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Neural correlates of out-group bias predict social impairment in patients with schizophrenia

J.U. Blackford [a,*], L.E. Williams [b], S. Heckers [a]

[a] Department of Psychiatry, Vanderbilt University School of Medicine, 1601 23rd Avenue South, Nashville, TN 37212, United States
[b] Department of Psychiatry, University of Wisconsin–Madison, Wisconsin Psychiatric Institute & Clinics, 6001 Research Park Blvd., Madison, WI 53719, United States

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ABSTRACT

Background: Social impairments are a hallmark feature of schizophrenia and are a key predictor of functional disability. Deficits in social information processing likely underlie social impairment; however, this relationship is understudied. We previously demonstrated that patients with schizophrenia fail to habituate to neutral faces, providing evidence for an alteration in basic social information processing. It remains unknown whether patients with schizophrenia also show deficits in processing of more complex social information. Out-group bias provides an excellent opportunity to test complex social information processing because the bias requires basic face processing skills, the ability to discriminate between groups, as well as the ability to categorize oneself into a salient social group.

Methods: Study participants were 23 patients with schizophrenia and 21 controls. Using functional magnetic resonance imaging, habituation of response to 120 s of repeated presentations of faces was assessed in participants who viewed either same-gender faces or opposite-gender faces. The interaction between face gender (same/opposite) and group was examined in three key regions: amygdala, hippocampus, and visual cortex. Social impairment was measured using the PANSS and correlations between social impairment and out-group effect (main effect of face type) were performed in patients.

Results: Patients with schizophrenia had aberrant neural responses to opposite-gender faces (interaction, $p < .05$ corrected). Healthy controls showed an immediate heightened response to opposite-gender faces relative to same-gender faces; but in patients this effect was substantially delayed (~70 s). In patients with schizophrenia, the out-group bias was significantly correlated with social impairment. Patients with no social impairment showed a heightened neural response to opposite-gender faces after 30 s, whereas patients with mild–moderate social impairment failed to ever show a heightened response.

Conclusion: Alterations in neural responses during out-group processing predicted degree of social impairment in patients with schizophrenia; thus, neural responses to opposite-gender faces may provide a novel measure for studies of treatment response and disease outcome.

1. Introduction

Deficits in the processing of social information are paramount in schizophrenia and are thought to underlie the observable deficits in social impairment. A growing body of research demonstrates that patients with schizophrenia have deficits in social information processing (Lee et al., 2013). For example, patients have a well-established deficit in emotion perception, typically demonstrated as an impaired ability to recognize or label emotional facial expressions (Chan et al., 2010), which is accompanied by reduced activation in several brain regions implicated in social and emotional information processing (Li et al., 2010). However, emotional faces confound emotion processing with processing of the social information inherent in faces. To directly investigate neural processing of a socially relevant stimulus in patients with schizophrenia, we recently measured neural response to repeated presentation of neutral faces (Williams et al., 2013).

Decreased responding to repeated presentations of a stimulus over time, or habituation, is one of the most basic learning processes and provides an ideal opportunity to observe social information processing. In controls, neural responses to repeated faces habituated over time; however, patients failed to show habituation. Importantly, the habituation deficits were specific to faces as they were not observed when participants viewed neutral objects, providing compelling evidence for a basic deficit in social information processing. Failure to habituate may represent a trans-diagnostic biomarker for social impairments as other groups characterized by social deficits, including autism and high social anxiety, also show habituation deficits to social stimuli (Kleinhans et al., 2009; Blackford et al., 2013; Swartz et al., 2013).

* Corresponding author at: 1601 23rd Avenue South, Suite 3057J, Nashville, TN 37212, United States. Tel.: +1 615 343 0715.
E-mail address: j.blackford@vanderbilt.edu (J.U. Blackford).

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Human faces convey a multitude of information critical for social interactions. In addition to emotion, faces provide salient information about identity, race, and gender. This additional information is used to quickly categorize others according to salient social groups. An interesting aspect of both race and gender is that humans show "out-group" biases; that is, behaviors and neural responses that differ when viewing someone that differs from oneself on either race (Hart et al., 2000; Olsson et al., 2005) or gender (Shapiro and Penrod, 1986; Shaw and Skolnick, 1994; Wright and Sladden, 2003). For gender bias, recognition memory is lower for out-group faces relative to in-group faces (Shaw and Skolnick, 1994).

The out-group phenomenon suggests that face properties such as gender elicit a level of social information processing that goes beyond basic face processing. Out-group bias likely requires several abilities, including the ability to discriminate between groups (Dunham et al., 2013) and to categorize oneself in to a salient social group (Turner et al., 1987). Patients with schizophrenia have intact gender discrimination (Bediou et al., 2005) but models of schizophrenia (i.e. ipseity-disturbance model) propose that patients with schizophrenia lack a consciousness of self (Nelson et al., 2014), which may produce deficits in self-categorization and social impairments. The neutral faces employed in our previous study did not vary in their race (all Caucasian), but did vary in gender, such that participants viewed faces of either the same or opposite gender to themselves. This provides a unique opportunity to test for differences in the neural processing of complex social information in schizophrenia and the impact on social functioning.

In the present study, we analyzed fMRI habituation data with a focus on gender out-group effects in schizophrenia. We hypothesized that patients with schizophrenia would fail to display the typical neural pattern of out-group bias—delayed habituation to opposite-gender faces. We further predicted that within patients, deficits in social information processing would predict social impairment.

2. Methods

This study is a novel analysis of a data set previously used to examine neural habituation in schizophrenia. Here we examine the role of face gender, which was not previously analyzed, on habituation in healthy controls and patients with schizophrenia, and incorporate measures of social impairment.

2.1. Participants

Participants were 25 patients with schizophrenia (schizophrenia n = 18; schizoaffective disorder n = 7) and 23 healthy controls. Patients were recruited from an academic medical center inpatient unit and outpatient clinics. Healthy controls were recruited from the local community using advertisements. Diagnosis was determined using the Structured Clinical Interview for DSM-IV. Patients with schizoaffective disorder met criteria A, B, and C for schizophrenia and clinical variables did not differ between the two patient subgroups. Participants were excluded for: history of drug or alcohol dependence, substance abuse in the past 6 months, head injury, significant medical or neurological illness, and/or uncorrected vision deficits.

All participants completed the National Adult Reading Test as a measure of premorbid IQ. Patients with schizophrenia were also assessed with the Positive and Negative Syndrome Scale (PANSS), the Hamilton Depression Rating Scale, and the Young Mania Rating Scale. To assess social impairment we used two items from the PANSS: 1) active social avoidance defined as diminished social involvement associated with unwarranted fear, hostility or distrust; and 2) passive social withdrawal defined as diminished interest and initiative in social interactions. Whether these two items represent distinct or shared constructs remains unclear as some studies find they are distinct (Hansen et al., 2013) and others show they load on a common factor (Van den Oord et al., 2006). In our sample the two items were modestly correlated (r = .48, p = .02), therefore we analyzed them separately. Both items showed sufficient range for correlation analyses: social withdrawal (minimum = 1, maximum = 6) and social avoidance (minimum = 1, maximum = 7). This research was conducted in accordance with the Vanderbilt Human Research Protection Program and all participants provided written informed consent. Participants received financial compensation.

Table 1
Participant characteristics.

	Schizophrenia N = 23		Control N = 21	
	Mean	SD	Mean	SD
Age	43.4	11.8	42.4	10.0
Education, years*	13.7	2.5	15.8	2.3
Parental education, years	13.2	2.7	13.4	2.4
IQ/NART score	106.2	8.5	109.3	8.3
PANSS—total	51.4	13.0		
PANSS—passive social withdrawal	2.4	1.5		
PANSS—active social avoidance	2.4	1.7		
Chlorpromazine equivalent dose	521.1	261.8		
Hamilton Depression Rating Scale	3.4	3.5		
Young Mania Rating Scale	1.0	2.3		
	%	N	%	N
Sex (% female)	48	11	47	10
Race (% black/white/other)	43/57/0	10/13/0	33/62/5	7/13/1

Note: PANSS = Positive and Negative Syndrome Scale.
* Controls > patients, p < .05.

2.2. fMRI task

Habituation to faces was assessed using fMRI and a repeated faces task (also known as repetition suppression or functional magnetic resonance adaptation). In this task, participants reviewed one 2-minute run of the same face. The run consisted of 120 face presentations (500-ms presentation, 500-ms inter stimulus interval). A fixation cross was presented for 10 s at the beginning of the run and 20 s at the end of the run to provide a baseline. Stimuli were black and white faces with neutral expressions obtained from standard stimulus sets (Lundqvist et al., 1998; Gur et al., 2001; Minear and Park, 2004; Tottenham et al., 2009). Face gender was counterbalanced across participant gender so that half of the participants saw a face that was the same gender and half saw a face that was an opposite gender. Stimuli were presented using Eprime 2.0. Eye-movements were monitored during the MRI session to ensure participants were awake and fixating the screen. To promote and quantify attention during the task, small versions of the faces (25% of original size) were presented on 10% of the trials and detected by participants with a button press. A brief pre-scan training was used to familiarize participants with the task. Participants were excluded for detecting less than 66% of targets (2 controls, 2 patients with schizophrenia).

2.3. Final analysis sample characteristics

Participant characteristics for the final analysis sample are presented in Table 1. Of the 23 patients with schizophrenia, 12 (6 female) viewed a same gender face and 11 (5 female) viewed an opposite gender face. In the sample of 21 controls, 10 (5 female) viewed a same gender face and 11 (5 female) viewed an opposite gender face. There were no significant differences in age or race by group, face gender, nor the group × face gender interaction (all p > .30). The two groups of schizophrenia patients viewing either same or opposite gender faces did not differ in education, parent education, IQ, PANSS total, PANSS active social avoidance, PANSS passive social withdrawal, depression, mania, or chlorpromazine equivalent dose.