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Functional activation abnormalities during facial emotion perception in schizophrenia patients and nonpsychotic relatives

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ABSTRACT

Background: Deficits in facial emotion perception in schizophrenia may be a marker of disorder liability. Previous functional magnetic resonance imaging (fMRI) studies investigating these deficits have been limited by task demands that may recruit other impaired cognitive processes in schizophrenia.
Methods: We used a family study design along with a passive viewing task during fMRI to investigate brain activation abnormalities underlying facial emotion perception in schizophrenia and examine whether such abnormalities are associated with the genetic liability to the disorder. Twenty-eight schizophrenia patients, 27 nonpsychotic relatives, and 27 community controls passively viewed images of facial emotions during an fMRI scan.
Results: Analyses revealed hypoactivation in face processing areas for both patients and relatives compared to controls, and hyperactivation in relatives compared to both patients and controls for frontal regions implicated in emotion processing.
Conclusions: Results suggest that activation abnormalities during facial emotion perception are manifestations of the genetic liability to schizophrenia, and may be accompanied by compensatory mechanisms in relatives. Studying mechanisms in nonpsychotic relatives is a valuable way to examine effects of the unexpressed genetic liability to schizophrenia on the brain and behaviour.

1. Introduction

A core impairment in schizophrenia is perceiving emotional information from faces (Chan et al., 2010; Kohler et al., 2010). These deficits are present and relatively stable across illness phases (i.e., prodromal, first-episode, chronic) (Addington et al., 2006; Green et al., 2012). Furthermore, several studies report impaired facial emotion perception performance compared to controls in nonpsychotic first-degree relatives of schizophrenia patients (Lavoie et al., 2013), suggesting that deficits in facial emotion perception are associated with the genetic liability to schizophrenia. The current study investigates the neural basis of impaired facial emotion perception with the aim of understanding the effect of the genetic liability to schizophrenia on the brain and behaviour.

Neurobiological models of facial emotion perception postulate a "core system" of visual regions involved in the analysis of facial features [occipital face area (OFA), fusiform face area (FFA), posterior superior temporal sulcus (pSTS)], and an "extended" system comprised of regions that are recruited to process socially meaningful information contained in faces (Haxby et al., 2000). The most studied region of the extended system is the amygdala; however other regions involved in emotion processing and higher-order cognition, including the prefrontal cortex, insula, and putamen, have also been implicated (Fusar-Poli et al., 2009).

In schizophrenia, functional magnetic resonance imaging (fMRI) studies report activation abnormalities associated with impaired facial emotion perception; however, results are inconsistent. For example, some studies report under-recruitment of the amygdala in schizophrenia (Das et al., 2007; Gur et al., 2002), while others have found intact activity (Holt et al., 2005; Seiferth et al., 2008) or hyperactivity (Holt et al., 2006; Kosaka et al., 2002). Two meta-analyses (Li et al., 2010; Taylor et al., 2012) attempted to synthesize this literature, and although the findings of the two analyses converged for several regions (e.g., hypoactivity in FFA and amygdala in schizophrenia vs. controls), they diverged with respect to functional abnormalities in other regions of the neural system for facial emotion perception, and only one meta-analysis (Taylor et al., 2012) reported significant hyperactivation in schizophrenia patients. Similarly, the handful of previous fMRI studies of facial emotion perception to include nonpsychotic relatives have reported conflicting results, including reduced (Barbour et al., 2010; Habel et al., 2004), increased (Li et al., 2012; van Buuren et al., 2011), or comparable (Rasetti et al., 2009) activation patterns compared to controls.

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A likely explanation for the inconsistent findings concerns the large variety of tasks used in previous fMRI studies of facial emotion perception in schizophrenia. The assortment of primarily explicit evaluative tasks (e.g., recognition, labelling, matching, discrimination, intensity rating) vary in the degree to which they measure the sensory/perceptual and appraisal processes involved in facial emotion perception, as well as in the recruitment of cognitive mechanisms relied on for task completion. Overall, these differences may influence the observed patterns of neural activation. Support for this explanation comes from several lines of evidence: 1) findings of prefrontal cortex–amygdala modulation induced by linguistic vs. non-linguistic labelling of facial emotion in healthy participants (Hariri et al., 1999); 2) the widespread pattern of neurocognitive impairment in schizophrenia (Reichenberg and Harvey, 2007) and the range of cognitive processes recruited by the majority of facial emotion perception tasks (e.g., context processing, set shifting, working memory); 3) fMRI evidence of strategy use differences between schizophrenia patients and controls on tasks of facial emotion recognition (Fakra et al., 2008); and 4) direct evidence that the effects of context on emotional appraisal, driven by task demands, exert differential effects on neural activation in schizophrenia patients and controls (Leitman et al., 2011).

In sum, the varied activation abnormalities observed in schizophrenia during task performance may in part reflect the influence of study-specific task demands and/or impaired generalized neurocognitive processes in schizophrenia. In the present study, we used a passive viewing fMRI task of facial emotion perception in order to minimize task demands and examine brain activation associated with sensory/perceptual (as opposed to appraisal) processes involved facial emotion perception in schizophrenia. Furthermore, we used a family study design, in which nonpsychotic relatives are assessed in addition to patients and controls, in order to investigate whether activation abnormalities are associated with the genetic liability to schizophrenia. We hypothesized that patients and relatives would display reduced activation compared to controls in key regions of interest (ROIs) from the neural system for face perception, with relatives displaying activation intermediate between patients and controls.

2. Methods

2.1. Participants

Participants were 28 individuals with schizophrenia or schizoaffective disorder (hereafter referred to as schizophrenia patients), 27 nonpsychotic first-degree biological relatives, and 27 community controls. Schizophrenia patients were recruited through outpatient clinics at the Foothills Medical Centre and community support programmes in Calgary, Canada. Research staff identified first-degree relatives by completing a pedigree with patients and obtaining permission to contact. Controls were recruited through advertisements posted online and in the Calgary community. Participants gave written informed consent before participating and the study protocol was approved by the University of Calgary Research Ethics Board.

Exclusion criteria were: 1) age below 18 or above 65 years, 2) an estimated Intelligence Quotient (IQ) less than 70, 3) current alcohol or drug abuse/dependence, 4) history of head injury resulting in unconsciousness greater than 20 min or hospital visit, 5) past/current central nervous system or neurological condition, 6) history of electroconvulsive therapy, 7) less than normal/corrected-to-normal vision, and 8) MRI contraindications. Additional exclusion criteria for relatives and controls were: 1) personal history of psychotic/bipolar disorders, 2) current major depressive episode, 3) Axis II Cluster A personality disorder, and 4) previous/current use of antipsychotic medication. A further exclusion criterion for controls was a family history of psychotic/bipolar disorders.

Diagnoses were confirmed by the Structured Clinical Interview for DSM-IV (First et al., 2002), and symptomatology was assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987). The Structured Interview for Schizotypy (Kendler et al., 1989), with supplemental questions, was administered to assess for Axis II Cluster A personality traits in relatives and controls. The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was used to estimate IQ.

2.2. Tasks

2.2.1. Passive viewing facial emotion perception task

Participants were presented with individual full-colour images representing one of five categories of facial expressions (happy, sad, angry, fearful, neutral) or images of scrambled faces, obtained from the Penn Emotion Recognition Test (ER40) (Carter et al., 2009). Each stimulus category contained eight different images, for a total of 48 stimuli, which were balanced for age, sex, and ethnicity. An event-related design was used, where stimuli were presented for 3000 ms in random order and each stimulus was preceded by a fixation cross (jittered inter-stimulus interval mean: 4500 ms; range: 3750–5500 ms). Total task duration was 390 s. Participants were instructed to simply pay attention to the series of images as they appeared.

2.2.2. Functional localizer

A block-design functional localizer task consisting of video-clips of nonliving objects and dynamic displays of facial expressions (Fox et al., 2009) was used to localize ROIs on a single-subject basis. For each trial, participants made a key press to indicate whether the current video-clip was identical to the previously viewed clip (see the Supplementary material).

2.3. Image acquisition

Scanning was performed on a 3T General Electric Discovery MR750 scanner (General Electric Healthcare, Waukesha, Wisconsin, USA) equipped with an 8-channel head coil, at the Seaman Family MR Research Centre, University of Calgary. Functional EPI data were acquired with 40, 3.4 mm slices, TE = 30 ms, TR = 2500 ms, flip angle = 77°, FOV = 22, and matrix = 64 × 64. One hundred and fifty-six volumes were acquired during the facial emotion perception task run and 159 volumes were acquired during the functional localizer run. Additionally, an MPRAGE anatomical scan was acquired to register the functional data (236, 1 mm slices, TE = 3.1 ms, TR = 7.4 ms, TI = 650 ms, FOV = 25.6, matrix = 256 × 256).

2.4. Data analysis

Analyses were performed using tools from the FMRIB Software Library (www.fmrib.ox.ac.uk/fsl), version 5.0.6. Image preprocessing included non-brain tissue removal, motion and slice-timing correction, spatial smoothing (7 mm FWHM Gaussian kernel), grand-mean intensity normalization, and highpass temporal filtering. Functional images were registered to the structural image and then standard Montreal Neurological Institute space using non-linear transformations. Generated time-series plots of each participant's estimated translations and rotations were carefully inspected for excessive motion.

2.4.1. Functional localizer and ROI analyses

A detailed description of the functional localizer model fitting and ROI definition is found in the Supplementary material. Functional ROIs included bilateral OFA, FFA, and pSTS, while structural amygdala ROIs were used due to the low number of participants with functionally identified amygdalae. For each participant, *z*-statistic images from the facial emotion perception contrasts (described below) were extracted for each ROI, and averaged across the group level. Group differences were assessed using one-way analysis of variance (ANOVA) and followed by planned pairwise comparisons. Independent *t*-tests were used instead of pairwise comparisons when the homogeneity of variance assumption

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