Progress in Neuro-Psychopharmacology & Biological Psychiatry 71 (2016) 90–96

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Decreased neural response for facial emotion processing in subjects with high genetic load for schizophrenia

Hye Yoon Park [a,1], Je-Yeon Yun [a,1], Na Young Shin [b], So-Yeon Kim [c], Wi Hoon Jung [b], Ye Seul Shin [c], Kang Ik K. Cho [c], Youngwoo Bryan Yoon [c], Kyung-Ok Lim [a], Sung Nyun Kim [a], Jun Soo Kwon [a,b,c,*]

[a] Department of Psychiatry, Seoul National University College of Medicine, Seoul 03080, Republic of Korea
[b] Institute of Human Behavioral Medicine, SNU-MRC, Seoul 03080, Republic of Korea
[c] Department of Brain & Cognitive Sciences, College of Natural Science, Seoul National University, Seoul 03080, Republic of Korea

ARTICLE INFO

Article history:
Received 9 April 2016
Received in revised form 16 June 2016
Accepted 27 June 2016
Available online 30 June 2016

Keywords:
Schizophrenia
First-degree relatives
Facial emotion processing
Amygdala
Functional magnetic resonance imaging

ABSTRACT

Background: Patients with schizophrenia show impairment in facial emotion processing which is essential for successful social cognition. Using a functional magnetic resonance imaging (fMRI), this study aimed to investigate the implicit facial emotion recognition processing in participants with high genetic load for schizophrenia (GHR) as a possible trait marker of developing schizophrenia.
Methods: Block design fMRI of implicit facial emotion processing was used in 20 participants with GHR aged 16–35, and 17 age, sex, and education year-matched healthy controls (HC). During the facial emotional processing for fearful, happy, and neutral face stimuli, participants were asked to explicitly determine the gender per stimuli.
Results: Occipito-temporo-limbic area in fearful face condition and involvement of broader region including prefrontal cortex in neutral face condition revealed significant attenuation of BOLD signal activation in GHR compared to HC. The GHR demonstrated less activity in right amygdala during fearful and neutral face condition.
Conclusion: The study presented that GHR displayed abnormal brain activity in occipito-temporo-limbic-frontal network implicated in facial emotion processing. It indicates that abnormal facial emotion processing may be influenced by a genetic factor and could be a trait marker in schizophrenia.

1. Introduction

Patients with schizophrenia are known to have abnormal decoding of facial emotion, which impairs social functioning (Kee et al., 2003; Rauch et al., 2010). Abnormal facial emotion recognition is relatively stable over the trajectory of the illness from the first episode to chronic stage regardless of symptom improvement (Addington and Addington, 1998; Edwards et al., 2001) and not improved by antipsychotic treatment (Herbener et al., 2005). Adolescents at increased risk for psychosis showed abnormal facial emotion recognition (van Rijn et al., 2011). These evidences support that facial emotion processing might have a genetic vulnerability in developing schizophrenia.

Patients with schizophrenia have repetitively demonstrated abnormal brain functional activation in regions such as amygdala, hippocampus, parahippocampal gyrus, temporal gyrus, fusiform gyrus, basal ganglia, and prefrontal cortex during face emotion processing (Gur et al., 2007; Holt et al., 2006; Johnston et al., 2005). Specifically, a recent meta-analysis study for brain activity during facial emotion processing revealed that patients with schizophrenia show hypoactivation of "social brain network" comprised of amygdala, ventral temporal lobe, basal ganglia and prefrontal cortex (Li et al., 2010). Among these regions of "social brain network", amygdala dysfunction has been investigated as its key role in abnormal facial emotion recognition of schizophrenia. Specifically, two recent meta-analyses demonstrated amygdalar underrecruitment in facial emotion processing in schizophrenia (Li et al., 2010; Anticevic et al., 2012). These findings may result from amygdalar hyperactivity in neutral condition, called 'amygdala overactivation hypothesis' (Hall et al., 2008; Seiferth et al., 2008; Gur and Gur, 2015). It suggests that abnormal emotion processing to salient stimuli might be one of the mechanisms related to biased interpretation of social context in psychosis.

Likewise, previous studies for family members of patients with schizophrenia have reported abnormal emotion recognition for face stimuli (Janssen et al., 2003), suggesting the possibility that abnormal processing of facial emotion might be related to the genetic basis of

Abbreviations: GHR, genetic high-risk for psychosis; STAI, State Trait Anxiety Inventory; BOLD, blood-oxygenation-level-dependent.

* Corresponding author at: Department of Psychiatry, Seoul National University College of Medicine, and Department of Brain & Cognitive Science, College of Natural Sciences, Seoul National University, Seoul, Republic of Korea.
E-mail address: kwonjs@snu.ac.kr (J.S. Kwon).

[1] Drs. Hye Yoon Park and Je-Yeon Yun contributed equally to this article.

http://dx.doi.org/10.1016/j.pnpbp.2016.06.014
0278-5846/

psychosis. In contrast, several neuroimaging studies for family members of patients with schizophrenia have shown mixed results; Amygdala showed reduced activity during induction of sad mood (Habel et al., 2004) or in response to happy faces (Barbour et al., 2010), indistinguishable degree of functional activation compared to healthy controls during explicit (Li et al., 2012) or implicit (Rasetti et al., 2009) processing of emotion as reflected in the face stimuli. The participants of previous studies for family members of schizophrenia were siblings or offspring of schizophrenia patients. As sporadic cases with weak genetic influence in their family were not excluded in these studies, those previous studies could not detect abnormality of family group. Furthermore, to determine genetic contribution for amygdala hyperactivity during implicit processing of neutral face stimuli, this study included investigation of neutral face processing in family of schizophrenia.

This study aims to investigate an influence of schizophrenia-related genetic factors for facial emotion processing including neutral face as one of the target valence. To increase the probability of capturing a genetic contribution in facial emotion processing, we recruited schizophrenia family with high genetic load who have at least two affected family members. Our hypothesis was that subjects with genetic high-risk for psychosis (GHR) would show changed patterns of amygdala activation including hypoactivation during fearful face processing and hyperactivation during neutral face processing, with alteration of emotional processing network; which have been already demonstrated in patients with schizophrenia.

2. Materials and methods

2.1. Participants

A total of twenty participants of GHR, individuals who had two first-degree relatives diagnosed with psychosis ($n = 7$) or who had one first-degree relative diagnosed with psychosis and at least one other family members of psychosis as their third-degree relatives ($n = 13$), were recruited from a prospective longitudinal project of Seoul Youth Clinic during August 2011 and March 2014. Using the Structured Interview for Prodromal Syndromes (SIPS) (Jung et al., 2010), the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005), the Positive and Negative Symptom Scales (PANSS) (Kay et al., 1987), Hamilton Rating Scale for Depression (HAM-D) (Muller and Dragicevic, 2003), and Hamilton Anxiety Rating Scale (HAM-A) (Bruss et al., 1994), certified psychiatrists evaluated the profile of psychopathology for GHR participants. Furthermore, seventeen participants of healthy controls (HC) were recruited using on-line advertisement and assessed using SCID-NP to confirm the absence of lifetime history of psychiatric illness. In addition, a self-report questionnaire named State Trait Anxiety Inventory (STAI) (Spielberger, 1983) was used for all of the participants including the GHR as well as the HC. Exclusion criteria for all participants were as follows: history of significant head injury; presence of neurological disease, significant medical illness, substance use disorder or intelligence quotient (IQ; as measured using the Korean version of the Wechsler Adult Intelligence Scale [K-WAIS] (Yum et al., 1992)) < 70.

2.2. MR acquisition and preprocessing

2.2.1. MR acquisition & task design

All task-related functional magnetic resonance imaging (fMRI) were performed using a 3 Tesla MAGNETOM Trio Tim Syngo (Siemens, Erlangen, Germany). Functional data were acquired using a T2*-weighted gradient echo sequence (TR = 2000 ms, TE = 30 ms, FOV = 220 × 220 mm, FA = 90°, voxel size = 3.44 × 3.44 × 4.00 mm^3, inter-slice gap = 1.04 mm, interleaved, and 27 axial slices) positioned parallel to the anterior–posterior commissure plane covering the whole brain. The design and preparation of face stimuli for task-related fMRI were described previously (Shin et al., 2015); In short, the task-block for implicit recognition of facial emotion [fearful, happy, or neutral] while conducting explicit gender identification of face stimuli (Hall et al., 2008) was composed of six different Korean facial identities (three males and three females; each presented with pseudo-random order for 3 s and were followed by a fixation cross for 0.5 s between different facial stimuli) and was interleaved with the baseline blocks showing a fixation cross for 12 s (Fig. 1).

The 11-minute task was composed of two runs. Each run consisted of three fearful, three happy, and three neutral face blocks (22 s each), in which each block included six different face trials. The emotion blocks were arranged in different pseudo-random orders across the run, and each run had different orders. The face stimuli used in this study were selected from Extended ChaeLee Korean Facial Expressions of Emotions (C-KFEE) (Lee et al., 2013) and Korean Facial Expressions of Emotion (KOFEE). The mean score of accuracy of emotion identification had been reported as 99% for happy faces, 97% for neutral faces, and 79% for fearful faces (Shin et al., 2015)). In addition, T1-weighted anatomical volume reference images for each subject was also acquired (TR = 1670 ms, TE = 1.89 ms, FOV = 250 × 250 mm, FA = 9°, voxel size = 1.0 × 1.0 × 1.0 mm^3).

2.2.2. Statistical analyses of MR data

The preprocessing and general linear modeling (GLM) analyses for task-related T2*-images were conducted using Statistical Parametric Mapping 8 (SPM 8) software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). After discarding the first three images for minimizing

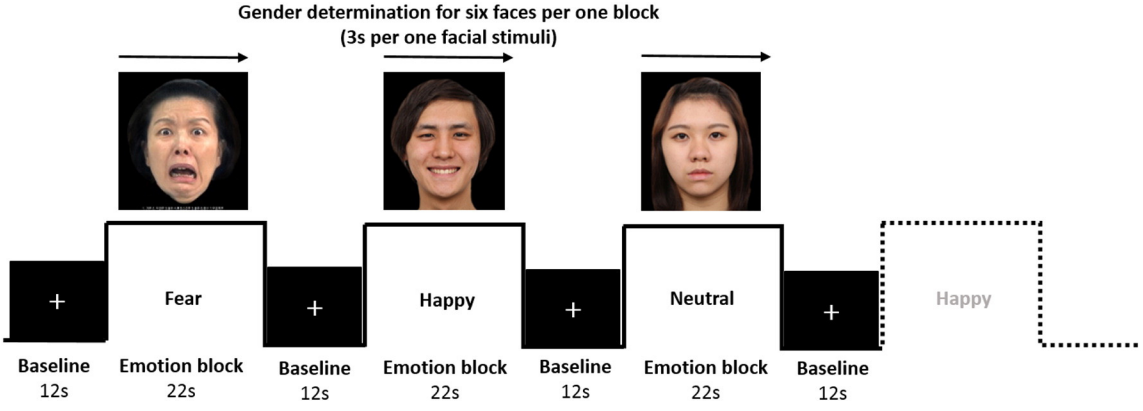

Fig. 1. fMRI paradigm. Subjects conducted gender determination of face stimuli while seeing three emotional face block [fearful, happy, or neutral] composed of six different Korean facial identities with pseudo-random order for 3 s and were followed by a fixation cross for 0.5 s between different facial stimuli.