ for each category. The result revealed a significant difference between patient and control groups for the measure of $ratioAcc_{img3}$ ($F(1,74) = 6.223$, $P = 0.015$) (see Figure 2). The mean (SD) scores of $ratioAcc_{img3}$ for the patient and control groups in the visible session were 0.995 (0.1452) and 1.067 (0.1479), respectively. No other significant group differences were found in the response accuracy ratios for the other two types of images or in response time differences for all the types of images.

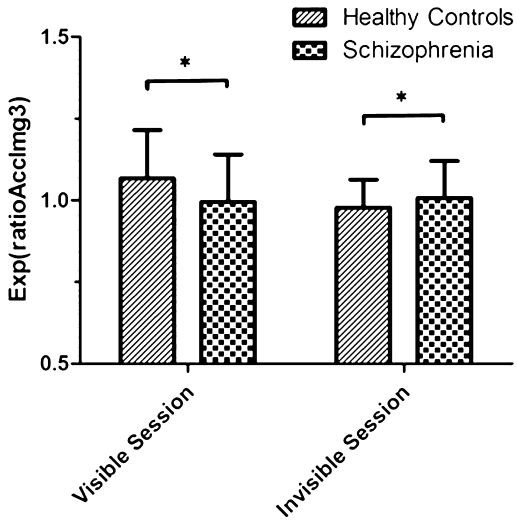

Figure 2. In the visible session, a significant difference was found between patient and control groups for the measure of ratioAccimg3 ($F(1,74) = 6.223$, $P = 0.015$). In the invisible session, a significant difference was found between patient and control groups for the measure of ratioAccimg3 ($F(1,92) = 4.466$, $P = 0.037$).

Invisible session

An ANCOVA with age, IQ score, BDI score, and SAS score as covariates was also conducted for the measures of $ratioAcc_{img}$ and $diffRT_{img}$ for each category in this session. The result yielded a significant difference between patient and control groups for the measure of ratioAccimg3 ($F(1,92) = 4.466$, $P = 0.037$) (see Figure 2). The mean (SD) scores of $ratioAcc_{img3}$ for the patient and control groups in the invisible session were 1.006 (0.1137) and 0.978 (0.0854), respectively. No other significant group differences were found in the response accuracy ratios for the other two types of images or in response time differences for all the types of images.

Correlation with clinical measures

In the invisible session, the measure of $diffRT_{img1}$ was found to be negatively correlated with the PANSS negative symptom score in the patient group (r=–0.383, $P = 0.004$). The duration of illness was

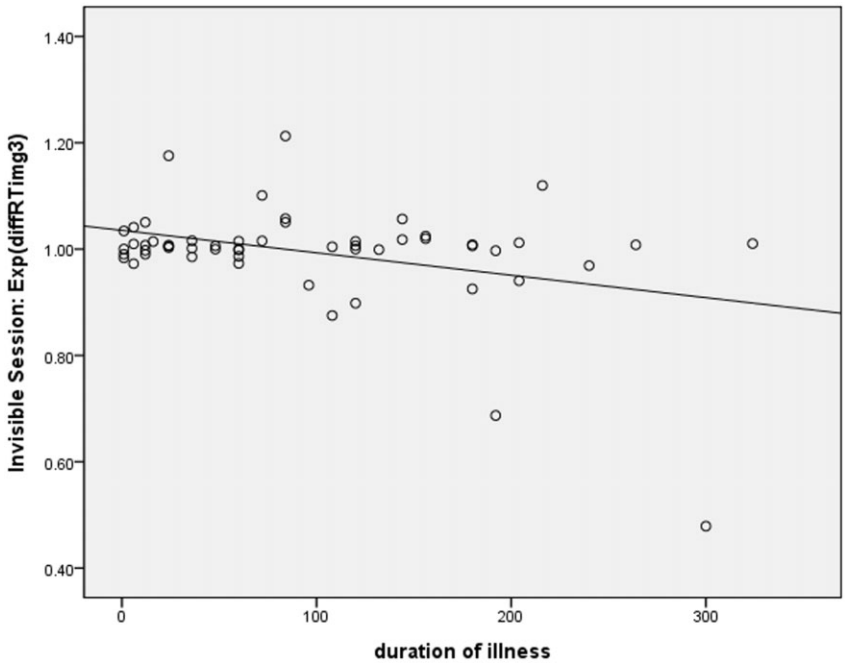

Figure 3. In invisible session, a negative correlation between the measure of diffRTimg3 and the duration of the illness was found in the patient group ($r = -0.355$, $P = 0.008$).

found to be negatively correlated with the measures of $diffRT_{img3}$ ($r=-0.355$, $P = 0.008$) (see Figure 3). In the visible session, there were no significant correlations between attention effect measures and clinical measures.

Correlation with image ratings

In both sessions, there were no significant correlations between attention effect measures and image ratings.

Discussion

The current study investigated the cognitive processing of interpersonal information under conscious or subconscious conditions in both schizophrenia patients and healthy controls using the CFS approach. This paradigm has been widely used in subconscious studies (Jiang *et al*., 2009; Tan *et al*., 2011; Yang *et al*., 2011; Anderson *et al*., 2012; Stein and Sterzer, 2012; Vizueta *et al*., 2012; Willenbockel *et al*., 2012; Gray *et al*., 2013; Troiani and Schultz, 2013; Akechi *et al*., 2014; Kring *et al*., 2014; Doi and Shinohara, 2015). As it was a demanding task that would be confounded by cognitive functions, mood, and anxiety, we included age, IQ score, BDI score, and SAS score as confounders.

The main findings are: in the visible mode of CFS tests, the accuracy ratio of the Gabor patch direction in the patient group was lower than that in the control group for the type 3 images, which indicates that patients with schizophrenia show a significant decrease in attention engagement to images with more than three communicating people in the conscious condition. In the invisible mode, the accuracy ratio of the Gabor patch direction in the patient group was higher than that in the control group for the type 3 images, which indicates that patients with schizophrenia show more attention engagement to images with more than three communicating people in the subconscious condition compared with controls. Another notable finding is that, either at a conscious or subconscious level, the healthy controls paid more attention to the images with more profoundly impacted people, while the patients with schizophrenia preferred to devote their attention to the images with people with lower depicted happiness. Therefore, the "negative" scene with people may attract the attention of the patients.

We also performed a correlation analysis between clinical measures and CFS tests. We found that, only in the invisible mode, the duration of illness was negatively correlated with the response time difference of the Gabor patch direction for the type 3 images, and there was an inverse correlation between the PANSS

negative symptom score and the response time difference of the Gabor patch direction for the type 1 images. Our results suggest that the patients with longer duration of illness show less attentional engagement to the images with more than three communicating people in the subconscious condition, which may indicate that interpersonal hypersensitivity under the subconscious condition decreased in the stable phase.

A recent study by Kring *et al*. (2014) used the CFS paradigm to examine the processing of affective information and found that patients with schizophrenia showed a deficit in explicit affect perception. The present study also used the CFS paradigm, but with neutral stimuli, to assess the conscious and subconscious processing of interpersonal information in patients with schizophrenia. Individuals with interpersonal sensitivity are able to perceive the emotions of a partner, infer the partner's thinking, decode the partner's attempts at communication, and behave appropriately in social interactions (Hall and Bernieri, 2001). We found that patients with schizophrenia showed attentional avoidance at the conscious level but hypersensitivity at the subconscious level toward interpersonal information, and interpersonal hypersensitivity at the subconscious level decreased along with the duration of illness.

The implications of our findings provide a better understanding of the relationship between clinical symptoms and the aberrant processing patterns of interpersonal information in schizophrenia. The symptoms of delusion in schizophrenia are usually accompanied with high interpersonal sensitivity to persons and things around the patient. On the basis of our findings, we presumed that this kind of hypersensitivity derived from the subconscious level, but it would decrease or disappear during the stable phase of the illness. Although no correlation was found between measurements and positive symptoms, this finding might be a clue to the underlying mechanisms of the paranoid symptom in schizophrenia. For future interventions, some research has started to use psychotherapy methods, such as cognitive behavioral therapy (Bell and Freeman, 2014; Freeman *et al*., 2015) and reasoning intervention (Garety *et al*., 2015), to treat the delusional symptoms in schizophrenia. The efficacy of these interventions requires further investigation.

Several limitations of the study should be taken into account. First, the CFS test was a demanding task, requiring a high level of concentration on the part of the participants. This may increase the difficulty of the tasks and limit the valid data size. We made the instructions as easy as possible to understand and added a practical trial to allow the participants to become familiar with the experiment sequence, but there were still some patients with severe thought disorders who could not perform the test according to the instructions. We excluded the data with accuracy less than 50%, which was regarded as invalid. Second, the experimental content involved the social cognitive functioning and attentional processing of patients with schizophrenia. It would be better to control for cognitive impairment using a neurocognitive scale. We assessed IQ for all the participants and included the IQ score as a confounder. Third, the side effects of antipsychotics, such as extrapyramidal side effects, may also affect reaction time. Due to the difference in the medications and dosages used in the patient group, we cannot exclude the influence of medication on the results. Moreover, the patients we enrolled in the present study were at different phases of the illness, so their levels of cognitive function might be different, leading to a large amount of invalid data that had to be excluded. As a next step, we would use this paradigm to test the subgroups of schizophrenia patients, for instance, first-episode patients or prodromal patients, to explore the dynamic alterations of the interpersonal processing patterns in schizophrenia.

Taken together, the ambivalence of interpersonal processing under conscious and subconscious conditions might be a clue to the paranoid symptom in schizophrenia. This aberrant interpersonal sensitivity altered along with the duration of the illness, which suggests that this pattern of interpersonal information processing might be a state, not a trait phenotype of psychopathology in schizophrenia. Further investigations combining Electroencephalogram (EEG) and Functional magnetic resonance imaging (fMRI) technologies should be conducted to examine the underlying mechanisms of the observed aberrant interpersonal processing in schizophrenia.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Experiment procedure.